Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guide-lines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

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CLINICOPATHOLOGIC CONFERENCE

A 36-Year-Old Man With Renal Failure, Fever, and Hypocomplementemia

Kimberly DeQuattro, Anatoly Urisman, and Mary Margaretten

CASE PRESENTATION

Chief symptoms

A 36-year-old man with recently diagnosed renal injury presented with fevers and dental pain.

History of present illness

For 15 months, the patient had experienced decreased appetite and malaise, and had missed work due to his symptoms. Two months prior, cough and ongoing malaise prompted a visit to the emergency department. At that time, routine laboratory evaluation revealed a blood urea nitrogen level of 105 mg/dl and a creatinine level of 7.01 mg/dl with estimated glomerular filtration rate of 9 ml/minute/1.73 m^2. The patient was examined and a renal biopsy was performed. A 16-day trial of oral prednisone was prescribed for presumed acute interstitial nephritis. The patient was discharged without undergoing dialysis and seen a week later in the renal clinic for follow-up. Seven weeks later, he returned to the emergency department with a report of fever and dental pain of 6 day's duration and was admitted. The results of the initial renal biopsy were limited due to a small sample; however, it showed non-specific findings of extensive interstitial fibrosis and tubular atrophy with scattered lymphoplasmacytic inflammation and a few globally sclerotic glomeruli.

Medical, social, and family history

The patient's medical history was notable for a gunshot wound to the left upper extremity requiring exploratory surgery 7 years earlier. At the time of the current admission, the patient had completed a course of oral prednisone (40 mg twice daily for 4 days, 30 mg twice daily for 4 days, 40 mg daily for 4 days, 20 mg daily for 4 days) and was taking sevelamer carbonate (800 mg) orally 3 times daily.

The patient was Hispanic, was married with one child, and worked as a dishwasher at a restaurant. He did not consume alcohol, or use tobacco or illicit drugs. There was no family history of autoimmune disease, renal disease, or malignancy. His mother died at a young age of "cirrhosis" of unclear etiology; she did not consume alcohol.

Review of systems

The patient had anorexia but no weight change. He denied pharyngitis, visual changes, oral or nasal ulcers, rash or nodules, weight loss, abdominal pain, dysuria, hematuria, flank pain, or edema. He had no history of tuberculosis, incarceration, or homelessness. He denied sick contacts, recent travel, and occupational exposures.

Physical examination

On examination, he was febrile with a body temperature of 39.4°C. His blood pressure was 138/84 mm Hg, pulse was 132 beats per minute, respiratory rate was 22 breaths per minute, and oxygen saturation was 96% on room air. Conjunctival pallor was noted, and an oral examination was significant for dental caries with normal salivary pool. There was no lacrimal gland swelling and no pain with extraocular movements. Neck examination revealed shotty, subcentimeter submandibular and anterior cervical lymphadenopathy without diffuse parotid or submandibular swelling. Cardiopulmonary examination demonstrated tachycardia with regular rate and rhythm. His carotid, brachial, radial, and femoral pulses were 2+. His lungs were clear to auscultation. His abdomen was soft and

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Kimberly DeQuattro, MD, MM, Anatoly Urisman, MD, PhD, Mary Margaretten, MD, MAS: University of California, San Francisco.

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Address correspondence to Kimberly DeQuattro, MD, MM, Division of Rheumatology, Department of Medicine, University of California San Francisco, 505 Parnassus Ave, Room 987, San Francisco, CA 94143. E-mail: Kimberly.DeQuattro@ucsf.edu.

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non-distended and hepatosplenomegaly was not present. The neurologic examination revealed 5/5 strength bilaterally in the flexors, extensors, abductors, and adductors of the upper and lower extremities, and the reflexes were 2+ throughout. There were no sensory deficits. The gait was normal and he had no synovitis or joint effusions and had full range of motion in all of his joints. The extremities were non-edematous, and no rash was present.

Table 1. Laboratory evaluation results at initial emergency department visit, 3 months later, and 15 months later*

	Initial	3 months	15 months	Normal range
WBC count, cells/mm^3	10,300	12,200	5,500	3,900–11,700
Hemoglobin, gm/dl	9.5	9.3	10.8	13.3–17.1
Hematocrit, %	30.2	28.0	30.7	39.8–52.2
Platelet count, cells/mm^3	135,000	138,000	125,000	150,000–400,000
ESR, mm/hour	122	106	26	0–15
Sodium, mmoles/liter	136	142	145	136–145
Potassium, mmoles/liter	4.5	4.0	4.4	3.5–5.1
Chloride, mmoles/liter	112	105	113	98–109
Carbon dioxide, mmoles/liter	11	22	22	22–29
BUN, mg/dl	105	48	59	6–20
Creatinine, mg/dl	7.01	4.44	4.91	0.7–1.3
Glucose, mg/dl	86	103	101	70–199
AST, units/liter	87	40	ND	10–48
ALT, units/liter	52	13	ND	10–40
Bilirubin, total mg/dl	0.3	0.3	ND	0–1.1
Alkaline phosphatase, units/liter	165	313	ND	56–119
Albumin, gm/dl	2.6	3.6	4.1	3.2–4.6
Total protein, gm/dl	9.4	7.5	ND	6.2–8.1
CRP, mg/liter	161.5	26.8	ND	<3.1
Serum C3, mg/dl	40	12	103	86–184
Serum C4, mg/dl	<1	1	24	12–40
IgG4, mg/dl	1,260	437	ND	86–135
Urine protein, mg/dl	93	68	195	0–15
Urine creatinine, mg/dl	101.4	58.6	91.6	ND
Protein:creatinine ratio	1.1	0.9	0.5	<0.02
Complement activity, CAE units	ND	1	ND	60–144
Urine specific gravity	1.011	1.006	1.011	1.003–1.030
Urine pH	7.0	7.0	6.5	5.0–7.0
Urine protein	1+	1+	1+	0
Urine nitrites	Negative	Negative	Negative	Negative
Urine leukocyte esterase	Negative	Positive	Negative	Negative
Urine glucose	Negative	Negative	Negative	Negative
Urine ketones	Negative	Negative	Negative	Negative
Urine blood	1+	ND	ND	0
Urine WBC cells/hpf	10–20	0–2	20–50	0–2
Urine RBC cells/hpf	10–20	2–5	0–3	0–3
Blood cultures 2/2 bottles	ND	*S pneumoniae*	ND	Negative
Urine culture, (colonies/ml)	ND	*S viridans* (15,000)	ND	Negative

* WBC = white blood cells; ESR = erythrocyte sedimentation rate; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ND = no data; ALT = alanine aminotransferase; CRP = C-reactive protein; C3 = compliment 3; hpf = high-power field; RBC = red blood cells; *S* = *Streptococcus.*

Laboratory evaluation

The results of the initial laboratory evaluation revealed normal peripheral smear and lactate dehydrogenase, non-reactive HIV-1/2 antigen/antibody combination test, hepatitis C virus antibody, and normal cryoglobulins, and serum protein electrophoresis with immunofixation. Additional results are shown in Table 1. Radiography of the chest did not show hilar lymphadenopathy. Abdominal and renal ultrasonography demonstrated a normal liver without nodularity or masses but was notable for bilateral nephromegaly with marked echogenicity in the medullary pyramids (Figure 1) and splenomegaly. Transthoracic echocardiogram (TTE) demonstrated normal systolic, diastolic, and valvular function without vegetations.

CASE SUMMARY

The patient is a 36-year-old man with acute fevers in the setting of fibrotic kidney injury, nephromegaly, and hypocomplementemia.

DIFFERENTIAL DIAGNOSIS

To synthesize this case, each of 3 key characteristics—fibrotic renal disease, nephromegaly, and hypocomplementemia—has a separate differential diagnosis to be considered. A unifying diagnosis will explain all features and guide further investigation.

Tubulointerstitial nephritis (TIN). TIN is an important cause of chronic kidney disease. Acutely, TIN is often reversible. Yet chronic disease can result in irreversible scarring due to interstitial fibrosis and tubular atrophy. These pathologic changes are a consequence of inflammatory and tissue repair mechanisms that promote fibrosis via cytokine production and recruitment of fibroblasts (1,2). Progressive loss of functional renal parenchyma due to interstitial fibrosis and tubular atrophy ultimately leads to end-stage renal disease. The degree of interstitial fibrosis and tubular atrophy is an important predictor of long-term renal survival (2).

Drug-induced TIN is the most common cause of chronic kidney disease and is typically associated with β-lactam antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), and other medications including rifampin, sulfonamides, and allopurinol. The clinical presentation is often allergic and can include fever (36%), eosinophilia (35%), rash (22%), or the full triad (11%) (3). Although our patient was exposed to NSAIDs and the presence of white blood cells in the urine supported this diagnosis; hypocomplementemia and nephromegaly are not seen in cases of TIN due to NSAID use.

Autoimmune disease–associated TIN can be associated with systemic lupus erythematosus (SLE), sarcoidosis, Sjögren's syndrome, and granulomatosis with polyangiitis (GPA) (4,5). Patients with SLE and GPA often have an interstitial nephritis accompanying the characteristic glomerular disease and may rarely present with acute interstitial nephritis, even in the absence of glomerular disease. Amyloidosis and IgG4-related disease (IgG4-RD) can also cause TIN (6,7). Despite hypocomplementemia, renal injury, and anemia, there was no other specific symptom, sign, positive antinuclear antibodies, or positive antineutrophil cytoplasmic antibodies to suggest SLE, Sjögren's syndrome, or GPA. Although the patient had poor dentition, Sjögren's syndrome was unlikely given the lack of xerostomia or xerophthalmia. Infiltrative processes such as sarcoidosis, amyloidosis, and IgG4-RD can go undiagnosed for months to years given the potential relative paucity of clinical symptoms until end-organ damage is manifested. There were no granulomas present on the renal biopsy sample to suggest sarcoidosis, and Congo red staining with birefringence was negative for the presence of amyloid.

TIN and uveitis (TINU) is an uncommon entity usually encountered by ophthalmologists and pediatric nephrologists. It is seen typically in young women and the pathogenesis is unknown. Patients with TINU may make autoantibodies against modified C-reactive protein, which is found both in uveal and renal tubular cells (8). Uveitis is initially treated with glucocorticoids and renal disease can be self-limited, although it may require additional immunosuppression (9). Our patient lacked ocular findings and his male sex and age made this diagnosis unlikely.

Infectious causes of TIN include bacterial (*Streptococcal* species, *Legionella*, *Leptospira*), viral (cytomegalovirus, adenovirus, polyomavirus), and fungal (histoplasma, Candida) pathogens. Although our patient was found to have *Streptococcus pneumoniae* in the blood and urine, which could raise suspicion for subacute bacterial endocarditis in the setting of hypocomplementemia, TTE was negative for vegetations, effectively ruling out endocarditis. However, the patient's profound hypocomplementemia and splenomegaly may have contributed increased susceptibility to encapsulated organisms, rather than the *Streptococcal* species directly causing tubulointerstitial injury (10).

Nephromegaly. Causes of nephromegaly are broad and can be categorized by type (Table 2), with the most common cause of nephromegaly being diabetes mellitus (11). Rheumatologists are more likely to encounter nephromegaly in patients with urate nephropathy from gout, some cases of lupus nephritis, and organ infiltration from sarcoidosis, amyloidosis, or IgG4-RD (12). As mentioned previously, the diagnoses of SLE, sarcoidosis, and amyloidosis were not suspected.

Hypocomplementemia. Complement is activated in several rheumatologic diseases, such as SLE. Complement defends against pathogens, promotes antibody responses, and clears immune complexes in concert with the innate and adaptive immune systems (13). In SLE, complement contributes to inflammation, reducing plasma complement levels while depositing in tissues (14). Other rheumatologic entities in which comple-

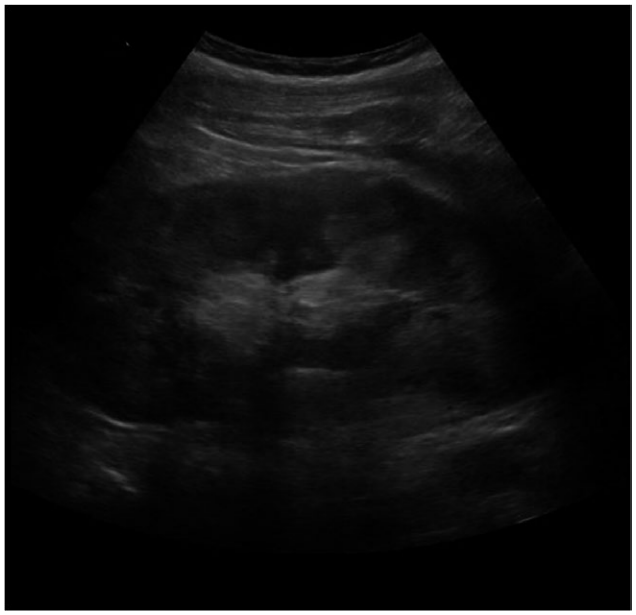

Figure 1. Renal ultrasound of the left kidney. Bilaterally, the kidneys were markedly echogenic, primarily within the medullary pyramids. There was bilateral nephromegaly (14.6 cm in the left kidney; and 13.8 cm in the right [not shown]. Normal range 10–13 cm).

ment is activated include hypocomplementemic urticarial vasculitis syndrome (HUVS) as well as cryoglobulinemic vasculitis, seen in patients with Type I (monoclonal IgG or IgM [e.g., multiple myeloma/Waldenstrom's macroglobulinemia]), Type II (mixed polyclonal IgG with monoclonal IgM rheumatoid factor [e.g., hepatitis B or C]), or Type III (polyclonal IgG and IgM rheumatoid factor [e.g., SLE, Sjögren's syndrome, hepatitis C]) (14). As the name suggests, a diagnosis of HUVS necessitates the presence of hypocomplementemia as well as the intermittent presence of urticarial wheals of at least 6 months' duration (15). The patient's lack of urticarial wheals, arthritis, uveitis, and abdominal pain made this an unlikely cause. The patient had no clinical or laboratory findings consistent with cryoglobulinemic vasculitis (16). Hypocomplementemia can also be seen in IgG4-RD (17).

DIAGNOSIS

Of the etiologies reviewed above, only IgG4-RD was a constant among the triad of fibrotic renal disease, bilateral nephromegaly, and hypocomplementemia. To confirm IgG4-RD, additional laboratory testing and tissue staining were essential.

CLINICAL COURSE

The serum IgG4 was 1,260 mg/dl, which measured more than 9-times the upper limit of normal (normal range 86–135 mg/dl). Given the concern for IgG4-RD, serum plasma IgG4 levels were obtained and a repeat renal biopsy was performed. The biopsy result showed storiform fibrosis, dense interstitial lymphoplasmacytic infiltrates with up to 40 IgG4-positive plasma cells/high-power field (hpf), and an IgG4-positive/total IgG-positive plasma cell ratio of >80%, which strongly suggested a diagnosis of IgG4-RD TIN (Figure 2). Electron microscopy and immunofluorescence studies performed on the biopsy tissue did not reveal evidence of an immune complex–mediated glomerulonephritis or paraprotein deposition. Blood cultures grew *S pneumoniae* in 2 out of 2 bottles, and urine cultures grew *S viridans*. Antibiotics were initiated for the patient's acute infection. After he completed the course of antibiotics, he was started on prednisone (60 mg/day) and rituximab (1,000 mg intrave-

Table 2. Causes of bilateral nephromegaly*

Causes
Obstructive
Urate nephropathy
Myoglobinuria
Hemoglobinuria
Cystic
Polycystic kidney disease
Tuberous sclerosis
Multicystic dysplastic kidney
Metabolic
Diabetes mellitus (most common)
Acromegaly
Storage diseases (GSD)
Inflammatory
Acute tubulointerstitial nephritis
Acute glomerulonephritis
Acute nephrotic syndrome
Abscess
Kawasaki disease
Hematologic
Sickle cell disease
Renal vein thrombosis
Oncologic
Leukemia/lymphoma
Multiple myeloma
Renal cell carcinoma
Infiltrative
Sarcoidosis
Aamyloidosis
IgG-4–related disease
Malakoplakia (histiocytic infiltration)
Infectious
Viral (HIV)
Fungal (histoplasmosis)
Bacterial (TB, PJP)

* GSD = glycogen storage disease; TB = tuberculosis; PJP = *Pneumocystis jiroveci* pneumonia (11,27).

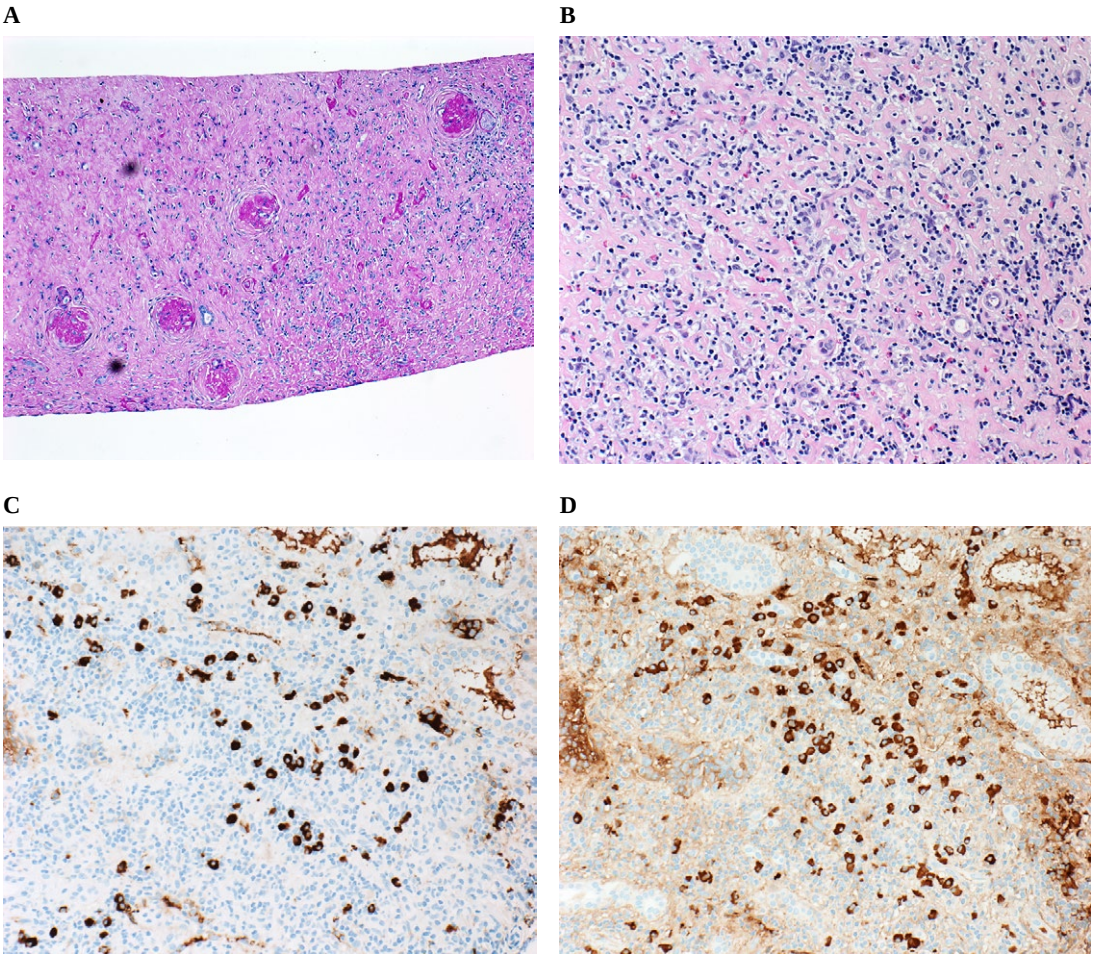

Figure 2. Photomicrographs showing renal biopsy findings. **A**, Several globally sclerotic glomeruli are seen within dense interstitial fibrosis without recognizable tubules; scattered interstitial inflammatory cells are noted. Periodic acid–Schiff stained; original magnification × 100. **B**, Storiform fibrosis (pink collagenous background) was diffuse with associated lymphoplasmacytic infiltrates. Hematoxylin and eosin stained; original magnification ×200. **C** and **D**, Immunohistochemical staining for IgG4 (**C**) and total IgG (**D**) demonstrates that most (>80%) of IgG-positive plasma cells are also positive for IgG4. Original magnification × 400.

nously at week 0 and week 2) for IgG4-RD TIN. C4 level was checked after 15 months and had normalized from <1 to 24. Fifteen months after the initial presentation, the creatine level (4.91 mg/dl) and urine protein-to-creatinine ratio (0.5) remained elevated despite the administration of a second cycle of rituximab and a slow prednisone taper.

DISCUSSION

IgG4-RD is a multi-organ, fibrotic, inflammatory condition that can affect nearly every organ (6). Renal involvement in IgG4-RD occurs in 15% of patients, most commonly as TIN or membranous glomerulonephritis (MGN) (18). Another renal manifestation of IgG4-RD includes retroperitoneal fibrosis causing impingement-related hydronephrosis (18,19).

IgG4-RD TIN is an increasingly recognized manifestation of IgG4-RD, although existing study sample sizes are small. IgG4-RD TIN is more common in men than women with an onset that is typically insidious rather than rapidly progressive, as reflected by a slowly rising average age at onset of 65 years. Concomitant extra-renal disease is frequent (18,20) and the creatinine level. Mild proteinuria is more common than nephrotic-range proteinuria (18). Frequently, urinalysis with microscopy demonstrates mild hematuria; pyuria and white blood cell casts are uncommon. Hypocomplementemia of C3, C4, and CH50 occurs in 60% of patients with IgG4-RD TIN (21). C4 deficiency from IgG4-RD TIN may have increased the patient's susceptibility to infection with encapsulated organisms. Low complement is unusual in IgG4-RD unless there is tubulointerstitial renal involvement. Therefore, hypocomplementemia in IgG4-RD should raise suspicion for IgG4-RD TIN (18). One hypothesis for hypocomplementemia in IgG4-RD TIN is that although IgG4 itself may not bind complement, other IgG subclasses, which are often elevated in patients with IgG4-RD, bind complement (21,22). Weakly positive antinuclear antibodies may be present, although specific serologies for SLE and Sjögren's

Table 3. Comparison of IgG4 renal disease: tubulointerstitial versus membranous nephritis*

Characteristic	Tubulointerstitial nephritis	Membranous nephritis
Males	Common, 80%	Common
Age >65 years	Common	Common
Proteinuria, gm	<3.5	>3.5
Hypocomplementemia	Common, 60%	Rare
Anti-PLA_2R autoantibodies	Absent	Absent
Bilateral nephromegaly	Common	Rare
Renal mass lesions	25%	Rare
TBM immune complex deposits	80%	30%
Proteinuria resolution with treatment	Brisk	Delayed
Other IgG4-RD organ involvement	80%	80%
Acute or progressive chronic renal failure	75%	Reported, % unknown

* Anti-PLA_2R = antiphospholipase A_2 receptor; TBM = tubular basement membrane (7,21,24).

syndrome are typically negative. Elevated serum IgG4 greater than 6- to 8-times the normal upper limit should raise concern for IgG4-RD; and multi-organ disease may elevate IgG4 levels to 40 to 50-times the normal range (18). Normal serum IgG4 does not exclude the diagnosis and an elevated IgG4 level requires clinicopathologic correlation.

Radiographic features of IgG4-RD TIN include bilateral nephromegaly in 20% of patients as well as bilateral lesions of the renal cortices in 40%. These hypodense masses can mimic renal cell carcinoma. Two features of renal parenchymal lesions in IgG4-RD TIN include clear demarcation between affected and unaffected parenchyma, and infiltration that invades into and beyond the renal capsule (19).

Hallmark histopathologic features in IgG4-RD are dense inflammatory lymphoplasmacytic infiltrates composed of polyclonal CD20 B lymphocytes, T cells, and IgG4+ plasma cells and storiform fibrosis, so-called for its irregular whorled appearance. A third pathologic feature, obliterative phlebitis, is an uncommon finding in renal biopsy. Mild tissue eosinophilia may be present but is not required for diagnosis (6). Two or more of the above pathologic features on kidney biopsy in combination with >10 IgG4-positive plasma cells/hpf is highly suggestive of IgG4-RD and confirmed when a background of >40% IgG4-positive/IgG-positive plasma cell ratio is also met (6,23).

IgG4-RD MGN is rare and can co-occur with IgG4-RD TIN (7%) (17). Patients with IgG4-RD MGN tend to be older males with elevated creatinine, hypoalbuminemia, and nephrotic-range proteinuria at diagnosis (24). Typically, in IgG4-RD MGN, complement levels are normal and nephromegaly is not a feature. A comparison of the features of IgG4-RD TIN and MGN is shown in Table 3.

Prompt treatment of IgG4-RD TIN is crucial to prevent progression of fibrosis and to preserve long-term renal function. Randomized controlled trials are lacking owing to the rarity of the disease. Glucocorticoids are first-line therapy, and in some cases monotherapy has led to renal improvement (25). Despite treatment with steroids, relapse can occur in 15–20% of patients, leading to progressive chronicity and end-stage renal disease (7,25).

In cases of IgG4-RD, rituximab has been used with the rationale that it will interfere with short-lived plasma cells, plasmablasts, and B cells contributing to IgG4-RD pathology (26). An open-label prospective, single-arm trial of rituximab in 30 individuals with varied organ involvement resulted in complete remission in 40% of the subjects at 12 months. In that cohort, 4 of 30 subjects (13%) had IgG4-RD TIN (27). Refractory cases of IgG4-RD may fail to recover organ function if fibrosis is too extensive, despite aggressive treatment with multiple cycles of rituximab (28).

Although glucocorticoids are first-line therapy for IgG4-RD due to a lack of randomized controlled trials providing evidence for other therapies, there were several reasons for concurrent treatment with prednisone and rituximab. The major concern in this patient with severe disease and delayed diagnosis was the inability to predict long-term renal response. With both inflammation and fibrosis present on biopsy, there was some possibility of reversibility. Frequency of relapse while receiving glucocorticoid monotherapy in IgG4-RD is well-described (22) as is long-term renal atrophy in those with IgG4-RD renal disease who present with low estimated glomerular filtration rate at baseline (29).

Case series and open-label data suggest that rituximab may be well-tolerated and effective for active inflammation in IgG4-RD (27,28), even in the absence of glucocorticoid therapy (27). The results are less clear in cases of advanced fibrosis, and no trials have specifically addressed IgG4-RD TIN. The patient was treated simultaneously with glucocorticoid and rituximab in hopes of avoiding irreversible end-stage renal disease leading to dialysis.

FINAL DIAGNOSIS

IgG4-RD TIN with associated hypocomplementemia leading to *S pneumoniae* sepsis and *S viridans* urinary tract infection.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. DeQuattro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. DeQuattro, Margaretten.
Acquisition of data. DeQuattro, Urisman, Margaretten.
Analysis and interpretation of data. DeQuattro, Urisman, Margaretten.

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BRIEF REPORT

Has Rheumatology Become a More Attractive Career Choice? Comparison of Trends in the Rheumatology Fellowship Match From 2008 to 2013 With Those From 2014 to 2017

Huynh W. Tran, Lauren M. Mathias, and Richard S. Panush

Objective. Rheumatology has previously been a less attractive career choice than other internal medicine (IM) subspecialties. Recent fellowship data from the National Resident Matching Program (NRMP) has suggested that this may have changed. Therefore, we evaluated the current attractiveness of rheumatology as a career choice and compared it with other medical subspecialties.

Methods. Data from the NRMP from 2008 to 2017, the 2015 American College of Rheumatology workforce study, and Medscape physician salaries from 2010 to 2017 were used to determine annual numbers of fellowship applicants, availability of positions, and post-fellowship salary trends. Data from 2008 to 2013 were compared with those from 2014 to 2017, and rheumatology was compared with other IM subspecialties.

Results. The total number of annual fellowship applicants to rheumatology for 2008–2013 decreased by 3% (average annual mean ± SEM percentage change of –1.9 ± 2.6%), from 251 to 244 applicants. However, for 2014–2017, annual rheumatology applications increased by 44% (average annual mean ± SEM percentage change of 20.7 ± 10.5% [$P = 0.03$]), from 230 to 332 applicants. Other nonprocedural and procedural IM subspecialties did not exhibit a similar increase. For rheumatology, the increases in the ratio of annual applicants to positions ($P = 0.02$) and in the percentage of US medical graduates applying ($P = 0.03$) were statistically significant, and mean post-fellowship salary also rose.

Conclusion. The aforementioned observations suggest that rheumatology has become a more attractive career choice since 2014. We speculate that the increasing popularity of the field is multifactorial, likely reflecting lifestyle, job satisfaction and availability, influence of mentors, and other elements. This salutary and exciting potential opportunity for rheumatology should be exploited.

INTRODUCTION

We consider rheumatology to be a cognitive subspecialty that combines diagnostic and management challenges with rewarding and particularly humanistic patient care (1–4). A recent survey found rheumatologists to be the happiest physicians (5,6). Yet despite these potentially appealing aspects, for many years rheumatology has been a less popular career choice than other internal medicine (IM) subspecialties. This perception may have contributed to the limited growth of rheumatologists in the US. The 2015 American College of Rheumatology/Association of Rheumatology Health Professionals Workforce Study, based on 2005–2013 data, projected a notable discrepancy between expected supply and demand of rheumatologists in the future—a shortfall of 2,329 rheumatologists in 2020, 3,845 in 2025, and 4,729 in 2030 (7). Recent fellowship NRMP data has, however, suggested that interest in rheumatology may have changed. We therefore evaluated the current attractiveness of rheumatology as a career choice and compared it with other medical subspecialties.

MATERIALS AND METHODS

This retrospective study examined annual numbers of applicants to fellowships, numbers of fellowship positions, applicant-to-fellowship position ratios, percentage of offered positions filled, percentage of applicants matched, percentage of US medical

Huynh W. Tran, MD, Lauren M. Mathias, MD, Richard S. Panush, MD, MACP, MACR: University of Southern California and Los Angeles County + University of Southern California Medical Center, Los Angeles.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Dr. Richard Panush, 2011 Zonal Avenue, Los Angeles, CA 90022. E-mail: panush@usc.edu.

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SIGNIFICANCE & INNOVATIONS

- The increase in annual applicants to rheumatology fellowship positions since 2014 was significantly greater than during prior years. Other internal medicine nonprocedural and procedural subspecialties did not exhibit similar changes.
- The annual ratio of applicants to positions and percentage of US medical graduates applying to rheumatology also increased significantly, while mean post-fellowship salary rose.
- These observations suggest that rheumatology has become a more attractive career choice since 2014. We speculate that the reason for increasing popularity of the field is multifactorial, and likely includes elements such as lifestyle, job satisfaction, perceived availability of jobs, influence of mentors, and perhaps other elements. We perceive this as a salutary and potentially exciting opportunity for rheumatology that should be exploited.

graduates in fellowships, and post-fellowship salary trends in rheumatology and other IM subspecialties from 2008 to 2017. We compared trends from 2008 to 2013 with those from 2014 to 2017, because interest in rheumatology appeared to have changed since 2014. Data were obtained directly from the National Resident Matching Program (NRMP) for these years (8). Salary trends were obtained from the Annual Medscape Physician Compensation Reports from 2010 to 2017 (9).

All rheumatology programs and other IM subspecialties in the US and Puerto Rico that reported to the NRMP were included. Popular IM subspecialties were divided into procedural oriented (cardiology, pulmonology/critical care, and gastroenterology) and nonprocedural oriented (hematology/oncology, infectious disease, endocrinology, and nephrology). Geriatrics, allergy and immunology, sports medicine, and palliative care were excluded due to relative small size and/or multiple pathways to fellowship.

Depending on the data, descriptive statistics of fellowship program and subspecialties salaries were presented as percentage change (from a baseline year of 2008 for the 2008–2013 period, and from a baseline year of 2014 for the 2014–2017 period) or mean ± SEM. Based on an assumption of normality, the unpaired *t*-test compared the mean of groups in 2008–2013 to groups in 2014–2017, and rheumatology with other IM subspecialties. All statistical analyses were conducted using GraphPad Online QuickCals software. The study utilized de-identified publically available summary data.

RESULTS

For rheumatology, the annual total number of applicants from 2008 to 2013 decreased from 251 to 244, a 3% decrease with an average annual mean ± SEM percentage change of –1.92 ± 2.6%; however, from 2014 to 2017 the annual total number of applicants increased from 230 to 332, a 44% increase with an average annual mean ± SEM percentage change of 20.7 ± 10.5% (compared with 2008–2013) ($P = 0.03$) (Figures 1 and 2).

Other IM subspecialties did not demonstrate the increase seen for rheumatology ($P = 0.09$) (Figures 1 and 2). For nonprocedural IM subspecialties, the annual total number of applicants from 2008 to 2013 decreased from 1,940 to 1,820 applicants, which is a 6.2% decrease with an average annual mean ± SEM percentage change of –1.8 ± 1.5%. However, from 2014 to 2017, the annual total number of applicants increased from 1,594 to 1,714, an 8% increase with an average annual percentage change of 0.9 ± 2.3% ($P = 0.33$) (Figures 1 and 2). For procedural medical subspecialties, the annual total number of applicants from 2008 to 2013 increased from 2,455 to 2,582, a 5.2% increase with an average annual percentage change of –0.2 ± 1.4%. From 2014 to 2017 the annual total number of applicants increased from 2,562 to 2,631, a 3% increase with an average annual percentage of 1 ± 1.1% ($P = 0.55$) (Figures 1 and 2).

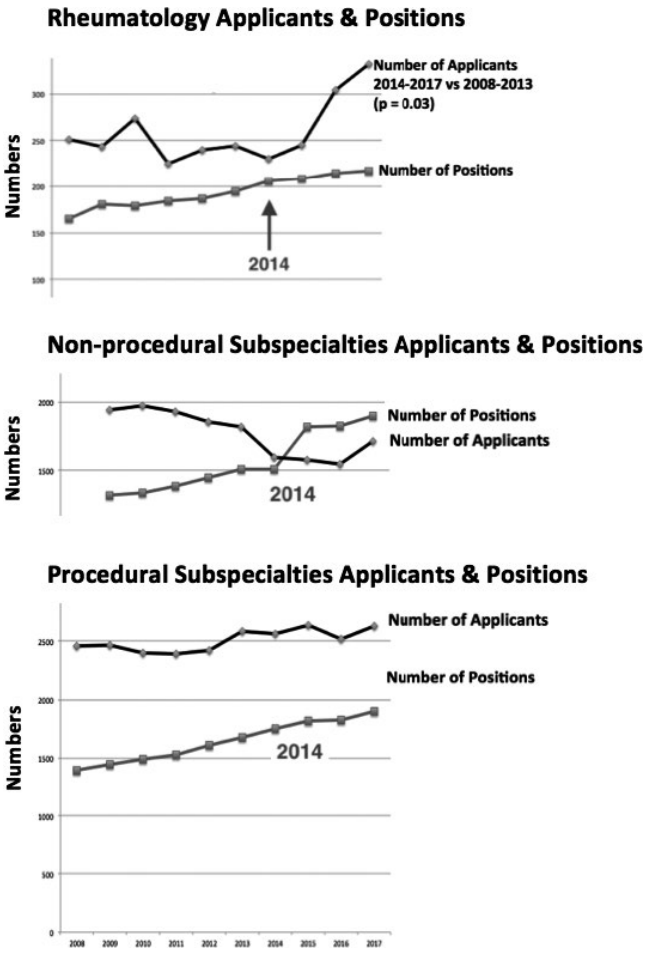

Figure 1. The number of applicants and fellowship positions for rheumatology and other medical subspecialties from 2008 to 2013 and from 2014 to 2017. The increase in the number of applicants to rheumatology after 2014, which was not seen for other medical subspecialties, was statistically significant.

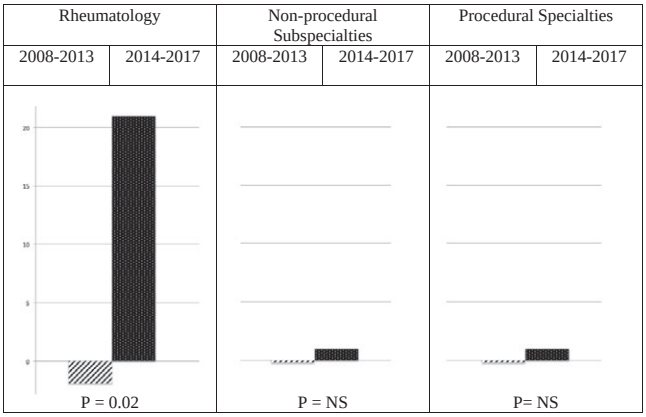

Figure 2. Percentage change of number of applicants to rheumatology and other medical subspecialties from 2008 to 2013 versus 2014 to 2017. Only rheumatology showed a statistically significant percentage change for 2014 to 2018 compared with 2008 to 2013.

For rheumatology from 2014 to 2017, compared with 2008 to 2013, there was also an increased ratio of applicants to positions (Figure 3A), an increased percentage of offered positions filled (data not shown), and an increased percentage of US medical graduate applicants (Figure 3B). The annual increase of applicants to position ratio in rheumatology from 2008 to 2013 versus 2014 to 2017 was statistically significant ($P = 0.03$) (Figure 3A); other IM subspecialties exhibited a decrease in ratio of applicants to positions during that same time (Figure 3A). The annual increase of US medical graduates applying to rheumatology from 2008 to 2013 compared with the increase from 2014 to 2017 was statistically significant ($P = 0.02$) (Figure 3B). Procedural IM subspecialties exhibited a decrease in US medical graduates applications during that same time while nonprocedural IM subspecialties showed a statistically significant increase ($P = 0.03$) (Figure 3B).

Rheumatologists' post-fellowship average annual salary increased 30%, from $180,000 in 2010 to $235,000 in 2017, while the average nonprocedural subspecialists' salaries increased 25%, from $212,500 to $264,500, and the average procedural subspecialists' salaries increased 32%, from $283,333 to $375,000. Data calculations, comparisons, results, and statistical analyses were similar when made with 2008 as the single baseline comparator year.

DISCUSSION

Rheumatology has long been regarded as a relatively unpopular career choice due to lower compensation than procedural specialties, working with patients with disorders thought to be complicated and sometimes "incurable," low exposure to the field in medical school and residency (1–4), and lower remuneration than other IM specialties (9).

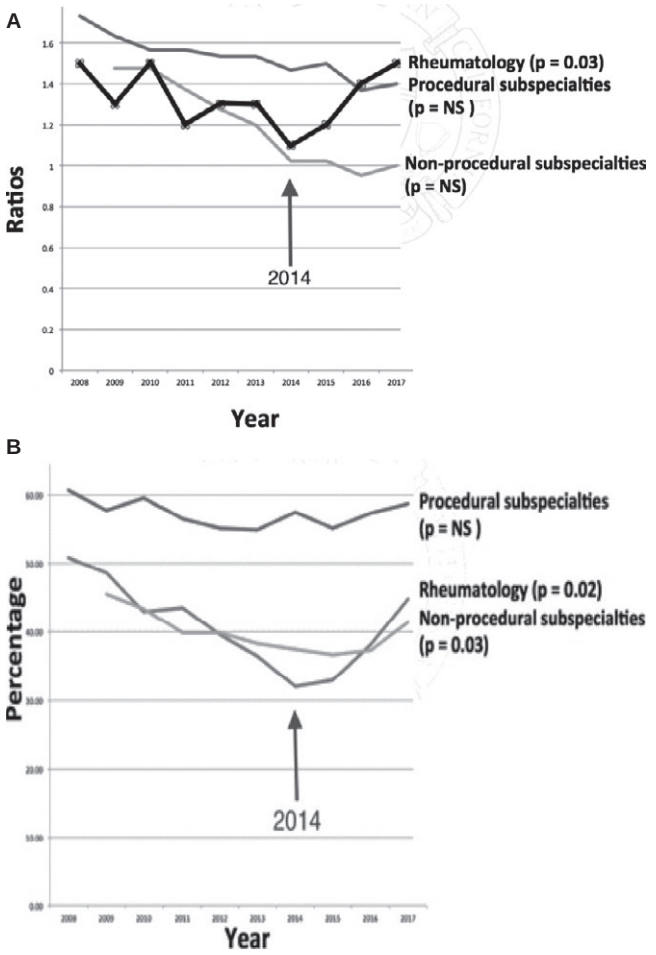

Figure 3. **A,** Ratios of application to positions in rheumatology and other medical subspecialties from 2008 to 2013 and from 2014 to 2017. The increase in the ratio of applicants to rheumatology positions after 2014, which was not seen for other medical subspecialties, was statistically significant. **B,** Changes in percentage of US medical graduates applying to rheumatology and other medical subspecialties from 2008 to 2013 and from 2014 to 2017. The increases in the percentage of US medical graduates (USMGs) applying to fellowship positions after 2014 for both rheumatology and nonprocedural subspecialties were statistically significant. NS = not significant.

There are certainly many unique and appealing aspects to rheumatology. These include increasingly attractive investigative opportunities and diverse career opportunities. Rheumatologists develop lifelong meaningful relationships with their patients, due to the chronicity of most rheumatic diseases. There are satisfying intellectual challenges. And the "compleat" rheumatologist will provide particularly humanistic care (1–4). Additionally, income disparities, compared with other subspecialties, decreased in 2016. For example, rheumatology tied with general internal medicine for the largest increase in (post-fellowship) salaries (9).

Our findings suggest that since 2014 the number of applicants and the ratio of applicants to offered positions in rheumatology

have increased in comparison with other medical subspecialties. Furthermore, the percentage of US medical graduates applying for careers in rheumatology has grown. Rheumatology seems to be becoming a more attractive and competitive subspecialty. We are unaware of similar data from other countries.

The reasons for these changes are speculative, as we did not formally study them. They might reflect factors such as improvements in compensation, attractive lifestyle, perceived availability of jobs, and influence of mentors. A recent survey from the American College of Cardiology emphasized that work-life balance considerations were paramount in trainees' career decisions (10,11). Rheumatologists tend to have regular hours and professional responsibilities that are conducive to more control over schedules and perhaps less stress than some of the other IM subspecialties. In fact, the 2012 Medscape Physician Lifestyle Report (12) indicated that rheumatologists were the happiest physicians. According to the report, rheumatologists had better social and health indicators, including normal weight, excellent health, and stable income. Rheumatology has also experienced notable scientific advances, which may make the discipline more appealing to potential applicants. Treatment of rheumatologic conditions has seen enormous progress in recent years, due to increased understanding of the pathogenesis of these diseases at the cellular and molecular levels. With the advent and efficacy of targeted therapies, achieving sustained remission for inflammatory arthritis is now a realistic goal (13,14). Intellectual interest is an important factor for applicants choosing rheumatology (3). Also, medical school curricula may now include more and more appealing presentation of rheumatic, immunologic, and musculoskeletal disorders.

Our study has several possible limitations. This is an observational, uncontrolled, study with short time trends. The data were derived from multiple publicly available databases, namely the NRMP, the ACR Workforce study, and Medscape. These data may be of limited quality, and the response rate of participants surveyed is unknown; responses to the Medscape survey were 4%. We did not include the 2018 NRMP information in our study because the entirety of Fellowship Match data for the year was not available at the time of our analysis. Preliminary information suggested that similar trends will continue in the 2018 Fellowship Match (8). There is no direct information about reasons for the changes noted. While the NRMP Match data adequately evaluates the actual rate of change in fellowship competitiveness, the forces driving this increase are less clear and merit further directed study. Lastly, US medical graduate status is not necessarily a good surrogate for the "quality" of a fellowship applicant pool, although it is often used in this manner.

Strengths of our study are that the NRMP and Medscape data are clear and respected. This study is simple and straightforward. Numbers and trends are apparent. The study did not include any guesses, manipulation of data (other than calculating percentages of change), or inferences.

Our observations complement and extend the 2015 ACR workforce report (7). We believe that the observations we have presented suggest a salutary change in the attractiveness of rheumatology in recent years. We note that more rheumatology fellowship positions would need to be offered in order to lead to more rheumatologists in the workforce, regardless of changes in the attractiveness of rheumatology. We should take advantage of this opportunity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Tran had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tran, Panush.
Acquisition of data. Tran, Panush.
Analysis and interpretation of data. Tran, Mathias, Panush.

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Connecting Rheumatology Patients to Primary Care for High Blood Pressure: Specialty Clinic Protocol Improves Follow-up and Population Blood Pressures

Christie M. Bartels,[1] Edmond Ramly,[2] Heather M. Johnson,[1] Diane R. Lauver,[3] Daniel J. Panyard,[1] Zhanhai Li,[1] Emmanuel Sampene,[1] Kristin Lewicki,[1] and Patrick E. McBride[1]

Objective. Recognizing high blood pressure (BP) as the most prevalent cardiovascular risk factor in patients with rheumatic diseases and all adults, experts recommend clinic protocols to improve BP control. The aim of this study was to adapt and implement a specialty clinic protocol, "BP Connect," to improve timely primary care follow-up after high BP measurements in rheumatology clinics.

Methods. We examined BP Connect in a 6-month preimplementation and postimplementation quasi-experimental design with 24-month follow-up in 3 academic rheumatology clinics. Medical assistants and nurses were trained to 1) check (re-measuring BPs ≥140/90 mm Hg), 2) advise (linking rheumatic and cardiovascular diseases), and 3) connect (timely [<4 weeks] primary care follow-up using protocoled electronic health record [EHR] orders). We used EHR data and multivariable logistic regression analysis to examine the primary outcome of timely primary care follow-up for patients with in-network primary care. Staff surveys were used to assess perceptions. Interrupted time series analysis was performed to examine sustainability and BP trends in the clinic populations.

Results. Across both 4,683 preimplementation and 689 postimplementation rheumatology visits by patients with high BP, 2,789 (57%) encounters were eligible for in-network primary care follow-up. Postimplementation, the odds of timely primary care BP measurement follow-up doubled (odds ratio 2.0, 95% confidence interval 1.4–2.9). Median time to follow-up decreased from 71 days to 38 days. Moreover, rheumatology visits by patients with high BP decreased from 17% to 8% over 24 months, suggesting significant population-level declines ($P < 0.01$).

Conclusion. Implementing the BP Connect specialty clinic protocol in rheumatology clinics improved timely follow-up and demonstrated reduced population-level rates of high BP. These findings highlight a timely strategy to improve BP follow-up amid new guidelines and quality measures.

INTRODUCTION

High blood pressure (BP) is the most prevalent and reversible cardiovascular disease (CVD) risk factor among all adults (1), and the risk is even higher in patients with rheumatic disease, such as those with rheumatoid arthritis (RA) (2,3). Nonetheless, we previously reported that only 10% of eligible rheumatology clinic visits resulted in documented recommendations for follow-up in patients with high BP (4), and that patients with RA were less likely to have hypertension diagnosed despite more visits than their peers meeting identical longitudinal BP thresholds (5). Although it has been shown that treating high BP in

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[1]Christie M. Bartels, MD, MS, Heather M. Johnson, MD, MS, Daniel J. Panyard, BS, Zhanhai Li, MS, PhD, Emmanuel Sampene, PhD, Kristin Lewicki, MD, Patrick E. McBride, MD, MPH: University of Wisconsin School of Medicine and Public Health, Madison; [2]Edmond Ramly, PhD: University of Wisconsin School of Medicine and Public Health and College of Engineering, Madison; [3]Diane R. Lauver, PhD: University of Wisconsin School of Nursing, Madison.

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Address correspondence to Christie M. Bartels, MD, MS, 1485 Highland Avenue, #4132, Madison, WI 53705. E-mail: cb4@medicine.wisc.edu.

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SIGNIFICANCE & INNOVATIONS

- Engaging staff nurses and medical assistants with protocols to address high blood pressure (BP) is feasible but had not been previously adapted for rheumatology clinics despite heightened cardiovascular disease risk in rheumatology patient populations.
- Following implementation of the BP protocol adapted for rheumatology clinic staff, visits in patients with high BP declined from 17% to 8% over 24 months, showing efficacy, with a significant population-level decrease.
- Engaging rheumatology clinic staff with BP protocols was an effective, evidence-based strategy to improve guideline-concordant BP follow-up among at-risk rheumatology patient populations.

11 at-risk patients could prevent 1 CVD-related event (6), half of US adults with hypertension lack BP control (7). To address this, many primary care clinics have used staff-led protocols, executed by nurses or medical assistants during vital sign assessment, to improve BP control (8), reduce variability, and save time for clinicians (9). However, BP protocols have not been adapted for rheumatology or other specialty clinics visits, which, at >423 million annual visits, outpaced primary care visits in 2013 (10).

As of 2017, 24 specialty organizations, as well as the American College of Rheumatology, endorsed screening and follow-up of high BP as a quality measure in Medicare Merit-based Incentive Payment System (MIPS) measure 317 (11). Specifically, "timely BP follow-up," defined as ≤4 weeks (12), is relevant across specialties, and referral back to a primary care clinic for follow-up meets this MIPS quality measure (11). We sought to adapt an evidence-based primary care clinic protocol (8) for use by specialty clinic staff to improve timely follow-up of patients after high BP measurements in rheumatology clinics.

Our multidisciplinary team developed a specialty BP protocol intervention and implementation plan adapted for rheumatology nurses and medical assistants (8,13–15). Based on the Chronic Care model (16) and Self-Regulation Theory (14), we hypothesized that when staff and patients were supported by a protocol, they would acquire BP data, compare them to norms, and take action to reach goals. A clinic rooming protocol empowers staff to work at the top of their licensure (17) by clarifying staff target behaviors, such as re-measuring high BPs and ordering primary care follow-up when BP is confirmed as being high. Likewise, patients who receive clinic feedback regarding high BPs could follow up with primary care, and, or modify behaviors, to improve antihypertensive medication adherence or lifestyle factors for BP control. We hypothesized that implementing a protocol would improve timely primary care follow-up after confirmed high BP readings at rheumatology visits and potentially improve population trends versus usual care.

PATIENTS AND METHODS

We evaluated preimplementation and postimplementation and clinic population outcomes of our specialty clinic BP protocol, BP Connect, at 3 academic rheumatology clinics. We compared timely primary care BP follow-up and population-level rates of high BP readings during the protocol project compared to preimplementation usual care. For the study period, ≥140/90 mm Hg (18) was the guideline-based high BP threshold for protocol steps and performance feedback (19), although now ≥130/80 mm Hg meets the definition of high BP (20). The institutional review board (IRB) certified exemption, and neither individual written consent nor full IRB approval was required for this standard-of-care improvement initiative, and certification included permission to publish.

Setting and participants. The project was conducted in 3 rheumatology specialty clinics attended by adults, within the tenth largest US academic multispecialty group. These 3 sites were in separate buildings with separate staff (medical assistants, nurses, and schedulers). We compared a baseline 2-year period (January, 2012 to September, 2014) to a staggered-start 6-month intervention period (November, 2014 to June, 2015). Outcomes were followed for 24 months, through 2016.

Intervention. The BP Connect specialty clinic protocol consisted of 3 steps: 1) check, 2) advise, and 3) connect, based on successful primary care protocols (8,15). First, adults visiting a rheumatology clinic who had a BP ≥140/90 mm Hg were eligible for protocol initiation with BP re-measurement checks. Next, if a BP of ≥140/90 mm Hg was confirmed, patients were eligible for brief advice regarding follow-up due to associations between BP, CVD, and rheumatic diseases. Finally, staff offered to connect patients to primary care follow-up. Specialty clinic patients with in-network primary care were eligible for the primary end point of timely primary care follow-up (≤4 weeks) (12). Clinic schedulers directly scheduled in-network follow-up, while all patients were eligible for printed primary care follow-up recommendations. Staff cues and patient eligibility were automated within the electronic health record (EHR) Health Link (Epic Systems Corporation). For comparison, we examined visits in patients with a BP ≥140/90 mm Hg in the same clinics, 2 years before implementation.

Primary outcome and process measures. Process measures were used to compare the 3 BP Connect steps (re-measurement checks, educational advice, and primary care follow-up connection offers) across eligible visits. The primary outcome measure was timely primary care follow-up (within 4 weeks) in patients with confirmed high BPs and in-network primary care. Preimplementation and postimplementation rates were compared among patients eligible for timely in-network primary care fol-

low-up to assure capture in our data set. Additional analyses were performed to examine the sustainability of improved follow-up using multivariable models and time series analysis of monthly clinic population-level rates of high BPs over 24 months, before and after implementation.

Implementation methods. BP Connect was supported by an evidence-based implementation package (21,22). We used 4 evidence-based implementation strategies (23): 1) engage, 2) educate, 3) remind, and 4) feedback. First, we engaged nursing staff clinic providers and administrative leadership using presentations and focus groups. Second, we educated staff on high BP including links between rheumatic diseases and CVD risk and steps of the protocol. Next, we reminded staff of the BP Connect steps using EHR decision support alerts. Last, we fed back performance data to individual staff through brief monthly audit and feedback.

Staff engagement. We engaged rheumatology clinic nurses, medical assistants, and schedulers in co-designing and implementing the BP Connect specialty clinic protocol. We obtained broad buy-in and identified supporters (24) at multiple levels, through presentations to system leaders (ambulatory administrators and primary care chiefs) and clinic staff. Preimplementation focus groups engaged with staff as partners in designing the workflows and supporting materials such as patient brochures, electronic reminders, and staff talking points. Midpoint focus groups engaged with staff in identifying clinic-specific barriers and sharing best practices.

Staff education. First, an expert nurse educator offered a 45-minute didactic and skills training session with each of the 3 clinic staff groups. The session refreshed participants knowledge regarding the rationale for BP control in at-risk patients with rheumatic diseases, proper BP measurement, and the BP Connect protocol steps. Training content was driven by preimplementation focus group recommendations from nurses and medical assistants. The nurse educator also observed each participant's technique for measuring BP on a peer, while other pairs practiced 3 scenarios with protocol talking points. On the first intervention day, we offered individual staff a 10-minute hands-on computer training session to practice navigating the EHR alerts and steps. Each clinic received a manual, and a laminated reminder card with protocol steps was placed in each room.

Reminders to staff. Co-designed EHR tools and desktop brochures provided staff with reminders and talking points for the 3 BP Connect protocol steps. The initial EHR decision support alert triggered when clinic staff recorded a BP ≥140/90 mm Hg, prompting them to check, re-measuring the BP after 3–5 minutes. If BP was again ≥140/90 mm Hg, a second alert triggered. This prompted staff to advise the patient on rheumatology-specific high-risk BP and to offer to connect the patient with timely follow-up in a primary care setting. If the patient agreed, staff clicked the EHR protocolized order to send the scheduler follow-up orders or documented refusal to participate. Upon checking out of the clinic, the patient received assistance scheduling with their in-network primary care clinic if applicable, and all patients received printed follow-up recommendations.

Staff feedback. A team member (CB) provided staff with 4 monthly one-on-one performance feedback sessions during the 6-month intervention period. Sessions included participatory audit, feedback, and action planning with individual nurses and medical assistants based on the Cochrane Database of Systemic Reviews and data regarding audit and feedback (19,25). These brief sessions were designed to support staff needs for relationship, autonomy, and competence consistent with the self-determination theory (26). Staff were offered a choice of whether to discuss how things were going or to view their data first. They were shown individual data, clinic data, and anonymized peer data regarding re-measurement and follow-up orders. Individual patients were then asked to set goals for the following month and to identify a plan to reach new goals in light of challenges they identified. Sessions averaged 7 minutes each during months 2–5, with monthly individual feedback emails thereafter.

Data sources. We used preimplementation and postimplementation EHR data to assess timely primary care follow-up after rheumatology clinic visits in patients with high BPs among patients with an in-network primary care provider. EHR data also provided patient-level covariate data. The same data were used to generate monthly audit and feedback reports. Time study (27) provided baseline workflows and preimplementation and postimplementation data, and staff completed a 14-item postimplementation survey.

Measures and covariates. We used the RE-AIM framework (28), which is commonly used to evaluate health intervention implementation, to define measures of Reach, Effectiveness, Adoption, Implementation, and Maintenance. We assessed protocol initiation checks re-measuring high BPs and connection offers for referrals for BP follow-up visits. We also measured the proportion of accepted referrals. Our primary outcome was timely primary care follow-up, using a national definition for timely follow-up within 4 weeks (12). We examined maintenance over 24 months, including these process measures, outcomes, and population-level BP trends.

We used EHR data to establish baseline patient-level control variables defined over the year prior to the index visit with high BP. Covariates included patient sociodemographics such as age, sex, race, marital status, tobacco use history, and ever receiving Medicaid and were used as socioeconomic markers. Composite comorbidity was calculated using the Johns Hopkins Adjusted Clinical Groups (ACG) System (version 10) (29), and baseline healthcare utilization included counts of visits the year prior to the rheumatology index visit with high BP. The model also included the clinic where the index visit occurred. We used published algorithms reviewing inpatient and outpatient encounters prior to the index visit date for International Classification of Diseases

codes to control for baseline RA (30), hypertension (codes [31] or antihypertensive medication), cardiovascular disease (myocardial infarction, ischemic heart disease, heart failure, peripheral vascular disease, or transient ischemic attack or stroke) (32–35), diabetes mellitus (36), and chronic kidney disease (37).

Statistical analysis. To compare preimplementation and postimplementation data, we calculated *P* values using 2-sample *t*-tests for numeric variables and chi-square tests for categorical data. To examine our primary end point, we performed multivariable logistic regression to estimate the odds ratio (OR) and 95% confidence interval (95% CI) of timely primary care follow-up during the intensive 6-month implentation period versus the 2 years before implementation, while controlling for baseline sociodemographics, comorbidities, utilization, year, and clinic. These analyses were executed for primary care follow-up for patients with in-network providers. Given the visit-level structure of the data set, we used robust estimates of variance for conservative interpretation.

A sensitivity analysis with clustering by individual did not change the results. A priori, we planned an as-treated analysis (including only patients in whom the protocol was initiated as indicated by re-measurement) for this pragmatic design (38), although we also performed intent-to-treat analysis. The intent-to-treat analysis included all patients eligible for re-measurement, regardless of whether it occurred, unless BP was re-measured and normalized. We estimated that 239 eligible preimplementation and 239 postimplementation visits would offer 80% power to demonstrate a timely follow-up increase from baseline of 33–45%, with a 2-sided test with a significance level of 0.05. A secondary analysis was performed to examine any timely follow-up at either a primary care or specialty clinic. Kaplan-Meier analysis was used to compare time to primary care follow-up after high BP visits between preimplementation and postimplementation visits among patients with in-network primary care. Last, we used interrupted time series regression with Newey-West standard errors to compare clinic-wide population-level BP trends in the 2 years before and

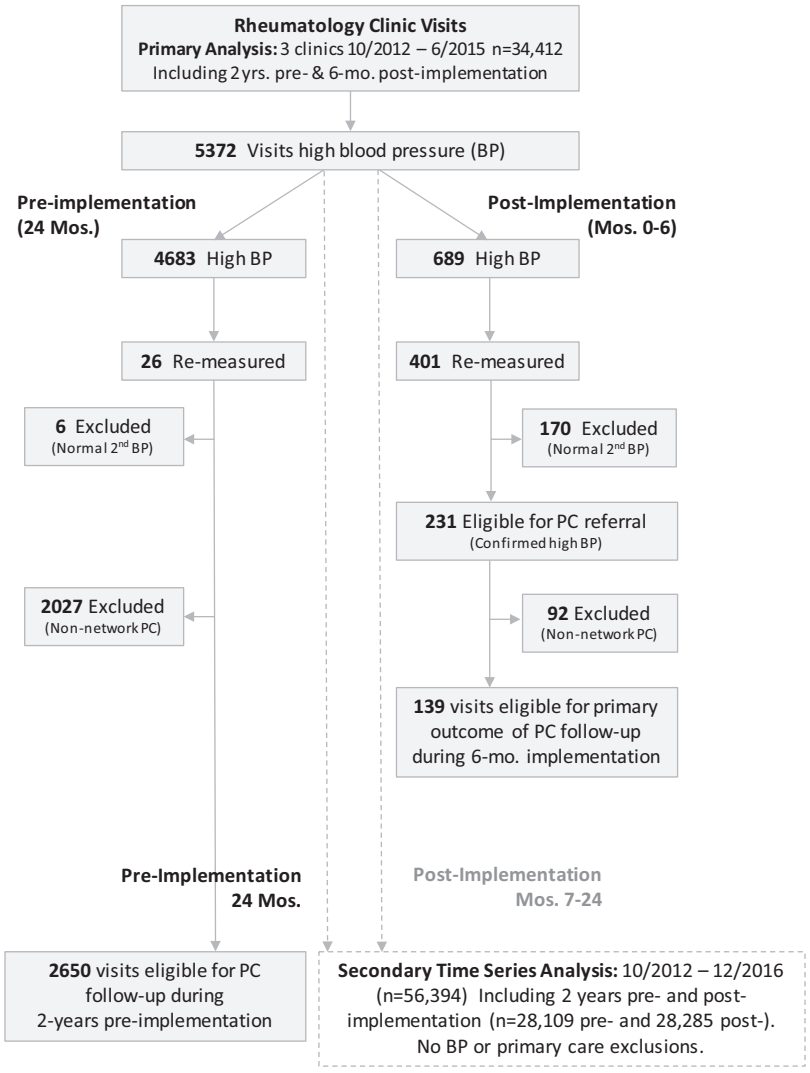

Figure 1. Flow diagram of project design and inclusion. BP = blood pressure.

Table 1. Description of visit-level patient characteristics preimplementation and postimplementation (protocol eligible)*

	Visits with high blood pressure measurement (n = 5,372)		
	Preimplementation (n = 4,683)	Postimplementation protocol-eligible (n = 689)	*P*†
Demographics			
Age, mean ± SD years	59.1 ± 14.1	60.4 ± 13.6	0.03
Age group			
18–39 years	390 (8.3)	43 (6.2)	0.02
40–59 years	1,949 (41.6)	261 (37.9)	
60–79 years	1,981 (42.3)	332 (48.2)	
≥80 years	363 (7.8)	53 (7.7)	
Female sex	3,105 (66.3)	458 (66.5)	0.93
Race			
White	4,210 (90.5)	604 (88.6)	0.26
Black	261 (5.6)	47 (6.9)	
Other	179 (3.9)	31 (4.6)	
Language			
English	4,637 (99)	685 (99.4)	0.31
Non-English	46 (1)	4 (0.6)	
Marital status			
Married/partnered	2,714 (58.1)	416 (60.5)	0.37
Single	1,046 (22.4)	152 (22.1)	
Separated/divorced/widowed	913 (19.5)	120 (17.4)	
Medicaid ever	572 (12.2)	81 (11.8)	0.73
Tobacco use			
Never	2,287 (49.8)	333 (49.5)	0.6
Current	474 (10.3)	70 (10.4)	
Quit	1,797 (39.2)	262 (38.9)	
Passive	32 (0.7)	8 (1.2)	
BMI quartile, mean ± SD	32.3 ± 8.3	31.6 ± 8.0	0.054
Underweight/normal	865 (19.0)	139 (20.5)	0.42
Overweight	1,210 (26.5)	187 (27.6)	
Obese	2,487 (54.5)	352 (51.9)	
Baseline comorbidities and healthcare utilization			
Rheumatoid arthritis	1,414 (30.2)	224 (25.2)	0.22
Hypertension	3,078 (65.7)	464 (67.3)	0.40
Cardiovascular disease	1,165 (24.9)	181 (26.3)	0.43
Diabetes mellitus	800 (17.1)	114 (16.6)	0.73
Chronic kidney/ESRD	287 (6.1)	52 (7.6)	0.15
ACG comorbidity score, mean ± SD	1.1 ± 0.8	1.1 ± 0.9	0.98
Mean ± SD annual ambulatory visits	7.6 ± 6.9	6.8 ± 5.8	<0.01
Mean ± SD annual primary care visits	2.4 ± 3.3	2.1 ± 2.6	<0.01
Mean ± SD annual rheumatology visits	2.1 ± 1.9	1.9 ± 1.7	<0.01
In-network primary care	2,650 (56.9)	393 (57.3)	0.83

* Except where indicated otherwise, values are the number (%). BMI = body mass index; ESRD = end-stage renal disease; ACG = Johns Hopkins Adjusted Clinical Group.
† By 2-sample *t*-test (numeric variables) and chi-square test (categorical variables).

2 years after implementation. Data set construction and the final analysis were performed using SAS version 9.4.

RESULTS

The primary analysis compared 689 intensive 6-month post-implementation visits to 4,683 2-year preimplementation visits, all of which included patients with BP ≥140/90 mm Hg (Figure 1). Overall, patient visits were comparable before and during the intervention (Table 1). There was a 1-year difference in the mean age between patients in the 2 groups, and a lower mean number of ambulatory, primary care, and rheumatology visits during the intervention period. In both groups, 57% of patients had in-network primary care; after exclusion due to a normal second BP

Table 2. Odds of timely primary care follow-up after specialty clinic visit with high blood pressure measurement*

	Per-protocol (n = 2,789)		Intent-to-treat (n = 3,043)
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)†
Protocol	1.88 (1.33, 2.66)	2.04 (1.42, 2.92)	1.50 (1.15, 1.95)
Age, years			
18–39	Ref.	Ref.	Ref.
40–59	0.91 (0.66, 1.27)	0.96 (0.67, 1.37)	0.99 (0.70, 1.41)
60–79	1.07 (0.77, 1.48)	1.09 (0.75, 1.59)	1.14 (0.79, 1.66)
≥80	1.42 (0.95, 2.12)	1.43 (0.89, 2.32)	1.41 (0.88, 2.25)
Female sex	1.16 (0.97, 1.39)	1.00 (0.82, 1.22)	1.01 (0.83, 1.22)
Race			
White	Ref.	Ref.	Ref.
Black	2.25 (1.62, 3.13)	1.72 (1.18, 2.49)	1.60 (1.12, 2.28)
Other	1.32 (0.89, 1.95)	1.40 (0.93, 2.12)	1.30 (0.88, 1.93)
Marital status			
Married/partnered	Ref.	Ref.	
Single	1.17 (0.95, 1.44)	0.96 (0.77, 1.20)	0.91 (0.73, 1.14)
Separated/divorced	1.43 (1.16, 1.75)	1.02 (0.81, 1.29)	1.00 (0.80, 1.26)
Medicaid ever	1.51 (1.18, 1.94)	1.26 (0.93, 1.70)	1.25 (0.93, 1.68)
Tobacco use			
Never	Ref.	Ref.	Ref.
Current	1.04 (0.77, 1.39)	1.05 (0.76, 1.44)	1.08 (0.80, 1.47)
Quit	1.17 (0.98, 1.39)	1.07 (0.89, 1.29)	1.05 (0.88, 1.25)
BMI			
Underweight/normal	Ref.	Ref.	Ref.
Overweight	0.73 (0.57, 0.94)	0.73 (0.56, 0.96)	0.76 (0.59, 0.98)
Obese	1.01 (0.81, 1.26)	1.01 (0.80, 1.28)	1.05 (0.83, 1.32)
Baseline comorbidities and utilization			
Rheumatoid arthritis	0.93 (0.78, 1.09)	0.87 (0.74, 1.06)	0.89 (0.75, 1.07)
Baseline hypertension	1.37 (1.12, 1.67)	0.90 (0.72, 1.13)	0.95 (0.76, 1.18)
Cardiovascular disease	1.66 (1.40, 1.98)	1.28 (1.04, 1.58)	1.28 (1.04, 1.56)
Diabetes mellitus	1.61 (1.33, 1.96)	1.25 (0.99, 1.56)	1.23 (0.99, 1.53)
Chronic kidney/ESRD	1.47 (1.10, 1.95)	0.85 (0.59, 1.23)	0.81 (0.57, 1.16)
ACG comorbidity	1.43 (1.30, 1.57)	1.12 (0.96, 1.29)	1.12 (0.97, 1.28)
Baseline mean annual ambulatory visits‡	1.06 (1.04, 1.07)	1.04 (1.02, 1.05)	1.04 (1.03, 1.05)

* Primary care (PC) follow-up analysis required in-network PC. The intent-to-treat analysis included all patients eligible for re-measurement, regardless of whether it occurred, unless blood pressure was re-measured and had normalized; per-protocol analysis included only patients in whom the protocol was initiated as indicated by re-measurement. 95% CI = 95% confidence interval; BMI = body mass index; ESRD = end-stage renal disease; ACG = Johns Hopkins Adjusted Clinical Group.

† Models also included clinic; data for non–English-speaking patients was insufficient to allow estimation.

‡ Baseline mean ambulatory visits indicates odds ratio (OR) per 1-visit increase.

measurement or lack of in-network primary care, 2,789 encounters were eligible for primary outcome assessment.

Process measures. Compared to <1% of preimplementation visits, >80% of eligible visits re-measured BP during intervention months 4–6. Over the entire 6-month postimplementation period, improvement was indicated by 60% re-measurement ($P < 0.001$). After implementation, follow-up orders were offered to 77% of eligible patients (84% either received education, or follow-up was offered), in contrast to only 10% of visits even recommending follow-up in our prior published abstraction study from these clinics (4). Protocol visit rooming averaged 4 minutes longer than that at baseline.

Primary outcome. As hypothesized and shown in Table 2, more eligible patients received timely primary care follow-up after high BP measurements in rheumatology clinics during implementation of the intervention compared to preimplementation (rates of timely follow-up after implementation 42% versus 29% before $P < 0.001$). Multivariable logistic regression showed that visits with protocol intervention had 2-fold higher odds of timely primary care follow-up compared to preimplementation (OR 2.04 [95% CI 1.42, 2.92], $P < 0.001$) (Table 2). Sensitivity testing with intent-to-treat analysis remained significant (OR 1.50 [95% CI 1.15, 1.95]). As predicted, virtually all prespecified subgroups benefited from the protocol. Notable improvements were observed among black patients and those with a prior CVD. Only overweight predicted slightly worse primary care follow-up. Overall, postimplementation, 57% of patients completed timely follow-up at either primary or specialty care clinics versus 46.5% at baseline (adjusted OR 1.73 [95% CI 1.20, 2.49]). Moreover, the median number of days until BP follow-up decreased from 71 days to 38 days postimplementation among those with protocol initiation (Figure 2), leading to a statistically significant difference in time to primary care follow-up ($P < 0.001$ by log rank test).

Other measures and maintenance. This 6-month project was limited by sample size, and no difference was noted in individual BP control within 6 months of the index visit when comparing those with protocol-confirmed high BP to preimplementation (data not shown). Analysis of the primary end point over 24 months showed maintained improvement in timely primary care follow-up (adjusted OR 1.9 [95% CI 1.4, 2.5]). Low rates of declined follow-up offers over the entire period (6–13%) suggested sound implementation fidelity.

Population impact and staff perspectives. Finally, we examined the clinic population-level impact using interrupted time series analysis of BP trends in the 2 years before and 2 years after implementation. We compared the proportion of monthly rheumatology visits in patients with initially high BPs before and during the intervention period. We observed an associated decrease from a monthly mean of 17% of visits with high BPs to a mean of 8% during the intervention period ($P < 0.001$) (Figure 3). Moreover, we observed a continued significant decrease in the postimplementation period (slope –0.15 [95% CI –0.24, –0.05], $P = 0.03$) through 24 months.

Staff favorably reviewed the protocol on postimplentation surveys. Comparing self-efficacy for BP care, 90% postimplementation versus 20% preimplementation reported being very or extremely confident in their ability to address high BP. Rheumatol-

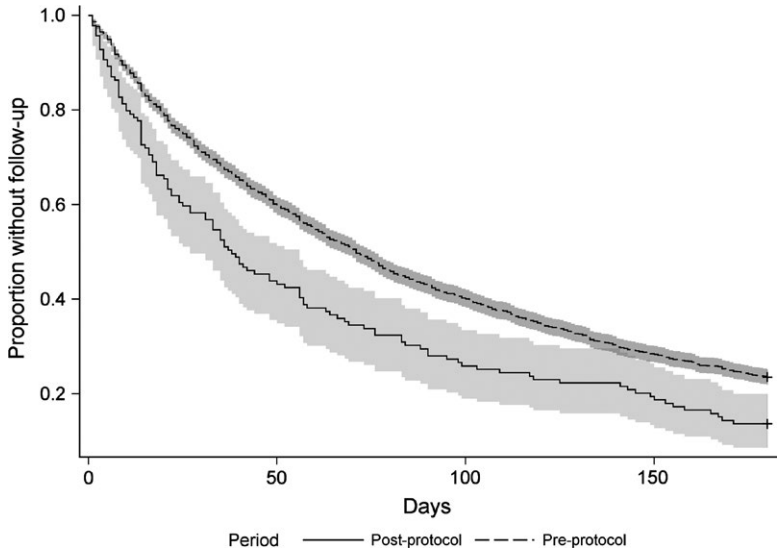

Figure 2. Kaplan-Meier survival curve comparing time to primary care (PC) follow-up visits between preimplementation and postimplementation visits for patients with high blood pressure (BP) and in-network PC (n = 2,650 preimplementation visits; n = 139 postimplementation visits with confirmed high BP). Median time to follow-up decreased from 71 days to 38 days during the protocol period ($P = 0.0003$ by log rank test). Shaded areas indicate 95% confidence intervals. + = censored.

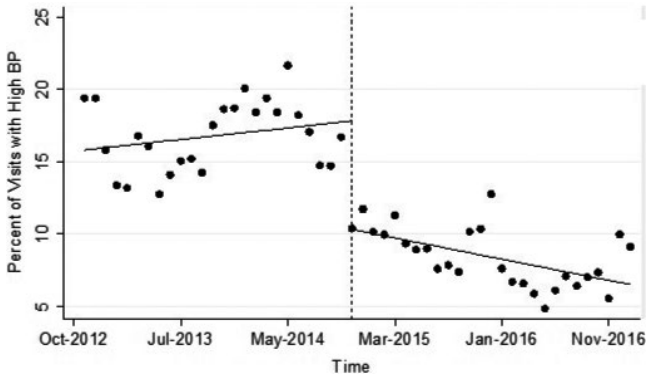

Figure 3. Interrupted time series graph of the percentage of monthly rheumatology clinic visits with high blood pressure (BP) (n = 56,394), before (n = 28,109) and after (n = 28,285) protocol implementation. Average monthly rates of high BP decreased from 17% preimplementation to 8% postimplementation, with a significant decline after implementation and continued improvement over time ($P < 0.003$ and $P = 0.03$, respectively). Each symbol represents the rate for each month.

ogy care providers were pleased by favorable outcomes without additional burdens on them.

DISCUSSION

Our BP Connect protocol intervention significantly increased timely follow-up of patients after high BP measurements in rheumatology clinics, doubling baseline rates of timely primary care follow-up. Moreover, using the clinic protocol strategy particularly benefited black patients and those with prior CVD, consistent with evidence that protocol-driven strategies can reduce health disparities in CVD treatment and prevention (39). Building on the literature about hypertension protocols from primary care (8), we added important features for specialty clinics, including rheumatology staff co-design, rheumatology-targeted training, EHR alerts with talking points, cross-specialty follow-up orders, and participatory audit and feedback to facilitate behavior change. We ultimately observed a significant population-level decline in the number of clinic visits by patients with high BP, suggesting support for our approach to adapt BP protocols for use in rheumatology or other specialty clinics.

Our positive results for clinic intervention contrast with negative results observed in a provider-focused educational EHR reminder study in rheumatology (40). This contrast demonstrates the limits of education alone to change provider behavior (41) and the value of engaging clinic staff (42,43) to systematically support primary care with population management using protcol-defined steps. Postimplementation, staff self-reported high feasibility and improved competence (44,45). Our evidence-based implementation strategies (23,46) also support future dissemination.

These findings also have timely practice and policy relevance. Experts estimate that 31 million more Americans have high BP based on new guidelines (20,47), and 24 different medical specialties now report BP follow-up for MIPS quality (48). Our baseline quality performance mirrored observed rates in a national American College of Rheumatology RISE registry report, and our improvement would have moved us from the fifth to the ninth decile (with tenth being best) for MIPS quality performance (49). Despite strong relative improvements and comparisons to RISE registry data, moderate timely follow-up postimplementation might be explained by access limitations or patient preference. Although in the current study the median time to follow-up decreased by 46% (from 71 days to 38 days), it was still outside our stated goal (<4 weeks, ≤28 days), which might have been attributable to primary care follow-up appointment availability or scheduling "around 4 weeks later." Patient preference to avoid travel, time off work, or co-payments, and gaps in understanding the importance of timely follow-up might also explain our results.

For rheumatology and other specialties, BP is a wise population health target given that it is measured at all visits and is the leading modifiable predictor of CVD (1). When discussing the potential impact of wider dissemination of BP protocols, the former Centers for Disease Control and Prevention director stated "Nothing would save more lives" (1,9). Healthcare system leaders welcomed our specialty clinic protocol to improve group BP metrics. Primary care providers—who were previously penalized for patients deemed uncontrolled after specialty visits outside their clinics—also welcomed follow-up protocol interventions.

Despite strengths of our adaptation and implementation of an evidence-based BP protocol in rheumatology clinics, limitations must be considered. First, we used a pre–post comparison design without blinding or randomization. However, as shown in Table 1, the preimplimentation and postimplementation groups were comparable. A reduced number of annual visits in the postimplementation period would conservatively bias the outcome of timely follow-up toward the null. Moreover, blinding and patient-level randomization were not feasible, because the intervention targeted the clinic staff.

Use of a contemporaneous control clinic could have some advantages, and a future multisite trial could match or randomize clinics, which in the current study was limited by the number of clinics. Likewise, although the timing of changes and comparison with system-wide trends supported evidence of change specific to the protocol, other system changes cannot be excluded. Although initial declines for follow-up might have reflected improved BP measurement, a positive outcome in itself, ongoing declines after initial training offer further support that the BP Connect protocol was effective for improving primary care follow-up. Primary outcome analysis was limited to patients with in-network primary care, but results of the intent-to-treat analysis across the entire population remained significant and may have in fact underestimated timely out-of-network primary care follow-up. Notably, because this project predated publication of the MIPS measures, eligibility and out-

comes were not identical to the BP follow-up measure, yet the project demonstrates a new evidence base for future improvement interventions in rheumatology or other specialty clinics (11). Last, this single-center project with a predominantly white English-speaking population may not be directly generalizable; therefore, future studies are planned to study protocol implementation in more diverse and vulnerable populations.

Currently, we are implementing BP Connect in a rheumatology clinic in another healthcare system, using our dissemination toolkit (https:www.hipxchange.org/BPCConnect) (50). The toolkit contains engagement and training materials, workflows, EHR build instructions, and audit and feedback tools. A future multisite study will examine the scalability and efficacy of the intervention for individual patient BP self-management and BP control, which were beyond the scope of this project.

Our findings highlight a timely population health strategy to improve guideline-based BP care and quality measures across rheumatology clinics and other specialties. Use of BP Connect doubled the rates of timely primary care follow-up after high BPs, and we observed reduced population-level rates of visits by patients with high BP, suggesting efficacy and feasibility of use of the protocol by specialty clinic staff. Future studies should examine BP Connect in other specialties and healthcare systems, including its impact on BP control to reduce CVD risk for patients attending rheumatology or other specialty clinics.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bartels had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bartels, Ramly, Johnson, Lauver, Lewicki, McBride.

Acquisition of data. Bartels, Ramly, Johnson.

Analysis and interpretation of data. Bartels, Ramly, Panyard, Li, Sampene.

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Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood

Kirsten Minden,[1] Gerd Horneff,[2] Martina Niewerth,[3] Eva Seipelt,[4] Martin Aringer,[5] Peer Aries,[6] Ivan Foeldvari,[7] Johannes-Peter Haas,[8] Ariane Klein,[9] Stefanie Tatsis,[10] Klaus Tenbrock,[11] Angela Zink,[1] and Jens Klotsche[1]

Objective. To study juvenile idiopathic arthritis (JIA) long-term outcomes in relation to the time of initiation of biologic disease-modifying antirheumatic drug (bDMARD).

Methods. Outcomes of JIA patients prospectively followed by the Biologika in der Kinderrheumatologie (BiKeR) and Juvenile Arthritis Methotrexate/Biologics Long-Term Observation (JuMBO) registers were analyzed with regard to drug-free remission and inactive disease, functional status and quality of life, and surgery. To analyze the influence of early bDMARD therapy on outcomes, patients were assigned to 3 groups based on the time from symptom onset to bDMARD start (G1: ≤2 years, G2: >2 to ≤5 years, and G3: >5 years). Propensity score–adjusted outcome differences were analyzed by multinomial logistic regression analyses among the groups.

Results. A total of 701 JIA patients were observed for mean ± SD 9.1 ± 3.7 years. At the last follow-up (disease duration mean ± SD 14.3 ± 6.1 years), 11.7% of patients were in drug-free remission, and 40.0% had inactive disease. More than half of the patients reported no functional limitation, while 5% had undergone arthroplasty, and 3% had eye surgery. At the 10-year time point, patients in G1 (n = 108) were significantly more likely to be in drug-free remission than those patients who began treatment later (G2, n = 199; G3, n = 259), with 18.5%, 10.1%, and 4.9%, respectively. Patients in G1 had significantly lower disease activity (clinical Juvenile Arthritis Disease Activity Score in 10 joints = 4.9), a better overall well-being (18.2% patient global assessment score = 0), and higher functional status (59.2% Health Assessment Questionnaire score = 0), compared to patients in G3 (7.1, 8.4%, and 43.7%, respectively). G1 patients required arthroplasty significantly less frequently than G3 patients and had significantly lower disease activity over time than patients in both G2 and G3.

Conclusion. Early DMARD treatment is associated with better disease control and outcomes, which supports the concept of a "window of opportunity" for JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous, immune-mediated disorder with a prevalence of approximately 1:1,000 (1,2). Up to 50% of JIA cases exhibit a polyarticular disease course and are therefore at high risk of disease activity into adult life, permanent functional disability, and progressive joint damage (3–8). In an effort to reduce long-term

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[1]Kirsten Minden, MD, Angela Zink, PhD, Jens Klotsche, PhD: German Rheumatism Research Center and Charité–University Medicine Berlin, Berlin, Germany; [2]Gerd Horneff, MD: Asklepios Clinic Sankt Augustin GmbH, Sankt Augustin, and University Hospital of Cologne, Cologne, Germany; [3]Martina Niewerth, MPH: German Rheumatism Research Center, Berlin, Germany; [4]Eva Seipelt, MD: Immanuel Krankenhaus, Berlin, Germany; [5]Martin Aringer, MD: University Medical Center Carl Gustav Carus at the Technische Universität Dresden, Dresden, Germany; [6]Peer Aries, MD: Rheumatologie im Struensee-Haus, Hamburg, Germany; [7]Ivan Foeldvari, MD: Centre for Pediatric and Adolescent Rheumatology, Hamburg, Germany; [8]Johannes-Peter Haas, MD: German Centre for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany; [9]Ariane Klein, MD: Asklepios Clinic Sankt Augustin GmbH, Sankt Augustin, Germany; [10]Stefanie Tatsis, MD: Kath. Marienkrankenhaus, Hamburg, Germany; [11]Klaus Tenbrock, MD: Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany.

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Address correspondence to Kirsten Minden, MD, German Rheumatism Research Center, Epidemiology Unit, Charitеplatz 1, 10117 Berlin, Germany. E-mail: minden@drfz.de.

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SIGNIFICANCE & INNOVATIONS

- The outcomes of juvenile idiopathic arthritis (JIA) in adulthood are significantly related to the time from JIA onset to the start of a biologic disease-modifying antirheumatic drug (bDMARD).
- Patients with an early DMARD start are more likely to be in drug-free remission in adulthood.
- Patients with an early DMARD start have a lower likelihood of requiring joint or eye surgery.
- Patients treated early with bDMARDs have better disease control over time.

morbidity, treatment paradigms have changed over the years (9). Disease-modifying antirheumatic drug (DMARD) treatment has moved toward the institution of more aggressive therapy, including the use of biologic DMARDs (bDMARDs) early in the course of the disease. Early intervention and the consequent suppression of disease activity may hamper disease progression in such a way that chronicity is reduced. However, the optimum time for initiating bDMARDs has not yet been determined (10), as reflected by a prescription rate of approximately 20% within the first 5 years of the disease (11–13).

Weak evidence of the efficacy of early bDMARD therapy was provided by 3 randomized controlled studies on JIA (14–16). All the studies found that early intensive treatment approaches resulted in a high likelihood of disease control within the first year of the disease. An impact on the patient's long-term prognosis can be assumed, because achieving a clinically inactive disease (CID) at least once within the first years of the disease has been associated with better outcomes (17,18). To analyze whether the time of bDMARD start determines the outcomes of JIA in young adulthood, we used data from the German JIA biologic register BiKeR (Biologika in der Kinderrheumatologie [biologics in pediatric rheumatology]) and JuMBO (Juvenile Arthritis Methotrexate/Biologics Long-Term Observation).

PATIENTS AND METHODS

Data were retrieved from BiKeR and JuMBO, which are both ongoing multicenter, prospective, observational cohort studies (19,20). These studies aim to monitor the safety and effectiveness of conventional synthetic DMARDs (csDMARDs) and bDMARDs (21–23). JuMBO is the follow-up register to BiKeR and monitors patients who have reached the age of 18 or left pediatric rheumatology care.

Patients. Patients were eligible for this study if they had JIA as defined by the International League of Associations for Rheumatology criteria (24), were enrolled in BiKeR during childhood and were subsequently transferred to JuMBO, and began their first bDMARD course and had at least 1 physician assessment during young adulthood. Written informed consent was obtained from both the parents and patients (age ≥8 years) for participation in BiKeR and again from the patients (age ≥18 years) for further follow-up in JuMBO. Patients were assessed every 6 months in both registers. At each follow-up, the physician recorded details on the patient's disease status and therapy. Patients were assessed with standardized questionnaires. BiKeR was approved by the ethics committee of the Medical Council of North Rhine-Westphalia, Duesseldorf, Germany. JuMBO was approved by the ethics committee of Charité University Medicine Berlin. Both registers are conducted in accordance with the Declaration of Helsinki.

Assessments and outcome parameters. The following outcomes were assessed at the 10-year follow-up and at the last available follow-up: drug-free remission and inactive disease, patient-reported outcomes, such as functional status and quality of life, and surgery. Physician-reported outcomes comprised the number of joints with swelling, range-of-motion limitations, tenderness or pain with motion (72-joint count), erythrocyte sedimentation rate, and C-reactive protein levels, as well as the physician's global assessment (PhGA) of the patient's disease activity on a 10-cm visual analog scale (VAS) in BiKeR and a numerical rating scale (NRS, range 0–10) in JuMBO. Disease activity was additionally assessed by the clinical Juvenile Arthritis Disease Activity Score in 10 joints (cJADAS-10), calculated according to Consolaro et al (25). Because information about active uveitis and systemic JIA features was not requested at every JuMBO visit before 2014, CID in young adulthood in JuMBO was defined by the best possible PhGA on the scale used (NRS = 0), and by cJADAS-10 score ≤1 (25). Remission off drugs was defined as CID for at least 12 months without any treatment, in accordance with the criteria by Wallace et al (26).

The patients' functional status was assessed using the Childhood Health Assessment Questionnaire (C-HAQ) (27) in BiKeR and the HAQ (28) in JuMBO. Other patient-reported outcomes included overall well-being and pain, globally assessed either with a VAS in BiKeR or an NRS in JuMBO. The adult patients' health-related quality of life (HRQoL) was measured via the Medical Outcomes Study Short Form 36 (SF-36) (29). The SF-36 survey yields 2 comprehensive HRQoL indexes, the physical component summary and the mental component summary scores. Both summary scores were obtained from normalized and Z-transformed domain scores. Operations, such as synovectomy, arthroplasty, or eye surgery due to uveitis complications, were reported by the patients and/or the physicians as adverse events in BiKeR and JuMBO, or as operative history at the first JuMBO visit.

Statistical analysis. The association between outcomes and the time between JIA onset and first bDMARD start was nonparametrically estimated by a local polynomial

Table 1. Patient characteristics at the time of BiKeR inclusion for the whole cohort and for the 3 patient groups by the time from symptom onset to bDMARD start*

Characteristics	Total group	Time from symptom onset to bDMARD start			*P*†
		G1 ≤2 years	G2 >2 to ≤5 years	G3 >5 years	
No. (%)	701 (100)	161 (23)	216 (31)	324 (46)	–
Age, years	14.3 ± 3.1	14.1 ± 3.0	14.1 ± 3.0	14.6 ± 3.3	0.616
Female, no. (%)	464 (66.2)	93 (57.8)	139 (64.4)	232 (71.6)	0.105
JIA category, no. (column %/ raw %)					0.001
Systemic JIA	40 (5.7/100)	10 (6.2/25.0)	11 (5.1/27.5)	19 (5.9/47.5)	–
RF-negative polyarthritis	179 (25.5/100)	45 (28.0/25.1)	54 (25.0/30.2)	80 (24.7/44.7)	–
RF-positive polyarthritis	76 (10.8/100)	31 (19.3/40.8)	28 (13.0/36.8)	17 (5.3/22.4)	–
Enthesitis-related arthritis	151 (21.5/100)	44 (27.3/29.1)	51 (23.6/33.8)	56 (17.3/37.1)	–
Psoriatic arthritis	65 (9.3/100)	15 (9.3/23.1)	24 (11.1/36.9)	26 (8.0/40.0)	–
Persistent oligoarthritis	43 (6.1/100)	4 (2.5/9.3)	16 (7.4/37.2)	23 (7.1/53.5)	–
Extended oligoarthritis	128 (18.3/100)	4 (2.5/3.1)	26 (12.0/20.3)	98 (30.3/76.6)	–
Other arthritis	19 (2.7/100)	8 (5.0/42.1)	6 (2.8/31.6)	5 (1.5/26.3)	–
HLA-B27–positive, no. (%)	192 (27.4)	56 (34.8)	63 (29.2)	73 (22.5)	0.114
ANA-positive, no. (%)	307 (43.8)	57 (35.4)	79 (36.6)	171 (52.8)	0.042
History of uveitis, no. (%)	63 (9.0)	7 (4.4)	9 (4.2)	47 (14.5)	0.002
Disease duration, years‡	5.2 ± 4.4	1.0 ± 0.7	2.8 ± 1.2	8.8 ± 3.9	0.368
Prior csDMARD, no. (%)	663 (94.6)	143 (88.8)	209 (96.8)	311 (96.0)	0.033
Time between JIA onset and csDMARD start, months	25.0 ± 34.3	5.3 ± 5.5	15.4 ± 12.7	40.4 ± 43.5	<0.001
Number of csDMARDs before bDMARD start	1.9 ± 1.1	1.3 ± 0.6	1.7 ± 0.9	2.3 ± 1.2	0.018
csDMARD treatment duration before bDMARD start, months	37.9 ± 38.1	7.3 ± 5.1	22.9 ± 14.0	62.0 ± 42.3	<0.001
Physician global assessment of disease activity§	5.5 ± 2.6	5.5 ± 2.7	5.3 ± 2.5	5.7 ± 2.6	0.492
cJADAS-10¶	15.7 ± 6.5	15.2 ± 7.2	14.2 ± 5.9	14.6 ± 6.5	0.327
C-HAQ total#	0.7 ± 0.6	0.8 ± 0.7	0.7 ± 0.6	0.7 ± 0.6	0.130
Patient global assessment of overall well-being**	4.8 ± 2.7	4.9 ± 2.7	4.7 ± 2.7	4.8 ± 2.8	0.537
Patient-reported pain††	4.3 ± 2.8	4.6 ± 3.0	4.3 ± 2.8	4.3 ± 2.8	0.604
Year of BiKeR enrollment, no. (%)					0.009
≤2004	199 (28.4)	31 (19.3)	65 (30.1)	103 (31.8)	–
2005–2008	316 (45.1)	68 (42.2)	97 (44.9)	151 (46.6)	–
≥2009	186 (26.5)	62 (38.5)	54 (25.0)	70 (21.6)	–

* Values are the mean ± SD unless indicated otherwise. BiKeR = Biologika in der Kinderrheumatologie; bDMARD = biologic disease-modifying antirheumatic drug; JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; ANA = antinuclear antibodies; csDMARD = conventional synthetic DMARD; cJADAS-10 = clinical Juvenile Arthritis Disease Activity Score in 10 joints; C-HAQ = Childhood Health Assessment Questionnaire.
† Group differences were tested by analysis of variance for continuously distributed parameters and by logistic regression analyses for categorical parameters weighted by the generalized propensity score.
‡ Missing values 5 (0.7%).
§ Missing values 17 (2.4%).
¶ Missing values 72 (10.3%).
# Missing values 1 (0.1%).
** Missing values 62 (8.8%).
†† Missing values 53 (7.6%).

approximation in preliminary analyses. These analyses showed a continuous and approximately linear association between the outcomes and the duration between JIA onset and the first bDMARD start, with an even stronger association within the first 2 years (see Supplementary Figures 1a and 1b, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23709/abstract). Based on the visual analyses of the data and the availability of a sufficient number of patients within each category for the propensity score–adjusted multivariable analyses, the time from JIA onset until the start of bDMARD treatment was categorized into 3 treatment groups (G1, ≤2 years [early]; G2, >2 to ≤5 years [medium]; and G3, >5 years [late]). A generalized propensity score (30) was estimated for the statistical comparison of young adulthood outcomes between the 3 groups. The generalized propensity score is the conditional density of the 3 groups given in the covariates JIA category, DMARD use before the first bDMARD course, age at JIA onset, C-HAQ score, cJADAS-10 score, and history of uveitis at BiKeR inclusion, with sex and year of enrollment in BiKeR estimated by maximum likelihood. The Box-Cox transformation was applied for continuously distributed treatment variable duration from the onset of JIA to the start of the bDMARD in the propensity score estimation process.

The balancing property of the generalized propensity score was tested by using the algorithm suggested by Hirano and Imbens (30). The following outcomes were considered: CID (by PhGA and cJADAS-10 score) and drug-free remission, and patient-reported outcomes (patient's functional status [HAQ], global assessments of overall well-being and pain [NRS], and HRQoL [SF-36]) and joint and eye surgery. Linear and logistic regression models were applied to analyze the relationship between outcomes and the time until bDMARD start and to compare outcome variables between the 3 groups (G1, G2, and G3), adjusting for the generalized propensity score. The outcomes were evaluated 10 years after JIA onset and at the last available follow-up. Survival analyses were used to investigate the probability that a synovectomy, arthroplasty, or eye surgery would be required after disease onset, including the Cox proportional hazards model. Additionally, a nested case–control study was conducted as a sensitivity analysis. Patients from G1, G2, and G3 were matched according to disease duration at the last follow-up in JuMBO, with a maximum difference of 1 year to permit pairing with comparable disease duration. Missing values in categorical predictor variables were recoded by including an additional response category. The level of significance was 5%, and analyses were performed using SAS software, version 9.4.

RESULTS

Patients and disease characteristics. A total of 701 JIA patients with a first bDMARD course were eligible for inclusion in this analysis by December 15, 2016. These participants corresponded to 60% of all patients (n = 1,169) included in BiKeR who have ever been treated with bDMARDs and could have potentially been enrolled in JuMBO. The study patients were not different from those who were potentially eligible but who were not transferred to JuMBO, based on disease severity at their last BiKeR documentation (e.g., mean ± SD PhGA 2.45 ± 2.83 and 2.31 ± 2.85, respectively; $P = 0.440$).

The patients' first bDMARD course most commonly comprised anti–tumor necrosis factor drugs (i.e., etanercept [n = 638, 91.0%] and adalimumab [n = 57, 8.1%]), followed by tocilizumab (n = 5, 0.7%) and anakinra (n = 1, 0.1%). A total of 78% of patients were enrolled in BiKeR at the start of bDMARD therapy, while the other 22% of patients started taking bDMARDs an average of 14 months after inclusion in BiKeR. At that time point, their disease activity (cJADAS-10 score mean ± SD 11.3 ± 5.8) and functional status (C-HAQ score mean ± SD 0.55 ± 0.49) were comparable to those at baseline. The total average observation period was mean ± SD 9.1 ± 3.7 years. The mean ± SD disease duration was 5.2 ± 4.4 years at BiKeR inclusion, and 14.3 ± 6.1 years at the last follow-up in JuMBO. Patient characteristics are shown in Table 1. Approximately 80% of patients (n = 566) had a disease duration of ≥10 years. In these cases, the first bDMARD treatment was started in 23% of patients within 2 years of JIA onset (G1), in 31% after 2 to 5 years of disease (G2), and in 46% later in the disease course (G3).

There were significant differences among the 3 patient groups categorized according to disease duration at the first bDMARD start. Despite weighting analyses by generalized propensity score, significant differences among the 3 groups remained in the JIA category distribution (and accordingly, the proportion of patients with antinuclear antibody positivity and a history of uveitis), as well as in the percentage of patients enrolled in BiKeR in different years.

Patient outcomes and treatments at the last follow-up in JuMBO. The outcomes after the mean follow-up of 14.3 years for the entire study group and for the different JIA categories are shown in Table 2. At the last follow-up, the median PhGA was 1 (interquartile range [IQR] 0–3), and the median cJADAS-10 score was 4.5 (IQR 1.5–6.5). More than half of the patients (n = 361, 57.6%) reported no functional limitations (HAQ score = 0, median 0 [IQR 0–0.45]), and 135 patients (21.6%) had no pain (pain = 0, median 2.0 [IQR 1–4]). The patients' global assessment median overall well-being was 2 (IQR 1–4), and 88 patients (14.0%) reported an optimal well-being (NRS = 0). At the last follow-up, 83% of patients were still using DMARDs, 43% were taking csDMARDs, and 72% were taking bDMARDs (Table 3). At the last follow-up, patients with an early bDMARD start (G1) were significantly more likely to be in drug-free remission and had a better functional status

Table 2. Outcomes at the time of the last JuMBO follow-up*

Parameters	Total group (n = 701)	Systemic JIA (n = 40)	RF– PA (n = 179)	RF+ PA (n = 76)	ERA (n = 151)	PsA (n = 65)	Persistent oligoarthritis (n = 43)	Extended oligoarthritis (n = 128)	Other arthritis (n = 19)	*P*†
Age, years	23.4 ± 3.9	24.9 ± 4.7	23.2 ± 4.0	24.3 ± 4.2	23.3 ± 3.8	23.5 ± 3.9	22.2 ± 2.5	23.0 ± 3.8	26.5 ± 4.1	<0.001
Disease duration, years	14.3 ± 6.1	16.9 ± 6.5	14.5 ± 6.1	12.3 ± 4.9	11.9 ± 4.9	13.7 ± 5.7	14.2 ± 4.7	17.9 ± 5.1	13.5 ± 5.4	<0.001
PhGA of disease activity	1.8 ± 2.0	1.4 ± 1.3	1.7 ± 2.0	2.4 ± 2.2	1.6 ± 1.8	2.0 ± 2.1	1.5 ± 1.9	2.1 ± 2.3	1.1 ± 1.2	0.011
PhGA CID, no. (%)	269 (40)	17 (42.5)	78 (44.8)	23 (31.9)	58 (40.3)	21 (36.2)	15 (36.6)	49 (39.5)	8 (42.1)	0.369
PhGA remission off drugs, no. (%)	74 (10.6)	5 (12.5)	23 (12.9)	6 (8.0)	17 (11.3)	7 (11.3)	0 (0.0)	14 (10.9)	2 (10.5)	0.576
cJADAS-10	4.9 ± 4.5	4.4 ± 4.1	4.7 ± 4.5	6.2 ± 5.2	4.0 ± 3.5	5.1 ± 3.8	4.3 ± 5.0	5.7 ± 5.2	4.5 ± 4.2	0.014
cJADAS-10 CID, no. (%)	166 (23.9)	13 (32.5)	48 (26.8)	15 (20.0)	41 (27.3)	7 (11.3)	14 (33.3)	22 (17.2)	6 (31.6)	0.072
cJADAS-10 remission off drugs, no. (%)	47 (6.7)	5 (12.5)	15 (8.4)	4 (5.3)	11 (7.3)	1 (1.6)	1 (2.4)	8 (6.3)	2 (10.5)	0.071
HAQ total	0.30 ± 0.51	0.34 ± 0.61	0.36 ± 0.59	0.37 ± 0.51	0.24 ± 0.43	0.29 ± 0.43	0.15 ± 0.40	0.26 ± 0.42	0.48 ± 0.83	0.348
Patient global assessment of overall well-being	2.7 ± 2.2	2.3 ± 2.3	2.8 ± 2.3	3.0 ± 2.0	2.5 ± 2.2	3.0 ± 2.5	1.8 ± 2.0	2.9 ± 2.1	3.0 ± 2.5	0.165
Patient-reported pain	2.7 ± 2.4	2.0 ± 2.2	2.7 ± 2.5	3.0 ± 2.4	2.6 ± 2.4	2.9 ± 2.8	1.8 ± 2.3	2.9 ± 2.3	2.8 ± 2.6	0.083
SF-36 PCS	46.5 ± 10.6	47.3 ± 11.5	46.3 ± 10.7	46.8 ± 9.5	47.3 ± 10.0	44.5 ± 11.5	49.7 ± 9.4	45.7 ± 10.6	44.2 ± 14.1	0.379
SF-36 MCS	50.0 ± 8.9	51.3 ± 7.2	48.8 ± 9.8	49.5 ± 8.5	50.6 ± 8.8	51.0 ± 9.2	50.4 ± 9.1	49.7 ± 8.6	53.3 ± 8.7	0.044
Surgery ever, no. (%)‡	151 (21.5)	11 (27.5)	39 (21.8)	14 (18.4)	21 (13.9)	13 (20.0)	8 (18.6)	38 (29.7)	7 (36.8)	0.255
Synovectomy	112 (16.0)	7 (17.5)	30 (16.8)	12 (15.8)	15 (9.9)	9 (13.9)	7 (16.3)	27 (21.1)	5 (26.3)	0.542
Arthroplasty	36 (5.1)	9 (22.5)	13 (7.3)	2 (2.6)	3 (2.0)	3 (4.6)	0 (0.0)	5 (3.9)	1 (5.3)	<0.001
Eye surgery	22 (3.1)	0 (0.0)	4 (2.2)	0 (0.0)	3 (2.0)	2 (3.1)	1 (2.3)	10 (7.8)	2 (10.5)	0.016

* Values are the mean ± SD unless indicated otherwise. The percentages refer to the number of patients with a valid measurement. JuMBO = Juvenile Arthritis Methotrexate/Biologics Long-Term Observation; JIA = juvenile idiopathic arthritis; RF– PA = rheumatoid factor–negative polyarthritis; RF+ PA = rheumatoid factor–positive polyarthritis; ERA = enthesitis-related arthritis; PsA = psoriatic arthritis; PhGA = physician's global assessment; CID = clinically inactive disease; cJADAS-10 = clinical Juvenile Arthritis Disease Activity Score in 10 joints; HAQ = Health Assessment Questionnaire; SF-36 = Medical Outcomes Study Short Form 36; PCS = physical component summary score; MCS = mental component summary score.

† Estimated by analysis of variance for continuously distributed variables and logistic regression for categorical variables.

‡ Disease-related.

Table 3. Treatment at the time of the last JuMBO follow-up*

Treatment	Total group (n = 701)	Time from symptom onset to bDMARD start: G1 ≤2 years (n = 161)	G2 >2 to ≤5 years (n = 216)	G3 >5years (n = 324)	P†
Any DMARD	579 (82.6)	115 (71.4)	178 (82.4)	286 (88.3)	<0.001
csDMARD	302 (43.1)	54 (33.5)	104 (48.2)	144 (44.4)	0.014
Methotrexate	231 (33.0)	47 (29.2)	87 (40.3)	97 (29.9)	0.022
Leflunomide	32 (4.6)	3 (1.9)	7 (3.2)	22 (6.8)	0.027
Sulfasalazine	34 (4.9)	5 (3.1)	9 (4.2)	20 (6.2)	0.285
Other csDMARD	30 (4.3)	3 (1.9)	9 (4.2)	18 (5.6)	0.167
bDMARD	505 (72.0)	104 (64.6)	147 (68.1)	254 (78.4)	0.002
Etanercept	226 (32.4)	44 (27.3)	72 (33.3)	110 (34.0)	0.312
Adalimumab	138 (19.7)	29 (18.0)	44 (20.4)	65 (20.1)	0.828
Other bDMARD	36 (5.1)	8 (4.9)	5 (2.3)	23 (7.1)	0.021
Tocilizumab	71 (10.1)	15 (9.3)	17 (7.9)	39 (12.0)	0.241
Canakinumab	26 (3.7)	7 (4.4)	4 (1.9)	15 (4.6)	0.219
Anakinra	8 (1.1)	1 (0.6)	5 (2.3)	2 (0.6)	0.001
NSAID	187 (26.7)	32 (19.9)	59 (27.3)	96 (29.6)	0.071
Glucocorticoid	150 (21.4)	20 (12.4)	36 (16.7)	94 (29.0)	<0.001

* Values are the number (%). JuMBO = Juvenile Arthritis Methotrexate/Biologics Long-Term Observation; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD; NSAID = nonsteroidal antiinflammatory drug.
† Group differences were tested by logistic regression analyses.

and well-being than those with a bDMARD start >2 years (G2) and 5 years (G3) after disease onset (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23709/abstract). However, the patients' disease duration was significantly different among the 3 groups.

Patient outcomes at the 10-year follow-up. Ten-year outcome analyses were conducted for 566 patients. The clinical and patient-reported outcomes for the 3 patient groups are categorized by the amount of time from symptom onset to bDMARD start in Table 3. Patients with an early bDMARD start (G1) were significantly more likely to be in drug-free remission, based on PhGA ($P = 0.005$) and cJADAS-10 score ($P = 0.014$), than those patients with a bDMARD start >2 years (G2) and 5 years (G3) after disease onset. Patients in G1 also had a significantly lower mean disease activity and had less frequent functional limitations and restrictions to overall well-being than those patients with a bDMARD start after 5 years (G3) (Table 4). Patients in G1 had significantly lower mean disease activity as determined by PhGA (beta –0.4 [95% confidence interval (95% CI) –0.66, –0.17]; $P < 0.001$) and cJADAS-10 score (beta –1.1 [95% CI –1.72, –0.52]; $P < 0.001$) over the observation period than those patients in G2 and G3. The outcomes at the follow-up, i.e., disease activity, the state of inactive disease, or remission off drugs, and functional limitations were significantly related to the time from JIA onset to bDMARD start (Table 4).

Surgery. Compared with patients in G3 (n = 67 [20.7%] with synovectomy), the risk of a synovectomy was significantly lower in patients with an earlier start of bDMARD therapy (G2: n = 31 [14.4%], hazard ratio [HR] 0.32; $P < 0.001$; G1: n = 14 [8.7%], HR 0.17; $P < 0.001$), as shown in Figure 1. Patients in G3 had also undergone joint arthroplasty (n = 24 [7.4%]) more frequently than those in G2 (n = 9 [4.2%], HR 0.44; $P = 0.099$) and G1 (n = 3 [1.9%], HR 0.34; $P = 0.043$) (Figure 2). Significant differences among the 3 groups were not observed with respect to eye surgery, even though more patients in G3 had eye surgery (n = 18 [5.6%]) than in G2 (n = 2 [0.9%], HR 0.19; $P = 0.068$) and G1 (n = 2 [1.2%], HR 0.3; $P = 0.087$). In addition, patients with an ongoing higher disease activity (mean cJADAS-10 score) during the observation period had a higher risk for a joint replacement (HR 2.25 [95% CI 1.05, 5.37]) or a synovectomy (HR 1.76 [95% CI 1.26, 2.47]).

Sensitivity analysis. To verify the robustness of results, additional analyses were performed in 1) patients of G1 separated into 2 groups, 1 with a duration of ≤1 year (G1a) between JIA onset and bDMARD start and another with a duration of >1 to 2 years (G1b) (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23709/abstract), 2) a more homogeneous JIA collective, i.e., patients with rheumatoid factor–negative polyarthritis (RF– PA), 3) patient groups by year of enrollment in BiKeR (≤2006 and ≥2007), and 4) patients matched for disease duration

Table 4. Outcomes after 10 years of disease duration for the 3 patient groups by time from symptom onset to bDMARD start*

Outcomes	G1 ≤2 years†	G2 >2 to ≤5 years			G3 >5 years			Continuous time from symptom onset to bDMARD start	
	Values (n = 108)	Values (n = 199)	Beta/OR (95% CI)	*P*	Values (n = 259)	Beta/OR (95% CI)	*P*	Beta/OR (95% CI)	*P*
PhGA of disease activity	1.7 ± 2.1 (1)	1.7 ± 2.0 (1)	−0.05 (−0.62, 0.53)	0.874	2.6 ± 2.5 (1.9)	0.85 (0.21, 1.48)‡	0.010‡	0.16 (0.07, 0.25)‡	<0.001‡
PhGA inactive disease (NRS = 0), no. (%)	45 (45.9)	71 (44.9)	1.02 (0.56, 1.84)	0.950	72 (34.6)	0.66 (0.35, 1.22)	0.185	0.92 (0.85, 1.00)‡	0.044‡
PhGA remission off drugs, no. (%)	20 (18.5)	20 (10.1)	0.46 (0.21, 0.99)‡	0.048‡	9 (4.9)	0.24 (0.09, 0.65)‡	0.005‡	1.10 (0.89, 1.36)	0.392
cJADAS-10	4.9 ± 5.3 (3.5)	4.7 ± 4.2 (4)	−0.13 (−1.50, 1.24)	0.852	7.1 ± 6.6 (5)	2.18 (0.60, 3.76)‡	0.007‡	0.44 (0.22, 0.65)‡	<0.001‡
cJADAS-10 inactive disease (≤1), no. (%)	27 (27.0)	42 (25.9)	1.20 (0.62, 2.35)	0.584	42 (20.1)	0.58 (0.30, 1.10)	0.096	0.90 (0.83, 0.97)‡	0.009‡
cJADAS-10 remission off drugs (≤1), no. (%)	17 (15.7)	12 (6.0)	0.34 (0.14, 0.85)‡	0.020‡	7 (3.8)	0.25 (0.08, 0.75)‡	0.014‡	0.78 (0.64, 0.94)‡	0.009‡
HAQ total	0.3 ± 0.5 (0)	0.3 ± 0.5 (0)	0.02 (−0.10, 0.14)	0.732	0.4 ± 0.5 (0.125)	0.14 (0.00, 0.28)	0.052	0.03 (0.01, 0.05)‡	0.003‡
No functional limitations (HAQ = 0), no. (%)	58 (59.2)	90 (57.7)	1.05 (0.57, 1.92)	0.871	86 (43.7)	0.49 (0.26, 0.93)‡	0.030‡	0.87 (0.80, 0.94)‡	<0.001‡
Patient-reported well-being	2.3 ± 2.0 (2)	2.6 ± 2.5 (2)	0.49 (−0.15, 1.12)	0.134	2.3 ± 2.3 (1.7)	0.37 (−0.23, 0.98)	0.226	0.06 (−0.03, 0.14)	0.183
Optimal well-being (NRS = 0), no. (%)	18 (18.2)	28 (18.2)	1.22 (0.58, 2.57)	0.597	17 (8.4)	0.34 (0.14, 0.79)‡	0.012‡	0.84 (0.74, 0.94)‡	0.003‡
Patient-reported pain	2.3 ± 2.4 (1.3)	2.6 ± 2.6 (2)	0.42 (−0.26, 1.11)	0.223	2.4 ± 2.6 (1.5)	0.42 (−0.26, 1.10)	0.226	0.09 (−0.01, 0.18)	0.072
Absence of pain (NRS = 0), no. (%)	20 (20.4)	37 (23.7)	1.63 (0.80, 3.30)	0.176	35 (18.8)	1.04 (0.48, 2.28)	0.918	0.96 (0.87, 1.07)	0.475
SF-36 physical component summary	48.1 ± 9.7 (50.95)	45.7 ± 11.3 (49.15)	−2.54 (−5.72, 0.63)	0.116	47.2 ± 9.1 (48.97)	−2.47 (−6.05, 1.10)	0.175	−0.76 (−1.40, −0.11)‡	0.022‡
SF-36 mental component summary	50.6 ± 8.7 (53.52)	49.1 ± 9.1 (51.48)	−1.20 (−3.99, 1.58)	0.396	51.3 ± 9.0 (53.5)	0.80 (−2.86, 4.46)	0.668	−0.01 (−0.66, 0.66)	0.997

* Values are the mean ± SD (median), unless indicated otherwise. Linear models (continuously distributed parameters) and logistic regression models (categorical parameters) were applied to analyze the continuous time from symptom onset to biologic disease-modifying antirheumatic drug (bDMARD) start and to compare outcome variables between the 3 groups, adjusting for the generalized propensity score. The percentages refer to the number of patients with a valid measurement. OR = odds ratio; 95% CI = 95% confidence interval; PhGA = physician's global assessment; NRS = numerical rating scale; cJADAS-10 = clinical Juvenile Arthritis Disease Activity Score in 10 joints; HAQ = Health Assessment Questionnaire; SF-36 = Medical Outcomes Study Short Form 36.

† Reference.

‡ Significant.

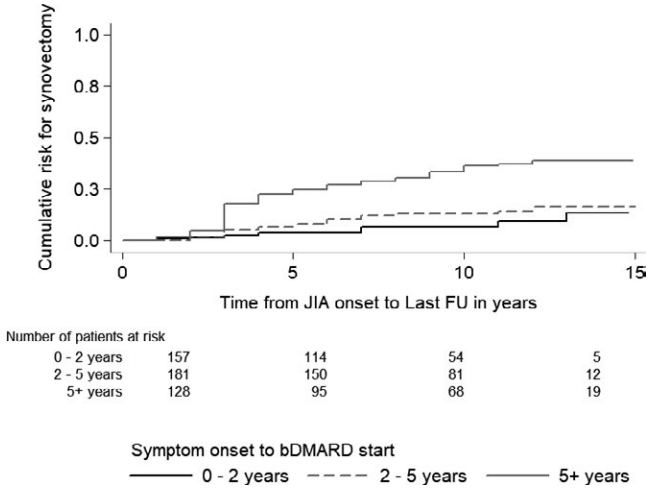

Figure 1. Time to first synovectomy in relation to initiation of a biologic disease-modifying antirheumatic drug (bDMARD). The projected rates of synovectomy differed among the 3 groups (log rank test $P < 0.0001$). JIA = juvenile idiopathic arthritis; FU = follow-up.

(nested case–control study). The additional analyses supported the results by also showing significantly better outcomes (or at least trends toward better outcomes) in terms of drug-free remission, functional ability, and overall well-being in early-treated patients (G1) compared to patients treated later (G2 and G3) (see Supplementary Tables 2a and 2b, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23709/abstract). The results were also confirmed after excluding systemic JIA patients (data not shown).

DISCUSSION

Over the past 18 years, the availability of effective therapies for children and adolescents with JIA has steadily grown (31,32),

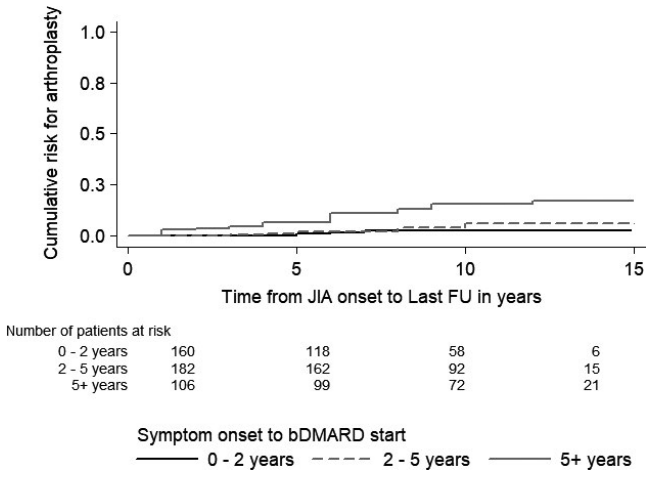

Figure 2. Time to first arthroplasty in relation to initiation of a biologic disease-modifying antirheumatic drug (bDMARD). The arthroplasty rates only significantly differed between G1 and G3 (log rank test $P = 0.043$). JIA = juvenile idiopathic arthritis; FU = follow-up.

and disease management has changed tremendously (33,34). Biologic therapies, which are highly effective at slowing the inflammatory cascade (14,16), have become an integral part of JIA therapy. However, therapy escalation is still taking place at very different times during the course of JIA, as this analysis shows. Almost half of the total study population as well as those with RF– PA did not start their first bDMARD course until they had been ill for >5 years. According to the study results, however, an early start would very likely have led to better long-term outcomes. We found that patients who were refractory to or intolerant of conventional treatment and who started bDMARDs within the first 2 years of JIA diagnosis had a significantly higher likelihood of having a drug-free remission and full functional capability in early adulthood and a significantly lower likelihood of requiring joint or eye surgery.

Especially important is the finding that after 10 years of disease, 19% of patients with early bDMARD use were in a state of medication-free remission as defined by PhGA, compared to 10% and 5% of those with bDMARD treatment after 2–5 years and after 5 years of JIA, respectively. The same result was obtained when remission was defined according to the cJADAS-10 score, with a slightly lower proportion of patients considered to be in remission in each group. Lower remission rates when using the cJADAS score instead of PhGA to define CID were also observed and discussed in a recent study (35).

The higher rate of drug-free remission in patients treated early is important, because it supports the concept of a window of opportunity for JIA. At present, a drug-free remission is the closest available proxy for being cured. This outcome is therefore most suited to evaluate whether an early period exists in which the disease is most susceptible to treatment (36). For rheumatoid arthritis (RA), the presence of a window of opportunity has convincingly been shown (36–38). This information has driven approaches for early and tight disease control in RA with the treat-to-target strategy that is now also proposed for JIA (10,16,39). Patients treated early in this study spent the observation period of approximately 9 years with a lower overall disease activity than those who started bDMARD therapy later. A late bDMARD start was associated with higher cumulative disease activity over time, which is a known predictor of disease damage in JIA (18). The importance of early aggressive treatment and the strong predictive ability of an early, robust response for achieving CID was already shown by the Trial of Early Aggressive Therapy study (26,40). The authors found that the likelihood of achieving CID in patients with polyarticular JIA by 6 months increased by >30% for each month earlier that aggressive treatment was started following disease onset (26,40,41).

In the current study, patients treated earlier also had lower mean disease activity, and had fewer functional and overall well-being restrictions than those who started bDMARDs later, despite less frequently using DMARDs and/or glucocorticoids in young adulthood. Significant differences in other patient-reported outcomes were not observed. However, the HRQoL was relatively good overall. Even patients treated with bDMARDs late in their

disease had a mental health score similar to that of the general population and a physical health score similar to population-based adult JIA collectives (5,7). Pain, HRQoL, and disease activity are known to dissociate (42,43).

When interpreting the results of the current study, one has to consider that the study included only patients with severe, mainly polyarticular, JIA, all of whom qualified for bDMARD treatment. Therefore, the drug-free remission rate in adulthood cannot be transferred to the whole JIA spectrum. However, 40% of these patients were in CID at their last follow-up, and the median cJADAS-10 score of 4.5 was similar to that of adult patients in population-based JIA cohorts (6,7).

To investigate the effects of early DMARD therapy on long-term prognosis, we used the first bDMARD instead of the first csDMARD, since most patients were enrolled in BiKeR at the start of bDMARD therapy. However, this distinction very likely does not affect our results because patients with an early bDMARD course also started csDMARDs early. Possible effects of the treatment decision on JIA outcome (confounding by indication) were modeled by propensity score methods, for which the patients' BiKeR baseline parameters were taken into account. Despite weighting by generalized propensity score, the 3 groups were quite different, especially with regard to JIA category distribution. For example, patients with enthesitis-related arthritis were overrepresented in G1 and more frequently included in BiKeR in recent years. This overrepresentation can be explained by the limited evidence for csDMARD efficacy in this patient group (44) as well as by approval of bDMARDs for enthesitis-related arthritis only in 2012.

The proportion of patients with RF+ PA was also greater in G1 (19%) than in G2 (13%) or G3 (5%). This finding reflects the treatment approach of pediatric rheumatologists, who treat patients with poorer prognosis more intensively from the outset. RF+ PA patients are less likely to reach remission, have poorer outcomes, and are more likely to be treated with glucocorticoids and biologic agents than patients of other JIA categories (6,7,11,12). However, even though the proportion of RF+ PA patients was highest in G1, this group still had the best long-term outcome. In contrast, patients with extended oligoarthritis were found more often in the late bDMARD start group G3 (30%) than in G1 (3%). Later evolvement to polyarthritis may be a reason for this finding. However, extension mainly occurs during the first 2 years of JIA (45). We have previously shown that patients with oligoarthritis are treated less intensively than patients with polyarticular JIA. Today, their outcomes are similar to or even worse than those of polyarticular JIA (11). This result was also found in the study of Nordal et al (6) for patients with extended oligoarthritis, who had a relatively poor prognosis, comparable to patients with RF+ PA. These findings raise questions about the current treatment approach for oligoarthritis. Ravelli et al (46) have recently published a randomized controlled trial that investigated the early use of methotrexate in these patients. The data in the current study underscore the need for more research and new treatment strategies for this group of patients.

Weaknesses of this observational study from real life include the problems of missing values and of loss to follow-up, especially during transfer from pediatric to adult care. Patients who were lost during the transfer period had a slightly less severe disease course than the patients who did not. A further limitation is the absence of a randomized design. Study strength lies in the prospective, standardized, and well-monitored observation of a large group of bDMARD-exposed JIA patients up to adulthood and the use of propensity score methods to take into account possible effects of treatment decision on the outcome. In summary, we believe that this study demonstrates the benefits of early intervention and effective disease activity control for optimal JIA long-term prognoses. In patients who have failed csDMARDs, an escalation to bDMARDs within the first 2 years of disease seems beneficial. Which patients are to be escalated early should be further investigated.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Minden had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Minden, Horneff, Niewerth, Zink, Klotsche.

Acquisition of data. Minden, Horneff, Seipelt, Aringer, Aries, Foeldvari, Haas, Klein, Tatsis, Tenbrock.

Analysis and interpretation of data. Minden, Niewerth, Zink, Klotsche.

ROLE OF THE STUDY SPONSORS

AbbVie, MSD, Pfizer, Chugai, and Roche had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. The companies received the manuscript 30 days prior to submission for the purpose of information. Publication of this article was not contingent upon approval by AbbVie, MSD, Pfizer, Chugai, or Roche.

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Childhood Arthritis and Rheumatology Research Alliance Consensus Treatment Plans for Juvenile Idiopathic Arthritis–Associated and Idiopathic Chronic Anterior Uveitis

Sheila T. Angeles-Han,[1] Mindy S. Lo,[2] Lauren A. Henderson,[2] Melissa A. Lerman,[3] Leslie Abramson,[4] Ashley M. Cooper,[5] Miriam F. Parsa,[6] Lawrence S. Zemel,[7] Tova Ronis,[8] Timothy Beukelman,[9] Erika Cox,[10] H. Nida Sen,[11] Gary N. Holland,[12] Hermine I. Brunner,[1] Andrew Lasky,[13] and C. Egla Rabinovich,[14] on behalf of the Juvenile Idiopathic Arthritis Disease-Specific and Uveitis Subcommittee of the Childhood Arthritis Rheumatology and Research Alliance

Objective. Systemic immunosuppressive treatment of pediatric chronic anterior uveitis (CAU), both juvenile idiopathic arthritis–associated and idiopathic anterior uveitis, varies, making it difficult to identify best treatments. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans (CTPs) for CAU for the purpose of reducing practice variability and allowing future comparison of treatments using comparative effectiveness analysis techniques.

Methods. A core group of pediatric rheumatologists, ophthalmologists with uveitis expertise, and a lay advisor comprised the CARRA uveitis workgroup that performed a literature review on pharmacologic treatments, held teleconferences, and developed a case-based survey administered to the CARRA membership to delineate treatment practices. We held 3 face-to-face consensus meetings using nominal group technique to develop CTPs.

Results. The survey identified areas of treatment practice variability. We developed 2 CTPs for the treatment of CAU, case definitions, and monitoring parameters. The first CTP is directed at children who are naive to steroid-sparing medication, and the second at children initiating biologic therapy, with options for methotrexate, adalimumab, and infliximab. We defined a core data set and outcome measures, with data collection at 3 and 6 months after therapy initiation. The CARRA membership voted to accept the CTPs with a >95% approval (n = 233).

Conclusion. Using consensus methodology, 2 standardized CTPs were developed for systemic immunosuppressive treatment of CAU. These CTPs are not meant as treatment guidelines, but are designed for further pragmatic research within the CARRA research network. Use of these CTPs in a prospective comparison effectiveness study should improve outcomes by identifying best practice options.

INTRODUCTION

Pediatric chronic anterior uveitis (CAU) is an inflammatory ocular disease that can lead to vision loss and ocular complications in up to 60% of affected children (1–15). Idiopathic uveitis, i.e., without associated systemic illness, constitutes approximately 50% of pediatric CAU (1,2,16–19). Juvenile idiopathic arthritis (JIA) is the most common systemic disease associated

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[1]Sheila T. Angeles-Han, MD, MSc, Hermine I. Brunner, MD, MSc: Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio; [2]Mindy S. Lo, MD, PhD, Lauren A. Henderson, MD, MMSc: Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; [3]Melissa A. Lerman, MD, PhD, MSCE: The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [4]Leslie Abramson, MD: Vermont Children's Hospital and University of Vermont Medical Center, Burlington; [5]Ashley M. Cooper, MD: Children's Mercy, Kansas City, Missouri; [6]Miriam F. Parsa, MD: University of California Los Angeles; [7]Lawrence S. Zemel, MD: Connecticut Children's Medical Center, Hartford, Connecticut; [8]Tova Ronis, MDCM: Children's National Health System, Washington, DC; [9]Timothy Beukelman, MD, MSCE: University of Alabama at Birmingham; [10]Erika Cox, BS: parent partner, Camas, Washington; [11]H. Nida Sen, MD, MHS: National Eye Institute, National Institutes of Health, Bethesda, Maryland; [12]Gary N. Holland, MD: Stein Eye Institute and David Geffen School of Medicine, University of California Los Angeles; [13]Andrew Lasky, MD: Randall Children's Hospital at Legacy Emmanuel, Portland, Oregon; [14]C. Egla Rabinovich, MD, MPH: Duke University Medical Center, Durham, North Carolina.

Drs. Angeles-Han and Lo contributed equally to this work.

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Address correspondence to C. Egla Rabinovich, MD, MPH, Box 3212 DUMC, Durham NC 27710. E-mail: egla.rabinovich@duke.edu.

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SIGNIFICANCE & INNOVATIONS

- Systemic immunosuppressive treatment of children with juvenile idiopathic arthritis–associated anterior uveitis and idiopathic chronic anterior uveitis varies significantly among pediatric rheumatologists.
- Consensus treatment plans for pediatric chronic anterior uveitis were developed by the Childhood Arthritis and Rheumatology Research Alliance to standardize systemic therapies for children with chronic anterior uveitis and enable comparison of treatments, with the goal of ultimately improving visual outcomes.

with pediatric CAU, in which 10–15% of these children will develop CAU (20,21). Early detection and appropriate timely treatment may prevent sight-threatening complications such as cataracts, glaucoma, and synechiae (22).

Presently, there are no widely accepted approaches to the treatment of CAU. Few pediatric randomized controlled trials have been conducted, except for adalimumab in JIA-associated uveitis (23,24). Topical steroids are typical initial therapy, but prolonged use can lead to complications such as cataracts and increased intraocular pressure. Inadequate response to, and/or toxic effects from, steroids necessitate the addition of steroid-sparing immunosuppressive therapy. However, evidence for specific agents is lacking.

Best practice guidelines for management of pediatric CAU have been developed by multiple groups but are not widely adopted in North America (25–27). Examination of JIA-associated patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, a large registry of North American pediatric rheumatology patients, demonstrated that a broad range of biologic and nonbiologic medications is prescribed (28). Additionally, the lack of pediatric standardized outcome measures for CAU limits the comparison of treatment strategies. Management is further complicated by the need for close collaboration between ophthalmologists and rheumatologists, with disease assessment by ophthalmologists, while steroid-sparing systemic treatment typically is prescribed by rheumatologists.

Through CARRA, we developed standardized treatment approaches, i.e., consensus treatment plans (CTPs), for children with typical JIA-associated and idiopathic CAU. These CTPs are meant for use in pragmatic research within the CARRA network and are not intended as standard treatment guidelines. We chose to include idiopathic CAU because systemic treatment approaches are the same as for JIA-associated uveitis, ocular complications are similar, and this condition affects an underserved population for research. In addition, the antinuclear antibody plus CAU may represent a forme fruste of JIA. These CTPs were developed through a robust consensus process and represent current clinical practice of North American pediatric rheumatologists, with expert input from ophthalmologists specializing in uveitis care. These CTPs, as with other CTPs developed by CARRA, differ from expert guidelines in that they are treatment strategies developed by consensus methods among CARRA members, with the primary goal of streamlining care and reducing practice variability (29). Ultimately, formal implementation of these CTPs in the treatment of patients enrolled in the CARRA registry will facilitate comparative effectiveness studies of different treatment approaches (29–33). We developed 2 CTPs with multiple treatment options intended for common CAU scenarios: initiation of methotrexate (MTX) therapy and initiation of biologic therapy.

MATERIALS AND METHODS

Core workgroup. A core workgroup of 10 board-certified pediatric rheumatologists with special interest in CAU, 2 ophthalmologists with expertise in uveitis, and a parent of a child with JIA-associated uveitis was formed. Tasks of the workgroup included defining a target population, identifying similarities and disparities among treatment approaches, reviewing the literature on comparative efficacies of treatment approaches, and achieving consensus on criteria to assess inflammation and treatment response. To identify relevant literature on uveitis treatment strategies, we performed a search of the PubMed database using the terms “juvenile arthritis,” “uveitis,” “treatment,” “subcutaneous,” “oral,” “dose,” “methotrexate,” “TNF inhibitor,” “etanercept,” “adalimumab,” and “infliximab” through April 1, 2014 and updated in July 2016. Besides face-to-face meetings, workgroup interactions occurred via teleconferences, surveys, and e-mail discussions between April 2012 and June 2016 (Figure 1).

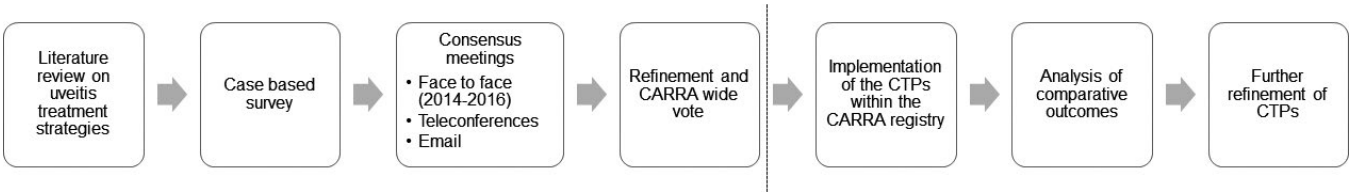

Figure 1. Flow chart of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) process. CTPs = consensus treatment plans.

Delphi survey. To better understand existing practice patterns in the treatment of CAU by the pediatric rheumatology community, we administered an anonymous web-based survey to CARRA voting members who actively treat children with CAU (trainees were ineligible). We presented clinical scenarios to identify common approaches for selection of an initial steroid-sparing agent in CAU, a second-choice steroid-sparing agent in the event of initial treatment failure in patients with and without complications from CAU, and a second-choice steroid-sparing agent in the event of intolerance to initial therapy (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23610/abstract).

Consensus meetings. The first face-to-face meeting of the workgroup was held in April 2014. One ophthalmologist participated via conference call (HNS). A syllabus consisting of a summary of the preconsensus survey, prior phone discussions, literature review, and existing guidelines was presented. Two CTPs were drafted for 2 scenarios of uncontrolled CAU: initiation of MTX in children naive to steroid-sparing agents and initiation of biologic therapy in children with inadequate response or intolerance to MTX.

Modified nominal group technique was used to seek consensus (defined as ≥75% agreement) on the 2 draft CTPs (30–33). The nominal group technique discussion was facilitated by an experienced moderator (HIB), and responses were tabulated by a non-voting CARRA member (LAH).These postconsensus CTPs were further refined by the uveitis workgroup during follow-up calls and via nominal group technique in face-to-face discussion in April 2015. An ophthalmologist (GNH) specializing in uveitis was present for these discussions.

The CTP strategies on the use of MTX and tumor necrosis factor inhibitor (TNFi) for CAU were presented to the CARRA JIA research committee in April 2016. Approval was obtained after members reviewed patient characteristics, data collection items, collection time points, primary and secondary outcomes, and the final CTP strategies. Consensus was based on a show of hands or on anonymous formal voting when needed. The number of voting members varied at each session, and thus our vote numbers varied. We disseminated final CTPs to the CARRA-wide membership as an anonymous online survey to confirm willingness to use at least 1 of the treatment plans to support comparative effectiveness research.

RESULTS

Delphi survey results. Our case-based survey was sent to all CARRA members (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23610/abstract). We received 129 responses (50% response rate). Five respondents indicated that they did not provide care for children with uveitis and were excluded from the analysis.

For a child with CAU that is not controlled by topical glucocorticoids, MTX was most frequently selected as the initial systemic drug. Respondents could select more than 1 response; half of the respondents (n = 60 of 120; 50%) selected oral dosing as the initial mode of administration, while subcutaneous dosing was selected more frequently (79 of 120; 66%). Therapy with a TNFi, with or without concomitant use of MTX, was less frequently selected (1–6%).

For patients with continued uncontrolled uveitis despite MTX, most (114 of 120; 95%) would add, instead of substitute, a systemic immunosuppressive agent. Adalimumab (73 of 117; 62%) was favored over infliximab (40 of 117; 34%). In contrast, in a child with uncontrolled uveitis and uveitis-related complications despite MTX, infliximab (63 of 120; 53%) was favored over adalimumab (52 of 120; 43%).

In the case of MTX intolerance requiring drug discontinuation in a child with inactive uveitis, adalimumab was the most frequently selected alternative (66 of 112; 59%), followed by mycophenolate mofetil (29 of 112; 26%), and infliximab (13 of 112; 11%). Less frequently selected systemic therapies included abatacept (2 of 112; 2%), azathioprine (1 of 112; 1%), and etanercept (1 of 112; 1%). Key questions considered important to address through a CTP were the timing of and criteria for initiation of a systemic agent, selection of first-line and second-line therapies, and criteria for assessing response to therapy.

Face-to-face consensus meetings. Based on the practice variability noted in the preconsensus survey, the workgroup agreed to develop CTPs that would determine the preferred form of MTX administration and preferred biologic therapy for CAU. Accordingly, we developed 2 CTPs for children with uncontrolled CAU: 1 for initiation of MTX in patients who have failed topical steroids, and 1 for initiation of TNFi therapy. Consensus on these CTPs was achieved by the JIA research committee at the 2016 CARRA annual meeting (27 of 28 [96%] and 25 of 25 [100%], respectively).

Target population. Table 1 defines the patient population targeted for these CTPs. There was consensus among the uveitis workgroup at the 2014 meeting and the CARRA JIA research committee in 2016 that these CTPs are appropriate for CAU that is idiopathic or JIA-associated, the most common categories of pediatric noninfectious uveitis. Although enrolling 2 distinct patient populations may introduce heterogeneity in the observed response to therapy, both are treated similarly, and a diagnosis of JIA does not influence outcomes (21). Two distinct target populations emerged from the consensus discussions, each with their own CTPs. The first CTP is for children naive to steroid-sparing therapy and compares oral versus subcutaneous MTX administration. The second CTP is for a heterogeneous population of children initiating a TNFi: failed MTX, intolerant of MTX, or naive to MTX but with need for urgent treatment as determined

Table 1. Characteristics of patients for use of the consensus treatment plans

Patients should have
Anterior uveitis only, idiopathic or juvenile idiopathic arthritis–associated
Age <18 years at enrollment
Uncontrolled chronic active uveitis, as evidenced by any of the following:
Ongoing uveitis activity, ≥1 (6–15 cells/high-power field) despite use of topical steroids or if unable to adhere to are or intolerant of topical steroids
Worsening uveitis activity while using topical steroids
Recurrent disease (≥1) with taper of topical steroids to twice per day or less
Development of new ocular complications attributable to inflammation or treatment during topical therapy*
Patients should not have
Panuveitis, intermediate uveitis, or posterior uveitis
Acute unilateral anterior uveitis
Retinal vasculitis
Active systemic infection or infectious uveitis
Uveitis associated with systemic disease other than juvenile idiopathic arthritis (e.g., Behçet's disease, sarcoidosis)
Contraindication to either methotrexate or anti–tumor necrosis factor therapy
Exposure to biologic therapy within prior 3 months
Ocular comorbidity not due to uveitis
Corrected visual acuity <20/200 not due to active uveitis
Pregnancy
History of malignancy

* Complications include increased intraocular pressure, hypotony, cataracts, posterior synechiae, band keratopathy, and cystoid macular edema.

by the clinician (e.g., patients presenting with acute uveitis and ocular complications from either uveitis or steroid therapy). This CTP compares adalimumab weekly, adalimumab every other week, and infliximab. Based on expert opinion, the more severely affected eye will dictate treatment in bilateral disease.

Both CTPs are suitable for the treatment of children who fulfill any of the following criteria: ongoing uveitis activity despite the use of topical steroids, worsening uveitis activity while using topical steroids, recurrent uncontrolled disease (≥1+ anterior chamber [AC] cell) with tapering of topical steroids to twice daily or less, development of new ocular complications attributable to either inflammation or treatment during topical steroid therapy, or intolerance or inability to adhere to therapy with topical glucocorticoid drops. Examples of complications include increased intraocular pressure, hypotony, cataracts, posterior synechiae, band keratopathy, and cystoid macular edema. While a twice-daily dosage of topical steroids is not preferred for long-term management, it is acceptable based on expert opinion, because this dosage is accepted by the ophthalmology community for patients who do not have glucocorticoid-induced ocular hypertension (34). There was consensus that these CTPs could also be applied to children taking systemic steroids or with a history of unsuccessful subtenon steroid injections.

Experts agreed that the CTPs were not designed for the treatment of children in other uveitis categories, i.e., intermediate and posterior uveitis, symptomatic acute unilateral anterior uveitis, uveitis attributable to other inflammatory conditions (e.g., sarcoidosis, Behçet's disease), the presence of ocular comorbidities that could affect interpretation of outcomes, and contraindications to therapy (Table 1). There was ≥80% consensus on all points. The CTPs were restricted to CAU, because this condition is most common in children, along with the lack of generally accepted criteria to assess disease activity in intermediate, posterior, or panuveitic uveitis. Patients with previous exposure to a biologic agent within 3 months prior to enrollment are also not appropriate for these CTPs.

Categorization of uveitis disease activity. Consensus was achieved to adopt the Standardization of Uveitis Nomenclature (SUN) Working Group methods of reporting clinical data (35) (Table 2). These methods include a grading scheme for AC cells and flare, uveitis activity, ocular complications, and outcomes. There was consensus that the course of uveitis can be categorized as inactive, worsened, improved, or controlled based on the degree of AC cells (35).

There was consensus to define adequately controlled CAU as follows: not using systemic steroids, ≤0.5+ AC cells, using topical steroids ≤2 drops/day, and no new ocular complications for at least 3 months. We agreed with the consensus that although 0.5+ AC cells is considered active by SUN criteria, we would not necessarily escalate therapy based on the presence of 0.5+ cells. For the purposes of these CTPs, the presence of AC cells ≥1+ (6–15 cells/high-power field) constitutes uncontrolled uveitis.

Table 2. Grading scheme for anterior chamber cells*

Grade	Cells in field†
0	0
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

* Adapted Standardization of Uveitis Nomenclature definitions of disease activity (ref. 22): inactive (grade 0 cells in anterior chamber), worsening activity (2-step increase in inflammation by anterior chamber cells, or 3+ to 4+), improved activity (2-step decrease in level of inflammation by anterior chamber cells, or decrease to 0), remission (inactive disease for ≥3 months after discontinuing all treatments for eye disease).
† Field size is 1 mm × 1 mm slit beam.

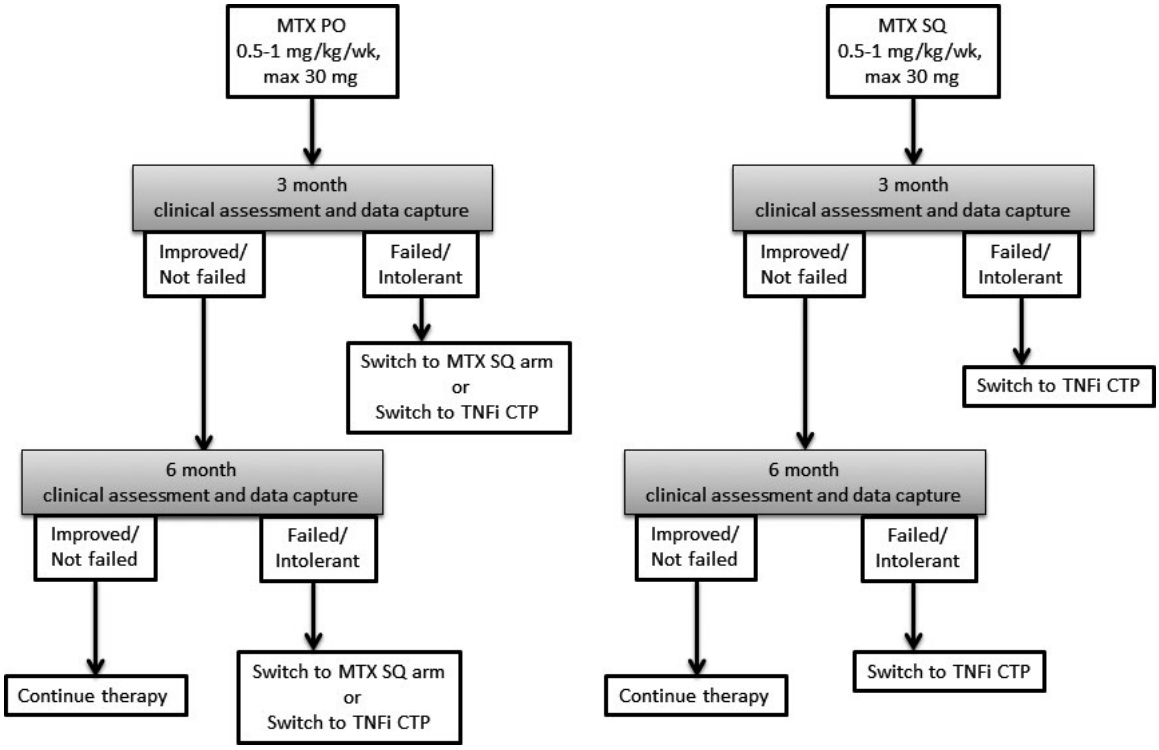

Figure 2. Dosing scheme for methotrexate (MTX). PO = by mouth; SQ = subcutaneous; TNFi = tumor necrosis factor inhibitor; CTP = consensus treatment plan.

MTX therapy CTP. Patients with CAU as defined, naive to steroid-sparing therapy, are appropriate for the MTX CTP. Although the majority of the uveitis workgroup agreed that subcutaneous MTX has higher bioavailability and is preferred over oral administration, data for superior efficacy of subcutaneous administration are lacking. In addition, a survey of pediatric rheumatologists indicated both routes are used equally (28). Therefore, both oral and subcutaneous MTX are treatment options. Dosing for MTX is 0.5–1 mg/kg/week, with a maximum of 30 mg/week; doses closer to 1 mg/kg/week are preferred (Figure 2).

Consensus was reached that 3 months of treatment are necessary before assessing MTX efficacy. After 3 months, the recommendation is for patients who failed MTX to change to the TNFi CTP. For children receiving oral MTX, an alternative is to enter the subcutaneous MTX treatment arm. In addition, JIA patients who develop new uveitis while taking MTX for arthritis would be considered to have failed MTX; the TNFi CTP should be considered.

TNFi CTP. Patients who fail MTX should be considered for the TNFi CTP using monoclonal antibody TNFi. For patients who are not intolerant of MTX, TNFi should be added to, rather than replace, MTX. The TNFi CTP can also be considered for MTX-naive patients with uncontrolled uveitis (≥1+ AC cells) and severe disease (e.g., ocular structural complications due to uveitis or complications of topical steroid therapy on presentation). MTX should be started simultaneously, using either the subcutaneous or oral MTX options from the MTX CTP. Consensus was achieved at the 2015 meeting that we would not specifically define "severe disease" at this time but that the TNFi CTP should be considered at the provider's discretion. Although inclusion of patients who are MTX naive and who failed MTX may confound the analysis of outcomes, we should be able to correct for this problem in analysis and do not want to limit therapy in children for whom the clinician has determined that TNFi initiation is necessary.

There was unanimous agreement that etanercept has no role in the treatment of pediatric uveitis and that there are insufficient data to recommend either adalimumab or infliximab as the preferred agent. Selection is left open to the treating provider, acknowledging that there may be individual factors influencing this decision, such as patient preference for medication route, insurance coverage, and adherence concerns.

The TNFi CTP includes 3 treatment options: adalimumab subcutaneous injections weekly, adalimumab subcutaneous injections every other week, and infliximab infusions every 4 weeks after loading. Dosing for adalimumab parallels that for polyarticular JIA: 10 mg for patients 10 kg to <15 kg, 20 mg for patients 15 kg to <30 kg, 40 mg for patients ≥30 kg (Figure 3). The workgroup agreed that the adalimumab dose can be escalated 8 weeks after initiation if uveitis remains uncontrolled (≥1+ AC) or if the patient is unable to begin tapering steroids after 4 weeks due to persistent CAU. Dose escalation through either doubling the every-other-week dose (if the patient is taking 10 or 20 mg) or increasing the frequency to weekly are equally acceptable.

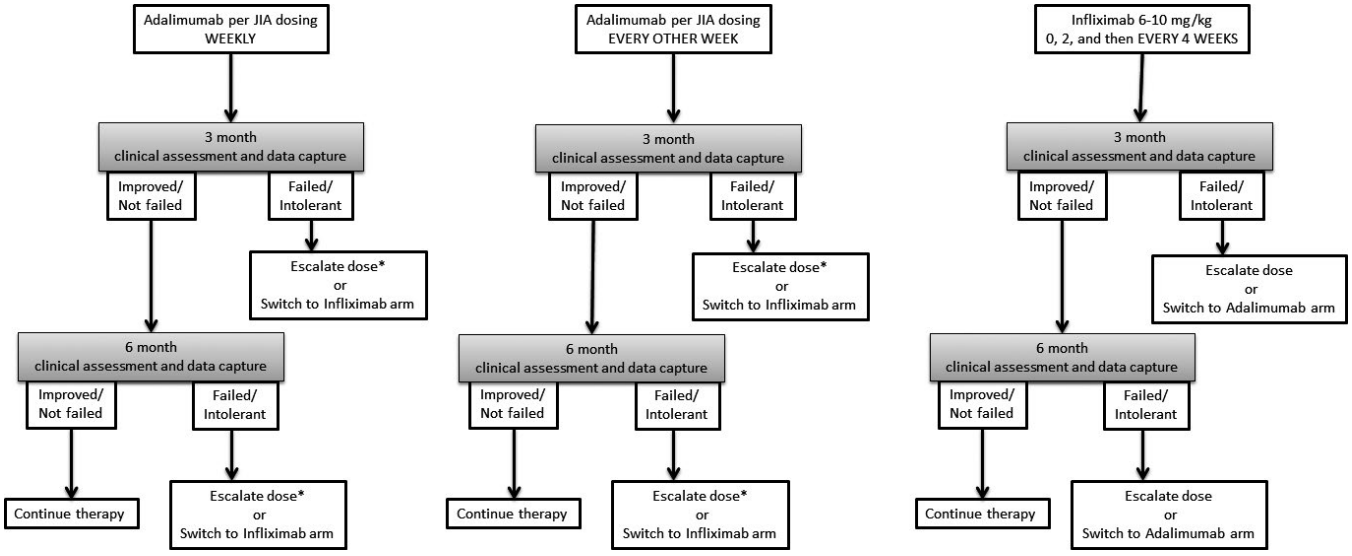

Figure 3. Dosing scheme for adalimumab and infliximab. JIA = juvenile idiopathic arthritis; * = Dose escalation: either doubling the every-other-week dose (if patient is taking 10 or 20 mg) or increasing frequency to weekly are equally acceptable.

Dosing for infliximab starts at 6–10 mg/kg (Figure 3). A loading regimen is recommended, giving infusions at 0 and 2 weeks, followed by every 4 weeks thereafter. Dose escalation is permitted based on a physical examination after 8 weeks, up to a maximum dose of 20 mg/kg. The MTX dose can be lowered while the patient is receiving a TNFi. The CARRA JIA research committee agreed with an infliximab dosing range of 6–10 mg/kg (27 of 28; 96%), and with both a weekly and every other week adalimumab dosing arm (27 of 28; 96%).

Core documentation for children with CAU. We defined the data collection items, time points, and outcome measures for data collection through consensus discussions at the 2015 meeting (10 of 13; 77%), and obtained approval by the JIA committee (26 of 26; 100%). Data will be collected at enrollment, 3 months, and 6 months. An eye examination should occur within 6 weeks after starting therapy but will not be considered a separate study visit. All eye examination records in between study visits should be reviewed. Data points include demographics, uveitis clinical data (duration, age at uveitis onset, JIA-associated or idiopathic uveitis, anatomic location, laterality, AC cells by SUN criteria, visual acuity, ocular complications, and ocular surgeries), reason for nonadherence to topical steroids if applicable, current and maximum daily steroid use (topical and systemic), start and stop dates of medications, and patient-reported outcome measures (Table 3). Patient-reported outcomes will include the Patient-Reported Outcome Measurement Information System global health scale, and the Effects of Youngsters' Eyesight on Quality of Life instrument (36,37). Adverse effects of therapy, such as leukopenia and hepatorenal toxicity from MTX, will be recorded. The schedule for monitoring the toxicity of medications is deferred to the prescribing physician. Definitions of disease activity, recurrence, flare, and complications will be

Table 3. Data collection points at 0, 3, and 6 months and/or end of study*

Variables	0 months	3 and 6 months and/or end of study
Baseline		
Disease duration	X	–
Age at disease onset	X	–
JIA subtype or idiopathic uveitis	X	–
Uveitis		
Anatomic location	X	X
Laterality	X	X
Anterior chamber cells by SUN criteria	X	X
Visual acuity	X	X
Ocular complications	X	X
Ocular surgeries	X	X
Patient-reported outcomes		
Visual analog scale	X	X
Overall QOL: PROMIS global health score	X	X
Uveitis related QOL: EYE-Q	X	X

* JIA = juvenile idiopathic arthritis; SUN = Standardization of Uveitis Nomenclature; QOL = quality of life; PROMIS = Patient-Reported Outcome Measurement Information System; EYE-Q = Effects of Youngsters' Eyesight on Quality of Life.

based on SUN criteria (35) (Table 2). Ophthalmology examination results will be included.

Interpretation of patient response. The primary outcome is defined as improvement or worsening of AC cells at 6 months as defined by SUN criteria. Secondary outcome measures include the proportion with inflammation of <1+ cells, visual acuity, eye complications, eye surgeries, patient-reported outcomes, adverse events, and glucocorticoid use. Most uveitis specialists have a goal of reducing AC cells to below a threshold of 1+ cells.

Treatment failure is defined as ongoing uncontrolled uveitis, development of damage/eye complications, or intolerance/nonadherence to treatment. Another CTP treatment arm can be considered for patients who fail initial treatment. If treatment changes for arthritis but not uveitis, or if the patient chooses not to continue in the CTP, this fact will be captured by the CTP.

MTX intolerance. Suggestions for management of MTX intolerance were considered beyond the scope of these CTPs. The workgroup emphasizes that MTX intolerance can often be managed through the use of anti-emetics, folic acid, and/or leucovorin and through dose adjustment, but children experiencing MTX intolerance can also be considered for the TNFi CTP.

Systemic steroids. The workgroup acknowledged that provision and dosing of systemic and topical glucocorticoids are typically made by the treating ophthalmologist, rather than the rheumatologist. Therefore, this CTP does not include glucocorticoid recommendations. However, based on expert opinion, systemic steroids should be avoided in the treatment of CAU. Systemic steroids should be used only as a temporizing measure while awaiting efficacy of steroid-sparing therapy, and steroid taper should begin no later than 2 weeks after initiation of a steroid-sparing agent. This approach was unanimously agreed upon by the CARRA JIA committee (27 of 27; 100%).

Ophthalmology screening. Although the American Academy of Pediatrics has guidelines for ophthalmology screening of children with JIA, no guidelines exist for children with a history of CAU. Expert consensus was reached that children with uncontrolled uveitis should be monitored at least every 2–6 weeks (27 of 28; 96%).

Third-line therapy. Insufficient data exist to support recommending treatment of uveitis refractory to MTX and TNFi. Although consensus was not achieved, members considered 1 or more of these medications: mycophenolate mofetil (13 of 18; 72%), abatacept (10 of 18; 56%), cyclosporine (7 of 18; 39%), tocilizumab (6 of 18; 33%), golimumab (1 of 18; 5%), azathioprine (1 of 18; 5%), leflunomide (1 of 18; 5%), and rituximab (1 of 18; 5%). These preferences may change as experience with these agents grows.

Post-consensus survey. The workgroup sought approval from the CARRA-wide membership through an online survey. The response rate was 81% (n = 247 of 306); among the respondents, 10% (24 of 247) reported that they did not manage uveitis, and their responses were excluded. Consensus was achieved on the target population (216 of 223; 97%) and on the criteria for application of the TNFi CTP (215 of 223; 97%). A total of 96% (215 of 223) reported willingness to use at least 1 arm of the MTX CTP and 99% (220 of 223) at least 1 arm of the TNFi CTP. There was broad consensus on the data collection measures outlined above.

DISCUSSION

Informed by the available medical evidence, expert consensus was achieved among pediatric rheumatologists and ophthalmologists participating in CARRA on treatment strategies for children with CAU. Thus, these CTPs may provide general guidance for the management of typical pediatric CAU, but they are not meant as treatment guidelines. Rather, as with CTPs developed for other rheumatologic conditions, these CTPs are primarily intended to facilitate future comparative effectiveness research within the CARRA network (29).

Two CTPs were developed for use in patients enrolled in the CARRA registry: 1 for MTX in children without prior exposure to disease-modifying antirheumatic drugs, and the other for TNFi therapy in children who failed MTX, are MTX intolerant, or are in need of urgent treatment as determined by the clinician. These CTPs may not be relevant for cases that do not fit the most common scenarios described here. Active uveitis may be associated with active arthritis; these plans are intended to be used in situations where uveitis is guiding the choice of therapy.

In general, MTX is the first-line agent for children with uveitis in need of systemic immunosuppression. In complicated or refractory disease, infliximab and adalimumab are equally preferred, and few data support superiority of either TNFi (38–43). Small studies suggest that adalimumab may be as effective as or superior to infliximab in achieving remission, but differences in the dose and frequency were given (41,44–46). Doses of infliximab >7.5 mg/kg and as high as 20 mg/kg/dose every 4 weeks may be necessary for recalcitrant disease (42,47–49). Our CTPs are intended to help standardize treatment approaches while also allowing future comparison of different treatment strategies in observational comparative effectiveness studies. Accordingly, our CTPs provide options that allow for comparatively higher dose regimens of TNFi than previously published guidelines.

In addition to standardization of care, a need also exists for standardized outcome measures. The SUN criteria can be used for measuring treatment response. Heiligenhaus et al (50) proposed outcome measures specific for children with JIA-associated uveitis. We propose an expanded group of outcome measures through these CTPs (Table 3).

Regular monitoring by an ophthalmologist experienced in uveitis is crucial. Although guidelines for children with JIA exist, none exist for children with idiopathic uveitis, because this condition typically falls within the treating ophthalmologist's purview. We suggest that children with uncontrolled uveitis or who are undergoing therapy changes be monitored at least every 2–6 weeks. In addition, if access to a uveitis specialist is available, all children should be evaluated at least once. We emphasize the importance of close communication between pediatric rheumatologists and ophthalmologists to ensure the best visual outcomes. This coordination can be done through shared medical records, combined subspecialty clinics, and/or standardized communication forms.

These CTPs address 2 important issues in CAU treatment. First, the preferred route of MTX administration is unknown. Subcutaneous administration has higher bioavailability and may have fewer gastrointestinal side effects (51,52). Since the route of administration will be based on the provider's and patient's preference, we may be able to optimize the route through the conduct of observational studies of patients treated with these CTPs, which will also enable comparative study of adalimumab and infliximab.

A limitation of these CTPs is the inability to recommend a tapering schedule for topical steroids, as this decision is made by ophthalmologists. Collaboration between subspecialties is crucial. As with any analysis of JIA-associated uveitis therapy, treatment may be guided by arthritis. This confounder would be captured in data collection and outcomes would not be used for comparison. Since data on treatment using other TNFi drugs are lacking, they were not included in this CTP. With implementation of these CTPs using the CARRA registry in comparative effectiveness research, we can address factors associated with treatment success, including preferred duration of therapy and the risk of relapse after medication discontinuation (49,53,54).

There is significant variability in current treatment strategies of CAU. We outline a consensus-based strategy to standardize the initial care of children with JIA-associated and idiopathic CAU. Standardizing care will enable comparative effectiveness studies and future clinical trials, as well as identification of preferred treatment, and will ultimately optimize visual outcomes for children with CAU.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rabinovich had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Angeles-Han, Lo, Lasky, Rabinovich.

Acquisition of data. Angeles-Han, Lo, Henderson, Lerman, Brunner, Lasky, Rabinovich.

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BRIEF REPORT

Association Between Nailfold Capillary Density and Pulmonary and Cardiac Involvement in Medium to Longstanding Juvenile Dermatomyositis

Zoltan Barth,[1] Thomas Schwartz,[2] Berit Flatø,[3] Trond M. Aaløkken,[4] Akos Koller,[5] May B. Lund,[6] Ivar Sjaastad,[2] and Helga Sanner[7]

Objective. To explore the associations between microvascular abnormalities as assessed by nailfold capillaroscopy (NFC) and pulmonary and cardiac involvement in patients with juvenile dermatomyositis (DM) who are assessed after medium- to long-term follow-up.

Methods. Fifty-eight patients with juvenile DM were examined a mean ± SD of 17.0 ± 10.6 years after symptom onset. Nailfold capillary density (NCD) and a neovascular pattern (defined as an active or late scleroderma pattern) were analyzed, with blinding to clinical data. Pulmonary involvement was assessed by pulmonary function tests including spirometry, diffusing capacity for carbon monoxide (DLco), and body plethysmography. High-resolution computed tomography (HRCT) was also performed. Cardiac involvement was assessed by electrocardiography, Holter monitoring (heart rate variability), and echocardiography.

Results. Patients with low NCD (<6 capillaries/mm) (n = 21), compared to patients with normal NCD (≥6 capillaries/mm) (n = 37) had lower forced vital capacity (89.7% versus 98.5% predicted), total lung capacity (87.8% versus 94.5% predicted), and more often had low DLco values (15 [71%] of 21 patients versus 14 [38%] of 37 controls) (all $P < 0.05$). Use of HRCT to assess airway disease was more frequent in the group with low NCD (6 [30%] of 20 patients versus 3 [8%] of 36 patients in the normal NCD group; $P = 0.034$). No associations between NCD and cardiac parameters or between neovascular pattern and pulmonary or cardiac parameters were observed.

Conclusion. In patients with juvenile DM, low NCD was associated with lung involvement, which was mostly subclinical. No significant associations with cardiac involvement were observed. These results shed light on possible mechanisms underlying organ involvement, but further and preferably larger studies are needed to identify NCD as a potential biomarker for lung and cardiac involvement in juvenile DM.

INTRODUCTION

Juvenile dermatomyositis (DM) is a rare autoimmune myopathy with a childhood origin and is characterized primarily by pathognomonic skin rashes and muscle weakness. Juvenile DM is considered to be a multisystemic vasculopathy in which autoimmune mechanisms target small vessels. Systemic vasculopathy and the consequent microvascular remodeling might play an important role in the involvement of various organs, including the heart and lungs.

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[1]Zoltan Barth, MD: Institute for Experimental Medical Research and K. G. Jebsen Center for Cardiac Research, Oslo University Hospital–Ullevål and University of Oslo, Oslo, Norway, Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary, and Bjørknes University College, Oslo, Norway; [2]Thomas Schwartz, MD, PhD, Ivar Sjaastad, MD, PhD: Institute for Experimental Medical Research and K. G. Jebsen Center for Cardiac Research, Oslo University Hospital–Ullevål and University of Oslo, Oslo, Norway; [3]Berit Flatø, MD, PhD: Oslo University Hospital–Rikshospitalet and Institute for Clinical Medicine, University of Oslo, Oslo, Norway; [4]Trond M. Aaløkken, MD, PhD: Oslo University Hospital–Rikshospitalet, Oslo, Norway; [5]Akos Koller, MD, PhD: Medical School, University of Pécs, Pécs, Hungary, and University of Physical Education, Budapest, Hungary; [6]May B. Lund, MD, PhD: Institute for Clinical Medicine, University of Oslo and Oslo University Hospital–Rikshospitalet, Oslo, Norway; [7]Helga Sanner, MD, PhD: Bjørknes University College and Oslo University Hospital–Rikshospitalet, Oslo, Norway.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Helga Sanner, MD, PhD, Department of Rheumatology, Oslo University Hospital–Rikshospitalet, 0027 Oslo, Norway. E-mail: helga.sanner@medisin.uio.no.

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SIGNIFICANCE & INNOVATIONS

- In patients with juvenile dermatomyositis (DM) assessed after medium- to long-term follow-up, low nailfold capillary density (NCD) is associated with impaired pulmonary function tests and high-resolution computed tomography–detected airway disease.
- NCD is not significantly associated with cardiac involvement, including systolic and diastolic dysfunction, echocardiographic abnormalities, and heart rate variability.
- These findings shed light on the role of microvascular remodeling for organ involvement, but further and larger studies are needed to assign a possible role of NCD as a biomarker for organ involvement in juvenile DM.

Pulmonary involvement is a relatively infrequent complication in patients with juvenile DM and is associated with a poor prognosis (1). Interstitial lung disease (ILD) and impaired pulmonary function tests (PFTs) are the most frequent findings. Although pulmonary involvement is mostly subclinical, rapidly progressive ILD has been shown to be a major cause of death in Japanese patients with juvenile DM (2). Clinically important cardiac involvement is even more sporadic in patients with juvenile DM; however, abnormal findings assessed by electrocardiography (ECG) and echocardiography have been observed both early (3) and late (4,5) in the disease course. Notably, even if the clinical relevance of these subtle cardiac abnormalities has yet to be determined, cardiac monitoring is recommended for patients with juvenile DM (6).

Nailfold capillaroscopy (NFC) is a simple, noninvasive technique that can be used to evaluate the microvascular architecture. It has been hypothesized that NFC might be a putative biomarker in autoimmune rheumatic diseases; pilot studies in patients with systemic sclerosis (SSc) have shown associations with peripheral vascular and pulmonary involvement (7). Additionally, microvascular changes in the nailfolds are associated with pulmonary involvement (7–9) and might be predictive of future severe organ involvement in SSc (9). Patients with SSc with striking microvascular abnormalities also more frequently presented with cardiac involvement and decreased heart rate variability (HRV), although the findings are conflicting (7). In adults with DM, NFC findings were associated with pulmonary but not cardiac involvement (10,11). Of note, cardiac-related pathologies were uncommon in most of these studies (7,10). Thus, there are data suggesting that NFC may be a useful tool to investigate organ involvement in adults with rheumatic diseases; however, there are no studies addressing this issue in juvenile DM or in other pediatric rheumatic diseases.

Our group has established a cohort of Norwegian patients with juvenile DM. Patients in this cohort (which has been thoroughly described with regard to NFC [12], pulmonary involvement [13], and cardiac involvement [4,5,14]) were clinically examined after medium- to long-term follow-up. Patients showed more abnormal findings in all NFC measures compared to age- and sex-matched controls. Nailfold capillary density (NCD), low NCD (defined as <6 capillaries/mm), and neovascular pattern (defined as an active or late scleroderma pattern) were shown to be the most applicable NFC measures (12). Compared to controls, patients had smaller lung volumes and reduced gas diffusion capacity. In addition, 37% of patients showed abnormalities as assessed by high-resolution computed tomography (HRCT) (13). Moreover, in our cohort, patients had cardiac abnormalities including decreased systolic (4) and diastolic function (5), reduced HRV (14), and more ECG-detected pathologies (5) compared to matched controls.

No studies have investigated the association between NFC findings and pulmonary or cardiac involvement in patients with juvenile DM. Thus, the objective of the current study was to investigate the possible relationship between NFC and pulmonary and cardiac measures in patients with juvenile DM who were examined after medium- to long-term follow-up.

PATIENTS AND METHODS

Study design and cohort. Our established Norwegian juvenile DM inception cohort consists of 60 patients in whom juvenile DM was diagnosed between January 1970 and June 2006 (15). Inclusion criteria included a probable or definitive diagnosis of DM according to the Bohan and Peter criteria, disease onset before age 18 years, ≥24 months from symptom onset to follow-up, and age at follow-up ≥6 years. Informed consent was obtained from all patients (and parents, for patients ages >16 years), and the Regional Ethics Committee approved the study (S-05144).

Data collection and clinical and laboratory measurements. Patients were clinically examined after a mean disease duration of 17 years. Disease onset was defined as the time of the first muscle or skin symptom, and disease duration was defined as the time from disease onset to the follow-up examination. We have previously published data on NFC in relation to general disease variables in this cohort (12), as well as data on pulmonary (13) and cardiac outcomes (4,5,14).

NFC. A Scalar video microscope (VideoCap; DS MediGroup) was used for NFC examinations (performed by HS) (12). The analyses were performed by ZB, who was blinded to clinical information. VideoCap 8.20 software (VideoCap; DS MediGroup) was used for image analysis. NCD

and neovascular pattern (defined as active or late scleroderma pattern) were assessed, as previously described in detail (12). The cutoff used for low NCD was <6 capillaries/mm (12). In our inception cohort, 1 patient was not examined with NFC, and 1 patient was excluded due to a limited number of available NFC recordings of good quality; thus, data for 58 patients were used for further analyses.

Pulmonary assessment. *PFT*. All PFT measurements, including spirometry (forced vital capacity [FVC]), measurements of gas diffusion (diffusing capacity for carbon monoxide [DLco]), and body plethysmography (total lung capacity [TLC]), were performed on a computerized Vmax pulmonary function unit (Viasys). All spirometry variables were measured in accordance with current guidelines (13). The PFT variables were expressed as percent predicted (13). Low FVC, TLC, and DLco values were defined as less than the 5th percentile of predicted values, and PFT abnormality was defined as low TLC and/or low DLco values.

HRCT. HRCT was performed in 56 patients, using a LightSpeed 16 scanner (GE Healthcare). An experienced radiologist (TMA) who was blinded to clinical information read the images and scored the presence of ILD (reticular pattern with or without traction bronchiectasis, and/or ground-glass opacity), and airway diseases (bronchiectasis, and/or air trapping, and/or micronodules) (13).

Table 1. Characteristics and pulmonary and cardiac measures in patients with juvenile dermatomyositis, stratified by normal and low NCD*

	All patients (n = 58)	Normal NCD (n = 37)	Low NCD (n = 21)	*P*
Patient characteristics				
Female	36 (62)	21 (57)	15 (71)	0.268
Age, mean ± SD years	25.4 ± 12.5	27.9 ± 12.9	19.8 ± 8.8	0.013†
Disease duration, mean ± SD years	17.0 ± 10.6	19.8 ± 10.9	12.1 ± 8.4	0.008‡
NCD, mean ± SD capillaries/mm	6.4 ± 2.1	7.7 ± 0.9	4.2 ± 1.6	NA
PFTs				
FVC, mean ± SD percent predicted	95.3 ± 12.4	98.5 ± 12.3	89.7 ± 10.6	0.008‡
Low FVC	10 (17)	4 (11)	6 (29)	0.085
TLC, mean ± SD percent predicted	92.0 ± 10.4	94.5 ± 10.9	87.8 ± 8.2	0.020†
Low TLC	14 (24)	8 (24)	6 (30)	0.600
DLco, mean ± SD percent predicted	81.6 ± 14.8	84.3 ± 16.2	76.7 ± 10.6	0.059
DLco/VA, mean ± SD percent predicted	96.2 ± 15.4	96.0 ± 17.1	96.7 ± 12.3	0.866
Low DLco	29 (50)	14 (38)	15 (71)	0.014†
PFT abnormality§	33 (57)	17 (50)	16 (80)	0.036†
HRCT				
ILD	8 (14)	5 (14)	3 (15)	0.909
Airway disease	9 (16)	3 (8)	6 (30)	0.034†
Cardiac measures				
LAS, mean ± SD percent	16.6 ± 2.5	16.3 ± 2.7	16.9 ± 2.3	0.383
e', mean ± SD cm/second	11.2 ± 2.7	11.0 ± 3.0	11.6 ± 2.1	0.433
Pathologic ECG	10 (17)	7 (19)	3 (15)	0.710
cSDNN, mean ± SD msec	39.1 ± 16.3	41.3 ± 17.1	36.8 ± 15.1	0.402

* Values are the number (%) except where indicated otherwise. Normal nailfold capillary density (NCD) was defined as ≥6/mm; low NCD was defined as <6 mm. The following measures were missing in patients with normal and low NCD, respectively: total lung capacity (TLC) in 4 patients (3:1), high-resolution computed tomography (HRCT) in 2 patients (1:1), early diastolic tissue velocity (e') in 1 patient (1:0), electrocardiogram (ECG) in 1 patient (0:1), and standard deviation of all normal-to-normal intervals corrected to the heart rate (cSDNN) in 4 patients (4:0). PFTs = pulmonary function tests; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; VA = alveolar volume; ILD = interstitial lung disease; LAS = long axis strain.
† $P < 0.05$, normal vs. low NCD.
‡ $P < 0.01$, normal vs. low NCD.
§ Low TLC and/or low DLco.

Cardiac assessment. *Electrocardiography*. Two-dimensional and Doppler echocardiography were performed and analyzed, with the assessors blinded to patient information (4,5). Diastolic function was measured by early diastolic tissue velocity (e′), which was recorded in the mitral ring in 2-chamber and 4-chamber views (5). Systolic function was measured by long-axis strain (LAS) (mitral annulus displacement as the percent of end-diastolic left ventricular length) (4). A lower value for early diastolic tissue velocity and LAS suggests poorer diastolic and systolic function, respectively.

ECG. A 12-channel ECG and 24-hour ambulatory Holter monitoring were carried out as previously described in detail (5,14). ECGs were analyzed by investigators blinded to clinical information and classified as normal or pathologic. Calculation of HRV (standard deviation of all normal-to-normal intervals corrected to the heart rate) was performed using HolterSoft Ultima version 2.44 software (Novacor) (14).

Statistical analysis. Differences between patients and controls were tested using Student's *t*-test for continuous and normally distributed variables and the Mann-Whitney U test for continuous non-normally distributed variables, as appropriate. Chi-square tests were used to test differences between 2 groups for categorical variables. Correlations were determined using Spearman's correlation coefficient (r_s).

NCD is known to be dependent on age and possibly disease duration; therefore, multivariate logistic regression analysis was used to age-adjust the associations between low NCD (dependent variable) and cardiac parameters as well as HRCT findings (with age used as an independent variable). PFT variables are presented as the percent predicted; thus, values were already corrected for age.

To explore the possible effect of disease duration on the association between PFT variables and NCD and low NCD, respectively, multivariate linear and logistic regression analyses were performed with disease duration and various PFT variables as independent variables. Due to a strong intercorrelation between age and disease duration (r_s = 0.938, P < 0.001), both variables could not be included as independent variables in the regression analyses. Two-tailed tests were used for all calculations, and P values less than 0.05 were considered significant. Statistical analysis was performed using SPSS v.24SA. Due to the explorative nature of the study, we did not adjust P values for multiple comparisons.

RESULTS

The characteristics of the patients have previously been described in detail (15), and selected parameters are shown in Table 1 as background information. Of 58 patients, 21 (36%) had low NCD (Table 1), and a neovascular pattern was observed in 24 (41%) of 58 patients (12). Table 1 also shows data for selected pulmonary tests in all patients with juvenile DM patients as well as in patients with normal and low NCD. Low NCD was associated with lower FVC and TLC values (percent predicted) (Figure 1). Moreover, low NCD was associated with low DLCO values (percent predicted). Signs of airway disease on HRCT were also more prevalent in the group with low NCD. There were weak-to-moderate correlations between NCD (as a continuous variable) and the following variables: FVC (r_s = 0.262, P = 0.047) and HRCT-assessed airway disease (r_s = –0.359, P = 0.007) but not with any of the other PFT or HRCT variables included in Table 1 (data not shown).

When adjusting for the association between NCD/low NCD and all PFT variables (that were already age-adjusted) for disease duration, FVC was no longer significantly associated with NCD (standardized β = 0.219, P = 0.080), but an association between TLC and NCD was observed (standardized β = 0.295, P = 0.018). Both FVC and TLC remained associated with low NCD (odds ratio [OR] 0.936, P = 0.18 and OR 0.931, P = 0.006, respectively), while low DLCO lost significance (data not shown). Additionally, we analyzed the differences in HRCT measures after adjusting for age; airway disease was more frequently observed in the group with low NCD than in the group with normal NCD.

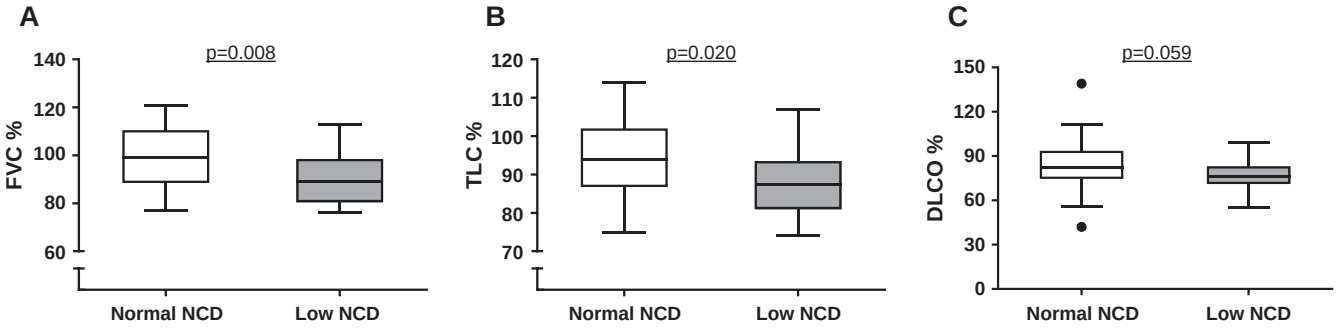

Figure 1. Pulmonary function measures, including forced vital capacity (FVC), percent predicted (**A**), total lung capacity (TLC), percent predicted (**B**), and diffusing capacity for carbon monoxide (DLCO), percent predicted (**C**), in patients with normal nailfold capillary density (NCD) and patients with low NCD. Data are shown as box plots (using Tukey's method). Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes are error bars. Circles indicate outliers.

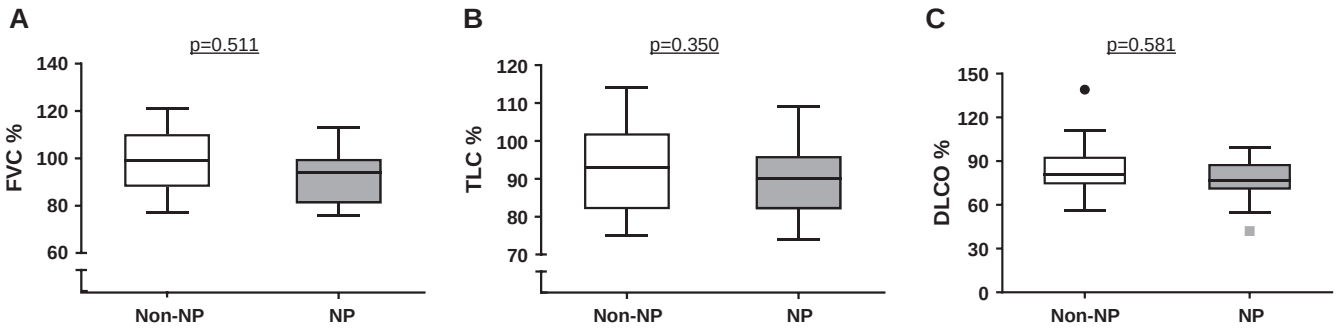

Figure 2. Pulmonary function measures, including forced vital capacity (FVC), percent predicted (**A**), total lung capacity (TLC), percent predicted (**B**), and diffusing capacity for carbon monoxide (DLCO), percent predicted (**C**), in patients with non-neovascular pattern (non-NP) and patients with NP. Data are shown as box plots (using Tukey's method). Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes are error bars. The circle and shaded box indicate outliers.

Table 1 also shows selected cardiac data for patients with juvenile DM as well as patients with normal NCD and those with low NCD. We observed no significant differences between patients with low NCD and those with normal NCD, including ECG findings, HRV, and systolic or diastolic function as assessed by echocardiography. Also, no significant associations between low NCD and cardiac measures were observed after adjusting for age. No significant correlations between cardiac parameters and NCD (as a continuous variable) were observed (data not shown). Additionally, no associations between neovascular pattern and any pulmonary or cardiac variables were found (selected data are shown in Figure 2; remaining data are not shown).

DISCUSSION

To our knowledge, this is the first study to investigate the relationship between NFC findings and pulmonary and cardiac involvement in patients with juvenile DM. We observed associations between NFC variables and lung involvement: low NCD was associated with smaller lung volumes, reduced gas diffusion capacity, and HRCT-detected airway disease. No significant associations between NFC and cardiac involvement were detected. The representativeness of our juvenile DM cohort has been described previously (15); we believe it covers the vast majority of patients with juvenile DM diagnosed from 1970 to 2006 in Norway.

Our key finding is the relationship between low NCD and smaller lung volumes (FVC and TLC) and reduced gas diffusion (low DLCO) in patients with juvenile DM. A recent study in SSc showed results consistent with our findings (8) when comparing patients with low NCD (<7 capillaries/mm) and those with normal NCD: both FVC values (87% versus 101%) and DLCO values (71% versus 86%) were decreased in patients with low NCD. These findings are comparable to our results showing that FVC (percent predicted) was decreased (90% versus 99%) and DLCO was borderline decreased (77% versus 84%) in patients with low NCD versus those with normal NCD.

HRCT-assessed airway disease was more prevalent in patients with low NCD than in patients with normal NCD. There was no significant difference in the prevalence of HRCT-detected ILD between the groups. Numerous studies in SSc have shown an association between NFC measures and lung involvement (9); reduced NCD was associated with ILD (8), and SSc patients with lung fibrosis showed decreased NCD and more bushy capillaries compared to patients with idiopathic pulmonary fibrosis (9). Thus, even if a few SSc studies did not demonstrate an association between capillaroscopic variables and lung involvement (9), microvascular changes seem to reflect pulmonary involvement in SSc (7,8). In our cohort, although decreased lung volumes and a higher incidence of HRCT-detected airway disease were observed in patients with low NCD, a considerable proportion of patients with normal NCD also showed lung involvement. Thus, even if microvascular involvement appears to be relevant in the development of pulmonary manifestations, other factors are likely to contribute to the process in juvenile DM.

No significant association between low NCD and cardiac involvement was demonstrated. None of the NFC parameters correlated significantly with systolic or diastolic function or with ECG-detected pathologies or HRV. Although clinically relevant cardiac disease is rare in patients with idiopathic inflammatory myopathies including juvenile DM, we previously showed that subclinical cardiac involvement was present in approximately one-fourth of the patients with juvenile DM (4,5,14). The exact mechanism underlying cardiac involvement is unknown, but atherosclerosis, small vessel vasculopathy, and myocardial as well as systemic inflammation may play a role in the process (16). Because we did not observe any significant association between NCD and parameters of cardiac dysfunction, our data do not support the notion that vasculopathy is an important underlying mechanism for cardiac involvement in juvenile DM. However, our study was limited by a small sample size, which made it challenging to study rare outcomes. Thus, the

study may have been underpowered to demonstrate associations between cardiac involvement and NFC.

There is a known relationship between age and NCD (17), and age, and possibly disease duration, might influence the associations between pulmonary and cardiac variables and NCD. In our study, age and disease duration were strongly intercorrelated (r_s = 0.938). Adjustment for these factors did not substantially influence the results; we observed robust associations between lung volumes and NCD. We previously studied NFC findings in the same cohort and compared findings with those in age- and sex-matched controls. Notably, the correlations between NCD and age were comparable in patients (r_s = 0.407, P = 0.002) and controls (r_s = 0.431, P = 0.003) (12), which supports the idea that this association was mainly an effect of aging and not an effect of disease duration.

In conclusion, patients with juvenile DM with low NCD had impaired pulmonary function and more frequent HRCT-detected abnormalities compared to controls. In contrast, we did not observe significant associations between capillaroscopic variables and cardiac involvement. Our results suggest that systemic microvascular remodeling might be an underlying mechanism for pulmonary involvement in juvenile DM. However, further and preferably larger studies are needed to identify NCD as a potential biomarker for organ involvement.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sanner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Barth, Sjaastad, Sanner.
Acquisition of data. Aaløkken, Sjaastad, Sanner.
Analysis and interpretation of data. Barth, Schwartz, Flatø, Aaløkken, Koller, Lund, Sjaastad, Sanner.

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Incidence and Risk of Glucocorticoid-Associated Adverse Effects in Patients With Rheumatoid Arthritis

Jessica C. Wilson,[1] Khaled Sarsour,[2] Sara Gale,[2] Attila Pethö-Schramm,[3] Susan S. Jick,[4] and Christoph R. Meier[5]

Objective. Using the UK Clinical Practice Research Datalink, we examined the incidence of glucocorticoid (GC)-related serious adverse events (SAEs) in rheumatoid arthritis (RA) and non-RA patients and quantified the risk of SAEs in patients with RA.

Methods. We matched incident patients with RA to an age- and sex-matched, non-RA comparison group of equal size. In a cohort analysis, we estimated incidence rates (IRs) and IR ratios (IRRs) for GC-related AEs (i.e., diabetes mellitus [DM], osteoporosis, fractures, glaucoma, hypertension, gastrointestinal [GI] perforation or bleeding, thrombotic stroke or myocardial infarction [MI], or death), stratified by GC use. We conducted a series of nested case–control analyses among patients with RA, evaluating the effects of increasing cumulative and average daily GC dose. Cases of each outcome were matched to controls for age, sex, and general practice. We calculated adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) for each outcome.

Results. Patients with RA had a higher incidence for all investigated SAEs except glaucoma, compared to non-RA patients. IRRs were greater in those patients prescribed a GC than in those without. In patients with RA, GCs were associated with an elevated risk of DM (adjusted OR 1.33 [95% CI 1.14–1.56]), osteoporosis (adjusted OR 1.41 [95% CI 1.25–1.59]), thrombotic stroke or MI (adjusted OR 1.28 [95% CI 1.07–1.52]), serious infection (adjusted OR 1.28 [95% CI 1.11–1.48]), and death (adjusted OR 1.33 [95% CI 1.19–1.48]). There was a trend of increasing risk with increasing cumulative and average daily GC dose for all outcomes other than glaucoma, hypertension, and GI perforations or bleeding ($P < 0.05$).

Conclusion. Patients with RA had an increased incidence of GC-related AEs. Increasing cumulative and average daily GC doses were found to be associated with an increasing risk of developing an AE.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, erosive, inflammatory arthritis characterized by a distinctive pattern of bone and joint destruction (1). Approximately 1% of the worldwide population is affected by RA (2). In the UK, the estimated incidence rates (IRs) of RA are approximately 25 and 54 per 100,000 person-years in men and women, respectively (3).

Oral glucocorticoids (GCs), primarily prednisolone and prednisone, play an important role in routine management of RA, alongside conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and more recent biologic therapies. Their temporary use is recommended to control episodes of increased disease activity (4). However, GC use is controversial because it is associated with an increased risk of serious adverse events (SAEs), particularly in patients exposed to high doses and extended use (5–7).

For many GC-treated diseases, the risk of associated AEs is debated in relation to the effect attributable to GCs compared to those effects occurring due to the underlying disease (8). In recent years, efforts have been undertaken to understand the relationship between GC use and the risk of related AEs in patients with RA. Meta-analyses conducted for widely studied AEs such as fracture/osteoporosis, infections, and cardiova-

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[1]Jessica C. Wilson, PhD, MSc: University of Basel, Basel, Switzerland; [2]Khaled Sarsour, PhD, MPH, Sara Gale, PhD, MPH: Genentech, South San Francisco, California; [3]Attila Pethö-Schramm, MD, PhD: F. Hoffmann-La Roche, Basel, Switzerland; [4]Susan S. Jick, DSc: Boston University School of Public Health, Lexington, Massachusetts; [5]Christoph R. Meier, PhD, MSc: University of Basel and University Hospital Basel, Basel, Switzerland, and Boston Collaborative Drug Surveillance Program, Lexington Massachusetts.

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Address correspondence to Christoph R. Meier, PhD, MSc, Basel Pharmacoepidemiology Unit, Hospital Pharmacy, University Hospital Basel, University of Basel, Spitalstrasse 26, CH-4031 Basel, Switzerland. E-mail: christoph.meier@usb.ch.

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SIGNIFICANCE & INNOVATIONS

- The results suggest that rheumatoid arthritis (RA) patients have a substantially increased incidence for glucocorticoid (GC)-related adverse events, and increasing cumulative and average daily GC doses are associated with an increasing risk of developing an adverse event.
- Our findings highlight the clinical burden associated with current and long-term, high-dose oral GC use in patients with RA and reinforce the importance of clinical awareness for GC-related adverse events in this patient group.

scular events, and findings from lesser studied outcomes such as diabetes mellitus (DM), gastrointestinal (GI) events, or glaucoma, suggest an increased risk of AEs with GC use (9–12). However, many studies are limited by restricted subpopulations, narrow outcome definitions (e.g., specific infections), small sample size, and limited information on GC dose effects (11–16). Thus, there is a need for large-scale, well-powered studies quantifying the relationship between GC dose and duration and related AE risk in patients with RA.

In the current study, we explored the incidence of developing DM, osteoporosis, fractures, glaucoma, hypertension, GI perforation or bleeding, thrombotic stroke or myocardial infarction (MI), or of dying, and to quantify the associated risk of GC use and the above-mentioned AEs in patients with RA. These outcomes were chosen based on their known associations with GCs found in the literature.

MATERIALS AND METHODS

Data sources. The Clinical Practice Research Datalink (CPRD) is a well-validated database that contains anonymized health care information on more than 10 million patients in the UK. General practitioners (GPs) record relevant information on demographics, consultations, diagnoses, specialist referrals, hospitalizations, prescribed medications, and some lifestyle parameters. Read codes are used to code medical diagnoses. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency Database Research (Protocol No 15_152R).

Hospital Episode Statistics (HES) data contain information on patient admissions to NHS hospitals in England. Medical diagnoses are coded using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes. HES data are only available for English practices participating in the linkage scheme (currently 75% of English practices), constituting approximately 58% of all patients in the CPRD (17). At the time of this study, the most up-to-date HES data were available from 1997 to 2012.

Study population. We defined the RA cohort population as patients age ≥18 years with a first-time Read code for RA between January, 1995 and January, 2015. Read codes are listed in Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract. We identified at random a comparison group of equal size of non-RA patients, matched for age (year of birth), sex, GP, study entry date (i.e., the date of the first recording of RA), and years of history in the CPRD before study entry. All patients were required to have at least 3 years of recorded medical history prior to entry. We excluded subjects with a diagnosis of cancer, alcoholism, drug abuse, or HIV diagnosis prior to study entry, because of increased comorbidity and to reduce possible ascertainment bias from regular GP visits.

Follow-up analysis (RA versus non-RA population). The outcomes of interest were incident DM (a first DM code and/or a new prescription for a drug to treat DM, whichever occurred first), an incident osteoporosis code, a bone fracture code, incident glaucoma (an incident glaucoma code and/or a newly-prescribed therapy to lower intraocular pressure, whichever occurred first), an incident hypertension code, an incident code for thrombotic stroke or MI, an incident code for GI perforation or bleeding, serious infection requiring hospitalization, or death (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract). We examined each outcome of interest independently of the others. We followed patients and accumulated person-time from study entry, until the first of the following occurred: an incident diagnosis for an outcome of interest, the patient's medical record ended, death, or the end of the study.

For the HES linkage subset, we linked CPRD and HES data to assess the outcome of serious infection requiring hospitalization. We excluded patients with an entry date outside the dates of available HES data. To be included in the final HES cohort, both the RA and matched non-RA comparison subjects were required to have available HES data linkage ensuring that both had the possibility of the outcome being captured. For the outcomes DM, osteoporosis, glaucoma, hypertension, thrombotic stroke or MI, and GI perforation or bleeding, we established a separate subcohort in which we excluded subjects in both the RA and non-RA comparison group if they ever had a diagnosis of the outcome under evaluation prior to cohort entry. We recorded a prior history of comorbidities and comedication at study entry. Information recorded closest and prior to study entry was used to evaluate alcohol status, body mass index, and smoking status in the RA and in the non-RA groups. Age was assessed at cohort entry.

Oral GC (prednisolone and prednisone) exposure. We defined GC exposure as ≥1 prescription for oral prednisolone

Table 1. Baseline characteristics of the study population, rheumatoid arthritis (RA) patients and age- and sex-matched non-RA patients (n = 34,050)*

Characteristics	With RA			Without RA	*P*
	All patients	GC Rx (n = 13,770)	No GC Rx (n = 20,280)		
Sex					
Men	10,059 (29.5)	4,021 (29.2)	6,038 (29.8)	10,059 (29.5)	–
Women	23,991 (70.5)	9,749 (70.8)	14,242 (70.2)	23,991 (70.5)	–
Age, years					
<30	1,871 (5.5)	436 (3.2)	1,435 (7.1)	1,872 (5.5)	–
30–49	9,825 (28.9)	3,083 (22.4)	6,742 (33.2)	9,821 (28.8)	–
50–69	14,464 (42.5)	6,230 (45.2)	8,234 (40.6)	14,458 (42.5)	–
≥70	7,890 (23.2)	4,021 (29.2)	3,869 (19.1)	7,893 (23.2)	–
Age, mean ± SD years	56.2 ± 16.0	56.2 ± 16.0	56.2 ± 16.0	56.2 ± 16.0	0.999
Smoking					
Never use	15,428 (45.3)	5,702 (41.4)	9,726 (48.0)	16,635 (48.9)	–
Former smoker	7,940 (23.3)	3,622 (26.3)	4,318 (21.3)	6,680 (19.6)	–
Current smoker	7,696 (22.6)	3,347 (24.3)	4,349 (21.4)	6,537 (19.2)	<0.0001†
Missing	2,986 (8.8)	1,099 (8.0)	1,887 (9.3)	4,198 (12.3)	–
Alcohol					
Never use	6,914 (20.3)	3,104 (22.5)	3,810 (18.8)	5,949 (17.5)	–
Former use	503 (1.5)	247 (1.8)	256 (1.3)	363 (1.1)	–
Current use	22,170 (65.1)	8,721 (63.3)	13,449 (66.3)	22,208 (65.2)	<0.0001†
Missing	4,463 (13.1)	1,698 (12.3)	2,765 (13.6)	5,530 (16.2)	–
Body mass index, kg/m^2					
<18.5	594 (1.7)	246 (1.8)	348 (1.7)	511 (1.5)	–
18.5–24.9	11,207 (32.9)	4,335 (31.5)	6,872 (33.9)	11,333 (33.3)	<0.0001†
25–29.9	10,052 (29.5)	4,150 (30.1)	5,902 (29.1)	9,470 (27.8)	–
≥30	6,659 (19.6)	2,936 (21.3)	3,723 (18.4)	5,690 (16.7)	–
Missing	5,538 (16.3)	2,103 (15.3)	3,435 (16.9)	7,046 (20.7)	–
Follow-up time, mean ± SD years	8.1 ± 5.7	–	–	8.1 ± 5.7	0.3180
Comorbidity (prior to follow-up)‡					
Non-RA rheumatic disease	2,418 (7.1)	1,654 (12.0)	764 (3.7)	494 (1.5)	<0.0001†
Systemic lupus erythematosus	167 (0.5)	95 (0.7)	72 (0.4)	28 (0.1)	–
Polymyalgia rheumatic	1,524 (4.4)	1,217 (8.8)	307 (1.5)	256 (0.8)	–
Scleroderma	41 (0.1)	21 (0.2)	20 (0.1)	8 (<0.1)	–
Polymyositis	24 (0.1)	15 (0.1)	9 (<0.1)	7 (<0.1)	–
Other rheumatic disease§	665 (2.0)	307 (2.2)	358 (1.8)	195 (0.6)	–
Renal disease	1,150 (3.4)	548 (4.0)	602 (3.0)	995 (2.9)	0.0007†
Peripheral vascular disease	681 (2.0)	342 (2.5)	339 (1.7)	630 (1.9)	0.1549
Peptic ulcer disease	1,322 (3.9)	617 (4.5)	705 (3.5)	1,010 (3.0)	<0.0001†
Myocardial infarction	946 (2.8)	470 (3.4)	476 (2.4)	915 (2.7)	0.4662
Mild liver disease	141 (0.4)	65 (0.5)	76 (0.4)	98 (0.3)	0.0053†
Hemiplegia	47 (0.1)	25 (0.2)	22 (0.1)	60 (0.2)	0.2085
Diabetes mellitus	2,061 (6.1)	876 (6.4)	1,185 (5.8)	1,966 (5.8)	0.1227
Diabetes mellitus with complications	419 (1.2)	161 (1.2)	258 (1.3)	400 (1.2)	0.5042

(Continued)

Table 1 *(Cont'd)*

Characteristics	With RA			Without RA	*P*
	All patients	GC Rx (n = 13,770)	No GC Rx (n = 20,280)		
Dementia	89 (0.3)	35 (0.3)	54 (0.3)	154 (0.5)	<0.0001†
Congestive heart disease	764 (2.2)	409 (3.0)	355 (1.8)	651 (1.9)	0.0024†
Chronic pulmonary disease	7,123 (20.9)	4,072 (29.6)	3,051 (15.0)	5,499 (16.2)	<0.0001†
Cerebrovascular disease	1,076 (3.2)	516 (3.8)	560 (2.8)	1,094 (3.2)	0.6945
Comorbidities, average no.	0.5	0.7	0.4	0.4	<0.0001†
Other GC use (during follow-up)¶					
Other oral GC Rx	147 (0.4)	80 (0.6)	67 (0.3)	91 (0.3)	<0.001†
Parenteral GC Rx	3,959 (11.6)	2,230 (16.2)	1,729 (8.5)	1,472 (4.3)	<0.001†

* Values are the number (%) unless indicated otherwise. GC = glucocorticoid; Rx = prescription.
† Statistically significant between RA and non-RA cohort.
‡ The mean ± SD period for patient record history was 10.1 ± 5.1 years.
§ Not including osteoarthritis.
¶ Other oral GCs included hydrocortisone, cortisone, triamcinolone, methylprednisolone, dexamethasone, and betamethasone; parenteral GCs included methylprednisolone (MP) and MP acetate injections. The mean ± SD number of prescriptions in the RA cohort was 2 ± 4 and in the non-RA cohort 2 ± 3.

or prednisone. Cumulative oral prednisolone or prednisone dose was calculated by combining information from tablet strength (i.e., 10 mg or 5 mg) and prescription quantity, summed across all prednisolone prescriptions (in mg). Average daily dose was calculated by dividing the cumulative dose by the duration of use in days. We did not apply a cut-off duration of use or dose. Full details are described in Supplementary Appendix C, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract).

Case–control analysis. Cases were patients with RA with an outcome of interest as detailed above. Each outcome was examined separately. For each case, we randomly identified from the RA cohort up to 4 control patients with no recorded history of the outcome of interest prior to the index date (i.e., the date of the case event). We matched controls to cases by index date (i.e., the date the case developed the outcome of interest), GP, year of birth, and sex. If no eligible controls were found from the same practice, we selected a matched control from another practice. We excluded patients with a diagnosis of cancer, HIV/AIDS, alcoholism, and drug abuse prior to the index date for all outcomes. For the outcome serious infections requiring hospitalization, we restricted cases and controls to patients in the HES-linked RA cohort. For each outcome, we assessed the prevalence of comorbidities and comedications at any time prior to the index date. For other covariates including body mass index, smoking, and alcohol use, we used the closest information recorded in the patient record prior to the index date.

Statistical analyses. *Follow-up analysis.* We described the cumulative and average daily GC dose for RA and non-RA patients, with the exposure period for GC use defined as the period from study entry until the end of follow-up. We calculated IRs with 95% confidence intervals (95% CIs) for all outcomes of interest among the RA group and the non-RA comparison group, stratified by age, sex, and GC use, and we calculated estimated incidence rate ratios (IRRs) with 95% CIs.

Case–control analysis. Conditional logistic regression was used to estimate the effect of GC exposure on each outcome separately, calculating unadjusted and multivariate adjusted odds ratios (ORs) with 95% CIs. We defined the period of GC exposure as time between (and including) the date of the first prescription at or following the RA diagnosis and the index date. We compared categories of increasing cumulative and average daily GC dose to no GC use. We also examined the timing of GC use (current or past use versus non-use). Unless otherwise stated, we defined past use as a last GC prescription recorded >180 days prior to the index date, and current use as a last GC prescription within the 180 days preceding the index date. For each outcome, we performed a stepwise regression analysis to include covariates found to be associated with the outcome in the univariate analyses, and we included them in the final model if they altered the main risk estimate by >10%. For the outcomes mortality, stroke, and serious infection, we assessed a Charlson Comorbidity Index score and included it in the model to account for the burden of comorbidity (18).

A number of sensitivity analyses were also conducted, described in full in Supplementary Appendix D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract. These analyses attempted to assess RA disease severity in the case–control analyses for thrombotic stroke or MI, infection and mortality; to assess the

case validity of osteoporosis, hypertension, and thrombotic stroke or MI; and to assess the RA disease definition through the inclusion of only patients with RA who met a more stringent definition of RA. We used SAS software (version 9.4) for the analyses.

RESULTS

RA versus non-RA population follow-up analysis. *Study population and characteristics.* We identified 34,050 patients with a first-time Read code for RA, and a 1:1 matched comparison group of patients without an RA diagnosis. Table 1 shows the characteristics of the study population. Figure 1 shows the numbers for each of the separate cohorts. Approximately 70% of patients with RA were women, and the majority were age >50 years at cohort entry (mean 56.2 years). Approximately 80% of patients with RA had at least two RA codes or a prescription for a DMARD or GC on or after their RA diagnosis. During the follow-up period, 40.3% and 15% of the RA and non-RA cohorts, respectively, were prescribed oral GC therapy. The median cumulative GC dose and duration of use was greater in the RA cohort (1,650 mg, 284 days) than in the non-RA cohort (500 mg, 55 days). The median average daily GC dose was smaller in the RA cohort (5.5 mg) compared to the non-RA cohort (8.7 mg), likely reflecting short-term and acute prescribing patterns.

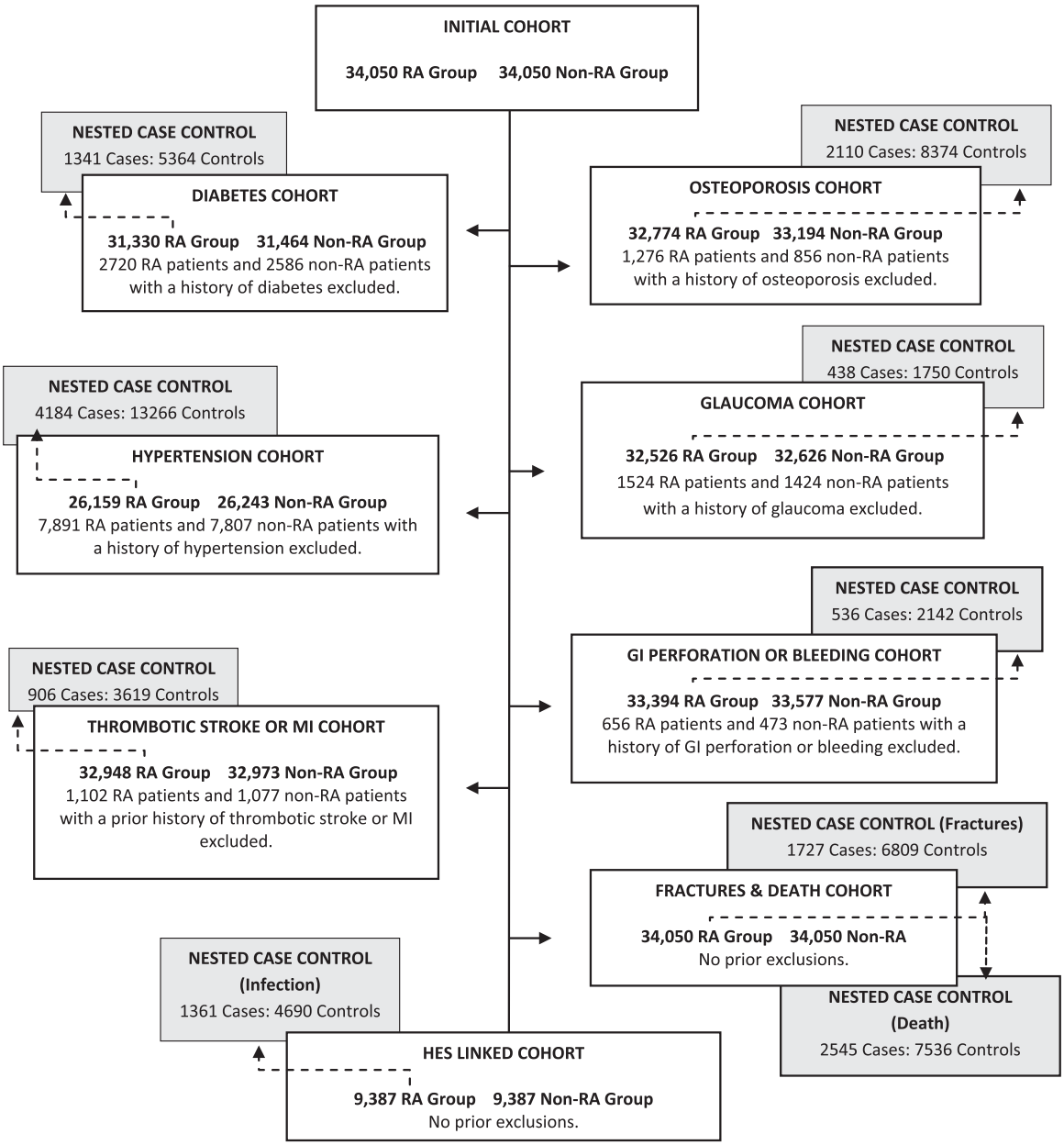


Figure 1. Exclusions prior to follow-up in the rheumatoid arthritis (RA) cohort and corresponding patients with RA included the nested case–control analyses. GI = gastrointestinal; MI = myocardial infarction; HES = Hospital Episode Statistics.

Incidence of the clinical outcomes of interest. IRs and IRRs in the RA cohort compared to the non-RA comparison cohort, stratified by GC-exposure, are shown in Table 2. IRs were significantly increased for DM, osteoporosis, fractures, hypertension, thrombotic stroke or MI, GI perforation or bleeding, death, and serious infection in the patients with RA compared to age-

Table 2. Incidence rates (IRs) per 1,000 person-years and incidence rate ratios (IRRs) for adverse events in RA and age- and sex-matched non-RA patients during the period 1995–2015, stratified by GC exposure*

Outcomes and GC prescription (during follow-up)	With RA			Without RA			RA vs. non-RA IRR (95% CI)
	Outcomes, no.	Person-time, years	IR (95% CI)	Outcomes, no.	Person-time, years	IR (95% CI)	
Diabetes mellitus							
All cohort	1,462	248,690.4	5.88 (5.59–6.19)	1,235	251,903.4	4.90 (4.64–5.18)	1.20 (1.11–1.29)†
No GC prescription	908	146,058.1	6.22 (5.83–6.63)	1,044	205,006.8	5.09 (4.79–5.41)	1.22 (1.12–1.33)†
GC prescription	554	102,632.3	5.40 (4.97–5.87)	191	46,896.62	4.07 (3.54–4.69)	1.33 (1.12–1.56)†
Osteoporosis							
All cohort	2,275	256,387.3	8.87 (8.52–9.24)	1,125	266,532.8	4.22 (3.98–4.47)	2.10 (1.96–2.26)†
No GC prescription	1,151	152,751.2	7.54 (7.11–7.98)	891	216,801.6	4.11 (3.85–4.39)	1.83 (1.68–2.00)†
GC prescription	1,124	103,636.1	10.85 (10.23–11.49)	234	49,731.28	4.71 (4.14–5.35)	2.30 (2.00–2.65)†
Fractures							
All cohort	1,890	267,675.1	7.06 (6.75–7.39)	1,609	270,429.9	5.95 (5.67–6.25)	1.19 (1.11–1.27)†
No GC prescription	1,090	156,213.2	6.98 (6.58–7.40)	1,336	219,383.5	6.09 (5.77–6.42)	1.15 (1.06–1.24)†
GC prescription	800	111,462	7.18 (6.70–7.69)	273	51,046.48	5.35 (4.75–6.02)	1.34 (1.17–1.54)†
Glaucoma							
All cohort	473	261,910.5	1.81 (1.65–1.98)	461	263,621.4	1.75 (1.60–1.92)	1.03 (0.91–1.17)
No GC prescription	278	152,824.1	1.82 (1.62–2.05)	415	213,656.4	1.94 (1.76–2.14)	0.94 (0.80–1.09)
GC prescription	195	109,086.4	1.79 (1.55–2.06)	46	49,965.01	0.92 (0.69–1.23)	1.94 (1.41–2.68)†
Hypertension							
All cohort	4,440	193,244.5	22.98 (22.32–23.65)	3,960	195,421.6	20.26 (19.65–20.90)	1.13 (1.09–1.18)†
No GC prescription	3,101	119,676.5	25.91 (25.03–26.83)	3,541	163,115.1	21.71 (21.01–22.43)	1.19 (1.14–1.25)†
GC prescription	1,339	73,568.02	18.20 (17.26–19.19)	419	32,306.45	12.97 (11.79–14.26)	1.40 (1.26–1.57)†
Thrombotic stroke or MI							
All cohort	986	265,055.1	3.72 (3.50–3.96)	808	266,900.8	3.03 (2.83–3.24)	1.23 (1.12–1.35)†
No GC prescription	560	154,844.9	3.62 (3.33–3.93)	674	216,711.4	3.11 (2.88–3.35)	1.16 (1.04–1.30)
GC prescription	426	110,210.1	3.87 (3.52–4.25)	134	50,189.39	2.67 (2.25–3.16)	1.45 (1.19–1.76)†
GI perforations or bleeding							
All cohort	602	268,736.7	2.24 (2.07–2.43)	451	272,280.1	1.66 (1.51–1.82)	1.35 (1.20–1.53)†
No GC prescription	363	156,060	2.33 (2.10–2.58)	382	220,626.6	1.73 (1.57–1.91)	1.34 (1.16–1.55)†
GC prescription	239	112,676.7	2.12 (1.87–2.41)	69	51,653.54	1.34 (1.06–1.69)	1.59 (1.21–2.08)†
Serious infection with hospitalization							
All cohort	1,553	92,222.45	16.84 (16.03–17.69)	1,060	69,593.18	15.23 (14.35–16.17)	1.11 (1.02–1.20)†
No GC prescription	816	54,211.74	15.05 (14.06–16.11)	849	56,153.2	15.12 (14.14–16.16)	1.00 (0.90–1.10)
GC prescription	737	38,010.71	19.39 (18.05–20.82)	211	13,439.98	15.70 (13.73–17.94)	1.24 (1.06–1.44)†
Mortality							
All cohort	3,653	276,116.2	13.23 (12.81–13.66)	2,924	277,595.2	10.53 (10.16–10.92)	1.26 (1.20–1.32)†
No GC prescription	1,579	159,401.6	9.91 (9.43–10.40)	2,171	224,038.4	9.69 (9.29–10.10)	1.02 (0.96–1.09)
GC prescription	2,074	116,714.6	17.77 (17.03–18.54)	753	53,556.85	14.06 (13.10–15.09)	1.26 (1.16–1.37)†

* GC = glucocorticoid; RA = rheumatoid arthritis; 95% CI = 95% confidence interval; MI = myocardial infarction; GI = gastrointestinal.
† Statistically significant at $P < 0.05$ for IRRs for the non-RA cohort comparison group, i.e., for GC exposure, IRRs are reported for the RA versus the non-RA cohort in patients with and without GC exposure. <1% of patients had a medical record that ended before the end of follow-up

and sex-matched non-RA patients. For all outcomes, the IRRs were elevated among the GC-treated patients compared to the non-GC–treated patients (Table 2), shown in Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract. Additional IRs and IRRs stratified by age and sex are shown in Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract.

Nested case–control analyses. From the RA cohort, the numbers of included cases and controls for each outcome are shown in Tables 3 and 4. For the thrombotic stroke or MI cases, 69% had MI and 31% had thrombotic stroke. Over 80% of cases of osteoporosis, hypertension, and thrombotic stroke or MI received a subsequent prescription for an associated therapy, supporting the case validity. The mean time from RA diagnosis for the occurrence of the outcomes of interest in cases ranged from 4.5 years for serious infections requiring hospitalization to 6.6 years for the outcome death. Demographic and lifestyle characteristics are shown in Tables 3 and 4.

Effect of GCs on the risk of developing an SAE. In the multivariate analyses, compared to patients with RA with no GC use, we found an elevated risk for patients exposed to any GC: DM (adjusted OR 1.33 [95% CI 1.14–1.56]), osteoporosis (adjusted OR 1.41 [95% CI 1.25–1.59]), thrombotic stroke or MI (adjusted OR 1.28 [95% CI 1.07–1.52]), serious infection requiring hospitalization (adjusted OR 1.28 [95% CI 1.11–1.48]), and death (adjusted OR 1.33 [95% CI 1.19–1.48]). There was a weakly increased risk of fracture (adjusted OR 1.14 [95% CI 1.01–1.29]). Adjusted ORs for either MI or thrombotic stroke were 1.35 (95% CI 1.09–1.67) and 1.15 (95% CI 0.84–1.58), respectively. The inclusion of indirect measures of severity (i.e., a recording for total joint replacement and the number of prescriptions for a DMARD and biologic) did not alter the adjusted ORs (Table 5, footnotes). Current GC use was associated with an increased risk of GI perforation and bleeding risk and with the risk of osteoporosis, serious infection, death, and particularly DM (Table 5).

Compared to patients with RA who did not have a prescription for GCs, we observed increasing ORs for DM, osteoporosis, fractures, thrombotic stroke or MI, serious infection, and death with increasing cumulative GC dose ($P < 0.05$ for trend) (Table 5), with the greatest increase observed in the highest cumulative dose category (≥7,000 mg). We found a dose-dependent trend of increasing risk for DM, osteoporosis, fractures, glaucoma, thrombotic stroke or MI, serious infection, and death with increasing average daily GC dose ($P < 0.05$ for trend) (Figure 2).

We observed no association between GC use and the risk of hypertension (Table 5 and Figure 2). When restricted to cases with a subsequent osteoporosis medication and antihypertensive drugs, the risk estimates associated with GC use hardly changed for osteoporosis (adjusted OR 1.48 [95% CI 1.31–1.67]) and hypertension (adjusted OR 0.94 [95% CI 0.86–1.030]). The magnitude of the risk for thrombotic stroke or MI was marginally reduced in the highest cumulative and average daily GC dose categories when we only included cases with a subsequent prescription for a stroke or MI-related medication (results not shown).

When we restricted the analysis to patients with RA with the much stricter RA definition (i.e., those with a more specific RA Read code and ≥1 additional RA read code, or those with a prescription for a DMARD on or after the date of the diagnosis) approximately 55% of the cases and controls remained. With the exception of glaucoma, infection, and death, which increased to adjusted OR 1.57 (95% CI 1.09–2.27), 1.49 (95% CI 1.22–1.83), and 1.53 (95% CI 1.30–1.81), respectively, there were no material differences in the risks for the examined AEs in patients with any GC use compared to no use (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23611/abstract).

DISCUSSION

Consistent with some existing literature (19–23), the results of this large-scale population-based study found the incidence of GC-related outcomes (DM, osteoporosis, fractures, hypertension, thrombotic stroke or MI, GI perforation or bleeding, serious infection, and death) to be higher in patients with RA compared to age- and sex-matched non-RA patients. The IRs in the RA group were somewhat lower than those reported in other UK-based studies. This variation may be due to differences in the age of study populations (the current study using patients who were on average marginally younger than other cohorts) and differing RA definitions (the current study being more comprehensive than other studies). However, IRs observed in the non-RA group were generally comparable to those reported in similarly aged UK populations (19). For all investigated AEs, the IRRs were higher in the GC-treated patients than in the non-GC–treated patients, suggesting that the increase in the investigated outcomes was not related only to RA disease.

Exploring the effect of GC exposure on the development of SAEs in the nested case–control analyses yielded increased results showing risks of DM, osteoporosis, fractures, thrombotic stroke or MI, serious infections requiring hospitalization, and death in patients with RA prescribed GCs. For all the above outcomes, including GI perforations, the magnitude of the risk was increased in patients who were current GC users. These findings are consistent with many previous studies (10,12,20,24–27), but not all (11,28), that examined the association between GC use and the development of AEs in patients with RA. In addition, related studies using CPRD data have found comparable risks to those shown in the current study. Movahedi et al (29) found a 35% increase in DM risk in patients with RA prescribed GCs,

Table 3. Demographic and lifestyle characteristics for outcomes of interest of cases and controls in the nested analysis: part I*

	Diabetes mellitus			Osteoporosis			Fractures			Glaucoma			Hypertension		
Characteristics	Cases (n = 1,341)	Controls (n = 5,364)	OR (95% CI)	Cases (n = 2,110)	Controls (n = 8,374)	OR (95% CI)	Cases (n = 1,727)	Controls (n = 6,809)	OR (95% CI)	Cases (n = 438)	Controls (n = 1,750)	OR (95% CI)	Cases (n = 4,184)	Controls (n = 13,266)	OR (95% CI)
Sex															
Men	34.3	34.3	–	13.4	13.5	–	16.1	16.3	–	34.2	34.2	–	30.6	31.2	–
Women	65.7	65.7	–	86.6	86.5	–	83.9	83.7	–	65.8	65.8	–	69.4	68.8	–
Age, years															
<30	0.9	8.9	–	0.3	0.4	–	0.6	0.6	–	0	0	–	0.3	0.4	–
30–49	14.8	14.9	–	3.8	3.9	–	5.9	6.0	–	5.3	5.7	–	14.2	18.1	–
50–69	57.4	57.9	–	43.1	44.2	–	33.6	34.6	–	37.4	37.5	–	55.5	55.6	–
≥70	26.9	26.3	–	52.7	51.4	–	59.9	58.7	–	57.3	56.8	–	30.0	26.0	–
Smoking															
Never use	38.8	43.9	1.0	44.2	47.8	1.0	45.3	48.1	1.0	44.5	43.9	1.0	50.0	43.7	1.0
Former smoker	37.9	30.8	1.4 (1.3–1.7)†	33.7	32.2	1.1 (1.0–1.3)	34.5	33.1	1.1 (1.0–1.3)	35.6	34.9	1.0 (0.8–1.3)	31.3	28.3	1.1 (1.0–1.2)
Current smoker	20.6	20.6	1.1 (1.0–1.3)	18.5	15.8	1.3 (1.1–1.5)†	16.6	14.8	1.2 (1.0–1.4)	15.8	16.3	1.0 (0.7–1.3)	19.3	23.0	0.8 (0.8–0.9)†
Missing	2.8	4.8	0.6 (0.4–0.9)†	3.6	4.1	1.0 (0.7–1.2)	3.6	4.0	1.0 (0.7–1.3)	4.1	4.9	0.8 (0.5–1.4)	4.4	5.0	0.9 (0.7–1.0)
Alcohol															
Never use	30.4	20.1	1.0	29.4	26.0	1.0	59.0	27.0	1.0	27.2	25.3	1.0	22.0	20.3	1.0
Former use	3.6	2.5	0.9 (0.7–1.3)	3.4	2.5	1.2 (0.9–1.6)	3.6	2.7	1.3 (1.0–1.8)	1.6	2.4	0.6 (0.3–1.4)	2.4	1.9	1.2 (0.9–1.5)
Current use	62.1	68.6	0.6 (0.5–0.7)†	58.9	62.6	0.8 (0.7–0.9)†	28.0	61.6	0.9 (0.8–1.0)	61.6	64.1	0.9 (0.7–1.1)	68.7	66.8	1.0 (0.9–1.1)
Missing	3.8	8.8	0.3 (0.2–0.4)†	8.3	8.8	0.8 (0.7–1.0)	9.4	8.7	1.1 (0.9–1.3)	9.6	8.3	1.1 (0.7–1.6)	6.9	11.0	0.6 (0.5–0.7)†
Body mass index, kg/m^2															
<18.5	0.4	1.7	0.8 (0.3–2.0)	4.3	1.9	1.7 (1.3–2.2)†	4.6	2.5	1.6 (1.2–2.1)†	2.3	2.2	1.0 (0.5–2.1)	1.1	2.2	0.6 (0.5–0.9)†
18.5–24.9	9.4	33.5	1.0	43.6	30.7	1.0	38.0	33.6	1.0	34.7	34.0	1.0	26.4	36.1	1.0
25–29.9	29.8	33.9	3.2 (2.6–4.0)†	29.4	32.5	0.6 (0.6–0.7)†	30.4	31.7	0.9 (0.8–1.0)	33.1	34.6	0.9 (0.7–1.2)	32.4	31.7	1.4 (1.3–1.6)†
≥30	55.0	20.0	10.8 (8.7–13.4)†	13.3	24.8	0.4 (0.3–0.4)†	18.0	21.5	0.7 (0.6–0.9)†	21.2	20.0	1.0 (0.8–1.4)	30.3	17.3	2.6 (2.4–2.9)†
Missing	5.5	10.8	1.6 (1.1–2.1)†	9.4	10.0	0.7 (0.6–0.8)†	9.0	10.7	0.8 (0.6–0.9)†	8.7	9.1	0.9 (0.6–1.4)	9.8	12.6	1.0 (0.9–1.2)
GC use	37.6	29.1	1.5 (1.3–1.71)†	49.0	32.9	2.1 (1.9–2.3)†	41.9	35.9	1.3 (1.2–1.5)†	40.2	33.1	1.4 (1.1–1.7)†	27.3	26.7	1.0 (0.9–1.1)
Total GC duration, median (IQR) days	208 (840)	252 (784)		344 (889)	246 (739)		420 (1195)	313 (960)		347 (946)	336 (920)		224 (750)	203 (641)	

* Values are the percentage, unless indicated otherwise. OR = odds ratio; 95% CI = 95% confidence interval; GC = glucocorticoid; IQR = interquartile range.
† Statistically significant at P <0.05.

Table 4. Demographic and lifestyle characteristics for outcomes of interest of cases and controls in the nested analysis: part II*

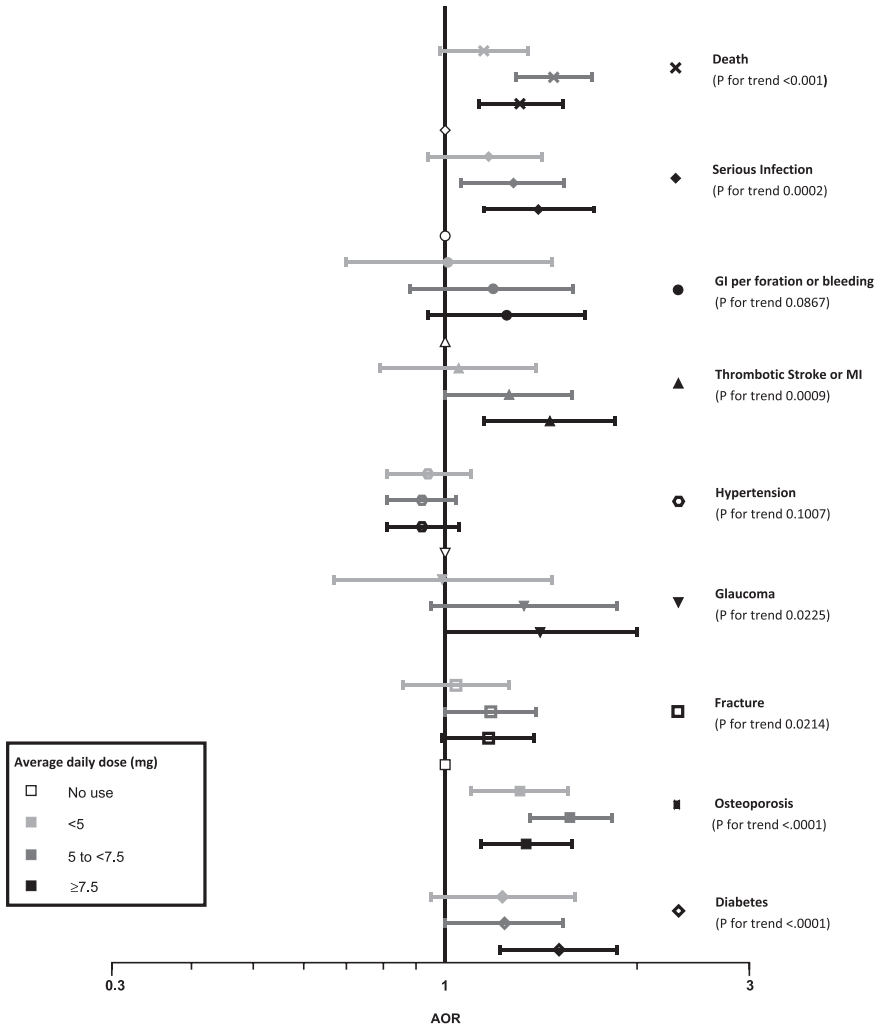
Characteristics	Thrombotic stroke or MI			GI perforation or bleeding			Serious infection			Death		
	Cases (n = 906)	Controls (n = 3,619)	OR (95% CI)	Cases (n = 536)	Controls (n = 2,142)	OR (95% CI)	Cases (n = 1,361)	Controls (n = 4,690)	OR (95% CI)	Cases (n = 2,545)	Controls (n = 7,536)	OR (95% CI)
Sex												
Men	41.2	41.2	–	31.7	31.7	–	28.7	27.6	–	33.2	33.8	–
Women	58.8	58.8	–	68.3	68.3	–	71.3	72.4	–	66.8	66.2	–
Age, years												
<30	0	0	–	2.6	2.8	–	1.4	1.5	–	0.1	0.2	–
30–49	4.7	4.6	–	14.6	15.0	–	11.8	13.5	–	1.7	2.2	–
50–69	39.7	40.3	–	36.9	35.7	–	29.5	35.1	–	16.1	22.5	–
≥70	55.6	55.1	–	45.9	46.5	–	57.4	49.9	–	82.0	75.1	–
Smoking												
Never use	33.8	46.0	1.0	38.6	46.5	1.0	39.1	44.7	1.0	35.0	44.9	1.0
Former smoker	34.0	33.7	1.4 (1.2–1.7)†	34.1	31.0	1.4 (1.1–1.7)†	40.6	35.1	1.3 (1.1–1.5)†	45.4	40.1	1.5 (1.4–1.7)†
Current smoker	27.0	15.5	2.5 (2.1–3.0)†	21.6	16.9	1.5 (1.2–2.0)†	16.9	16.5	1.3 (1.1–1.5)†	16.0	12.1	2.2 (1.9–2.6)†
Missing	5.2	4.8	1.4 (1.0–2.1)	5.6	5.6	1.2 (0.8–1.9)	3.5	3.6	1.1 (0.8–1.6)	3.5	3.0	1.7 (1.3–2.2)†
Alcohol												
Never use	27.0	23.0	1.0	23.7	22.7	1.0	27.0	22.5	1.0	31.2	25.2	1.0
Former use	2.9	2.0	1.2 (0.8–2.0)	2.4	2.2	1.0 (0.5–2.0)	3.8	3.0	1.1 (0.8–1.5)	4.6	3.4	1.1 (0.9–1.4)
Current use	62.1	65.8	0.8 (0.7–1.0)	63.4	65.3	0.9 (0.7–1.2)	59.6	64.8	0.8 (0.7–0.9)†	51.9	63.6	0.7 (0.6-0.8)†
Missing	7.9	9.1	0.7 (0.5–1.0)	10.4	9.8	1.0 (0.7–1.5)	9.6	9.7	0.8 (0.7–1.1)	12.3	7.8	1.3 (1.1–1.5)†
Body mass index, kg/m^2												
<18.5	3.3	2.0	1.6 (1.1–2.5)†	3.7	2.6	1.7 (1.0–2.9)	3.5	2.5	1.3 (0.9–1.9)	8.1	2.6	2.7 (2.1–3.3)†
18.5–24.9	31.5	32.1	1.0	27.6	33.6	1.0	33.1	33.2	1.0	37.6	33.3	1.0
25–29.9	32.4	34.7	1.0 (0.8–1.2)	33.8	31.3	1.3 (1.0–1.7)	28.1	32.4	0.9 (0.8–1.0)	24.5	35.2	0.7 (0.6–0.7)†
≥30	21.5	19.1	1.2 (0.9–1.4)	22.8	20.7	1.4 (1.0–1.8)	24.4	21.9	1.2 (1.0–1.5)	17.2	20.5	0.9 (0.8–1.0)†
Missing	11.3	12.1	0.9 (0.7–1.2)	12.1	11.7	1.3 (0.9–1.8)	10.9	10.0	1.1 (0.9–1.3)	12.7	8.4	1.4 (1.2–1.7)†
GC use	42.4	33.3	1.5 (1.3–1.8)†	38.8	32.2	1.4 (1.1–1.7)†	47.2	35.8	1.6 (1.4–1.8)†	56.8	41.5	1.8 (1.7–2.0)†
Total GC duration median (IQR) days	347 (1,080)	334 (871)		286 (936)	297 (849)		390 (965)	308 (816)		652 (1,540)	372 (996)	

* Values are the percentage, unless indicated otherwise. MI = myocardial infarction; GI = gastrointestinal; OR = odds ratio; 95% CI = 95% confidence interval; GC = glucocorticoid; IQR = interquartile range.
† Statistically significant at $P < 0.05$.

Table 5. Risk of outcomes associated with glucocorticoid (GC) use in patients with rheumatoid arthritis in the nested analysis, stratified by timing of GC use and by increasing cumulative dose*

	Diabetes mellitus†	Osteoporosis‡	Fractures§	Glaucoma¶	Hypertension#	Thrombotic stroke or MI**	GI perforation or bleeding††	Serious infection‡‡	Death§§
GC use									
No use	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
GC use¶¶	1.33 (1.14–1.56)##	1.41 (1.25–1.59)##	1.14 (1.01–1.29)##	1.26 (0.98–1.62)	0.93 (0.85–1.01)	1.28 (1.07–1.52)##	1.17 (0.95–1.45)	1.28 (1.11–1.48)##	1.33 (1.19–1.48)##
Timing of GC***									
Past GC use	1.09 (0.91–1.29)	1.02 (0.95–1.09)	1.00 (0.93–1.08)	1.25 (0.95–1.64)	0.96 (0.91–1.02)	1.09 (0.98–1.21)	0.98 (0.86–1.12)	0.96 (0.88–1.05)	1.03 (0.97–1.10)
Current GC use	2.24 (1.76–2.83)##	1.77 (1.54–2.04)##	1.29 (1.10–1.51)##	1.27 (0.87–1.84)	1.02 (0.90–1.16)	1.31 (1.05–1.64)##	1.52 (1.15–2.01)##	1.63 (1.37–1.95)##	1.80 (1.59–2.04)##
Cumulative dose, mg)†††									
<700	1.24 (1.00–1.53)	1.31 (1.11–1.54)##	1.08 (0.91–1.29)	1.07 (0.74–1.55)	0.93 (0.82–1.06)	1.35 (1.06–1.72)##	1.15 (0.83–1.59)	1.11 (0.91–1.36)	0.90 (0.76–1.07)
700 to <3,500	1.35 (1.08–1.69)##	1.52 (1.30–1.77)##	1.11 (0.94–1.31)	1.53 (1.10–2.13)##	0.93 (0.82–1.06)	1.03 (0.80–1.32)	1.06 (0.79–1.43)	1.17 (0.93–1.45)	1.27 (1.10–1.48)##
3,500 to <7,000	1.39 (1.03–1.88)##	1.43 (1.16–1.76)##	1.00 (0.79–1.27)	0.76 (0.45–1.28)	0.92 (0.76–1.11)	1.56 (1.14–2.14)##	1.38 (0.92–2.09)	1.30 (1.01–1.68)##	1.42 (1.18–1.71)##
≥7,000	1.53 (1.12–2.10)##	1.56 (1.24–1.97)##	1.57 (1.25–1.96)##	1.71 (1.07–2.72)##	0.91 (0.74–1.12)	1.60 (1.13–2.28)##	1.29 (0.84–1.99)	1.62 (1.23–2.15)##	2.33 (1.95–2.77)##
P for trend	0.0003##	<0.0001	0.0027##	0.0560	0.1174	0.0032##	0.1021	<0.0001##	<0.0001##

* Values are the adjusted odds ratios (ORs) (95% confidence interval [95% CI]). All models were adjusted for alcohol status (non, current, former, unknown), smoking status (non, current, former, unknown), body mass index (≤18.4, 18.5−24.9, 25−29.9, ≥30 kg/m^2, unknown) and RA disease duration. MI = myocardial infarction; GI = gastrointestinal.
† Additionally adjusted for prior history of osteoporosis, coronary heart disease (CHD), asthma, a prior prescription for a proton-pump inhibitor (PPI), diuretic, statin, and opioid.
‡ Additionally adjusted for prior history of chronic obstructive pulmonary disease (COPD), a past fracture, a prior prescription for a PPI, calcium supplement, and disease-modifying antirheumatic drug (DMARD).
§ Additionally adjusted for prior history of epilepsy, osteoporosis, a past fracture, a prior prescription for a DMARD, and calcium supplement.
¶ Additionally adjusted for prior history of asthma, autoimmune disease, a prior prescription for a DMARD, and ocular steroid.
# Additionally adjusted for prior history of diabetes mellitus, cardiovascular disease, COPD, asthma, a prior prescription for opioid, statin, and cyclooxygenase 2 inhibitor.
** Additionally adjusted for prior history of diabetes mellitus, hypertension, peripheral vascular disease, Charlson Comorbidity Index (CCI) score, a prior prescription for a bisphosphonate, aspirin, and DMARD.
†† Additionally adjusted for a prior prescription for a nonsteroidal antiinflammatory drug, aspirin, PPI, and opioid.
‡‡ Additionally adjusted for prior history of diabetes mellitus, COPD, CCI score, a prior prescription for aspirin, opioid, PPI, and bisphosphate.
§§ Additionally adjusted for prior history of COPD, prior history of CHD, CCI, a prior prescription for vitamin D supplements, and steroid injections.
¶¶ Sensitivity analysis for severity (adjusted ORs serious infection requiring hospitalization 1.26 [95% CI 1.09–1.46], thrombotic stroke or MI 1.28 [95% CI 1.07–1.53], and death 1.32 [95% CI 1.18–1.47]).
Statistically significant at *P* <0.05.
*** For diabetes mellitus and glaucoma, past use defined as a last prescription recorded >30 days prior to the index date and current use as a last prescription ≤30 days prior to the index date.
††† Cumulative dose stratified into tertiles, with the final dose category split.



Outcome/ ADD (mg)	Diabetes	Osteoporosis	Fracture	Glaucoma	Hypertension	Thrombotic Stroke/ MI	GI Perforation /Bleeding	Serious Infection	Death
<5	1.23	1.31	1.04	0.99	0.94	1.05	1.01	1.15	1.15
5 to <7.5	1.24	1.57	1.18	1.33	0.92	1.26	1.19	1.28	1.48
>=7.5	1.51	1.34	1.17	1.14	0.92	1.46	1.25	1.40	1.31

Figure 2. Risk of adverse events associated increasing average daily dose (ADD) glucocorticoid dose in rheumatoid arthritis (RA) patients among the nested case–control patients with RA matched for index date, age, sex, and general practice. GI = gastrointestinal; MI = myocardial infarction; AOR = adjusted odds ratio.

while Souverein et al (27) noted a 25% risk increase in cardiovascular and cerebrovascular events in patients receiving GCs. Conversely, a CPRD-based retrospective cohort study showed a 96% increased mortality risk with any GC use, but the risk was substantially reduced after accounting for comorbidities at death, which was noted to be largely due to malignancy diagnoses (26). Exclusion of prevalent cancers prior to the index date in the current study may explain the differences in the observed risk increases. Our findings for current and cumulative GC dose were largely comparable to those reported by these authors after accounting for this bias (26).

A trend of increasing risk was observed with increasing cumulative GC dose for DM, osteoporosis, fractures, thrombotic stroke or MI, serious infection, and death. Studies examining the effect of prolonged or cumulative GC dose in patients with RA have shown similar dose-dependent effects on AE risk (9,12,25,26,30–33). In the current study, the highest dose category (≥7,000 mg) was associated with the highest increase in risk. Consistent with this finding, a number of large-scale studies examining the effect of cumulative dose showed significantly increased risks of DM, infection, cardiovascular events, and mortality for high cumulative GC doses (>5,400 mg) (26,27,29,34). For most AEs, we found no

association with cumulative doses below 700 mg. However, in the case of osteoporosis, the risk did not substantially change between the lowest and the highest cumulative dose category. This finding may reflect an increase in risk with short-term, high-dose GC treatment, where GC dose may be high, but the overall cumulative dose is low, compared to those developing an AE after prolonged use. Supporting this possibility, the median duration of total prednisolone use in the lower cumulative dose was <50 days, and the adjusted ORs associated with high average daily GC dose echo those observed in the lower cumulative dose category.

Increasing average daily GC dose was associated with an increasing risk of DM, osteoporosis, fractures, glaucoma, thrombotic stroke or MI, serious infection, and death ($P < 0.05$ for trend). Additionally, a trend was suggested for GI perforation or bleeding, however, results were not significant, but the number of patients in the analysis was low. The observed dose-dependent trend with increasing average daily dose is consistent with the existing literature (7,12,24,25,29,34,35). Current evidence for a threshold dose for GC–related AEs in patients with RA remains relatively inconclusive, perhaps due to the heterogeneity of the study populations (different treated diseases) and the absence of dose-effect analyses. Doses of <7.5 mg may be generally well tolerated, but mortality and infection risk may be increased at lower doses (36,37). Our results corroborated this possibility: average daily doses of ≥7.5 mg were associated with a significantly increased risk of DM and thrombotic stroke or MI, while doses ≥5 mg were associated with serious infections requiring hospitalization and with death. Our findings reinforce the importance of clinical awareness for GC-related AEs even at relatively low doses. No association was observed for most AEs at doses of <5 mg.

In the current study, no association was observed between GC use and hypertension, neither with increasing cumulative dose nor with high average daily dose. Prolonged daily doses of ≥7.5 mg have been associated with an increased prevalence of hypertension and heightened blood pressure levels (38,39). In contrast, a number of clinical trials examining low-dose GC use in patients with RA showed no effect of prednisolone on blood pressure (9). GC-induced hypertension is possibly dose related and less likely to occur with medium or low GC doses (9). This possibility would explain the lack of association in the current analysis, because included patients had a relatively low average daily GC dose (median 5.63 mg, interquartile range 5.02), and the total GC duration in the highest daily dose category was short (<49 days).

The major strength of this study is the large size of the CPRD and the high data quality. Furthermore, due to the prospective nature of data collection, independent of any study hypothesis, our results are not influenced by recall bias.

The study does have some limitations. The possibility of competing risks, such as death following MI or infection impeding the development of other outcomes, appeared low, with <0.3% of patients in the RA and non-RA cohort having a record of death closely following an MI or infection diagnosis. Because GC use tends to be a marker for RA severity, and because disease severity is an important risk factor in the development of outcomes such as infection, cardiovascular events, or mortality, there is some question as to whether the increased risk of these outcomes, especially cardiovascular events, is due to GCs or RA activity (40,41). Controlling for disease severity is difficult because no direct measure of disease activity is routinely recorded in the CPRD. To overcome this limitation, we included indirect measures of severity in the models for infection, thrombotic stroke or MI, and mortality. The inclusion of this parameter did not alter the observed association for these outcomes.

With respect to the risk of developing the other outcomes of interest, confounding by severity is likely to be minimal but cannot be ruled out completely. Additionally, there is a possibility for misclassification in the RA group from patients misdiagnosed with RA, which could potentially lead to a dilution of the strength of the estimated association. However, approximately 80% of patients with RA had 2 or more RA codes, or a prescription for a DMARD or GC, and when we restricted the analysis to those patients with RA with a more stringent RA definition, we found little difference in the risks. This result provides confidence in our findings and reassurance that any misclassification is likely to be minimal. Some misclassification in the SAE outcomes is possible. However, studies show high positive predictive values of diagnosis (>80%) for coding in the CPRD for MI, fractures, GI bleeding, and DM (42), and our sensitivity analyses validating osteoporosis, hypertension, and thrombotic stroke or MI found little difference in the risk estimates. Furthermore, nearly 90% of patients had a run-in period of at least 5 years, reducing the possibility of misclassifying prevalent cases as incident cases. In addition, detection bias may be present for some outcomes, for example osteoporosis; patients receiving GCs tend to be screened for conditions known to be possibly GC-related. However, because a fracture risk assessment is recommended for all individuals with RA, this assessment may reduce the extent of this bias.

Regarding exposure assessment, information on prednisolone use was related to medication prescribed but did not account for whether the prescription was dispensed or taken. Furthermore, we cannot fully account for medications dispensed in secondary care such as biologics or DMARDs, or for drugs bought over the counter, such as nonsteroidal antiinflammatory drugs (NSAIDs). DMARDs are often prescribed, or at least initiated, by specialists, and possibly not all such exposure is properly transferred by the GP to the medical record of a patient. Thus, we cannot rule out some misclassification of DMARD exposure and a possible unknown impact on the regression model when we included DMARD use as a potential confounding variable. However, in the case of RA, NSAIDs likely would be prescribed by GPs, thus minimizing misclassification (4). Finally, although information on the strength of prednisolone or prednisone medication was available in the RA cohort, information on the exact daily dose was not avail-

able for many patients with RA, where the instruction was written to take as directed. Thus, some assumptions were made when calculating dose, which could have led to some misclassification.

The findings of this large observational study suggest that patients with RA are at a substantially increased incidence of GC-related AEs. Both increasing cumulative and average daily GC doses were associated with increased risks of DM, osteoporosis, fractures, infections, thrombotic stroke or MI, and mortality. Increasing average daily GC dose was also associated with increasing glaucoma risk. These findings highlight the clinical burden associated with current and long-term, high-dose oral GC use in patients with RA. Clinical awareness of oral GC safety in this patient group is important for improving patient care.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Meier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wilson, Sarsour, Gale, Pethö-Schramm, Meier.

Acquisition of data. Wilson, Jick, Meier.

Analysis and interpretation of data. Wilson, Sarsour, Pethö-Schramm, Meier.

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F. Hoffmann-La Roche and Genentech, Inc. had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by F. Hoffmann-La Roche and Genentech, Inc.

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Subsequent Cardiovascular Events Among Patients With Rheumatoid Arthritis, Psoriatic Arthritis, or Psoriasis: Patterns of Disease-Modifying Antirheumatic Drug Treatment

Jeffrey A. Sparks,[1] Tamara Lesperance,[2] Neil A. Accortt,[3] and Daniel H. Solomon[1]

Objective. To examine disease-modifying antirheumatic drug (DMARD) treatments and estimate the risk of a subsequent cardiovascular (CV) event following an initial CV event in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or psoriasis.

Methods. We analyzed data from MarketScan claims databases (January 1, 2006 to June 30, 2015) for adults with RA, PsA, or psoriasis and an initial/index CV event (acute myocardial infarction, stroke, or coronary revascularization) while receiving DMARDs (tumor necrosis factor inhibitor [TNFi] biologic DMARDs [bDMARDs], conventional synthetic DMARDs [csDMARDs], or non-TNFi bDMARDs). We studied DMARD treatment patterns following the index event and rates of subsequent CV events. We used Cox regression to investigate predictors of DMARD discontinuation and risk factors for subsequent CV events.

Results. Among 10,254 patients, 15.3% discontinued and 15.5% switched DMARD therapy after the index CV event. Independent predictors of DMARD discontinuation included a psoriasis diagnosis, renal disease, hypertension, heart failure, diabetes mellitus, older age, and baseline csDMARD or non-TNFi bDMARD use (versus TNFi bDMARDs). Rates per 1,000 patient-years of subsequent events were 75.2 (95% confidence interval [95% CI] 54.4–96.0) for patients taking TNFi bDMARDs, 83.6 (95% CI 53.3–113.9) for csDMARDs, and 122.4 (95% CI 60.6–184.3) for non-TNFi bDMARDs. A diagnosis of RA (versus psoriasis) and heart failure at baseline, but not a DMARD pattern after the index event, were independently associated with an increased risk of subsequent CV event.

Conclusion. In this large nationwide study, nearly one-third of patients with RA, PsA, or psoriasis switched or discontinued DMARD therapy following a CV event. There was no association between DMARD class and the risk of a subsequent CV event.

INTRODUCTION

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and psoriasis are systemic inflammatory diseases that manifest primarily in joints, skin, or both (1). Patients with RA, PsA, or psoriasis have increased rates of cardiovascular (CV) disease as well as excess traditional CV risk factors, increased risk of an initial CV event, and worse outcomes after CV events (2–4). A recent population-based cohort study reported adjusted hazard ratios (HRs) for a major acute CV event (composite outcome) of HR 1.58 (95% confidence interval [95% CI] 1.46–1.70) for patients with RA, HR 1.17 (95% CI 0.95–1.46) for patients with PsA, and HR 1.42 (95% CI 1.17–1.73) for patients with psoriasis treated with disease-modifying antirheumatic drugs (DMARDs) compared with matched controls (5). RA, PsA, and psoriasis are associated with increased prevalence and incidence of traditional CV risk factors of hypertension, diabetes mellitus, hyperlipidemia, and obesity (6). The high systemic inflammatory burden associ-

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[1]Jeffrey A. Sparks, MD, MMSc, Daniel H. Solomon, MD, MPH: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Tamara Lesperance, MPH: DOCS Global Inc., North Wales, Pennsylvania; [3]Neil A. Accortt, PhD: Amgen Inc., Thousand Oaks, California.
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Address correspondence to Jeffrey A. Sparks, MD, MMSc, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, #6016U, Boston, MA 02115. E-mail: jsparks@bwh.harvard.edu.
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SIGNIFICANCE & INNOVATIONS

- Patients with the systemic inflammatory diseases rheumatoid arthritis, psoriatic arthritis, and psoriasis have a high risk of cardiovascular (CV) events, and the effect of treatment for these diseases on the risk of a subsequent CV event is unclear.
- In this large nationwide study reflecting typical clinical care, disease-modifying antirheumatic drug (DMARD) discontinuation and class switches after an initial CV event were common.
- We found that treatment with different classes of DMARDs did not significantly affect the risk of subsequent CV events.

ated with these diseases, which is mediated by proinflammatory cytokines (7), is linked to accelerated atherosclerosis (8,9). Compared with the general population, patients with RA or PsA have excess CV mortality (10–14).

Patients with RA, PsA, or psoriasis are treated with similar classes of medications, including conventional synthetic DMARDs (csDMARDs; e.g., methotrexate, hydroxychloroquine, sulfasalazine), and biologic DMARDs (bDMARDs; e.g., tumor necrosis factor inhibitors [TNFi]), often in combination with a csDMARD (15–17). Some DMARDs may have cardioprotective effects. In patients with RA, for example, the use of methotrexate (versus non-use) was associated with a reduced CV risk of 21% (18), and TNFi bDMARD therapy (versus csDMARD therapy) was associated with a reduced risk of 46% (19). Larger studies to examine this issue are needed (20,21).

After a CV event in patients with RA, PsA, or psoriasis, adverse events may be more likely to occur and to have serious clinical consequences, or DMARDs may be contraindicated because of organ dysfunction resulting from the CV event. However, DMARD therapy may be required for underlying rheumatic disease control. Moreover, recent data support the potential benefit of immunomodulators in patients who have experienced a CV event (22). The aims of this study were to describe patterns and predictors of changes in DMARD treatment patterns after an initial CV event, to estimate the risk of subsequent CV events, and to compare the risk of subsequent CV events among patients with RA, PsA, or psoriasis.

PATIENTS AND METHODS

Study design. This retrospective cohort study used administrative claims data from the MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases. The study period was January 1, 2006 through June 30, 2015. The index date was the hospital discharge date for the first nonfatal CV event during the study period. Index CV events included acute myocardial infarction (MI), stroke, or coronary revascularization procedure (percutaneous coronary intervention, stent, or coronary artery bypass grafting). The baseline period was the 12 months preceding (and including) the index date. Follow-up started on the day after the index date and continued for at least 30 days until disenrollment from MarketScan, a CV event of interest, diagnosis of an exclusionary event, or the end of the study period. During follow-up, patients were assessed for treatment and subsequent CV events.

Patients. Patients were adults (age ≥18 years) with a diagnosis of RA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 714.0), PsA (ICD-9-CM code 696.0), or psoriasis (ICD-9-CM code 696.1) and an index CV event. Patients with RA were identified using a previously validated algorithm (23). All patients had ≥1 claim for a TNFi bDMARD, csDMARD, or a non-TNFi bDMARD within 12 months before the index event. Continuous enrollment for the 12-month baseline period and ≥30 days of follow-up after the index event were required. Patients with inflammatory bowel disease, juvenile idiopathic arthritis, ankylosing spondylitis, cancer (except nonmelanoma skin cancer), HIV, systemic lupus erythematosus, organ transplant, or dialysis utilization were excluded.

Diagnoses of RA, PsA, and psoriasis were based on ≥1 inpatient diagnosis or outpatient diagnosis claim, a practice that is known to accurately classify patients with RA (23). Outpatient claims had to be accompanied by another RA, PsA, or psoriasis outpatient diagnosis claim within ≥30 days and ≤365 days of the original outpatient claim; the latter claim was defined as the diagnosis date. Patients with multiple diagnoses were classified according to a hierarchy. Patients with a dual diagnosis of RA and either PsA or psoriasis were included in the RA cohort. Patients with a dual diagnosis of PsA and psoriasis on the same date were assigned to the PsA cohort; if the psoriasis diagnosis preceded the PsA diagnosis, the patients were assigned to the psoriasis cohort until the PsA diagnosis, and were then censored from the psoriasis cohort and included in the PsA cohort.

Outcomes. Study outcomes included DMARD treatment patterns across all patients after an initial CV event and the incidence of subsequent CV events in patients who received DMARD therapies after the initial CV event. We grouped patients by DMARD class (TNFi bDMARD, csDMARD, or non-TNFi bDMARD) because of the limited number of subsequent CV events for each individual DMARD.

Outcome 1: DMARD treatment patterns after initial CV event. Treatment pattern outcomes included the proportion of patients receiving TNFi bDMARD therapy, csDMARD therapy, or non-TNFi bDMARD therapy at the time of the initial CV event, and whether patients persisted with initial therapy, switched to another therapy, or discontinued all DMARD therapy following the index CV event. Treatment assessments were based on pharmacy claim records

(National Drug Codes) for medications administered subcutaneously or orally and procedure claim records (Current Procedure Terminology [CPT] and/or Healthcare Common Procedure Coding System) for intravenously administered medications.

The csDMARD therapies included methotrexate, hydroxychloroquine, leflunomide, azathioprine, cyclophosphamide, cyclosporine, D-penicillamine, gold, mycophenolate mofetil, or sulfasalazine as monotherapy or in combination with another csDMARD. TNFi bDMARD therapies included adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab with or without a csDMARD. Non-TNFi bDMARD therapies included abatacept, anakinra, rituximab, secukinumab, tocilizumab, tofacitinib, or ustekinumab with or without a csDMARD. Tofacitinib, a small molecule, was included with the non-TNFi bDMARD group because it is a targeted medication with biologic effects that are more similar to bDMARDs than to csDMARDs. Baseline therapies during the 12 months before the index event were based on the last 2 treatments before the index date (all patients were taking at least 1 DMARD). Postindex therapies were based on the first 2 treatments after the index date. Patients who were using combination therapies with csDMARDs and bDMARDs were included in the bDMARD cohorts based on the type of bDMARD (TNFi or non-TNFi).

Outcome 2: subsequent CV events. Following the initial CV event, subsequent CV events were identified based on inpatient ICD-9-CM codes for MI (410.x) or stroke (430.x, 431.x, 432.x, 433.x1, 434.x1, 435.x, 436.x, 437.1x, 437.9x). Subsequent CV events were also identified based on procedure codes for coronary revascularization (ICD-9-CM procedure codes: 36.10–36.17, 36.19, 36.2, 36.3x, 36.0x, 00.66; and/or CPT procedure codes: 33510–33523, 33533–33536, G0290, G0291, 92980, 92981, 92982, 92995).

Statistical analysis. Descriptive statistics for categorical variables were presented as proportions, and for continuous variables were presented as mean ± SDs or as medians and interquartile ranges. Proportions of patients who persisted with, switched, or discontinued DMARD therapy following the index CV event were calculated. Rates of subsequent CV events were calculated and age- and sex-standardized to the MarketScan general population. Rate ratios (RRs) with 95% CIs were calculated using TNFi bDMARD therapy as reference.

Logistic regression was used to estimate odds ratios (ORs) with 95% CIs for discontinuation from all DMARD therapy following the index CV event. Covariates used in regression analyses included demographic characteristics (age and sex), disease indication (RA, PsA, or psoriasis), comorbid conditions (obesity, hyperlipidemia, hypertension, diabetes mellitus, chronic pulmonary disease, and unstable angina), DMARD treatment prior to the index CV event, medication use in the baseline period (oral glucocorticoids, statins, and antihypertensives), and the type of index CV event (MI, stroke, or coronary revascularization procedure). Only patients who were receiving TNFi bDMARDs, csDMARDs, or non-TNFi bDMARDs after the initial CV event were included in the analyses of subsequent CV events.

Cox proportional hazards models were fit to estimate adjusted HRs and 95% CIs for the risk of subsequent CV events. The proportional hazards assumption was tested by plotting standardized score residuals over time and was met in all analyses. Data were standardized by age and sex using standard methods (24). For each sex category, 4 age strata were examined: ≤54 years, 55–64 years, 65–74 years, and ≥75 years, for a total of 8 strata.

Model 1 was adjusted for age (per 10 years) and sex. Model 2 was adjusted for age (per 10 years), sex, disease indication (RA, PsA, and psoriasis), index CV event (acute MI, stroke, coronary revascularization), baseline comorbidities (heart failure, chronic pulmonary disease, diabetes mellitus, hyperlipidemia, hypertension,

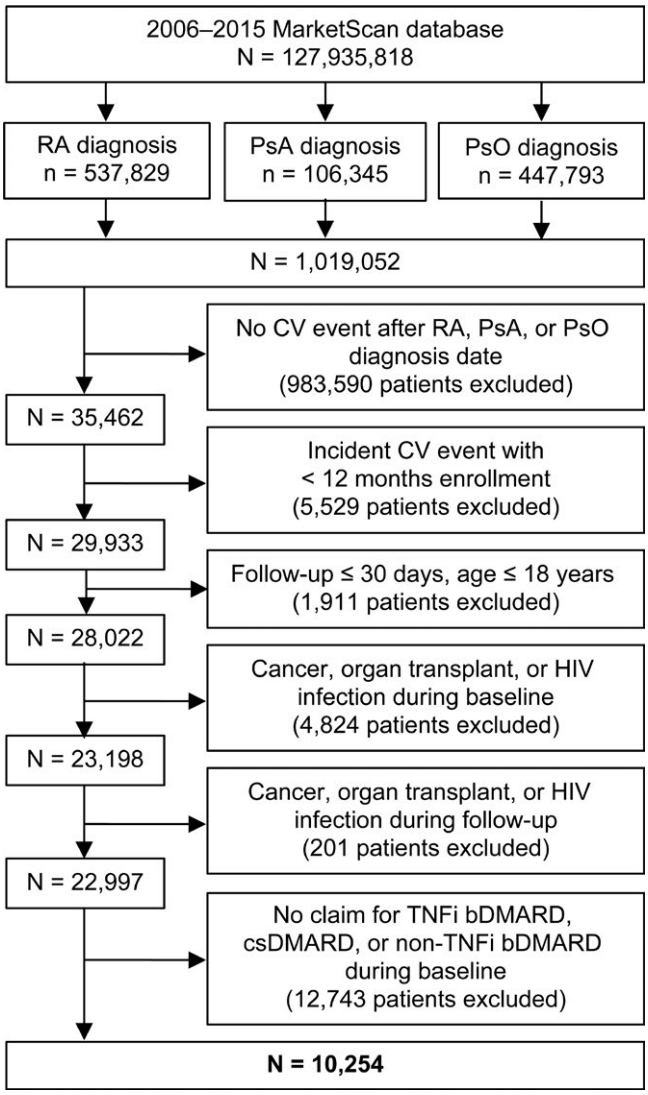

Figure 1. Identification of study sample. RA = rheumatoid arthritis; PsA = psoriatic arthritis; PsO = psoriasis; CV = cardiovascular; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD.

obesity, unstable angina, and renal disease), the number of baseline unique DMARDs used, and baseline medication exposures (statins, oral glucocorticoids, angiotensin-converting enzyme inhibitor, and beta blockers). Model 3 used backward elimination, retaining covariates of age, sex, disease indication, baseline comorbidities (heart failure, diabetes mellitus, renal disease), and baseline oral glucocorticoid use.

RESULTS

Patients and baseline medication. Data from 10,254 patients were analyzed (Figure 1), including 8,475 patients (82.7%) with RA, 794 patients (7.7%) with PsA, and 985 patients (9.6%) with psoriasis (Table 1). In the total study sample, the mean ± SD age was 67.2 ± 11.9 years, and 59.1% were women. The most common index CV event was stroke (42.7%), followed by coronary revascularization (39.2%) and acute MI (18.1%). The most commonly used medication class to treat RA, PsA, or psoriasis in the baseline period was csDMARDs (76.8%). Nearly one-half of all patients (48.7%) were receiving a statin during the baseline period, and 52.2% were receiving oral glucocorticoids. Patients taking csDMARDs were older (mean ± SD age 69.7 ± 11.4 years) compared to patients taking TNFi bDMARDs (63.7 ± 11.1 years) or non-TNFi bDMARDs (64.6 ± 12.0 years). Fewer women were in the TNFi bDMARD cohort (53.4%) than in the csDMARD cohort (61.3%) or non-TNFi bDMARD cohort (59.4%).

Treatment patterns after index CV event and predictors of DMARD discontinuation. Across all therapies, most patients persisted with their index DMARD following the index CV

Table 1. Pre-index demographic and clinical characteristics of patients according to the class of DMARD treatment after an initial cardiovascular event (n = 10,254)*

Characteristics	TNFi bDMARD (n = 3,077)	csDMARD (n = 4,663)	Non-TNFi bDMARD (n = 947)	No DMARD (n = 1,567)
Age, mean ± SD years	63.7 ± 11.1	69.7 ± 11.4	64.6 ± 12.0	68.7 ± 12.9
Women	1,642 (53.4)	2,860 (61.3)	563 (59.4)	990 (63.2)
Disease indication				
Rheumatoid arthritis	2,315 (75.2)	4,223 (90.6)	750 (79.2)	1,187 (75.7)
Psoriatic arthritis	411 (13.4)	218 (4.7)	54 (5.7)	111 (7.1)
Psoriasis	351 (11.4)	222 (4.8)	143 (15.1)	269 (17.2)
Index event				
Acute myocardial infarction	452 (14.7)	883 (18.9)	184 (19.4)	342 (21.8)
Stroke	1,196 (38.9)	2,014 (43.2)	378 (39.9)	787 (50.2)
Coronary revascularization	1,429 (46.4)	1,766 (37.9)	385 (40.7)	438 (28.0)
Comorbidities				
Chronic pulmonary disease	689 (22.4)	1,294 (27.8)	280 (29.6)	494 (31.5)
Diabetes mellitus	928 (30.2)	1,336 (28.7)	326 (34.4)	571 (36.4)
Heart failure	433 (14.1)	979 (21.0)	212 (22.4)	429 (27.4)
Hyperlipidemia	1,435 (46.6)	1,983 (42.5)	506 (53.4)	751 (47.9)
Hypertension	1,968 (64.0)	3,109 (66.7)	662 (69.9)	1,200 (76.6)
Obesity	292 (9.5)	351 (7.5)	142 (15.0)	198 (12.6)
Renal disease	237 (7.7)	472 (10.1)	115 (12.1)	272 (17.4)
Unstable angina	414 (13.5)	532 (11.4)	128 (13.5)	146 (9.3)
Medication exposure during baseline				
TNFi bDMARD	2,883 (93.7)	332 (7.1)	153 (16.2)	386 (24.6)
csDMARD	1,788 (58.1)	4,607 (98.8)	487 (51.4)	997 (63.6)
Non-TNFi bDMARD	158 (5.1)	168 (3.6)	766 (80.9)	361 (23.0)
Oral glucocorticoids	1,457 (47.4)	2,655 (56.9)	479 (50.6)	763 (48.7)
Statin	1,479 (48.1)	2,454 (52.6)	393 (41.5)	669 (42.7)
ACEi	939 (30.5)	1,550 (33.2)	241 (25.5)	447 (28.5)
Beta blocker	1,341 (43.6)	2,429 (52.1)	401 (42.3)	744 (47.5)

* Values are the number (%) unless indicated otherwise. DMARD = disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; ACEi = angiotensin-converting enzyme inhibitor.

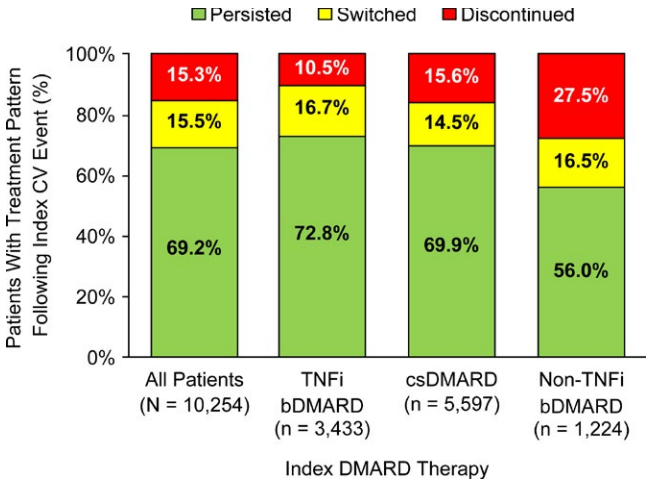

Figure 2. Treatment patterns following index cardiovascular (CV) event. The percentages of patients who persisted with the index disease-modifying antirheumatic drug (DMARD) (green bars), switched to a different DMARD (yellow bars), or discontinued all DMARD therapy (red bars) are shown. bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; TNFi = tumor necrosis factor inhibitor.

event (Figure 2). Nearly one-third of patients (30.8%) discontinued or switched from index therapy following the index CV event. There were 540 infliximab users (18.5% of TNFi bDMARDs) during the baseline period; of these, 382 patients (70.7%) re-initiated infliximab as their first DMARD after the index date. There were 100 rituximab users (11.5% of non-TNFi bDMARDs) during the baseline period; of these, 39 patients (39.0%) re-initiated rituximab as their first DMARD after the index date.

Regression analyses showed that older patients and those with a comorbidity of renal disease, hypertension, heart failure, or diabetes mellitus were more likely to discontinue DMARD therapy following the index CV event (Figure 3). Compared to patients taking TNFi bDMARDs after the index CV event, patients taking csDMARDs (odds ratio [OR] 1.61 [95% CI 1.41–1.85]) or non-TNFi bDMARDs (OR 2.61 [95% CI 2.19–3.11]) were more likely to discontinue DMARD therapy after the index CV event.

Risk of subsequent CV events. Age- and sex-standardized rates for a subsequent CV event were highest for patients taking non-TNFi bDMARDs (rate 122.4 [95% CI 60.6–184.3] events per 1,000 patient-years) followed by patients taking csDMARDs (rate 83.6 [95% CI 53.3–113.9] events per 1,000 patient-years) and patients taking TNFi bDMARDs (rate 75.2 [95% CI 54.4–96.0] events per 1,000 patient-years) (Table 2). Compared to TNFi bDMARDs, the RRs for subsequent CV events were 1.11 (95% CI 0.70–1.75) for csDMARDs and 1.63 (95% CI 0.92–2.90) for non-TNFi bDMARDs.

The type of DMARD used after the initial nonfatal CV event was not associated with an increased risk for subsequent CV events among patients with RA, PsA, or psoriasis in any of the models tested (Table 3). The model 3 multivariable HR for risk of subsequent CV events was 0.98 (95% CI 0.82–1.17) for csDMARDs (versus TNFi bDMARDs), and 1.16 (95% CI 0.86–1.57) for non-TNFi bDMARDs (versus TNFi bDMARDs). Patients with RA (HR 1.55 [95% CI 1.00–2.39] versus patients with psoriasis) and patients with heart failure (HR 1.39 [95% CI 1.13–1.72]) had an increased risk of a subsequent CV event independent of other factors, including age, sex, medication use, type of index CV event, and other baseline comorbidities.

DISCUSSION

Patients with RA, PsA, or psoriasis have an inherently high risk for CV disease, and our study showed that these patients are

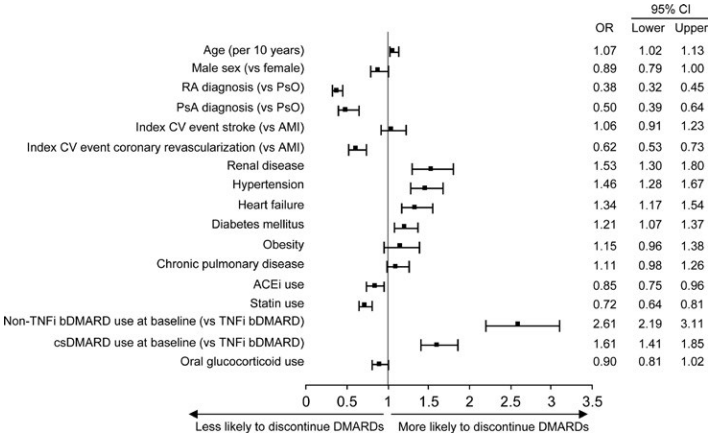

Figure 3. Predictors of discontinuation from all disease-modifying antirheumatic drugs (DMARDs) following the index cardiovascular (CV) event. Odds ratios (ORs) with 95% confidence intervals (95% CIs) for the risk of discontinuation are shown. The vertical line represents OR = 1. RA = rheumatoid arthritis; PsO = psoriasis; PsA = psoriatic arthritis; AMI = acute myocardial infarction; ACEi = angiotensin-converting enzyme inhibitor; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD.

Table 2. Subsequent CV events (acute myocardial infarction, stroke, or coronary revascularization) in patients receiving DMARD therapy following the index CV event*

	TNFi bDMARD	csDMARD	Non-TNFi bDMARD
Follow-up			
Patient-years	2,744.4	2,984.7	482.0
Mean ± SD years	0.99 ± 1.21	0.69 ± 0.87	0.69 ± 0.92
Subsequent CV events, no.	230	288	53
Rate per 1,000 patient-years (95% CI)†	75.2 (54.4–96.0)	83.6 (53.3–113.9)	122.4 (60.6–184.3)
RR (95% CI)†	Ref.	1.11 (0.70–1.75)	1.63 (0.92–2.90)

* CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; 95% CI = 95% confidence interval; RR = rate ratio.
† Rates and RRs are age- and sex-standardized to the MarketScan general population.

also at high risk for a subsequent CV event following an initial CV event. Clinicians may focus on the CV disease immediately following an initial event, and management of other chronic illnesses may have low priority. The frequent discontinuation observed in this study of all DMARD therapies (over 15% of all patients) following the initial CV event suggests that RA, PsA, and psoriasis disease management was secondary to CV disease management in many patients. Notably, the risk of a subsequent CV event did not differ by type of DMARD therapy in this analysis.

Although high rates of CV risk factors and the high risk of CV disease in patients with RA, PsA, or psoriasis have been thoroughly documented, few studies have examined recurrent or subsequent CV events in these patient populations. Of the few studies conducted in patients with RA, all showed that patients with RA and a prior CV event had worse outcomes compared to patients without RA. For example, a small study of patients with acute coronary syndrome from a coronary care admission register showed that recurrent cardiac events were more common in patients with RA (57.5%) compared to controls (30%; $P = 0.013$) (25). An increased risk for acute coronary syndrome recurrence in RA patients was also found in a cohort study (HR 1.30 [95% CI 1.04–1.62]) versus matched controls (26). In a cohort study of statin use, crude event rates for a nonfatal MI were 81.6 events per 1,000 patient-years (95% CI 30.6–217.5) for secondary prevention patients with RA who were statin-naive (27). Notably, statin use was associated with a reduced rate of nonfatal MI in RA patients (47.6 [95% CI 24.8–91.5] events per 1,000 patient-years) (27). In a recent analysis of nationwide health claims data in Taiwan, patients with RA were significantly more likely to have a subsequent major acute coronary event compared to controls (HR 1.20 [95% CI 1.07–1.34]; $P < 0.01$) (28). These results are consistent with our observation that patients with RA are at high risk for a subsequent CV event, and that CV risks in patients with RA, PsA, or psoriasis need to be aggressively managed.

After a CV event, patients may experience a profound decline in functional status and worsened organ function that are not adequately captured in administrative claims database studies such as ours. These complex factors likely affect the decision for DMARD treatment for both clinicians and patients. For example, patients with systemic rheumatic disease in remission or low disease activity may not resume medications after a CV event, particularly if disease activity remains stable or if new medical complications persist after the CV event. Patients may also experience a flare from their underlying rheumatic disease but be hesitant to restart DMARD treatment because of a perceived risk of adverse events, such as serious infection. Clinicians may be reluctant to prescribe DMARDs if new contraindications have developed, such as heart failure or renal insufficiency. While our study could not investigate the complexities of these treatment decisions, we were able to capture an overall view of DMARD treatment patterns following CV events. We found that >30% of patients switched or discontinued DMARD therapy after an initial CV event. In our study, patients taking non-TNFi bDMARDs at baseline were at much higher risk to discontinue DMARD therapy after the index CV event compared to those patients taking TNFi bDMARDs. This finding is perhaps surprising given some conflicting evidence of the effect of TNFi on heart failure (29,30), which presumably occurred in some patients after the index CV event. Some residual confounding may have occurred, because patients in the TNFi group may have been slightly healthier based on the inclusion of heart failure in the warnings and precautions on TNFi labels (31).

Patients with multimorbidities at baseline were more likely to discontinue all DMARDs after a CV event, perhaps because these patients were in relatively poor health both before and after the CV event, which made prescribers and patients reluctant to continue DMARDs. Patients with RA and PsA were less likely to discontinue all DMARDs compared to patients with psoriasis. While we were not able to determine levels of disease activity, we used glucocorticoid therapy as a surrogate. While there was no statistically significant association between glucocorticoid use and DMARD discontinuation, the point estimate

Table 3. Hazard ratios for risk of subsequent cardiovascular events*

	Model 1 (age, sex, DMARD type)	Model 2 (multivariable)	Model 3 (multivariable, parsimonious)
csDMARD vs. TNFi bDMARD	1.03 (0.86–1.23)	0.97 (0.80–1.18)	0.98 (0.82–1.17)
Non-TNFi bDMARD vs. TNFi bDMARD	1.23 (0.91–1.66)	1.17 (0.86–1.58)	1.16 (0.86–1.57)
Age per 10 years	1.05 (0.97–1.13)	1.01 (0.93–1.10)	1.02 (0.94–1.10)
Men vs. women	1.11 (0.94–1.31)	1.15 (0.96–1.37)	1.13 (0.96–1.34)
Rheumatoid arthritis vs. psoriasis	–	1.58 (1.01–2.46)	1.55 (1.00–2.39)
Psoriatic arthritis vs. psoriasis	–	1.45 (0.86–2.44)	1.43 (0.85–2.40)
Stroke vs. acute MI	–	1.20 (0.93–1.56)	–
Coronary revascularization vs. acute MI	–	1.14 (0.88–1.56)	–
Chronic pulmonary disease	–	0.97 (0.80–1.18)	–
Heart failure	–	1.42 (1.41–1.77)	1.39 (1.13–1.72)
Diabetes mellitus	–	1.16 (0.96–1.40)	1.16 (0.97–1.39)
Hyperlipidemia	–	0.95 (0.80–1.14)	–
Hypertension	–	0.99 (0.83–1.19)	–
Obesity	–	1.09 (0.80–1.49)	–
Unstable angina	–	0.96 (0.75–1.25)	–
Renal disease	–	1.28 (0.96–1.69)	1.27 (0.96–1.67)
No. of unique baseline DMARDs	–	0.98 (0.88–1.10)	–
Baseline oral glucocorticoid use	–	1.14 (0.96–1.35)	1.14 (0.96–1.35)
Statin use	–	0.98 (0.82–1.17)	–
ACEi use	–	1.00 (0.84–1.21)	–
Beta blocker use	–	1.12 (0.94–1.22)	–

* Values are the hazard ratio (95% confidence interval). DMARD = disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; MI = myocardial infarction; ACEi = angiotensin-converting enzyme inhibitor.

suggested that patients taking glucocorticoids were less likely to discontinue DMARDs, perhaps because of active inflammation requiring continuation of DMARDs even after a CV event. Our findings describe the result of these complex clinical scenarios on a nationwide scale, but we cannot make conclusions about the validity of those clinical decisions.

In the present study, we investigated the risk of a subsequent CV event using a large nationwide database of patients with rheumatic diseases taking DMARDs prior to the initial CV event. The secondary prevention of CV diseases using antiinflammatory drugs is currently being investigated in large randomized clinical trials as a way to understand the contribution of inflammation to CV disease. A large placebo-controlled trial recently showed that canakinumab lowered the risk of recurrent CV events independent of lipid-lowering effect, providing evidence supporting the "inflammatory hypothesis" underlying CV disease (22). A similarly designed placebo-controlled randomized clinical trial is investigating the safety and efficacy of methotrexate for risk of recurrent CV events (32,33). However, these studies were conducted in patient populations without systemic rheumatic diseases, because large-scale placebo-controlled trials with lengthy follow-ups are not feasible for patients with systemic rheumatic disease who require DMARDs.

We investigated the risk of a subsequent CV event among patients with rheumatic diseases who were taking DMARDs prior to the index CV event. We did not analyze patients who discontinued DMARD therapy after their index CV event because these patients may have been more likely to die or have new contraindications to DMARDs. We found no significant differences between the classes of DMARDs for risk of a subsequent CV event after controlling for confounders. All DMARDs investigated possibly had truly similar cardioprotective effects, but perhaps there were subtle differences that we were unable to detect. Because of the number of outcomes, we grouped different DMARDs into the same class. For example, we grouped tocilizumab and abatacept as non-TNFi bDMARDs even though they have different mechanisms of action and therefore may have different effects on CV disease. However, a recent large

observational study comparing tocilizumab to TNFi bDMARDs reported no difference in CV event rates, consistent with our results (34). We also found no difference for risk of a subsequent CV event between csDMARDs and bDMARDs. Patients receiving bDMARDs may be inherently different from patients who can be maintained only using csDMARDs. Since we found no difference between these DMARD classes, confounding by indication or channeling bias probably does not explain these null results. Overall, our study does not provide guidance on DMARD class and risk of CV event, so the decision of DMARD use should be related to the relative risks and benefits for a given patient's clinical scenario.

The current study was subject to inherent limitations of analyses of claims databases and observational studies. The study population was not randomized, but selected from the database based on claims codes. A preliminary review of data from patients who discontinued all DMARD therapy following the index CV event suggested that those patients were clinically different from patients who continued to receive DMARD therapy, and therefore the data from those patients would not be generalizable to the overall RA, PsA, or psoriasis populations. Additionally, the study population was insured, and results of the analysis may not be generalizable to uninsured or underinsured patients. Obesity, a risk factor for CV disease, was identified based on coded diagnoses, and rates of obesity may have been underestimated. Similarly, smoking, another risk factor for CV disease, was not well captured in the database. Information on disease activity and severity is not available from claims databases, which may affect the interpretation of the results. To address this issue, glucocorticoid use at baseline was used as a surrogate for moderate to severe disease prior to initial CV event. There was no adjudication of CV outcomes. Deaths are not well captured in this type of database. This limitation was mitigated in the analysis of subsequent CV event risk by requiring 30 days of follow-up after the initial CV event and excluding patients who did not receive DMARDs after the initial CV event. Although patients in this database filled these prescriptions, there were no measures of medication adherence, and we could not determine whether medications were used as prescribed. Discontinuation of treatment was assumed when prescriptions were not refilled, but patients possibly could have continued taking their medications from a home supply; a 60-day window around medication supply was used to minimize this possibility. Mean follow-up after the initial CV event was <1 year for each class of DMARD; this duration of follow-up may have been too short to detect a true biologic effect on subsequent CV events.

In conclusion, patients with RA, PsA, or psoriasis remain at high risk for a subsequent CV event following an initial CV event. Our study suggests that DMARD therapy for the underlying RA, PsA, or psoriasis does not appear to affect the risk for subsequent CV events, and clinicians should carefully consider continuing DMARD therapy as well as appropriate therapies for CV disease.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Sparks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sparks, Lesperance, Accortt, Solomon.
Acquisition of data. Sparks, Lesperance, Accortt.
Analysis and interpretation of data. Sparks, Lesperance, Accortt, Solomon.

ROLE OF THE STUDY SPONSOR

Amgen Inc. designed the study in collaboration with the non-Amgen authors and was involved in the collection, analysis, and interpretation of the data. Both the Amgen and non-Amgen authors participated in writing the manuscript and provided approval to submit the manuscript for publication.

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Responsiveness of Patient-Reported Outcomes Measurement Information System Measures in Rheumatoid Arthritis Patients Starting or Switching a Disease-Modifying Antirheumatic Drug

Alyssa Wohlfahrt,[1] Clifton O. Bingham, III,[2] Wendy Marder,[3] Kristine Phillips,[4] Marcy B. Bolster,[5] Larry W. Moreland,[6] Zhi Zhang,[1] Tuhina Neogi,[7] and Yvonne C. Lee[1]

Objective. The Patient-Reported Outcomes Measurement Information System (PROMIS) is a calibrated item bank used to assess patient-reported outcomes across multiple domains. The purpose of this study was to describe the performance of selected PROMIS measures in patients with rheumatoid arthritis (RA) with active disease who were initiating a disease-modifying antirheumatic drug (DMARD).

Methods. Participants in an ongoing prospective observational study completed 8 PROMIS measures before and after DMARD initiation. Linear regression models were performed to identify cross-sectional associations between baseline PROMIS measures and disease activity, measured using the Clinical Disease Activity Index (CDAI). Paired *t*-tests were performed to evaluate responsiveness after 12 weeks of DMARD treatment. Associations between changes in PROMIS measures and changes in the CDAI score were assessed using linear regression.

Results. Among the 156 participants who completed the first study visit, the mean ± SD baseline CDAI score was 25.5 ± 14.0. Baseline scores for PROMIS measures of physical health, pain, and sleep were associated with the baseline CDAI score ($P \leq 0.05$). Among the 106 participants with 12-week data, all PROMIS scores improved after DMARD initiation ($P \leq 0.05$). With the exception of depression, changes in all assessed PROMIS measures were correlated with changes in the CDAI score (standardized βs from |0.23| to |0.38|).

Conclusion. These data provide support for the utility of PROMIS measures for the assessment of physical and mental health in individuals with active RA. All PROMIS measures improved significantly after DMARD initiation, with the magnitudes of association between changes in PROMIS measures and changes in the CDAI score in the low-to-moderate range.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic illness that can significantly impact daily life when not aggressively managed. To evaluate disease activity, physicians rely heavily on assessment of swollen joints, measurement of blood inflammatory markers, and radiographs. Physicians cannot, however, gain a full understanding of disease activity and its effects without direct feedback from patients. Hallmark symptoms of RA, such as pain and fatigue, are necessarily evaluated through patient self-report. Additionally, other factors, including the patient's physical function, are often assessed through patient report (1).

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[1]Alyssa Wohlfahrt, BA, Zhi Zhang, MS, Yvonne C. Lee, MD, MMSc (current address: Northwestern University Feinberg School of Medicine, Chicago, Illinois): Brigham and Women's Hospital, Boston, Massachusetts; [2]Clifton O. Bingham III, MD: Johns Hopkins University, Baltimore, Maryland; [3]Wendy Marder, MD: University of Michigan Medical School, Ann Arbor; [4]Kristine Phillips, MD, PhD: Vanderbilt University, Nashville, Tennessee; [5]Marcy B. Bolster, MD: Massachusetts General Hospital, Boston, Massachusetts; [6]Larry W. Moreland, MD: University of Pittsburgh, Pittsburgh, Pennsylvania; [7]Tuhina Neogi, MD, PhD: Boston University School of Medicine, Boston, Massachusetts.

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Address correspondence to Yvonne C. Lee, MD, MMSc, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611. E-mail: yvonne.lee@northwestern.edu.

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this is the first study to assess 8 Patient-Reported Outcomes Measurement Information System (PROMIS) computerized adaptive tests and 2 short forms (yielding a total of 10 different scores) of physical and mental health in rheumatoid arthritis (RA) patients starting a disease-modifying antirheumatic drug (DMARD) for active disease.
- PROMIS measures can detect change in symptoms of global health, pain, sleep, fatigue, and emotional health among RA patients with active disease who are starting a new DMARD.
- Changes in PROMIS measures of physical global health, mental global health, pain, sleep, fatigue, and anxiety were significantly associated with changes in disease activity after 12 weeks of DMARD treatment.

The importance of patient-reported outcomes (PROs) has been recognized in multiple realms, including clinical trials, clinical care, and insurance authorizations (2). Recommendations from the American College of Rheumatology (ACR) and the European League Against Rheumatism incorporate the use of composite indices (e.g., the Clinical Disease Activity Index [CDAI], the Disease Activity Score in 28-joints instrument, and the Simplified Disease Activity Index), which include patient global assessment, for reporting disease activity in all clinical trials (3). In addition, the Outcome Measures in Rheumatology group is composing guidelines for the assessment of additional PROs within clinical trials (4). For the treatment of RA, an international task force has recommended that physicians rely on composite measures of disease activity to evaluate a patient's progress toward a treatment target and that physicians incorporate the patient perspective in developing a management strategy (5). Insurance companies are also pushing physicians to be patient-centered in their care, because good outcomes are, in part, being defined as value-adding activities for patients. Physician recognition of what patients consider value-adding activities can come from PROs (6).

Although the value of PROs is widely recognized, researchers and clinicians are often faced with the conundrum of deciding which measures to use. This study focused on 1 option for PRO assessment, the Patient-Reported Outcomes Measurement Information System (PROMIS). PROMIS was developed to provide a standardized set of assessments of PROs, which allows for comparability across diseases and direct translation from research to clinical settings (7). Assessments are administered as fixed-item short forms or via computer adaptive testing (8).

The successful implementation of PROMIS measures for RA patients in research and clinical care settings requires establishment of their validity and ability to detect changes in symptoms. Bartlett et al (9) provided preliminary evidence of the reliability and construct validity of PROMIS measures to assess RA symptoms in a general RA clinic cohort, finding that PROMIS domain measures correlated well with established measures for assessment of disease activity and RA symptoms in cross-sectional analyses (10). In addition, Katz et al (11) reported on the performance of the static 29-item PROMIS profile in a large population of individuals with rheumatic disease, including RA. The findings presented in the current article aim to provide additional evidence for the feasibility of using PROMIS in a research setting, examine the distribution of PROMIS scores within an RA cohort with mostly moderate-to-high levels of disease activity, and provide the first evidence demonstrating the responsiveness of PROMIS measures to changes in RA disease activity associated with starting a disease-modifying antirheumatic drug (DMARD).

PATIENTS AND METHODS

Study population. Data for this study were from the first 156 participants enrolled in the ongoing multisite, prospective, observational Central Pain in Rheumatoid Arthritis (CPIRA) study, which began enrollment in January 2014. All data obtained on or before September 16, 2016 were included in this set of analyses. Participants were recruited from 5 academic medical centers. Inclusion criteria required participants to have active disease necessitating a start or switch to a new DMARD based on physician judgment. Subjects starting hydroxychloroquine or switching from 1 tumor necrosis factor (TNF) inhibitor to another were not eligible for inclusion. All participants had to meet the 2010 ACR criteria for a diagnosis of RA (12). No subjects could be taking >10 mg of prednisone or long-term opioid pain medications. Those subjects using central acting pain medications (e.g., tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants) had to be taking stable doses for the past 3 months and planning to continue the same usage for the study duration. Patients with fibromyalgia were included in the study population. Patients with peripheral neuropathy or severe peripheral vascular disease were excluded. Patients with a diagnosis of another autoimmune disease were excluded. Written informed consent was obtained from all participants. This study was approved by the institutional review board at each study site.

Procedures. Subjects were evaluated before starting the new DMARD and 12–24 weeks after taking their first dose of medication. Because the onset of action of methotrexate is 3–6 weeks, subjects starting methotrexate were eligible for enrollment if they had taken 1 dose before the baseline evaluation (13). Since not all participants had completed follow-up visits at the time of this analysis, follow-up data are presented on a subset of the baseline cohort.

RA patients were registered as study participants at the time of their baseline visit in the PROMIS assessment center (www.

assessmentcenter.net). Participants answered questionnaires using a desktop or tablet computer. At the baseline and follow-up study visits, subjects completed the PROMIS global health, version 1.1, and the PROMIS pain intensity 3a short forms (14). Subjects also completed the following PROMIS physical and mental health domains, assessed using computerized adaptive tests: pain interference, pain behavior, sleep disturbance, sleep-related impairment, fatigue, anxiety, and depression (15–20). Computerized adaptive tests use item-response theory to provide tailored and precise assessment across the continuum of experience (21). Answering questionnaires took participants typically between 5 and 10 minutes. Research coordinators measured height and weight at each visit. Trained research coordinators also performed swollen and tender joint counts (28 joints) at both visits and provided global assessments on a 0–100 numerical rating scale (NRS) of the patients' health with respect to their RA. These coordinators were trained in the joint examination during a 1-day orientation session at the beginning of the study. In addition, each coordinator was provided with a training video to review the joint count. Additional training in the joint examination was provided at each site, supervised directly by the site principal investigators (COB, WM, KP, TN, YCL), who are all board-certified rheumatologists.

The presence of fibromyalgia symptoms and the diagnosis of fibromyalgia were assessed using the 2010 modified ACR Preliminary Diagnostic Criteria for Fibromyalgia (22). Patients also provided their own global assessment of disease activity using a 0–100 NRS (where 0 = very well and 100 = very poorly). Medication information was obtained from participants at both visits. Use of a DMARD at baseline was defined as having taken the DMARD within the 6 weeks prior to the baseline visit. Serologic status of subjects was obtained from chart review of each participant's electronic medical record.

Scoring. Instrument scores were calculated by the PROMIS Assessment Center and reported as T scores standardized to a general population mean ± SD of 50 ± 10. High scores indicated more of the concept measured. Higher physical and mental global health scores indicated better health, whereas higher scores on the pain, sleep, anxiety, and depression measures indicated worse outcomes. The CDAI score was calculated as the sum of the swollen and tender joints (0–28 for swelling and 0–28 for tenderness), patient global assessment (0–10), and assessor global assessment (0–10) (23). Scores ≤10 indicated low disease activity, scores from >10 to 22 indicated moderate disease activity, and scores >22 indicated high disease activity (24).

Statistical analysis. We created histograms of the distributions of scores for all PROMIS measures and compared means in our population to the general population mean of 50. Multivariable linear regression models were used to compute adjusted mean PROMIS scores according to the CDAI category. Multivariable adjusted linear regression models were also used to determine baseline associations between each PROMIS measure, the CDAI score, and its components. All multivariable models were adjusted for site, sex, race, age, seropositive status, and RA disease duration. Among participants with follow-up data, paired *t*-tests were used to assess for change in CDAI and PROMIS measure scores with DMARD treatment. We used multivariable linear regression models to evaluate associations between changes in PROMIS scores and changes in CDAI and its components. Associations were presented as standardized betas. Approximate *P* values (e.g., $P \leq 0.05$, $P \leq 0.01$, and $P \leq 0.001$) were reported rather than exact *P* values according to the recommendations of Boos and Stefanski (24). To assess for evidence of a floor effect, a subgroup analysis was performed among subjects with a moderate-to-high CDAI score at baseline.

RESULTS

Participant characteristics. A total of 156 RA patients were enrolled in the CPIRA study at the time of this analysis. The majority of participants were women (82.1%) and white (95.5%) (Table 1). Mean ± SD age was 54.6 ± 13.6 years, and mean ± SD

Table 1. Baseline characteristics of rheumatoid arthritis (RA) patients initiating a new DMARD (n = 156)*

Characteristic	Values
Female, %	82.1
Age, years	54.6 ± 13.6
White, %	95.5
RA disease duration, years	10.0 ± 12.6
Seropositive, %	81.4
CDAI (0–100)	25.5 ± 14.0
Swollen joints (0–28)	5.8 ± 5.6
Tender joints (0–28)	11.8 ± 9.2
Patient global (0–10)	4.1 ± 2.3
Assessor global (0–10)	3.8 ± 2.3
Average pain rating (0–10)	5.2 ± 2.2
Pain catastrophizing score (0–52)	18.5 ± 13.6
Medication use	
DMARDs, %	60.9
Nonbiologic DMARDs†	44.2
Biologic DMARDs†	26.3
Glucocorticoids, %	43.0
Mean prednisone dose, mg‡	6.7 ± 3.0
NSAIDs, %	46.2

* Values are the mean ± SD unless indicated otherwise. DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; CDAI = Clinical Disease Activity Index; NSAID = nonsteroidal anti-inflammatory drug.
† Percentages reflect a denominator of the whole population.
‡ Of patients taking prednisone.

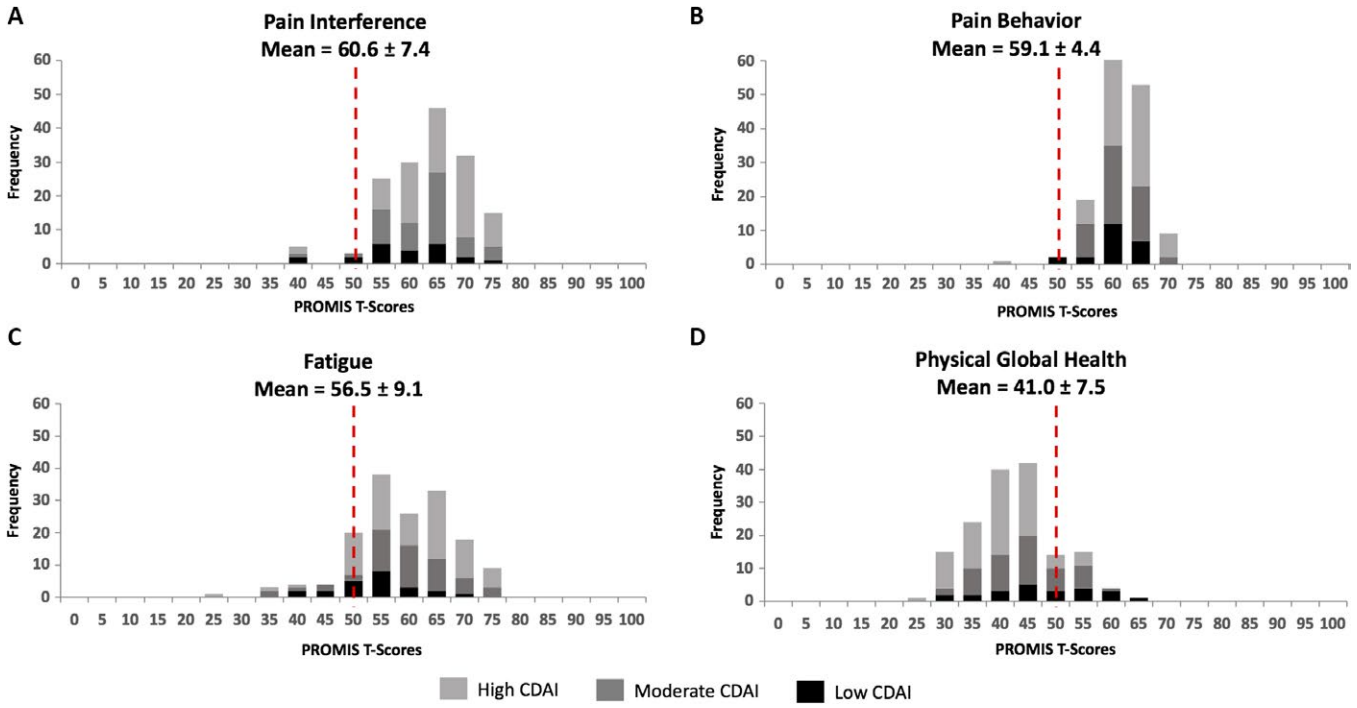

Figure 1. Distributions of **A**, Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference, **B**, pain behavior, **C**, fatigue, and **D**, physical global health T scores for study participants, showing scores by Clinical Disease Activity Index (CDAI) at baseline (n = 156). The red dotted line shows the general population mean score of 50.

disease duration was 10.0 ± 12.6 years. Overall, the population was overweight, with a mean ± SD body mass index of 31.1 ± 16.4.

The majority of participants were seropositive (81.4%) and had high disease activity, indicated by a mean ± SD CDAI score of 25.5 ± 14.0. The average numbers of swollen and tender joints were 5.8 ± 5.6 and 11.8 ± 9.2, respectively. The mean ± SD patient global assessment score was 4.1 ± 2.3. The mean ± SD assessor global assessment score was 3.8 ± 2.3. Within the study population, 33.3% of participants had fibromyalgia as defined by the 2010 modified ACR Preliminary Diagnostic Criteria for Fibromyalgia.

At baseline, 60.9% of participants were taking ≥1 DMARD. Forty-four percent were using nonbiologic DMARDs, and 26.3% were taking biologic DMARDs. Slightly less than half of participants (43.0%) were taking glucocorticoids at their baseline visit. Among those taking glucocorticoids, the mean ± SD prednisone dose was 6.7 ± 3.0 milligrams per day. Forty-six percent of participants received nonsteroidal antiinflammatory drugs on a regular basis.

Means and distributions of baseline PROMIS measures. All PROMIS T scores exhibited a normal distribution. The PROMIS measures with the greatest shifts in distribution from the general population (mean ± SD of 50 ± 10) were pain interference (60.6 ± 7.4), pain behavior (59.1 ± 4.4), fatigue (56.5 ± 9.1), and physical global health (41.0 ± 7.5) (Figure 1). The means for sleep disturbance and sleep-related impairment were close to one-half of an SD above the general population mean ± SD of 50 ± 10, at 54.2 ± 9.1 and 55.1 ± 10.0, respectively (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23617/abstract). The distributions of the depression, pain intensity 3a, anxiety, and mental global health measures were similar to those of the general population, with means ± SDs of 53.7 ± 8.8, 51.5 ± 6.0, 50.5 ± 9.2, and 47.9 ± 8.4, respectively (see Supplementary Figure 2, at http://onlinelibrary.wiley.com/doi/10.1002/acr.23617/abstract). Participants with fibromyalgia had significantly worse scores on all assessed PROMIS measures ($P < 0.0001$) (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23617/abstract).

Cross-sectional associations between baseline PROMIS and disease activity measures. In multivariable analyses, mean scores for all PROMIS measures were significantly worse ($P < 0.001$) across categories of increasing disease activity (Table 2). Mean physical global health scores ranged from 45.3 among those with low disease activity to 38.8 among those with high disease activity, whereas mental global health scores ranged from 51.2 among those with low disease activity to 46.1 among those with high disease activity. Of the individual PROMIS domains, sleep disturbance showed the widest range in scores (7.9 points), whereas pain behavior showed the smallest difference (2.1 points).

In multivariable models examining the relationship between PROMIS measures and CDAI scores, significant

Table 2. Patient-Reported Outcomes Measurement Information System (PROMIS) T scores by CDAI category*

PROMIS measure†	Low ≤10 (n = 23)	Moderate 10–22 (n = 51)	High >22 (n = 82)
Physical global health‡	45.3 (44.4–46.1)	42.6 (41.9–43.3)	38.8 (38.3–39.3)
Mental global health§	51.2 (50.6–51.8)	49.3 (48.7–49.9)	46.1 (45.6–46.5)
Pain intensity 3a‡	48.5 (47.8–49.2)	50.7 (50.2–51.2)	52.9 (52.5–53.3)
Pain interference§	57.2 (56.5–57.9)	59.6 (59.0–60.1)	62.2 (61.8–62.6)
Pain behavior¶	57.7 (56.9–58.5)	58.7 (58.1–59.3)	59.8 (59.3–60.2)
Sleep disturbance‡	48.9 (48.2–49.7)	52.6 (51.9–53.2)	56.8 (56.4–57.2)
Sleep-related impairment§	50.0 (48.9–51.0)	53.1 (52.3–53.9)	57.8 (57.2–58.4)
Fatigue§	52.9 (52.1–53.7)	55.0 (54.4–55.6)	58.4 (57.9–58.9)
Anxiety§	50.5 (49.2–51.8)	52.4 (51.6–53.2)	55.3 (54.7–56.0)
Depression¶	47.7 (46.5–48.8)	49.2 (48.5–49.8)	52.1 (51.5–52.7)

* Values are the mean (95% confidence interval). Multivariable models adjusted for study site, sex, race, age, seropositivity, and rheumatoid arthritis disease duration to predict means by Clinical Disease Activity Index (CDAI) category and to determine trend across categories. Differences between groups were all significant at P <0.001.
† Global health and pain intensity 3a scores were collected using short forms. All other instruments were collected using computerized adaptive tests. Lower global health scores indicate worse global health. For all other measures, high scores indicate worse symptoms. All PROMIS scores range from approximately 20 to 80 and are standardized to a general population mean ± SD of 50 ± 10.
‡ P ≤0.001.
§ P ≤0.01.
¶ P ≤0.05.

associations (βs ranging from |0.21| to |0.34|; $P < 0.05$) were found with physical global health, pain intensity 3a, pain interference, pain behavior, sleep disturbance, and sleep-related impairment (Table 3). Tender joints, patient global assessment, and assessor global assessment were also significantly associated (βs ranging from |0.18| to |0.43|; $P \leq 0.05$) with these PROMIS measures. The swollen joint component of the CDAI was only significantly associated ($\beta = 0.18$; $P < 0.05$) with

Table 3. Standardized betas showing associations between Patient-Reported Outcomes Measurement Information System (PROMIS) T scores and disease activity measures at baseline (n = 156)*

PROMIS measure	CDAI	Swollen joints	Tender joints	Patient global	Assessor global
Physical global health†	−0.25‡	0.019	−0.21§	−0.43¶	−0.28‡
Mental global health†	−0.14	0.073	−0.12	−0.30‡	−0.24‡
Pain intensity 3a†	0.30¶	0.063	0.25§	0.38¶	0.27¶
Pain interference	0.27‡	0.016	0.25§	0.35¶	0.27‡
Pain behavior	0.21§	0.018	0.22§	0.25‡	0.18§
Sleep disturbance	0.34¶	0.18§	0.27‡	0.30¶	0.23‡
Sleep-related impairment	0.27‡	0.045	0.26‡	0.29¶	0.26‡
Fatigue	0.17	−0.065	0.23§	0.26‡	0.16
Anxiety	0.14	−0.040	0.12	0.28¶	0.18§
Depression	0.026	−0.10	0.021	0.17§	0.14

* Multivariable models adjusted for study site, sex, race, age, seropositivity, and rheumatoid arthritis disease duration. Standardized betas reflect the amount of SDs a dependent variable changes per SD change in the independent variable.
† Global health and pain intensity 3a scores were collected using short forms. All other instruments were collected using computerized adaptive tests. Lower global health scores indicate worse global health. For all other measures, high scores indicate worse symptoms. All PROMIS scores range from approximately 20 to 80 and are standardized to a general population mean ± SD of 50 ± 10.
‡ P ≤0.01.
§ P ≤0.05.
¶ P ≤0.001.

Table 4. Mean Patient-Reported Outcomes Measurement Information System (PROMIS) T scores pre- and post-DMARD treatment (n = 106)*

	Pre-DMARD	Post-DMARD
Physical global health	41.4 ± 7.3	45.1 ± 8.7†
Mental global health	48.0 ± 8.2	49.7 ± 9.0‡
Pain intensity 3a	51.5 ± 6.0	45.5 ± 7.7†
Pain interference	60.6 ± 7.3	55.5 ± 8.0†
Pain behavior	59.2 ± 4.7	54.8 ± 8.0†
Sleep disturbance	55.2 ± 8.5	50.9 ± 8.8†
Sleep-related impairment	55.2 ± 9.8	52.0 ± 10.5†
Fatigue	56.8 ± 8.6	52.3 ± 8.8†
Anxiety	54.3 ± 8.8	51.2 ± 9.5†
Depression	50.8 ± 9.7	48.5 ± 9.2§

* Values are the mean ± SD. Global health and pain intensity 3a scores were collected using short forms. All other instruments were collected using computerized adaptive tests. Lower global health scores indicate worse global health. For all other measures, high scores indicate worse symptoms. All PROMIS scores range from approximately 20 to 80 and are standardized to a general population mean ± SD of 50 ± 10. DMARD = disease-modifying antirheumatic drug.
† $P \leq 0.001$ from paired *t*-tests.
‡ $P \leq 0.05$ from paired *t*-tests.
§ $P \leq 0.01$ from paired *t*-tests.

sleep disturbance. The directionality of all associations was such that increases in the CDAI score or the components of the CDAI were associated with worsening PROMIS scores.

Changes in PROMIS measures and CDAI score from baseline to 12 weeks post-DMARD initiation. At the time of this analysis, 106 subjects had data from a follow-up visit. With 12–24 weeks of DMARD treatment, disease activity significantly decreased with a mean ± SD decrease in the CDAI score of 10.8 ± 13.1. The 52 subjects with high baseline disease activity experienced a mean ± SD improvement in the CDAI score of 17.6 ± 14.6. The 38 participants with moderate baseline disease activity experienced a mean ± SD improvement in the CDAI score of 5.8 ± 6.6, and 16 participants with low baseline disease activity experienced an average improvement in the CDAI score of 0.8 ± 6.3.

All PROMIS measures improved significantly ($P < 0.05$) with DMARD treatment (Table 4). The greatest improvement was seen in the pain intensity 3a scores (6.0 points), and the smallest improvement was seen in mental global health scores (1.7 points). In a sensitivity analysis examining only subjects with moderate-to-high CDAI scores at baseline, the results were similar.

Changes in all PROMIS measures, except depression, were significantly associated (βs ranging from |0.23| to |0.38|; $P \leq 0.05$) with changes in the CDAI score and changes in tender joint count (βs ranging from |0.24| to |0.36|; $P \leq 0.05$) (Table 5). Changes in all PROMIS measures, except mental global health, were significantly associated with changes in patient global assessment (βs ranging from |0.21| to |0.35|; $P \leq 0.05$). Changes in physical global health, mental global health, pain interference, sleep disturbance, sleep-related impairment, and fatigue were significantly associated with changes in assessor global assessment (βs ranging from |0.22| to |0.34|; $P \leq 0.05$). Changes in PROMIS measures were not significantly associated with changes in the swollen joint count. A sensitivity analysis among those subjects with a moderate-to-high baseline CDAI score showed similar results, with some associations being slightly stronger in the subgroup of individuals with moderate-to-high disease activity (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23617/abstract).

DISCUSSION

To our knowledge, this is the first prospective, longitudinal study to examine changes in PROMIS measures among RA patients starting a DMARD. This study is also unique in that it provides data regarding PROMIS measures among RA patients with moderate-to-high disease activity, whereas previous studies included RA patients following established DMARD regimens with lower average disease activity (9,11).

At baseline, mean PROMIS physical global health, pain interference, and pain behavior scores differed by approximately 1 SD from general population norms, indicating that these measures are able to differentiate RA patients with active disease from the general population. In contrast, mean PROMIS pain intensity and depression T scores were similar to population norms. This finding may be due to habituation, meaning that patient perception of their symptoms may change over time as they habituate to the new reality of their chronic illness. In other words, a rating of 0 may equate to baseline symptoms instead of a complete lack of symptoms (9). Further research is needed to examine the role of habituation in the assessment of pain and depression in patients with active RA. In the meantime, investigators wanting to compare symptoms of pain and depression between RA patients and the general population should consider including other assessments of these domains and/or supplement the assessments with related PROMIS measures (e.g., pain interference and pain behavior).

In cross-sectional analyses, all of the evaluated PROMIS instruments, including pain intensity and depression, differentiated between groups of RA patients with different levels of disease activity. Pain intensity and depression scores were significantly higher among those with higher disease activity compared to those with lower disease activity, despite similar mean scores in the total cohort compared to general population norms. This observation underscores the distinction between comparing

Table 5. Standardized betas showing associations between changes in Patient-Reported Outcomes Measurement Information System (PROMIS) T scores and changes in disease activity measures (n = 106)*

PROMIS measure	CDAI	Swollen joints	Tender joints	Patient global	Assessor global
Physical global health†	−0.29‡	−0.12	−0.30‡	−0.21§	−0.24§
Mental global health†	−0.34‡	−0.20	−0.33‡	−0.18	−0.22§
Pain intensity 3a†	0.27§	0.12	0.24§	0.23§	0.20
Pain interference	0.33‡	0.12	0.31‡	0.30‡	0.28‡
Pain behavior	0.27§	0.059	0.28‡	0.28‡	0.20
Sleep disturbance	0.38¶	0.12	0.36¶	0.35‡	0.34‡
Sleep-related impairment	0.33‡	0.11	0.34‡	0.27‡	0.30‡
Fatigue	0.33‡	0.086	0.35‡	0.29‡	0.27§
Anxiety	0.23§	0.048	0.24§	0.24§	0.16
Depression	0.088	−0.039	0.067	0.24§	0.10

* Multivariable models adjusted for study site, sex, race, age, seropositivity, and rheumatoid arthritis disease duration to predict means by Clinical Disease Activity Index (CDAI) category and to determine trend across categories. Standardized betas reflect the amount of SDs a dependent variable changes per SD change in the independent variable.
† Global health and pain intensity 3a scores were collected using short forms. All other instruments were collected using computerized adaptive tests. Lower global health scores indicate worse global health. For all other measures, high scores indicate worse symptoms. All PROMIS scores range from approximately 20 to 80 and are standardized to a general population mean ± SD of 50 ± 10.
‡ $P \leq 0.01$.
§ $P \leq 0.05$.
¶ $P \leq 0.001$.

subgroups within a population versus comparing 2 different populations. Even though RA patients may have a different frame of reference than the general population for gauging symptoms of pain severity and depression, these measures were able to differentiate between RA patients with different disease activity levels.

Congruent with the finding that baseline PROMIS scores were associated with baseline CDAI categories, the baseline scores for physical global health, pain intensity 3a, pain interference, pain behavior, sleep disturbance, and sleep-related impairment were correlated with each component of the CDAI, except the swollen joint count. The absence of association between PROMIS measures and the swollen joint count may be due to multiple factors, including the relative insensitivity of the swollen joint count as an independent measure of inflammatory disease activity (25,26) and the multifaceted nature of these PROs. The patient-reported measures of disease activity likely capture more intangible aspects of the patient experience, which may variably reflect actual inflammation, depending on individual circumstances (27–29).

One of the most novel findings of this study was the observation that all PROMIS measures improved with DMARD treatment. In our study, the largest change was seen with pain intensity, whereas the smallest change was seen in the mental global health scores. The changes in the physical health domains were larger than those for the mental health domains. This observation is consistent with reports for legacy instruments assessing PROs in clinical trials (30). A meta-analysis of the effect of TNF inhibitor therapy in chronic illnesses, including RA, showed that although depression and anxiety improved with treatment, effect sizes were small (31). Whether the improvements observed in this study were clinically meaningful is still unclear. Research is underway to determine the minimal clinically important differences in PROMIS scores for RA patients.

Changes in all PROMIS measures, except depression, were associated with changes in the CDAI score, though the magnitudes of correlation were generally low. In a subgroup analysis, including only those subjects with baseline moderate-to-high disease activity, some correlations were slightly stronger, suggesting a possible mild floor effect among individuals with low disease activity at baseline. Of the physical health domains, the strongest associations with changes in disease activity were noted for the measures of sleep and fatigue (PROMIS sleep disturbance, sleep-related impairment, and fatigue). These findings highlight the important relationship between sleep, fatigue, and disease activity in RA and are consistent with reports of significant reductions in sleep problems and fatigue in clinical trials of RA patients treated with DMARDs (32–34).

The lack of association between changes in depression and changes in the CDAI score is notable in the context of growing interest in the impact of inflammation on depressive symptoms. Others have reported that depression and inflammatory disease activity have a reciprocal relationship. Whereas depressive symptoms decrease with effective treatment of inflammatory disease activity, prevalent depression also decreases the likelihood of

response to DMARDs (35). Multiple factors, including the complex relationship between depression, pain, and inflammation, the absence of severe depressive symptoms at baseline, and the small magnitude of change in depression scores, may have limited our ability to detect associations in this study.

The strengths of our study include the large sample size of RA patients with active disease and the comprehensive assessment of these patients after initiation of a DMARD. Limitations of this study include the absence of a comparison group of RA patients who were not starting DMARDS. In addition, we were not able to examine associations between PROMIS measures and serum markers of inflammation. Although blood samples were obtained from these subjects, these measures have not been assayed, because this study is ongoing. We also did not include assessments of physical function, which could be an important determinant of irreversible components of disease. Other studies, however, have shown that PROMIS measures of physical function are valid and responsive in RA (36,37).

Another limitation may be generalizability, because only 60.9% of the participants were taking a DMARD at the time of the baseline study visit. The relatively low number taking DMARDs at baseline reflects the inclusion criterion requiring patients to have active disease, necessitating a start or switch to a new DMARD. Many subjects had previously been taking DMARDs but had discontinued their DMARD at least 6 weeks prior to the study visit for various reasons (e.g., insurance changes, infection/other comorbidities, history of remission) and, as a result, were experiencing increased disease activity, requiring initiation of a new DMARD.

This study contributes new information regarding the role of PROMIS measures in the longitudinal assessment of RA patients with active disease treated with DMARDs. The PROMIS global health, pain intensity, pain interference, pain behavior, sleep disturbance, sleep-related impairment, fatigue, anxiety, and depression measures were all able to differentiate between RA patients with different levels of disease activity. The PROMIS physical global health, pain, and sleep measures were correlated with the CDAI score and each of its components, except swollen joint count. With respect to statistical significance, all the aforementioned PROMIS measures improved with initiation of a DMARD. However, from a clinical standpoint, whether these changes were meaningful is not known. While the majority of improvements in PROMIS measures were associated with improvements in the CDAI score, the magnitudes of association were not strong. Further research is needed to determine minimal clinically important changes in these measures for RA patients and to clarify the effects of baseline RA disease activity on the responsiveness of these measures.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Impact of High-Intensity Interval Training on Disease Activity and Disease in Patients With Psoriatic Arthritis: A Randomized Controlled Trial

Ruth S. Thomsen,[1] Tom I. L. Nilsen,[1] Glenn Haugeberg,[2] Anja Bye,[1] Arthur Kavanaugh,[3] and Mari Hoff[1]

Objective. To evaluate the impact of high-intensity interval training (HIIT) on disease activity and disease perception in patients with psoriatic arthritis (PsA) and to evaluate whether a potential effect could be sustained for a longer period of time.

Methods. We randomly assigned 67 patients with PsA (43 women and 24 men) to an intervention group in which patients performed HIIT for 11 weeks or a control group of patients who were instructed not to change their physical exercise habits. Outcomes were assessed at 3 months and 9 months with the patient's global assessment (PGA), fatigue, and pain scores measured on a 100-mm visual analog scale (VAS), and the composite Disease Activity Score in 44 joints (DAS44) was calculated. We used linear mixed models to calculate the mean difference (95% confidence interval [95% CI]) between groups according to the intent-to-treat principle.

Results. At 3 months, there was no clear difference in the PGA score (–0.49 [95% CI –10.91, 9.94]), DAS44 (–0.08 [95% CI –0.36, 0.20]), or pain intensity (5.45 [95% CI –4.36, 15.26]) between the groups. However, patients in the intervention group reported less fatigue (–12.83 [95% CI –25.88, 0.23]) than those in the control group. There was no evidence of long-term effects of HIIT on outcomes measured at 9 months.

Conclusion. HIIT showed no clear effects on disease activity markers in patients with PsA, but the intervention (exercise) group reported meaningfully less fatigue after the intervention period. The results of this study suggest that patients with PsA tolerate HIIT without deterioration of disease activity and with improvement in fatigue.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic heterogeneous inflammatory disease. Inflammation in the musculoskeletal system may present as enthesitis, dactylitis, arthritis, or spondylitis. The consequences for the patient may include fatigue, pain, impaired physical function, and reduced quality of life (QoL) (1–3). The aim of standard treatment using synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) is to reduce inflammatory activity (4). However, medical treatments do not always appear to eliminate symptoms such as fatigue and pain, both of which are significantly related to QoL (4).

Physical exercise is recommended as a supplement to medical therapy for all patients with arthritis, although there is little evidence for its utility in patients with PsA (5). High-intensity interval training (HIIT) is a system of organizing cardiorespiratory training with repeated bouts of short duration, high-intensity exercise intervals at 80–95% of maximum heart rate (HR_{max}) interrupted by periods of lower-intensity intervals of active recovery (6). The impact and tolerability of HIIT in patients with PsA is unknown. Furthermore, there are no recommendations regarding the type and intensity of exercise for patients with PsA. There is also a concern that vigorous physical exercise may cause increased disease activity in patients with PsA, by generating more enthesitis. This concern is related to the notion that mechanical strain can drive entheseal inflammation (7,8).

The aim of this randomized controlled trial (RCT) in patients with PsA was to evaluate the impact of HIIT on disease activity and patients' disease perception and to evaluate whether a potential effect could be sustained for a longer period of time.

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[1]Ruth S. Thomsen, MD, Tom I. L. Nilsen, PhD, Anja Bye, PhD, Mari Hoff, MD, PhD: Norwegian University of Science and Technology, and St Olavs Hospital, University Hospital of Trondheim, Trondheim, Norway; [2]Glenn Haugeberg, MD, PhD: Norwegian University of Science and Technology, Trondheim, Norway, Hospital of Southern Norway Trust, Kristiansand, Norway, and Martina Hansens Hospital, Bærum, Norway; [3]Arthur Kavanaugh, MD: University of California, San Diego.

Address correspondence to Ruth S. Thomsen, MD, NTNU, Faculty of Medicine, Department of Public Health and Nursing, Post Box 8905 Medical Research Centre (MTFS), N-7491 Trondheim, Norway. E-mail: ruth.thomsen@ntnu.no.

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SIGNIFICANCE & INNOVATIONS

- Physical exercise is recommended for all patients with arthritis, although there is little evidence for its utility in patients with psoriatic arthritis (PsA). Furthermore, there are no recommendations regarding the type and intensity of exercise for patients with PsA.
- High-intensity interval training did not result in deterioration of disease activity or disease perception in patients with PsA.
- Fatigue improved after high-intensity interval training.
- High-intensity interval training may be a relevant mode of physical exercise for patients with PsA.

PATIENTS AND METHODS

Design. We conducted an RCT in 2 parallel groups, comparing an intervention group in which patients performed HIIT 3 times per week for 11 weeks to a control group in which patients made no change in their pre-study physical exercise habits. The study was performed according to Good Clinical Practice and Declaration of Helsinki principles. The trial was approved by the regional ethics committee (RECnr 2012/1646) and is registered in ClinicalTrials.gov (identifier: NCT02995460). Results are presented according to the CONSORT (Consolidated Standards of Reporting Trials) statement (see Supplementary Material, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23614/abstract) (9).

Participants. All eligible patients with PsA, ages 18–65 years, fulfilled the Classification of Psoriatic Arthritis (CASPAR) Study Group criteria. Exclusion criteria included inability to exercise, unstable ischemic cardiovascular disease or severe pulmonary disease, an anticipated need for a change in synthetic or biologic DMARDs during the intervention period (however, a change of DMARDs was possible during the follow-up period, from 3 months to 9 months, and a change in glucocorticoid doses as well as injections with intraarticular glucocorticoid were allowed until 4 weeks before any follow-up), pregnancy, breastfeeding, and drug or alcohol addiction. In addition, the investigator interviewed the patients about their physical exercise habits. Those who reported vigorous endurance training (e.g., running or bicycling) at least once weekly for the last 3 months were excluded. Patients were recruited through local advertisement at the Department of Rheumatology, St. Olavs Hospital, the Psoriasis and Eczema Association of Norway; and the Norwegian Rheumatism Association. The study was conducted at St. Olavs Hospital and Norwegian University of Science and Technology (NTNU), Trondheim, Norway, from 2013 to 2015.

Intervention. At baseline, the patients performed a max test measuring their HR_{max} and maximum oxygen uptake ($V_{O_{2\ max}}$) on a stationary bicycle (10). All tests were carried out at the Cardiac Exercise Research Group (CERG) facilities at NTNU. The exercise intervention was performed as a supervised HIIT workout starting with a 10-minute warm-up period followed by 4 × 4 minutes of exercise at 85–95% of HR_{max} interrupted by 3 minutes of exercise at 70% of the HR_{max} (11). The supervised HIIT was performed on a stationary bicycle at CERG twice weekly, with an intermitting day of rest. The supervisors were physiotherapy and physiology students who were experienced in guiding an HIIT. One supervisor guided a maximum of 6 patients at a time. Additionally, the patients did one self-guided HIIT a week. They were instructed in using the HIIT concept by, e.g., running, bicycling, or walking uphill. All exercises were supported by using a heart rate monitor.

During the follow-up period from 3 to 9 months, patients in the HIIT group were encouraged to continue exercising but without guidance. To reinforce adherence to the training program, diaries were obtained from the HIIT group every week during the intervention period from baseline to 3 months and included information on the type of exercise, time, location, and with whom it was performed. Moreover, the intensity was rated by the registered pulse and by the 15-point Borg scale (from 6 to 20), the latter being a method of rating perceived exertion (12,13). Patients in the control group were instructed not to change their pre-study physical exercise habits. However, during the follow-up period from 3 to 9 months, they were allowed to start exercising.

Assessment of outcome measures. Outcome measures were assessed at baseline and at 3 and 9 months of follow-up. These assessments included questionnaires, clinical examinations, and laboratory measurements. An experienced rheumatologist (RST) performed the clinical examinations, including joint and enthesis assessment. Blood samples and the baseline body mass index were assessed at the Department of Research and Development, St. Olavs Hospital. Demographics, disease measures, comorbidities, and medication data were obtained using the medical journal system and the GoTreatIT Rheuma software program (14), the latter of which was developed for use in daily clinical care and for research purposes (www.diagraphit.com).

Main outcome measure. The main outcome was patient's global assessment (PGA) score based on the question "In all the ways in which your PSORIASIS and ARTHRITIS, as a whole, affect you, how would you rate the way you felt over the past week?" and reported on a 100-mm VAS. The PGA has been found to be a reliable tool for the assessment of both joint and skin disease (15), and a PGA score ≤20 is defined as low disease activity (16).

Secondary outcome measures. Patients reported fatigue and pain intensity on a 100-mm VAS. Fatigue was based on the question "To what degree has unusual tiredness or exhaustion been a problem for you the last week?" and pain on the question "How much pain did you experience during the last week?" A change of ≥10 mm on a 100-mm VAS is considered as the minimal clinically important difference (17). Peripheral joint inflammation was assessed by the Disease Activity Score in 44 joints (DAS44) (18). This is a composite score combining information on the number of tender and swollen joints, PGA, and high-sensitivity C-reactive protein (hsCRP) level (19). The DAS44 was chosen instead of the DAS in 28 joints, because joints in the ankle and feet are included.

Axial inflammation was evaluated by the Ankylosing Spondylitis Disease Activity Score using the CRP level (ASDAS-CRP), which is a continuous score based on 4 questions and the hsCRP level (20). The burden of enthesitis was defined by the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index, in which 18 enthesial sites are examined for the presence or absence of tenderness, providing a score ranging from 0 to 16 (21,22).

Sample size. A difference in the main outcome measure (PGA) of 10 mm on a 0–100-mm VAS was considered clinically important (17), and based on a standard deviation of 15 and a correlation of 0.4 between repeated measures (23), we estimated that 30 patients were required in each group to achieve a power of 90% at an alpha level of 0.05.

Randomization and blinding. Patients were randomized to either a HIIT group or a control group according to a 1:1 allocation in permuted blocks after signed consent was given and a clinical investigation was performed, using a computer random-number generator (Unit for Applied Clinical Research, St. Olavs Hospital). Patients were stratified according to sex. The block randomization did not allow the researchers to reveal the next allocations. The rheumatologist (i.e., one of the researchers) was blinded to group allocation at the time of baseline evaluations but not at 3 months and 9 months of follow-up. The assessors at the biochemical laboratory at St. Olavs Hospital (who analyzed blood samples) were blinded throughout all follow-ups.

Statistical analysis. The main analyses of both primary and secondary outcomes were conducted according to an intent-to-treat strategy, using all available data from all time points. We used a linear mixed model for repeated measures to estimate mean differences with 95% confidence intervals (95% CIs) in outcome variables between the HIIT group and the control group at 3 months and 9 months after randomization. Changes from baseline at 3 months and 9 months were calculated using a joint baseline level of the outcome measure, assuming that any baseline differences between groups are due to chance. From these models, we also estimated the mean change in outcome variables within each group.

All measures of effect were adjusted for sex (male and female) and age (continuous). Due to non-normal distribution of the hsCRP level, we used a logarithmic transformation of the variable in the regression model before transforming back the estimates. The results for hsCRP are thus expressed as geometric means. Logistic regression analysis was performed to calculate the odds ratios (ORs) with 95% CIs for worsening in the SPARCC Enthesitis Index in the HIIT and control groups. The difference in the SPARCC Enthesitis Index between baseline and 3 months was used to classify patients as having a worse or same/improved enthesitis burden. The diaries were reviewed to find the number of accomplished supervised and self-guided exercises. The mean intensity, as rated using the Borg scale, was calculated according to the values recorded in the diaries.

Descriptive statistics are presented as the mean ± SD or as the median and interquartile range for non-normally distributed variables. All statistical analyses were conducted using Stata version 14.2.

RESULTS

Participant flow and characteristics. Among 102 patients who were assessed for eligibility, 35 were excluded based on the exclusion criteria, withdrawal, or other reasons (Figure 1). Thus, 67 patients were eligible for randomization and allocation to either the

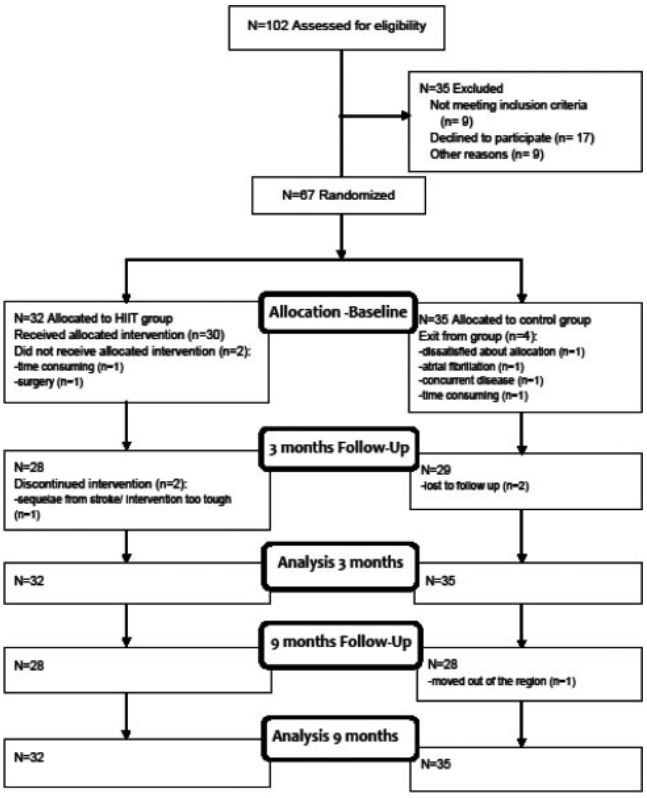

Figure 1. Diagram showing the flow of participants through the study. HIIT = high-intensity interval training.

HIIT group (n = 32) or the control group (n = 35). More women than men were included in the study (66% and 63% in the HIIT and control groups, respectively), and the mean ± SD age of patients in the HIIT group was 50.7 ± 11 years, and that of patients in the control group was 45.6 ± 11.5 years. Baseline characteristics of the patients are shown in Table 1.

Patients in the HIIT group turned in completed diaries for 95% of all weeks. They completed the guided exercises in 78% of all sessions. However, patients in the HIIT group did more self-guided endurance exercises than requested (i.e., 1.2 times/week). According to diaries, the mean ± SD intensity during guided exercise was 16.4 ± 3.3, which according to the 15-point Borg scale is considered "very hard" effort. The mean ± SD intensity during self-guided exercise was 12.8 ± 3.4, which according to the Borg scale is considered "moderate" effort. At 9 months of follow-up, 28 patients remained in each group. Of these, 12 (4%) in the HIIT group and 5 (18%) in the control group reported that they were doing endurance exercise.

Effect on outcome measures at 3 months. Overall, there was no clear difference in the PGA score (–0.49 mm [95% CI –10.91, 9.94]), the DAS44 (–0.08 mm [95% CI –0.36, 0.20]), pain intensity score (5.45 mm [95% CI –4.36, 15.26]), ASDAS-CRP level (–0.14 [95% CI –0.53, 0.25]), or hsCRP level (–0.11 mg/liter [95% CI –0.97, 0.75]) between the groups at 3 months (Table 2). Although there were no differences between groups in measures of disease activity and pain, patients in the HIIT group reported lower fatigue than that reported by patients in the control group (–12.83 mm [95% CI –25.88, 0.23]). Moreover, within-group analyses showed that both groups experienced reductions in PGA, pain intensity, DAS44, and fatigue from baseline to 3 months. There was no difference in change in the SPARCC Enthesitis Index between the 2 groups, with an OR of 0.80 (95% CI 0.19, 3.35) for worsening when comparing the HIIT group with the control group.

Outcome at 9 months of follow-up. At 9 months of follow-up, there were no clinically important differences between the 2 groups for all outcome measures (Table 3). Similar to the 3-month data, there was some decline in most of the outcome variables from baseline to 9 months, although the magnitude of change was small.

Safety. During the period of intervention from baseline to 3 months, 2 patients in the HIIT group and none in the control group had intraarticular injections. Injections were given 1 month after the start of the intervention. At the 3-month follow-up, 4 patients in the HIIT group and 3 in the control group had intraarticular injections. During the 3 month to 9 month follow-up, 4 patients in the HIIT group and 7 patients in the control group had intraarticular injections. None of the injections were administered later than 4 weeks prior to DAS44 evaluations. One patient left the HIIT group due to sequelae after a stroke previous to the study and found that participation in the intervention was too difficult. No other adverse events were reported during the intervention.

Table 1. Baseline characteristics of the patients with psoriatic arthritis in the intervention and control groups*

	Intervention (n = 32)	Control (n = 35)
Age, mean ± SD years	50.7 ± 11.0	45.6 ± 11.5
Female, no. (%)	21 (66)	22 (63)
Disease duration, median (IQR) years	5.5 (2–12)	3 (2–11)
Synthetic DMARDS, no. (%)	29 (91)	28 (80)
Biologic DMARDS, no. (%)	11 (34)	10 (29)
Vo_2 max, mean ± SD ml/kg/minute†	28.73 ± 6.41	30.75 ± 7.95
Current smoker, no. (%)	6 (19)	5 (14)
BMI, mean ± SD kg/m^2	28.6 ± 4.1	28.0 ± 4.5
hsCRP, median (IQR) mg/liter‡	1.67 (0.9–4.5)	1.87 (0.86–4.74)
PGA score, mean ± SD (0–100-mm VAS	37.4 ± 23.4	42.9 ± 20.8
DAS44, mean ± SD§	1.98 ± 0.77	2.00 ± 0.74
Tender joint count in 66 joints, median (IQR)	4.5 (1–9)	6 (1–9)
Swollen joint count in 68 joints, median (IQR)	0 (0–1)	0 (0–2)
Fatigue score, mean ± SD (0–100-mm VAS)#	43.5 ± 30.7	52.9 ± 28.2
Pain score, mean ± SD (0–100-mm VAS)	35.3 ± 21.0	39.2 ± 22.8
ASDAS-CRP, mean ± SD§	2.08 ± 0.96	2.18 ± 0.89
SPARCC Enthesitis Index, median (IQR)	3 (1–6)	3 (0–5)
M-HAQ score, median (IQR)	0.32 (0–0.69)	0.38 (0.25–0.63)
PASI score, median (IQR)	0 (0–1)	0.5 (0–2.7)

* IQR = interquartile range; DMARDs = disease-modifying antirheumatic drugs; Vo_2 max = maximum oxygen uptake; BMI = body mass index; hsCRP = high-sensitivity C-reactive protein; PGA = patient's global assessment; DAS44 = Disease Activity Score in 44 joints; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using the CRP level; SPARCC = Spondyloarthritis Research Consortium of Canada; M-HAQ = modified Health Assessment Questionnaire; PASI = Psoriasis Area Severity Index.
† Baseline data were missing for 4 patients in the control group and 2 patients in the intervention group.
‡ Baseline data were missing for 4 patients in the control group and 1 patient in the intervention group.
§ Calculated based on ordinary CRP values for those with missing hsCRP data at baseline.
# Baseline data were missing for 1 patient in the control group.

Table 2. Changes in outcome between patients in the control group (n = 35) and patients in the intervention group (n = 32) and changes within the groups from baseline to 3 months of follow-up*

	Baseline mean, both groups	Changes within groups		Mean between-group difference
		Control	Intervention	
PGA	40.41	−5.37	−5.86	−0.49
95% CI	34.79, 46.02	−13.12, 2.37	−13.74, 2.02	−10.91, 9.94
P	–	0.17	0.15	0.93
Fatigue	48.74	−3.03	−15.86	−12.83
95% CI	41.74, 55.73	−12.82, 6.75	−25.66, −6.75	−25.88, 0.23
P	–	0.54	0.002	0.05
DAS44	2.00	−0.30	−0.38	−0.08
95% CI	1.84, 2.16	−0.50, −0.09	−0.59, −0.17	−0.36, 0.20
P	–	0.004	<0.001	0.56
Pain	37.57	−11.03	−5.58	5.45
95% CI	32.49, 42.65	−18.38, −3.68	−13.06, 1.90	−4.36, 15.26
P	–	0.003	0.14	0.28
ASDAS-CRP	2.14	−0.17	−0.31	−0.14
95% CI	1.91, 2.36	−0.46, 0.12	−0.60, −0.02	−0.53, 0.25
P	–	0.24	0.04	0.49
hsCRP†	1.87	−0.00	−0.11	−0.11
95% CI	1.33, 2.42	−0.65, 0.64	−0.74, 0.52	−0.97, 0.75
P	–	0.99	0.73	0.81

* Scores for PGA, fatigue, and pain were measured on a 0–100-mm visual analog scale. Baseline data for PGA, DAS44, pain, and ASDAS were available for 67 patients; baseline data for hsCRP were available for 62 patients. All measures were adjusted for age and sex. See Table 1 for abbreviations.
† Expressed as the geometric mean.

DISCUSSION

In this RCT, we observed that although HIIT in patients with PsA had no effect on markers of disease activity, patients performing HIIT had a clinically relevant improvement in fatigue at 3 months compared with controls. Unfortunately, there were no longer clinically relevant effects of HIIT at 9 months. To our knowledge, this is the first study investigating the impact of HIIT on disease activity and PsA patients' disease perception. The results of previous studies in rheumatoid arthritis (RA) and spondyloarthritis (SpA) have suggested reduced inflammatory activity after HIIT (24–26). Otherwise, the concept of HIIT, performed at 85–95% of HR_{max}, has been associated mainly with increased cardiorespiratory fitness (11,27).

Disease activity as assessed by both the primary outcome measure PGA and the secondary outcome measures DAS44, ASDAS-CRP, and HS-CRP was either reduced or stable within both the HIIT group and the control group. It is conceivable that vigorous exercise in patients with PsA might increase disease activity, in particular enthesitis (7). Encouragingly, this was not observed.

At inclusion, the PGA score indicated higher disease activity than that judged by the DAS44 and hsCRP. Discrepancy between physicians' and patients' perception of disease activity is a well-known phenomenon (28–30). Both physicians' and patients' perception of disease activity as well as the hsCRP level influence the DAS. Furthermore, PGA could also be influenced by factors other than disease activity (31,32) (e.g., experience of pain for reasons other than inflammatory disease activity). Results of a recent study suggest an association between physical exercise and skeletal damage related to the Achilles tendon insertion in patients with PsA (33). However, the type of exercise was not defined. In our patients, SPARCC Enthesitis Index did not increase more in the HIIT group compared with the control group, and the ASDAS-CRP level showed a reduction after 3 months. A partial explanation may be that the supervised exercise was performed on a stationary bicycle versus a treadmill, minimizing mechanical stress to the lower limbs and back.

Interestingly, we observed that patients in the HIIT group had a clinically relevant improvement in fatigue at 3 months compared with controls. However, this difference in the fatigue score was not evident at 9 months when physical activity was not maintained. Although fatigue is a major problem in PsA (1), its etiology is not well understood. It could be partially explained by inflammation (34), and a higher degree of fatigue has been associated with higher disease activity as measured by enthesitis, joint count, and skin disease (1,35). In a multicenter cross-sectional study, it was shown that fatigue in patients with PsA was associated with female sex, level of education, skin psoriasis, enthesitis, as well as tender and swollen joints (1).

Table 3. Changes in outcome between patients in the control group (n = 35) and patients in the intervention group (n = 32) and changes within the groups from baseline to 9 months of follow-up*

	Baseline mean, both groups	Change from baseline to 9 months		Mean between-group difference at 9 months
		Control	Intervention	
PGA	40.41	−6.35	−5.36	0.99
95% CI	34.79, 46.02	−14.20, 1.50	−13.24, 2.52	−9.51, 11.49
P	–	0.11	0.18	0.85
Fatigue	48.74	−7.92	−2.72	5.20
95% CI	41.74, 55.73	−17.92, 2.08	−12.52, 7.08	−8.00, 18.41
P	–	0.12	0.59	0.44
DAS44	2.00	−0.34	−0.16	0.18
95% CI	1.84, 2.16	−0.54, −0.13	−0.37, 0.05	−0.10, 0.46
P	–	0.001	0.13	0.22
Pain	37.57	−7.94	−4.29	3.64
95% CI	32.49, 42.65	−15.39, −0.49	−11.77, 3.18	−6.23, 13.51
P	–	0.04	0.26	0.47
ASDAS-CRP	2.14	−0.17	−0.01	0.16
95% CI	1.91, 2.36	−0.46, 0.12	−0.30, 0.29	−0.23, 0.56
P	–	0.26	0.96	0.42
hsCRP†	1.87	−0.04	0.63	0.67
95% CI	1.33, 2.42	−0.69, 0.61	−0.22, 1.48	−0.39, 1.72
P	–	0.92	0.11	0.20

* Scores for PGA, fatigue, and pain were measured on a 0–100-mm visual analog scale. Baseline data for PGA, DAS44, pain, and ASDAS were available for 67 patients; baseline data for fatigue were available for 66 patients; and baseline data for hsCRP were available for 62 patients. All measures were adjusted for age and sex. See Table 1 for abbreviations.
† Expressed as the geometric mean.

Among our patients with PsA, the association between fatigue and female sex was possibly because two-thirds of the patients were women, but an association with disease activity was not apparent. In patients with RA, increased fatigue seems to be associated with increased pain (32). We observed no strong effect on pain intensity in parallel with the reduction in fatigue in our study. However, the baseline pain score among our patients was mild to moderately high (36), and thus the potential for a reduction in pain could be lower than that among patients with higher pain intensity levels. Another explanation for the reduction in the fatigue score could be an exercise-induced endorphin response (37) or improvement in aerobic capacity (38). Nevertheless, the effect of exercise on fatigue in our study is consistent with results of previous studies investigating physical exercise in patients with SpA and those with RA (39–41). Furthermore, graded aerobic exercise at 40–70% of HR_{max} has been reported to reduce fatigue in individuals with chronic fatigue syndrome (42).

After the 3-month intervention period, the patients were responsible for the exercise themselves, and less than one-half of patients in the HIIT group continued exercising. Moreover, in those who did exercise, the intensity level was usually reduced. Patients in the control group were encouraged to exercise, but only 18% managed to start with endurance exercises. The lack of persistence could explain why the effect on fatigue in the HIIT group was not sustained. This lack of persistence may emphasize that PSA patients need continuous motivation to perform physical exercise, and this notion has also been suggested by other investigators (41,43). The observed minor reduction in all of the outcome measures in both groups may be explained by the Hawthorne effect—that people change their behaviors when they know they are being observed (44).

A strength of the current study was the randomized design. Both groups had the same type and amount of follow-up, and the diagnosis was confirmed by an experienced rheumatologist before enrollment. In the HIIT group, adherence to the guided exercises was good, and the exercises were performed with a high intensity, according to the diaries. The withdrawal rate was only 12.5% in the HIIT group but was a little higher in the control group (17.1%). Moreover, disease duration and disease activity measured by the PGA score were comparable to those observed in other PsA patients in Norway (45), indicating that the external validity of our results is high. The baseline median swollen joint count was low, but a risk of flare caused by mechanical stress would be likely even with low disease activity. On the other hand, an improvement in disease activity would be less likely in patients with a low baseline swollen joint count.

The need for intraarticular injections during the study could be considered an adverse event. However, a total of 10 intraarticular glucocorticoid injections in each group during the total study period could be due to flares caused by a natural disease course. The injections were given at least 4 weeks prior to any follow-up and therefore should not affect the DAS44. Other limitations included the relatively small sample size, which reduces the precision of the estimated effects. Furthermore, ideally all of the HIIT sessions should be guided, but for practical reasons and time constraints of the participants, only 2 of 3 exercise sessions were supervised. This could have resulted in lower exercise intensities for the unsupervised sessions and consequently a smaller observed effect of HIIT between the groups. In addition, the control patients were allowed to practice endurance exercises from 3 to 9 months to enhance their willingness to participate in the study, which could mask potential long-term effects. However, only 5 of the 28 participants in the control group reported engaging in vigorous exercise during this period.

Furthermore, patients who volunteer to participate in a trial involving physical exercise might be more experienced with physical activity and exercise compared with those who do not participate, thereby reducing the generalizability of our results. In addition, the lack of blinded intervention and assessment could potentially have influenced the results. Moreover, patient-reported outcome measures might be difficult to interpret, because issues other than actual disease activity, such as permanent damage, psychological distress, and comorbidities, could influence the reporting (46). In addition, we cannot rule out the possibility that control patients might have performed endurance exercise during the intervention period. Finally, HIIT is a method of exercise that may be difficult to perform without guidance over time.

No clear effects on disease activity markers and pain were observed after HIIT in patients with PsA. However, fatigue improved during the period of HIIT. Thus, we conclude that HIIT was well tolerated in patients with PsA, as evaluated by measures of both disease activity and patients' disease perception. However, the benefit does not last if HIIT is not maintained. A challenge (and goal) for health care providers is to motivate and encourage patients to remain physically active.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Thomsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Thomsen, Bye, Hoff.

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Relationship of Joint Hypermobility With Ankle and Foot Radiographic Osteoarthritis and Symptoms in a Community-Based Cohort

Yvonne M. Golightly,[1] Marian T. Hannan,[2] Amanda E. Nelson,[1] Howard J. Hillstrom,[3] Rebecca J. Cleveland,[1] Virginia B. Kraus,[4] Todd A. Schwartz,[1] Adam P. Goode,[4] Portia Flowers,[1] Jordan B. Renner,[1] and Joanne M. Jordan[1]

Objective. To explore associations of joint hypermobility (a condition where range of motion is greater than normal) with ankle and foot radiographic osteoarthritis (OA) and symptoms in a large community-based cohort of African American and white adults ages 55–94 years old.

Methods. Ankle and foot radiographs and joint hypermobility data (Beighton score for joint hypermobility criteria) were available for 848 participants (from 2003 to 2010) in this cross-sectional study. General joint hypermobility was defined as a Beighton score ≥4 (range 0–9); knee hypermobility was defined as hyperextension of at least 1 knee. Standing anteroposterior and lateral foot radiographs were read with standard atlases for Kellgren-Lawrence grade, osteophytes, and joint space narrowing (JSN) at the tibiotalar joint, and for osteophytes and JSN to define OA at 5 foot joints. Ankle or foot symptoms were self-reported. Separate person-based logistic regression models were used to estimate associations of ankle and foot OA and symptom outcomes with hypermobility measures, adjusting for age, sex, race, body mass index, and history of ankle/foot injury.

Results. This sample cohort included 577 women (68%) and 280 African Americans (33%). The mean age of the participants was 71 years, with a mean body mass index of 31 kg/m^2. The general joint hypermobility of the participants was 7% and knee hypermobility was 4%. Having a history of ankle injury was 11.5%, and foot injury was 3.8%. Although general joint hypermobility was not associated with ankle and foot outcomes, knee hypermobility was associated with ankle symptoms, foot symptoms, and talonavicular OA (adjusted odds ratios of 4.4, 2.4, and 3.0, respectively).

Conclusion. Knee joint hypermobility may be related to talonavicular OA and to ankle and foot symptoms.

INTRODUCTION

Joint hypermobility is a condition in which the range of motion is greater than normal at most joints. The Beighton scoring system is the most commonly used measure for assessing joint hypermobility in clinical and research settings. This 9-point test assesses hypermobility of the trunk (forward bending with straight knees) and bilaterally of the first and 5th fingers, elbows, and knees (1). Typically, a cutoff point of 4 is used to define general joint hypermobility. Joint hypermobility is common in youth and is a lifelong condition, but its frequency in the population declines with older age due to the common joint stiffening that occurs with aging (2,3). Prevalence of joint hypermobility is estimated between 2% and 57% of the population, depending on the criteria used and

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[1]Yvonne M. Golightly, PT, PhD, Amanda E. Nelson, MD, MSCR, Rebecca J. Cleveland, PhD, Todd A. Schwartz, DrPH, Portia Flowers, PhD, Jordan B. Renner, MD, Joanne M. Jordan, MD, MPH: University of North Carolina, Chapel Hill; [2]Marian T. Hannan, DSc, MPH: Institute for Aging Research, Hebrew Senior Life and Harvard Medical School, Boston, MA; [3]Howard J. Hillstrom, PhD: Hospital for Special Surgery, New York, New York; [4]Virginia B. Kraus, MD, PhD, Adam P. Goode, DPT, PhD: Duke University School of Medicine, Durham, North Carolina.

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Address correspondence to Yvonne M. Golightly, PT, PhD, Thurston Arthritis Research Center, University of North Carolina, 3300 Thurston Building, Campus Box #7280, Chapel Hill, NC 27599-7280. Email: golight@email.unc.edu.

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SIGNIFICANCE & INNOVATIONS

- Reports of associations of joint hypermobility and osteoarthritis (OA) vary widely, potentially because hypermobility may affect each joint site differently.
- To our knowledge, this is the first large cohort study to examine the relationship of joint hypermobility with OA and symptoms at the foot or ankle.
- In a large cohort of adults ages ≥45 years, the associations of joint hypermobility and radiographic OA and symptom outcomes appear to differ by specific ankle and foot joints, even when considering age, race, sex, obesity, and injury.

the population studied (4–8). Joint hypermobility is more frequent among women than men (8), may differ by race (8,9), and is linked to obesity (10) and joint injury (11,12).

Key risk factors for osteoarthritis (OA), the most common form of arthritis and a leading cause of disability (13), include older age, female sex, obesity, and joint injury, which are similar risk factors to those seen in joint hypermobility. Of the lower body joints, most community-based OA studies have examined the knee and hip, and less is known about OA of the ankle and foot and their risk factors. In a previous study, which was, to our knowledge, the first community-based cohort study of older African American and white men and women (14), we demonstrated associations of older age, obesity, prior injury, and ankle symptoms (i.e., pain, aching, and stiffness) with radiographic ankle OA, but the relationship of joint hypermobility with ankle OA or symptoms was not investigated. No prior published cohort study has examined the association of joint hypermobility with foot OA or foot or ankle symptoms.

In clinical settings, joint hypermobility appears to be associated with OA, but evidence from larger cohort studies does not readily support this observation (15–19). Among these few published cross-sectional cohort studies, associations of joint hypermobility and OA vary. For the hand, positive associations between metacarpophalangeal joint hypermobility and first carpometacarpal joint OA were demonstrated in a population-based study of older adults in Reykjavik, Iceland (n = 384) (17), while inverse associations of general joint hypermobility and hand OA were noted in a study of a cohort of sibling pairs from the US and the UK (n = 1,043) and in an extended family of African American and American Indian descent (from a single founder born in the 1700s; n = 280) (18). In the same extended family, general joint hypermobility was inversely associated with knee OA (15), yet a positive association was observed among 100 women ages ≥50 years in a clinical population in the UK (19). No apparent associations were seen between general joint hypermobility and lumbar or thoracic spine OA in a study of 716 older white women in a community study in the UK (16). This lack of agreement may be due in part to differences in joint hypermobility definitions used in these studies, but also may suggest differences in the association of hypermobility and OA outcomes by joint site, as well as differences in the samples. Potentially, joint sites that are vulnerable to the biomechanic impact of joint hypermobility, such as weight-bearing joints of the foot or ankle, might contribute to poorer joint health. A study of 112 female soccer players demonstrated that joint hypermobility was associated with greater midfoot loading attributed to medial foot collapse, a condition that is linked to joint injuries (20). Furthermore, hypermobility of the knee is associated with altered neuromuscular strategies during walking, which may affect multiple joints along the kinetic chain including the ankle and foot (21).

The purpose of this study was to explore the associations of joint hypermobility with ankle and foot OA and symptoms in a large community-based cohort. Our primary hypermobility measure was general joint hypermobility, based on the commonly used Beighton score of ≥4. We also chose to examine knee hypermobility (the ability to complete the knee maneuver on the Beighton score criteria in at least one knee) because of: 1) the biomechanical connection of the knee with the ankle-foot complex, as supported by the altered lower body joint moments observed with knee hypermobility (21) and the poorer ankle joint health among knees with poor joint health (22,23); and 2) the possibility that older adults with general joint hypermobility may be less likely to achieve ≥4 Beighton score maneuvers due to joint stiffness with aging. We hypothesized that joint hypermobility (general and knee) would be associated with foot and ankle OA and symptoms.

MATERIALS AND METHODS

Study participants. The Johnston County Osteoarthritis Project is a prospective, ongoing, community-based study of OA and OA risk factors that began in 1991 (24). Participants included in this cohort are African American and white men and women ages ≥45 years who resided in 1 of 6 townships in Johnston County, North Carolina for at least one year. Baseline data were collected from 1991 to 1997 for the original cohort (n = 3,187) and from 1999 to 2003 for the enrichment cohort (n = 1,015), and follow-up visits of these cohorts were completed approximately every 5 years. Measurement of joint hypermobility (Beighton score criteria) was conducted during the 2003–2004 and 2006–2010 clinical examinations, but not during the 2013–2015 examination. Radiographs of the feet and ankles were first collected in the Johnston County Osteoarthritis Project (2013–2015). Radiographic, joint symptoms, and participant characteristics data collected during the 2013–2015 study visit for 908 individuals were used in the present analyses (Figure 1), at which time participants had aged to be ≥55 years old. For its duration, the Johnston County Osteoarthritis Project has been continuously approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill and the Centers for Disease Control and Prevention.

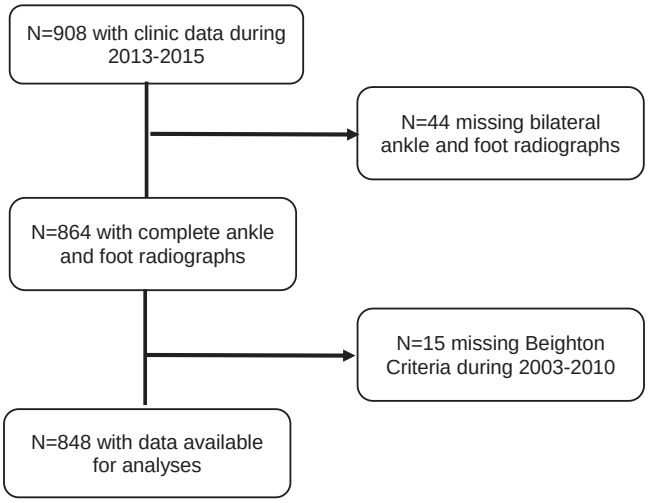

Figure 1. Johnston County Osteoarthritis Project participants available for analyses.

Joint hypermobility. The Beighton scoring system for hypermobility was used during the 2003–2004 and 2006–2010 clinical examinations in the Johnston County Osteoarthritis Project. The Beighton score criteria have demonstrated high intrarater and interrater reliability (Spearman's correlation coefficient r = 0.81–0.86 and 0.75–0.87, respectively) among women ages 15–45 years (25) and a high intraclass correlation of 0.91 among 20 patients with benign joint hypermobility syndrome or Ehlers-Danlos syndrome compared to 20 controls (26). The Beighton score criteria determine the ability to complete 9 maneuvers: passive dorsiflexion of the right/left 5th finger ≥90 degrees, passive apposition of the right/left thumbs to the forearm, right/left elbow hyperextension ≥10 degrees, passive right and left knee hyperextension ≥10 degrees, and palms on floor during forward trunk flexion with knees extended (1). As described by Beighton et al, one point is assigned for each completed maneuver (total score: 0 [unable to perform any maneuver] to 9 [performed all maneuvers]). Two examiners were trained by an expert in musculoskeletal assessment to conduct each of the Beighton score maneuvers; interrater reliability was high (κ >0.80) (27).

General joint hypermobility was defined as a Beighton score ≥4. Additionally, knee hypermobility, based on the ability to complete the knee maneuver in at least one knee, was examined specifically because of the biomechanical association of the knee with the ankle and foot.

Ankle OA. Ankle images in the Johnston County Osteoarthritis Project included standardized mortise and lateral views in standing during 2013–2015. Using an atlas (28), radiographs were read by an expert musculoskeletal radiologist (JBR) (intrarater reliability kappa value of 0.91) for Kellgren-Lawrence (K/L) grade, osteophyte (grade 0–3), and joint space narrowing (JSN; grade 0–3) grades of the tibiotalar joints. In this atlas, the K/L grades were slightly modified; 0 was selected for no radiographic findings of OA, 1 indicated "minute osteophytes of doubtful clinical significance"; 2 was selected when definite osteophytes and mild JSN were present; 3 was designated for definite osteophytes and moderate JSN; and 4 indicated both definite osteophytes and severe JSN. For the present analyses, ankle (tibiotalar joint) radiographic OA was defined as a K/L grade ≥2 (28). Radiographic features of OA were examined separately for osteophytes (grade ≥1 versus 0) and JSN (grade ≥1 versus 0) (29).

Foot OA. During 2013–2015, standing anteroposterior and lateral foot x-rays were read with a La Trobe atlas for foot radiographic OA (30) in order to measure osteophytes (0–3) and JSN (0–3) at 5 joint sites: first metatarsophalangeal, first cuneometatarsal, second cuneometatarsal, navicular-first cuneiform, and talonavicular. A joint with a score ≥2 osteophytes or ≥2 JSN was considered radiographic OA (30). According to the La Trobe Foot Atlas, foot radiographic OA was defined as ≥1 joint with radiographic OA within the same foot.

Ankle and foot symptoms. In order to evaluate the presence of symptoms consistent with OA, during the 2013–2015 follow-up visit participants were asked, separately for each ankle and foot, "On most days of any one month in the last 12 months did you have pain, aching or stiffness in your left/right ankle/foot?" (yes/no). This question has been supported for OA pain at other joint sites (knee and hip) (31) and considers the chronic pain experience and the fluctuations in symptom intensity over the course of a year. Symptoms were categorized as present separately for each foot and ankle based on an affirmative response to the above question. Additionally, the presence of ipsilateral symptoms and radiographic OA were examined for both the ankle (ankle symptoms + ankle K/L grade ≥2, along with an alternative definition of ankle symptoms + ankle osteophyte) and foot (foot symptoms + foot radiographic OA).

Demographic and clinical characteristics. Potential confounders included self-reported sex (men/women), race (African American or white), age (in years, continuous), body mass index (BMI) (weight [kg]/height [m^2]; continuous, calculated from clinical measures), and self-reported history of ankle/foot injury, which were collected during the 2013–2015 follow-up visit. History of injury was asked separately for each ankle and foot and was considered present based on an affirmative response to the question, "Have you ever injured your (right/left) (ankle/foot) badly enough that it limited your ability to walk for at least 2 days?"

Analysis. Participants with complete radiographic and Beighton score data were included in analyses (Figure 1). Chi-square statistics for categorical variables and *t*-tests for continuous variables were used to compare demographic and clinical characteristics (sex, race, age, BMI, injury) by hypermobility status. Separate logistic regression person-based models were used

to estimate associations of hypermobility (general and knee) with each ankle (K/L grade, osteophytes, JSN, symptoms, symptoms + K/L grade) and foot outcome (radiographic OA, symptoms, symptoms + radiographic OA), adjusting for covariates of sex, race, age, BMI, and history of injury at the joint site. Pairwise interactions between hypermobility and each covariate were examined at the 0.10 significance level.

RESULTS

Study participants. Of the 908 participants who attended a clinic visit from 2012 to 2015, 864 participants had complete ankle and foot radiographs. Of those participants, Beighton score data was collected for 848 (joint hypermobility) from 2003 to 2010. Those who were able to participate in the 2012–2015 clinic visit for whom Beighton score data was available were generally similar to nonparticipants in this analytic sample in regard to sex, race, and BMI, but were typically younger at their baseline visit (age 56 versus 62 years) and were more likely to have completed high school (85% versus 58%). Primary reasons for not participating in the clinic visit included death, moving outside of the study area, or being physically or mentally unable to participate.

Of the 848 participants available for these analyses, 68% were women and 33% were African American and had a mean ± SD age of 71.2 ± 7.6 years and a mean ± SD BMI of 30.9 ± 6.4 kg/m^2 (Table 1). More than 11% reported a history of an ankle injury, and 3.8% reported a history of a foot injury. General joint hypermobility was present in 59 participants (7%) and was most common among those ages <55 years (12.1%); 4.0% of participants had knee hypermobility in at least one knee. Presence of ankle osteophytes was defined in 74.5% of participants, while 6.6% had an ankle K/L grade ≥2, and 7.7% had ankle JSN.

Table 1. Characteristics of participants*

Characteristic	Total sample (n = 848)	Beighton score ≥4 (n = 59 [7.0%])	Beighton score <4 (n = 789 [93.0%])
Age, mean ± SD years			
55–94	71.2 ± 7.6	–	71.3 ± 7.6
56–88	–	70.2 ± 8.2	–
BMI (kg/m^2), mean ± SD (range)	30.9 ± 6.4 (16.1–60.2)	29.1 ± 6.1 (17.8–51.1)	31.0 ± 6.4 (16.1–60.2)
Sex, women	577 (68.0)	48 (81.4)	529 (67.1)
Race, African American	280 (33.0)	12 (20.3)	268 (34.0)
History of ankle injury	96 (11.5)†	10 (17.0)‡	87 (11.1)§
History of foot injury	32 (3.8)†	17 (28.8)	33 (4.2)§
Joint hypermobility, knee maneuver	34 (4.0)¶	12 (20.3)‡	22 (2.8)#
Ankle outcomes			
KLG ≥2	56 (6.6)	2 (3.4)	54 (74.3)
OST ≥1	632 (74.5)	48 (81.4)	584 (74.0)
JSN ≥1	65 (7.7)	2 (3.4)	63 (8.0)
Ankle symptoms	146 (17.2)	14 (23.7)	132 (16.7)
Ankle symptoms + KLG ≥2	18 (2.1)	1 (1.7)	17 (2.2)
Ankle symptoms + OST	119 (14.2)	12 (20.3)	107 (13.6)
Foot outcomes			
Foot rOA	189 (22.3)	12 (20.3)	177 (22.4)
First metatarsophalangeal rOA	88 (10.4)	7 (11.9)	81 (10.3)
First cuneometatarsal rOA	21 (2.5)	0 (0.0)	21 (2.7)
Second cuneometatarsal rOA	59 (7.0)	5 (8.5)	54 (6.8)
Navicular-first cuneiform rOA	41 (4.8)	4 (6.8)	37 (4.7)
Talonavicular rOA	49 (5.8)	4 (6.8)	45 (5.7)
Foot symptoms	176 (20.8)	17 (28.8)	159 (20.2)
Foot symptoms + foot rOA	46 (5.4)	4 (6.8)	42 (5.3)

* Values are the number (%) of participants unless indicated otherwise. BMI = body mass index; KLG = Kellgren/Lawrence grade; OST = osteophytes; JSN = joint-space narrowing; rOA = radiographic osteoarthritis
† N = 838 participants.
‡ N = 29 participants.
§ N = 787 participants.
¶ N = 845 participants.
# N = 786 participants.

Table 2. Ankle and foot outcomes with hypermobility measures*

Outcome	Beighton score			Knee maneuvers		
	Score ≥4 (n = 59)	Score <4 (n = 789)	Adjusted OR (95% CI)	Yes (n = 34)	No (n = 811)	Adjusted OR (95% CI)
Ankle KLG ≥2	2 (3.4)	554 (6.8)	0.55 (0.13–2.39)	3 (8.8)	53 (6.5)	1.45 (0.42–5.13)
Ankle OST ≥1	48 (81.4)	584 (74.0)	1.87 (0.92–3.80)	27 (79.4)	602 (74.2)	1.50 (0.62–3.66)
Ankle JSN ≥1	2 (3.4)	63 (8.0)	0.47 (0.11–2.03)	3 (8.8)	61 (7.5)	1.32 (0.38–4.56)
Ankle symptoms	14 (23.7)	132 (16.7)	1.55 (0.80–3.01)	15 (44.1)	131 (16.2)	4.41 (2.06–9.44)
Ankle symptoms + KLG ≥2	1 (1.70)	17 (2.15)	0.87 (0.11–6.97)	3 (8.8)	15 (1.9)	5.34 (1.37–20.79)
Ankle symptoms + OST	12 (20.3)	107 (13.6)	1.67 (0.81–3.42)	13 (38.2)	106 (13.1)	4.65 (2.07–10.45)
Foot rOA	12 (20.3)	177 (22.4)	1.08 (0.55–2.12)	7 (20.6)	181 (22.3)	0.91 (0.38–2.15)
First metatarsophalangeal rOA	7 (11.9)	81 (10.3)	1.36 (0.59–3.14)	3 (8.8)	85 (10.5)	0.82 (0.25–2.77)
First cuneometatarsal rOA	0 (0)	21 (2.7)	†	0 (0)	21 (2.6)	†
Second cuneometatarsal rOA	5 (8.5)	54 (6.8)	1.55 (0.57–4.22)	3 (8.8)	56 (6.9)	1.32 (0.38–4.65)
Navicular-first cuneiform rOA	4 (6.8)	37 (4.7)	2.16 (0.70–6.67)	2 (5.9)	39 (4.8)	1.23 (0.27–5.59)
Talonavicular rOA	4 (6.8)	45 (5.7)	1.65 (0.55–4.95)	5 (14.7)	43 (5.3)	3.05 (1.10–8.51)
Foot symptoms	17 (28.8)	159 (20.2)	1.54 (0.84–2.83)	12 (35.3)	163 (20.1)	2.40 (1.15–5.04)
Foot symptoms + Foot rOA	4 (6.8)	42 (5.3)	1.43 (0.48–4.28)	3 (8.8)	42 (5.2)	2.04 (0.56–7.21)

* Values are the number (%) of participants unless indicated otherwise. Adjusted for age, gender, race, ankle injury, and body mass index. OR = odds ratio; 95% CI = 95% confidence interval; KLG = Kellgren Lawrence grade; OST = osteophytes; JSN = joint space narrowing; rOA = radiographic osteoarthritis.
† No participants with hypermobility (Beighton ≥4 or able to complete knee maneuver) had first cuneo-metatarsal rOA.

Foot radiographic OA was present in 22.3% of participants; the first metatarsophalangeal joint was the most common site for radiographic OA (10.4%) of the 5 foot joint sites. Ankle and foot symptoms were present in 17.2% and 20.8% of participants, respectively. The combination of ankle symptoms + K/L grade ≥2 was rare (2.1%); 14.2% had ankle symptoms + osteophytes, and 5.4% had foot symptoms + radiographic OA.

General joint hypermobility. Overall, associations of general joint hypermobility and ankle and foot outcomes were not statistically significant (Table 2). No association was observed for foot radiographic OA with general joint hypermobility (adjusted odds ratio [OR_{adj}] 1.08, 95% confidence interval [95% CI] 0.55–2.12), There were no statistically significant interactions for general joint hypermobility with any covariate.

Knee hypermobility. There was a statistically significant increase in the adjusted odds of ankle symptoms, ankle symptoms + K/L grade ≥2, and ankle symptoms + osteophyte (OR_{adj} 4.41–5.34) in association with knee hypermobility (Table 2). Compared to those without knee hypermobility, the adjusted odds of talonavicular radiographic OA and of foot symptoms indicated a statistically significant increase (OR_{adj} 3.0 and 2.4, respectively) in associations with knee hypermobility. No associations were noted for foot radiographic OA or first metatarsophalangeal radiographic OA with knee hypermobility. No statistically significant interactions for knee hypermobility with sex, race, age, BMI, or injury were observed.

DISCUSSION

The results of this cross-sectional study demonstrated that the relationships of joint hypermobility with OA and symptoms outcomes at the ankle and foot vary by joint site. Notably, ankle symptoms, ankle symptoms + ankle radiographic OA, foot symptoms, and talonavicular radiographic OA were strongly associated with knee hypermobility. The foot radiographic OA definition that considered radiographic OA at 5 joint sites of the foot was not associated with general joint hypermobility nor knee hypermobility based on the Beighton score criteria. Associations of general joint hypermobility and ankle outcomes were not statistically significant.

Although general joint hypermobility has been considered a risk factor for increased musculoskeletal pain (2), we did not

find any objective evidence for an association between general joint hypermobility and ankle or foot symptoms. This differs from findings from a previous study (10) with a large cohort of 2,901 adolescents, which reported 82% higher odds of ankle/foot pain among individuals with general joint hypermobility versus those without hypermobility, but was consistent with results from the present study of an association of knee hypermobility and ankle and foot symptoms. This is interesting considering that a hypermobile joint may have altered biomechanics, and this joint, along with other joints in the kinetic chain, may become overloaded during repetitive motions occurring with daily or occupational activities (5). The joints may thus experience microtrauma resulting in increased joint pain (5). With knee hypermobility specifically, the reduced stability of the knee may contribute to malalignment of the knee, along with other lower body joints, altering knee joint loads and contributing to joint pain. In fact, both radiographic knee OA and knee malalignment have been associated with bone scintigraphic abnormalities of the contralateral ankle (associated with ankle joint symptoms) and forefoot (22). These data, taken together with findings from the present study, suggest that therapeutic interventions targeting mechanical factors, particularly for knee hypermobility, may be needed to prevent ankle and forefoot symptoms.

For radiographic OA, the only significant result was an association of knee hypermobility with the talonavicular joint. Our results suggested a possible link of joint hypermobility with a radiographic ankle outcome that relied on the presence of osteophytes (i.e., ankle osteophytes). Similar results were not seen for radiographic outcomes related to cartilage degeneration (e.g., JSN), but these analyses were limited considerably by small sample sizes. Additional investigations are needed to clarify whether joint hypermobility has a varying relationship with different joint tissue processes at the ankle. Local foot or ankle hypermobility is not assessed as part of the Beighton score criteria, and associations of joint hypermobility and radiographic OA in our analyses may have been different if validated measures for hypermobility of the foot and ankle were a part of the assessment of general joint hypermobility. Joint hypermobility of the first ray, which includes the first metatarsophalangeal, cuneometatarsal, and interphalangeal joints, has been considered by clinicians to be associated with hallux valgus, although there is debate as to whether hypermobility is the cause or the result of the deformity (32). The first ray has been clinically considered as hypermobile when it translates ≥1 cm superiorly and inferiorly with respect to the second ray, and this type of hypermobility has been qualitatively described and suggested to be related to hallux valgus and hallux rigidus, 2 conditions seen with first metatarsophalangeal joint OA (33,34).

Strengths of the present study include the use of a large community-based sample, inclusion of African American and white men and women participants ages ≥45 years, and the use of detailed data for these analyses (e.g., Beighton score criteria, foot and ankle radiography, foot and ankle symptoms). To our knowledge, this is the first large cohort study to explore associations of joint hypermobility with ankle and foot osteoarthritis and symptoms.

An important limitation of this study is that there were small numbers for some analyses due to low frequency of hypermobility and certain outcomes; thus, results should be considered preliminary rather than definitive. Additionally, the analyses were not conducted over time, and thus, we were unable to determine how joint hypermobility may contribute to the progression of ankle and foot symptoms and radiographic features of OA. Individuals in this cohort who were hypermobile in their youth may have experienced stiffening in the joints that is typically seen with aging. At the time of this study, our participants were over the age of 45 years when we assessed their joint hypermobility status with the Beighton score criteria; therefore, participants who at one time had general joint hypermobility (Beighton score criteria ≥4) now may be classified as not having this condition. The occurrence of joint hypermobility was 7% in this study, which is within the range of frequencies reported in other large cohorts of adults in this age group (15–18), but less than what is observed in younger populations (with up to 57% joint hypermobility occurrence) (5,35–37). It is important to note that the hypermobility measures (conducted from 2002 to 2010) were collected several years before the ankle and foot radiographs were acquired (2013–2015), and the presence of joint hypermobility may have been less frequent at the time of outcome assessment. Also, participants included in these analyses likely were not fully representative of the overall Johnston County Osteoarthritis Project cohort because they were more likely to be younger and to have completed more years of school than those who did not participate, although sex, race, and BMI were comparable for participants and nonparticipants.

In summary, joint hypermobility may be linked to ankle and foot symptoms and talonavicular radiographic OA. These findings should be further examined in other populations and in longitudinal analyses, particularly studies that may include data on joint hypermobility during younger ages, to determine the contribution of joint hypermobility over time to the incidence and progression of ankle and foot OA outcomes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Golightly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Golightly, Jordan.
Acquisition of data. Renner.
Analysis and interpretation of data. Golightly, Hannan, Nelson, Hillstrom, Cleveland, Kraus, Schwartz, Goode, Flowers, Jordan.

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"I Was Really Pleasantly Surprised": Firsthand Experience and Shifts in Physical Therapist Perceptions of Telephone-Delivered Exercise Therapy for Knee Osteoarthritis–A Qualitative Study

Belinda J. Lawford, Clare Delany, Kim L. Bennell, and Rana S. Hinman

Objective. To explore physiotherapists' perceptions before and after delivering exercise advice via telephone to patients with knee osteoarthritis (OA).

Methods. We performed a descriptive qualitative study (based on interpretivist methodology) embedded within a randomized controlled trial. Before and after providing exercise therapy to patients with knee OA, all 8 physiotherapists who were involved in the trial participated in semi-structured interviews via telephone. Interviews were audio recorded, transcribed verbatim, and thematically analyzed.

Results. Prior to delivering the intervention, physiotherapists thought that the telephone should be used only for follow-up rather than as the primary mode of providing care. They believed that telephone-delivered care would be convenient and cost-saving for patients, would provide increased opportunity for patient education, and also increase access to services, but that the lack of visual and physical contact with patients would be problematic. After delivering the intervention, physiotherapists reflected that telephone-delivered care exceeded their expectations, noting positive patient outcomes including improved pain, function, and confidence. The focus on communication allowed more personal conversations with patients and shifted patient expectations of care away from manual therapies and toward self-management. Numerous implementation considerations were identified, including the need for clinician training in communication skills, written resources for patients to supplement telephone calls, and careful deliberation of how to schedule telephone consultations during the usual in-person consultations in the clinic.

Conclusion. Although physiotherapists were initially skeptical about the effectiveness of telephone-delivered service models to patients with knee OA, perceptions shifted once they experienced delivery of care via this nontraditional method. Our findings suggest that firsthand experience may be necessary for physiotherapists to embrace new models of service delivery.

INTRODUCTION

Knee osteoarthritis (OA) is prevalent, affecting approximately one-fourth of adults (1). Clinical guidelines recommend exercise as a core component of nonsurgical management of OA irrespective of patient age, comorbidity, pain severity, or disability (2–5). Therapeutic exercise, particularly muscle strengthening, is associated with improvements in pain, function, and quality of life in patients with knee OA (6). In addition, given that patients with knee OA who are sedentary have poorer physical function (7,8), advice to increase physical activity is also imporant.

Of all allied health care professionals, general practitioners most commonly refer their patients with OA to physiotherapists (9,10). Physiotherapy care is typically provided in-person in clinics,

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Belinda J. Lawford, BMedSci, BHlthSci(Hons), PhD, Clare Delany, BPhysio, MHlth&Med Law, MPhysio, PhD, Kim L. Bennell, BAppSci(Physio), PhD, Rana S. Hinman, BPhysio(Hons), PhD: University of Melbourne, Victoria, Australia.

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Address correspondence to Rana S. Hinman, Centre for Health Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, University of Melbourne, Parkville, Victoria, 3010. E-mail: ranash@unimelb.edu.au.

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SIGNIFICANCE & INNOVATIONS

- There is some evidence that physiotherapists do not agree that telephone-delivered exercise therapy for patients with osteoarthritis (OA) is an acceptable, safe, or effective mode of service delivery, yet it is not clear why they hold these perceptions or whether these perceptions change after firsthand experience delivering care in this manner.
- Prior to delivering care for patients with knee OA over the telephone, physiotherapists believed that the telephone should be used only for follow-up with patients, and although they thought it would be convenient and cost-saving for patients, they expressed concern about the lack of physical and visual contact.
- After delivering care for patients with knee OA over the telephone, physiotherapists found that the lack of physical and visual contact was less of an issue than they had initially anticipated and were pleasantly surprised by the positive outcomes they were able to achieve with patients.
- Although physiotherapists may initially be skeptical about new models of service delivery such as telephone-delivered care, our findings suggest that firsthand experience helps to shift perceptions and may help facilitate future implementation of novel service models.

yet there is evidence that patients experience difficulties accessing these services (11,12). For example, although patients with OA believe that exercise therapy and physiotherapy are important, a range of system barriers contribute to poor uptake (e.g., lack of service provision, inconvenient appointment times, or venue location) (11,13). In addition, common barriers to participation in exercise in patients with OA include lack of access to facilities, conflict with routines, and transportation difficulties (12).

Telerehabilitation, which is the remote provision of rehabilitation services via telecommunication technology (14), is one way in which accessibility to services such as physiotherapy could be improved. Providing care via telephone is a potentially accessible and inexpensive option, allowing patients to consult with their care provider from their own home or workplace. In addition, the "hands-off" nature of telerehabilitation consultations might help foster patient self-management skills (15). There is emerging evidence that telephone-delivered care is effective and comparable to in-person consultation in patients with musculoskeletal conditions (e.g., those with OA and those who have undergone knee/hip arthroplasty) (16). For example, the UK physiotherapist-led telephone service PhysioDirect has been shown to be equally effective as usual care for improving physical health and to provide faster access to physiotherapy for patients with musculoskeletal problems (17).

Although there is evidence that telerehabilitation is effective, successful implementation is dependent on the perceived acceptability and usefulness of these services among patients and health care providers (18–20). We recently conducted a survey and found that physiotherapists in Australia, most of whom had no prior experience with delivering telerehabilitation, did not agree that telephone-delivered care would be acceptable, effective, or useful for patients with OA (21). In contrast, patients with knee and/or hip OA believed that telephone-delivered care would be safe, useful, acceptable, and would improve their OA symptoms (22). However, because our data from physiotherapists was collected via an online survey, it is not clear why they held these perceptions or whether their perceptions could be shifted with firsthand experience of delivering care via this nontraditional method. Thus, the aim of this study was to qualitatively explore whether physiotherapists' perceptions about telephone-delivered exercise therapy for patients with knee OA shifted once they had delivered exercise management advice to patients with knee OA over the telephone.

MATERIALS AND METHODS

Study design. This study had a longitudinal, descriptive, qualitative design based on interpretivist methodology and was nested within an ongoing randomized controlled trial (RCT) (Australian New Zealand Clinical Trials Registry ANZCTRN 12616000054415) evaluating the effectiveness of incorporating exercise advice and support by physiotherapists for adults with knee OA into an existing Australian, nurse-led, national musculoskeletal telephone service (23). The Consolidated Criteria for Reporting Qualitative Research checklist was used to ensure complete and transparent reporting of this qualitative study (24).

Participants. All 8 physiotherapists who delivered the intervention for the RCT were invited and participated in this qualitative study. Physiotherapists were recruited from Victoria, Australia, through the research team's clinical networks. Selection criteria included physiotherapy qualification, at least 2 years of professional experience treating patients with musculoskeletal disorders, and current Australian registration to practice. All participants provided written informed consent, and the institutional ethics committee approved the study.

Intervention. Details of the intervention have been described elsewhere (23). Briefly, research patients with knee OA were randomly assigned to 1 of the 8 physiotherapists and received 5–10 telephone consultations over a 6-month period. Physiotherapists devised goals and an action plan for each patient that involved both a structured home exercise program and a physical activity plan. The program and goals were adjusted as necessary throughout the intervention. Physiotherapists sought to provide support by increasing patient knowledge and understanding of

knee OA and the benefits of exercise and also worked to increase patients' motivation and confidence in completing, and adhering to, an exercise program. Before the first consultation, each patient completed a pretreatment questionnaire that provided information for the physiotherapists about clinical history, knee symptoms, physical limitations, and personal goals.

Each patient was provided with a detailed information folder, 3 resistance bands for home exercises, and access to a study website containing video demonstrations of each exercise. The information folder contained material about OA and its effective management, the role and benefits of physical activity, and strategies for fatigue management. The patients were also provided with exercise instructions and photographs, a diary to record exercise adherence and knee symptoms, and a template for a self-management plan. Each physiotherapist was also provided with an identical information folder with which to refer while speaking to the patients. Physiotherapists used online treatment notes to record health literacy topics discussed, clinical history, personal motivators, prescribed exercises, action plan strategies, and ratings of patient's confidence to carry out the action plan.

During the 3 months prior to the start of the intervention, physiotherapists underwent training in person-centered practice and behavior change support using HealthChange Methodology (http://www.healthchange.com/). This involved an initial 2-day training workshop, a period of practice consultations over 3 months, and a final training day. Briefly, the methodology involves: 1) a set of practice principles to guide effective communication and knowledge transfer, 2) a set of techniques used to identify and address barriers to behavior change, and 3) a 10-step decision framework that acts as a health behavior change clinical pathway to guide decision-making. To assist physiotherapists in using these skills throughout the intervention, a structured consultation framework (part of the HealthChange Methodology) was embedded in the online treatment notes. The training program and its impacts on the physiotherapists have been described in detail elsewhere (25).

Interviews. Two semi-structured interviews with each physiotherapist were conducted, including one in the week prior to the training program, and the other after participant recruitment for the trial was complete and the physiotherapist had completed all consultations with 75% of their allocated participants. The pre-intervention interview guide was used to ascertain the physiotherapist's beliefs about the likely effectiveness of delivering exercise therapy via telephone and their expectations about delivering the intervention (Table 1). The post-intervention interview guide was drawn from the Donabedian framework (26) (Table 1), which is used for quality assessment in health care and has been advocated as a useful model for reviewing physiotherapy services (27). According to the Donabedian framework, information about quality of care can be drawn from 3 categories: 1) structure (environment in which the service is provided), 2) process (clinician and patient activities involved in delivering/receiving care, including the clinician–patient relationship), and 3) outcome (effects of the care provided).

All interviews lasted ~40 minutes and were conducted over the telephone by the same investigator (BJL), a graduate research student who was trained in qualitative methodologies, is not a clinician, and had no other interactions with the physiotherapists. Interviews were audio recorded and externally transcribed verbatim. Pseudonyms were assigned to each participant for confidentiality purposes. All data were de-identified and stored in digital format on a password-protected university server.

Data analysis. The first stage of data analysis involved a more deductive content analysis approach in which the data were coded using the elements of the Donabedian framework as an overarching guide (28). Consistent with the aims of the study, a thematic analysis approach was used to examine both pre-interview and post-interview data (29). The purpose was to identify common patterns and ideas, which we subsequently grouped as themes. Interview transcripts were read by BJL after transcription and then re-read to identify topics and concepts within the data (i.e., coded). Similar or related topics were organized into categories and combined to form themes. Categories for post-intervention data were organized under each of the 3 elements of the Donabedian framework (i.e., process, structure, and outcome) (26). Categories and themes were separately reviewed and revised by both BJL and a qualitative expert (CD) who had no contact with the physiotherapists at any stage of the research. Overall themes were divided into subthemes, which were reviewed, discussed, and deliberated by all members of the research team (30). For reporting purposes, final themes were loosely grouped according to the Donabedian framework. To ensure credibility and confirmability of the data, another researcher (RSH) read all transcripts prior to discussion of the themes/subthemes that were developed by BJL and CD. All analytical steps were performed using standard word processing rather than qualitative analysis software.

RESULTS

Characteristics of the participants. The cohort (Table 2) was composed of an equal number of male and female physiotherapists, most of whom worked exclusively in private practice (63%), with a mean ± SD of 14 ± 8 years of clinical experience. At the time of the interview, physiotherapists had consulted with a mean ± SD of 9 ± 1 participants during the study and had completed a mean ± SD of 64 ± 22 telephone consultations.

Table 1. Pre-intervention and post-intervention interview guides

Pre-intervention	Post-intervention
1. Tell me what you think about telephone-delivered physiotherapy care. (How do you think telephone-delivered care fits into physiotherapy practice [not just for OA])? 2. Can you tell me about why you wanted to be involved in this study? 3. Telerehabilitation is defined as the delivery of rehabilitation services over telecommunication technology. Do you have any experience with telerehabilitation? Tell me about that. (Did you like it? What were the outcomes for you/the patient?) 4. Can you tell me what you think telephone-based physiotherapy services could offer people with knee OA? (How might it help people with OA? Do you see any advantages it could have over face-to-face physiotherapy?) 5. Do you see any potential disadvantages of telephone-based physiotherapy for people with knee OA? (What do you think might be challenging? Why?) 6. How do you think providing physiotherapy exercise advice and support over the telephone will compare to the way you usually treat a patient with knee OA in the clinic when you consult with them face-to-face? (In what ways will it be different? How will it be similar?) 7. I'm interested in your ideas about how you might gain an understanding of the patient and their knee condition over the phone. Tell me about that. (Is there anything that you think you would like to do but might not be able to?) 8. Tell me a bit about how you normally prescribe exercise to a patient in the clinic, and how you think prescribing exercise over the telephone will be different? (How will you teach the patients their exercise programs over the phone? What do you expect will be easy/difficult?) 9. Tell me a little bit about your typical communication style and the methods you use to build a relationship with your patients. 10. What sort of relationship do you think you will develop with the patient over the telephone in the Telecare trial, knowing that you won't see your patients face-to-face? (How will the telephone influence your normal communication style? How will you pick up on nonverbal cues?) 11. Tell me about what impact you think the Telecare intervention will have on people with knee OA? 12. How confident are you feeling about delivering exercise counselling and advice to people with knee OA over the phone? (Do you hope to learn anything yourself from this trial? Do you have anything else you would like to add about your expectations of being involved in the Telecare trial?)	1. What stands out most about your experience of being a physiotherapist delivering care in the trial? 2. During our first interview before the trial started, I asked you about your expectations of the study. Overall, do you think your experiences matched those expectations? (How did it meet/not meet your expectations? Was there anything that took you by surprise, that you weren't expecting? [prompt using their transcripts if necessary].) 3. What stood out to you as the best things about delivering care over the phone? (Did you think there were any clear advantages of delivering care via phone? Were there things you liked about it?) 4. Was there anything challenging about delivering care over the phone? (Was there anything you didn't like about providing care via phone? Did you have any difficulties at any time? Can you remember a particular conversation/treatment that went well or not so well? and why it went well/not so well.) 5. How do you think it compares to consulting with patients face-to-face in your rooms? (How/why was it different/the same or better/worse? If required, reflect specifically on patients with knee OA.) 6. How did the calls fit into the structure of your working day? (Did you make the calls in your usual working hours? Did you make the calls from your usual workplace or elsewhere? How did you feel about these locations? Which locations were easier/more difficult?) 7. Tell me how about you assessed each patient… How did you feel about the depth of understanding you gained of each patient's problem? (How did this differ from face-to-face practice? Anything you couldn't do that you wanted to? How did being unable to touch or see the patient influence your assessment? Did you refer to the pre-treatment survey/information that the patient provided? Was it useful?) 8. Tell me about your experiences prescribing a structured exercise program and general physical activity plan over the phone. (How did you instruct/teach the patients their exercise programs? What was easy and what was difficult? Did you do anything different compared to what you would normally do face-to-face?) 9. How well do you think your patients understood the exercises and physical activity plan you prescribed? (How confident were you that your patients could perform the exercises safely and effectively at home on their own? How confident were you that your patients would adhere to the exercise/activity programs?) 10. I would like you to reflect on your communication with your patients and the relationships you developed. What are your thoughts about this? (Did you change anything from what you normally do? What was easy/what was challenging?) 11. What do you think the main outcomes were for your patients in this study? (Did patient symptoms change? Did patient function change? Did patient knowledge/attitudes/confidence change? Did they achieve/not achieve their goals?) 12. Based on your experiences, what would you think about using the phone in the future to consult patients with knee OA? What about other patients, not just ones with knee OA? (What advantages/disadvantages do you see that the phone offers over in-person visits? What would your preference be for delivery of exercises? Why? Is there anything you would change about such a service, based on your experience in this study? If you were in charge of training physios to give advice and treatment over the phone for OA, what would you introduce to the training? Do you have anything else to add?)

Table 2. Characteristics of the 8 physiotherapists*

Pseudonym	Sex	Work setting	Years of clinical experience	Previous experience delivering telerehabilitation	No. of patients (no. of telephone consultations completed)†
Karen	Female	Private and public	20	Yes (via Skype)	10 (92)
Luke	Male	Private	4	No	9 (61)
Simon	Male	Private	15	No	7 (42)
Jane	Female	Private	7	No	10 (83)
Maria	Female	Public	28	No	10 (81)
Emma	Female	Private and public	14	No	8 (27)
Gavin	Male	Private	5	Yes (via Skype)	9 (74)
Ian	Male	Private	17	No	8 (52)

* The mean ± SD years of experience was 14 ± 8. The mean ± SD number of patients (number of telephone consultations completed) was 9 ± 1 (64 ± 22).
† At the time of the interview.

Pre-intervention perceptions of telephone-delivered care (Table 3). The following 5 themes arose at the pre-intervention stage.

Telephone is only for follow-up. Most physiotherapists tended to use the telephone in their clinical practice only to check in on their patients and for follow-up after an in-person consultation. The telephone was not viewed as a primary mode of providing care.

Patient convenience and cost-savings. Physiotherapists believed that telephone-delivered care would be convenient for patients, and that allowing patients to consult from their own home could make patients feel more comfortable talking about their condition and/or engaging in an exercise program. Some of the physiotherapists also thought that telephone-delivered care could reduce patient costs associated with accessing physiotherapy services.

New opportunities. Physiotherapists believed that telephone-delivered care could provide increased opportunities to educate patients about OA. In addition, they thought that telephone-delivered care could allow a wider variety of patients to access physiotherapy, such as those living in remote areas or those who would otherwise find it difficult to attend clinics in person.

Unable to see or touch patients. Physiotherapists were concerned about being unable to see or touch patients when consulting via telephone. They believed that this could make assessment of patients difficult, due to inability to observe exercise techniques or quality of movement. Physiotherapists thought that relationships with patients might be adversely impacted, and that it could be difficult to develop rapport. They also believed that they might experience difficulties communicating, particularly if the patient was unable to clearly describe his or her condition or movement difficulties. Physiotherapists thought that the lack of visual and physical contact would limit the strategies available to them when teaching patients an exercise program.

Improved communication skills needed. Physiotherapists believed that, compared to traditional in-person consultations, more effective communication skills would be needed to consult via telephone, including clear questioning and careful listening by both themselves and the patient. Physiotherapists believed that, in order to supplement this, it would be necessary to provide patients with pictures or videos of each exercise so that patients could gain an adequate understanding of the exercise technique.

Post-intervention perceptions of telephone-delivered care (Table 4). The following 4 themes arose post-intervention.

Exceeded expectations. Physiotherapists found that their experiences providing telephone-delivered care exceeded their expectations, resulting in new enthusiasm for this model of service delivery. The lack of physical and visual contact was "less of an issue" than anticipated. Physiotherapists were also surprised to discover that they had developed a strong rapport with patients over the telephone, and that patient adherence to their exercise program was high.

Focus on communication. Physiotherapists acknowledged that consulting via telephone forced them to focus on effective conversations with their patients. This allowed them to talk at a more personal level with patients compared to talking to them in person in their usual clinical setting. Consulting via the telephone, with its inherent focus on communication, caused a noticeable shift in patients' expectations of physiotherapy care, in that they did not expect to receive "hands-on" therapy and seemed more willing to self-manage their condition.

Positive outcomes. Some physiotherapists were surprised by how effective the intervention was for their patients.

Table 3. Pre-intervention quotes relating to physiotherapists' expectations about delivering exercise therapy via telephone*

Theme, subtheme	
Telephone is only for follow-up	
Check in on patients	Karen: "I guess it's usual in practice that you end up having phone calls with some of your patients – often when things aren't going so well or they want to call you to check with something." Luke: ". . . telephone care the way I see it is probably more of a follow-up call after you've seen someone." Emma: "I think a lot of follow-up stuff could be done over the phone – checking in terms of checking how people are complying with exercise programs and monitoring whether they're having flare ups and things."
Not primary mode of providing care	Jane: "All of my experiences in physio have been in-person–home visits in the clinic. You certainly do liaise with people over the phone, but not really any – I don't think telephone-based consultations has been widely used at the moment as a way of treating people." Maria: ". . . with my work at the [hospital] I probably do call some patients . . . but it's not sort of – it's more about follow-up." Luke: ". . . you would see someone face-to-face and then you may ring them three days later and just go 'look, how are you going?'. . . So I suppose from that point of view I do use it, but I don't use it as a primary source of care."
Patient convenience and cost-savings	
Convenience	Karen: "I guess cost, time, no travel obviously, convenience I think is a big thing I think people find it really difficult to schedule appointments . . . People find it really difficult to fit in their jobs, they've got family responsibilities, those kinds of things, whereas a phone call you can basically do anywhere – I think that's convenient, it would be a big help." Emma: "I think certainly for people who are working or are busy and they can't get to a clinic, I think that's often a limiting factor for some people attending the physio and this can make it more convenient and fit into what works for their lifestyle I think there'll be a lot better compliance and a lot better engagement."
Reduced cost for patients	Karen: "I think cost is a big issue with physio, particularly when you want to see someone over a bigger period of time . . . I think potentially having a reduced cost with phone-based physio presumably might be more cost-effective and might give an opportunity for a bigger chunk of input to get people you know at a higher functional level." Luke: ". . . potentially some physio clinics might go ok so we'll offer it at a cheaper rate because well you know there's no overheads there's no equipment, there's no administration stuff that I'm paying, I'm literally just jumping on a call and I can make that call potentially after hours or when it's suitable for me as well."
Patient comfort	Jane: "I think also people are often a little bit more comfortable in their own home, so they might be more willing to participate with home-based exercises than some people. I know some people don't like getting out and coming in to clinics." Maria: "I'm thinking that maybe the contact would be more regular, and once again at a time and place that's more convenient for the patient, so they're sort of in the mindset that this is what they're there to do at that point in time."
New opportunities	
Advice and education	Karen: "[telephone-delivered care] offers them an opportunity to ask questions, I think when people have got chronic diseases or knee OA, people often really want some clarity about – particularly related to exercise – but also related to what's reasonable related to symptoms and I think [phone-delivered care] would give them structure" Emma: "I think [telephone-delivered care is] possibly a big way of the future. I think a lot of what I guess current research into back pain at least shows that advice is one of the most powerful things you can give the patient, and obviously in terms of patients being busy and time poor, being able to do that over the phone at times that suit them. . . I think there's a big market for it."
Access	Jane: "I think that we'd be able to access clients – or different clients, so people that have difficulty accessing the community, difficulty with transport, non-ambulant. I think a lot of people who struggle with appointments – we'd be able to reach a wider variety of the population." Emma: "[over the phone] you're not limited by where people live, so if people are living more remotely you can still provide them with good treatment over the phone. And areas where they might not have access to physio, that's a bit advantage. And I guess people with children and people who just can't get to the physio. It opens up a whole new market."
Unable to see or touch patients	
Difficult to assess patients	Karen: "I think that physios do a lot of observation, I feel like that's a normal thing to do when you're assessing someone obviously, but also looking at their treatment and their quality of movement and those sorts of things. So they're the things I feel a little bit less clear about – how that fits in [to telephone-delivered care]." Luke: "I think that [telephone-delivered care] really I suppose takes out the power of our observation skills . . .just trying to get an understanding of what the patient capabilities are over the phone, because obviously I can't see them, so you know are we going to give them something that's far too hard or far too easy, you probably won't be able to regress or progress quickly, and then what's the quality of that movement pattern like . . . you know all the things that we've got that we take for granted face-to-face might be a little bit of a challenge." Maria: ". . . in terms of just the objective assessments we're going to have to rely on what that patient is telling us . . . obviously it's not quite the same as actually eyeballing someone and, you know, possibly putting your hand on someone or watching what they're doing or, you know, watching how well they move . . . I think just getting used to having no eye contact for me personally might be a bit of a hurdle."

(continued)

Table 3. *(Cont'd)*

Theme, subtheme	
Relationships and rapport will suffer	Karen: "I think also there may be issues with the relationship you build . . . I can see on the phone that you don't know what someone looks like, they don't know – they're only working off how you express yourself verbally." Gavin: ". . . it's going to be hard to develop that sort of close relationship I suppose, because when we're so used to meeting people and visualizing them and seeing them and having sort of a face to a name and that sort of thing as well, and sort of things we'll traditionally do as far as meeting people is concerned, and that's a tricky bridge." Ian: "I think [a strong relationship] comes down to being able to see that person face-to-face, so again we'll lose that in a phone call. . . [it] will feel distant, I think it will feel very removed, and maybe a bit colder to start with, because you can't use other cues or body language to express yourself."
Difficulties communicating	Karen: "I guess you're just relying on the patient to give you clear information, and if they don't have very good – some people just aren't very clear communicators or they don't have very good body awareness, and I think there could be issues with some patients." Jane: "I think the disadvantage is a little bit in the assessment, where without being able to see and touch and feel as a physio we rely on that information we get from the client a lot more. Which in some cases might be a disadvantage if they're not very good at self-reporting or not very aware at understanding questions you're asking." Ian: "I think it will be different, and I think there'll be a lot more explanation needed over the phone and clarification about what we're trying to get that person to do . . . So yeah we're going to have to rely a lot on good communication skills I think, on both parties."
Limits ways to teach exercise	Karen: "I guess you can't demonstrate, and you can't observe the patient doing it, and you can't touch them to ask them to move in a different way – all the feedback is going to have to be verbal, and they're going to have to tell you whether they think they're doing it in the way that you want them to . . . So I guess you've just got limited – more limited options, in terms of how you would go about prescribing exercise." Luke: "In terms of exercise delivery and getting the specific exercises I think, from my point of view, that might be a little bit of a challenge because of how physios are all about getting exercise quite detailed and specific to our patient, when that's over the phone that might be a bit of a challenge" Emma: "I guess with some exercises, a demonstration often helps, or taking the patient through the actual exercise and showing them how to do it . . . I guess describing exercises over the phone will be a skill I'll have to learn as well."
Improved communication skills needed	
Clear questioning	Karen: "I can only assume that you need to compensate for the fact that you can't smile, nod and give them eye contact by being a better verbal communicator or there must be ways that you can show that you're an active listener and they've got your attention, verbally that's just going to have to be a stronger component of what you say." Jane: "Asking them lots of questions about what makes them worse, what makes them feel a bit better, can they do – get them to do some things while they're on the phone with you – get up and down from the chair, get them to do some functional activities while they're on the phone. . . I guess some of the things that we would normally want to do from an assessment side of things we just have to ask them to do it."
Careful listening	Simon: "I think we take a lot of cues from facial expression, body position, all those sorts of things I think that's certainly something that's going to be, picking up all those sorts of things and tone of voice and those sorts of things may be slightly more difficult to sort of make sure you are hitting the mark." Gavin: "You can listen for obviously some cues, with pauses and their language and – it's not something that I've had any training with but you tend to pick up a couple of things along the way and if they're emotive about what they're talking about it will often come up across with their tone or their rate of talk."
Providing pictures or videos of exercises*	Karen: "I think with the right type of extra audiovisual pictures or other material that I can still see that it should be relatively straight-forward to talk someone through something." Luke: ". . . even maybe you know a booklet of exercise is really good but maybe even a – I'm just thinking – some kind of visual sort of DVD or something of actually forming the exercises through range and then actually potentially someone talking verbally how you do the exercise." Jane: ". . . that would be ideal – if they've already got some resources with some pictures, so they know those details, for example if they've got something at home with an exercise quads over fulcrum, then I can get them to refer to the diagram, the equipment that they either do or don't have, and then just talk them through the set-up, as to how it works."

* At the time of interviewing, physiotherapists were not aware that participants would be provided with images of each exercise as well as access to exercise videos.

In particular, physiotherapists noticed improvements in patient pain and function and increased confidence to self-manage. Physiotherapists found that telephone-delivered care was convenient for their patients, because they did not have to travel to clinics in-person and could easily fit the consultations into their lifestyle.

Implementation considerations. Physiotherapists believed that, in some circumstances, it would have been helpful for them to see the patient's knee or observe the patient walking in order to get a better understanding of his or her condition and to observe the exercise technique used. However, physiotherapists found that they were able to work around the lack

Table 4. Post-intervention quotes relating to physiotherapists' experiences delivering exercise therapy via telephone

Theme, subtheme	
Exceeded expectations	
Fewer issues than expected	Emma: "I guess I was really pleasantly surprised with how well the program worked with the patients that I had through. I thought there'd be more difficulty communicating just via phone and getting people to comply . . . it probably exceeded my expectations, to be honest." Ian: "Initially I thought [the lack of face-to-face contact] would be hard. I thought there'd be some more barriers to being able to achieve the physio service that we wanted. But I actually found it a lot easier than what I expected. And I think patients were also on board and willing." Simon: "I guess I was concerned that [exercise prescription] was going to be tricky, but it was probably really easy and clients seemed to be pretty comfortable with getting the exercises done. So the one challenge that I thought was going to be, that it really didn't exist."
Strong rapport	Emma: "I was pleasantly surprised at how well rapport could be built just over the phone. And that you don't really need that visual – I was surprised by that." Karen: "I don't think you lose anything on an interpersonal relationship level which, in the past . . . that had been my biggest concern: you lost some connection you have with the participant. But I don't think you'd lose anything – I think that you can gain someone's trust and you can develop a good working relationship as a patient and therapist through the phone . . . I don't know that it matters that they can't see you." Jane: "I think the thing that surprised me the most was how much rapport you could build with people over the phone. I expected that to be not quite the same as the way you would build rapport with someone in person, but I felt like I was able to do that over the phone."
Patient compliance	Karen: "I think the compliance with the exercise routine [in this trial] I think is definitely a standout compared to what I would consider my usual experience . . . I think the participant being in their own home probably helps to reinforce to them that being at home and doing the exercises themselves is actually something that they do have to tackle by themselves." Simon: "They were a really easy and positive cohort to work with and seemed to all report really good changes really quickly, and certainly implemented all of the specific exercise stuff really easily into their lifestyle . . . probably compliance was really easy, rather than complex or difficult." Luke: "[Before the intervention] I would have had doubts about the impact that we could have made and if we could make changes and I was potentially questioning the compliance of our patients and things like that, but I think I have been overly surprised with it."
New enthusiasm	Maria: "I think it would be a fantastic program to roll out . . . it is a relatively easy and I would hope, cost effective way, of getting that information out to these people and assisting them to make significant changes to their lifestyle, positive changes." Emma: "I think that it's something we, as physios, should be doing. It's so easy, it makes the physio so accessible to so many people and you realise that a lot of the time the most important treatment from a physio is actually that discussion and the talking through problems and the educating. If we can, as a profession, get on top of that I think the chronic disease – especially knee OA and back pain and things like that – there is such a scope to have such a huge impact with very little cost." Jane: "I think it was very effective. I'd happily do that . . . I definitely think in those instances where the general course of treatment is exercise and advice, I think that would be perfectly effective over the phone."
Focus on communication	
More personal conversations	Emma: "I was trying not to talk too much at the patient which is kind of what I do in clinics. Like, you get there and you have your thrall of – the lecture of 'I'll tell you what's wrong with you.' And actually holding back and letting them talk a lot more [over the phone] has been quite powerful as well as a good lesson for me." Maria: "You had the time to really investigate what was motivating them or what their main issues were. Whereas I guess if you were more face-to-face and doing more of a traditional role you would be more focussed on their range of movement and their strength . . . it is more about finding out more about them as a person and helping them to remain motivated to continue with the program. I think over the phone facilitated that to a certain degree."
Shifts patient expectations	Emma: "It changes everyone's expectations, especially for patients, when treatment is delivered over the phone . . . probably when I treat face-to-face I guess there's the expectation that a physio has to treat. So you've got to get your hands on, you've got to touch and probably reinforce that whole disability illness behaviour. Whereas, on the phone . . . you're straight into discussing [health] management and exercises and it just works so much better. It's probably influenced how I'm treating in the clinic a lot more as well. I'm doing a lot more exercise coaching, really, as opposed to actual treatment." Jane: "I think it did take away from that expectation of manual therapy. I know when people come into the clinic and they're coming in for a similar issue . . . because you're in the room with them quite often there is an expectation of manual therapy and being on the phone it just completely takes it out of the equation. You don't have to quite justify why you're not doing the manual therapy quite as much because it's just not an option."

(continued)

Table 4. *(Cont'd)*

Theme, subtheme	
Positive patient outcomes	
Improved pain and function	Emma: "Definitely increased functional capacity. A lot of them – nearly all of them – couldn't walk far, couldn't do stairs, couldn't walk up hills. And the majority by the end of it, were doing that . . . functional improvements probably more so than pain, but learning to function better with the pain." Jane: "I find with a lot of the people I saw, I feel like we had some great effectiveness. The best part is I feel like I was effective and that I've been able to help the majority of people have been dealing with . . . A lot of them have returned to things they haven't been able to do for a very long time."
Confidence	Maria: "I am thinking of a couple of clients who it seems to have made a huge difference to their lives. For example, one client, she was in tears the first time I spoke to her and was so terrified about her knee pain and then by the end of it she was very much a different person, was really happy, was really positive and felt quite capable to continuing and working on the exercises and found great benefit from that." Jane: "The biggest difference is a lot of them have a lot more confidence that they went into the program with the attitude of, 'I'm going to have surgery,' and at the end, 'I might be able to do this.' I think that was the biggest difference and got that with pretty much everybody; that they do feel confident that they will be able to self-manage if they do the right thing."
Convenience	Gavin: ". . . obviously the flexibility for the participant and the fact that, you know, obviously they don't have to be at a location at any particular time . . . And for the most participants they sort of just were in the comfort of their own home, and that's certainly a perk." Ian: "The best things are the flexibility with appointment times, so you can access people at various times of the day, and I guess it becomes a little bit easier for patients who can't get into a clinic at a certain time or are restricted with hours of the day."
Implementation considerations	
Desire to see some patients	Maria: "Sometimes I felt with certain clients that I would really like to have been able to see exactly what they were describing and perhaps see what their knee joints looked like and how they were actually walking." Emma: "I guess, some patients – there's a couple that were getting aggravated by a similar exercise, and I get the – trying to describe over the phone what they were doing – that was probably the hardest thing. If I could have got eyeballs on them and said, 'You're doing XYZ wrong.' That may have made it easier, but you can work around it."
Erring on side of caution	Maria: "There was one patient in particular who was quite elderly and her knees sounded like they were pretty bad in terms of arthritis. I ended up erring on the side of caution very much with her and being very gentle in terms of what we were doing." Jane: ". . . for me, I do like watching people walk. I like to watch people get out of the chair. They're the two things I really like being able to do. I guess I would ask people about those activities and just ask them to describe what's happening – I think if I wasn't sure I'd just play it safe with my advice." Luke: ". . . sometimes I would just, particularly that first week, deliberately start low level as well to really start on the easier bands just because I wanted to know the next week when I called them how they responded. Even if I thought they could have handled more, I just wanted to know. So I always felt we'd started lighter than what I should have."
Need written material and resources	Jane: "The ability to do it over the phone was dependent on having those resources . . . I think the effect and the ability to do it on the phone is, in part, dependant on them having access to resources. I'm not sure it would go quite as well if you just called someone and they didn't have anything else in front of them." Ian: ". . . having the information already in the patient's hand is definitely an advantage because they've got the tools that they can just refer to at their fingertips. That works in our favour, so we don't have to provide that information or put together the exercise programmes. They've got all the advice and the exercises there with them. That's definitely an advantage."
Safety net	Gavin: ". . . obviously because they're in the program they've generally been screened pretty well to being specific to one condition. So, I don't know how well that would go in a different context if we were trying to treat different conditions." Karen: "There has to be some criteria or tightness around people's diagnosis and their issues . . . If you've got a patient – they're there to see you for knee OA and there's some clarity around that and this studies their biggest functional limitation or technical issue, then they're stable to do exercise and you're confident they do exercise then I think it's a great medium to treat people with."
Training is necessary	Maria: "I certainly think the health coaching training we had was really useful because that was all about, I guess, assisting patients to become self-managed themselves, basically. It is kind of what we do in physio but I don't think we are really trained specifically to do that as well as it could be and that needs to be the emphasis with this sort of [telephone] program." Karen: "For most physios, [telephone-delivered care] would be a very big departure from their standard clinical practice face-to-face. I think there's a huge amount of training that would need to be done . . . Communication skills or health coaching kind of things."

(continued)

Table 4. *(Cont'd)*

Theme, subtheme	
Scheduling	Luke: "I work quite fast-paced in private practice so if I got a little bit behind or things like that then I'd be calling my patients late . . . So I found it a convenient thing just being able to [do the telephone calls] from home." Ian: "Probably the time and the paperwork [was a challenge] . . . trying to fit the service into what we do here day to day, so, with getting ready for the telephone call, there's a bit of preparation time, there's opening up files, there's getting documents ready, and then there's the paperwork to do afterwards. So, trying to get that done within a normal working day in the clinic was probably a little bit of a challenge at times." Simon: "... probably for me as a clinician, doing a one-off call here or there probably used up a lot of time. It probably wasn't as time efficient as I thought it could be... So, tricky for me going forwards in regards to thinking about this application of it in private practice. I think you'd almost have to be all in and have a day or two a week with lots of clients and lots of referral and continuity to that to make it applicable."

of visual contact, often by "erring on the side of caution." They valued the written materials that were provided to patients, including exercise instructions, pictures, and video links, which helped them to prescribe exercises effectively. Physiotherapists acknowledged that there was a "safety net" in place with the trial, because each patient had been screened prior to receiving the telephone-delivered care. Physiotherapists expressed some difficulty scheduling telephone consultations during their usual day of face-to-face consultations, with most opting to make the telephone calls on days on which they were not working in the clinic or after hours. Physiotherapists believed that training in communication and/or health coaching is important to effectively deliver care over the telephone.

DISCUSSION

The aim of this study was to investigate whether the experience of providing telephone-delivered exercise therapy to patients with knee OA shifts physiotherapists' perceptions about such services. We observed that although physiotherapists may initially be skeptical about new models of service delivery such as telephone-delivered care, firsthand experience can help shift their perceptions about the challenges associated with delivering these services, which may therefore help facilitate the future implementation of such services.

Prior to the intervention, the physiotherapists participating in our study expressed some concern about the lack of physical and visual contact with patients when consulting via telephone and believed that their relationship and rapport with patients would suffer. These expectations of telephone-delivered care reflect those revealed in a recent qualitative study that aimed to explore service provider's perceptions of telerehabilitation for patients referred to public neurosurgical and orthopedic specialist services (31). The 15 physiotherapists who were interviewed in that study, most of whom had no prior experience with telerehabilitation, believed that telerehabilitation would have some limitations when compared to standard in-person care. These limitations included difficulties building rapport, inability to perform hands-on techniques, and having reduced treatment options at their disposal. These findings also broadly reflect the findings from our recent survey of physiotherapists' perceptions of telephone-delivered exercise therapy, in which most respondents did not agree that telephone-delivered care by a physiotherapist would be effective, safe, or acceptable for managing patients with knee and/or hip OA (21).

However, we found that our physiotherapists' perceptions about the challenges associated with providing telephone-delivered care shifted after firsthand experience. After delivering the intervention, physiotherapists believed that they experienced fewer problems than anticipated, they developed a strong rapport with patients, and adherence with prescribed exercise was high. Consequently, most physiotherapists had developed increased enthusiasm for telephone-delivered care. This disparity between expectations and experiences may be partly due to the fact that physiotherapists traditionally are not trained to provide care remotely or without physical and visual contact with their patients. In fact, entry-level physiotherapy training typically focuses on biomedical models of care (i.e., biologic aspects of injury or pain), with particular emphasis on assessment and treatment of physical strength, movement, and function (32). This focus is also apparent in the current "culture" of physiotherapy practice, which emphasizes "hands-on" anatomical, biomedical, and biomechanical models of care (32). Inaccurate beliefs about the benefits of exercise for patients with knee OA may also have contributed to the mismatch between expectations and experience, given that a survey of UK-based physiotherapists showed that only 56% of physiotherapists largely/totally agree that knee problems are improved by exercise (33).

The importance of firsthand experience is highlighted by research investigating how clinicians change their practice. For example, one study involved interviews with 23 clinicians (nurses, allied health care professionals, and an Aboriginal health worker) to explore how attitudes and beliefs influence the implementation of lifestyle risk factor management in primary health care (34). Interviewees believed that to feel confident providing an intervention, they needed to understand how to do so through direct experience with patients. In another qualitative study, 15 primary care physicians were interviewed in order to explore their perceptions about changing their clinical practice (35). These phy-

sicians believed that in order to overcome feelings of discomfort when introducing new practices or ceasing current practices, direct experience was required. They also believed that successful "unlearning" of habits (e.g., prescribing exercise without visual or physical contact as required by our study physiotherapists) required repeated experience using the practice change. Our findings suggest that for physiotherapists to feel confident and comfortable delivering care via nontraditional methods, exposure or direct firsthand experience is required.

Another previous study qualitatively explored physiotherapists' perceptions about delivering care via telephone. Sixteen physiotherapists who delivered care via the UK PhysioDirect telephone service, which provides initial assessment and advice for patients with varied musculoskeletal problems, were interviewed before and after experience (36). Prior to the experience, the main concerns expressed by physiotherapists included being limited to providing only generalized treatment, given their inability to observe patients, and being unable to communicate effectively or develop rapport via telephone. After experience, physiotherapists found that they were indeed able to provide only generalized advice, that telephone calls restricted their normal therapeutic relationship and rapport, that telephone-delivered care impaired continuity of care (because patients in the PhysioDirect service are unlikely to speak to the same physiotherapist more than once), and that it disengaged patients (because few tried to re-contact the service). However, they felt that PhysioDirect was a useful way in which to provide patients with advice about self-management. Somewhat similarly, before experience our physiotherapists also expressed concerns about the lack of physical and visual contact with patients when consulting via telephone and felt unsure about how this might impact rapport. However, our physiotherapists' perceptions changed after experience and contrasted with those of the PhysioDirect therapists. This might be because the PhysioDirect service is designed to provide initial advice for a broad range of patients, including those presenting with acute conditions and those seeking a diagnosis. Our intervention was tailored for a specific group of patients who did not require diagnosis and involved numerous consultations with the same physiotherapist over an extended period of time, during which the aim was to develop a long-term self-management program involving exercise and physical activity. In addition, our physiotherapists were intensively trained in behavior change techniques and person-centered practice prior to starting the trial (25), which likely helped them provide more personalized and supportive care.

Our physiotherapists identified numerous advantages of telephone-delivered care. For example, they believed that it was convenient for patients, helped improve exercise adherence, and led to improvements in confidence, pain, and function. This reflects the findings of our qualitative study exploring the experiences of the patients in the trial who received care via telephone (n = 20) (37). Importantly, and somewhat paradoxically, both physiotherapists and patients found that they were able to talk at a more personal level via telephone compared with an in-person consultation, and that they developed a strong sense of rapport. These findings challenge misconceptions that Telehealth is "impersonal" (38) and suggest that personalized care can be provided remotely via telephone and that a strong rapport can develop between patients and therapists even without physical or visual contact. In fact, there is evidence that the therapeutic alliance is strengthened when patients and therapists talk in more detail about the patient's specific needs (39).

Our findings have clinical implications. Physiotherapists believed that the "hands-off" nature of telephone consultations helped shift patient expectations of care, leading to better patient engagement in self-management and improved adherence to prescribed exercise. There is evidence that patients with low back pain expect to receive hands-on treatment procedures and physical examinations from physiotherapists (40,41) and are more satisfied when they receive hands-on therapy (42–44). Physiotherapists often feel as though they have to provide hands-on therapy in order to meet patient expectations (32). Our findings suggest that remotely delivered consultations can help shift patient expectations away from being a passive recipient of hands-on therapies to being a more active participant in self-management of their condition. It is thus possible that remotely delivered consultations may also be applicable to other chronic conditions in which hands-on therapies are less effective and active self-management involving exercise is recommended (e.g., chronic low back pain).

Our findings also have implications for the design of future telerehabilitation services. Physiotherapists, as well as the patients in our other qualitative study (37), expressed a preference for some visual contact during telephone consultations. This suggests that video conferencing for consultations may be the ideal mechanism for implementing remote models of service delivery. In that study, both physiotherapists and patients emphasized that comprehensive written resources, including educational material and exercise instructions/photographs, were essential to the effectiveness of the intervention. As such, future service providers should ensure that these elements are incorporated into service models.

Our physiotherapists found that it was difficult to prepare for and schedule telephone consultations during the days when they were seeing patients in the clinical setting, preferring to do the telephone consultations after hours or on days when they were not working in their clinics. Future service providers may consider scheduling "blocks" of telephone consultations rather than interspersing them among in-person consultations; however, this approach may adversely impact patient convenience. Careful screening of patients is also required prior to booking telephone consultations to ensure the patients' safety and that their health condition is amenable to a self-management approach. Similarly, telephone services should not replace in-person consultations with a physiotherapist for patients who require a diagnosis of their health condition.

It is important that future telerehabilitation service providers consider training their clinicians in communication skills prior to delivering care via telephone (45). The physiotherapists in our study believed that training in communication skills or health coaching was necessary. Currently, there is no evidence to inform appropriate training for improving clinicians' telephone consultation skills (46). Our physiotherapists completed an intensive training program in person-centered care and behavior change techniques prior to the trial, which included 2 initial training days, a 3-month practice phase, and a final follow-up training day. After training, all of the physiotherapists felt confident and prepared to begin the trial and believed that they were better able to provide care that was person-centered (25). Physiotherapists who provide care via the UK telephone service PhysioDirect are also required to complete training to enhance listening and interviewing skills (47), involving 1½ days of workshop, a practice period, and a competency check involving observation of telephone consultations.

The strengths of our study include the use of pre-intervention and post-intervention interviews to gain a better understanding of how physiotherapists' perceptions of telephone-delivered exercise therapy shifted after they experienced delivery of care via this nontraditional method, and our evaluation of a robust, clearly described intervention (23) that can be replicated outside of the research setting. Our study also has a number of limitations. It was nested within an RCT, which constrained our sample to the physiotherapists who participated in the trial. Our physiotherapists volunteered to participate in the trial, and their perceptions and experiences may not be transferable to the broader population of physiotherapists. Only one researcher (BJL) coded all transcripts, and therefore data analysis may have been influenced by her own attitudes or perspectives.

In conclusion, we found that although physiotherapists were initially skeptical about the effectiveness of telephone-delivered service models for patients with knee OA, perceptions shifted once they experienced delivering care via this nontraditional method. Our findings suggest that firsthand experience may be necessary for physiotherapists to embrace new models of service delivery.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms Lawford had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lawford, Delany, Bennell, Hinman.
Acquisition of data. Lawford.
Analysis and interpretation of data. Lawford**,** Delany, Hinman.

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BRIEF REPORT

A Prediction Model for the 40-Year Risk of Knee Osteoarthritis in Adolescent Men

Karin Magnusson,[1] Aleksandra Turkiewicz,[2] Simon Timpka,[3] and Martin Englund[4]

Objective. To simplify the previously published Nottingham 12-year risk prediction model for knee osteoarthritis (OA) and examine whether it can be used to predict the 40-year risk of knee OA in young men.

Methods. Our cohort included 40,118 men who were 18 years of age and had undergone military conscription in Sweden from 1969 to 1970. Diagnostic OA codes were obtained from the Swedish National Patient Register for persons registered from 1987 to 2010. The original Nottingham model included as predictors age, sex, body mass index (BMI), knee injury, occupational risk, and family history of OA, with a receiver operating characteristic area under the curve (AUC) of 0.70 (95% confidence interval [95% CI] 0.61–0.79) in the model development sample, and AUC 0.60 (95% CI 0.58–0.63) in an external validation sample. In our sample, we used predictors that were available only in adolescence (age, BMI, and knee injury) and evaluated the discrimination of the simplified model using AUC.

Results. The AUC statistic of the modified knee OA model to predict 40-year risk was 0.60 (95% CI 0.59–0.61). Hence, using the reduced model, an 18-year-old man with a BMI of 30 and a knee injury would have 3 times the risk of developing knee OA within 40 years when compared to a man of similar age having a BMI of 25 and no knee injury (predicted risks 22% and 7%, respectively).

Conclusion. The 40-year risk of knee OA on individual and population levels can be predicted in 18-year-olds from a few easily measured covariates with moderate discrimination. The discrimination of this simplified model based on data available in adolescents was comparable to that of the full Nottingham model in middle-aged individuals.

INTRODUCTION

Prediction modeling in knee osteoarthritis (OA) allows for the calculation of total individual and population lifetime risk of incident disease in order to encourage risk reduction and the prevention of OA. Attempts at diagnostic prediction in knee OA have so far mainly considered the elderly, using radiographic knee OA as the outcome. A prediction study among 2,628 individuals ages >55 years reported that minor radiographic changes at baseline gave the best prediction of radiographic OA at follow-up (1). The main focus of other prediction studies in OA was on the predictive ability of genetic factors only (2,3) or they considered knee pain with no structural OA changes (4). These studies neither included younger participants nor candidate predictors that could be self-reported and, thus, easily obtained at a young age.

To our knowledge, the Nottingham 12-year risk prediction model (5) is the only study that has predicted knee OA using easily obtainable candidate predictors. The study sample in which it was developed comprised middle-aged persons and the model included age, female sex, body mass index (BMI), physically demanding work, family history of OA, and knee injury as predictors. The discriminative ability was fair in the original sample, with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.70 (95% confidence interval [95% CI] 0.61–0.79), and moderate when externally validated (AUC 0.60 [95% CI 0.58–0.63]). The lower AUC in the external validation

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[1]Karin Magnusson, PhD: Lund University, Lund, Sweden, and Diakonhjemmet Hospital, Oslo, Norway; [2]Aleksandra Turkiewicz, PhD: Lund University, Lund, Sweden; [3]Simon Timpka, PhD: Lund University, Malmö, Sweden; [4]Martin Englund, PhD: Lund University, Lund, Sweden, and Boston University School of Medicine, Boston, Massachusetts.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Karin Magnusson, PhD, Lund University, Faculty of Medicine, Department of Clinical, Sciences Lund, Orthopaedics, Clinical Epidemiology Unit, Lund, Sweden, Remissgatan 4, Wigerthuset 221 85 Lund, Sweden. E-mail: karin.magnusson@med.lu.se.

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SIGNIFICANCE & INNOVATIONS

- The long-term risk of knee OA is predictable in 18-year-old men using a modified version of the Nottingham model.
- The modified Nottingham model includes only the predictors age, BMI, and previous knee injury.
- Risk prediction of knee OA may become a readily available and useful tool for risk reduction at individual and population levels.

of the Nottingham model might be an indicator of overfitting, which suggests that a model with fewer predictors might perform equally well. Additionally, the Nottingham model is the basis for an online knee OA risk prediction tool for adults ages ≥25 (6). This tool is not available for younger persons.

The extent to which a simple model including variables available in adolescents can predict the long-term risk of knee OA is currently unknown. Therefore, we aimed to study the discriminatory power of an existing prediction model in a cohort of young men who were all 18 years of age, using only variables that were available at baseline. In doing so, we modified the 12-year Nottingham risk prediction model (5) and investigated the extent to which it could also be used to predict the 40-year risk of knee OA in adolescents.

MATERIALS AND METHODS

We used data of 41,886 men who were 18 years of age and had undergone mandatory conscription in Sweden between September 1969 and May 1970. At the time, the main reason for not undergoing the conscription examination was severe disability. The examination was performed at 6 centers nationwide and included standardized physical and mental health examinations and performance tests. Height and weight were measured, and BMI was calculated as weight (kg)/height (m^2). We reviewed data on knee injury as registered at the examination with International Classification of Diseases, Eighth Revision [ICD-8] codes and included codes 836 (dislocation of knee), 924 (knee contusion), 820 (fracture of patella), and 724 (internal derangement of knee).

These baseline data were linked to medical diagnoses on knee OA of persons registered between 1987 and 2010 in the Swedish National Patient Register (NPR). The NPR contains information about every hospitalization (from 1987 to 2010), 1-day surgery (from 1997 to 2010) and specialist outpatient care visits (from 2001 to 2010).

Incident knee OA was defined as the first record of an OA diagnosis in inpatient or specialist care between the year 1987 (typical age 35 years) and 2010 (typical age 59 years), including ICD-10 code M17 gonarthrosis (arthrosis of knee) and corresponding ICD-9 codes (if diagnosed before 1997). We included only men who were alive and were residents of Sweden at age 35 years (i.e., by January 1, 1987, which corresponds with the start of the registration of diagnostic codes in the NPR). The study was approved by the regional ethical review board in Lund, Sweden.

The Nottingham models were developed to predict Kellgren/Lawrence grade 2 or more and knee pain at 12 years follow-up in persons with mean ± SD age 56.8 ± 7.9 at baseline (4). The original model included the following predictors and regression coefficients (5), with the logit of the probability of knee OA as outcome [logit(p) = log (p/1-p)]:

$$\text{Logit(knee OA)} = -7.7 + 0.06^{*}\text{age} + 0.03^{*}\text{female} + 0.25^{*}\text{occupational risk} + 0.87^{*}\text{knee injury} + 0.09^{*}\text{BMI} + 0.54^{*}\text{family history of OA}$$

It can be assumed that occupational risk and family history of OA are less readily available data in 18-year-olds than current height, weight, and presence of knee injury. Hence, in our sample, we simplified the model to include only variables that were available at baseline, i.e., assuming the deletion of sex, occupational risk, and family history of OA had no impact on the magnitude of effect of BMI and knee injury as predictors. The regression coefficients of age, knee injury, and BMI were thus constrained to 0.06, 0.87, and 0.09, respectively. To take into account the difference in case mixing between our study sample

Table 1. Participants' characteristics and case-mix with the study population in which the prediction model was developed*

Characteristics	Swedish Conscription Registry, no knee OA (n = 38,066)	Swedish Conscription Registry, knee OA (n = 2,052)	Nottingham sample, knee OA and no knee OA (n = 424)
Age, mean ± SD	18 ± 0.3	18 ± 0.3	56.8 ± 7.9
Men	38,066 (100)	2,052 (100)	153 (36)
Knee injury†	208 (0.6)	39 (2.0)	51 (12.0)
BMI (kg/m^2), mean ± SD ‡	20.9 ± 2.6	21.7 ± 2.7	25.5 ± 3.5
Overweight (≥25–29.9 kg/m^2)	2,178 (5.7)	177 (8.6)	–
Obese (≥30 kg/m^2)	296 (0.8)	30 (1.5)	–

* Values are the no. (%) unless indicated otherwise. OA = osteoarthritis; BMI = body mass index.
† For the Swedish Conscription Registry, diagnostic code at time of conscription examination.
‡ Calculated from measured height and weight at conscription examination; measurements performed in the Nottingham model sample are described by Zhang et al (5).

and the sample used to develop the Nottingham model, we did not constrain the model intercept. Hence, we updated the model intercept to reflect the baseline risk of incident OA in our sample:

$$\text{Logit(knee OA)} = -5.92 + 0.06^{*}\text{age} + 0.87^{*}\text{knee injury} + 0.09^{*}\text{BMI}$$

Using this modified model, we studied calibration plots showing the agreement between observed and predicted values by sample deciles, where perfect predictions align along the 45° line (7). We also examined the discriminative ability (i.e., the model's ability to discriminate between men affected and those not affected by knee OA) using the C statistic by Harrell et al (AUC) (7). Finally, we assessed whether a model with recalculated regression coefficients, which fitted our sample better, showed improved discrimination (bias-corrected using bootstrapping). All analyses were performed in Stata MP software, version 14.

RESULTS

Of the 41,886 eligible recruits, we excluded 677 and 779 men due to death and emigration before 1987. After further exclusion of 312 men (0.07%) with missing data on predictors, we included in total 40,118 participants. Participants' characteristics are shown in Table 1.

The first cases with knee OA were diagnosed in 1987, i.e., when participants were 35 years of age. In total, 2,052 men (5.1%) were diagnosed with knee OA before 2010 (when 59 years of age). The calibration of the modified Nottingham risk model when it is applied to our sample to predict the 40-year risk is shown in Figure 1.

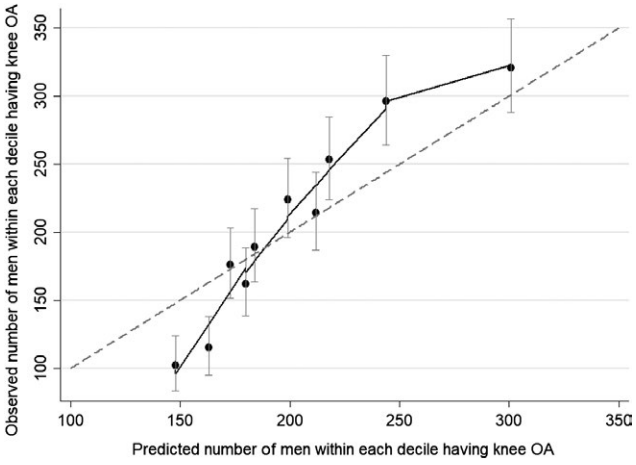

Figure 1. Calibration plots for the prediction model for knee osteoarthritis (OA). Circles represent the observed versus predicted knee OA; horizontal lines and error bars show the median and interquartile range. The broken line (45°) represents perfect predictions. The solid line is a smoothed calibration line (locally weighted scatterplot smoothing), fitted to the scatterplot. In a perfect model, this line would overlie the broken line. In a poor model, this line would be parallel to the x-axis.

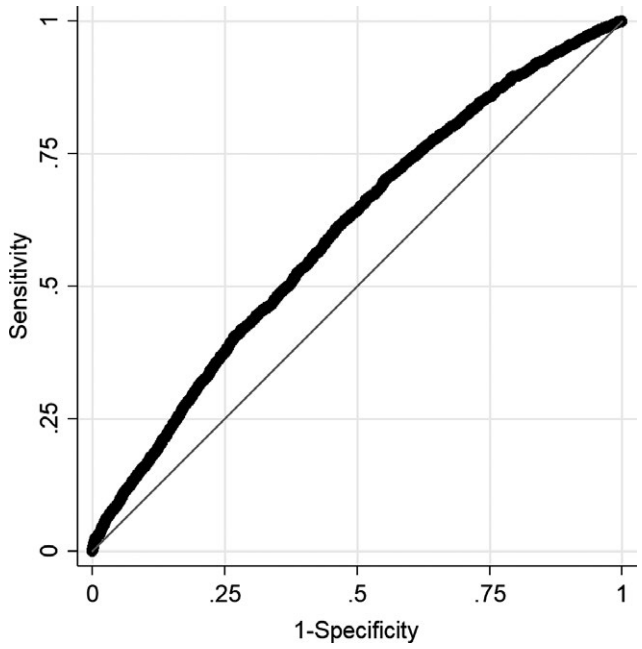

Figure 2. Discrimination curve showing the area under the curve for the prediction model for knee osteoarthritis.

The ROC statistic of the modified knee OA model was AUC 0.60 (95% CI 0.59–0.61), indicating that the model performed moderately (Figure 2). The AUC was similar with recalculated regression coefficients (AUC 0.60 [95% CI 0.59–0.61]), beta coefficients 0.04, 0.11, and 1.28 for age, BMI, and knee injury, respectively, with constant –5.92. The sensitivity and specificity (calculated with a cutoff of population prevalence 0.0511) was 50.4% and 62.5%, respectively. The proportion correctly classified was 61.9%. Our findings imply that an 18-year-old man with a BMI of 30 and a knee injury would have 3 times the risk of having knee OA within 40 years as compared to a similarly aged recruit with a BMI of 25 and no knee injury (predicted risks 22% and 7%, respectively).

DISCUSSION

In the current study of more than 40,000 men who had undergone conscription, we externally validated a simple prediction model for incident knee OA by middle age that included only 3 predictors: age, knee injury, and BMI. The externally validated model that was originally developed for the prediction of 12-year risk suggested similar discrimination in our sample as in its original sample (5). However, the discrimination was of moderate strength in both samples because it was closer to 0.5 than 1 (AUC 0.60–0.70). Moderate discrimination has also been found in other prediction studies of knee OA with shorter follow-up (1,2). In a prediction model that included age, gender, BMI, questionnaire variables, genetic scores, and a biochemical marker urinary C-terminal cross-linked telopeptide of type II collagen, the AUC was similar to that in our findings as well as to the Nottingham risk models (AUC 0.60–0.70) (1,4).

To our knowledge, the present study is the first to predict the long-term risk (i.e., the lifetime risk over 40 years) using only 3 easily obtainable predictors with similar discrimination as the previous knee OA prediction models. The predicted risks will likely increase over the life course as information on more predictors becomes available. For example, there may be no incidence of OA in one's closest family members when the offspring is 18 years old because of the still relatively young age of the mother and father. Similarly, at age 18, there has not been much occupational load that may influence the risk of knee OA. In contrast, etiological studies have demonstrated that the effects of BMI and knee injury on the risk of later knee OA have been reported to be rather constant from puberty (8,9). The difference in presence of predictors may explain the differences in predicted risks using the original Nottingham model and the modified model. Indeed, in the original Nottingham model, the predicted risk for a 50-year-old man having all the predictors and a BMI of 30 was 30% higher than for a similarly aged man with a BMI of 25 having no other predictors. In comparison to our modified model, the similar difference in predicted risks for an 18-year-old man using our modified model was 15%. The age from which the original prediction model is useful, and, for instance, the degree to which OA in close relatives can predict future knee OA need further investigation.

The simplicity of the model in the present study may increase its utilization in the prevention of knee OA. We had a different study population and a more clinically relevant outcome than used in the development study. Thus, the current validation study contributes to an improved understanding of the transportability of the Nottingham model (i.e., to what extent the model performs well in a different situation). Because the model was developed in a different sample, and has also been externally validated in other samples, there is growing evidence for this model to be actively used for risk reduction and OA prevention at the individual and population levels (5,6). For example, our modified model may be of relevance to general practitioners and physiotherapists who meet young men with knee injuries in their clinics. According to our findings, such patients may be encouraged to reduce their BMI to reduce their long-term risk of knee OA, and therefore, increase the longevity of their knees for further lifetime active sports participation. Further, our findings highlight the relevance of knee injury prevention programs in sports to reduce the risk of lifetime knee OA in young men. The extent to which our findings are applicable to young women is currently unknown and should be topic for further study.

A strength of the present study was the homogenous study population which ensured that age and sex could not mask potentially important influences of other variables. We also had a long follow-up time of 40 years, covering the total lifespan from adolescence and early adulthood to late middle age (18–58 years). Since conscription was mandatory at the time of study inclusion, we evaluated virtually the entire male population living in Sweden with limited selection bias. Other strengths were the inclusion of a large range of OA risk factors and the use of diagnostic codes to indicate OA, ensuring clinical symptoms were a part of the diagnosis.

Importantly, our study also had limitations. First, we could only include OA diagnosed within inpatient or outpatient specialist care and we might have studied only the more severe cases of OA. Indeed, the population prevalence was somewhat higher in a Swedish study, which also included primary care, than in the current study (9.2% versus 5.1%) (10). A prediction model for OA developed for diagnostic codes set in primary care might have looked different from the model found in the current study. Additionally, we cannot exclude that the organization of the Swedish health care system may have influenced our findings. Thus, it is unclear how the model would perform in other countries with other health care systems. Another limitation is that data were only available for men. Consequently, we could not study whether the model had similar discrimination in women.

In conclusion, we have simplified and externally validated a risk prediction model to be used for the prediction of knee OA with moderate discrimination in young men. Further studies are required in order to find a predictive model that effectively discriminates between persons with and without high risk of knee OA. Yet, so far, the Nottingham risk prediction model has been externally validated in at least 3 different samples including our study. Risk prediction tools may become increasingly important for encouraging risk reduction at the individual and population levels.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Magnusson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Magnusson, Turkiewicz, Timpka, Englund.

Acquisition of data. Turkiewicz, Timpka, Englund.

Analysis and interpretation of data. Magnusson, Turkiewicz, Timpka, Englund.

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Applications Invited for *Arthritis & Rheumatology* Editor-in-Chief (2020–2025 Term)

The American College of Rheumatology Committee on Journal Publications announces the search for the position of Editor, *Arthritis & Rheumatology*. The official term of the next *Arthritis & Rheumatology* editorship is July 1, 2020–June 30, 2025; however, some of the duties of the new Editor will begin during a transition period starting April 1, 2020. ACR members who are considering applying should submit a nonbinding letter of intent by May 1, 2019 to the Managing Editor, Jane Diamond, at jdiamond@rheumatology.org, and are also encouraged to contact the current Editor-in-Chief, Dr. Richard Bucala, to discuss details; initial contact should be made via e-mail to richard.bucala@yale.edu. Applications will be due June 21, 2019 and will be reviewed during the summer of 2019. Application materials are available on the ACR web site at https://www.rheumatology.org/Learning-Center/Publications-Communications/Journals/A-R.

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Ultrasonography for the Assessment of Skin in Systemic Sclerosis: A Systematic Review

Tânia Santiago,[1] Mariana Santiago,[1] Barbara Ruaro,[2] Maria João Salvador,[1] Maurizio Cutolo,[2] and J. A. P. da Silva[1]

Objective. To identify and synthesize the best available evidence on the use of ultrasound to assess skin involvement in systemic sclerosis (SSc).

Methods. We conducted a systemic review of the literature on PubMed Medline and Embase, using the vocabulary terms ("systemic sclerosis OR scleroderma") AND ("ultrasonography" OR "elasticity imaging techniques") AND ("skin" OR "dermis"). Two independent reviewers selected articles, collected data from studies, and carried out a manual search of the references from the studies included. This search was further enhanced by a review of bibliographic references extrapolated from these studies. The quality of the evidence was assessed by the Effective Public Health Practice Project system.

Results. A total of 30 studies were identified, enrolling 1,171 SSc patients, predominantly middle-aged (mean age 55.5 years) females (88.8%). The ultrasound skin measurements that were reported included thickness in 28 studies and/or echogenicity (7 studies), and/or stiffness (6 studies), and/or vascularity (1 study). The main comparator was the global and site-specific modified Rodnan skin thickness score. Reported interrater and intrarater reproducibility appeared to be excellent, but this reproducibility was assessed by a small number of studies. Moreover, there were no published evaluations of construct or criterion validity of skin ultrasound assessment. The responsiveness to change of ultrasound elastography has not been assessed.

Conclusion. Published reports have strong limitations and are highly heterogeneous, hindering the evidence to support the use of skin ultrasound assessment in clinical practice. Further studies, with modern devices and appropriate methodology, are needed to establish the real value of skin ultrasound assessment in the early diagnosis and monitoring of SSc patients.

INTRODUCTION

Skin involvement is of major clinical and prognostic relevance in systemic sclerosis (SSc) and is often the primary outcome in clinical trials (1,2). Skin thickness is usually measured by the modified Rodnan skin thickness score (MRSS), a palpation-based semiquantitative score (3). However, MRSS has some limitations, such as requiring specific examiner skills and having a high interobserver variability (3). Moreover, MRSS may not be sensitive enough to detect small, but relevant, changes in skin thickness over time (3,4). Therefore, an unmet need exists for an objective and sensitive method for skin assessment in clinical practice and research. This assessment is especially required to support the development of new therapies.

Interest has been stimulated by skin high-frequency ultrasound and ultrasound elastography. Indeed, several studies suggest that high-frequency ultrasound provides a quantitative and reliable evaluation of dermal thickness (5,6). Recently, ultrasound elastography, i.e., shear-wave elastography, has become the focus of increasing research and may well be an innovative method for the quantitative assessment of skin involvement in SSc patients (7,8).

The aim of this systematic literature review was to identify and synthesize the best available evidence on the use of ultrasound to assess skin involvement in SSc. This review follows the OMERACT (Outcome Measures in Rheumatology) filter of validity, reproducibility, responsiveness to change, and feasibility (9).

[1]Tânia Santiago, MD, Mariana Santiago, MD, Maria João Salvador, MD, J. A. P. da Silva, MD, PhD: Centro Hospitalar e Universitário de Coimbra and University of Coimbra, Coimbra, Portugal; [2]Barbara Ruaro, MD, Maurizio Cutolo, MD, PhD: University of Genoa, IRCCS San Martino Polyclinic Hospital, Genoa, Italy.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Tânia Santiago, MD, Serviço de Reumatologia, Centro Hospitalar e Universitário de Coimbra, Praceta Prof. Mota Pinto, 3030-075 Coimbra, Portugal. E-mail: tlousasantiago@hotmail.com.

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SIGNIFICANCE & INNOVATIONS

- Ultrasound has the potential to become a reliable tool to assess skin involvement in systemic sclerosis (SSc).
- This systematic literature review highlights remarkable heterogeneity in several aspects of ultrasound skin examination in SSc that hinders evidence supporting its use in clinical practice.
- Skin ultrasound examination still lacks criterion validity, and further studies correlating skin biopsy findings with ultrasound skin measurements are required.

MATERIALS AND METHODS

Literature search. A systematic literature review protocol was uploaded to the PROSPERO database (registration number CRD42017077048). A Population, Intervention, Comparator, Outcomes–structured search was made to identify relevant studies in the PubMed Medline and Embase databases. The search considered the factors Population: SSc population; Intervention/test: ultrasound and/or ultrasound elastography; Comparator/control: any comparator (such as the Rodnan skin score [RSS], MRSS, or biopsy) or none; Outcome: correlations between skin ultrasound measurements (such as thickness, echogenicity, stiffness, and vascularity) and other parameters (such as RSS, MRSS, the Health Assessment Questionnaire [HAQ], nailfold capillaroscopy, and others); and Design: observational studies (including cohort and case–control studies) and randomized trials.

The search was performed using free terms and medical descriptors (e.g., medical subject headings [MeSH] terms). The terms used were "scleroderma, systemic," scleroderma, ultrasonography, "elasticity imaging techniques," skin, and dermis. The complete electronic string used for PubMed is shown in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract.

Selection criteria and search strategy. A study was eligible if it included ≥1 defined group of patients with SSc and reported a structured evaluation of the skin with ultrasound and/or ultrasound elastography. Published articles up to and including July 2017, written in English, Spanish, French, Italian, or Portuguese were searched. The last search was done on September 6, 2017, with monthly automatic email updates, until January 15, 2018, and a manual search for recent publications without attribution of MeSH terms was added on this final date.

Any studies that were already known to the authors of this review (based on previous work or familiarity with the research area) were also included. Publications reporting no original data and/or those without a clear description of the research methods were excluded. No search was made on conference abstracts or unpublished studies. Duplicates were removed and the selected references were imported into Microsoft Excel.

Study selection. The selection of the studies to be included was made by 2 independent rheumatologists (TS and MS), who assessed the electronic search results by title and abstract. Only relevant abstracts were deemed eligible. In case of doubt, the full text of the article was retrieved and discussed. Only 2 cases required arbitration by a third author (MJS). Exclusion criteria were recorded after the full text screening. The interrater agreement between TS and MS for selection based on abstract and full text, measured by Cohen's kappa coefficient, was 0.98.

Data collection and extraction. Two reviewers (TS and MS) independently extracted the data into a Microsoft Excel spreadsheet. There was arbitration by a third author (MJS) whenever there was persistent disagreement. The following data were collected: publication data (title of the article, first author, publication date, country), methods (study design, inclusion and exclusion criteria, follow-up, intervention), patient characteristics (age, sex, SSc subsets, disease duration), ultrasound measures (thickness, echogenicity, stiffness, vascularity, skin sites imaged), comparator (biopsy, MRSS, others), technical aspects (probe, MHz, ultrasound device, sonographer experience), intrarater and interrater variability, contextual factors (time of day, room temperature), and feasibility (cost, time taken). During the data collection and extraction, the author of 1 study (10) was contacted for additional information.

Grading the quality of evidence of the studies included. The Effective Public Health Practice Project method was used to rate the quality of the evidence in the reviewed studies (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract) (11). Each study was assigned a score category of strong, moderate, or weak.

RESULTS

Study selection and characteristics. The selection of articles is shown in Figure 1. A total of 196 articles were identified from 2 databases, and 30 articles were included in this systematic review. The selected articles included 21 observational cross-sectional studies investigating the relationship of ≥1 skin ultrasound measurement with diverse disease parameters and 9 longitudinal studies (see Supplementary Tables 3 and 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract).

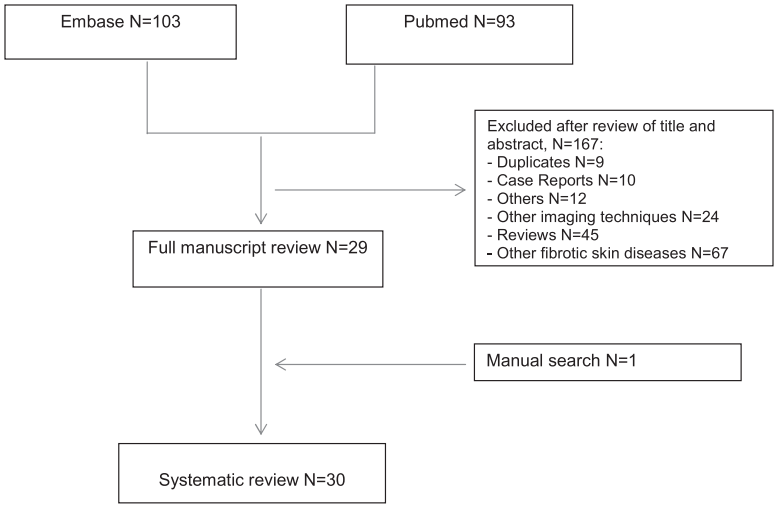

Figure 1. Search strategy and exclusion process for studies on skin ultrasound assessment in patients with systemic sclerosis.

Five of these studies evaluated ultrasound skin responsiveness to spontaneous change over time (5,12–15) and 4 evaluated specific interventions: urokinase (16), photochemotherapy (17), bosentan (18), and extracorporeal shockwave therapy (19). All studies were single-center based. Of the 30 total studies, 9 (30%) were performed in Italy and 7 (approximately 23%) in Sweden.

The studies included a total of 1,171 patients with SSc, varying between 8 and 106 patients per study. Females represented 88.8% of the total sample (range 47.0% to 100.0% in different reports). A total of 59% of the patients had the limited form of SSc. The mean age was 55.5 years (range 15.0–83.0 years) and the mean time lapse since SSc diagnosis varied from 0.9 to 17.5 years. Case definition of SSc was based on 3 different sets of criteria (see Supplementary Table 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract). Few studies reported the details of ongoing therapy (5,12,14,20).

Ultrasound protocol. Overall, the technical aspects of the ultrasound machine, probe, and frequency were well described (Table 1), and 19 studies (63%) performed skin ultrasound assessment with a probe of at least 18 MHz. Only 3 studies described the level of the sonographer's experience as an "experienced sonographer" (21), or an "experienced ultrasound physician, who was engaged in superficial organ examination for more than 18 years" (22), or as "experienced in ultrasound" (10). Only 7 studies described that the sonographers were blinded to clinical data and local MRSS (6–8,15,22–24).

Ultrasound measurements. The ultrasound skin measurements reported in the 30 studies included were thickness in 16 (6, 10, 14, 16, 18, 20, 23, 25–33), thickness and echogenicity in 7 (5,12,13,15,17,34,35), thickness and stiffness in 3 (8,21,36), stiffness in 2 (7,24), thickness, echogenicity, and stiffness in 1 (22), and thickness and vascularity in 1 (19).

Although a total of 28 studies reported on ultrasound skin thickness (Table 1), there was a high heterogeneity in definition of this parameter. In 2003, Moore et al (30), emphasized that ultrasound skin thickness should be focused on the dermis, due to the lack of precision of epidermal measurements, as reflected by a low reproducibility across skin sites. The articles included in our study showed that ultrasound skin thickness was greater in SSc patients than in control subjects, in almost all Rodnan skin sites (6,12,14,22,27,30,32,34).

Moreover, patients with diffuse cutaneous SSc also had thicker skin on the hands, forearms, legs, and chest than did patients with the limited cutaneous form, whereas the differences in the finger sites did not reach significance (13). One important aspect relates to the subclinical dermal involvement in SSc, i.e., ultrasound evaluation of clinically uninvolved skin. Interestingly, in a recent study, Sulli et al (6) reported that ultrasound was able to detect increased dermal thickness in skin areas with an MRSS score of 0, in patients classified as having limited cutaneous SSc.

Although the ultrasound skin thickness values are generally reported in millimeters, the methods adopted to establish the measurement were highly heterogeneous between different studies: some used the average of 3 ultrasound measurements, others the average of 2 ultrasound measurements (19), while other groups adopted the median of 3 ultrasound measurements (34), or the average of 3 ultrasound measurements by 3 readers (29).

Eight studies contained data on skin echogenicity (Table 1). Hesselstrand et al (13) reported an inverse relationship between skin echogenicity and thickness in patients with SSc with a duration <2 years, supposedly reflecting the edematous phase

Table 1. Main characteristics of the included studies*

First author, year (ref.)	US settings			Construct validity			Site examined		Reliability		Responsiveness to change†	Feasibility
	Mode	Machine	Probe, MHz	US measure-ment	Skin layers examined	Comparator	Skin	No.	Intra	Inter		
Serup, 1985 (25)	A	NR	15	Thickness	Soft tissue	Ring size	Finger	1	NR	NR	NA	NR
Akesson, 1986 (14)	B	DRF-12, Diasonics	10	Thickness	Skin (beginning of skin surface echo and beginning of underlying bone echo)	RSS	Finger	4	NR, controls only	NR	6,12,18 months	NR
Myers, 1986 (26)	B	NR	25	Thickness	Skin	Soft tissue radio-graph	Forearm	1	1 patient: coefficient of variance 2.7% (vs. radiograph 3.9%)	r = 0.98, mean difference = 0.02 mm	NA	NR
Ihn, 1995 (27)	B	UX-01 Rion Co.	30	Thickness	Skin (distance between skin surface and skin-fat interface)	Biopsy	Hand, forearm, chest	3	NR	NR	NA	NR
Seidnari, 1996 (28)	A, B	DermaScan C, Cortex Technology	20	Thickness	Skin	NR	Hand, cheek, forehead	3	NR	NR	NA	NR
Ciompri, 1996 (16)	A, B	Bruel & Kjaer apparatus, Diagnostic Ultrasound System 3535	7.5	Thickness	Skin and subcutis	Handprint	Chest, bicipital groove, forearm, leg	5	NR	NR	Pre and after urokinase, 4 months	NR

(Continued)

Table 1. (*Cont'd*)

First author, year (ref.)	US settings			Construct validity			Site examined		Reliability		Responsiveness to change†	Feasibility
	Mode	Machine	Probe, MHz	US measurement	Skin layers examined	Comparator	Skin	No.	Intra	Inter		
Scheja, 1997 (34)	A, B	DermaScan	20	Thickness, echogenicity	Skin	MRSS	Finger, hand, forearm	3	NR	1.0% (proximal phalanx), 4.2% (hand), and 0.0016% (forearm), over 4 sites in 10 controls	NA	NR
Brocks, 2000 (29)	A, B	DermaScan, Cortex Technology	20	Thickness	Skin (distance between dermal/epidermal junction and dermal/subcutaneous interphase)	MRSS	Finger, hand, forearm, chest	5	NR	NR	NA	NR
Hesselstrand, 2002 (12)	A, B	DermaScan	20	Thickness, echogenicity	Skin	RSS biopsy	Forearm	1	NR	NR	1–3 years follow-up	NR
Moore, 2003 (30)	B	Diasus, Dynamic Imaging	22	Thickness	Epidermis vs. dermis	MRSS	Rodnan sites	17	ICC 0.65–0.94	ICC 0.55–0.96	NA	NR
Akesson, 2004 (15)	A, B	DermaScan, Cortex Technology	20	Thickness, echogenicity	Skin (epidermis plus dermis)	MRSS	Finger, hand, forearm, leg, chest	5	Thickness ICC 0.92 0.98, echogenicity ICC 0.92–0.98	Thickness ICC 0.66–0.88, echogenicity ICC 0.92–0.99	12–24 months (3 4×)	NR
Hashikabe, 2005 (17)	B	DermaScan, Cortex Technology	20	Thickness, echogenicity	Dermis	MRSS	Finger, hand, forearm	3	NR	NR	Pre and after photo chemotherapy	NR

(Continued)

Table 1. (*Cont'd*)

	US settings			Construct validity			Site examined		Reliability			
First author, year (ref.)	Mode	Machine	Probe, MHz	US measurement	Skin layers examined	Comparator	Skin	No.	Intra	Inter	Responsiveness to change†	Feasibility
Kissin, 2006 (31)	B	SonoSite	10	Thickness	Skin	MRSS durometry	Finger, hand, forearm, upper arm		NR	NR	NA	NR
Hesselstrand, 2008 (13)	A, B	DermaScan, Cortex Technology	20	Thickness, echogenicity (0–100)	Skin	MRSS	Finger, hand, forearm, leg, chest	5	NR	NR	Mean ± SD 3.9 ± 2.9 years	NR
Hesselstrand, 2008 (35)	B	DermaScan, Cortex Technology	20	Thickness, echogenicity (0–255)	Skin	Serum COMP	Finger, hand, forearm, leg, chest	5	NR	NR	NA	NR
Kuhn, 2010 (18)	B	NR	20	Thickness	Skin	MRSS	Finger, hand, forearm, legs	4	NR	NR	Pre and after bosentan, 24 weeks	NR
Kaloudi, 2010 (32)	B	MyLab 25 US system, Esaote	6–18	Thickness	Skin	MRSS HAQ phase of skin involvement	Finger	2	ICC 0.92–0.96	ICC 0.92–0.97	NA	NR
Iagnocco, 2010 (7)	Comp. elasto.	HiVision 8500, Hitachi	18	Stiffness (color scale)	Skin	MRSS	Finger, forearm	2	100% forearm	100% forearm	NA	NR
Tinazzi, 2010 (19)	B and color Doppler	LOGIQ Book XP, GE	12	Thickness vascularity (1–3)	Skin	MRSS VAS	Upper arm	2	NR	N	Pre and after ESW, 7, 30, 60, and 90 days	NR
Di Geso, 2011 (21)	B and comp. elasto.	MyLab70 XVG, Esaote	6–18	Thickness, stiffness (color scale)	Skin	MRSS, Raynaud's phenomenon score	Finger	2	ICC 0.904 for B-mode US; B-mode plus UE ICC 0.979	ICC 0.59 for B mode US; 0.88 for B mode and UE	NA	US took ≤5 min. per patient

(Continued)

Table 1. (*Cont'd*)

First author, year (ref.)	US settings			Construct validity			Site examined		Reliability		Responsiveness to change†	Feasibility
	Mode	Machine	Probe, MHz	US measurement	Skin layers examined	Comparator	Skin	No.	Intra	Inter		
Sedky, 2013 (33)	B	ATL Philips	6–18	Thickness	Skin and subcutaneous	MRSS total severity score clinical parameters	Finger, hand, forearm, leg, chest	5	NR	NR	NA	NR
Sulli, 2014 (23)	B	MyLab 25, Esaote	12	Thickness	Dermis	MRSS, LDF, NVC, MES	Finger	2	95%	NR	NA	NR
Hou, 2015 (8)	B and SWE	Siemens S2000	6–18, 4–9	Thickness, stiffness (SWV)	Skin (epidermis plus dermis)	MRSS	All Rodnan sites	17	NR	SWV ICC 0.25 0.91	NA	NR
Hesselstrand, 2015 (5)	B	DermaScan, Cortex Technology	20	Thickness, echogenicity (0–255)	Skin	MRSS serum COMP, HAMIS	Finger, hand, forearm, chest, leg	5	Not specified	NR	12 months	NR
Santiago, 2016 (24)	SWE	Siemens S3000	4–9	Stiffness (SWV)	Skin	MRSS	All Rodnan sites (except face)	16	ICC 0.47–0.98	NR	NA	UE (ARFI) required <2 min. per skin site
Liu, 2017 (22)	B and SWE	Siemens S2000	4–9	Thickness, echogenicity, stiffness (SWV)	Skin	MRSS	All Rodnan sites	17	NR	Echogenicity ICC 0.608	NA	NR
Sulli, 2017 (6)	B	MyLab 25, Esaote	18	Thickness	Dermal	MRSS, NVC	All Rodnan sites	17	95.0%	NR	NA	20–25 min. per US Rodnan site

(Continued)

Table 1. (*Cont'd*)

First author, year (ref.)	US settings			Construct validity			Site examined		Reliability		Responsiveness to change†	Feasibility
	Mode	Machine	Probe, MHz	US measurement	Skin layers examined	Comparator	Skin	No.	Intra	Inter		
Sousa-Neves, 2017 (10)	B	LOGIQ S8, GE	6–15	Thickness	Skin (epidermis plus dermis plus subcutaneous tissue)	MRSS, HAMIS, SScSS	Finger	2	NR	NR	NA	NR
Cildag, 2017 (36)	B and comp. elasto.	Aplio 500, Toshiba	15	Thickness, stiffness (color scale)	Skin	Pulmonary involvement (HRCT)	Forearm	1	NR	NR	NA	NR
Ruaro, 2018 (20)	B	MyLab 25, Esaote	18	Thickness	Dermis	MRSS, LASCA, NVC	Finger, hand, zygoma	3	95.0%	NR	NA	NR

* US = ultrasound; NR = not reported; NA = not applicable; RSS = Rodnan skin thickness score; MRSS = modified Rodnan skin thickness score; ICC = intraclass correlation coefficient; COMP = cartilage oligomeric matrix protein; HAQ = Health Assessment Questionnaire; Comp. elasto. = compression elastography; VAS = visual analog scale; ESW = extra-corporeal shock waves; UE = ultrasound elastography; LDF = laser Doppler flowmetry; NVC = nailfold videocapillaroscopy; MES = microangiopathy evolution score; SWE = shear-wave elastography; SWV = shear-wave values; HAMIS = Hand Mobility in Scleroderma; ARFI = acoustic radiation force impulse; SScSS = scleroderma severity scale; HRCT = high-resolution computed tomography; LASCA = laser speckle contrast analysis.
† Change due to time or intervention.

of the disease (6). This relationship disappeared when the disease evolved into the indurative phase, which was reflected by a decrease in skin thickness and an increase in skin echogenicity, as observed in serial measurements (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract) (5,15).

Six studies described skin stiffness: 3 were based on compression elastography (7,21,36) and the other 3 on shear-wave elastography, by acoustic radiation force impulse imaging (Table 1) (8,22,24). The degree of tissue elasticity was graded using a qualitative color scale in compression elastography. Shear-wave velocity values were significantly higher in SSc patients than in controls in almost all the MRSS sites. Interestingly, clinically unaffected skin of patients with SSc could also be differentiated from healthy skin (8,24). Only 1 study assessed vascularity through color Doppler analysis, reporting a significant improvement in skin vascularization 90 days after treatment (extra-corporeal shock waves) (Table 1 and Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract) (19).

Skin sites examined. There was a substantial discordance in the number and definition of skin sites examined among the reports included in our study. The finger (proximal and/or middle phalanx) was the most frequently scanned site (20 of 29 studies). Three studies (8,22,30) examined the same 17 MRSS sites. Four studies examined a similar set of 5 skin sites (5,13,15,33). Overall, the sites examined were in line with the Rodnan skin sites, or at least in the same body area, although there was high heterogeneity in the exact definition and landmarks for each site scanned. Moreover, ultrasound measurements were reported for 1 body side, usually the right or the dominant side (5,13,15,21,33), or as the average of left and right sides (10,23), or separately for right and left sides (6,14,24,30).

Validity/comparator. One of the studies included (28) was merely descriptive, i.e., it did not contrast skin ultrasound measurements with other parameters. Most of the studies, i.e., 21 of 30, established criterion validity for skin ultrasound assessment by assuming RSS/MRSS as the gold standard, with MRSS (19 studies) or RSS (12,14). Other studies considered the relationship between ultrasonography measurements and the following parameters: serum cartilage oligomeric matrix protein (COMP) (5,13), the HAQ (32), hand mobility (Hand Mobility in Scleroderma [HAMIS] scale) (5,10), Raynaud's Condition Score (21), and nailfold videocapillaroscopy (6,23), among others. Only 3 articles considered the skin clinical phases, i.e., edematous, fibrotic, and atrophic (10,13,32).

Only 1 study assessed the correspondence between the ultrasound data and histologic parameters (24). Ihn et al (27) reported that increased ultrasound thickness observed in clinically uninvolved skin in SSc patients did not correspond to identifiable histologic changes. However, unfortunately, that article failed to detail this conclusion. Hesselstrand et al (12) compared the change in ultrasound parameters during 1–3 years with the production of proteoglycans by skin fibroblasts collected at baseline and cultured ex vivo. During this period, ultrasound skin thickness values increased while ultrasound skin echogenicity values decreased. Cultured fibroblasts from patients with greater changes in thickness and echogenicity produced more versican, whereas the production of biglycan and decorin was higher only in patients with greater decreases in skin echogenicity.

The correlation between ultrasound skin thickness and MRSS, measured at the same site, was evaluated in an interesting group of studies (13,29,33,35), using a similar set of 5 skin sites. All the studies reported a mild-to-moderate positive correlation between these parameters in all 5 sites studied (r = 0.37 [$P < 0.001$] to 0.72 [$P < 0.001$]). Although Sousa-Neves et al (10) did report a significant positive correlation between these parameters in the fingers (r = 0.698 [$P < 0.001$] and rs = 0.645 [$P < 0.001$], for right and left sides, respectively), this observation was not confirmed in 2 other studies (20,29).

The total MRSS had a mild-to-moderate positive correlation (r = 0.48 [$P < 0.001$] to 0.66 [$P = 0.001$]) to the added skin thickness values, revealed at ultrasound in the same 17 sites (5,13,30). Two studies reported a weak but significant positive correlation ($\rho = 0.056$ [$P = 0.001$]) between the ultrasound skin thickness of the fingers and the total MRSS (10,29).

Interestingly, 1 study showed a strong correlation between skin stiffness and local MRSS in 4 of 16 skin sites examined (24). No correlation was found between dermal finger thickness and HAQ (32) or Raynaud's Condition Score (21). Changes in the total sum of skin thickness were correlated with changes in serum COMP (r = 0.3, $P = 0.034$), in MRSS (r = 0.43, $P < 0.001$) and in HAMIS (r = 0.53, $P = 0.001$) during the follow-up (5).

Moreover, dermal finger thickness as assessed by ultrasound was associated with the severity of microangiopathic changes, as assessed by nailfold videocapillaroscopy (6,23). In another 2 studies (20,23), the authors demonstrated a relationship between dermal thickness, evaluated by ultrasound and MRSS, and the peripheral blood perfusion in SSc patients only at finger level.

Variability. The studies that reported intra- and intervariability are included in Table 1 and detailed in Supplementary Table 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract. Four studies (15,30,32,34) assessed the interrater variability for dermal thickness based on ultrasound measurements performed by 2 independent observers. Three studies (15,30,32) described an intraclass correlation coefficient (ICC) for dermal thickness, often >0.8 for interobserver variability and >0.9 for intraobserver variability (15,30,32). Scheja et al (34) reported an interobserver variability for skin thickness of 1.0% for the phalanx, 4.2% for the hand, and 0.0016% for the forearm, by comparing the results obtained by 2 independent investigators in 10 healthy controls.

Hou et al (8) measured the skin stiffness in 17 skin sites, in 15 SSc patients and 15 controls and reported an ICC for interobserver variability between 0.25 (right middle phalanx) and 0.91 (right forearm). Unfortunately, the authors did not report the methodology used for ICC calculation. In another study (24), intraobserver variability for skin stiffness varied between 0.48 (chest) and 0.98 (left phalanx), in 4 SSc patients and 2 controls (24). In a study by Liu et al (22), the ICC for skin echogenicity classification by 2 reviewers was 0.608 ($P < 0.001$), based on the reading of static ultrasound images.

Ambient conditions: time of day and room temperature. A total of 7 studies showed the time of day when the ultrasound assessments were performed: between 9:00 and 12:00 a.m. in 6 studies and in the afternoon for the remaining study (29). Two studies contained data concerning the room temperature (30,33).

Reference data. If ultrasound is to be used for early diagnosis of the disease and/or determination of local site involvement, reference normality data are required. Akesson et al (15) reported that the skin ultrasound parameters (thickness and echogenicity) vary between different skin sites of healthy individuals. In 2000, Brocks et al (29) reported that the skin of healthy controls of Danish origin was thicker on ultrasound examination than that of Japanese controls, raising the question of ethnic background. The influence of other variables, such as age or sex, has not been addressed in literature. We were unable to identify any attempt to define normal ultrasound skin reference data.

Responsiveness to change. A total of 9 studies assessed the longitudinal changes of skin involvement as evaluated by ultrasound. Five of these studies described a change in skin thickness over time (5,12–15) and 4 reported changes with therapy (16–19). None of the ultrasound elastography studies assessed the responsiveness to change over time. Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract, shows the main results of the above-mentioned studies.

Feasibility (time consumption, cost, ease of measurement). Only a few studies described how long the ultrasound examinations took. Di Geso et al (21) reported that ultrasound dermal measurements in the finger (proximal and middle phalanx), using both grey-scale and ultrasound elastography, took no longer than 5 minutes per site. Our group previously reported (24) <2 minutes per site for each examination with shear-wave elastography. Sulli et al (6) stated that ultrasound is more time consuming than total MRSS assessment and takes 20–25 minutes (including skin capture image and manipulation to measure dermal thickness).

DISCUSSION

This systematic literature review highlights, first and foremost, a remarkably high heterogeneity in several aspects of the published studies on ultrasound skin assessment in SSc, including: the ultrasound protocol used, i.e., the probe frequency, devices used, and skin layers of interest to be imaged and measured; the number and location of skin sites examined; the definition of outcomes and the number of measurements taken; the patient and disease characteristics (disease stage/duration, drug exposure); the criterion validity; cross-sectional versus prospective studies; and the methods used to assess reproducibility.

Many studies fail to describe aspects that may be essential to allow reproduction of their results, such as age (37), sex, skin site (15), time of the day (30), room temperature (30,33), or the blinding of observers. Notably, a large number of different ultrasound devices were used, which may contribute to variability. In approximately 40% of the studies, the probe frequency (i.e., space discrimination) was below what is now considered adequate for skin evaluation (≥18 MHz). The overall quality of the reported studies, as assessed by the Effective Public Health Practice Project quality assessment tool, was weak to moderate on average (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23597/abstract). The accrual of knowledge and the robustness of evidence supporting the use of ultrasound to assess the skin in SSc are strongly hindered by this remarkable literature heterogeneity and the limited quality of most studies.

The need for a better tool than MRSS to assess the skin in SSc has been repeatedly emphasized, especially due to its low sensibility to change (1,3,38,39). Additionally, the variability for the MRSS is considered very high (intraobserver 12% and interobserver 25%) (40).

Published data, albeit limited in quantity and quality, suggest that ultrasound may provide much needed progress in the noninvasive assessment of skin involvement in SSc, both in clinical practice and research settings. This technology may allow for earlier detection of skin involvement, as suggested by positive findings in apparently unaffected skin areas (6,13,24,27). An objective distinction between the edematous versus indurative phases in the early stages of SSc would also be useful (13,30,32). Potential advantages of skin ultrasound assessment include the quantitative and continuous nature of the data and a higher reproducibility and sensitivity to early disease and to change over time. Innovative techniques, such as the ultrasound elastography, may add greater precision and objectivity to ultrasound B-mode in SSc. These techniques may provide for more reliable correlations with specific histologic and pathogenetic features, e.g., the level of fibrosis, content of elastin, collagen, or extracellular matrix.

As to feasibility, skin ultrasound examination is well-accepted by patients, widely available, noninvasive, and easily affordable, and in addition, it would require only minimal additional training by

experienced sonographers. Skin ultrasound assessment (combining different parameters) of the 17 Rodnan skin sites is probably not realistic in daily practice today, because of time constraints.

Taken together, these observations suggest that ultrasound examination may represent an important step forward in the search for a sensitive and reliable method to assess skin involvement in SSc. Moreover, it may also become an invaluable tool to support the development of much needed new therapeutic interventions. However, if that promise is to be adequately addressed, future research in the area should be aimed at resolving the main issues that undermine the currently available evidence: a clear definition and standardization of the number and exact location of skin sites to be examined; a description of the US protocol (probe frequency and type); an exact definition of outcomes of interest (thickness, echogenicity, stiffness, and vascularity); the establishment of the intrarater and interrater variability of the outcomes and their sensitivity to change, taking into account the site of measurement; clarification of the importance of contextual factors (age, sex, ethnicity, profession, room temperature and time of the day); the issue of the blinding of the assessors, which must be appropriately addressed, despite the obvious difficulties; and the appropriateness of the devices (i.e., probe ≥18 MHz).

Early detection of skin involvement would be strongly favored by the establishment of reference intervals/normality values for the relevant anatomic sites, taking into account the significant contextual factors. Additional value would be added by further studies on the biologic and/or histopathologic correlations of ultrasound measurements, especially regarding stiffness. Indeed, ultrasound measurements may actually reflect properties of the skin that are different from those assessed by the currently validated gold standard of MRSS, rendering their direct comparison meaningless.

In summary, although skin ultrasound assessment has a strong rationale and addresses a very important unmet need in SSc, the strong heterogeneity and limitations of published reports limit its current use in clinical practice. However, recent studies contain very promising data (e.g., good reliability and the possibility to detect subclinical skin involvement) that support further investigation into the use of skin ultrasound assessment in SSc. Further evidence-based studies are required to validate the use of skin ultrasound assessment in the early diagnosis and monitoring of SSc patients. These studies may overcome the important limitations of the current gold standard, MRSS, and become crucial to improve our understanding of the disease process and to foster the development of much-needed new intervention strategies.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. T. Santiago had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. T. Santiago, da Silva.

Acquisition of data. T. Santiago, M. Santiago

Analysis and interpretation of data. T. Santiago, M. Santiago, Ruaro, Salvador, Cutolo, da Silva.

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Erratum

In several articles by Polachek et al published in *Arthritis Care & Research*, one of the institutional affiliations of the first author was inadvertently omitted. Dr. Ari Polachek's affiliations should have read: "University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada and Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. The articles in *Arthritis Care & Research* on which Dr. Polachek was first author were as follows: January 2017 (Risk of Cardiovascular Morbidity in Patients With Psoriatic Arthritis: A Meta-Analysis of Observational Studies [pages 67–74]), March 2017 (Reply [page 457]), July 2017 (Defining Low Disease Activity in Systemic Lupus Erythematosus [pages 997–1003]), and November 2017 (Clinical Enthesitis in a Prospective Longitudinal Psoriatic Arthritis Cohort: Incidence, Prevalence, Characteristics, and Outcome [pages 1685–1691]).

We regret the error.

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LETTERS

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Do not disregard diagnostic clues of endocarditis: comment on the article by Garg et al

To the Editor:

We read with great interest the recent report by Garg et al about a patient with *Bartonella*-related endocarditis (1). However, we regret that the "petechial pruritic rash" on the lower extremities and the presence of an elevated rheumatoid factor (RF) level were initially neglected in the context of glomerulonephritis.

Indeed, the rash was poorly described. It was bilateral and petechial, but it is not mentioned whether it was symmetric, distal, palpable, or necrotic, for instance. Because no cutaneous biopsy was performed (with direct immunofluorescence and cultures), we can only hypothesize that the rash was related to a leukocytoclastic vasculitis. Indeed, a careful dermatologic examination is mandatory in patients with suspected infective endocarditis in order to find the portal of entry present in more than 20% of cases. Moreover, minor criteria for infective endocarditis include not only vascular phenomena with conjunctival hemorrhages, Janeway lesions and major arterial emboli, and immunologic phenomena such as Osler nodes but also glomerulonephritis, Roth spots, and RFs, according to the Duke criteria (2) and the modified Duke criteria (3).

Of note, in a recent study that included 497 definite cases of infective endocarditis, 487 had known dermatologic status. Among these 487 cases, 11.9% had skin manifestations, including 8.0% with purpura, 2.7% with Osler nodes, and 1.6% with Janeway lesions (4). However, the 2 latter lesions, which were formerly considered to be the result of small vessel vasculitis, are currently considered to be the result of minute septic emboli to the dermis originating from valvular vegetation, with septic microemboli and dermal microabscess (5). Finally, petechiae, which were considered as a criterion in the 1981 definitions proposed by von Reyn et al (6), were excluded from new criteria, because these lesions can be observed in other conditions and are not specific to infective endocarditis (2,3).

The presence of RF, an antibody directed against the Fc fragment of IgG, is frequent in patients with infective endocarditis. It is considered to be a minor criterion for infective endocarditis, related to a complex stimulation of humoral and cellular immunity of the host to control the infection. Rheumatoid factor is found in more than half of patients with subacute endocarditis lasting more than 6 weeks (7) and in 24% of patients with acute endocarditis (8) and therefore seems to be related to the duration of infection. Of course, the previous presence of RF cannot be considered to be a minor criterion. As suggested by the authors, other autoantibodies may be present (1).

In conclusion, a high index of suspicion of infective endocarditis in patients with a petechial rash is required, and subtle data should not be neglected in order to establish an early diagnosis and adapted treatment.

Claude Bachmeyer, MD
Victoire Dubourdieu, MD
Barthélémy Poignet, MD
Service de Médecine Interne, Hôpital Tenon, Assistance Publique Hôpitaux de Paris
Paris, France

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Reply

To the Editor:

We thank Dr. Bachmeyer and colleagues for their interest in and comments regarding our clinical scenario. The presentation of endocarditis with a cutaneous vasculitis has been well reported. The concern expressed by Bachmeyer et al regarding the description of the rash is valid, but as noted in our report, the rash was first observed when the patient was admitted to an "outside" hospital. Given that the patient had altered mental status when he was transferred to our hospital, it was difficult to obtain a detailed history with regard to the distribution, symmetry, and characteristics of the skin rash. Our concern for petechial rash (leukocytoclastic vasculitis) was based on his past medical records and postinflammatory scarring on his lower extremities.

The other concern raised by Bachmeyer et al was that petechial rash is no longer included in the diagnostic criteria for infective endocarditis because the presence of petechiae is a nonspecific finding. We agree regarding the nonspecificity of this type of skin manifestation but still believe that petechial rash (leukocytoclastic vasculitis) is an important diagnostic clue for infective endocarditis. Several studies in similar cases have highlighted the importance of including infective endocarditis in the differential diagnosis list, because it is a more commonly reported presentation in comparison to other specific skin manifestations of infective endocarditis (1). Although the specificity of petechial rash in patients with infective endocarditis is low, its prevalence is high, leading researchers to underscore the need to consider a diagnosis of infective endocarditis before pursuing a diagnosis of autoimmune disease; patients with autoimmune disease require treatment with immunosuppressive medications, which can be detrimental in patients with infective endocarditis (1,2). A similar scenario was reported in our case presentation.

Another notable finding, as pointed out by Bachmeyer et al, was the important relationship between RF IgM/IgG and infective endocarditis. Other investigators have shown that 97% of patients with infective endocarditis had immune complex deposition, and that these patients had elevated levels of IgM-RF, IgG-RF, or both (3). Both IgG-RF and IgM-RF have been reported to be a part of polyvalent antibody response to elevated levels of circulating immune complexes that might or might not contain RF. Elevated IgG-RF levels have been reported not only in patients with infective endocarditis but also in patients with uncomplicated sepsis, chronic liver disease, or chronic viral infections such as hepatitis C virus (3).

Shivani Garg, MD, MS
University of Wisconsin
Madison, WI

1. Loricera J, Blanco R, Hernández JL, Calvo-Río V, Ortiz-Sanjuán F, Mata C, et al. Cutaneous vasculitis associated with severe bacterial infections: a study of 27 patients from a series of 766 cutaneous vasculitis. Clin Exp Rheumatol 2015;33(Suppl 89):S36–43.
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Hypothesis: can neuroendocrine immune testing in individual rheumatoid arthritis patients guide the benefits-to-harms ratio in glucocorticoid therapy? Comment on the article by Palmowski et al

To the Editor:

We compliment Palmowski and colleagues and endorse the "official view" expressed in their review of guidelines for glucocorticoid (GC) therapy in patients with rheumatoid arthritis (RA) (1). The international guidelines were generally in agreement that GCs are an appropriate option for RA therapy, especially at low doses and for a short duration (1). However, the recommendations lacked evidence and guidance regarding doses, timing, and duration of GC treatment. The authors concluded that high-quality studies of GCs in RA are urgently needed (1).

In an accompanying editorial, Mahajan and O'Dell (2) referenced a study by Hench and Kendall (3) describing the first use of cortisone to treat a patient with RA. In that study, the patient received daily intramuscular injections of GCs (100 mg of cortisone), based on the belief that the drug could help to correct a deficiency (2). Mahajan and O'Dell also stated that the optimal GC dose or duration of GC treatment in patients with early RA is not known either in general or for individual patients (2). It is also not known whether adverse risks or benefits are related to linear or threshold doses of GCs, in general or individually (2).

A previous systematic literature review was conducted with the aim of defining conditions under which long-term GC therapy in patients with rheumatic disease could result in an acceptably low level of harm in relation to beneficial effects (4). Robust evidence regarding the risk of harm was often lacking, and there was uncertainty about patient-specific characteristics (e.g., age, sex, disease activity) that could influence the risk/benefit ratio. The authors concluded that future high-quality data are needed, including data on patient-specific conditions (4).

An ongoing randomized trial of prednisolone 5 mg/day for 2 years versus placebo in elderly patients with RA is being conducted to determine whether it is a highly cost-effective and safe therapy (1). A complementary hypothesis for individual RA patients is whether or not baseline serum neuroendocrine immune (NEI) profile testing can be cost-effective in guiding GC therapy to achieve improved benefits:harms outcome? Research on individual benefits and harms of GC therapy in individual patients with RA is necessarily challenging. Little is known about the complex and varied interactions of genetic/epigenetic, behavioral (smoking), age, sex, and NEI influences.

A PubMed search (conducted on September 1, 2017) for "rheumatoid arthritis mechanisms" and "hypothalamic pituitary" yielded 35 citations (https://www.ncbi.nlm.nih.gov/pubmed/?term=%22mechanisms+in+rheumatoid+arthritis%22+AND+%22hypothalamic+pituitary%22). The preceding articles indicated a relative adrenocortical insufficiency in a minority of premenopausal-onset RA patients versus control subjects, before and after the onset of RA. Previous reports also suggest that baseline dynamic testing of adrenal function (e.g., using adrenocorticotropic hormone stimulation), in addition to adrenal glucocorticoid and androgenic-anabolic steroid measurements, could be predictive biomarkers in individual RA patients who may benefit the most from long-term, low-dose GC therapy. The immunologic component of NEI factors in RA would also require selective baseline and periodic monitoring of inflammatory bio-

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Shivani Garg, MD, MS
University of Wisconsin
Madison, WI

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Hypothesis: can neuroendocrine immune testing in individual rheumatoid arthritis patients guide the benefits-to-harms ratio in glucocorticoid therapy? Comment on the article by Palmowski et al

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markers serum biomarkers (acute-phase reactants [high-sentivity C-reactive protein and serum amyloid A]) and inflammatory cytokines [e.g., interleukin-6]).

GCs are not simply drugs, but also are potent hormones. When relative adrenocortical insufficiency is identified, GC therapy deserves physiological consideration in terms of doses, diurnal variation, delivery, and other factors that best conform to the concept of chronic, individualized "hormone replacement therapy." In addition, when GC treatment is needed for antiinflammatory effects, the treatment should be monitored for personalized chronic long-term benefits:harms outcomes. Research is needed to evaluate whether monitoring of endogenous hypothalamic–pituitary–adrenal function and the inflammatory component of NEI mechanisms in RA can achieve both improved efficacy and safety coupling and individualized cost-effective GC therapy guidelines.

Alfonse T. Masi, MD, DrPH
University of Illinois College of Medicine at Peoria
Peoria, Illlinois
Richard Imrich, MD, PhD
Slovak Academy of Sciences
Bratislava, Slovak Republic
Maurizio Cutolo, MD
University of Genoa
Genoa, Italy

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Reply

To the Editor:

We would like to thank Masi and colleagues for their interest in our study as well as for their interesting comments regarding the potential usefulness of NEI testing in patients with RA.

When GCs were first used in 1948 to treat a patient with RA, the effect was overwhelming for that time. The impact on the treatment of rheumatic diseases was so tremendous that it was captured in a previous review article by dividing the history of rheumatology into "BC" and "AC" (before cortisol and after cortisol) (1). Although the discovery was originally guided by the idea of correcting an existing GC deficiency (2), the great enthusiasm about the effects produced by the new miracle drug led to the administration of dosages by far exceeding a mere "substitution therapy" in the following years (3). Inevitably, this extensive use soon revealed the serious downsides of GC use: the striking antiinflammatory effects were contrasted by substantial adverse events in many patients, and the initial enthusiasm rapidly turned into an equally great skepticism. GCs gradually lost their importance as first-line treatment in uncomplicated RA (4).

With such great concerns regarding GC therapy prevailing for a long period of time, it took several decades for their disease-modifying potential as a low-dose co-medication to come to light (4). But even today, more than 65 years after the first administration of cortisone to a patient with RA, the optimal dose and the adequate treatment duration as well as the actual risk/benefit ratio remain unclear. Therefore, many researchers continue to see the role of GCs primarily as that of a short-term bridging therapy until conventional synthetic disease-modifying antirheumatic drugs reach full effect (5,6). In a recent systematic literature review, authors concluded that the risk of harm of long-term GC treatment is acceptably low for doses of up to 5 mg of prednisone in the majority of patients, although robust evidence is still missing (7). The currently ongoing Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) trial, the aim of which is to prove the safety and cost-effectiveness of additional low-dose GCs (5 mg/day of prednisone) in patients ≥65 years of age, will hopefully provide valuable new evidence.

Yet, a better clarification of the general risk/benefit profile is only one of several steps still necessary for safer and more efficient GC therapy. Further steps include the introduction and in-depth evaluation of new GC formulations (e.g., modified-release prednisone, liposomal prednisone, and selective GC agonists/modulators) as well as a more individualized adjustment of the treatment regimen, for which NEI testing may indeed play a major role. A significant proportion of the complexity of GC treatment derives from its close interdependency with endogenous cortisol production, and changes in the circadian rhythm have long been observed in RA patients (8). Low baseline adrenal function may serve as a valuable predictor of a positive individual risk/benefit ratio, while hypercortisolism might be indicative of a higher risk for undesired side effects—even more so in the case of low-dose regimens. Interestingly, the dosage of 5 mg/day of prednisone used in the GLORIA trial and proposed by Strehl et al (7) is not only within the range of physiological endogenous cortisol production (9–11 mg/day of cortisol [equal to ~4–5 mg of prednisone in an average adult] [9]) but also in accordance with recommendations for substitution therapy in patients with pituitary insufficiency (10). Therefore, we actually might already

be closer than we thought to the originally intended purpose of GC therapy.

At the same time, this observation might also offer a solution to another issue raised by Mahajan and O'Dell (2): because it has proven difficult to identify clinically relevant cut-offs that can be agreed on for a uniform nomenclature, wouldn't it be an obvious solution to use the natural cut-off of endogenous production for a clear and plausible definition of low-dose GC treatment?

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Yannick Palmowski, MD
Frank Buttgereit, MD
Universitätsmedizin Berlin
Berlin, Germany
Maarten Boers, MD, MSc, PhD
University of Twente, Enschede,
The Netherlands and VU
University Medical Center
Amsterdam, The Netherlands

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Differences in management style between pediatric and adult rheumatologists: comment on the article by Van Mater et al

To the Editor:

According to the Arthritis Foundation, more than 300,000 children in the US have juvenile arthritis, and there are many more children with musculoskeletal conditions who could benefit from rheumatologic care. However, there are only approximately 350 board-certified pediatric rheumatologists in this country, and 8 states do not have a single board-certified practitioner. As a consequence, more than 75% of children with rheumatic disease are cared for by an adult certified rheumatologist. A recent article (Van Mater H, Balevic SJ, Freed GL, Clark SJ. Prescribing for children with rheumatic disease: perceived treatment approaches between pediatric and adult rheumatologist. Arthritis Care Res [Hoboken] 2018;70:268–74) highlights some differences in management style between pediatric and adult rheumatologists, although data reflecting outcome differences are not presented.

The reality is that pediatric subspecialty programs are poorly enrolled, and pediatric rheumatology programs are especially under-enrolled. More than 20 years after the availability of certification in pediatric rheumatology (established in 1992), there is still a desperate need for pediatric rheumatology specialists. This is compounded by increasingly common restrictions on faculty appointments to pediatric departments without pediatric rheumatology board certification. As an adult trained rheumatologist who spends most of his clinical effort caring for children, I would like to make the following recommendations: 1) that training programs in adult rheumatology require some exposure to pediatric rheumatic disease, 2) that programs are established for adult trained rheumatologists to gain additional training and certification status in pediatric rheumatology, and 3) that adult rheumatologists with faculty appointments in pediatric departments be granted status within the pediatric rheumatology community.

Although it is arguable whether training in pediatrics is absolutely necessary for the practice of pediatric rheumatology, such training would at least represent an attempt to fill the gap until there are sufficient numbers of trained pediatric rheumatologists, if that indeed ever happens.

Daniel Albert, MD
Dartmouth Hitchcock Medical Center
Lebanon, NH

ARP Announcements

Association of Rheumatology Professionals
2200 Lake Boulevard NE, Atlanta, Georgia 30319
www.rheumatology.org

ACR/ARP Annual Meeting

November 8–13, 2019, Atlanta

Applications Invited for *Arthritis & Rheumatology* Editor-in-Chief (2020–2025 Term)

The American College of Rheumatology Committee on Journal Publications announces the search for the position of Editor, *Arthritis & Rheumatology*. The official term of the next *Arthritis & Rheumatology* editorship is July 1, 2020–June 30, 2025; however, some of the duties of the new Editor will begin during a transition period starting April 1, 2020. ACR members who are considering applying should submit a nonbinding letter of intent by May 1, 2019 to the Managing Editor, Jane Diamond, at jdiamond@rheumatology.org, and are also encouraged to contact the current Editor-in-Chief, Dr. Richard Bucala, to discuss details; initial contact should be made via e-mail to richard.bucala@yale.edu. Applications will be due by June 21, 2019 and will be reviewed during the summer of 2019. Application materials are available on the ACR web site at https://www.rheumatology.org/Learning-Center/Publications-Communications/Journals/A-R.

New Division Name

Rheumatology is truly a people specialty: We often develop lifelong relationships with our patients as well as our colleagues. We increasingly recognize that providing the best rheumatologic care requires a team effort. The collegial nature of our specialty is reflected in the ACR's mission statement: To empower rheumatology professionals to excel in their specialty.

In keeping with this mission, we are pleased to announce that our health professionals' membership division is changing its name to Association of Rheumatology Professionals (ARP). This name change highlights the dedication of the ACR to serve the entire rheumatology community. It also reflects our broadened base of interprofessional members (administrators, advanced practice nurses, health educators, nurses, occupational therapists, pharmacists, physical therapists, physician assistants, research teams, and more).

The name is new, but our commitment and promise remain the same: We are here for you, so you can be there for your patients.

ARP Membership

The Association of Rheumatology Professionals (ARP), a division of the American College of Rheumatology, appreciates your continued membership and looks forward to serving you another year. Membership costs range from $30 to $140. ARP welcomes nurse practitioners, nurses, physician assistants, office staff, researchers, physical therapists, occupational therapists, assistants, and students. Student membership is complimentary; the Annual Meeting registration fee is waived for students who submit the required student verification letter. For information, go to www.rheumatology.org and select "Membership" or call 404-633-3777 and ask for an ARP staff member.

New for 2019: Education for Rheumatology Professionals

Whether you are new to a rheumatology practice or just need a rheumatology refresher, kick off 2019 with high-quality education for the entire interprofessional team. All 19 Advanced Rheumatology Course activities have been updated with all-new interactive content, including mini-quizzes. You can also register for 11 brand new Advanced eBytes, which are complimentary to ARP members. For information on pricing, credits hours, and registration go to www.rheumatology.org, click the drop down box "I AM A" next to the Membership tab and select "Health Professional Education."