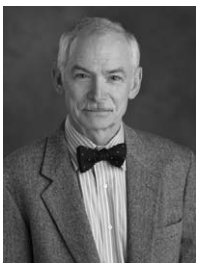
Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

SECTION EDITORS

W. Joseph McCune



Dr Joseph McCune is a graduate of Harvard College, and the University of Cincinnati Medical School, USA. Following residency at the University of Michigan, USA, and fellowship Brigham and Women's Hospital, USA, he joined the faculty of the University of Michigan, where he is the Michael and Marcia Klein Professor of Rheumatic Diseases and Director of the Lupus Program.

Dr McCune has devoted much of his research career to systemic lupus. He reported the clinical and immunologic effects of monthly bolus cyclophosphamide for severe lupus using methods that were subsequently adopted as standard treatment for lupus nephritis and has since focused on improving the efficacy and safety of immunosuppressive therapy, including the use of leuprolide for ovarian protection in women receiving cyclophosphamide. His work in medical imaging helped establish the importance of MRI in neurological complications of lupus and rheumatoid arthritis, and he was the first to describe ultrasound imaging of articular cartilage. Current interests include the pathogenesis of cardiovascular disease in SLE, advanced MRI in SLE, and detailed population-based epidemiologic studies of the SLE in southeastern Michigan.

Jon T. Giles

Dr Giles's research interests are centered primarily within the inflammatory arthritides. Current projects center around understanding the inflammatory and non-inflammatory determinants of body composition abnormalities in rheumatoid arthritis and psoriatic arthritis, and their subsequent effects on health outcomes. Other current and past research involve the investigation of accelerated atherosclerosis and myocardial dysfunction in rheumatoid arthritis patients, understanding the determinants of rheumatoid arthritis-associated interstitial lung disease, and exploring the musculoskeletal side-effects of a class of medications used to suppress estrogen in women with certain forms of breast cancer.

He is the recipient of grant support from the National Institutes of Health, the Arthritis Foundation, the Rheumatology Research Foundation, the Marianne Legato Foundation, and the Arthritis National Research Foundation.

IgG4-related disease

Emanuele Bozzalla Cassione and John H. Stone

Purpose of review
Remarkable insights have been gleaned recently with regard to the pathophysiology of IgG4-related disease (IgG4-RD). These findings have direct implications for the development of targeted strategies for the treatment of this condition.

Recent findings
Oligoclonal expansions of cells of both the B and T lymphocyte lineages are present in the blood of patients with IgG4-RD. Oligoclonal expansions of plasmablasts are a good biomarker for disease activity. An oligoclonally expanded population of CD4+ cytotoxic T lymphocytes is found not only in the peripheral blood but also at tissue sites of active disease. This cell elaborates cytokines that may drive the fibrosis characteristic of IgG4-RD. T follicular helper cells (Tfhc), particularly the Tfhc2 subset, appear to play a major role in driving the class switch to IgG4 that typifies this disease. The relationship between malignancy and IgG4-RD remains an area of interest.

Summary
Advances in understanding the pathophysiology of IgG4-RD have proceeded swiftly, leading to the identification of a number of potential targeted treatment strategies. The completion of classification criteria for IgG4-RD, an effort supported jointly by the American College of Rheumatology and the European League Against Rheumatism, will further facilitate studies on this disease.

Keywords
CD4+ cytotoxic T lymphocyte, IgG4-related disease, plasmablast, T follicular helper cell

INTRODUCTION

IgG4-related disease (IgG4-RD) is a chronic fibroinflammatory condition characterized by tumefactive lesions, dense lymphoplasmacytic infiltrates, and abundant IgG4-bearing plasma cells in the affected tissues. Serum IgG4 concentrations in patients' sera are often elevated dramatically, yet are normal in approximately one-third of patients with clinicopathologically confirmed disease. IgG4-RD was described first in the pancreas – the condition once termed 'lymphoplasmacytic sclerosing pancreatitis' or sometimes just 'sclerosing pancreatitis', among other designations [1].

Common histological features are now known to characterize IgG4-RD in essentially every organ in the body [2]. Broader experience with this condition, however, has led to the recognition that the diagnosis is critically dependent upon careful correlation between clinical, pathological, and often radiological findings. American College of Rheumatology/European League Against Rheumatism Classification Criteria are now being developed on the basis of this recognition.

The immunopathogenesis of IgG4-RD remains incompletely defined. B cells at first and subsequently T cells have been recognized to be key players in disease pathogenesis, but their full contributions to IgG4-RD remain to be elucidated. Moreover, other elements of the immune system are also likely to play important roles. Treatment of IgG4-RD to date has been predicated primarily on glucocorticoids, but the growing recognition of this approach's shortcomings has spawned earlier consideration of either nonspecific 'disease-modifying' agents or targeted treatments, both of which are intended as steroid-sparing strategies.

ROLE OF B CELLS

A first reliable advance into the pathophysiology of IgG4-RD was made when preliminary studies with rituximab (RTX) showed that B-cell depletion

Rheumatology Clinic/Yawkey 2, Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence to Dr John H. Stone, MD, MPH, Rheumatology Clinic/Yawkey 2, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA. Tel: +1 617 726 7938; e-mail: jhstone@mgh.harvard.edu

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KEY POINTS

- Oligoclonal expansions of cells of both the B and T lymphocyte lineages are present in the blood of patients with IgG4-RD.
- Blood plasmablast concentrations correlate well with disease activity – better even than do serum IgG4 levels.
- An oligoclonally expanded population of CD4+ CTLs, found not only in the peripheral blood but also at tissue sites of active disease, elaborates cytokines that may drive the fibrosis characteristic of IgG4-RD.
- Tfhc2 appears to play a major role in driving the IgG4 class switch.
- Data from a recent study suggest that a history of malignancy may be a risk factor for IgG4-RD rather than vice versa.
- The completion of classification criteria for IgG4-RD, an effort supported jointly by the American College of Rheumatology and the European League Against Rheumatism, will further facilitate studies on this disease.

induced disease remission and led to improvement in tissue fibrosis [3▪]. Clinical improvement was accompanied by a reduction in serum IgG4 levels. Further studies in IgG4-RD patients with active, untreated disease identified an oligoclonally expanded population of circulating $CD19^+CD20^-CD27^+CD38^+$ bright plasmablasts (cells that are the precursors of tissue-resident, antibody-producing plasma cells). Flow cytometry studies following treatment demonstrated that clinical improvement correlated with selective depletion of this B-cell subpopulation [4▪▪]. Many patients achieved clinical remissions without normalizing their serum IgG4 concentrations, even though substantial declines in serum IgG4 levels following treatment were the rule.

The B-cell compartment of patients with IgG4-RD has been studied extensively because the striking serum IgG4 elevation in many patients and the abundance of IgG4+ plasma cells at sites of disease initially suggested the possibility of an underlying lymphoproliferative condition. The latter hypothesis has then been excluded because of failure to identify monoclonal plasma cells populations in the affected tissues [2], but the issue of a potential relationship between malignancy and IgG4-RD risk – and vice versa – remains an important topic.

At least two lines of evidence from the humoral immune system have suggested that an antigen-driven immune response is present in IgG4-RD. Studies on the cerebrospinal fluid of patients with IgG4-related pachymeningitis revealed the presence of oligoclonal IgG4 [5]. In addition, next-generation sequencing analysis on tissue biopsy samples and on the peripheral blood of IgG4-RD patients demonstrated oligoclonal expansions of somatically hypermutated $IgG4^+$ B-cell clones [4▪▪].

The oligoclonally expanded B cells were identified by flow cytometry as being $CD19^+CD20^-CD27^+CD38^+$ plasmablasts. Plasmablasts arise in germinal centers following affinity maturation from naïve CD20+ precursors. Once in the bloodstream, plasmablasts differentiate into antibody-secreting short-lived or long-lived plasma cells, accounting for the excess IgG4 production in this disease [6]. Plasmablast concentrations in the blood correlate well with disease activity, decreasing sharply after RTX-induced remission and reemerging during relapse. It is worth noting that the plasmablasts reemerging during disease relapses express distinct V-J repertoires compared with samples from the same patients before their initial treatment. This phenomenon, known as 'clonal divergence', further supports the hypothesis of hypermutation driven by the selection of specific antigens.

ROLE OF T CELLS

T-cell responses have long been considered to be central to the pathophysiology of IgG4-RD, but the focus of interest within the T-cell population has shifted within recent years. Th2 immune responses were once believed critical to IgG4-RD pathways, partly because of the high frequency of atopic symptoms observed in many patients with IgG4-RD [7] and partly because of the detection of mRNA from cytokines frequently linked to Th2 responses, for example, IL-4, IL-5, and IL-13 [8]. More recent studies, however, have demonstrated expansions of Th2 cells only in the circulation of IgG4-RD patients with an atopic history, not in those without histories of atopy [9▪]. It seems, therefore, that despite initial appearances, the role of Th2 cells in IgG4-RD is marginal. Other subpopulations of T cells, however, are involved more directly in IgG4-RD pathogenesis.

A novel population of effector memory CD4+ T cells with cytotoxic function [CD4+ cytotoxic T lymphocytes (CTLs)] has then been described in IgG4-RD patients [10▪▪]. Substantial evidence suggests that this population of cells plays an important role in the pathophysiology of this disease. CD4+ CTLs are expanded in both the peripheral blood and in affected organs of IgG4-RD patients. Moreover, together with circulating plasmablasts (though at a slower rate), these CD4+ CTLs decline following RTX treatment, supporting the

concept that cells of the B-cell and T-cell lineages cooperate closely in mediating this condition [10▪▪].

Cytotoxicity associated with CD4+ T-helper lymphocytes is a concept that has emerged progressively in the past few years. The concept contrasts with the traditional view that cytotoxic T cells arise only from major histocompatibility complex (MHC) class I-restricted CD8+ T lymphocytes. During thymic development, lineage commitment toward CD4+ or CD8+ T-cell fate is driven by the action and counteraction of the key transcription factors, ThPOK and Runx3, respectively [11]. CD4+ CTLs seem to represent highly differentiated, antigen-experienced (memory) T cells with features of both CD4+ and CD8+ T lymphocytes (though there are CD8−) [12]. It is likely that this cell population arises from chronic antigenic stimulation. Indeed, in response to repeated antigenic stimulation, ThPOK is downregulated, resulting in a cytolytic gene expression program in activated CD4+ T cells, with differentiation into MHC class II-restricted CD4+ CTLs and an effector cell phenotype [11].

The CD4+ CTLs identified express high levels of CD11a and CD11b integrins, and CD45 isoform-RO and isoform-RB. They lack the costimulatory receptors CD27, CD28, the chemokine receptor CCR7, and CD45-RA. Small numbers of CD4+ CTLs can be detected in the blood of healthy individuals [13], and they significantly increase during chronic viral infections (such as cytomegalovirus [14], Epstein–Barr virus [15], and HIV [13]), malignancies [16], and autoimmune disorders [17]. CD4+ CTLs seem to bear protective functions such as control of infected cells or elimination of transformed cells, thanks to their cytolytic MHC class II-restricted action. Nevertheless, the accumulation of CD4+ CTLs in the setting of autoimmune conditions such as rheumatoid arthritis [18] and inflammatory bowel disease [19] suggests that these cells might also contribute to chronic inflammation. Indeed, CD4+ CTLs numbers correlate with disease severity in rheumatoid arthritis and ankylosing spondylitis, and decrease after treatment with anti-TNFalpha agents [20].

In summary, the CD4+ CTLs identified in the context of IgG4-RD represent the most carefully phenotyped such cell studied to date. The cell appears to have significant potential to contribute to chronic inflammation of a variety of forms.

ROLE OF T FOLLICULAR HELPER CELLS

The powerful evidence of class-switching in IgG4-RD has led to substantial interest in the role of T follicular helper (Tfh) cells in this condition. Tfh cells are known to be involved in the differentiation of B cells during their development and to contribute significantly to class switching [21]. Akiyama *et al.* [22,23▪▪] have reported that among Tfh cells subsets, Tfh2 cells induce the differentiation of naïve B cells into plasmablasts, subsequently promoting the production of IgG4 in active, untreated IgG4-RD. Circulating Tfh2 cells are expanded IgG4-RD and their concentrations are linked to disease activity, the concentrations of circulating plasmablasts, and serum IgG4 levels.

In contrast, although circulating activated Tfh1 cells were also found to be expanded in IgG4-RD, their levels correlated with disease activity but not with serum IgG4 levels. These findings support the hypothesis of a greater role for Tfh2 cells in the class switch observed in IgG4-RD. It is known that Tfh cells in germinal centers cooperate with B cells in the formation and antibody production. Therapy with glucocorticoids did not affect Tfh2 cell counts, but did result in a decrease in numbers of plasmablasts and levels of serum IgG4 and IL-4. As IL-4 is believed to be produced by Tfh2 cells and not by the other Tfh cell subsets, it is possible that glucocorticoid treatment affects the function and not the number of these cells.

PLASMACYTOID DENDRITIC CELLS

Plasmacytoid dendritic cells (pDCs) were shown to be important in the development of pancreatic inflammation through production of IFN-alpha [24▪▪]. Autoimmune pancreatitis (AIP) in IgG4-RD patients is associated with an infiltration of pDCs. Peripheral pDCs from IgG4-RD patients were shown to enhance IgG4 antibody production by cells through IFN-alpha-mediated signaling. Demonstration of a role for IFN-alpha in this disease comes from studies conducted on experimental AIP models in which regression of the inflammation was seen to occur with depletion of IFN-alpha production or signaling.

Final proof of its relevance in AIP in humans requires studies with pDC-depleting antibodies or neutralizing IFN-alpha receptor antibodies. In addition to pDCs, inflamed pancreata also harbor NETs. These structures have been seen to be involved in the activation of pDCs [25–26]. In fact, cocultures of pDCs and neutrophils, forced to express NETs by monosodium urate (MSU) crystals or antilactoferrin antibodies (NET component protein), showed increased production of IFN-alpha and the B lymphocyte-activating factor known as BAFF. Moreover, when these cells were cocultured together with B cells, they led to increases in IgG4 production.

Some data do support the notion that antilactoferrin antibodies contribute to IgG4-RD. Serum

antilactoferrin antibody titers, especially those of the IgG4 subclass, were elevated in the serum of IgG4-RD patients. In contrast, there has to date been no demonstration of MSU deposition in the IgG4-related pancreatic lesion.

THERAPY

A group of international experts published a Consensus Guidance Statement on the Management of IgG4-RD [27]. This effort grew out of the Second International Symposium on IgG4-RD and Associated Conditions, held in 2014. The Third such Symposium is scheduled for 2017, and it is there that the ACR/EULAR Classification Criteria will be completed.

RTX was used initially in patients who did not respond to glucocorticoids, conventional steroid-sparing agents, or both, under the assumption that B-cell depletion might ameliorate the condition through decreasing serum IgG4 concentrations [28]. The fundamental assumption underlying this approach now seems not entirely true. Indeed, careful mechanistic studies of patients with IgG4-RD treated with RTX have led to novel insights about the pathophysiology of this disorder. First, B-cell depletion targets the subset of plasma cells that produce IgG4 in IgG4-RD [29], by depleting all circulating CD20− positive B cells, the precursors of short-lived plasma cells. Second, IgG4+ plasmablasts (CD38+CD27+CD19+CD20−IgG4+ cells) seem to be a good biomarker for IgG4-RD and are superior to serum IgG4 concentrations for diagnosis and monitoring of disease activity [30▪].

Yamamoto *et al.* [31] described the use of abatacept (cytotoxic T lymphocytes-associated protein 4-immunoglobulin) to treat one patient with IgG4-RD whose condition had been refractory to RTX. Given the recognition of the importance of T cells in this disease now emerging, greater attention to treatment strategies directly targeting T-cell function may be of value.

TUMOR ASSOCIATION

Discussions of a possible link between IgG4-RD and malignancy have emerged recently. Evidence against such a relationship, however, came from a retrospective study showed that history of malignancy was 2.5 times more likely in IgG4-RD patients compared with the general US population [32▪]. Moreover, a history of malignancy was three times more common among IgG4-RD patients than among control patients in a case–control analysis performed as part of the same study. Prostate cancer was the most common malignancy in both the IgG4-RD patients and the controls, a point not surprising given the demographics of IgG4-RD and its tendency to afflict middle-aged to elderly men. It is worth noting, however, that lymphoma was responsible for 19% of the malignancies in the IgG4-RD cohort, compared with only 4% in the control cohort. These data may suggest a possible interplay between the immune dysregulation found in IgG4-RD and lymphomagenesis.

Disease history of IgG4-RD seems to differ between IgG4-RD patients with malignancy and those without. IgG4-RD patients with malignancy history develop IgG4-RD at a later age and had higher serum IgG4 concentrations compared with the subgroup without malignancy. It should be noted that no cases of IgG4-RD involving the organ previously affected by cancer were reported.

Malignancy may therefore be a predisposing condition, at least in some patients. One hypothesis is that treatment of malignancy (e.g., radiation and chemotherapy) favors immune deregulation. Alternatively, there might be a common genetic predisposing background behind both malignancy and IgG4-RD. However, the fact that no IgG4-RD manifestation occurred at the site of a prior malignancy suggests that local changes deriving from the tumor itself or from its treatment are not a likely explanation. We anticipate further discussion about the potential connections between IgG4-RD and malignancies in the future.

CONCLUSION

The large increase in literature production on IgG4-RD in these past years reflects the increasing interest of scientific community about this topic. Despite the increased efforts, the exact pathophysiology standing behind this fibroinflammatory condition still remains enigmatic. Studies in the last years, highlighting a role for T-cell subpopulations, namely CD4+ CTLs and Tfh cells, as well as plasmablasts and pDCs in IgG4-RD, seem to open new vistas from which to explore further the biological processes leading to fibrosis. We anticipate increasing interest in targeted disease therapies based on emerging pathophysiological insights.

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Conflicts of interest

There are no conflicts of interest.

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Calls into question the idea that IgG4-RD is a precursor of malignancy. In fact, the opposite may be true.

Diagnostic and therapeutic considerations in patients with hypogammaglobulinemia after rituximab therapy

Ruba Kado[a], *Georgiana Sanders*[b], *and W. Joseph McCune*[a]

Purpose of review
There are no established guidelines for evaluating and treating hypogammaglobulinemia in patients with rheumatic disease who receive B-cell depleting agents. The purpose of this article is to review findings in the work-up and treatment of common variable immunodeficiency (CVID) that can guide our evaluation of patients with autoimmune disease who develop hypogammaglobulinemia after rituximab/B-cell depleting therapy.

Recent findings
Infection rates are higher in rheumatic disease patients who develop hypogammaglobulinemia than those who do not. However, not all patients who develop hypogammaglobulinemia are at increased risk of developing infection after B-cell depleting therapy. Recent consensus statements have helped refine the diagnosis of impaired immune responses in patients with CVID, and can provide guidance for the diagnostic work-up and therapeutic decision making for patients with secondary drug induced hypogammaglobulinemia.

Summary
Based on findings in studies of CVID, assessment of vaccine response in patients with hypogammglogulinemia after rituximab therapy in the setting of recurrent infections can help predict propensity for infection and thus guide decision making with regards to intravenous immunoglobulin supplementation and retreatment with rituximab.

Keywords
antibody deficiency, hypogammaglobulinemia, rituximab therapy

INTRODUCTION

In a previous article, the authors of this study outlined the immunologic consequences of immune suppression with rituximab. We noted that preexisting hypogammaglobulinemia has been linked to increased risk of further reduction of immunoglobulin G (IgG) levels and serious infections after rituximab therapy; concomitant cyclophosphamide therapy has been associated with an increased risk of developing hypogammaglobulinemia [1,2]. Immunoglobulin M (IgM) depletion postrituximab is more frequent and prolonged than IgG depletion, but less clinically significant. Early and late-onset neutropenia has been described, but appears to be transient [1]. The following review is focused on patients treated with cyclophosphamide and/or rituximab and should also be applicable to assessing the component of immunosuppression attributable to hypogammaglobinemia when it occurs in the setting of treatment with other immunosuppressive drugs used to treat rheumatic diseases.

Important decisions in managing rheumatic disease patients treated with rituximab include: when to check immunoglobulin levels in rheumatic disease patients on rituximab and other immunosuppressive agents, whether or not to provide immunoglobulin replacement therapy (IGRT) to patients with prolonged hypogammaglobulinemia,

[a]Division of Rheumatology, Department of Internal Medicine and [b]Division of Allergy and Immunology, Departments of Internal Medicine and Pediatrics and Communicable Diseases, University of Michigan, Michigan, USA

Correspondence to Ruba Kado, MD, Suite 7C27 North Ingalls Building, 300 North Ingalls SPC 5422, Ann Arbor, MI 48109-5422, USA.
Tel: +1 734 232 6115; e-mail: kador@med.umich.edu

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KEY POINTS

- Findings in the work-up and treatment of CVID can guide evaluation of patients with autoimmune disease who develop hypogammaglobulinemia after rituximab/B-cell depleting therapy.
- In patients with hypogammaglobulinemia after rituximab therapy, assessing vaccine responses to protein and polysaccharide vaccines can help predict risk of infection.
- The subset of hypogammaglobulinemic patients with recurrent infections and failure to respond to protein and polysaccharide vaccines constitute a high-risk group and deserve consideration for administration of intravenous or subcutaneous immunoglobulin.

how to begin therapy and how long to continue IGRT in these patients, and whether to modify immunosuppressive therapy in these patients. There are no consensus guidelines for this population; however, there are recent articles outlining an approach to the patient with secondary antibody deficiency based on established guidelines, reviewed below [3,4▪▪,5▪▪]. We will also review guidelines for the evaluation and treatment of patients with primary antibody deficiencies, in particular common variable immunodeficiency (CVID) [6▪▪,7,8▪▪], which serves as a model for this population.

COMMON VARIABLE IMMUNODEFICIENCY, A MODEL FOR APPROACHING HYPOGAMMGLOBULINEMIA AND ANTIBODY DEFICIENCY SECONDARY TO MEDICATION

The immune response in CVID is variable and results from a complex interplay between the innate and adaptive immune systems causing impaired B-cell maturation. In contrast with hypogammaglobulinemia in patients with rheumatic diseases, CVID is not a consequence of pharmacologic B-cell suppression or depletion. However, some patients with rheumatic diseases may suffer from both the effects of immunosuppression and underlying CVID that has not previously been appreciated.

The phenotype of CVID is variable and there are different proposed consensus criteria for the diagnosis of CVID, including the recently developed International Consensus Document (ICON) from Europe, and the Joint Practice Parameters in the United States [6▪▪,8▪▪]. CVID is characterized by increased susceptibility to infections and low IgG levels as well as low immunoglobulin A (IgA) and/or IgM levels. Clinical features include recurrent, severe, or unusual infections; autoimmune manifestations; granulomatous disease; lymphoproliferative disorders; and poor response of infections to antibiotic therapy.

Low lgG levels are variously defined as IgG either below an absolute threshold of 450–500 mg/dl for adults or as IgG level more than two SD below the normal mean [7,9]. Supportive criteria, which have been less stringently applied in the setting of very severe IgG depression (below 300 mg/dl), include concomitant depression of IgA with or without IgM depression (2 SD below mean), and failure to respond to protein and/or polysaccharide vaccines [6▪▪,7,8▪▪]. Most criteria exclude children less than 4 years old from a diagnosis of CVID. CVID is a diagnosis of exclusion, and it is recommended that other causes of hypogammaglobulinemia should be ruled out [6▪▪,8▪▪].

Berglund *et al.* [10] outline the impaired maturation of B cells in CVID patients. Carsetti *et al.* [11] addressed the finding that some patients with profound hypogammaglobulinemia are protected against bacterial pneumonia; their findings suggest that in these cases, IgM memory B cells are present in adequate numbers. Additionally, Goldacker *et al.* [12] demonstrated that immune responses to polysaccharide and polypeptide were mounted in CVID patients who had adequate IgM memory B cells.

TESTING FOR IMPAIRED IMMUNITY AND SUSCEPTIBILITY TO INFECTION

It should be noted that there has been no standardization of diagnostic assessment when it comes to testing for response to immunization in CVID or in other forms of hypogammaglobulinemia. In addition, prior vaccinations and widespread use of Prevnar (pneumococcal-13 vaccine, manufactured by Wyeth Pharmaceuticals Inc., marketed by Pfizer Inc.) can alter the degree of increase in titers post-vaccination [3,13▪,14].

Protein containing (T-cell dependent) and pure polysaccharide (T-cell independent) vaccines are used in testing for an appropriate vaccine response. Pneumococcal polysaccharide 23 vaccine (Pneumovax-23, Merck and Co.,Inc) is most often used. Frequently used protein or conjugated vaccines include tetanus toxoid and diphtheria toxoid. However, Haemophilus influenzae B vaccines (conjugated), hepatitis A subunit, hepatitis B surface antigen, and meningococcal vaccines (polysaccharide or protein conjugate) are also used [14,15].

Studies have addressed interpretation of vaccine responses in CVID patients, and normal antibody responses are defined based on achieving known protective titers and/or a four-fold increase in titers, although there has been variability in the criteria used. Patients with CVID are more likely to maintain responsiveness to protein conjugate vaccines, thus most criteria focus on the polysaccharide vaccine response [7].

In 2007, Paris *et al.* [16] discussed the interpretation of pneumococcal polysaccharide antibody responses. They recommended assessing responses to specific serotypes included in the 23-valent polysaccharide vaccine. An adequate response was defined as a four-fold increase in the antibody titer and a resulting antibody concentration of 1.3 ug/ml for more than 70% of the serotypes tested in patients under 6 years of age [16]. In recent years, however, the definition of an adequate vaccine response has been supplanted. In contrast, in 2012, Orange *et al.* [14] provided new criteria for interpretation of pneumococcal polysaccharide antibody responses, defining adequate as the ability to reach a protective titer of 1.3 ug/ml for more than 70% of serotypes 4–8 weeks after immunization with pneumococcal polysaccharide vaccine. If a titer of 1.3 ug/ml is not reached, then an adequate response is doubling of the titer in more than 70% of phenotypes. Responses were further subdivided into mild, moderate, and severe impairment to pneumococcal polysaccharide vaccine based on inability to achieve protective titers or inability to achieve a two-fold increase in titers in 70% or more of serotypes tested [6▪▪,14]. There has been suggestion that testing with polysaccharide vaccines can be problematic because of the variable responses even in healthy individuals [12,15]. Thus, Chapel *et al.* [15] proposed that failure to mount protective titers to at least two protein antigens may be more useful. Some experts have suggested that vaccine responses should not be given as much weight in the diagnosis of CVID [13▪,17▪]. The 2015 European Society for Immunodeficiencies Working Definitions for clinical diagnosis of primary immunodeficiency diseases includes impaired antibody response to vaccine or low switched memory B cells (<70% age-related normal) as one of the criteria for a CVID diagnosis [9]. In 2016, an international consensus for CVID was published, suggesting that impaired vaccine response is a requirement for the diagnosis of CVID. The authors propose that immunization responses to protein/conjugated and polysaccharide vaccines be evaluated and cite the criteria established by Orange *et al.* [14] as a useful tool in evaluating for impaired immunity to pneumococcal polysaccharide vaccine [6▪▪].

HYPOGAMMAGLOBULINEMIA IN RHEUMATIC DISEASE PATIENTS TREATED WITH RITUXIMAB

Hypogammaglobulinemia may or may not occur after B-cell targeted therapy and does not always translate into impaired responses to antigens after vaccination or natural infection [10,11,17▪]. Conversely, after rituximab administration to patients treated with other B cell targeted therapy patients (including cyclophosphamide) patients with normal IgG levels may have impaired immune responses to vaccination due to B cell depletion [18]. Patients who have been previously treated with cyclophosphamide appear to be at greater risk for hypogammaglobulinemia after rituximab. It is therefore of particular interest to determine immunoglobulin levels in cyclophosphamide-treated patients before administering rituximab.

As in CVID, rituximab therapy has been associated with an increased risk of infection in rheumatic disease patients, and prolonged hypogammaglobulinemia after administration of rituximab increases the risk of infection further. Furthermore, the subset of patients who are hypogammaglobulinemic prior to treatment appear to be at the highest risk for subsequent infection. Studies have shown that patients with postrituximab hypogammaglobulinemia develop more serious infectious episodes when compared with patients who do not develop hypogammaglobulinemia [19▪▪,20,21]. Respiratory infections are among the most frequent. Hypogammaglobulinemia, however, does not necessarily result in recurrent infection [22]. A long-term study of rheumatoid arthritis (RA) patients over 11 years, reported that the risk of infections postrituximab did not increase over time, even with repeated rituximab infusions [19▪▪]. It should be noted that numbers are small and some RA trials have excluded patients with preexisting hypogammaglobulinemia, the highest risk group. Interestingly, a small study by Rehnberg *et al.* [23] reported that although humoral and cellular immune responses to vaccines are impaired after initial courses of rituximab, impairment was not compounded by repeated courses of rituximab.

As in CVID, studies have shown that the proportion of circulating immature B cells is elevated postrituximab [22,24]. Response to vaccines may be a surrogate marker of the presence of mature protective IgM memory B cells. In a study of RA patients treated with rituximab with or without methotrexate, higher levels of IgG2 were associated with a positive immunization response to pneumococcal polysaccharide, tetanus toxoid, and keyhole limpet hemocyanin vaccines [25].

Assessment of the immunologic status and risk for infection of rituximab-treated rheumatic disease patients is complicated by frequent use of additional immunosuppressive drugs ranging from biologic agents to methotrexate, mycophenolate, or cyclophosphamide, adding to risk for infection. In addition, vaccine responses are expected to be attenuated posttreatment with rituximab and suppression of vaccine responses at this time in patients who both do and do not develop hypogammaglobulinemia is frequent. It is unclear whether failure to respond to exogenous antigens following treatment with an immunosuppressive drug confers a risk which is similar at that time to the risk faced by an individual with CVID who is not on immunosuppressive agents who fails to mount an antibody response.

MAKING THE DECISION TO START IMMUNOGLOBULIN REPLACEMENT IN RHEUMATOLOGIC PATIENTS WITH HYPOGAMMAGLOBULINEMIA AFTER B-CELL TARGETED THERAPIES

In 2015, Wolf *et al.* [26▪▪] evaluated 49 patients with hypogammaglobulinemia (IgG below 500 mg/dl) referred for further evaluation to determine which would need replacement immunoglobulin and which would not. In this retrospective observational cohort study, they determined that IgG antibody responses correlated to the patient's future susceptibility to infection, whether or not they were initially referred for frequent infections. However, those with impaired antibody response had a history of more significant infectious episodes. Most guidelines suggest that the decision to provide intravenous immunoglobulin replacement in hypogammaglobulinemic patients should be supported by the presence of recurrent infections, as well as a failure to respond to polysaccharide and/or protein antigens postvaccination. However, profound depression of IgG levels (e.g., less than 200 or 100 mg/dl) may be interpreted as an indication for IgG replacement in the absence of a full set of the features of CVID noted above [6▪▪,8▪▪].

In a patient with secondary antibody deficiency because of medications effects, such as the rheumatologic patient treated with rituximab, this decision is complicated by the primary action of the drug on B cells. Recent articles address the issue of replacement immunoglobulin therapy in these secondary antibody deficiency states [3,4▪▪,5▪▪]. These authors recommend a detailed evaluation of the incidence, recurrence, and severity of infectious episodes occurring in the patient at the time of evaluation, as well as assessment of immunoglobulin levels and antibody responses to vaccines, as described above. In addition, an extensive evaluation similar to that for the suspected CVID patient is recommended, including complete complete blood count, flow cytometric determination of lymphocyte phenotypes, IgG subclasses, kidney and liver function tests, immunoelectrophoresis, and C-reactive protein. Complete pulmonary function testing, high-resolution chest computed tomography scan (CT), and sinus CT are recommended, as the majority of infections in these patients, as in CVID, are respiratory tract infections caused by encapsulated bacteria [3,4▪▪,11,17▪]. If there is hepatosplenomegaly noted on exam, further evaluation is indicated.

The decision to start IGRT for patients with secondary antibody deficiency and/or hypogammaglobulinemia is not made lightly. If the patient is hypogammaglobulinemic without frequent ongoing infectious episodes, it is reasonable to observe them with antibiotic therapy as indicated and recheck of immunoglobulin levels at 6–12 month intervals, or sooner if an increase in infections raises a concern [3]. The patients with hypogammaglobulinemia and a history of frequent infections will either have present or absent IgG antibody response to vaccines. Authors have recently outlined similar therapeutic decision pathways for this population, based on initial antibody responses [3,4▪▪]:

(1) A patient with adequate antibody responses can be followed, with appropriate antibiotic therapy, for infectious episodes. However, if there is waning of antibody response within a year and frequent, serious, or poorly resolving infections, a trial of IGRT is indicated. If there is persistent good response to vaccines, this person can be monitored for the burden of infection, and if infection becomes persistent or recurrent a full revaluation is indicated to look for other causes.
(2) A patient without a good antibody response at initial evaluation, and only minimal history of infection can also be monitored with appropriate antibiotic therapy for infectious episodes. If infectious episodes continue, however, IGRT should be considered. The patient without a good antibody response and with persistent, recurring, or severe infection at initial evaluation should be treated with IGRT for a period of 6–12 months, and then reassessed [3].
(3) When confronted with a patient with very low (<250 mg/dl) IgG levels on initial evaluation, consideration should be given to starting IGRT immediately [4▪▪].

IGRT can be given intravenously every 3–4 weeks or subcutaneously on a weekly or biweekly basis, depending on insurance coverage and patient preference. The goal of IGRT is to decrease infections and the amount of immunoglobulin needed to reach this goal varies with the individual. Guidelines for replacement therapy in CVID include starting with a dose of 400–600 mg/kg body weight every month and adjusting dosing based on infections and IgG trough level, or steady state level in subcutaneous administration. Goal IgG levels range from 600–900 mg/dl, although a higher level may be required in some patients to protect them from recurrent infections [27].

DISCUSSION

Detection of hypogammaglobulinemia in a rheumatic disease patient treated with an agent such as rituximab and/or cyclophosphamide is an indication to review the therapeutic plan and assess risk for secondary infection. Falling immunoglobulin levels over time may suggest that even more profound hypogammaglobulinemia with increased risk of infection may ensue if therapy is continued with the same intensity. Identification of additional risk factors for infection such as failure to respond to vaccines or a prior history of recurrent infections can further inform decision making about whether to modify treatment. In nonlife threatening diseases where multiple therapeutic agents are available (such as in RA), detection of hypogammaglobulinemia and additional risk factors for infection might reasonably prompt substitution a different disease modifying agent. Conversely, for patients with potentially life-threatening diseases such as pauci-immune vasculitis, the best option may be to continue treatment with or without supplemental intravenous immunoglobulin.

The subset of hypogammaglobulinemic patients with recurrent infections and failure to respond to protein and polysaccharide vaccines constitutes a high-risk group and deserves consideration of administration of intravenous or subcutaneous immunoglobulin

Because preexisting hypogammaglobulinemia increases posttreatment infectious risk, immunoglobulin levels should be assessed pretreatment and, especially if low, followed during treatment. We follow immunoglobulin levels periodically in all treated patients. Some insurance companies allow use of subcutaneous immunoglobulin for preexisting CVID but not for presumably acquired drug-induced hypogammaglobulinemia so documentation of low pretreatment levels may facilitate future treatment with subcutaneous (rather than intravenous) immunoglobulin, if needed.

Low IgG levels that are present prior to rituximab administration may prompt physicians to look for alternative means of treatment for rheumatic disease, if available. It will also raise concern for an underlying immune deficiency that could complicate the further treatment of autoimmune disease in general [28].

Based on the above we suggest the following approach to rheumatic disease patients with hypogammaglobulinemia associated with immunosuppression:

Immunosuppressed rheumatic disease patients with recurrent infections and hypogammaglobulinemia: Because there are potential causes of hypogammaglobulinemia (e.g., nephrotic syndrome) in patients with normal immune responses, and because there are often multiple additional risk factors for recurrent infections in rheumatic disease patients, these patients should be tested for suppression of antibody responses to vaccines, for example, tetanus toxoid and pneumovax. The presence of suppressed antibody responses and/or profound hypogammaglobulinemia (in the range of serum IgG <200 mg/dl) should prompt consideration of maintenance immunoglobulin administration

Immunosuppressed rheumatic disease patients hospitalized for severe infection: Especially if the globulin fraction on the routine biochemistry panel (which can be estimated by subtracting serum albumin from total protein) is low, or patients fail to respond to therapy, we suggest determining serum immunoglobulin. We are unaware of evidence-based guidelines for immunoglobulin administration in this setting in the absence of documented failure to respond to vaccination. Nonetheless, immunoglobulin replacement is arguably worth considering in profoundly hypogammaglobulinemic patients with severe infection

Hypogammaglobulinemia observed in immunosuppressed rheumatic disease patients who do not have a history of recurrent infections: Here, it is not possible to base recommendations on the CVID population as in CVID, recurrent infections are usually the reason they are evaluated. We suggest that the approach should be informed by the intensity of concomitant immunosuppression and severity of immunoglobulin deficiency. In the presence of significant depression of IgG, we suggest testing for antibody responses to vaccines. Arguably, patients with mild to moderate hypogammaglobulinemia who have normal responses to vaccines and have no history of infections are at lower overall risk than those who do not respond. It is less clear that all hypogammaglobulinemic patients who fail to

respond to immunizations, especially those tested during active immunosuppression such as recent administration of rituximab are at unacceptably high risk for infection but failure to respond raises additional concern.

CONCLUSION

Although there is a consensus guideline for evaluating and treating patients with hypogammaglobulinemia because of CVID, equivalent guidelines do not exist for patients with rheumatic disease who develop hypogammaglobulinemia with or without recurrent infections or inadequate antibody responses to vaccinations. It is clear that rituximab can result in hypogammaglobulinemia with consequent systemic infection, especially in patients with preexisting decrease in IgG. Thus, it should be the first duty of physicians to determine whether there is preexisting hypogammaglobulinemia before treatment with rituximab. Postrituximab decrease in IgG should be evaluated based on guidelines proposed for CVID and recent literature regarding secondary antibody deficiency.

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Conflicts of interest

There are no conflicts of interest.

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International collaboration including patients is essential to develop new therapies for patients with myositis

Ingrid E. Lundberg[a] *and Jiri Vencovsky*[b]

Purpose of review
To discuss the needs for international collaborations between investigators in different disciplines working with myositis and with patients with myositis.

Recent findings
Recent advances in detection of several myositis-specific autoantibodies that are associated with distinct clinical phenotypes, will enable studies in new well defined clinically homogenous subgroups of myositis This is likely to lead to development of new information on molecular pathogenesis that might be different in different myositis subgroups. Subgrouping patients according to autoantibody profile may also be important to assess outcome, to identify prognostic biomarkers and in clinical trials. As these are rare disorders international collaboration is essential to enrol large enough cohorts of the subgroups. To facilitate such collaboration we have developed a web-based international myositis register, www.euromyositis.eu, which includes validated outcome measures and patient reported outcome measures. This register is to support research but also to support decision-making in the clinic. We welcome investigators to join the Euromyositis register.

Summary
Myositis is a heterogeneous disorder with varying treatment response and outcome. There is a high unmet need for new therapies which can only be achieved by increased knowledge on molecular disease mechanisms. Subgrouping patients according to autoantibody profile may be a new way forward to get a better understanding on disease mechanisms and to develop novel therapies.

Keywords
autoantibodies, disease register, longitudinal cohorts, myositis

INTRODUCTION

Inflammatory myopathies, collectively named myositis, is a heterogeneous group of chronic inflammatory disorders affecting skeletal muscle leading to muscle weakness and impaired function. In addition, other organs are frequently involved like the skin, lungs, heart, joints, and the gastrointestinal tract contributing to morbidity and mortality and to low health-related quality of life for these patients. These are autoimmune diseases as supported by the association with HLA molecules and by the frequent presence of T lymphocytes in muscle tissue as well as by frequent presence of serum autoantibodies. Treatment of myositis is based on targeting the immune system by using high doses of glucocorticoids often in combination with other immunosuppressive drugs such as methotrexate, azathioprine, cyclosporine A, or mycophenylate mofetile; however, with varying and often disappointing results leading to persisting muscle weakness and irreversible damage not only in skeletal muscle but also in other organs. Only a small group of patients, approximately 20%, has a good effect of conventional immunosuppressive treatment with suppression of inflammation and recovery of muscle strength and a good health-related quality of life [1]. A clinical important problem is that we to date lack prognostic biomarkers for treatment response and outcome. Thus, some patients may have to test and fail several treatment options before they improve and other patients do

[a]Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Solna, Stockholm, Sweden and [b]Institute Institute of Rheumatology, Prague, Czech Republic

Correspondence to Ingrid E. Lundberg, Rheumatology Unit, Karolinska University Hospital, Solna, SE-171 76, Stockholm, Sweden.
Tel: +46 8 5177 6087; e-mail: Ingrid.lundberg@ki.se

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KEY POINTS

- Myositis is a heterogeneous disorder where different molecular disease mechanisms may predominate in different subgroups.
- Subgrouping patients according to autoantibody profile has identified clinically homogenous subgroups and is likely to identify shared molecular pathways.
- For future studies on myositis subgrouping of patients according to autoantibody profile seems important as these are rare diseases we need to collaborate across borders of disciplines and nations.
- We need to involve patients in our research to make sure that we measure patient relevant outcomes.
- A web-based register like www.eruomyositis.eu will support international collaborations and facilitate large clinical studies.

not improve their muscle performance at all despite various immunosuppressive treatment and they develop muscle atrophy and functional impairment and may also develop persisting damage in other organs such as in the lungs or skin. Thus we need to develop better treatment options and we need to identify prognostic markers to select the right treatment for the individual patient. For this means we need to develop a better understanding of the molecular pathogenesis in myositis and this is likely to be different in different clinical subgroups and may be different for different organ manifestations.

STUDIES ON PATHOGENESIS OF MYOSITIS

To get a better understanding of pathogenesis in autoimmune diseases you can study disease mechanisms in different ways. One approach is to use animal models. For myositis there are few animal models available. Some important information has been gained from these models, for example, the nonimmune mechanisms and the MHC class I expression in muscle fibres leading to muscle weakness from the MHC class I transgene mice and from the protein C immunized mice [2,3]. In these animal models, some details of the disease can be studied. However, none of the available mouse models reflect the different spectrum of myositis disease. Studies on muscle cell cultures in autologous cocultures, that is, with muscle cells cultured together with T lymphocytes from the same individual, some information as an example cytotoxic properties of different T-cell phenotypes can be investigated [4▪]. Still in-vitro experiments only reflect particular cellular mechanisms and may not reflect the in-vivo situation occurring in the patient with myositis disease. Yet another approach is to use longitudinal studies of carefully characterized patients with standardized registration of validated clinical outcome measures and treatment in longitudinal registries. To capture enough number of patients from different subgroups a large cohort needs to be defined. As myositis disorders are rare diseases a multicentre international collaboration is required. By such an international collaboration it will be feasible to collect data from a large number of patients. Patients with different ethnicities may facilitate comparisons that can be determined by genetics and or different environments.

MYOSITIS SUBGROUPS CLINICALLY DEFINED

Subgrouping of patients into clinically more homogenous subgroups is more likely to identify critical molecular pathways that can be targeted by specific therapies. Since decades the myositides have been subclassified into adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis based on difference in clinical and histopathological features. This subgrouping has several limitations as some patients, for example, with dermatomyositis without clinical evident muscle involvement, amyopathic dermatomyositis, are not included among these subgroups. Similarly, the recently identified so called immune-mediated necrotizing myopathy [5,6]. There are also some overlaps between these subgroups, for example, some patients have histopathological features with perifascicular atrophy which is suggestive of dermatomyositis but they do not have any dermatomyositis typical skin rash. This has caused confusion on how to subclassify such patients. Similarly, some patients with myositis have features compatible with other autoimmune diseases such as systemic sclerosis, mixed connective tissue disease, systemic lupus erythematosus, or Sjögren's syndrome so called overlap myositis. Whether patients with overlap myositis are all the same, if they have similar histopathology and if they respond to treatment similarly to myositis without overlap is not known.

MYOSITIS SUBGROUPS DEFINED BY AUTOANTIBODIES

Autoantibodies are common in patients with myositis. Some autoantibodies can also be seen in patients with Sjögren's syndrome and systemic lupus erythematosus such as anti-Ro52, anti-Ro60 and anti-La, and anti-U1RNP in mixed connective

tissue disease, or anti-PM/Scl in systemic sclerosis, these autoantibodies are often named myositis-associated autoantibodies. A major breakthrough in myositis research is the identification of autoantibodies that are specific for myositis and very rarely found in other diseases, thus called myositis-specific autoantibodies (MSA) [7] The MSA can be helpful in the diagnostic procedures of myositis disease in both adult and juvenile patients and they also identify distinct clinical subgroups [8▪▪,9▪▪]. The first identified MSAs, anti-Jo-1, anti-Mi-2, and anti-SRP were observed to identify distinct clinical phenotypes of myositis, anti-Jo-1 was associated with interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, and skin rash on the hands called mechanic's hands and was named antisynthetase syndrome (ASS). Anti-Mi-2 antibodies were associated with classical dermatomyositis skin rash and anti-SRP with a treatment-resistant myositis associated with heart involvement [7]. The anti-SRP antibodies have later been identified with a specific histopathological feature dominated by muscle fibre necrosis and scarce inflammation, so called necrotizing myopathy. The heart involvement with anti-SRP antibodies is controversial and may differ between different populations [10]. The clinical observations with anti-Jo-1 and anti-Mi2 antibodies have stood the test of time.

MYOSITIS-SPECIFIC AUTOANTIBODIES

During the last decade more than 15 new MSAs have been identified, as discussed in the review for adult myositis by Fujimoto *et al.* [11] and for juvenile onset myositis Tansley *et al.* [12]. These MSAs are associated with distinct clinical phenotypes such as ASS; skin rash typical of dermatomyositis (anti-Mi-2), or severe skin rash with calcinosis (anti-NXP2) or cancer associated myositis (anti-TIF1γ) or a rapidly progressive ILD (anti-MDA5) (Table 1) [8▪▪].

Autoantibodies associated with antisynthetase syndrome

Importantly, new subsets of chronic inflammatory disorder have been identified to be associated with some of the MSAs. One is the above mentioned ASS, which can present with ILD without myositis [13▪]. Besides anti-Jo-1 (antihistidyl tRNA synthetase) there are in addition seven other autoantibodies that are targeting different aminoacyl-tRNA synthetases anti-PL7, threonyl tRNA synthetase; anti-PL12, alanyl tRNA synthetase; anti-EJ, glycyl tRNA synthetase, anti-OJ, isoleucine tRNA synthetase,anti-KS, asparaginyl tRNA synthetase, anti-Zo, phenylalaninyl tRNA synthetase, and anti-Ha tyrosyl tRNA synthetase) (Table 1). Some of the antiaminoacyl tRNA synthetase autoantibodies are more often

Table 1. Myositis-specific autoantibodies, target autoantigens and associated clinical manifestations

Autoantibody	Target autoantigen	Clinical manifestations
Anti-Jo1	Histidyl tRNA synthetase	ASS
Anti-PL12	Alanyl tRNA synthetase	ASS
Anti-PL7	Threonyl tRNA synthetase	ASS
Anti-EJ	Glycyl-tRNA synthetase	ASS
Anti-OJ	Isoleucyl-tRNA synthetase	ASS
Anti-KS	Asparaginyl tRNAsynthetase	ASS
Anti-Ha	Tyrosyl tRNA synthetase	ASS
Anti-Zo	Phenylalanyl tRNA synthetase	ASS
Anti-Mi-2	Nucleosome-remodelling deacetyase complex	Characteristic DM skin rash
Anti-MDA5	Melanoma differentiation-associated gene 5	DM, may be amyopathic, rapidly progressive ILD
Anti-TIF1gamma	Transcription factor gamma	JDM and adult DM. In adults, cancer-associated DM
Anti-NXP2	Nuclear matrix protein 2	JDM and adult DM with calcinosis. Cancer-associated DM in adults
Anti-SAE	Small ubiquitin-like modifier activating enzyme	DM
Anti-SRP	Signal recognition particle	Necrotizing myopathy, high serum CK levels. Dysphagia. Cardiac involvement?
Anti-HMGCR	3-Hydroxy, 3 methylglutaryl-coenzyme A reductase	Necrotizing myopathy, high serum CK levels. Associated with statin exposure
Anti-c1NA	Cytosolic 5′ nucleotidase	IBM
Anti-FHL1	Four and half LIMB domain 1	Severe muscle weakness, muscle atrophy and dysphagia

ASS, anti-synthetase syndrome: myositis; CK, creatine kinase; DM, dermatomyositis; IBM, Inclusion body myositis; ILD, interstitial lung disease, arthritis, Raynaud's phenomenon and mechanic's hands; MSA, myositis-specific autoantibodies.

associated with ILD than with myositis, such as anti-PL12 or anti-PL7 [14,15].

Autoantibodies associated with amyopathic or hypomyopathic dermatomyositis

Another 'new' subset of diseases with MSAs is the amyopathic dermatomyositis, which in association with anti-MDA5 may be associated with rapidly progressive ILD associated [16] (Table 1). The anti-MDA5 autoantibody is sometimes associated with a severe skin rash with cutaneous vasculitis and palmar papules. Another MSA associated with DM that can be amyopathic at onset in anti-SAE.

Necrotizing myopathy and anti-FHL1 positive myositis

Anti-SRP and anti-HMGCR antibodies as are associated with a necrotizing myopathy, with little or no inflammation [17]. For a newly discovered autoantibody, anti-FHL1, we identified an association with muscle fibre necrosis, and inflammation [18▪▪]. Clinically there was an association with severe involvement of skeletal muscle with muscle atrophy and dysphagia. Anti-FHL1 antibodies are directed against muscle specific protein, FHL1, in contrast to most other MSAs which target ubiquitously expressed antigens. A possible role for anti-FHL1 autoantibodies in the pathogenesis of this subgroup of myositis disease spectrum is the observation from experimental studies in an animal model, using myositis prone mice, who were immunized with FHL1. In these mice we observed an aggravated muscle weakness and increased mortality compared to control mice. Another interesting autoantibody in relation to disease mechanisms is the anti-HMGCR antibody which is strongly associated with previous treatment with statins as the antigen, HMGCR, is the enzyme that is targeted by statins and then presumably becomes modified which could give it antigenic properties. There is also an association with DRB1∗11:01 [19] supporting the hypothesis of a T cell mediated immune response. Whether the anti-HMGCR antibodies can attack the muscle fibers and cause muscle fiber damage and necrosis needs to be demonstrated. Clearly more studies are needed to achieve a better understanding of the potential role of autoantibodies in causing myositis spectrum disease.

Myositis disease spectrum

These emerging different distinct clinical phenotypes of chronic multiorgan inflammatory diseases with MSAs has broadened the myositis subgroups to extend to include patients without clinical muscle inflammation but with typical skin rash of dermatomyositis, with rheumatoid like arthritis or with ILD suggesting a spectrum of clinical phenotypes of myositis diseases and a nomenclature of myositis spectrum diseases (MSD) has been proposed by Dr Neil McHugh (personal communication). A clinical consequence of this is that patients may present with lung problems seeing pulmonary physicians or in the arthritis clinic mimicking early rheumatoid arthritis, where the serology is helpful to classify patients into the MSD. A close collaboration between myologists and pulmonologists is important to promote diagnosis of these patients as delayed time to diagnosis and start of immunosuppressive treatment may affect the treatment response and prognosis of the lung disease. These patients are recommended to be referred to centres where patients with MSD are managed.

The distinct clinical phenotypes associated with the respective MSAs suggest that different molecular pathogenesis may be associated with different autoantibodies. Thus it will be important in future studies to determine MSAs and myositis-associated autoantibodies in studies of molecular pathogenesis. In addition, autoantibody profile will also be important to determine in clinical studies on prognosis and outcome as well as in clinical trials. Longitudinal studies in clinically homogenous groups defined by autoantibodies is a new way forward in our attempts to identify biomarkers to assist in treatment decision making and to identify biomarkers for prognosis.

Patients with myositis spectrum disease usually only have one MSA specificity but they may have one or more additional myositis-associated autoantibodies. The monospecificity of the MSA reactivity supports a specific immune response to epitopes of these autoantigens, but little information is available on antigen specific T and B cells. To identify antigen-specific T cells is important to develop therapies using tolerization to cure the patients. Furthermore, it is not known if the MSAs have a direct role in the pathogenesis of the myositis spectrum disease or if they are an epiphenomenon. Serum levels may vary with disease activity as demonstrated for one of the MSAs, anti-Jo-1 autoantibodies [20] which is one support of a role of the antibodies in the pathogenesis but little information is available from longitudinal studies of the other MSAs. To answer this question more functional studies are needed.

A support for the hypothesis that different autoantibodies are associated with different molecular pathogenesis would be if the molecular features in muscle tissue or skin biopsies are shared by patients

with one type of myositis-specific autoantibody. There is some emerging data suggesting that the MSAs are associated with distinct muscle histopathology, for example, anti-Jo-1 antibodies are associated with perifascicular necrosis, atrophy, and perimysial fragmentation [21].

MYOSITIS OUTCOME MEASURES

Taken together these observations suggest that different autoantibody profiles may be associated with different molecular pathogenesis affecting muscle tissue but potentially also the skin, and lungs, but more studies are needed including large enough patient cohorts to address this question. For such studies international multicentre collaborations are needed, and longitudinal follow-up using standardized and validated outcome measures are important. An international initiative the International Myositis Activities and Clinical studies, IMACS, group has made important contributions by defining disease activity core set, disease damage tool, and IMACS has also developed definitions of improvement to be used in clinical trials [22,23]. A development of improvement criteria is under way through the IMACS collaboration. Furthermore, collaboration involving patients is essential in clinical studies. One such collaboration between clinical investigators and patients is ongoing through the Outcome Measures in Rheumatology with the aim to develop patient reported outcome measures that capture items that are important to patients with myositis. This collaboration is ongoing under the lead of Dr L. Christopher-Stine [24] Dr Y. Son South Korea, and H. Alexanderson *et al.* [25] Sweden and involves patient representative.

AN INTERNATIONAL MYOSITIS REGISTER

To facilitate longitudinal studies based on clinical data from the everyday clinic we have taken the initiative to a web-based international electronic registry, Euromyositis, www.euromyositis.eu. This project started within an EU-funded project, Autocure, and has then developed with support from the European Science Foundation in collaboration with IT expertise in the Danish company ZiteLab Aps, creator of the Danish biologics register DANBIO represented by Niels Steen Krogh [26]. The Euromyositis register has two parts, one with basic data, demographic and disease specific to describe the patient cohort, and one longitudinal part with recording of visit data which include the IMACS disease activity score, the myositis damage, and treatment. This register was started among European collaborators in the UK, Czech Republic, and Sweden but has as expanded to become a truly international register with now 23 centres worldwide including Hanoi and Beijing and has enrolled more than 4500 patients (Fig. 1) [26]. The register has also been used to follow patients in investigators driven clinical trial where a case report form module was created within the register [27]. The basic data have so far been used in genetic studies with GWAS and Immunochip data [28▪▪]. The aim of the longitudinal part of the register is to identify prognostic

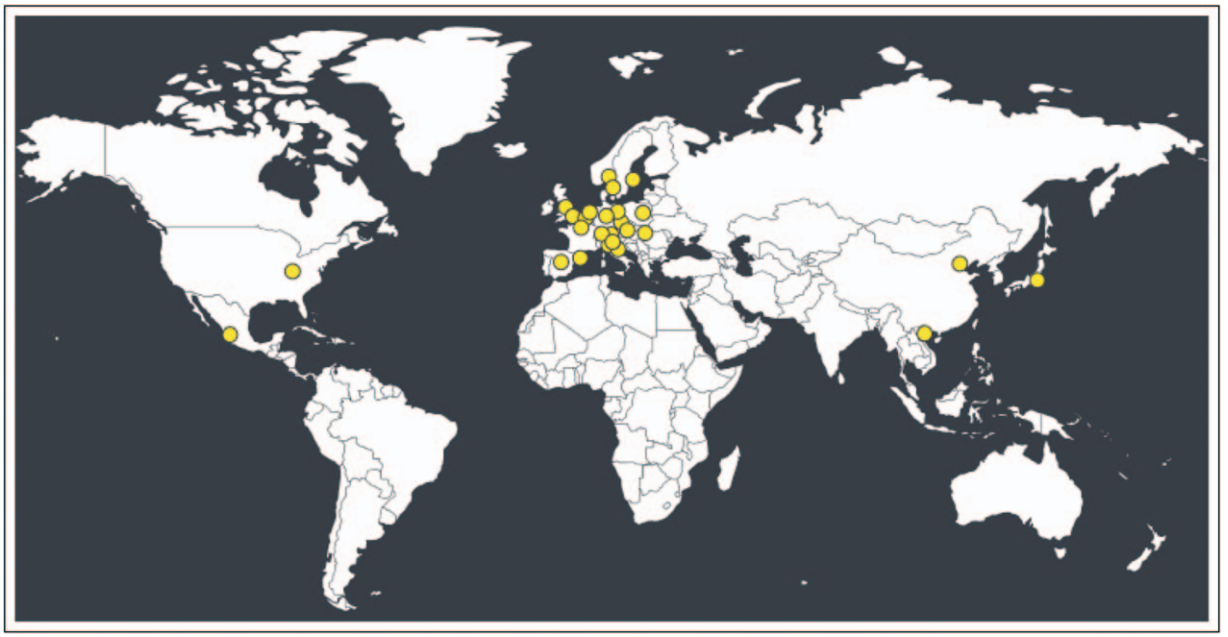

FIGURE 1. World map of Euromyositis, www.euromyositis.eu. Each grey dot indicates a centre that is collaborating within Euromyositis. In total, 23 centres and more than 4500 patients have been enrolled. Reproduced from [26] with permission.

markers for treatment response and outcome. To be part of the biomarker study at least two visits need to be registered. The idea with the longitudinal part of the register is that it should be simple to use in the everyday clinic, and that the data in the register shall not only be for research but also serve as a tool to support decision making in the clinic with the patient. We are planning to develop links between patient records and the register to avoid double registration, with the DANBIO, as a prototype [29]. We are also planning to develop the register so that patients will be able to report their outcome measures directly into the register through the website or by using a smart phone, which will ensure more longitudinal data. We will develop the tools for patients together with patients with myositis. We welcome clinicians who are interested in myositis to join the Euromyositis register. There is no cost for investigators to use the register, as we support it by funding sources, currently through a UK grant by Dr Hector Chinoy. Each investigator has access to her/his own data and can decide whether to be part of multicentre projects. A steering committee, chaired by Dr Chinoy makes decision on applications to join the register and on which research project to support. You can find more information on www.euromyositis.eu. To the register we have linked a DNA database, currently chaired by Dr Chinoy and Dr J Lamb in Manchester. We have also analysed sera for myositis specific and associated autoantibodies for more than 2000 patients using the immunoprecipitation assay by Dr Neil McHugh, Bath, UK and by a lineblot assay by Dr Peter Charles and Dr Johan Rönnelid, Uppsala, Sweden. We will continue to standardize the autoantibody tests. We also have an ongoing quality of care project to standardize the reading and interpretation of muscle biopsy features headed by Professor Jan De Bleecker [30], Gent, Belgium and Professor Marianne De Visser, Amsterdam, the Netherlands.

CONCLUSION

We strongly believe that working together with patients with myositis and across borders of disciplines and nations facilitate clinical, translational research in myositis and that we will accomplish novel and clinically important information on myositis disease spectrum with the intention to develop new treatment algorithms for different subgroups of myositis and hopefully new therapies.

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J.V. has received consulting fee from Servier.

Conflicts of interest

There are no conflicts of interest.

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Treatment of lupus nephritis: current paradigms and emerging strategies

Maria Dall'Era

Purpose of review
Lupus nephritis is the most common organ-threatening manifestation of lupus and continues to result in end-stage renal disease. This review describes the contemporary treatment of lupus nephritis as well as emerging therapeutic strategies.

Recent findings
Lupus nephritis management consists of an initial (induction) phase and a maintenance (extended) phase in which steroids are used in combination with another immunosuppressive medication. Current treatments are incompletely effective and associated with substantial toxicity. Despite disappointing results of several recent trials, novel therapies targeting diverse immunologic pathways are being actively studied in lupus nephritis. Two promising strategies include the use of B-cell depletion therapy and multitarget therapy with calcineurin inhibitors. In parallel with the conduct of these trials, there are ongoing efforts to improve trial design. Two recent studies of outcome measures reported that a level of proteinuria of less than 0.7–0.8 g at 12 months is most predictive of good long-term renal outcome, and that the inclusion of urine red blood cells worsens the predictive value of proteinuria alone.

Summary
Improved understanding of lupus nephritis pathogenesis, development of novel therapies, and optimization of clinical trial design are leading the path forward for successful drug development in lupus nephritis. The ultimate goal of these efforts is to treat our patients in a more strategic, personalized manner that improves long-term outcomes.

Keywords
lupus nephritis, novel therapies, renal outcome, trial design

INTRODUCTION

Lupus nephritis is the most common organ-threatening manifestation of systemic lupus erythematosus (SLE) and continues to result in significant morbidity and mortality [1]. A recent inception cohort study of 1827 patients followed in international lupus clinics reported an overall prevalence of lupus nephritis of 38% and an increased risk of end stage renal disease (ESRD) (hazard ratio (HR) 44.7) and death (HR 3.2) in those patients with lupus nephritis. Despite the best possible expert care and access to contemporary lupus therapies, patients with lupus nephritis had a 10-year cumulative incidence of ESRD of 10.1% and death of 5.9% [2▪▪]. These data support the fact that our current treatment regimens are incompletely effective. Only a small proportion of lupus nephritis patients achieve a complete renal response within the first 6–12 months of therapy [3,4], and renal flares are common during maintenance therapy [5–7]. Conventional therapies are also associated with substantial toxicity. For example, treatment regimens are still anchored to high-dose steroids which are contributors to long-term damage in SLE [8]. Cyclophosphamide (CYC) is associated with ovarian toxicity, an unacceptable side effect in young women [9]. The teratogenicity of mycophenolate mofetil (MMF) limits its use as a long-term maintenance agent. Thus, it is clear that more efficacious and safer treatment strategies are urgently needed to preserve good long-term kidney health in our lupus nephritis patients. Lessons learned from previous trials coupled with improved understanding of

Division of Rheumatology, Russell/Engleman Research Center, University of California, San Francisco, California, USA

Correspondence to Maria Dall'Era, MD, Division of Rheumatology, Russell/Engleman Research Center, University of California, 533 Parnassus Ave. U 384 Box 0792, San Francisco, CA 94143-0792, USA.
Tel: +1 415 476 0783; e-mail: maria.dallera@ucsf.edu

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KEY POINTS

- New treatment strategies for lupus nephritis are urgently needed to achieve a renal response, prevent renal flares, minimize treatment-related toxicity, and improve long-term kidney health.
- Contemporary treatment of lupus nephritis consists of an initial (induction) phase and a maintenance (extended) phase consisting of steroids combined with another immunosuppressive agent.
- Emerging treatment strategies include novel combinations of B-cell modulating therapies and multitarget therapy with calcineurin inhibitors.
- Ongoing studies assessing evidence-based renal outcome measures are leading to improved lupus nephritis trial design.

pathogenic mechanisms are paving the way for new drug development in lupus nephritis. Cutting-edge approaches include not only specific targeted medications, but also the context in which those medications are used. Issues including the most appropriate phase of treatment (initial or maintenance) and the best use of concomitant therapies are coming to the forefront. Even the need for oral steroids is being assessed. In this review, I will outline the evidence supporting current treatment strategies for lupus nephritis, and then discuss emerging approaches with a focus on B-cell depletion therapy and multitarget therapy.

Current treatment landscape

The contemporary treatment of lupus nephritis consists of two phases: an initial (induction) phase and a maintenance (extended) phase. During the initial phase, intensive treatment with steroids in combination with another immunosuppressive agent are given to quickly suppress immune complex-mediated renal inflammation and begin to alter underlying immune dysregulation to induce immune quiescence. The goal of this approach is to minimize early damage and preserve long-term kidney health (Fig. 1).

Initial (induction) treatment

Data from randomized, controlled trials support the use of CYC or MMF for initial treatment. CYC is typically administered in one of two regimens: National Institutes of Health (NIH) regimen of monthly intravenous (i.v.) pulses of 0.5–1.0 g/m^2 for 6 months, or Euro-Lupus Nephritis (ELNT) regimen of i.v. pulses of 500 mg every 2 weeks for six doses. In a randomized, controlled trial of 90 predominantly Caucasian lupus nephritis patients, the low dose ELNT regimen and the high dose NIH regimen resulted in similar rates of treatment failure, renal remission, and renal flare at a median of 41 months of follow-up [4]. In this trial, all patients received azathioprine (AZA) for maintenance. Subsequent analyses have reported continued favorable outcomes at 5 and 10 years of follow-up with no difference in rates of death, doubling of serum creatinine, and ESRD between the two i.v. CYC groups

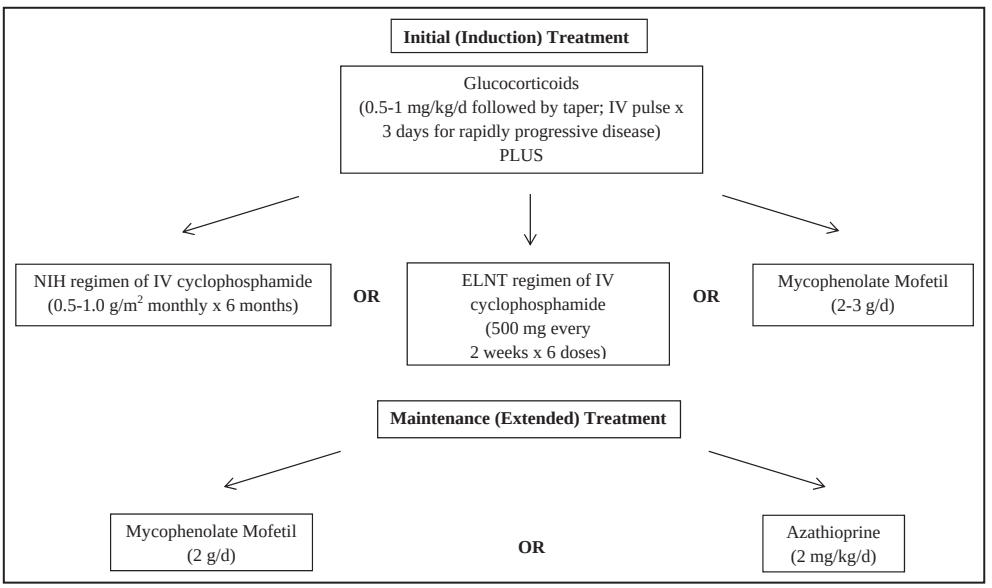

FIGURE 1. Contemporary, evidence-based initial (induction) and maintenance (extended) regimens for the treatment of LN. AZA, azathioprine; CYC, cyclophosphamide; ELNT, Euro-Lupus Nephritis; i.v., intravenous, LN, lupus nephritis; MMF, mycophenolate mofetil; NIH, National Institutes of Health.

[10]. Because the ELNT trial enrolled predominantly Caucasian patients, some rheumatologists have expressed concerns about the generalizability of the ELNT regimen to patients of other racial/ethnic backgrounds. To address this question, Wofsy and colleagues utilized primary data from several lupus nephritis trials including the Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis trial, in which 134 lupus nephritis patients were randomized to abatacept or placebo on a background of the ELNT regimen [11]. The Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis trial enrolled a racially/ethnically diverse population that was 37% Black and 41% Hispanic. After applying uniform response criteria, the investigators determined that rates of complete renal response at 24 weeks were similar in patients receiving the ELNT i.v. CYC regimen, the high-dose i.v. CYC regimen, or MMF [12▪▪]. Thus, this analysis lends supportive data for the use of the ELNT regimen for the initial treatment of lupus nephritis in diverse racial/ethnic groups.

The Aspreva Lupus Management Study (ALMS) trial firmly established the use of MMF as an alternative to i.v. CYC as initial treatment for lupus nephritis [3]. In this trial, 370 lupus nephritis patients were randomized to treatment with MMF or NIH monthly i.v. CYC, both in combination with steroids. The rates of renal response (56.2 versus 53%) and complete remission (8.6 and 8.1%) at 24 weeks were similar between the two groups. In a post hoc, exploratory analysis, more Black and Hispanic patients responded to MMF versus i.v. CYC [13].

Maintenance (extended) treatment

The goals of the maintenance phase are to continue immunosuppressive treatment to achieve a complete renal response and to prevent renal flares while minimizing potential toxicity of long-term exposure to immunosuppressive medications. Throughout the initial phase, steroids are tapered to a low dose such that they are typically not a prominent feature of the maintenance phase. Two contemporary randomized, controlled trials have provided data to inform our practice patterns for the maintenance phase. In the maintenance phase of ALMS, 227 patients who had a response to initial treatment with i.v. CYC or MMF were rerandomized to MMF or AZA. MMF was superior to AZA at 36 months in decreasing the frequency of treatment failure (16% in the MMF group versus 32% in the AZA group) [6]. The maintenance results from ALMS differ from those of the MAINTAIN (Mycophenolate Mofetil versus Azathioprine for Maintenance Therapy of Lupus Nephritis) trial, a European trial of 105 lupus nephritis patients randomized to MMF or AZA following induction therapy with the ELNT i.v. CYC regimen [7,14▪▪]. The cumulative incidence of renal flares at 5 years was not statistically different between the MMF group and the AZA group (19 versus 25%, respectively). Differences in sample size and study design may have influenced the discordant results between these two trials. The results of these trials support the use of MMF or AZA for maintenance treatment of lupus nephritis.

BIOLOGIC THERAPY

Several biologic therapies have been studied in lupus nephritis. An in-depth discussion of all of these agents is beyond the scope of this review. Table 1 lists recent clinical trials of interest using therapies targeting diverse immunologic pathways.

B-cell depletion therapy

B cells play a prominent role in the pathogenesis of lupus nephritis via a variety of mechanisms including production of autoantibodies, antigen presentation, cytokine production, and interactions with T cells. Thus, targeting B cells has emerged as a biologically plausible therapeutic strategy. Rituximab is a chimeric mAb against cluster of differentiation (CD)20 that depletes B cells from the pre-B cell to the memory B cell stage. Importantly, pro-B cells and plasma cells are spared because they do not express CD20. Initially, several open-label trials and numerous case reports generated great optimism about the potential benefit of rituximab in patients with lupus nephritis [20–24]. However, subsequent controlled trials were disappointing. The Lupus Nephritis Assessment with Rituximab trial was a randomized, controlled trial of 144 patients with proliferative lupus nephritis that assessed induction therapy with rituximab versus placebo on a background of MMF and steroids [15]. Although the trial failed to demonstrate a statistically significant difference between the two groups in the rate of renal response at 52 weeks, numerically more rituximab treated patients achieved a renal response (57 versus 46%). In a secondary analysis, more rituximab treated patients achieved at least 50% reduction in proteinuria at 78 weeks. This observation raises the possibility that trials of longer duration may be necessary to fully discern the differences between these treatments. The discrepancy between the disappointing Lupus Nephritis Assessment with Rituximab results and the positive community experience with rituximab in patients with persistently active, refractory disease has yet to be explained. In the absence of definitive data to

Table 1. Trials of biologic therapies for lupus nephritis

Study	Study drugs	Number of patients	Duration (weeks)	Primary result
Rovin *et al.* (LUNAR) [15]	Rituximab versus placebo on background MMF	144	52	No difference in renal response
Mysler *et al.* (BELONG) [16]	Ocrelizumab versus placebo on background ELNT or MMF	378	52	Study prematurely terminated because of excess serious infections in ocrelizumab groups ITT population (223 treated for 32 weeks): no difference in renal response
Ginzler *et al.* [17]	Atacicept versus placebo on background MMF	6	52	Study prematurely terminated because of hypo γ-globulinemia and excess serious infections in atacicept group
Furie *et al.* [18]	Abatacept versus placebo on background MMF	298	52	No difference in renal response
ACCESS trial group [11]	Abatacept versus placebo on background ELNT	134	24	No difference in renal response
Rovin BH *et al.* [19▪]	Sirukumab versus placebo	25	24	No difference in percentage change in proteinuria

ELNT, Euro-Lupus Nephritis; ITT, intention to treat; LUNAR, Lupus Nephritis Assessment with Rituximab; MMF, mycophenolate mofetil.

resolve this paradox, rituximab has emerged as the most commonly used off-label biologic therapy for refractory lupus nephritis [25▪]. Several studies have informed the practical use of rituximab in patients. For example, one study reported that repeated courses of rituximab may be effective in patients with refractory lupus and that poor response to the first cycle does not predict poor response to the second cycle [26]. Also, early B cell repopulation is associated with increased risk of renal flare [27]. The use of rituximab for the treatment of refractory lupus nephritis is supported by the American College of Rheumatology [28] and the European League against Rheumatism guidelines for the treatment of lupus nephritis [29].

Ocrelizumab is a humanized mAb that also targets CD20, and results in greater antibody-dependent cytotoxicity compared with rituximab. In the phase III BELONG (A Study to Evaluate Ocrelizumab in Patients with Nephritis Due to Systemic Lupus Erythematosus) trial, 381 patients with proliferative lupus nephritis were randomized to two different doses of ocrelizumab or placebo on a background of MMF or the ELNT regimen [16]. The trial was stopped prematurely because of increased infections in the ocrelizumab groups. Further development in rheumatic diseases has been discontinued. The quest to understand the role of CD20 targeted therapies for lupus nephritis is moving forward with obinutuzumab, a type II mAb that is reported to result in improved peripheral and tissue B-cell depletion compared with rituximab [30▪]. A phase II trial of obinutuzumab versus placebo on a background of MMF is currently ongoing in proliferative lupus nephritis.

Novel strategies using B-cell depletion therapy

Despite the disappointments with controlled clinical trials, the lupus community's continued interest in B-cell depletion therapy has led to the recent initiation of several investigator initiated trials in which rituximab is being studied in unique ways. Several of these trials are being conducted within the Lupus Nephritis Trials Network, a collaborative group of international lupus investigators committed to carrying out studies to improve outcomes for patients with lupus nephritis. The RITUXILUP (Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis) trial is designed to assess whether a rituximab containing regimen can effectively treat lupus nephritis without the use of oral steroids. A pilot study of 50 consecutive patients with class III, i.v., or V lupus nephritis (Class V lupus nephritis) reported that a regimen of two doses of rituximab 1 g and methylprednisolone 500 mg given 2 weeks apart followed by maintenance treatment with MMF (called the RITUXILUP regimen) resulted in complete or partial renal response in 90% of patients by a median of 37 weeks [31]. In total, 11 patients experienced a renal flare at a median of 65 weeks after achieving a renal response. Remarkably, only two patients required maintenance treatment with oral steroids, both for extrarenal manifestations. RITUXILUP is the first large-scale, randomized, controlled trial in lupus nephritis to study a treatment regimen that is completely free of oral steroids. If a steroid free regimen is proven to be successful, future patients may be spared from the well described multiple toxicities of long-term

steroid use. This would be a groundbreaking development in the lupus community.

The CALIBRATE (Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis) trial is designed to study a novel combination of B cell directed therapies for the initial and maintenance treatment of lupus nephritis. It is known that serum B Cell Activating Factor (BAFF) levels are elevated after B-cell depletion therapy and may contribute to a more autoimmune B-cell repertoire after repopulation as well as enhanced survival of plasmablasts [32]. Conversely, B-cell reconstitution in the setting of low BAFF levels may lead to a tolerized B-cell repertoire, resulting in a decreased rate of renal flares and improved renal outcomes. To test this hypothesis, the ongoing CALIBRATE trial is randomizing patients with class III or i.v. lupus nephritis to initial treatment with rituximab 1 g and i.v. CYC 750 mg on two occasions 2 weeks apart (in conjunction with oral steroids) followed by either monthly belimumab infusions or low-dose oral steroids alone. Unlike the completed phase III trials in nonrenal lupus (BLISS (A Study of Belimumab in Subjects with Systemic Lupus Erythematosus)-52 [33] and BLISS-76 [34]) and the ongoing phase i.v. trial in lupus nephritis in which belimumab is used as an initial therapy, CALIBRATE is testing sequential therapy with belimumab being used as a maintenance agent. Lastly, the ongoing RING (Rituximab for Lupus Nephritis with Remission as a Goal) trial is testing the use of rituximab as a maintenance treatment in patients with refractory disease. In this trial, patients are being randomized to the addition of rituximab to maintenance MMF or AZA in patients with persistently active lupus nephritis despite initial therapy with MMF or i.v. CYC. Taken together, the results of these trials will hopefully serve to better inform the rational use of B cell directed therapies for the treatment of lupus nephritis.

The aforementioned B-cell depletion strategies do not deplete long-lived plasma cells, which produce pathogenic autoantibodies and reside in survival niches within bone marrow and other tissues such as the renal interstitium. These plasma cells have become attractive therapeutic targets, with proteasome inhibitors playing a potential role. The proteasome inhibitor, bortezomib, was studied in 12 patients with refractory SLE, including eight patients with lupus nephritis. At 6 months, there was reduction in proteinuria, anti-double-stranded deoxyribonucleic acid levels, plasma cell counts, and type I interferon activity [35▪]. Notably, adverse events led to the discontinuation of bortezomib in 58% of patients. Newer generation proteasome inhibitors may be associated with less toxicity and are currently being studied in SLE and lupus nephritis.

MULTITARGET THERAPY WITH CALCINEURIN INHIBITION

Although combination immunosuppressive therapy with calcineurin inhibitors has been the norm for prevention of rejection after solid organ transplantation, this approach has not been widely utilized for lupus nephritis. Given the various immunologic mechanisms involved in the pathogenesis of lupus nephritis, the prospect of targeting more than one pathway is attractive. In a recent trial, 368 Chinese patients with class III-V lupus nephritis were randomized to monthly pulse i.v. CYC versus MMF 1 g/d and tacrolimus 4 mg/d, all in conjunction with steroids [36▪▪]. At 24 weeks, more patients in the combination group compared with the i.v. CYC achieved a complete response (45.9 versus 25.6%, respectively). As a cautionary note, it is important to interpret these results in the context of the pleotropic effects of tacrolimus and the fact that the primary endpoint of complete response was based on suppression of proteinuria. Tacrolimus decreases proteinuria through both immunologic and nonimmunologic effects including inhibition of T-cell proliferation, preventing release of cytokines, and stabilizing glomerular podocytes. Thus, in this short-term trial, it is possible that the rapid improvement in proteinuria was because of other factors besides attenuation of immunologic activity. To address this issue, repeat renal biopsies were performed in 23 study participants. Reassuringly, there was a similar reduction in the activity index between the two groups. It will be important to conduct longer-term trials with this regimen to better understand its efficacy and safety profile for the treatment of lupus nephritis. Of note, multitarget therapy is also being studied with voclosporin, a new generation, higher potency calcineurin inhibitor. Top-line results reported that the combination of voclosporin and MMF was superior to placebo plus MMF in attainment of complete response at 24 weeks, but that study also raised safety concerns that are yet to be fully evaluated.

OUTCOME MEASURES IN LUPUS NEPHRITIS TRIALS

Although, we continue to push forward with clinical trials of novel medications and treatment strategies in lupus nephritis, it is equally important to ensure that we understand how best to assess renal response to these therapies. Lupus nephritis trials use a wide variety of outcome measures, and it is unclear which, if any, are most able to differentiate between

treatment arms and which are reflective of good long-term kidney health [37,38]. Two recent studies by Lupus Nephritis Trials Network investigators using data from the ELNT and MAINTAIN trials reported that a level of proteinuria of less than 0.7–0.8 g at 12 months is most predictive of good long-term renal outcome, and that the inclusion of urine red blood cells worsens the predictive value of proteinuria alone [39▪,40▪]. These results are currently being validated in several large, multinational lupus nephritis cohorts. The expectation is that these data will enable improved design of future lupus nephritis trials such that we will be able to accurately assess the efficacy of novel treatments. Although these studies are a step in the right direction, the limitations of using proteinuria as a short-term outcome measure are well recognized. Proteinuria may reflect fixed renal damage and not ongoing activity. Thus, current studies are addressing whether histologic and molecular outcomes may be more beneficial. It is hoped that a major collaborative effort that was recently launched by the National Institutes for Health in partnership with several biopharmaceutical companies (the Accelerating Medicines Partnership) will shed light on this question in the upcoming months.

CONCLUSION

Despite our best efforts, a significant percentage of lupus nephritis patients still progress to ESRD and experience treatment related toxicity. Fortunately, there is remarkable clinical trial activity in lupus nephritis using molecules targeting various immunologic pathways believed to be important in the pathogenesis of lupus nephritis. As novel biologic medications are developed and new sequences and combinations of biologic and conventional medications are studied, the established paradigm for the treatment of lupus nephritis will continue to evolve. In parallel with drug development, ongoing work to create and validate renal response measures will lead to more rigorous clinical trial design. With this foundation, we will have the best opportunity to determine which treatment strategies are most effective for which patients at which time point in disease. The future is bright indeed.

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Conflicts of interest

There are no conflicts of interest.

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Update on maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis

Ora Singer and W. Joseph McCune

Purpose of review
The antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitides are a group of rare systemic diseases. The past several years have seen major therapeutic advances in the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The success rate in induction of remission is high, but reducing the high incidence of relapses remains a therapeutic challenge.

Recent findings
Studies have shown no improvement in relapse rates in GPA and MPA over the past 2 decades. This has prompted a recent focus on therapeutic strategies to maintain remission in these relapsing diseases. Low-dose rituximab (RTX) at fixed intervals has been shown superior to azathioprine for maintenance of remission. Despite this advance, longer follow-up periods have shown late-stage relapses with withdrawal of therapy suggesting a possible need for longer treatment regimens. Evaluation of prognostic indicators is also helpful in stratifying patients who might be more likely to relapse or to respond to a particular therapy.

Summary
Results from recent research have significantly advanced our approach to prevention of relapses in GPA and MPA. Newer maintenance agents have shown benefit in maintenance of remission and relapse-free survival.

Keywords
antineutrophilic cytoplasmic antibodies, granulomatosis with polyangiitis, maintenance therapy, microscopic polyangiitis, rituximab

INTRODUCTION

The antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) include granulomatosis with polyangiitis (GPA), formerly Wegener's granulomatosis, microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg–Strauss syndrome.

These rare systemic diseases defined by pauci-immune vasculitis can result in significant morbidity and even mortality. Treatment of AAVs follows a two-staged approach with induction of remission followed by maintenance of remission remove the worse phase. The past decade has seen major therapeutic advances in both phases of treatment. Overall survival and renal survival have improved [1▪]. Despite these advances, relapse rates and treatment toxicity remain high [2,3,4▪▪]. Rhee *et al.* [1▪] showed that between 1985 and 2009, the risk of death and end stage renal disease were reduced, but risk of relapse had not changed. Patients are living longer, but reducing the high incidence of relapses remains a therapeutic challenge.

Well tolerated and effective therapeutic strategies to maintain remission has been a recent focus in AAV research. This article reviews the current treatment strategies for maintenance of remission in GPA and MPA. It will highlight new approaches with an emphasis on the use of rituximab (RTX) as a maintenance agent. Recent data on withdrawal of therapy and tailoring therapy by disease characteristics will also be reviewed. EGPA, which is treated as a distinct entity and has not been included in most AAV clinical trials, will not be discussed in this article.

CONVENTIONAL MAINTENANCE THERAPY

For over 40 years, cyclophosphamide (CYC) combined with glucocorticoids has been the

University of Michigan, Ann Arbor, Michigan, USA

Correspondence to Ora Singer, MD, MS, University of Michigan, 300 N Ingalls, Ann Arbor, MI 48109, USA.
Tel: +1 734 936 5560; e-mail: singero@med.umich.edu

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KEY POINTS

- Despite advances in therapy, relapse rates for GPA and MPA remain high, and late relapses after withdrawal of therapy are common.
- Patients with PR3-ANCAs have higher risk of relapse.
- RTX is an effective and well tolerated alternative for maintenance therapy.
- Patients with PR3-ANCAs and relapsing disease have better response to RTX.

gold-standard induction regimen for severe disease with remission rates between 70 and 90% [3,5–7]. Attempts have been made to reduce CYC-related toxicity. The Rituximab in AAV (RAVE) and the Rituximab Versus cyclophosphamide for AAV (RITUXVAS) trials showed efficacy of two RTX induction regimens [8,9]. In the RAVE trial, RTX alone (375 mg/m^2 × 4 doses) and in RITUXVAS trial RTX in combination with two pulses of CYC (15 mg/kg) showed similar rates of remission to CYC alone with a more favorable safety profile. In limited AAV (nonlife or organ-threatening), methotrexate (MTX) can be used in place of CYC for induction of remission [10].

Randomized controlled trials (RCTs) have also shown CYC-sparing regimens to be effective in maintaining remission (Table 1) [2,3]. In the CYCAZAREM trial (a randomized trial of maintenance therapy for vasculitis associated with ANCAs), patients who had achieved remission after oral CYC induction were randomized to continue CYC or to switch to azathioprine (AZA) [3]. At 18 months, there was no difference in relapse rates. The WEGENT trial (AZA or MTX maintenance for AAV) compared AZA with MTX in patients in remission after intravenous CYC [2,4▪▪]. There was no difference in adverse events or relapse rates. Mycophenalate mofetil (MMF) showed higher rates of relapse compared with AZA in the IMPROVE trial (MMF versus AZA for remission maintenance in AAV) and should be considered a second-line agent [11].

It is important to note that these trials compared maintenance regimens after induction with CYC. It is clear, however, that use of RTX for induction does not lead to a sustained remission (8). At the 18-month follow-up of the RAVE trial, an unacceptable one-third of the participants in both arms relapsed, emphasizing the need for maintenance therapy after RTX induction [14].

Table 1. Granulomatous with polyangiitis and microscopic polyangiitis randomized controlled maintenance trials

Study	Induction regimen	Maintenance regimens	Steroid dosing	Duration of therapy	Results
CYCAZAREM [3]	PO-CYC	PO-CYC (1.5 mg/kg/day) versus AZA (2 mg/kg/day) for 12 months then both groups switched to AZA 1.5 mg/kg/day	Prednisolone 10 mg a day until 12 months then 7.5 mg a day	18 months	No difference in relapse rates between treatment groups Relapse rates were lower in patients with MPA
WEGENT [2,4▪▪]	IV-CYC	AZA 2 mg/kg/day versus MTX goal dose 25 mg/week	Prednisone tapered to 12.5 mg/day by 6 months and to 5 mg/day by 18 months. Withdrawn at 24 months	12 months	No difference in adverse events and relapse rates between treatment groups Late relapse common Relapse more common in PRS_ANCA
IMPROVE [11]	PO-CYC or IV-CYC	MMF (200 mg/day) versus AZA (2 mg/kg/day) until 12 months, 1500 mg or 1.5 mg/kg/day until 18 months, 1 mg/kg/day or 1000 mg/day until 24 months and withdrawn at 42 months	Prednisone tapered to 5 mg/day by 12 months and withdrawn by 24 months	42 months	Relapses were more common with MMF than with AZA
MAINRITSAN [12▪▪,13▪▪]	IV-CYC	RTX 500 mg at weeks 0 and 2 then 500 mg every 6 months versus AZA 2 mg/kg/day for 12 months, 1.5 mg/kg/day until 18 months and 1 mg/kg/day until 22 months	Prednisone 5 mg/day for at least 18 months	22 months (last RTX infusion at 18 months)	Relapse rates were higher in the AZA group

CYC, cyclophosphamide; MMF, mycophenalate mofetil; MTX, methotrexate; RTX, rituximab.

RITUXIMAB FOR MAINTENANCE

RTX is a chimeric monoclonal anti-CD20 (B-cell) antibody. In April 2011, it was approved for use by the United States Food and Drug Administration to treat severe GPA and MPA. Several retrospective cohort studies have suggested that maintenance therapy with RTX is well tolerated and effective [15–19]. The Maintenance of Remission using Rituximab in systemic AAV (MAINRITSAN) trial is the first RCT to show superiority of RTX over AZA in patients who had achieved remission after CYC induction [12▪▪]. At 28 months, the relapse rate was 5% in the RTX arm versus 29% in the AZA arm. RTX maintained superiority as far out as 60 months [13▪▪].

There is no consensus on the appropriate RTX maintenance dosing regimen. In the MAINRITSAN trial, a dose of 500 mg was given twice 2 weeks apart followed by 500 mg every 6 months. Other studies suggest dosing of 1000 mg every 4 or 6 months [15,16]. More information will be available from the RITAZAREM trial (Comparing Rituximab with AZA as Maintenance Therapy in Relapsing AAV), which is currently enrolling. A dose of RTX 1000 mg every 4 months is being compared with AZA in relapsing patients who achieved remission after RTX induction [20].

Two therapeutic strategies for RTX have been proposed – continuous B-cell depletion on a fixed dosing regimen versus dosing for rise in ANCA titers and reconstitution of B cells. In a Mayo clinic cohort, relapses were preceeded by the reconstitution of B cells and the rise in ANCA levels [18]. These findings do not agree with other cohorts in which relapses occurred despite ongoing B-cell depletion, and rise in ANCA titers did not correlate with flare [16,17]. In the MAINRITSAN trial, all three patients who flared in the first 28 months had not reconstituted their B cells [12▪▪]. The follow-up study, MAINRITSAN 2, will compare fixed dosing RTX 500 mg every 6 months to dosing based on B-cell recovery and ANCA level [21]. Hopefully, MAINRITSAN 2 and RITAZAREM will shed more light on the best way to dose this effective agent for maintenance of remission. The RITAZAREM trial will also provide data on use of RTX as maintenance after induction with the same agent.

As treatment paradigms change and more RTX is being prescribed, it is important be familiar with the potential side effects of long-term B-cell depletion. Infusion reactions are a well described complication of RTX but the risk does not seem to increase with repeated infusions [12▪▪,15,16,19]. In the RTX maintenance studies, infections are the most commonly reported adverse event. In cohort studies, serious infections were reported in 10–30% of patients [15,16,18,19]. Though not statistically significant, in the MAINRITSAN trial, there were more infections in the RTX arm due to higher incidence of pneumonia and bronchitis. Several cases of *Pneumocystis Jerovii* pneumonia (PJP) have been reported suggesting the need for PJP prophylaxis [12▪▪,17,18]. Another concern with the long-term use of RTX is hypogammaglobulinemia. In one retrospective study of patients treated with RTX 1000 mg every 6 months, one-third of patients developed hypogammaglobulinemia [22]. Immunoglobulin levels should be followed; however, no consistent link between levels and the occurrence of infections has been demonstrated. The role of immunoglobulin replacement therapies is still undefined but might be considered in patients with hypogammaglobulinemia and recurrent infections. Late-onset neutropenia has also been reported and has been associated with neutropenic fevers [15].

OTHER BIOLOGIC AGENTS

Several other biologic agents are in the investigative stage. Ofatumamuab, a fully humanized mAb to CD20 showed promise in a small cohort [23]. This agent might be an option for patients who have had anaphylactic reactions to RTX.

In an open-label study, the CTLA4-Ig agent Abatacept was used in patients with nonsevere relapsing disease with promising results. Patients were allowed to remain on a stable dose of MTX, AZA or MMF [24]. Abatacept might be a good option for patients who have mild flares on conventional therapy. The ABROGATE trial that will examine the efficacy of addition of Abatacept to standard therapy is currently enrolling [25].

Belimumab, a mAb directed against B-lymphocyte stimulator, is under investigation in combination with AZA and MTX in the BREVAS trial [26]. Avacopan (CCX168) is an oral small-molecule C5a receptor antagonist that blocks neutrophil activation. It has shown a good safety signal, and though not powered for efficacy, did show improved steroid-sparing effect when used with standard induction regimens [27,28].

WITHDRAWAL OF THERAPY

Prospective trials of conventional maintenance therapies for GPA and MPA have treated patients for 12–18 months [2,11,12▪▪]. Long-term follow-up data have shown high relapse rates with withdrawal and discontinuation of maintenance agents [4▪▪,13▪▪]. In the WEGENT trial, comparing AZA

with MTX in maintenance of remission for 12 months, 73% of the relapses occurred after discontinuation of the study drugs. In the IMPROVE trial, comparing maintenance MMF with AZA, relapse rates increased after 42 months when therapies were completely withdrawn [11]. Late relapses were also seen in the 60-month follow-up of the MAINRITSAN trial. Three relapses occurred in the first 28 months, and 13 relapses occurred between months 28 and 60 after discontinuation of RTX infusions [13▪▪].

Compelling support for the use of longer maintenance regimens comes from a retrospective review of a Cleveland Clinic cohort [29▪▪]. In a group of 157 patients with newly diagnosed disease who had maintained a sustained remission for 18 months after induction, 58% had late-onset relapse. Treatment with either AZA or MTX for more than 36 months reduced the hazard ratio of relapse by 66% versus a reduction of only 29% if treated for only 18–36 months. Furthermore, of those who relapsed while on therapy, 50–60% were on subtherapeutic doses of MTX or AZA. Of note, there was no difference in proportion of adverse events between the longer and shorter treatment groups. In contrast, a small prospective trial comparing AZA maintenance for 1 year versus for 4 years did not show a reduced risk of relapse with longer treatment [30]. This study however was underpowered, limiting the interpretation of these results.

Though the optimal duration of maintenance therapy remains unclear, consideration of long-term maintenance therapy might be appropriate in patients with worse prognostic indicators.

TAILORED THERAPY

Ideally, the identification of disease characteristics that respond to a particular therapy and identification of risk factors for relapse would allow for subsequent individualization of therapy. Tailored therapy would mean selecting the most appropriate agent and avoiding unnecessary treatment-related toxicity in patients with more favorable prognosis.

Post-hoc analysis of the RAVE trial showed that patients with proteinase 3 antibodies (PR3)-ANCAs and those with relapsing disease did better on RTX [31▪]. However, a retrospective study of 59 patients suggests that not all PR3-positive patients should be treated with RTX. The authors showed that of GPA patients treated with RTX, 86% of whom had +PR3-ANCAs, response to therapy was poor in the subset of patients with granulomatous lesions (orbital masses and pachymeningitis) versus those with vasculitic manifestations [32].

It is well demonstrated that relapses are more likely in patients with PR3-ANCAs [3,4▪▪,33,34]. This might indicate a subset of patients who warrant longer treatment. The relationship between ANCA titers and risk of relapse remains an area of intense debate. The reappearance of ANCA and the increase in titer have been shown to correlate with flare [35]. A post-hoc analysis of the RAVE trial, however, showed that rise in PR3 was poorly predictive of flare within the overall population [36]. In the subsets of patients with renal disease and/or diffuse alveolar hemorrhage and in those treated with RTX, rise in PR3 titer was predictive of relapse within 1 year but not in other subgroups. More studies are necessary to determine if ANCA type and following ANCA titers can be used to tailor therapy.

GLUCOCORTICOID DOSING

The optimal strategy for GC dosing and duration in the maintenance phase remains unknown. There has been no standardization of the approaches of the various RCTs to maintain GC leading to substantial practice variability (Table 1).

A 2010 meta-analysis of 13 RCTs concluded that in the studies in which participants were exposed to longer courses of GC, the relapse rates were lower [37]. The authors demonstrate a three-fold higher risk of relapse in patients on no GC compared with those on prednisone 5 mg a day. In contrast, a retrospective study of 147 patients showed no difference in time to relapse in patients in remission on 0, 5 or more than 5 mg of prednisone beyond 6 months [38]. Furthermore, steroid use was associated with higher incidence of new-onset diabetes and infection.

The Assessment of Prednisone In Remission (TAPIR) trial, which is currently recruiting, hopes to shed light on this unanswered question comparing prednisone 5 mg a day with no prednisone for 6 months in patients who have achieved remission [39].

CONCLUSION

The advances in the field have changed the AAVs from fatal diseases to ones with a chronic and relapsing course. As patients live longer, late-stage relapses are common, and longer treatment duration might

be warranted in certain patient subsets. RTX has emerged as an effective alternative for maintenance of remission. Due to its side effect profile and superiority in PR3-positive patients and those with nongranulomatous disease, perhaps not all patients are appropriate candidates for this drug. The optimal steroid dosing and duration as well as the best way to tailor therapy based on ANCA titer is still unknown. Researchers are continuing to address these questions moving us toward tailored treatment regimens based on patients' disease characteristics.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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Recent advances in the pathogenesis, prediction, and management of rheumatoid arthritis-associated interstitial lung disease

Cheilonda Johnson

Purpose of review
To provide an overview of recently published articles covering interstitial lung disease associated with rheumatoid arthritis (RA-ILD).

Recent findings
Over the past year, many studies replicated previous findings in more diverse and occasionally larger populations internationally. Specifically, the association among cigarette smoking, high rheumatoid factor titer, elevated anticitrullinated protein antibody (ACPA) levels, and RA-ILD was strengthened. Clinical characteristics, autoantibodies, and biomarkers to aid in RA-ILD development, progression, and mortality prediction were explored. Finally, direct and indirect treatment effects were highlighted.

Summary
The ability to identify risk factors for preclinical RA-ILD has been enhanced, but the proper management strategy for these patients is yet to be defined. ACPAs and cigarette smoking are highly associated with RA-ILD, but the mechanistic relationship between lung injury and autoantibody generation remains unknown. There is conflicting evidence regarding the significance of a usual interstitial pneumonia (UIP) versus non-UIP pattern on high-resolution computed tomography. The use of biologic agents in patients with rheumatoid arthritis does not appear to increase the risk of incident ILD or RA-ILD exacerbation. Randomized prospective studies of specific therapy for RA-ILD are still lacking.

Keywords
interstitial lung disease, pathogenesis, pulmonary fibrosis, rheumatoid arthritis, treatment

INTRODUCTION

Interstitial lung disease often complicates rheumatoid arthritis (RA-ILD) and remains a significant source of morbidity and mortality [1–5]. Subclinical RA-ILD is common, but factors that predict progression to clinically significant disease are poorly understood [1,6–8]. Further, prognostication in any individual patient following diagnosis is difficult due to significant clinical heterogeneity [9–11]. Finally, therapeutic management is highly variable and dependent on retrospective studies and case series, not well designed randomized control trials [12–14].

Several RA-ILD knowledge gaps in need of additional research have been identified [15]. Over the past year, the field addressed many of these areas including the need for screening guidelines, diagnostic criteria, biomarker development, predictive modeling, and response to therapy. This review will provide an overview of recently published articles investigating RA-ILD focusing on pathogenesis, prediction, and management.

RISK FACTORS

In the past year and a half, several RA-ILD risk factors were described across diverse highly characterized international populations [16▪,17▪▪,18▪▪,19–23] (Table 1). Once again, advanced age, male sex,

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Correspondence to Cheilonda Johnson, MD, MHS, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, 1830 E. Monument Street, Suite 500, Baltimore, MD 21224, USA. Tel: +1 410 955 4176; fax: +1 410 614 1652; e-mail: cjohn164@jhmi.edu

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KEY POINTS

- ACPAs and cigarette smoking are highly associated with RA-ILD.
- There is conflicting evidence regarding the significance of radiographic UIP versus non-UIP pattern in patients with RA-ILD.
- Randomized prospective studies of specific therapy for RA-ILD are needed.

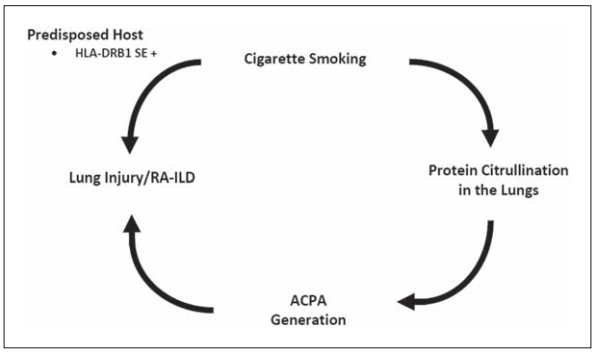

FIGURE 1. Theoretical framework for rheumatoid associated interstitial development. Depiction of potential risk factors for interstitial lung disease associated with rheumatoid arthritis. Susceptible individuals positive for human leukocyte antigen DRB1 shared epitope develop lung protein citrullination in the setting of cigarette smoking. Protein citrullination leads to the production of anticitrullinated protein antibodies that promote lung abnormalities including interstitial lung disease associated with rheumatoid arthritis. Smoking independently increases risk for lung injury and fibrosis.

rheumatoid arthritis disease activity, rheumatoid factor, and anticitrullinated protein antibody (ACPA) titers were found to be associated with RA-ILD. Many of these studies provided additional evidence in support of the leading hypothesis for one major RA-ILD risk pathway (Fig. 1).

Restrepo *et al.* [19] demonstrated a strong interaction among human leukocyte antigen DRB1 (HLA-DRB1) shared epitope, cigarette smoking, and the development of RA-ILD. They also demonstrated an association between high titer anticyclic citrullinated peptide (anti-CCP), a type of ACPA, and RA-ILD.

Song *et al.* [21] sought to explore whether polymorphisms in peptidyl arginine deiminase 4 (*PADI4*) and *HLA-DRB1* were associated with RA-ILD in 116 Korean patients with rheumatoid arthritis. Peptidyl arginine deiminase 4 catalyzes conversion of peptidyl arginine into peptidyl citrulline. *PADI4* single nucleotide polymorphisms (SNPs) have been found to be associated with rheumatoid arthritis in Asian populations. Susceptibility to airway abnormalities on high resolution computed tomography(HRCT) was noted in those with the recessive genotype padi4_92. RA-ILD susceptibility was seen in those with a tryptophan at position 9 of the HLA-DRB1 sequence.

A study by Park *et al.* [24] explored the association between anti-CCP and pulmonary abnormalities defined by ILD score (ILDS) from visual inspection of computed tomographies (CTs) in 83 patients with rheumatoid arthritis. Few patients had RA-ILD [$n = 7$ (8.4%)], but most had some pulmonary abnormality (RA-ILD, centrilobular nodules, or airway abnormality). Expiratory air trapping and bronchial wall thickening were significantly

Table 1. Clinical factors associated with interstitial lung disease associated with rheumatoid arthritis

		Clinical factor										
		Age	Male sex	Later onset RA	RA duration	RF titer	Anti-CCP	DAS 28	HLA-DRB1 SE	Cigarette smoking	Other pulmonary condition	Tumor markers
Study[a]	*n*											
Akiyama [16▪]	395	+	+			+	+			+		
Curtis [17▪▪]	11 219	+	+								+	
Doyle [18▪▪]	113	+	+			+	+			+		
Restrepo [19]	779	+	+		+	+	+	+	+			
Rocha-Munoz [20]	81				+	+	+	+		+		
Song [21]	116	+	+	+		+						
Wang [22]	111	+				+						+
Wang [23]	41											+

Anti-CCP, anticyclic citrullinated peptide; DAS, disease activity score; HLA-DRB1 SE, human leukocyte antigen DRB1 shared epitope; RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope.
[a]First author.

correlated with anti-CCP titer. There was no significant correlation with total ILDS and physiologic parameters, but the number of patients with RA-ILD and abnormal PFTs was small.

Automated CT interpretation has the potential to identify lung abnormalities before the development of clinically overt disease. Smoking has long been thought to play a role in the pathogenesis of rheumatoid arthritis and highly coincident RA-ILD. The association between high attenuation areas (HAA) based on CT densitometry and cigarette smoking was explored in 172 patients with rheumatoid arthritis and 3969 controls [25]. HAA, a surrogate for preclinical lung abnormalities that could represent ILD, was associated with cigarette smoking; this association was more pronounced in patients with rheumatoid arthritis [25].

Bernstein *et al.* [26] looked whether rheumatoid arthritis associated autoimmunity is associated with subclinical ILD in 6736 individuals without overt classifiable autoimmune disease. CT densitometry from cardiac CT (quantitative) and visual inspection from full lung CT (qualitative) were utilized. Increasing rheumatoid arthritis associated autoimmunity was associated with both quantitative and qualitative measures of subclinical ILD, this association was significantly magnified among ever-smokers.

In summary, the strong interaction among HLA-DRB1 alleles, citrulline autoimmunity, cigarette smoking, and both subclinical and clinical RA-ILD was reinforced.

DIAGNOSIS

Identification of diagnostic biomarkers was an intense area of focus in the field. Several groups investigated potential serum and bronchoalveolar lavage biomarkers to aid in RA-ILD diagnosis, severity grading, and prognostication [18▪▪,20,22,27–29].

Doyle *et al.* [18▪▪] evaluated factors associated with RA-ILD in 113 individuals and then validated those measures in a second population of 76 independent patients. Once again, age, sex, rheumatoid factor, anti-CCP, and cigarette smoking were associated with RA-ILD. Further, a biomarker signature composed of matrix metalloproteinase 7, pulmonary and activation-regulation chemokine, and surfactant protein D significantly increased the area under the curve for both subclinical and clinically overt RA-ILD.

Furukawa *et al.* [28] looked at anti-HLA antibody profiles in patients with connective tissue disease-associated ILD (CTD-ILD). They found that antimajor histocompatibility complex class I-related chain A (anti-MICA) antibodies were significantly in those with RA-ILD.

Hamada *et al.* [29] investigated serum B-cell activating factor (BAFF) levels in patients with CTD-ILD. BAFF is a member of the TNF family and is thought to play a role in autoantibody production. They compared CTD-ILD patients with undifferentiated CTD-ILD, chronic fibrosing interstitial pneumonia (CFIP), and healthy controls. Serum BAFF levels were significantly higher in those with CTD-ILD compared with those with CFIP and healthy controls. Further, levels inversely correlated with lung function. Finally, BAFF was overexpressed in the lung tissue of those with CTD-ILD.

Oguz *et al.* [30] looked at Krebs von de Lungen-6 (KL-6) levels in 113 patients with CTD and 45 healthy controls. KL-6 levels were higher in patients with CTD-ILD than those with CTD alone and healthy controls. In addition, smokers had significantly higher KL-6 levels than nonsmokers.

Elevated tumor markers can be found in patients with rheumatoid arthritis and ILD. Wang *et al.* [22] explored tumor markers and their ability to aid in the diagnosis of RA-ILD in 111 rheumatoid arthritis patients, 28 with ILD and 83 without. They looked specifically at carcinoembryonic antigen, carbohydrate antigen 15-3, carbohydrate antigen 125, and carbohydrate antigen 19-9. Carbohydrate antigen 15-3, carbohydrate antigen 125, and carbohydrate antigen 19-9 were elevated in patients with RA-ILD compared with patients with rheumatoid arthritis alone [22,23]. Only age and carbohydrate antigen 125 remained significantly associated with risk in the adjusted model.

In summary, KL-6 once again was demonstrated to be associated with RA-ILD. Longitudinal studies are needed to understand the exact role of tumor markers in patients with RA-ILD. BAFF may have clinical utility in distinguishing types of chronic fibrosing lung diseases [31]. The addition of biomarkers to current clinical RA-ILD prediction models has the potential to significantly improve diagnostic sensitivity even in the preclinical stage.

NATURAL HISTORY

Several groups sought to identify risk factors associated with disease progression and mortality. Zamora-Legoff *et al.* performed a retrospective study of 167 patients with RA-ILD to look for factors that predicted progressive disease. Progressive decline was common in the cohort (22–40%); usual interstitial pneumonia (UIP) HRCT pattern, severe disease at presentation, and rate of PFT change in the first 6 months following diagnosis were risk factors for progression [32].

Nurmi *et al.* [33] analyzed clinical disease course in 59 patients with RA-ILD based on HRCT pattern.

They found no significant difference in median survival between those with UIP (92 months) versus non-UIP patterns (137 months), but those with UIP had a greater number of hospitalizations, need for supplemental oxygen, number of deaths, and rate of decline in lung function.

A computer-based CT analysis prediction tool, CALIPER, Biomedical Imaging Resource Laboratory, Rochester, MN, USA, was used to predict mortality in a mixed population of over 200 patients with CTD-ILD, including 50 patients with RA-ILD [34]. Mortality was independently associated with age, smoking history, carbon monoxide transfer coefficient, and pulmonary vessel volume. The automated CT parameter, pulmonary vessel volume, identified by CALIPER performed better than visual inspection and age-adjusted and sex-adjusted PFT measures.

Lung physiology remains an attractive modality for risk prediction, given the ease of incorporation into standard clinical practice. Solomon *et al.* [35▪▪] evaluated 137 RA-ILD patients with NSIP ($n=29$) or definite/possible UIP ($n=108$) HRCT patterns for clinical predictors of mortality. Median follow-up was 4.8 years; for the entire group, median survival was 10.35 years. Those with UIP (44%, median survival 10.18 years) were more likely to die than those with NSIP (24%, median survival 13.62 years) with a significantly greater rate of lung function decline. In a multivariate model, low baseline forced vital capacity percentage predicted (FVC%) and a 10% decline in FVC% at any time during the following period were both independently associated with mortality. HRCT pattern (UIP versus NSIP) after adjustment for confounders (age, sex, smoking history, baseline FVC%, and change in FVC%) was not associated with mortality.

In summary, the evidence regarding HRCT pattern as a prognostic indicator were mixed. RA-ILD patients with a UIP pattern were repeatedly demonstrated to have more severe progressive disease, but this did not translate into worse survival after accounting for lung function. The potential for automated CT measures to augment the performance of currently available clinical prediction models is appealing but require external validation.

TREATMENT

Studies of medication treatment and RA-ILD were largely focused on exploring potential adverse effects of current empiric treatment for rheumatoid arthritis alone and RA-ILD; two studies did investigate direct response to therapy.

Rituximab, a B-cell depleting agent, has been given as salvage therapy for severe refractory RA-ILD based on small case series. Chartrand *et al.* [36] described their single-center experience with rituximab for the treatment of CTD-ILD in 24 patients, the majority had RA-ILD ($n=15$). Lung function response (FVC%) was highly variable, and rituximab had no appreciable effect on lung function over time. Further, a steroid-sparing effect was not seen.

Corticosteroids are at the foundation of empiric treatment for RA-ILD. Prolonged durations of even moderate doses are avoided if possible due to a wide variety of potential adverse effects [37,38]. The risk for serious infection (need for antimicrobials or hospitalization) was determined in 181 patients with RA-ILD from a single center with a median follow-up time of 3.1 years [38]. The risk of infection was highest in the first year and among those on 10 mg or more of prednisone daily with or without disease-modifying antirheumatic drugs (DMARDs) in combination. Pneumonia was seen most commonly (3.9 per 100 person-years) followed by opportunistic infections (1.5 per 100 person-years) and septicemia (1.0 per 100 person years). Overall infection rates were 7.4 per 100 person-years, which is similar to infection rates reported in rheumatoid arthritis patients without ILD.

Fibrotic lung disease regardless of underlying cause [i.e., idiopathic pulmonary fibrosis (IPF) versus RA-UIP] may behave similarly. Consequently, there is some concern that our current treatment strategies (i.e., prednisone/azathioprine combination therapy) may introduce harm as was shown in patients with IPF. Oldham *et al.* [39▪] studied adverse events related to azathioprine in patients with fibrotic CTD-ILD. Incident rates for death, lung transplantation, and hospitalization were compared for fibrotic CTD-ILD patients on azathioprine ($n=54$; RA-ILD $n=15$) compared with mycophenolate ($n=43$; RA-ILD $n=8$). Medication discontinuation for nonpulmonary side effects was much more common in those on azathioprine (27%) than on mycophenolate (5%). The adverse incident rates were similar in both groups and did not differ on the basis of HRCT pattern (UIP versus non-UIP). Both therapies were equally well tolerated (in those who tolerated them) and resulted in stability of lung function.

Biologic DMARDs have been described as risk factors for the development and or progression of interstitial pneumonitis. They have also been reported to have a therapeutic effect. Akiyama *et al.* [16▪] examined risk factors for acute ILD exacerbation in 395 patients with rheumatoid arthritis, 78 with RA-ILD, and 317 with RA alone, on tocilizumab, an IL-6 inhibitor. Six patients with RA-ILD developed acute exacerbations while on tocilizumab; none of the rheumatoid arthritis alone

patients had an acute presentation of ILD on therapy. Baseline characteristics did not distinguish between the exacerbation and nonexacerbation groups. Those who achieved remission or low disease activity after 24 weeks on tocilizumab were significantly less likely to develop RA-ILD exacerbation. This same pattern was not seen in patients who stopped tocilizumab before 24 weeks.

In a similar study, Curtis *et al.* [17▪▪] looked at the risk of incident ILD and ILD exacerbation in 11 219 patients with rheumatoid arthritis treated with TNFi, rituximab, tocilizumab, or abatacept (a T-cell costimulation blocker). Mean exposure time was 8.3 months. Unadjusted incident ILD ranged from 4.0 to 12.2 per 1000 person-years. ILD complications ranged from 65.8 to 127.7 per 1000 person-years. In the full Cox model, the relative hazard for incident ILD was not higher in those exposed to biologic DMARDS. Similarly, there were no differences in ILD-related hospitalization rates between the cohorts.

Detorakis *et al.* [40▪] looked prospectively at the evolution of CT findings in 82 rheumatoid arthritis patients after 1 year on TNFi. The goal was to assess the safety of TNFi compared with nonbiologic DMARDS. The study group comprised 42 patients with existing RA-ILD and 40 without known lung disease treated with TNFi [68 infliximab, 10 etanercept, and four with adalimumab) and methotrexate (MTX)]; the control population included 44 patients with RA-ILD and 44 patients without known lung disease treated with nonbiologic DMARDs (68 MTX alone, 20 MTX and hydroxychloroquine). All patients had moderately to severely active rheumatoid arthritis and underwent HRCT examination at baseline and 1 year. There were no episodes of incident ILD or ILD exacerbation in the TNFi group. In addition, TNFi patients showed improvement in bronchial wall thickening and air trapping over time based on imaging and pulmonary physiology.

In summary, small sample sizes and study group heterogeneity continue to limit our ability to draw a definitive conclusion regarding the utility of rituximab to treat RA-ILD. TNFi and other biologic DMARDS appear well tolerated with regard to the development of incident RA-ILD and RA-ILD progression/flare. The current management of RA-ILD with a UIP pattern with combination corticosteroids/steroid-sparing agents does not appear to introduce harm. Once again, the need for the judicious use of corticosteroids was highlighted.

CONCLUSION

Researchers in the field are advancing our understanding of RA-ILD, but many knowledge gaps remain. Key areas to address in future research include diagnostic and management strategies. The development of longitudinal multicenter consortia will be a crucial component of this important endeavor.

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Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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Biosimilars: implications for rheumatoid arthritis therapy

Stanley Cohen[a,b] *and Jonathan Kay*[c]

Purpose of review
Abbreviated pathways for the approval of biosimilars have been established in the European Union (EU), the United States, and other countries. Biosimilar TNF inhibitors have been available in South Korea and the EU since 2012 and 2013, respectively, and the first biosimilar infliximab was introduced to the clinic in the United States in November 2016. Five TNF inhibitor biosimilars have now been approved, and many other biosimilars to treat rheumatoid arthritis and other inflammatory diseases are in development.

Recent findings
Over the last 18 months, published results of randomized clinical trials (RCTs) have shown equivalent efficacy and comparable safety and immunogenicity of biosimilars with their reference products. 'Real world' experience with biosimilars in the EU continues to increase and provides evidence regarding the efficacy and safety of using biosimilars in the clinic and of switching from bio-originators to their biosimilars.

Summary
Cost implications of using biosimilars and extrapolation of their use to treat diseases in which they were not tested in RCTs are of great interest. We review the results of RCTs and available experience with biosimilars in the clinic.

Keywords
biosimilars, equivalence, extrapolation, interchangeability, nomenclature, rituximab, TNF inhibitors

INTRODUCTION

In 2005, the European Medicines Agency (EMA) proposed a pathway by which to approve similar biological products [1]. Five years later, as part of the Patient Protection and Affordable Care Act, the United States (US) Congress established an abbreviated pathway [351(k)] for the approval of biological products that are 'highly similar' to their reference products [2]. The EMA and the US Food & Drug Administration (FDA), as well as regulatory agencies in other countries, subsequently issued guidelines clarifying the process by which such biosimilars are approved [3–10]. In the US, the Biologics Price Competition and Innovation (BPCI) Act of 2009 defines a biosimilar as a biological product that is 'highly similar to the reference product notwithstanding minor differences in clinically inactive components' and that 'there are no clinically meaningful differences between the reference product and the biologic product in terms of the safety, purity and potency of the product' [2]. Likewise, in the European Union (EU), the EMA defines a biosimilar as 'a biological medicinal product that contains a version of the active substance of an already authorised' reference product, for which 'similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy' has been demonstrated [3].

These approval pathways have been utilized by multiple sponsors, and as of 23 September 2016, biosimilars had been approved in the EU and United States; most are commercially available. Following the initial approval of a biosimilar infliximab by the EMA in 2013, four additional biosimilar TNF inhibitors have been approved by the EMA or the US FDA for the treatment of rheumatoid arthritis and other inflammatory diseases. Many others are in development. We will review the reports published over the

[a]Clinical Professor of Internal Medicine, UT Southwestern Medical School, [b]Medical Director, Metroplex Clinical Research Center, Dallas, Texas and [c]Director of Clinical Research, Rheumatology Division, Professor of Medicine and Timothy S. and Elaine L. Peterson Chair in Rheumatology, Department of Medicine, UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, Massachusetts, USA

Correspondence to Stanley Cohen, MD, Clinical Professor of Internal Medicine, UT Southwestern Medical School, Dallas, Texas, USA. Tel: +1 214 707 1390; e-mail: Arthdoc@aol.com

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KEY POINTS

- Abbreviated pathways for the approval of biosimilars have been implemented successfully in the EU and United States, and 23 biosimilars have been approved, of which five are biosimilars of TNF inhibitors.
- For the approved TNF inhibitor biosimilars, RCTs comparing each biosimilar with its reference product have demonstrated equivalent pharmacokinetics and clinical efficacy and comparable safety.
- Even in diseases not studied, such as inflammatory bowel diseases, 'real world' and observational studies have confirmed comparable efficacy and safety.
- The issue of 'interchangeability' or 'nonmedical switching' from a bio-originator to its biosimilar remains a concern, but data from RCTs and accumulated clinical experience suggest that this will not be a significant problem. However, the potential effects of multiple switches have not been studied.
- In many countries, price reductions have been realized with biosimilars. We hope that these cost savings for healthcare systems will translate into greater access to effective biologic therapies for patients.

last 18 months on biosimilars that either have been approved or are in development to treat rheumatic diseases and will discuss the implications of their use in the clinic.

BIOSIMILARS DEVELOPMENT PATHWAY

Biopharmaceuticals are large, complex proteins that are manufactured by inserting a gene encoding the primary amino acid sequence into a producer cell line, using a DNA vector. These transfected cells are grown in culture and produce the biologic product, which is recovered from the culture medium, purified, and packaged [11]. In contrast to a generic drug, for which the active ingredient can be replicated exactly so that the generic drug is identical in chemical structure to its reference product, the complex structure of a biopharmaceutical and its posttranslational modifications make production of an identical protein virtually impossible. Thus, replicas of biopharmaceuticals typically are similar to, but not exactly the same as, their reference products.

The regulatory pathways for approval of a biosimilar differ somewhat between the EMA and the US FDA, but both follow a 'stepwise approach' and require extensive analytical studies followed by clinical studies comparing pharmacokinetic and pharmacodynamic parameters, immunogenicity, efficacy, and safety of the proposed biosimilar with its reference product to confirm that there are 'no clinical meaningful differences' between the reference molecule and the biosimilar [4,6] (Fig. 1). The US FDA has articulated a 'totality of the evidence' approach to evaluating the data accumulated, in which all of the information is considered in its entirety without conferring greater importance to any one aspect.

A wide range of analytical studies comparing multiple batches of the biosimilar and the reference product, acquired over time, must demonstrate no differences in the primary amino acid sequence and no consequential variations in charge isoforms, glycosylation, other posttranslational modifications, or impurities [6,12]. However, there may be minor differences, but these should not impact critical functional properties of the biopharmaceutical. For therapeutic monoclonal antibodies, these

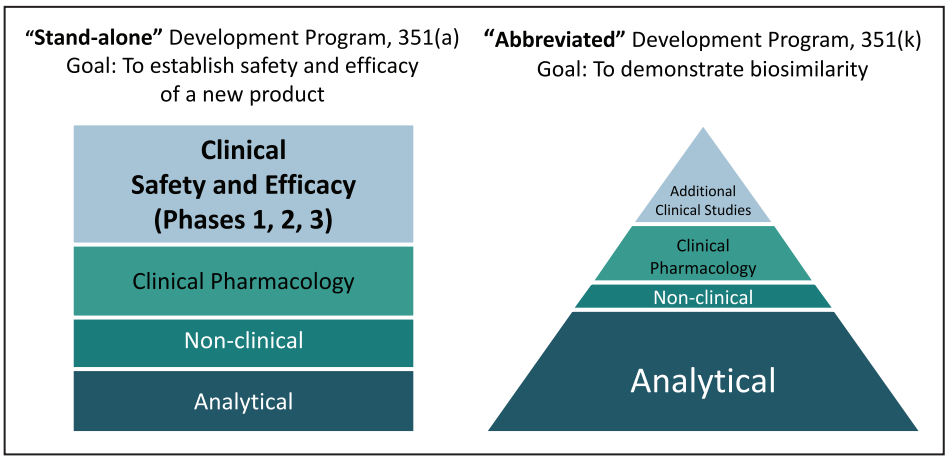

FIGURE 1. The goals of 'stand-alone' and biosimilar development are different. Reproduced from Christl, L. Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US. FDA Arthritis Advisory Committee meeting, 9 Feb 2016. Permission granted.

critical functional properties include Fc receptor binding, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity.

Pharmacokinetic parameters of a biosimilar must be equivalent to those of its reference product. Regulatory agencies have defined pharmacokinetic bioequivalence as when the 90% confidence intervals (CIs) for the ratio of geometric means for area under the curve and maximal concentration (C_{max}), between the biosimilar and its reference product fall within the log-transformed range of 80–125% (±20%) [4,10]. Pharmacokinetics typically is studied by comparing single doses of a biosimilar and its reference product in healthy patients. However, for drugs such as rituximab, which cannot safely be administered to healthy individuals, pharmacokinetics has been studied in patients with active rheumatoid arthritis [13,14]. In published pharmacokinetic studies of approved biosimilar TNF inhibitors, serum concentration–time profiles of the biosimilar and its reference product have overlapped closely, and variability of the ratio of geometric means for pharmacokinetic parameters has been much tighter than required by regulatory requirements [13,15–19].

Regulatory agencies require at least one clinical study to demonstrate equivalent efficacy and comparable safety and immunogenicity of the proposed biosimilar with its reference product, in contrast to novel agents for which two pivotal phase III placebo-controlled randomized clinical trials (RCTs) must be conducted in each indication for which approval of the novel agent is sought. Phase III RCTs of biosimilars of TNF inhibitors typically have been conducted in patients with rheumatoid arthritis, in combination with methotrexate, or in patients with plaque psoriasis, as monotherapy. Because the composite measures used to assess disease activity in clinical trials of drugs for Crohn's disease or ulcerative colitis rely upon patient's subjective assessment of disease activity and thus are less sensitive to detect potential differences between a biosimilar candidate and its reference product, manufacturers have been reluctant to pursue RCTs in inflammatory bowel diseases. This has frustrated the gastroenterology community.

The equivalence margin for RCTs comparing the clinical efficacy of a biosimilar with its reference product is derived from a meta-analysis of the therapeutic effect of the bio-originator in the original placebo-controlled RCTs, calculated as the risk difference in the endpoint of interest between active drug and placebo. For clinical trials in rheumatoid arthritis, that endpoint is usually the ACR20 (≥20% improvement in ACR response criteria), and for clinical trials in psoriasis, it is usually the PASI75 response rate. To preserve a proportion of the therapeutic effect of the bio-originator, the equivalence margin used in a comparative effectiveness RCT is usually half or less of the mean absolute difference derived in the meta-analysis [20]. This has yielded equivalence margins for the primary endpoint of ACR20 response rate in RCTs for TNF inhibitor biosimilars of ±15% [21–23], although the FDA recently proposed using an equivalence margin of ±12% that preserves a greater proportion of the therapeutic effect. Regulatory agencies have defined two-sided therapeutic equivalence in RCTs comparing a biosimilar with its reference product as when the 90% CI or 95% CI for the mean absolute difference in the primary endpoint between the biosimilar and the bio-originator falls within the predefined equivalence margin [20]. In the published clinical trials comparing biosimilar TNF inhibitors with their reference products, the absolute treatment differences for ACR20 and PASI75 responses in the per-protocol set analyses have ranged between 1 and 4%, with the 90% CI and 95% CI falling well within the predefined equivalence margins (Fig. 2).

In addition to having equivalent efficacy and comparable safety with its reference product, a biosimilar must be no more immunogenic than the bio-originator. The prevalence of both binding and neutralizing antidrug antibodies (ADAs) to each drug is assessed in RCTs that compare biosimilars with their reference products. Although neutralizing ADAs may impact pharmacokinetics, they produce only a modest but similar reduction in efficacy of both the biosimilar and the bio-originator.

Most of the studies comparing the immunogenicity of a biosimilar with its reference product have used an electrochemiluminescence bridging assay to detect ADAs, which yields higher rates of ADAs in the presence of drug than had been observed using

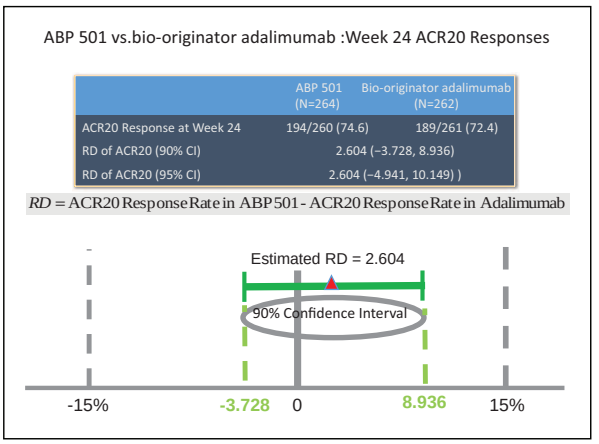

FIGURE 2. ABP 501 vs. bio-originator adalimumab week 24 ACR20 responses. RD, risk difference.

an enzyme immunoassay in the earlier placebo-controlled RCTs of the bio-originators. Immunogenicity of each of the approved infliximab biosimilars was similar to that of bio-originator infliximab [21,23], as was that of the approved adalimumab biosimilar ABP 501 and bio-originator adalimumab [24,25]. As etanercept is less immunogenic than the monoclonal anti-TNF antibodies, a much lower prevalence of ADAs was detected in the RCTs comparing the etanercept biosimilars, HD203, SB4, and GP2015, to bio-originator etanercept; these ADAs occurred transiently and none were neutralizing [22,26,27▪].

BIOSIMILARS APPROVED FOR INFLAMMATORY DISEASES

Infliximab

CT-P13 is an infliximab biosimilar developed and manufactured by Celltrion (Incheon, South Korea). Preclinical evaluation demonstrated it to be highly similar to both EU-sourced and US-sourced bio-originator infliximab. The 30-week results of the phase I PLANETAS study (5 mg/kg) and of the phase III PLANETRA study (3 mg/kg) each demonstrated equivalent efficacy and comparable safety and immunogenicity of the biosimilar with bio-originator infliximab, either as monotherapy in AS patients or with concomitant methotrexate in rheumatoid arthritis patients [23,28]. The 54-week results of both these trials, published in 2016, demonstrated continued comparability of pharmacokinetic parameters, efficacy, safety, immunogenicity, and adherence to treatment [15,29]. The outcomes of transitioning patients from bio-originator infliximab to the biosimilar in open-label extensions of both studies were also published in 2016 [30,31]. Patients who remained on treatment at week 54 were either continued on CT-P13 or switched to the biosimilar, if they had been receiving bio-originator infliximab. Although each extension study was open-label, investigators and patients remained blinded as to the initial treatment. ACR response rates were similar for the maintenance and switch groups in the PLANETRA extension study at week 102: ACR20 71.7 vs. 71.8%, ACR50 48.0 vs. 51.4%, and ACR70 24.3 vs. 26.1% (maintenance vs. switch) [30]. Similar findings were observed in the PLANETAS extension study at week 102: ASAS20 80.7 vs. 76.9% and ASAS40 63.9 vs. 61.5% (maintenance vs. switch) [31]. Safety and immunogenicity remained comparable between the two groups in both extension studies.

CT-P13 was approved in South Korea in July 2012, in the EU in September 2013, and subsequently in the United States in April 2016 to treat all of the conditions for which bio-originator infliximab is approved. It is available in more than 70 countries worldwide, marketed as Remsima by Celltrion, as Inflectra by Pfizer (New York, NY, USA), and as Flammegis by Egis Pharmaceuticals PLC (Budapest, Hungary). Inflectra (infliximab-dyyb) has been available in the United States since November 2016.

SB2 is a biosimilar infliximab developed by Samsung Bioepis (Incheon, South Korea). Pharmacokinetic equivalence of SB2 to both EU-sourced and US-sourced reference infliximab was demonstrated in a phase I randomized, single-blind, three-arm, parallel group pharmacokinetic study conducted in 159 healthy patients [16]. SB2 was shown to have equivalent efficacy and comparable safety to reference infliximab in a phase III RCT conducted in 584 rheumatoid arthritis patients with active disease despite methotrexate [21]. SB2 was approved in December 2015 in South Korea, where it is marketed as Renflexis, and in May 2016 in the EU, where it is marketed as Flixabi, to treat all of the conditions for which bio-originator infliximab is approved.

Etanercept

SB4 is biosimilar etanercept that was also developed by Samsung Bioepis. A phase I randomized, single-blind, three-arm, crossover study conducted in 138 healthy male patients demonstrated pharmacokinetic equivalence of SB4 to both EU-sourced and US-sourced bio-originator etanercept [32]. Equivalent efficacy and comparable safety with bio-originator etanercept were shown in a phase III RCT conducted in 596 patients with rheumatoid arthritis inadequately responsive to methotrexate [22]. SB4 was approved in September 2015 in South Korea, where it is marketed as Brenzys to treat patients with rheumatoid arthritis, ankylosing spondylitis (AS), plaque psoriasis, and psoriatic arthritis; and in January 2016 in the EU, where it is marketed as Benepali to treat patients with rheumatoid arthritis, axial spondyloarthritis (AS and nonradiographic axial spondyloarthritis), plaque psoriasis, and psoriatic arthritis.

GP2015 is another biosimilar etanercept that was developed by Sandoz (Holzkirchen, Germany). Pharmacokinetic parameters of GP2015 were shown to be equivalent to those of bio-originator etanercept in two phase I randomized, double-blind, single-dose, crossover studies, conducted in 105 healthy male patients [18]. Equivalent efficacy and comparable safety of GP2015 with bio-originator etanercept were demonstrated in a phase III RCT (EGALITY), in which 531 patients with active plaque psoriasis received either GP2015 or reference

etanercept as monotherapy [27▪]. GP2015 was approved by the US FDA in August 2016 as etanercept-szzs for all of the indications for which bio-originator etanercept is authorized [33]. Sandoz has given it the proprietary name, Erelzi. However, GP2015 has not yet become commercially available because of ongoing patent litigation.

Adalimumab

ABP 501 is a biosimilar adalimumab that was developed by Amgen (Thousand Oaks, CA, USA). Pharmacokinetic equivalence of ABP 501 to both EU-sourced and US-sourced reference adalimumab was demonstrated in a phase I randomized, single-blind, single-dose, three-arm, parallel-group study conducted in 203 healthy patients [34]. ABP 501 was shown to have equivalent efficacy and comparable safety to bio-originator adalimumab in two phase III double-blind RCTs: one as monotherapy in 350 patients with active plaque psoriasis and the other in combination with methotrexate in 526 patients with rheumatoid arthritis inadequately responsive to methotrexate [24,25]. ABP 501 was approved by the US FDA in September 2016 as adalimumab-atto for the treatment of rheumatoid arthritis, AS, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis [35]. Amgen has given it the proprietary name Amjevita. However, because of ongoing patent litigation, ABP 501 has not yet become commercially available.

Biosimilars in development for inflammatory diseases

Many other biosimilars of TNF inhibitors are being developed to treat inflammatory diseases. Several more infliximab biosimilars are in development, with at least four of the programs either conducting phase III RCTs or having been completed [36,37]. Multiple additional etanercept biosimilars are in development [38]. Data from phase III clinical trials of CHS-0214, a biosimilar etanercept developed by Coherus Biosciences Inc. (San Francisco, California, USA), in rheumatoid arthritis and in plaque psoriasis were presented in 2016, revealing equivalent clinical responses and comparable safety and immunogenicity to bio-originator etanercept [39,40]. Many other adalimumab biosimilars also are in development, with phase III RCTs ongoing [36,41]. Data from the phase III RCT of SB5, a biosimilar adalimumab developed by Samsung Bioepis, have been presented and demonstrate equivalent efficacy and comparable safety and immunogenicity to bio-originator adalimumab, as well as comparable efficacy, safety, and immunogenicity after a single transition from bio-originator adalimumab to SB5 [42,43]. At least one golimumab biosimilar is in preclinical development [44].

Rituximab biosimilars are being developed for both oncology and rheumatology indications and several have progressed to phase III RCTs in non-Hodgkin's lymphoma [45]. Two phase I pharmacokinetic studies comparing the rituximab biosimilar PF-05280586 to both EU-sourced and US-sourced bio-originator rituximab in 220 and 214 rheumatoid arthritis patients, respectively, each demonstrated pharmacokinetic equivalence, similarity in the pharmacodynamic measure of B-cell depletion, and comparable safety and immunogenicity [14,46]. Although not powered to demonstrate therapeutic equivalence, the latter trial showed the efficacy of PF-05280586 to be comparable with that of both EU-sourced and US-sourced bio-originator rituximab [46].

At least two abatacept [44,47] and one tocilizumab [48] biosimilars are in preclinical development or phase I trials.

IMPLICATIONS OF 'REAL WORLD' EXPERIENCE

Extrapolation of indications

'Extrapolation of indications' eliminates the need to perform multiple costly phase III RCTs in each different disease for which approval of a biosimilar is sought and facilitates the abbreviated approval pathway for biosimilars. To date, all regulatory agencies have granted the approved biosimilars of TNF inhibitors extrapolation to all indications for which the bio-originator is approved and that no longer are protected by patent. In the United States, it remains to be seen how this approach will impact utilization of biosimilars by gastroenterologists or dermatologists to treat indications in which their patients had not been studied. However, postmarketing experience in other countries suggests that this will not impede the adoption of biosimilars.

Cost

It was anticipated that the availability of biosimilars would significantly reduce the cost of biopharmaceuticals, allowing for greater utilization of these medications by patients. A 2014 RAND Corporation study estimated the potential cost savings of biosimilars in the United States market to be $44.2 billion over the subsequent decade, of which TNF inhibitors would account for 21% ($9.3 billion) [49]. This study assumed that market competition would result in the price of a biosimilar being 35% lower

than that of its reference product. However, at the time of the launch in September 2015 of filgrastim-sndz [Zarxio (Sandoz)], the first biosimilar approved in the US, its wholesale acquisition cost (WAC) was only 15% lower than that of bio-originator filgrastim [50]. Similarly, at the time of its launch in November 2016, the WAC of infliximab-dyyb (Inflectra) in the United States was only 15% lower than that of bio-originator infliximab [51]. However, discounts and ex-post rebates provided to third-party payers and pharmacy benefit management companies by bio-originator manufacturers might reduce or even eliminate the price differential between a biosimilar and its bio-originator. With multiple biosimilar TNF inhibitors likely coming to market over the next several years, competition may result in greater reductions in WAC. We expect that, in the US, payers ultimately will place a single biosimilar of each bio-originator on their formularies with cost being the major, if not the only, consideration in choosing that biosimilar.

In other countries, the price of biosimilars is lowest where market competition is greatest. In Canada, at the time of its launch in March 2015, the price of Inflectra was 34% lower than that of bio-originator infliximab [52]. The prices of biosimilars in the EU typically have been 20–30% lower than those of the corresponding bio-originators, but this is much less than the 80% price reduction realized with generic small molecule drugs [53]. However, in Norway, where the national hospital system has a competitive tender process for the exclusive contracts to supply medications that are administered in-hospital, the tender accepted for Remsima in 2014 was 39% lower than that offered for bio-originator infliximab and that accepted in 2015 was 69% lower [54]. As expected, the market share of biosimilar infliximab is much larger in those countries where the price of the biosimilar is markedly lower than that of bio-originator infliximab [55].

Interchangeability

The most contentious issue surrounding biosimilars is interchangeability and how this designation may impact safety and efficacy of both the biosimilar and the bio-originator. The BPCI Act, which established the pathway for biosimilars approval in the US, defines an 'interchangeable' biosimilar as one that 'may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product' [2]. Such an interchange might even take place on more than one occasion. In the EU, the designation of a biosimilar as being 'interchangeable' must be made by the regulatory agency in each member state, rather than by the EMA. In Canada, 'interchangeability' is determined by the provincial pharmacy boards and not by Health Canada [56]. The US FDA issued draft guidance in January 2017 regarding the data that will be required for a biosimilar to be granted the designation of being 'interchangeable' but, as of February 2017, no biosimilar yet has sought or received this designation. However, we expect that 'nonmedical switching' between bio-originator infliximab and its biosimilar, CT-P13 (infliximab-dyyb), will be encouraged by health insurers if the acquisition cost of the biosimilar is lower.

Most RCTs comparing biosimilars with their reference products have evaluated only a single transition from the bio-originator to the biosimilar. For approved biosimilars of TNF inhibitors, no loss of efficacy or increase in the incidence of adverse events or immunogenicity has been observed with such transitions. Only the phase III RCT (EGALITY), which compared the etanercept biosimilar GP2015 with bio-originator etanercept in patients with active plaque psoriasis, incorporated three switches between the two products, each of 6 weeks' duration, after assessment of the primary endpoint at week 12 [27▪]. Efficacy and safety was similar among patients who switched back and forth between the bio-originator and the biosimilar and those who continued either the bio-originator or the biosimilar throughout the 52-week study.

Over a decade of experience in the EU has shown that switching from bio-originator filgrastim, erythropoietin, or human growth hormone to the biosimilar has not been associated with significant loss of efficacy or new adverse events [57▪]. A recent systematic review of 11 published studies that included 1007 inflammatory bowel disease patients who initiated treatment with CT-P13 or who switched from bio-originator infliximab to the biosimilar CT-P13 found no significant difference in efficacy or safety between the therapies [58].

NOR-SWITCH was a study funded by the Norwegian government that evaluated a blinded switch from bio-originator infliximab to biosimilar infliximab CT-P13 compared with continuing treatment with bio-originator infliximab [59▪▪]. This 52-week noninferiority trial randomized 481 patients with AS, rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn's disease, or ulcerative colitis, who had been receiving bio-originator infliximab for a minimum of 6 months. Over 50% of patients enrolled had inflammatory bowel diseases. Study patients had a mean disease duration of 17.1 years and had been receiving infliximab for a mean of 6.8 years. The primary endpoint was worsening in disease-specific composite measures and/or agreement between the investigator and the patient that

increased disease activity required a change in treatment by week 52. In the per protocol population, disease worsening occurred in 26.2 and 29.6% of patients in the infliximab and CT-P13 arms, respectively. The 95% CI of the adjusted treatment difference (−4.4%) was −12.7 to 3.9, which was within the prespecified noninferiority margin. This study was not powered to compare the treatment strategies in patients with any individual disease. Similar proportions of patients in each group developed treatment-emergent adverse events and serious adverse events resulting in study drug discontinuation. The incidences of ADAs detected during the study was 7.1 and 7.9% in the infliximab-treated and CT-P13-treated patients, respectively, in the full analysis set.

Nomenclature

With concerns regarding the safety of therapeutic substitution, especially when multiple biosimilars become available, careful pharmacovigilance will be necessary. To facilitate postmarketing surveillance, biosimilars must have distinct names. In 2012, the World Health Organization proposed that a unique four-letter 'biological qualifier' code be appended as a suffix to the core name [60]. In 2015, the FDA issued draft guidance regarding nomenclature in which it proposed that the biological qualifier code suffix consist of four lowercase letters and that it be unique and 'devoid of meaning' [61]. The three biosimilars subsequently approved in the United States were designated as infliximab-dyyb, etanercept-szzs, and adalimumab-atto. This use of a biological qualifier code suffix appended to the core name should facilitate traceability of biosimilars and their reference produces and allow effective postmarketing surveillance of their safety and efficacy.

CONCLUSION

Biosimilars for rheumatoid arthritis and other inflammatory conditions are now available worldwide. The limited, but growing, 'real world' experience to date suggests that biosimilars and their bio-originators have similar efficacy and safety. If the cost of biosimilars is lower, we expect a rapid increase in their use to treat patients with inflammatory diseases. Concern about 'nonmedical switching' and 'interchangeability' persists, but will not be resolved until there is greater experience using biosimilars and appropriate postmarketing surveillance, both to assess efficacy and to detect potential safety signals. If the cost savings of biosimilars are realized, these should allow more patients to access effective biologic therapies and reduce the morbidity and mortality of rheumatoid arthritis and other inflammatory diseases.

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Causes and consequences of fatigue in rheumatoid arthritis

Patricia Katz

Purpose of review
To review current information on the causes, treatments, and consequences of fatigue in rheumatoid arthritis.

Recent findings
Disease activity (inflammation, pain, joint symptoms) is associated with greater fatigue. However, disease activity *per se* accounts for only a small portion of fatigue, and rheumatoid arthritis medications that reduce disease activity have small effects on fatigue. Instead, factors outside the direct effects of rheumatoid arthritis, such as obesity, physical inactivity, sleep disturbance, and depression, explain the majority of variation in fatigue. Some of these factors may be indirect effects of disease (e.g. pain can lead to sleep disturbance). Rheumatoid arthritis has significant effects on the quality of life of individuals with rheumatoid arthritis. The most effective approaches to reducing rheumatoid arthritis fatigue appear to be behavioral, such as increasing physical activity, or cognitive, such as cognitive behavioral interventions.

Summary
Fatigue in rheumatoid arthritis appears to be largely because of factors outside the direct effects of the disease, such as behavioral and psychological factors. In spite of the tremendous impact of fatigue on patient health and quality of life, effective treatments remain elusive, but existing data show that behavioral and cognitive approaches may be most effective.

Keywords
fatigue, patient-reported outcomes, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis fatigue is experienced as different from 'normal' tiredness [1], and is viewed by patients as overwhelming, uncontrollable, and, often, untreatable [2]. In defining a 'good day', 57% of patients with rheumatoid arthritis stated a day free of fatigue or having energy was one of the main indicators, a frequency equivalent to being pain free (58%) [3]. Fatigue was one of the top three domains that patients view as important to reflect remission, rated overall second to pain [4▪].

Although the American College of Rheumatology has made recommendations for measures of disease activity and physical functioning, no corresponding recommendations have been offered for measuring fatigue. In a recent compendium of rheumatology outcome measures, 11 measures were reviewed, all of which have been used in studies of rheumatoid arthritis fatigue [5]. Since then, at least one other instrument has come into prominent use, the PROMIS Fatigue scale [6], which has several short forms as well as a computer-adaptive testing form.

The construct of 'fatigue' varies in the multiple instruments being used in studies of rheumatoid arthritis fatigue. Some focus simply on fatigue severity, whereas others address the impact of fatigue on different aspects of life, or attempt to separate types of fatigue (e.g. cognitive vs. physical). Likewise, the time frame considered varies, ranging from, the present to the past 4 weeks.

The above information is provided as a backdrop to further discussion of rheumatoid arthritis fatigue to demonstrate that no consistency in definitions of fatigue exist. Fatigue is a construct that can only be measured through patient reports. In all types of

Division of Rheumatology, Department of Medicine and Institute for Health Policy Studies, University of California San Francisco, San Francisco, California, USA

Correspondence to Patricia Katz, PhD, University of California San Francisco, 3333 California St, Suite 270, San Francisco, CA 94143-0920, USA. Tel: +1 415 476 5973; fax: +415-476-9030; e-mail: patti.katz@ucsf.edu

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KEY POINTS

- Rheumatoid arthritis fatigue is associated with higher levels of disease activity and inflammation, but these factors actually explain a relatively small amount of variation in fatigue.
- Medications that effectively treat disease activity appear to have little effect on fatigue.
- A constellation of behavioral, psychological, cognitive, and other physiological factors may play important roles in rheumatoid arthritis fatigue. The greatest evidence supports the roles of physical inactivity, sleep disturbance, and depression. Many other potential sources of fatigue have received little attention.
- The most effective approaches to reducing fatigue identified to date are physical activity and cognitive behavioral interventions.

measures, even so-called 'hard' outcome measures such as laboratory values, there is a certain degree of measurement error. However, although many of the patient-reported measures of fatigue have been developed and tested according to rigorous psychometric standards, the lack of consistency in defining and measuring fatigue likely complicates any definitive conclusions regarding prevalence or causes of fatigue.

PREVALENCE OF FATIGUE IN RHEUMATOID ARTHRITIS

A total of 40–70% of people with rheumatoid arthritis report severe fatigue [7,8]. One recent study used the SF-36 Vitality scale to measure fatigue, defining severe fatigue as less than 10th percentile of the population distribution, and reported that 41% of individuals met the criterion [8].

Although recognition of the importance of fatigue is growing, physicians report that they lack knowledge about the cause of rheumatoid arthritis fatigue and about evidence-based interventions to prevent and treat it [9]. This lack of knowledge is perhaps because the source of rheumatoid arthritis fatigue is unclear.

IS FATIGUE IN RHEUMATOID ARTHRITIS BECAUSE OF THE RHEUMATOID ARTHRITIS DISEASE PROCESS?

Fatigue has long been considered a direct result of the disease process of rheumatoid arthritis, due either to the systemic effects of the disease, the primary manifestations of the disease – pain and joint symptoms – or to medications used to treat rheumatoid arthritis.

Inflammation and disease activity

Inflammation has been proposed as a source – both direct and indirect – of fatigue in rheumatoid arthritis. Several of the inflammatory biomarkers elevated in rheumatoid arthritis have been linked to fatigue, particularly tumor necrosis factor (TNF)-α and interleukin (IL-6) [10]. Cytokine-induced illness behavior, invoked by IL-1, IL-6, IL-2, and interferon (IFN)-α, is linked to fatigue [11▪▪]. Severe fatigue is not unique to rheumatoid arthritis. In addition to being present in other rheumatic diseases [e.g. systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), Sjögren's syndrome], it is also present in Parkinson's disease, multiple sclerosis, chronic obstructive pulmonary disease, and depression. In many of these diseases, fatigue is also proposed to be at least partially because of increased levels of pro-inflammatory cytokines, including IL-1β, IL-6, and IFN-α [11▪▪]. However, clinical studies of the relationship between inflammation and fatigue in rheumatoid arthritis have yielded inconsistent results [12]. For example, a recent systematic review reported that c-reactive protein (CRP) was positively correlated with fatigue ($P = 0.006$), but that erythrocyte sedimentation rate (ESR) was less strongly associated ($P = 0.09$) [13]. In this same review, one clinical measures of disease activity, DAS28, was significantly correlated with fatigue ($P = 0.04$), whereas another, swollen and/or tender joint count was not ($P > 0.4$). Evers reported that higher levels of specific cytokines (IL-1β and IFN-γ) predicted higher levels of fatigue one month later [14]. In another longitudinal study, patients with higher levels of inflammation (more tender/swollen joints, higher CRP) had greater fatigue, but effects sizes were small [12]

Inflammation has complex relationships with other factors that may lead to fatigue, such as sleep disturbance, and so may have indirect effects on fatigue. Both IL-6 and TNF-α are associated with alterations in the sleep–wake cycle [15]. In chronic insomniacs, difficulty sleeping at night and daytime fatigue are thought to be related to dysfunction in the circadian cycles of IL-6 and TNF-α, and in the general population, elevated IL-6 is associated with worse sleep [10]. Sleep deprivation and abnormalities can impair immune function [15].

A systematic review and meta-analysis reported that the effect of biotherapies on fatigue in rheumatoid arthritis is small [16], another factor diminishing the idea of a strong inflammation-fatigue link. Most patients reaching disease remission after anti-TNF therapy continue to report fatigue [17▪].

Pain

Studies generally show a direct link between rheumatoid arthritis pain and fatigue [13,18,19].

However, changes in pain and fatigue seem to vary concurrently rather than one predicting the other [20]. Indeed, Druce [21] reported that decreases in fatigue following anti-TNF therapy were linked to changes in pain. From a slightly different perspective, experimental pain thresholds were more consistently predictive of subsequent fatigue than current reported pain levels, suggesting that pain sensitization may be a crucial factor [22]. Lee [23] postulated that there may be a subgroup of patients with rheumatoid arthritis with high levels of fatigue and other symptoms but with low levels of inflammatory disease activity who have a centralized chronic widespread pain syndrome such as fibromyalgia. Others have also reported that comorbid fibromyalgia significantly increases the likelihood of severe fatigue [8].

Functional limitations

Fatigue is greater among individuals with greater functional limitations measured by the Health Assessment Questionnaire (HAQ) [18,24]. Functional impairments may decrease the efficiency of movement, requiring more energy or use of less developed muscles to avoid pain [25]. Joint deformities or swelling may increase the work required for specific activities [1].

Summary

Disease activity, whether measured biologically as inflammation or through patient reports of pain, does appear to influence fatigue. However, disease activity alone explains only a modest amount of variability in fatigue. Further, fatigue persists in many patients even after a low disease state or remission has been reached [26]. These findings suggest that other factors must be involved in rheumatoid arthritis fatigue.

IF NOT DISEASE, WHAT CAUSES FATIGUE IN RHEUMATOID ARTHRITIS?

Conceptual models of explaining rheumatoid arthritis fatigue have been developed (Fig. 1). The broadest of these models, proposed by Hewlett (Fig. 1, panel a), illustrates the idea that rheumatoid arthritis fatigue most likely has multiple and varied origins [27]. The model proposed by Louati and Berenbaum [28] is less comprehensive, but clearly illustrates the potential overlap of fatigue with other conditions common in rheumatoid arthritis – pain and depression (Fig. 1, panel b). Matcham [29▪] described a conceptual model focusing only on psychological and cognitive factors (Fig. 1, panel C). In the sections below, factors that are not directly related to rheumatoid arthritis *per se*, but have either demonstrated or potential connections with fatigue in rheumatoid arthritis, are reviewed, grouped into four major categories: behavioral, psychological, cognitive, and other physiological.

BEHAVIORAL

Sleep disturbance

A large proportion of individuals with rheumatoid arthritis, between 45 and 70%, report sleep problems, such as poor quality sleep, nonrestorative sleep, and nighttime awakenings [10,30]. Studies in patients with rheumatoid arthritis have linked sleep problems to a number of poor health outcomes, including greater fatigue [31–33]. Sleep problems may also have indirect effects on fatigue by on lowering pain thresholds and increasing systemic inflammation [34,35]. Ranjbaran [15] describes a vicious cycle whereby sleep problems can aggravate pain thresholds, which can in turn worsen sleep problems.

Obesity

Although obesity is linked to fatigue in other conditions, and obesity is common in rheumatoid arthritis [36], few studies have examined obesity as a predictor of rheumatoid arthritis fatigue. Of the two that have [22,37▪▪], both found a significant relationship between obesity and fatigue. Obesity is also linked to sleep disturbances [38] and higher levels of systemic inflammation [39] so may have both direct and indirect influences on fatigue.

Low physical activity

Many individuals with rheumatoid arthritis are physical inactive [37▪▪,40], and recent studies have identified direct correlations between inactivity and fatigue [41,42], as well as indirect links, with effects of inactivity mediated through sleep disturbance, obesity, and depression [37▪▪]. Regular physical activity also appears to decrease levels of inflammatory markers, including CRP, IL-6, and TNF-α [43,44].

PSYCHOLOGICAL

Depression or depressed mood is a strong predictor of fatigue in rheumatoid arthritis [18,22,29▪, 37▪▪,45]. In fact, fatigue/lack of energy is one of the diagnostic criteria for depression even among individuals without rheumatoid arthritis. Additional effects of depression on fatigue may be

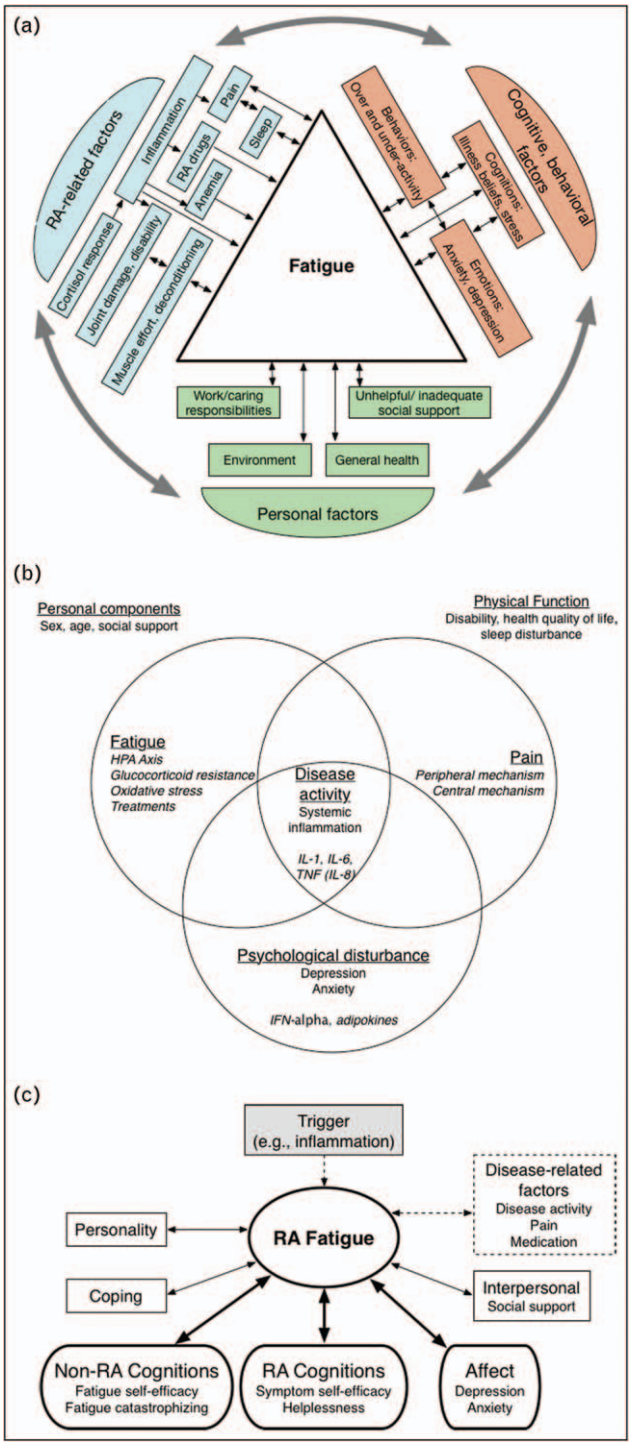

FIGURE 1. Conceptual models of rheumatoid arthritis fatigue. (a) Hewlett proposed interactions among three primary factors: rheumatoid arthritis-related disease processes, cognitive and behavioral factors (e.g. thoughts, feelings, and behaviors), and personal life issues. In addition, causes of fatigue were proposed to vary both among individuals and within individuals at different times. Source: Adapted from [27]. (b) This conceptual model illustrates clinical and physiological interactions between fatigue, pain, and psychological disturbance. Potential mechanisms in each domain are shown in italics. Increases in inflammatory cytokines could be because of fatigue, pain, or mood disorders. Source: Adapted from [28]. (c) This conceptual model was developed based on a systematic review of psychological variables associated with fatigue in rheumatoid arthritis. Six categories of variables were identified: affect and common mental disorders, including depression; rheumatoid arthritis-related cognitions such as self-efficacy; non-rheumatoid arthritis-related cognitions; personality traits; stress and coping; and interpersonal factors such as social support. However, as noted by bolded lines, empirical support was available only for affect, and rheumatoid arthritis and non-rheumatoid arthritis cognitions. Adapted from [29▪].

mediated by impaired sleep, which is often observed in depression [10,46]. Depression also has a recognized association with systemic inflammation, and cytokine-induced depression has been experimentally produced [47–49]. It is possible, then, that disease activity could act on fatigue indirectly through depression [50].

Perceived stress may also have direct and indirect effects on rheumatoid arthritis fatigue. Higher levels of self-perceived daily stressors predicted increases in fatigue one month later [14]. Chronic psychosocial stress has been associated with increased levels of IL-6, which, in turn, were associated with greater self-reported fatigue [51]. Perceived stress has also been linked to sleep disturbances in rheumatoid arthritis [30].

COGNITIVE

Certain cognitive styles seem to be associated with fatigue. Self-efficacy generally and for managing rheumatoid arthritis symptoms is associated inversely with fatigue, whereas learned helplessness is associated with greater fatigue and subsequent increases in fatigue [29▪,52]. Poor coping, particularly 'catastrophizing', is also linked to greater fatigue [29▪].

PHYSIOLOGICAL

Comorbid conditions

Individuals with rheumatoid arthritis who have more comorbid conditions tend to have higher levels of fatigue [24]. Some of these comorbid conditions themselves, especially cardiovascular conditions and anemia, may be associated with fatigue. Medications used to treat comorbid conditions may also increase fatigue or interfere with sleep.

Muscle wasting and weakness

Low muscle mass and muscle density have been noted in rheumatoid arthritis [53,54], and have been attributed to chronic inflammation [55]. In turn, low muscle mass or quality has been linked to weakness and poor functioning [53,56]. Impairment of muscle functioning and muscle wasting could therefore increase the functional burden of daily tasks and be a cause of fatigue [57].

Deconditioning and energy imbalance

Perhaps because of generally low levels of physical activity, individuals with rheumatoid arthritis often have decreased aerobic capacity [58]. Low levels of activity may also result in muscle weakness through deconditioning, which, with low aerobic capacity, reduce functional capacity. At the same time, energy required for tasks can be increased by pain, elevated fat mass, functional limitations, or structural abnormalities [1,25,59,60]. Combined, these factors mean that energy requirements for a given task may be greater for someone with rheumatoid arthritis, but that the individual's capacity for performing the task is decreased. This mismatch between task demands and physical capabilities may force individuals to dip into functional reserves to a greater extent than might be expected, which may then lead to elevated levels of fatigue.

Other

A fairly robust model of muscle fatigue based on contractile dysfunction in chronic inflammatory disease has been proposed [61▪▪]. However, the role of muscle fatigue in more generalized fatigue, and in rheumatoid arthritis fatigue specifically, has not been studied. Some evidence also suggests a role of oxidative stress; neurotransmitter, specifically glutamate and dopamine, impairment; and mitochondrial dysfunction in fatigue in other inflammatory or autoimmune conditions [11▪▪,50,62], but these have not been studied in rheumatoid arthritis.

PUTTING THE EVIDENCE TOGETHER: EMPIRICAL MODELS OF RHEUMATOID ARTHRITIS FATIGUE

Studies attempting to construct empirical models to explain the sources of rheumatoid arthritis fatigue have primarily focused on pain, inflammation or disease activity, and sleep. For example, Nicassio's cross-sectional structural equation model (Fig. 2, panel a) showed direct effects of disease activity, mood disturbance, and poor sleep on fatigue, as well as indirect effects of disease activity on mood disturbance, which was then related to poor sleep quality [63]. Druce (Fig. 2, panel b) included these same factors, adding female sex and disability, in a longitudinal model to explain changes in fatigue [64▪▪]. Although there was a small direct effect of disease activity on fatigue, 82% of the effects of disease activity was mediated through pain, mental health, and disability.

The study of rheumatoid arthritis that included the broadest array of potential explanatory variables examined inflammation (CRP), pain, functional limitations (HAQ), depressive symptoms, and sleep, as well as rheumatoid arthritis medications, obesity, smoking, low cardiorespiratory fitness, low lean mass, muscle weakness, and physical inactivity (Fig. 3) [37▪▪]. Each of these factors (except medications) was associated with fatigue in bivariate analyses. However, multivariate analyses showed direct and independent effects of disease activity (primarily pain), depression, obesity, and sleep

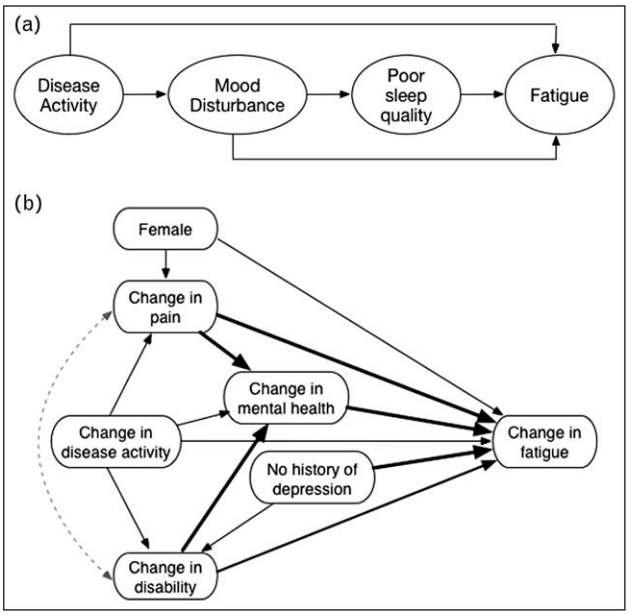

FIGURE 2. Empirical models of the causes of rheumatoid arthritis fatigue. (a) In a cross-sectional model, disease activity, mood disturbance, and poor sleep each had direct effects on fatigue. In addition, disease activity had an indirect effect, working through mood disturbance, which was in turn related to poor sleep quality. Source: Adapted from [63]. (b) Using a structural equation model, a longitudinal analysis showed the primary direct effects on changes in fatigue were changes in pain, disability (HAQ), and mental health (SF-36 MH). Eighty-two percent of the effect of disease activity (DAS28) was mediated through other variables. Adapted from [64▪▪].

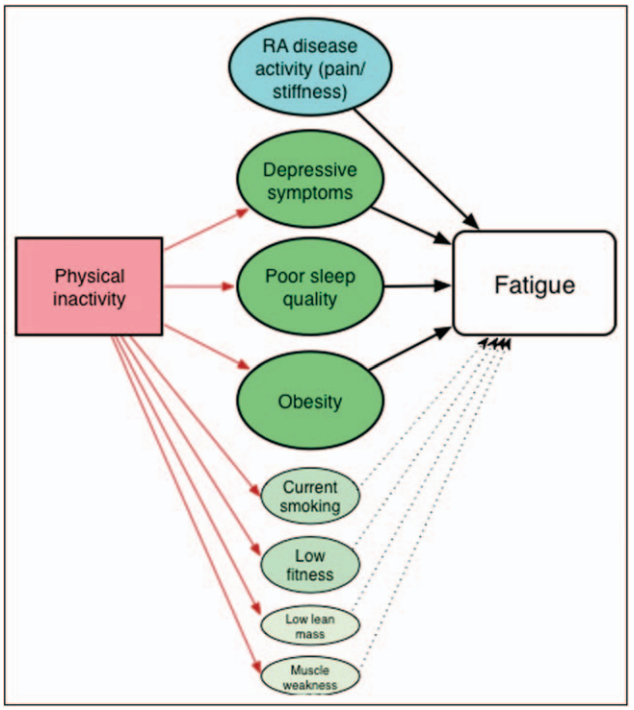

FIGURE 3. Empirical model of the causes of rheumatoid arthritis fatigue with the broadest range of potential explanatory variables tested to date. Solid lines extending from physical inactivity represent statistically significant correlations. Solid lines pointing to fatigue represent associations that were statistically significant in multivariate analyses. Broken lines represent associations that were statistically significant in bivariate analyses but not in multivariate. The size of each circle represents the relative contribution of that factor to fatigue. Adapted from [37▪▪].

disturbance. Physical inactivity had an indirect association with rheumatoid arthritis fatigue, with effects mediated by obesity, poor sleep, and depression.

IMPACT OF FATIGUE

The impact of fatigue is significant. Individuals with rheumatoid arthritis report that it influences everyday tasks, attitudes, and leisure time [2]. Fatigue among persons with rheumatoid arthritis is associated with declines in functioning, worse mental health status, higher levels of interpersonal stress, and greater healthcare utilization [18]. It can make management of other rheumatoid arthritis symptoms more challenging and interfere with participation in rehabilitation [25]. Fatigue also plays a significant role in patient global assessments, which are often used to make treatment decisions and determine treatment response [65▪].

TREATMENT OF FATIGUE

Individuals with rheumatoid arthritis report having to find their own fatigue management strategies by trial and error [2]. Most reported strategies are related to activity accommodations, such as pacing or rest [2], and may not address the root causes of fatigue. Many individuals with rheumatoid arthritis report that they do not discuss fatigue with clinicians and do not believe that there is effective treatment [2]. Some of the advice received from healthcare professionals is perceived as unrealistic (e.g. taking time for rest breaks with two small children at home) [9].

Effective treatments for fatigue appear to be limited. Drugs used to treat rheumatoid arthritis seem to have limited effects on reducing fatigue [16,17▪,66▪]. Trials of programs to focused on managing thoughts around fatigue have demonstrated improvements in fatigue [67,68]. Programs such as cognitive behavioral therapy appear to have a positive impact [69], but the likelihood of such programs becoming widely available is unknown because of the resources required for them. Two recent systematic reviews found that physical activity had beneficial effects on fatigue [68,70]. Recently tested exercise interventions specifically targeting rheumatoid arthritis fatigue have shown promising effects [71–73]. The challenge lies in identifying interventions that are both effective and feasible for wide-spread dissemination.

CONCLUSION

Severe fatigue present in 41% of individuals with rheumatoid arthritis, but is not unique to rheumatoid arthritis. Fifty-two percentage of individuals with SLE, 45% with AS, 35% with osteoarthritis, 51% with psoriatic arthritis, 48% with scleroderma, and 82% with fibromyalgia report fatigue [8]. Although fatigue is also proposed to be at least partially because of increased levels of pro-inflammatory cytokines, recent data suggest that rheumatoid arthritis fatigue is a complex phenomenon, due more to non-rheumatoid arthritis-specific factors as to the disease *per se*. Interventions targeting behavioral factors may have the most promise in reducing rheumatoid arthritis fatigue.

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Conflicts of interest

There are no conflicts of interest.

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Lipids and lipid changes with synthetic and biologic disease-modifying antirheumatic drug therapy in rheumatoid arthritis: implications for cardiovascular risk

Elena Myasoedova

Purpose of review
To highlight recently published studies addressing lipid changes with disease-modifying antirheumatic drug use and outline implications on cardiovascular outcomes in rheumatoid arthritis (RA).

Recent findings
Growing evidence suggests lower lipid levels are present in patients with active RA vs. general population, and significant modifications of lipid profile with inflammation suppression. Increase in lipid levels in patients with RA on synthetic and biological disease-modifying antirheumatic drugs may be accompanied by antiatherogenic changes in lipid composition and function. The impact of lipid changes on cardiovascular outcomes in RA is a subject of active research. The role of lipids in cardiovascular risk in RA may be overpowered by the benefits of inflammation suppression with antirheumatic medication use. Recommendations on lipid management in RA are evolving but uncertainty exists regarding frequency of lipid testing and goals of treatment.

Summary
Knowledge about quantitative and qualitative lipid changes in RA is expanding. The relative role of lipids in cardiovascular risk in the context of systemic inflammation and antirheumatic therapy remains uncertain, delaying development of effective strategies for cardiovascular risk management in RA. Studies are underway to address these knowledge gaps and may be expected to inform cardiovascular risk management in RA and the general population.

Keywords
cardiovascular risk, disease-modifying antirheumatic drugs, lipids

INTRODUCTION

There is convincing evidence of a substantially increased burden of cardiovascular disease and resulting increase in cardiovascular mortality in rheumatoid arthritis (RA) compared with the general population [1,2]. Unlike the general population where hyperlipidemia is strongly associated with adverse cardiovascular outcomes, the link between lipids and cardiovascular risk in RA is more complex because of the interplay between metabolic factors, inflammation, antirheumatic treatments, and genetic factors. In fact, the association between lipid levels and cardiovascular outcomes in RA may be weaker than in the general population [3]. A nonlinear association between total cholesterol (TC), low-density lipoprotein (LDL) levels and cardiovascular outcomes in RA has been shown with tendency to increased cardiovascular risk even in patients with low LDL in the setting of active inflammation, the so-called 'lipid paradox' [4,5].

The knowledge base linking antirheumatic medications, inflammation, lipids, and cardiovascular outcomes in RA is evolving. This review highlights recent findings on the topic of lipid changes with disease-modifying antirheumatic drug

Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to Elena Myasoedova, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, 200 1st St. SW, Rochester, MN 55905, USA. Tel: +1 507 284 4277; fax: +1 507 284 0564; e-mail: myasoedova.elena@mayo.edu

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KEY POINTS

- Lipid levels are decreased in active RA and may increase with inflammation suppression following antirheumatic treatment; improvement in lipid composition and function may also occur.
- The relative impact of lipid modifications on cardiovascular risk in RA is not well understood and may be offset by inflammation as a major driver of increased cardiovascular risk in RA.
- Studies assessing the interplay between lipids, inflammation, antirheumatic treatments, and cardiovascular risk are underway and expected to aid in optimization of cardiovascular disease management in RA.

(DMARD) therapy in RA and emerging implications for cardiovascular risk.

UNDERSTANDING THE PATTERN OF LIPID CHANGES WITH SYNTHETIC AND BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUG THERAPY IN RHEUMATOID ARTHRITIS

Several studies including our own have shown that patients with active RA have lower TC and LDL than the general population [6,7]. The nature of this change is not fully understood but decreased LDL synthesis and/or increased lipid clearance, as well as shared genetic factors of RA susceptibility and lower LDL have been suggested as potential explanations [8–10]. Advancing this knowledge, a recent study by Charles-Schoeman *et al.* [11] has demonstrated higher cholesterol ester fractional catabolic rate but no increase in cholesterol production in patients with active RA compared with healthy volunteers supporting the role of increased cholesterol clearance as a potential mechanism of downregulation of LDL and high-density lipoprotein (HDL) levels in active RA. These changes appeared to be reversible with the use of Janus kinase inhibitor tofacitinib and were associated with increase in HDL particle size, number, and improved HDL function in the setting of increased TC, LDL, and HDL levels with tofacitinib use observed in this and other studies [11,12▪].

A growing body of literature shows that reduction in inflammation after initiation of synthetic and biological DMARDs is associated with increased TC, LDL, and HDL levels toward normalization and beyond, and with improvement of the TC/HDL ratio [12▪,13–16]. The comparative impact of different antirheumatic regimens on lipid levels is unclear and randomized controlled trials (RCTs) are lacking. Addressing these gaps in knowledge, the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial assessed 2-year dynamics of lipid and inflammatory changes in DMARD-naive RA patients who were randomized to methotrexate vs. etanercept and methotrexate vs. triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine [17▪▪]. The study showed consistent increase in TC, LDL, and HDL with corresponding decrease in disease activity score of 28 joints (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) in the first 6 months and a subsequent decrease in lipid levels in all treatment groups (Fig. 1). Consistent with the notion that the severity of systemic inflammation is inversely proportional to the degree of lipid lowering [13,18], the magnitude of increase in lipid levels in the TEAR trial appeared to be proportional to the magnitude of reduction in inflammation.

Triple therapy in the TEAR trial was associated with lower LDL and TC/HDL and higher HDL at 2 years, possibly because of hydroxychloroquine use. Hydroxychloroquine has been previously suggested to have lipid-modifying properties [19]. Concordantly, a recent large retrospective cohort study of patients with early RA ($n = 17\,145$) showed a somewhat lower risk of incident hyperlipidemia [hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.63–1.04, adjusting for age, sex, cardiovascular risk factors and comorbidities] during 4770 person-years of follow-up, and significant reduction in TC and LDL with hydroxychloroquine vs. methotrexate [20]. The association of hydroxychloroquine with lower risk of hyperlipidemia was stronger when propensity score analyses were applied: HR 0.75, 95%CI 0.58–0.98.

TEAR trial also revealed that the use of anti-tumor necrosis factor (TNF) treatments was associated with slightly higher likelihood of hyperlipidemia (HR 1.41; 95%CI 0.99–2.00) vs. methotrexate in adjusted analyses, but the association attenuated with propensity score analysis (HR 1.18; 95%CI 0.80–1.73). Along the same lines, a recent systematic review and meta-analysis of RCTs of lipid profile changes in patients with chronic inflammatory arthritis showed a nonsignificant increase in proportion of patients with hypercholesterolemia, but no change in LDL or HDL, with anti-TNF therapy, including infliximab, adalimumab, or golimumab use for 12–24 weeks [odds ratio (OR) 1.54; 95%CI 0.9–2.66, $P = 0.119$] [12▪]. More recent individual studies show no significant changes in non-HDL cholesterol levels with anti-TNF treatment [13,21], although increase in HDL with adalimumab and etanercept has been noted by some authors [13,22].

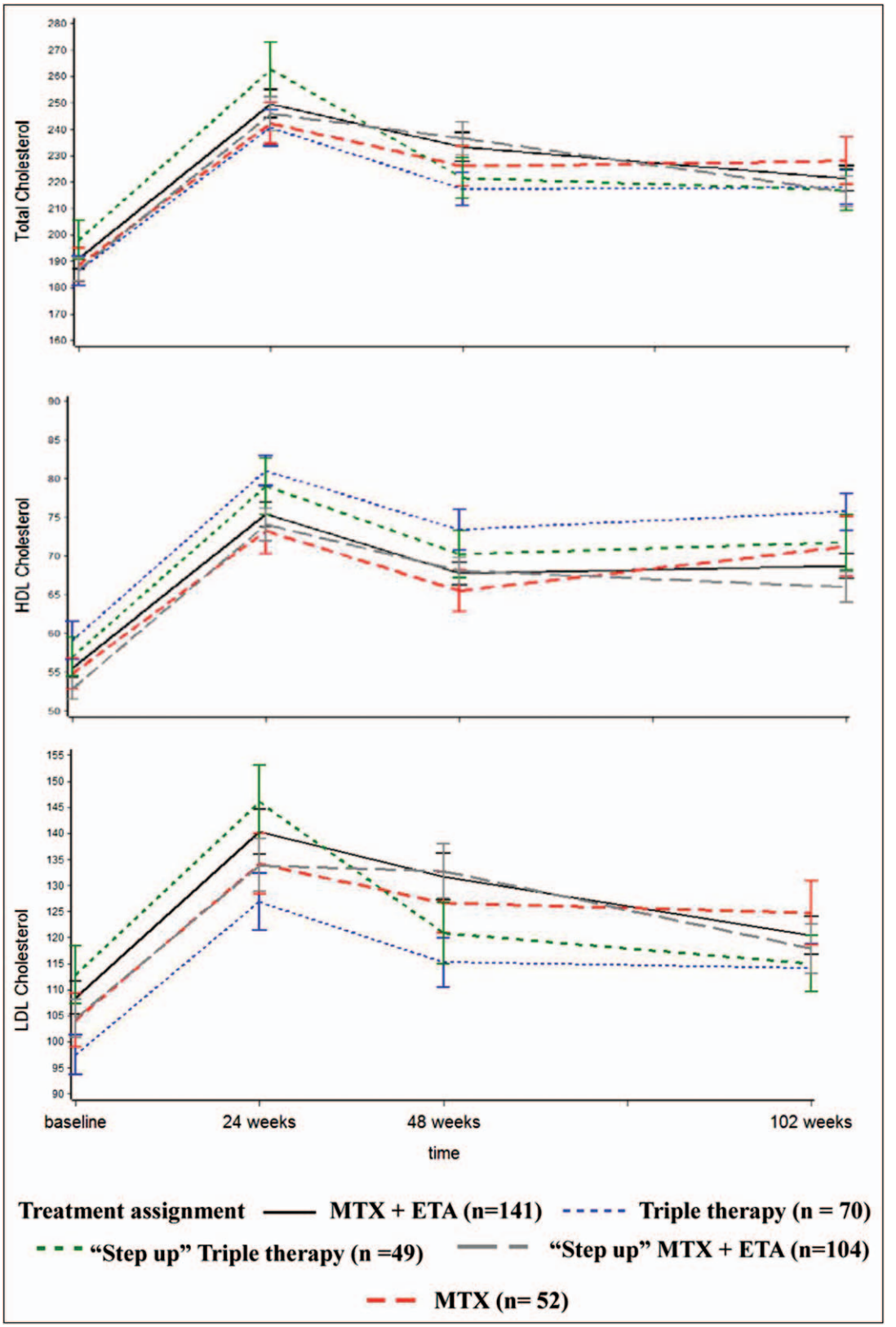

FIGURE 1. Mean ± standard error for LDL, HDL, and TC levels (mg/dl) in each treatment group over 2-year follow-up in the TEAR trial. Reprinted with permission from [17▪▪]. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TEAR, Treatment of Early Aggressive Rheumatoid Arthritis; TC, total cholesterol.

Knowledge about qualitative lipid changes with anti-TNF treatments is evolving. A prospective observational cohort study using the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) register showed that in patients with established RA treated with a synthetic DMARD or anti-TNF agent or combination of both, a decrease in CRP at 1-year follow-up was associated with increase in LDL and concurrent improvement in HDL-cholesterol efflux capacity (CEC) [23]. Larger reductions in CRP, regardless of medication used, were associated with larger improvements in HDL-CEC ($r = 0.24$, $P = 0.02$), although the association was attenuated following adjustment for HDL levels ($P = 0.06$).

HDL functional properties were also assessed in a recent study from Norway using serum of patients with RA treated with methotrexate ($n = 34$) vs. methotrexate and adalimumab ($n = 22$) [22]. The study suggests potential drug-specific antiatherogenic effects of methotrexate on HDL-CEC and of adalimumab on macrophage cholesterol uptake and serum cholesterol loading capacity with hypothetical complimentary benefits of these medications. Increase in HDL with treatments in this study may have affected the findings of HDL-CEC but no adjustment for HDL levels were made, complicating the understanding of the extent of beneficial changes of HDL function with treatments.

An increasing number of studies report elevated TC and LDL with the use of the interleukin-6 receptor antagonist tocilizumab [4,12▪,24]. To better understand implications of such changes on cardiovascular risk in RA, studies over the past year have investigated quantitative and compositional lipid changes with tocilizumab use. The results of a recent RCT 'MEASURE' using tocilizumab and methotrexate vs. placebo and methotrexate demonstrated a greater increase in TC, LDL, triglycerides (TG). and TC/HDL ratio with tocilizumab vs. placebo in the setting of decreased inflammation at 12 weeks of treatment. Despite these increased levels, qualitative lipid changes overall appeared to be antiatherogenic, including decrease in HDL-associated serum amyloid A and lipoprotein(a) with tocilizumab use [25▪]. Concordantly, a post hoc analysis of data from the adalimumab monotherapy for treatment of RA (ADACTA) trial showed greater increase in TC, LDL, TG, HDL, and TC/HDL ratio in patients with RA at 8 weeks of tocilizumab use vs. adalimumab [16]. Similar to the previous study, this increase in lipids was accompanied by reductions in lipid-associated markers of cardiovascular risk, including HDL-serum amyloid A, lipoprotein(a), and secretory phospholipase A2IIA which was also somewhat more pronounced with tocilizumab. Both treatment responders and nonresponders had similar dynamics of lipid changes suggesting that mechanisms not directly related to treatment response may be responsible for these changes.

The literature on effects of rituximab and abatacept on lipids remains scarce. Over the past year, two small studies have reported increase in TC and HDL with rituximab [14,15]. This increase was found to taper off by 12 months of rituximab treatment in one study [14], whereas the other study found that increase in lipid levels was limited to rituximab responders only [15]. Conclusive evidence is lacking with regard to the effects of these medications on lipid profile and their net cardiovascular effects.

In summary, growing evidence supports a decrease in lipids levels and tendency towards impaired HDL function in active RA. Lipid changes appear to be inversely proportional to the degree of inflammatory changes. Treatment with DMARDs is generally associated with increased lipid levels; data are most consistent for tocilizumab and tofacitinib. Improved HDL function has been suggested with the use of synthetic and biological DMARDs. Further studies are needed to understand whether the pathway of inflammation suppression in RA is linked to the pattern of lipid changes.

LINKING INFLAMMATION, LIPIDS, AND CARDIOVASCULAR EVENTS IN RHEUMATOID ARTHRITIS

Inflammation is an established key factor in cardiovascular risk in RA [13,24]. Antirheumatic treatments have been shown to improve cardiovascular outcomes which cannot be solely explained by seemingly adverse changes in lipid levels observed with these treatments and is thought to be largely attributed to inflammation suppression. Interpretation of lipid changes and their cardiovascular impact in the context of inflammation is a subject of ongoing interest. A retrospective post hoc analysis of RCTs, including pooled data for 3986 adults with moderate–severe RA using tocilizumab with synthetic DMARDs or as monotherapy suggests that only the baseline TC/HDL ratio, but not other lipid measures, was associated with major adverse cardiovascular events (MACE) during 3.6-year follow-up (14 683 patient-years) [24]. Confirming the pivotal role of inflammation in cardiovascular risk, this study showed that measures of RA disease activity and their changes over 24 weeks, but not changes in lipid levels, were strongly associated with MACE.

Along the same lines, a study of a large US veteran cohort, including predominantly male

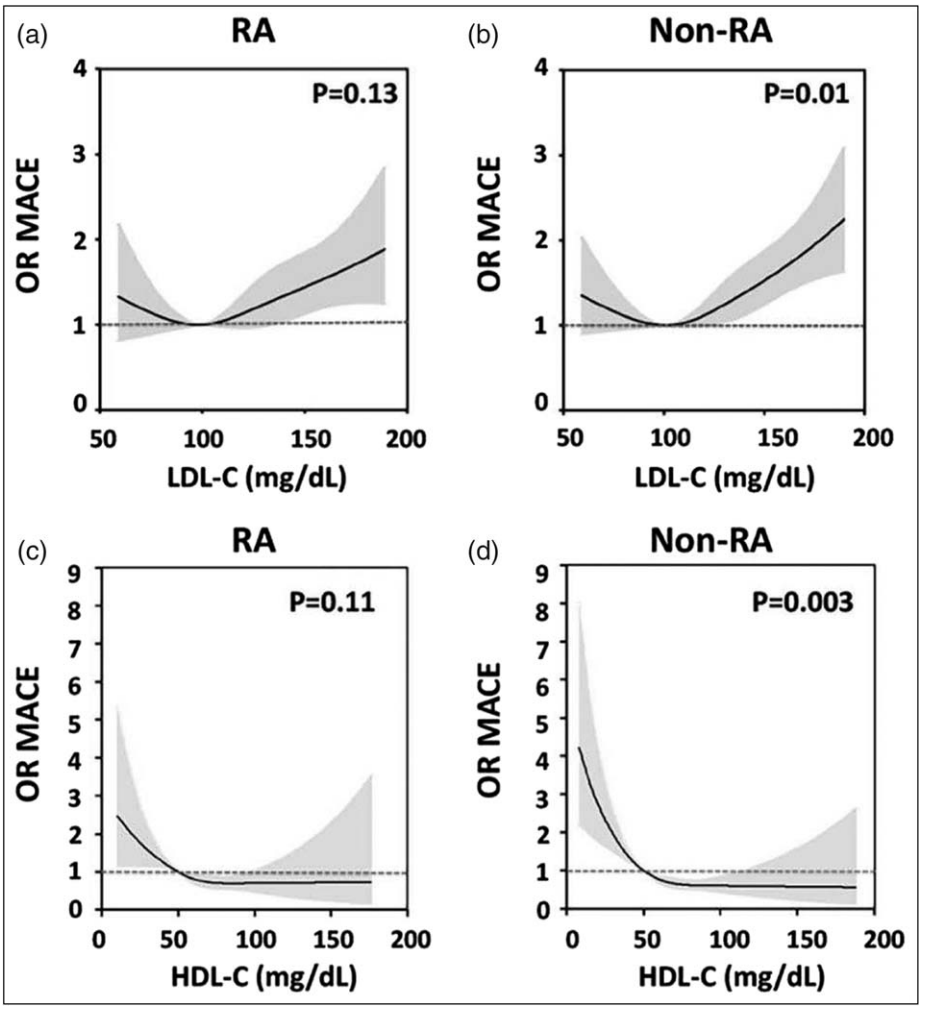

FIGURE 2. Relationship between low density lipoprotein cholesterol (LDL-C) and MACE (a and b), and high density lipoprotein cholesterol (HDL-C) and MACE (c and d) and *P* value testing for linearity in the RA and non-RA cohorts. Reprinted with permission from [27]. MACE, major adverse cardiovascular events; RA, rheumatoid arthritis.

patients with RA found that increased ESR (ESR >47 vs. ESR <8 mm/hr) and CRP (CRP >2.17 vs. CRP <0.26 mg/dl) were associated with about two-fold increase in risk of myocardial infarction (MI) and stroke over 4.5-year follow-up [26]. Higher HDL (HDL ≥54 vs. HDL <34 mg/dl) was inversely associated with MI (HR 0.68, 95%CI 0.55–0.85) and stroke (HR 0.69, 95%CI 0.50–0.96). Although other lipid measures were not statistically significantly associated with cardiovascular events, a nonlinear U-shaped trend was noted between LDL and risk of MI, controlling for comorbidities and antirheumatic medications.

Another recent study evaluating association of lipid levels with MACE in a US population of RA patients ($n = 16\,085$) vs. non-RA subjects ($n = 48\,499$) using insurance data also reported that nonlinear U-shaped association between LDL level and cardiovascular outcomes may affect both patients with RA and non-RA study participants (Fig. 2) [27]. The association between HDL and MACE was also nonlinear and similar in RA and non-RA study participants, with each successive quintile being associated with reduced risk of MACE compared with the lowest quintile. These findings suggest potential common mechanisms mediating the relationship between lipids and cardiovascular risk in both RA and the general population, to which inflammation is a likely contributor. This is consistent with our prior studies showing nonlinear relationship between LDL and cardiovascular risk in RA and interaction between lipid levels and inflammatory markers on cardiovascular outcomes in RA [4].

A large retrospective cohort study using US claims data showed an incremental increase in cardiovascular event rates in RA compared with matched non-RA study participants with hyperlipidemia defined per physician diagnosis/treatment, but not in those without hyperlipidemia [28]. No evidence for statistically significant interaction

between RA and hyperlipidemia was found. While binary stratification for the presence or absence of hyperlipidemia was used and individual lipid measures were not available, nonlinearity in the relationship between hyperlipidemia and cardiovascular outcomes was not observed.

In summary, inflammation is consistently associated with increased cardiovascular risk and the relative role of lipid modification related to the inflammatory burden is not fully understood in RA. Figure 3 schematically summarizes the changes in inflammatory and lipid measures in study participants with active vs. controlled RA and potential associated changes in cardiovascular risk. It is uncertain whether beneficial changes in lipid composition may counterbalance seemingly adverse changes in lipid levels with antirheumatic treatments and confer some cardiovascular benefits.

Studies to address these important questions are underway. A study aiming to elucidate the relationship between lipids, inflammation, and establish their relative contribution on cardiovascular risk in RA was initiated in 2016 in the United States with an estimated end-date in 2021 [28]; an RCT of Early Rheumatoid Arthritis COR Intervention (ERA-CORI) targeting cardiovascular risk factor management and assessing 5-year cardiovascular outcomes is ongoing in Denmark and is estimated to be completed in 2020 [29]. The results of these studies are expected to be of significant importance for cardiovascular risk management in both RA and the general population.

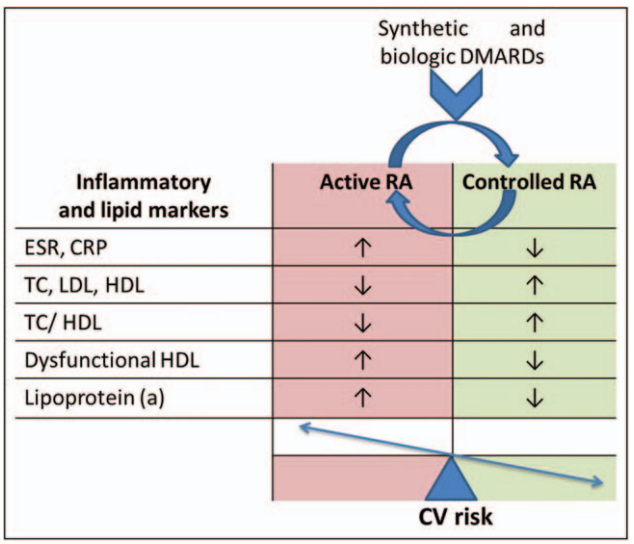

FIGURE 3. Changes in some inflammatory and lipid measures in active vs. controlled RA, and associated level of cardiovascular risk. CRP, C-reactive protein; CV, cardiovascular; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; TC, total cholesterol; TC/ HDL, total cholesterol to high-density lipoprotein cholesterol ratio.

CURRENT RECOMMENDATIONS ON LIPID MANAGEMENT IN RHEUMATOID ARTHRITIS AND FUTURE DIRECTIONS

Updated European League Against Rheumatism (EULAR) 2015/2016 recommendations continue to underscore the importance of optimal control of RA disease activity aiming at remission for cardiovascular risk reduction [30]. As the impact of lipids on cardiovascular outcomes in RA is less certain, the strength of recommendations on lipid management is lower than for inflammation control. Considering the significant variability of lipid levels with changes in inflammatory status in RA, recommendations from EULAR and the National Lipid Association suggest assessing lipid levels in a state of remission/stable disease activity [30,31▪▪,32]. Use of nonfasting lipid levels is acceptable [30]. It is reasonable to suggest that sustained elevations in LDL in remission and/or stable RA disease activity but not during the medication adjustment phase/active uncontrolled RA require treatment with a statin as a first-line lipid-lowering medication.

More studies support benefits of statin use in RA. Significant reduction in LDL levels with atorvastatin (40 mg/day) vs. placebo in RA has been shown in a Trial of Atorvastatin for the primary prevention of Cardiovascular Events in RA (TRACE-RA) [33]. Although nonsignificant, a 34% reduction of MACE has been noted with atorvastatin vs. placebo. Consistent with these findings, a recent study by An J. *et al.* [34] showed that in patients with RA who have hyperlipidemia on statin treatment, reduction in lipid levels are associated with similar degree of reduction in cardiovascular events as in the general population (HR of 0.68 for RA, 0.72 for general population).

Although the use of statins in RA is recommended, the thresholds for initiation of the medication and treatment goals are not clearly established and remain a subject of the EULAR group's research agenda [30]. Currently, no clear evidence exists that these should be different from the general population. Recommendations for specific frequency of lipid assessment in patients with RA on antirheumatic treatments are lacking, and are only included on package inserts for tofacitinib and tocilizumab, but not other antirheumatic medications [32]. It remains unclear whether assessing lipid composition and function has an additional value for cardiovascular risk assessment in RA, beyond that provided by lipid levels.

CONCLUSION

In summary, hyperlipidemia as a modifiable cardiovascular risk factor appears an attractive target for cardiovascular risk management in RA. The use of antirheumatic treatments is associated with quantitative and compositional lipid changes, which appear to be largely driven by associated decrease in inflammation, although some drug-specific effects have been suggested. The resulting 'net' cardiovascular benefits and the relative impact of lipid changes on cardiovascular risk in RA are not fully understood. Further, it is unclear whether lipid changes are of independent cardiovascular impact beyond that associated with inflammation suppression. Guidelines for assessment and management of hyperlipidemia in RA are evolving but uncertainty exists regarding frequency of testing and goals of treatment. Several studies are ongoing to address these gaps in knowledge and will be expected to inform cardiovascular risk management in RA and in the general population.

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Conflicts of interest

There are no conflicts of interest.

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