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

John Varga

John Varga, MD, is the John and Nancy Hughes Distinguished Professor at Northwestern University's Feinberg School of Medicine in Chicago, Illinois, USA.

Born in Budapest, Hungary, Dr Varga received his undergraduate education at Columbia University in New York, USA. He completed his medical studies at New York University, and following a rheumatology fellowship in Boston, USA, undertook post-doctoral research training with Professor Sergio Jimenez at the University of Pennsylvania, USA. In 2007, he was named the John and Nancy Hughes Distinguished Professor at the Feinberg School of Medicine in Chicago, USA, where he founded and directs the Northwestern Scleroderma Program. His research focusing on the pathogenesis and treatment of scleroderma and fibrosis bridges clinical and laboratory-based investigation.

Dr Varga is the author of more than 300 original articles, 40 book chapters and four books. His research has been funded by the National Institutes of Health, the Department of Defense and the Scleroderma Research Foundation. In 2007, he was elected to the Association of American Physicians.

Ingrid E. Lundberg

Doctor Ingrid E. Lundberg completed her medical education at Karolinska Institutet, Stockholm, Sweden in 1977. Her rheumatology residency was completed in 1985. In parallel with clinical rheumatology service, she completed her PhD with the title "Clinical and immunological studies of patients with anti-RNP antibodies" at Karolinska Institutet in 1991. After her PhD she spent one year as a post doc at the neuromuscular laboratory under Dr Andrew Engel at Mayo Clinic to learn more about muscle histopathology and new techniques to study molecular expression in muscle tissue. In 1998 she was appointed associate professor in rheumatology, and since 2003 she is full professor in rheumatology at Karolinska Institutet combined with a position as senior consultant at Karolinska University hospital. Since 2012 she is chair of the Rheumatology Unit, Department of Medicine, Karolinska Institutet.

After her return from Mayo clinic in 1993 she was recruited to Karolinska University hospital, and Karolinska Institutet in Stockholm, where she established a myositis clinic with a dedicated multidisciplinary team, and an associated translational research project with the aim to achieve improved understanding of molecular mechanisms that lead to muscle weakness in patients with myositis. Through her research she has demonstrated that physical exercise, in contrast to the recommendations at that time, leads to increased muscle strength and improved performance. Moreover, exercise can reduce muscle inflammation. She has also established national (SweMyoNet) and international (www.myonet.eu) multidisciplinary collaborations on myositis, important for this rare disorder. Through the international MyoNet, and together with Professor Vencovsky and Dr Chinoy, she has

established an international web-based myositis register (www.euromyositis.eu) which now has more than 4 500 patients from 23 centers world-wide enrolled. This is a longitudinal register to learn more about prognostic markers and outcomes. The register will also be a platform for future clinical trials. Until now the register's data has contributed to genetic studies exploring risk factors of myositis. Dr Lundberg has also been leading a multidisciplinary project to develop new classification criteria for myositis, EULAR-ACR classification criteria for myositis. She has published more than 200 papers in international peer-reviewed journals and more than 15 book chapters.

Dr Lundberg has served as Advisory Editor and Associate Editor of Arthritis & Rheumatology and served as ACR Abstract Category Co-Chair for Muscle Biology, Myositis and Myopathies. She joined the International Myositis Assessment and Clinical Studies (IMACS) from the start in year 2000. She has served the Swedish Society for Rheumatology, the Scandinavian Society for Rheumatology as president and EULAR as chair of Standing Committee of Education and Training (ESCET) and as member of the executive committee.

Jiří Vencovský

Jiří Vencovský received his MD in 1980 from the Charles University in Prague, Czechoslovakia. He completed specializations in internal medicine (1984), rheumatology (1987) and medical immunology (1994) while working in the Institute of Rheumatology in Prague. In 1988 he defended PhD thesis on ''Clinical and Immunological Characterization of Older Age Onset Rheumatoid Arthritis''. In the years 1988, 1991 and 1992–93 he was a visiting scientist at the Kennedy Institute of Rheumatology in London, UK, where he worked under supervision of Professor R.N. Maini. He was interested in autoantibodies against p70 antigen of nRNP complex in patients with connective tissue diseases and later on he also worked under Professor R. A. Mageed on rheumatoid factor immunoglobulin genes.

Since 1993 he has been the head of the Research and Clinical Laboratory Departments of the Institute of Rheumatology. He has become Associate Professor at Charles University in 1996 and full Professor of Medicine in 2002.

Jiří Vencovský is a current President of the Czech Society of Rheumatology. He was an editor of the journal ''Czech Rheumatology'' in 1998–2014. Professor Vencovsky is a member of Editorial boards of several scientific journals including Annals of Rheumatic Diseases, RMD Open and Clinical and Experimental Rheumatology. In 2002–2005 he was a member of the EULAR Scientific Committee and chairman of the Abstract Committee for European Congress of Rheumatology 2003/2004. Currently he serves as the treasurer for FOREUM Foundation for Research in Rheumatology. His research interests include inflammatory idiopathic myopathies, autoantibodies in rheumatic diseases and treatment of rheumatoid arthritis. He started myositis clinic in Prague and was one of the founding members of the European myositis registry. He organized/participated in several important studies in the field of inflammatory myopathies, including therapeutic, genetic and serological collaborations. Recently he was a member of the steering committee for the development of ACR/EULAR response criteria in dermatomyositis and polymyositis. He has published around 200 scientific papers, reviews and book chapters. He is also a busy clinician and enjoys both patient care and teaching.

Intestinal microbiome in scleroderma: recent progress

Elizabeth R. Volkmann

Purpose of review
Our evolving understanding of how gut microbiota affects immune function and homeostasis has led many investigators to explore the potentially pathologic role of gut microbiota in autoimmune diseases. This review will discuss the rapidly advancing field of microbiome research in systemic sclerosis (SSc), an incurable autoimmune disease with significant gastrointestinal morbidity and mortality.

Recent findings
Recent reports have identified common perturbations in gut microbiota across different SSc cohorts. Compared with healthy controls, patients with SSc have decreased abundance of beneficial commensal genera (e.g. *Faecalibacterium*, *Clostridium* and *Bacteroides)* and increased abundance of pathbiont genera (e.g. *Fusobacterium*, *Prevotella* and *Erwinia*). Certain genera may protect against (e.g. *Bacteroides*, *Clostridium*, and *Lactobacillus*), or conversely exacerbate (e.g. *Fusobacterium* and *Prevotella*) gastrointestinal symptoms in SSc. These genera represent potential targets to avert or treat gastrointestinal dysfunction in SSc.

Summary
Emerging evidence suggests that alterations in gut microbiota exist in the SSc disease state; however, future basic and clinical studies are needed to ascertain the mechanism by which these alterations perpetuate inflammation and fibrosis in SSc. Therapeutic trials are also needed to investigate whether dietary interventions or fecal transplantation can restore the gut microbial balance and improve health outcomes in SSc.

Video abstract
http://links.lww.com/COR/A38.

Keywords
gastrointestinal involvement, microbiota, systemic sclerosis

INTRODUCTION

Accumulating evidence suggests that gastrointestinal tract (GIT) microbiota has a profound effect on human health and disease. The burgeoning body of science investigating the microbiome has illuminated important relationships between alterations in GIT microbiota and specific rheumatic diseases, including systemic sclerosis (SSc). The present article reviews the evolving association between GIT microbiota and autoimmunity with a focus on the SSc disease state. Specifically, this review highlights recent reports revealing unique features of the GIT microbiome in patients with SSc and posits how these features may relate to clinical dimensions of this disease. The present review also describes the need for ongoing research in this area to better understand the mechanistic and clinical implications of SSc-related GIT microbiota alterations and how these data may inform the future discovery and assessment of novel therapeutic interventions, including fecal transplantation.

GASTROINTESTINAL TRACT MICROBIOTA AND AUTOIMMUNITY

The pathological hallmark of autoimmune disease is the loss of tolerance against nuclear self-constituents [1]. Although the biological underpinnings of this process are largely unknown, recent reports have demonstrated a link between commensal GIT flora and the production of pathogenic autoantibodies [2]. Furthermore, studies indicate that GIT microbiota plays a central role in the development of innate and adaptive immunity [3–6]. For example, the expression of nucleotide-binding

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KEY POINTS

- Emerging evidence suggests that GIT dysbiosis is a feature of the SSc disease state.
- Recent studies demonstrate that patients with SSc have decreased abundance of beneficial commensal organisms and increased abundance of pathobiont organisms.
- These organisms and their products offer potential targets for intervention to restore gastrointestinal microbial homeostasis in SSc.
- Future research is needed to determine how changes in the microbiome may affect immune function and clinical outcomes in SSc.

oligomerization domain 2, a protein associated with innate immune responses, depends on the presence of microbiota [7]. Moreover, the presence of microbiota also influences the peripheral differentiation of T helper (Th) cells, such as T regulatory (Treg) and Th17 cells [8].

However, the interplay between the microbiome and immune system is complex. Not only does GIT microbiota shape the development of the host immune system, but the immune system itself can alter GIT microbiota [4]. Aberrations in this cross-talk have been extensively explored in the study of the pathogenesis of inflammatory bowel disease (IBD). For instance, murine models deficient in key immune components cause changes in microbial communities, and when these communities are transferred to genetically normal mice, ulcerative colitis develops [9].

In addition to IBD, emerging evidence suggests that other diseases of the immune system affect GIT microbial composition, including psoriasis [10], rheumatoid arthritis (RA) [11] and graft-versus-host disease [12]. Treatments directed toward suppressing immune function in the aforementioned diseases further influence the interplay between microbiota and the immune system [13].

GASTROINTESTINAL DYSFUNCTION IN SYSTEMIC SCLEROSIS

Our evolving understanding of the intersection between immune function and microbiota has prompted researchers to investigate the GIT microbiota in SSc, a systemic inflammatory disorder with profound effects on GIT health and function. Unlike other connective tissue diseases (e.g. RA and systemic lupus erythematosus), GIT tract involvement occurs in the majority of patients with SSc [14,15]. In fact, after the skin, the GIT is the second most common organ system affected in SSc [16].

The symptoms of GIT dysfunction (e.g. esophageal reflux, dysphagia, constipation, abdominal pain, diarrhea, fecal incontinence and weight loss [17]) adversely affect patient quality of life and emotional well being [18–20]. However, treatments for managing this dimension of SSc (beyond temporizing measures to control symptoms) are lacking because of the fundamental dearth of knowledge regarding the pathogenesis of SSc-GIT dysfunction.

Historical data suggest that changes in the microvasculature, autonomic nervous system and immune system converge to cause smooth muscle atrophy and gut wall fibrosis [21,22]. The role of GIT microbiota in moderating these changes is unknown. Yet, many patients with SSc experience small intestinal bacterial overgrowth (SIBO) [15,17]. The primary cause of malabsorption in SSc, SIBO is defined as a microbial concentration greater than 10^5 CFU/ml in a jejunal aspirate culture. SIBO is more prevalent in patients with SSc compared with healthy controls [23]. Moreover, in an unselected cohort of patients with SSc, nearly half of all patients (43%) fulfilled criteria for SIBO using a glucose hydrogen methane (H_2CH_4) breath test and those presenting with SIBO had more severe GIT symptoms than those without [24].

Antibiotics seem to improve symptoms related to SIBO [23,24], albeit temporarily. In clinical practice, many patients receive frequent and rotating cycles of broad-spectrum antibiotics to treat GIT symptoms. The long-term effects of these repeated antibiotic courses on GIT microbiota are unclear. However, the observation that antibiotics generally improve GIT symptoms suggests that alteration in GIT microbiota is a feature of the SSc disease state.

GASTROINTESTINAL TRACT MICROBIOTA IS ALTERED IN SYSTEMIC SCLEROSIS

Our group and others have sought to characterize the lower GIT microbiota in SSc (Table 1) [25▪,26▪,27▪▪,28▪▪]. In a small, unselected cohort of patients with SSc, we demonstrated significant microbial community differences in SSc patients versus healthy controls in the cecum and sigmoid regions in patients undergoing colonoscopy [25▪]. We also observed significant genus-level differences between SSc patients and healthy controls, including decreased beneficial commensal genera such as *Faecalibacterium*, *Clostridium* and *Rikenella*, as well as increased potentially pathbiont genera, including *Fusobacterium*, *Prevotella*, *Ruminococcus*, *Akkermansia* and the uncommon γ-*Proteobacteria*, *Erwinia* and *Trabsulsiella*.

Table 1. Increased and decreased microbial taxa in systemic sclerosis patients versus controls

Study	Region	Design/sample	*N*	Increased in SSc[a]	Decreased in SSc[a]
Volkmann *et al.* [25▪]	Los Angeles, USA	Cross-sectional/colonic lavage sample	17[b]	*Lactobacillus; Bifidobacterium; Fusobacterium; Erwinia; Ruminococcus Prevotella*	*Faecalibacterium; Clostridium; Rikenella*
Volkmann *et al.* [26▪]	Oslo, Norway	Cross-sectional/fecal sample	17	*Lactobacillus*	*Clostridium; Bacteroides*
Volkmann *et al.* [26▪]	Los Angeles, USA	Cross-sectional/fecal sample	17[b]	*Lactobacillus; Fusobacterium; Erwinia; Ruminococcus*	*Faecalibacterium; Bacteroides*
Andréasson *et al.* [28▪▪]	Lund, Sweden	Cross-sectional/fecal sample	98	*Lactobacillus*	*Faecalibacterium prausnitzii; Clostridiaceae*
Bosello *et al.* [29]	Rome, Italy	Cross-sectional/fecal sample	66	*Lactobacillus; Ruminococcus; Roseburia; Faecalibacterium*	*Clostridium; Odoribacter; Veillonella; Prevotella*

[a]Relative to healthy controls.
[b]These are the same individuals. In Volkmann *et al.* [25▪], we collected lavage specimens from the cecum and sigmoid colon during colonoscopy; in Volkmann *et al.* [26▪], we collected fecal specimens. The healthy control groups were composed of different individuals in the two studies.

In the same SSc patient cohort, we analyzed stool samples and again found significant microbial community differences [26▪]. Patients with SSc had lower levels of the commensal genera, *Bacteroides* and *Faecalibacterium*, and higher levels of pathbiont genera, such as *Fusobacterium*, *Ruminococcus* and *Akkermansia*. In both studies, the genera, *Ruminococcus* and *Akkermansia*, had the highest fold change scores of all genera found to be enriched in the SSc samples relative to the controls. Interestingly, these two genera are associated with a fibrotic (stenozing) phenotype of Crohn's disease in a recent, relatively large, inception cohort study of pediatric patients with Crohn's disease [27▪▪]. These findings could suggest that *Ruminococcus* and *Akkermansia* (and their metabolic products) perpetuate fibrosis in SSc.

The SSc patients in this study varied with regard to disease duration, SSc subtype (i.e. limited versus diffuse disease), age, GIT symptom severity and SSc phenotype [i.e. the presence of interstitial lung disease (ILD)]. Very few patients in the study were consuming immunosuppressant medications. The small sample size precluded any statistically meaningful subgroup analyses, but a striking observation was that even patients with early disease (<3 years) had significant changes in their lower GIT microbiota compared with controls. In a separate cohort of SSc patients from Sweden, the extent of dysbiosis did not correlate with disease duration, and the presence of dysbiosis was prevalent among patients with both early (<2 years) and long-standing disease [28▪▪]. These findings suggest that dysbiosis may exist early in SSc, even prior to the development of symptoms or objective findings of dysmotility.

An unexpected finding from the aforementioned studies was that *Lactobacillus*, deemed a beneficial commensal genera by several host inflammatory and physiologic endpoints in animal models, was found in greater abundance in SSc patients compared with controls in the colonic lavage specimens from the sigmoid and cecum regions [25▪] and in the fecal specimens [26▪]. This observation has been appreciated in three other SSc cohorts in which fecal specimens were analyzed: Norwegian cohort [26▪], Swedish cohort [28▪▪] and Italian cohort [29]. Although the abundance of this genus is typically reduced in chronic inflammatory states [30], this finding is intriguing in light of recent evidence that *Lactobacillus reuteri* may moderate GIT motility [31,32]. For instance, administration of this species reduced the frequency and contractility of motor complexes, leading to diminished peristalsis, a common feature of SSc [31,32]. Increased abundance of *Lactobacillus* is unlikely to be related to probiotic use as very few patients in the University of California, Los Angeles and Norwegian cohorts consumed probiotics, and studies have demonstrated that ingestion of lactobacillus-bearing probiotics does not measurably influence fecal microbial composition [33]. Future studies are needed to determine whether members of the *Lactobacillus* genus and/or their metabolic products alter the broader intestinal microbial ecosystem gene expression and function in SSc.

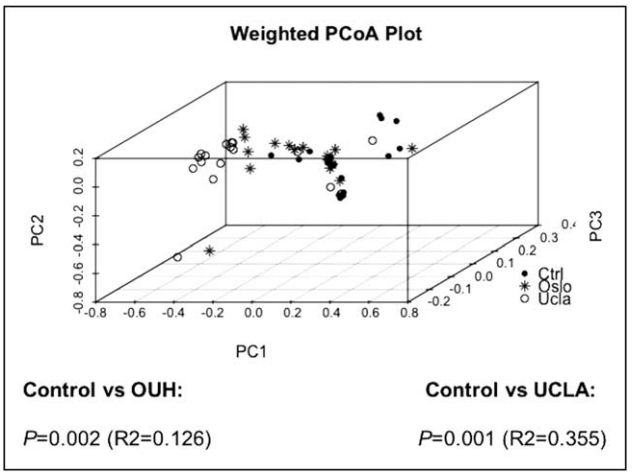

FIGURE 1. Significant differences in the β diversity of the SSc and healthy samples as demonstrated by principal coordinate analysis plots of the weighted UniFrac distance. Each dot represents a sample from a UCLA-SSc patient (open circle) or a healthy control (closed circle). Each star represents a sample from a Norwegian-SSc patient (abbreviated as OUH). The *P*-values provided were calculated by analysis of variance using distance matrices. The β diversity also differed between the UCLA-SSc and OUH-SSc cohort patients (R2 0.145; $P=0.002$). Reproduced with permission from [26▪].

THE EXTENT OF DYSBIOSIS IN SYSTEMIC SCLEROSIS MAY VARY GEOGRAPHICALLY

In an analysis of a cohort of unselected SSc patients from Norway [26▪], we demonstrated significant microbial community differences in SSc patients versus healthy controls. For instance, the commensal genera, *Clostridium* and *Bacteroides*, were depleted in SSc patients compared with healthy controls [26▪]. However, in a direct comparison of fecal specimens from the UCLA-SSc cohort and the Norwegian-SSc cohort, the overall extent of dysbiosis appeared greater in the UCLA-SSc cohort [26▪]. As demonstrated in Fig. 1, the β diversity, a measure of between-sample taxonomic diversity, was significantly different between the two SSc cohorts. Moreover, the relative abundance of *Bacteroidetes* was significantly decreased in both SSc cohorts compared with the healthy control cohort; however, the UCLA-SSc patients had the lowest proportion of *Bacteroidetes* (21.3%), followed by SSc patients in the Norwegian cohort (45.0%) and healthy controls (63.2%). Studies have found that the ratio of *Firmicutes* to *Bacteroidetes* may have an important effect on human health [34,35]; thus, the proportional difference in the abundance of *Bacteroidetes* between the two SSc cohorts may have clinical significance. It bears mentioning that *Bacteroidetes* was also depleted in SSc patients from an Italian cohort compared with controls in a recent abstract [29].

At the genus level, the commensal genera, *Faecalibacterium* and *Bacteroides*, were significantly more abundant in the Norwegian-SSc patients compared with the UCLA-SSc patients (Fold change scores of 4.85 and 3.75, respectively). Taken together, these findings suggest that GIT microbiota alterations in SSc may vary by region. Possible reasons to explain this disparity are numerous and may include genetic differences, dietary variation, as well as differences in the severity of SSc and/or the phenotypic expression of SSc. In support of the latter hypothesis, more SSc patients in the UCLA cohort had ILD than in the Norwegian cohort [26▪]. Emerging evidence suggests that GIT microbiota may influence immune responses in pulmonary disease, such as asthma [36]. It is plausible that patients with SSc-ILD may have distinct microbiota features compared with SSc patients without ILD. In fact, Andreasson *et al.* [28▪▪] demonstrated that the extent of GIT dysbiosis was more severe in patients with ILD compared with patients without ILD. Future studies are needed to further investigate this hypothesis, and these analyses should attempt to adjust for immunosuppressant use, which is likely more prevalent among patients with SSc-ILD and may also affect GIT microbiota.

ALTERATIONS IN GASTROINTESTINAL TRACT MICROBIOTA MAY AFFECT SYSTEMIC SCLEROSIS-GASTROINTESTINAL TRACT SYMPTOMS

Although no valid, objective measure of GIT dysfunction in SSc exists, the GIT 2.0 questionnaire is commonly used to measure SSc-GIT symptoms in both clinical practice and for research purposes [37]. The questionnaire consists of seven domains and has been translated and validated in several languages. Scores on the GIT 2.0 can indicate self-rated severity (i.e. none/mild versus moderate versus severe/very severe disease) of GIT involvement based on previously published score thresholds [37]. Application of this questionnaire in SSc microbiota studies has allowed researchers to begin to identify specific microbial taxa associated with SSc-GIT symptom severity (Table 2) [25▪,26▪,38].

In an analysis of colonic lavage specimens of UCLA-SSc patients, patients with none-to-mild GIT involvement (based on the total GIT score, diarrhea domain and bloating/distension domain) had increased abundance of the beneficial commensal species, *Bacteroides fragilis*, in the cecum and sigmoid compared with patients with moderate-to-severe GIT

Table 2. Summary of microbial taxa associated with systemic sclerosis-gastrointestinal tract symptoms

Study	Region	Design/sample	*N*	Increased GIT-symptoms[a]	Decreased GIT-symptoms[a]
Volkmann *et al.* [25▪]	Los Angeles, USA	Cross-sectional/ colonic lavage sample	17[b]	*Fusobacterium Actinobacillus*	*Bacteroides fragilis Candidatus arthromitus Clostridium*
Volkmann *et al.* [26▪]	Oslo, Norway & Los Angeles, USA	Cross-sectional/ fecal sample	17[b]	*Prevotella; Parabacteroides*	*Clostridium Lactobacillus*
Volkmann *et al.* [38]	Los Angeles, USA	Longitudinal/ fecal sample	17[b]		*Bacteroides*

[a]Increase abundance of these taxa is associated with increased/decreased GIT symptoms based on the GIT 2.0.
[b]These are the same individuals. In Volkmann *et al.* [25▪], we collected lavage specimens from the cecum and sigmoid colon during colonoscopy; in Volkmann *et al.* [26▪], we collected fecal specimens at baseline for the cross-sectional analysis [26▪] and every 3 months over 12 months for the longitudinal study [38].

involvement [25▪]. In the cecum, patients with none-to-mild scores for the GIT 2.0 diarrhea domain had increased abundance of the genus *Clostridium* compared with patients with moderate-to-severe diarrhea scores [25▪]. Similarly, in an analysis of fecal specimens from the UCLA-SSc and Norwegian-SSc cohorts, *Clostridium* was more abundant in patients with none-to-mild GIT involvement (for the total GIT score and the bloating/distension domain) compared with patients with moderate-to-severe GIT involvement [26▪]. *Lactobacillus* was also more abundant in patients with none–mild constipation compared with patients with moderate–severe constipation in an analysis of fecal specimens from the UCLA-SSc and Norwegian-SSc cohorts [26▪]. If *B. fragilis*, *Clostridum* and/or *Lactobacillus* are found in future studies to attenuate mucosal inflammation in SSc, therapy directed at increasing the growth or activity of these species may have a therapeutic benefit for alleviating SSc-GIT symptoms.

On the contrary, increased abundance of *Fusobacterium* was associated with more severe GIT disease in an analysis of the colonic lavage specimens of UCLA-SSc patients [25▪]. *Fusobacterium* species are deemed pathobionts given their invasive nature and ability to translocate into the blood and contribute to systemic disease states [39–41]. In both Crohn's disease and ulcerative colitis, for example *Fusobacterium* species are increased compared with controls [42,43], and when human isolates of *Fusobacterium varium* are introduced into mice, mucosal erosions develop in the colon [44].

Prevotella was also more abundant in patients with moderate–severe GIT symptom severity (bloating/distention domain and diarrhea domain) compared with patients with none–mild GIT symptom severity in an analysis of fecal specimens from the UCLA-SSc and Norwegian-SSc cohorts [26▪]. Like *Fusobacterium*, species of the *Prevotella* genus are increased in Crohn's disease [45]. Moreover, a recent study found that patients with early RA had increased abundance of *Prevotella copri*, and when fecal samples from these patients were introduced into germ-free, arthritis-prone mice, the mice developed severe arthritis and harbored an increased number of intestinal Th17 cells [46▪▪]. Understanding how *Fusobacterium* and *Prevotella* moderate immune responses in SSc may shed light on whether these genera contribute to the pathogenesis of SSc.

LONGITUDINAL ASSESSMENT OF GASTROINTESTINAL TRACT MICROBIOTA IN SYSTEMIC SCLEROSIS

The aforementioned microbiota analyses in SSc were cross-sectional. It is unclear whether the relationships observed between specific genera and GIT symptoms are causational and/or persist with time. To address this limitation, our group has recently embarked on a study to serially measure fecal specimens in SSc patients every 3 months over a 12-month period [38]. In the first analysis of these data, both the absolute and relative abundances of specific genera did not change over time within individual SSc patients. In addition, GIT 2.0 scores did not change significantly over the course of the 12-month study within each SSc patient. We did find that patients with lower abundance of *Bacteroides* throughout the study had increased GIT symptoms over time, even after controlling for age, sex, ethnicity, disease duration and SSc subtype (i.e. limited versus diffuse) [38]. However, larger and longer studies are needed to determine temporal patterns in the abundance of specific genera and their relationship to SSc-GIT symptoms.

FUTURE RESEARCH QUESTIONS IN SYSTEMIC SCLEROSIS GASTROINTESTINAL TRACT MICROBIOME STUDIES

The studies highlighted in the present review likely represent the tip of the iceberg in SSc microbiome

research. Ongoing research efforts in this area are greatly needed to better understand the relationships between GIT microbiota, immune responses and clinical outcomes in SSc. To adequately address these unanswered research questions, future studies should also explore how specific factors can moderate the GIT microbiota in SSc as outlined below.

Diet–microbe–host interactions

Additional research is needed to understand how diet affects microbial composition in SSc. In a relatively large study of Dutch patients ($N = 1135$), Zhernakova *et al*. [47] identified 60 dietary factors affecting variations observed in the interindividual distance of microbial composition. For example, this study found that drinking low-fat milk (e.g. buttermilk) was associated with higher diversity in microbial composition compared with drinking high-fat milk (e.g. whole milk) [47].

Moreover, while multiple factors affect GIT microbiome composition (e.g. age, genetics and diet), diet may represent the easiest factor to modify for therapeutic means. Changing dietary intake patterns can immediately and dramatically alter GIT microbial composition and metabolic output [48,49]. For instance, adoption of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) causes marked alterations in the microbiome and metabolome of patients with irritable bowel syndrome [50,51]. Although the low FODMAP diet is often prescribed for patients with SSc, this approach has never been formally studied in SSc. Future studies may consider evaluating how this dietary intervention affects microbial composition, as well as GIT symptoms in SSc.

The effects of dysmotility on microbiota

Impaired GIT motility is a hallmark of SSc. Precisely how dysmotility affects the microbiota in SSc is unclear. However, objective signs of intestinal stasis are associated with an increased risk of SIBO [24]. Moreover, Andreasson *et al*. [28▪▪] found that the degree of dysbiosis correlated with the degree of dysmotility (based on cineradiography of esophageal function). No studies have evaluated the effects of lower GIT dysmotility on microbiota in SSc. It is furthermore unknown whether dysmotility itself drives changes in microbial composition or changes in microbial composition influence GIT motility in SSc. To answer this question, longitudinal studies are needed, which evaluate changes in microbial composition and motility over time. These studies should also include patients with normal GIT motility perhaps by including SSc patients with very early disease.

Using probiotics to modify the gastrointestinal tract microbiota in systemic sclerosis

Although antibiotics are an obvious way to manipulate the microbiome in SSc, the long-term effects of this approach are unknown and may pose more harm than benefit [52]. A prospective study of patients with Crohn's disease found that antibiotics exposure was associated with increased dysbiosis over time [52]. Moreover, this approach is nonselective and may eliminate beneficial commensal organisms associated with improved SSc-GIT symptoms. Ingestion of selected strains of live bacteria (aka probiotics) may be a safer alternative to ameliorating dysbiosis in SSc. The majority of studies on probiotic use in autoimmune disease have focused on IBD. Unfortunately, the results of these studies have not been entirely promising [53,54]. One small ($N = 10$), uncontrolled study evaluated the effects of a 2-month course of daily probiotics [Align (*Bifidobacterium infantis*) or Culturelle (*Lactobacillus* GG)] on GIT 2.0 scores in SSc [55]. This study found that patients treated with probiotics had improved reflux, distention/bloating and total GIT scores; however, without a control group, the results are inconclusive. Interestingly, we found increased abundance of *Bifidobacterium* and *Lactobacillus* in our UCLA-SSc cohort relative to controls [25▪]. Thus, future efforts to evaluate the effects of probiotics in SSc may consider employing an approach to replenish genera depleted in SSc or genera associated with improved SSc-GIT symptoms.

Fecal microbial transplantation in systemic sclerosis

Fecal transplantation, intestinal microbiota transfer or fecal bacteriotherapy has recently gained interest as a potentially effective treatment modality in autoimmune diseases. Although the application of this approach dates back to the 4th century when human feces were used to treat various GIT diseases in Traditional Chinese Medicine [56], it was not until the 20th century that the Western world explored the use of fecal transplantation to manage pseudomembranous colitis [57]. In terms of autoimmune diseases, most fecal transplantation studies have been performed in patients with IBD. However, a recent review of the literature illustrated that while some studies have demonstrated promising findings, there are insufficient data to recommend fecal transplantation in IBD [58]. Questions remain

regarding the optimal route of administration, frequency of application, donor screening method, donor stool preparation and preparation procedures for the recipient (e.g. antibiotic administration prior to transplantation) [59]. No studies have evaluated fecal transplantation in the setting of SSc. However, the introduction of a stable and complete community of intestinal microorganisms may potentially restore intestinal microbial homeostasis in SSc and lead to improved clinical outcomes compared with the ingestion of probiotics containing limited bacterial species.

CONCLUSION

Until recently, the intestinal microbiota remained an unexplored area of SSc research. However, in the past 2 years, new reports have demonstrated that the SSc disease state is associated with alterations in lower GIT microbiota characterized by depletions in beneficial commensal genera (e.g. *Faecalibacterium*, *Clostridium* and *Bacteroides)*, as well as enrichments in potentially pathbiont genera (e.g. *Fusobacterium*, *Prevotella, Ruminococcus* and *Akkermansia* and the uncommon γ-*Proteobacteria*, *Erwinia* and *Trabsulsiella*) [25▪,26▪,28▪▪]. Furthermore, cross-sectional and longitudinal analyses have demonstrated that specific genera are associated with GIT symptom severity. Numerous questions remain regarding the role of GIT microbiota in perpetuating immune responses in SSc and affecting clinical outcomes. Future basic and clinical studies are needed to further define the GIT microbiota in SSc and identify specific strategies to modify microbial composition to improve health outcomes for patients with SSc.

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Conflicts of interest

There are no relevant conflicts of interest concerning this article.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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New insights into the recognition, classification and management of systemic sclerosis-associated pulmonary hypertension

Christopher J. Mullin and Stephen C. Mathai

Purpose of review
Pulmonary hypertension is a common complication of systemic sclerosis (SSc), and remains a leading cause of morbidity and mortality. We will review recent developments in the recognition, classification and treatment of pulmonary hypertension in SSc.

Recent findings
Advances in screening for pulmonary arterial hypertension (PAH) and use of exercise haemodynamics may help to identify pulmonary vascular disease earlier in SSc. Recent studies have led to changes in recommendations for adjunct therapy and selection of pulmonary vasodilators for the treatment of SSc-associated PAH.

Summary
Recent advances in the diagnosis, classification and management of pulmonary hypertension in SSc have continued to improve our understanding of this challenging disease. Ongoing investigation in the pathogenesis of this disease will afford the opportunity to develop targeted therapies to improve outcomes for SSc patients with pulmonary hypertension.

Keywords
exercise, pulmonary hypertension, screening, systemic sclerosis, therapy

INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (mPAP) at least 25 mmHg, pulmonary artery wedge pressure (PAWP) of 15 mmHg or less and pulmonary vascular resistance (PVR) more than 3 Wood units (WU) in the absence of parenchymal lung disease, chronic thromboembolic disease or other uncommon diseases [1,2▪▪]. Although rare in the general population, PAH is relatively common in systemic sclerosis (SSc), with an estimated prevalence of 7–12% [3–5]. PAH remains a leading cause of morbidity in SSc [5], and PAH related to SSc (SSc-PAH) carries a worse prognosis than idiopathic PAH (IPAH) and PAH related to other connective tissue diseases [6,7].

Given the significant morbidity and mortality with SSc-PAH, there is great interest in improving outcomes. There have been many advances in the specific therapies for PAH, which are also applicable specifically to SSc-PAH. However, because of the unique epidemiology of SSc-PAH, advances in improving the recognition and classification of pulmonary hypertension specifically in SSc are equally as important in improving outcomes in SSc-PAH.

RECOGNITION OF PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

Early detection of pulmonary vascular disease in SSc is widely considered to be essential to reduce the morbidity and mortality in SSc-PAH, particularly as PAH is often diagnosed late in disease progression [8,9▪]. There are two main considerations for detecting early pulmonary vascular disease in SSc to improve screening methods to identify SSc patients

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KEY POINTS

- Advances in screening protocols may lead to earlier identification of pulmonary hypertension in patients with scleroderma.
- Exercise challenges during right heart catheterization identify patients with early pulmonary vascular disease who may have outcomes as poor as those with resting pulmonary arterial hypertension.
- Oral anticoagulation should not be routinely prescribed for management of PAH in SSc-PAH patients.
- Combination therapy with ambrisentan and tadalafil in treatment-naive SSc-PAH patients reduces time to clinical worsening and improves measures of right ventricular function.
- Several clinical trials of novel therapies for PAH targeting pathways relevant to both PAH and SSc are ongoing and will offer new insights into clinical management of this disease.

with PAH as early as possible after they develop the disease, and to identify pulmonary vascular disease before it results in elevations of resting pulmonary artery pressures, typically with an exercise challenge.

Screening for pulmonary hypertension in systemic sclerosis

Current guidelines recommend annual screening of all patients with SSc for PAH [10]. The DETECT algorithm is a two-step process developed to screen for PAH in SSc [11] that uses a combination of clinical, laboratory, pulmonary function, electrocardiographic and echocardiographic parameters to determine referral for diagnostic right heart catheterization (RHC) (Fig. 1). This algorithm recommended RHC in 62% of the cohort of at-risk SSc patients from which it was derived, and missed only 4% of PAH cases [11]. Two recent studies have prospectively evaluated the performance of the DETECT algorithm in an unselected cohort of SSc patients [12,13]. In both studies, the DETECT algorithm recommended more patients be referred for RHC than per European Society of Cardiology (ESC)/European Respiratory Society (ERS) guideline criteria [14]. In one study, the four patients diagnosed with PAH screened positive by both criteria (i.e. a diagnosis was not missed by guideline criteria) [12], while in the other study, six patients who did not initially meet ESC/ERS guideline criteria were diagnosed with PAH after 2 years of follow-up. All of these patients screened positive by DETECT for at least a year before they were referred for RHC [13]. Taken together, this suggests that the DETECT algorithm may be more sensitive than current guideline screening criteria, although larger studies are still needed. Widespread use of the DETECT algorithm is somewhat challenging because the two required echocardiographic parameters are either not routinely measured (right atrium area) or technically feasible on every patient (tricuspid regurgitant jet velocity). In a large Australian SSc cohort, less than half of SSc patients underwent yearly echocardiograms [9▪], so practically speaking, the specific screening criteria used may be less important than simply improving adherence to any screening protocol.

Exercise pulmonary hypertension in systemic sclerosis

Although the definition of pulmonary hypertension is based on a resting mPAP at least 25 mmHg, it is estimated that 50–70% of the pulmonary vasculature needs to be affected or obstructed before resting mPAP is elevated [15]. An abnormal pulmonary haemodynamic response to exercise, or exercise pulmonary hypertension (Ex-PH), has been postulated to represent early pulmonary vascular disease, and thus exercise haemodynamics is an area of active research. Right ventricular function is worse in SSc-PAH compared with IPAH despite similar afterload [16], and more recent work has shown that right ventricular contractile reserve is depressed in SSc-PAH compared with IPAH, and is associated with right ventricular dilation and worsening ventricular-vascular coupling with exercise [17▪▪]. This difference in right ventricular function with exercise is one of many reasons why there is a strong interest in studying pulmonary vascular responses to exercise in SSc.

Ex-PH was previously defined as a mPAP more than 30 mmHg with exercise. These criteria were included in guidelines for the diagnosis of PH, but was removed in 2009 guidelines because of concerns about the pressure cut-off (upper limit of normal mPAP with exercise may exceed 30 mmHg) and lack of standardization of exercise protocol (modality, duration, workload) [18]. Since then, the importance of the relationship between mPAP and cardiac output during exercise has been further elucidated [19,20], and although there is currently no consensus definition of Ex-PH, a mPAP more than 30 mmHg and transpulmonary gradient (TPG) more than 3 WU at maximal exercise has been proposed as the most suitable definition [21▪▪,22]. A study of 72 SSc patients who underwent RHC with exercise haemodynamics showed that survival in the 28 Ex-PH patients (defined by mPAP >30 mmHg and TPG >3 WU at maximal exercise) was worse than those without resting or Ex-PH ($n=27$), but surprisingly was not different than those with resting PAH

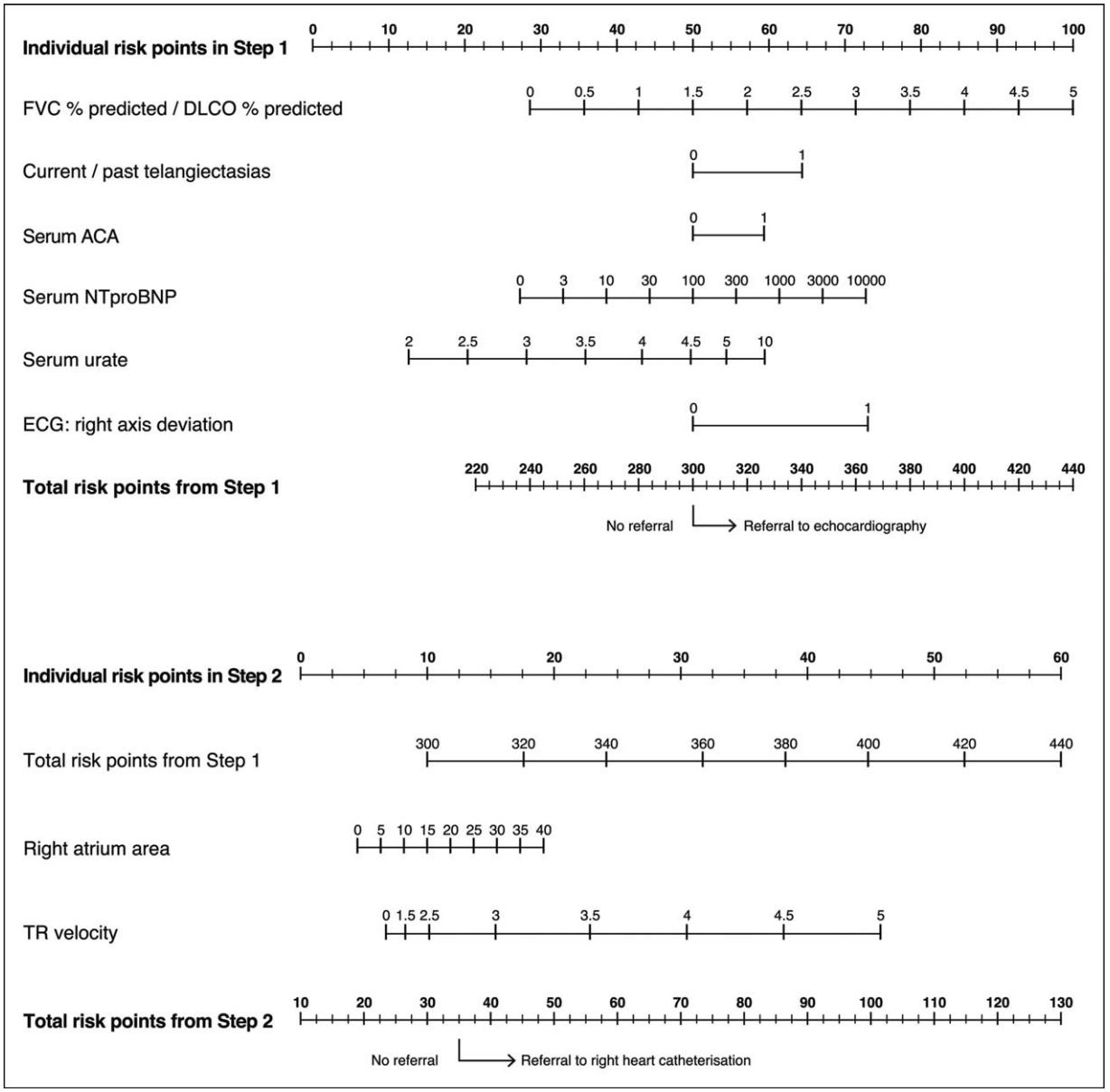

FIGURE 1. Nomograms for the DETECT algorithm. Two-step algorithm for determining referral for right heart catheterization for suspected pulmonary arterial hypertension in systemic sclerosis. At Step 1 (top), risk points for each of the six nonechocardiographic variables are calculated and summed. If the total risk points from Step 1 are >300, the patient is referred for echocardiography. Similarly, at Step 2, risk points for the carried forward and the two echocardiographic variables are calculated. If the total risk points from Step 2 is >35, the patient is referred to right heart catheterization. If a single Step 1 variable is missing, it should be assigned 50 risk points, with the exception of current/past telangiectasias, which should be assigned 65 points. If a single Step 2 variable is missing, it should be assigned 10 points. The nomograms cannot be reliably used if more than one variable out of the eight total variables is missing. ACA, anticentromere antibody; DLCO, pulmonary diffusing capacity for carbon monoxide; FVC, forced vital capacity; NTproBNP, N-terminal pro b-type natriuretic peptide; TR, tricuspid regurgitant jet. Reproduced from [11].

(Fig. 2) [23]. Although this was a single-centre, retrospective study, it highlights that Ex-PH is relatively common amongst SSc patients and has prognostic implications. Whether SSc patients with Ex-PH progress more rapidly to resting PAH, and if treatment with PAH-specific therapies is of any benefit in this population, remains to be studied.

TREATMENT OF PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

Recent observational cohort studies and randomized clinical trials have informed clinical management of PAH. These studies have led to changes in consensus guidelines in recommendations for adjunct therapy and selection of specific pulmonary

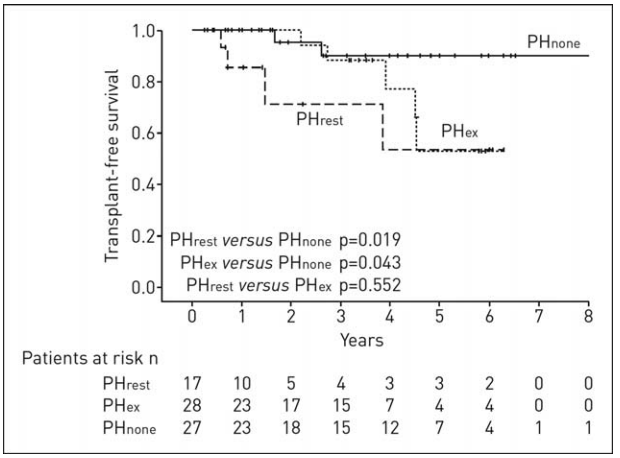

FIGURE 2. Survival in systemic sclerosis by haemodynamic classification in systemic sclerosis. Transplant-free survival by Kaplan–Meier method and number at risk of 72 patients according to their haemodynamic classification. PH_{rest}: resting, Precapillary pulmonary hypertension; PH_{ex}: exercise precapillary pulmonary hypertension (defined by mean pulmonary artery pressure >30 mmHg and total pulmonary resistance >3 Wood units at maximal exercise); PH_{none}: patients without resting or exercise pulmonary hypertension. Reproduced with permission from [23].

vasodilators for the management of this disease [2▪▪]. Importantly, these changes not only pertain to PAH in general but also specifically to SSc-PAH.

Adjunct therapy

For the past 30 years, oral anticoagulation has been recommended as adjunct therapy for PAH. Early pathologic studies demonstrated thrombotic lesions in the pulmonary arteries of IPAH patients with plexogenic arteriopathy and were thought to result from in-situ thrombosis related to pulmonary vessel endothelial damage [24,25]. Based upon these observations and several retrospective cohort studies of PAH patients that showed lower mortality in IPAH patients who received oral anticoagulation [26–28], consensus guidelines recommended the use of warfarin for PAH including SSc-PAH [14,29]. Data from more recent registry studies conducted in Europe and the United States provided evidence that routine anticoagulation in SSc-PAH may not be beneficial. In fact, data from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) demonstrated an increased risk of death for SSc-PAH patients who received oral anticoagulation [30,31]. Based upon these studies, the most recent treatment guidelines from the ESC/ERS advise against routine anticoagulation for SSc-PAH patients [2▪▪]. Although there are no randomized clinical trials to provide more definitive data on the role of anticoagulation in SSc-PAH, this recommendation marks a significant change in the management of SSc-PAH.

Recommendations for physical activity and exercise training have similarly been limited by the lack of prospective studies. However, the most recent guidelines do suggest that PAH patients participate in a supervised exercise programme such as pulmonary rehabilitation with Level 2b recommendation [2▪▪]. Included in the data supporting this approach was an observational cohort study of 21 patients with CTD-PAH, nine of whom had SSc-PAH, who underwent a 3-week inpatient rehabilitation programme followed by continued unsupervised exercise programs at home [32]. Improvements were noted in quality of life, 6-min walk distance (6MWD) and maximum work load achieved during exercise. Although further data from randomized clinical trials are needed to better define the ideal mode, session duration and length of exercise intervention programme in patients with SSc-PAH, these data support routine supervised exercise for PAH patients and, as such, should be incorporated into clinical management.

Pulmonary vasodilators

Recent clinical trials of PAH therapy have also led to important changes in the clinical management of SSc-PAH patients. First, the large, randomized clinical trial known as the AMBITION study (Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension) showed a more than 50% reduction in time to clinical worsening (a composite endpoint of death, hospitalization for worsening PAH, disease progression or unsatisfactory long-term clinical response) in the combination therapy arm of ambrisentan along with tadalafil compared with either agent alone [33]. A subsequent subgroup analysis of SSc-PAH patients included in this study showed persistence of this effect, with a more than 60% reduction in time to clinical worsening in the combination therapy arm [34▪▪]. Further, improvements in functional capacity and in the serum biomarker N-terminal pro-brain natriuretic peptide were also seen. In fact, when compared with IPAH patients included in the study, the outcomes for SSc-PAH patients were similar to even greater in magnitude, marking the first clinical trial of PAH therapy in which outcomes for SSc-PAH patients achieved this benchmark.

The benefit of this combination of therapy in SSc-PAH was further demonstrated in a multicentre observational study of SSc-PAH patients called the Ambrisentan and Tadalafil in Pulmonary Arterial

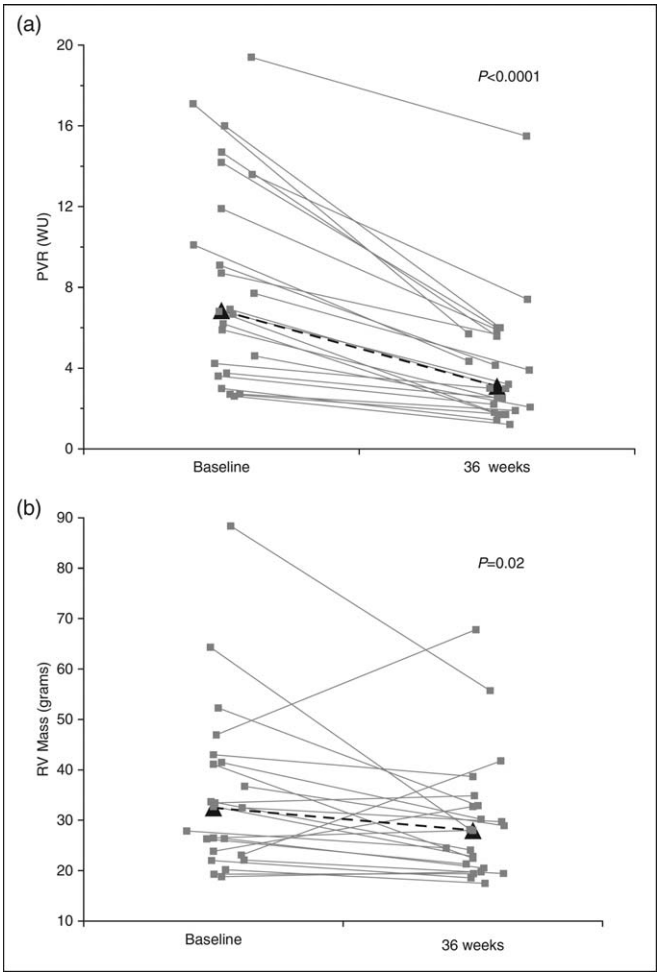

FIGURE 3. Effect of combination therapy in the ambrisentan and tadalafil in pulmonary arterial hypertension in scleroderma study (ATPAHSS). Effect of combination therapy with ambrisentan and tadalafil on pulmonary vascular resistance (PVR) (a) and right ventricular (RV) mass (b) from baseline to 36 weeks for 24 patients. PVR (mean $\pm$ SD) improved from 8.4 ± 5.4 Wood units (WU) to 4.1 ± 3 WU ($P > 0.01$), and RV mass [median (interquartile range)] improved from 32.5 (23.2–41.4) to 28.0 (20.6–32.9) g. The dashed line represented the change in median values for the group. Reproduced with permission from [35▪▪].

Hypertension in Scleroderma Study (ATPAHSS) [35▪▪]. This 36-week study of treatment-naive patients employed coprimary endpoints of change in right ventricular mass by cardiac MRI (CMR) and change in PVR. The study demonstrated dramatic reductions in both right ventricular mass and PVR, with more than a 50% reduction in the latter (Fig. 3). Measures of right ventricular function, functional capacity and quality of life all improved significantly as well.

Based upon these findings from the AMBITION study, current guidelines favour the use of initial combination therapy with ambrisentan and tadalafil for treatment-naive patients at low or intermediate risk with Class Ib recommendations [2▪▪]. These recommendations apply to SSc-PAH patients as well, and are further buttressed by the results of the ATPAHSS study, which offer insights into the mechanism of these observed clinical improvements in SSc-PAH patients.

Ongoing clinical trials

There are several ongoing clinical trials of novel therapies in PAH. Importantly, some of these studies are solely enrolling SSc patients. The Rituximab for Treatment of Systemic Sclerosis Associated Pulmonary Arterial Hypertension Trial (clinicaltrials.gov NCT01086540) is a randomized, placebo-controlled, phase-2 study with a primary outcome of change in PVR at 24 weeks. This study was motivated by basic research in animal models of pulmonary hypertension that demonstrated a potential pathogenic role of B cells in pulmonary hypertension, both through the development of antiendothelial antibodies thought to promote vascular injury and through an imbalance between T-cell and B-cell activity that leads to pulmonary vascular remodelling [36▪▪]. The study is currently enrolling at 26 centres across the United States and will examine the impact of rituximab on CMR measures of right ventricular function, TTCW, 6MWD and quality of life in addition to changes in PVR.

Ifetroban, a thromboxane A2/prostaglandin H2 receptor (TxA2/PGH2) antagonist, is also being studied in a SSc-specific clinical trial (clinicaltrials.gov NCT02682511). Based upon prior research demonstrating a role for TxA2/PGH2 in vascular remodelling and cardiac fibrosis and a recent study in a mouse model of right ventricular volume overload that showed abrogation of right ventricular fibrosis and cardiomyocyte hypertrophy compared with other inhibitors of the arachodonic acid pathway [37], investigators initiated a small randomized clinical trial designed to examine the safety of this intervention in SSc. The study, conducted at five centres in the United States, is currently enrolling patients with diffuse SSc without PAH, assessing the impact on lung function and skin thickening, and in SSc patients with PAH, assessing the impact on right ventricular function as assessed by CMR.

Mitochondrial dysfunction in PAH and its impact on cellular remodelling and tissue fibrosis is the focus of both basic research and now clinical trials [38]. Bardoxolone, an antioxidant inflammation modulator that restores mitochondrial energy production in experimental models, is being examined in a randomized clinical trial. The CATALYST study

(ClinicalTrials.gov identifier: NCT02657356) is currently enrolling patients with CTD-associated PAH, including SSc-PAH, who are on stable PAH therapy. The primary outcome of this 24-week, Phase 3 study is a change in 6MWD. Although other novel agents and treatment strategies are under investigation in PAH clinical trials, only the aforementioned are the only ones being studied exclusively in CTD-PAH or SSc-PAH patients.

Lung transplantation

Between 2005 and 2012, over 11 000 lung transplantations were performed in the United States; however, only 229 (less than 2%) were performed in patients with SSc [39]. This practice pattern reflects concerns about poor outcomes in SSc patients related to extrapulmonary involvement of the kidneys, immune dysregulation and the high prevalence of oesophageal reflux that is a risk factor for bronchiolitis obliterans syndrome (BOS), the most common cause of graft failure and death in lung transplantation [40]. However, two recent retrospective observational cohort studies have demonstrated excellent short and longer-term survival for SSc patients, comparable to outcomes in patients who undergo lung transplantation for interstitial lung disease who do not have SSc [41,42]. A substantial portion of the cohorts (nearly 50% in one, 70% in the other) had pulmonary hypertension associated with SSc, though none were reported to have SSc-PAH. These results, combined with prior cohorts of SSc patients who underwent lung transplantation, suggest that this intervention is a viable option for those SSc patients with end-stage disease, and thus, patients should be referred to a centre with expertise in the evaluation and management of SSc patients and lung transplantation.

CONCLUSION

Pulmonary hypertension remains a common complication of SSc. Advances in both screening for PAH and use of exercise haemodynamics in SSc may help to identify pulmonary vascular disease earlier in this at-risk population. Initial combination therapy with ambrisentan and tadalafil is now recommended as standard of care for treatment-naive, low or intermediate-risk PAH and SSc-PAH patients. Despite improvements in recognition, classification and treatment of pulmonary hypertension in SSc, there remains an ongoing need to improve outcomes in this challenging disease.

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Conflicts of interest

S.C.M. reports receiving consulting fees from Actelion, Bayer and United Therapeutics and serving on the Scientific Leadership Council of the Pulmonary Hypertension Association.
C.J.M. reports no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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Progress in the clinical classification of systemic sclerosis

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Purpose of review
Systemic sclerosis (SSc) subset classification criteria are a cornerstone of SSc research. Given changes in our understanding of the disease and limitations of the current criteria in the conduct of trials, the developments of new SSc subset criteria are underway.

Recent findings
This article summarizes previous iterations of SSc subset criteria, highlights current thinking about the construct underlying SSc subsets in the modern era and provides an overview of the development of new SSc subset criteria.

Summary
Using a combination of data-driven and expert-based innovative methodologies, a large international collaborative effort is developing new SSc subset criteria. It is anticipated that this new system of classification will shift the paradigm of how we study novel therapies in SSc.

Keywords
classification criteria, scleroderma, subset, systemic sclerosis

INTRODUCTION

The American College of Rheumatology (ACR) – European League Against Rheumatism (EULAR) classification criteria for systemic sclerosis (SSc) resulted in a paradigm shift in the concept of the disease, improving the classification of individuals with early, mild and the limited subtype of disease. Given the heterogeneity of SSc, numerous SSc subset criteria have been proposed to identify groups of SSc who are similar. Recent advances in the understanding of the disease and limitations in the current subsetting system(s) have resulted in an international collaborative effort to develop new classification criteria for SSc subsets. This article highlights progress in the clinical classification of SSc.

Criteria for SSc are an essential component of clinical research [1]. The heterogeneous clinical phenotype, autoantibody profile and prognosis of SSc result in the need for classification criteria to identify more homogenous groups of individuals for participation in research studies [2]. The ACR – EULAR classification criteria for SSc are a significant advancement in the field [3–5]. Building upon previous criteria, they add emphasis to the vasculopathic manifestations, introduce the concept of differential weighing of disease characteristics and include the early manifestation of puffy fingers. This criteria set has shifted the conceptual framework of the disease [6▪]. This is particularly evident among cases with early disease, mild disease and limited cutaneous subtype of disease resulting in demonstrable improvements in sensitivity and specificity [7–9]. This provides an unprecedented opportunity to intervene early in the disease process with novel therapeutic agents with the goals of preventing or reversing internal organ involvement [6▪].

Subset criteria are used to identify groups of patients within the spectrum of SSc. SSc subset criteria were historically based on the extent of skin involvement [10]. The most frequently used subset criteria are those of LeRoy *et al.* [11], which classify patients as limited or diffuse. This system is used as entry criteria for trials of new treatments. However,

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KEY POINTS

- This article summarizes previous iterations of SSc subset criteria.
- This article provides an overview of the development and validation of new SSc subset criteria.
- This article highlights current thinking about the construct underlying SSc subsets in the modern era.

many patients do not fit this system [12]. As a consequence, only patients with established disease have access to trials; and patients with early or limited disease are denied access to trials of potentially life-saving treatment [6▪]. Some have felt that individuals with the limited subset have been neglected [13]. There have been calls for development of a new subset classification system, which take into consideration other aspects of the disease [12,14]. There has also been increasing rigor in the methodology for the development of classification criteria. Recommendations for the development of classification criteria are considered the current standard [15,16]. An international collaborative effort is underway, using novel methods to develop new classification criteria to identify distinct subsets of SSc patients.

DEVELOPMENT OF NEW SYSTEMIC SCLEROSIS SUBSET CRITERIA

In phase 1, a systematic review of the literature is being conducted to identify systems of classification of SSc subsets; and comparatively evaluate them against standards of measurement science. In phase 2, a content analytic study evaluates the purpose and utility of SSc subset criteria, strengths and limitations of existing SSc subset criteria, and identifies areas of improvement. In phase 3, two data-driven approaches will be undertaken. Using similarity network fusion, homogeneous subsets of SSc patients will be identified through the combination of demographic, physiologic, immunologic and clinical data. Trajectory analysis will also be conducted to assess if differences in disease trajectory can inform the identification of SSc subsets. The goal is to define a system of criteria that produces a measure of the relative probability that a particular case falls within a distinct subset of SSc. In phase 4, consensus methods will be used to solicit input from the SSc international community to refine the draft system. Finally, in phase 5, the subset criteria system will be tested in a validation cohort, and compared against preexisting subset systems Fig. 1.

PREVIOUS SYSTEMIC SCLEROSIS SUBSET CRITERIA

A 2007 systematic review of the published literature found 13 unique systems of identifying clinically based SSc subsets [4,10,11,17–27] Table 1.

On the basis of their judgment, Goetz and Berne [28] proposed a two-subset criteria to classify a case series of patients in South Africa. Although not incorporated in the criteria, they were among the first to identify gastrointestinal involvement as a disease manifestation.

Tuffanelli and Winkelmann [18] reported a two-subset criteria to classify patients as acrosclerosis and diffuse, based on the extent of skin involvement and the presence of Raynaud's phenomenon. These criteria were an improvement compared to its predecessors as they included Raynaud's phenomenon as a differentiating manifestation. The authors reported good predictive validity as patients with diffuse disease have decreased survival [18].

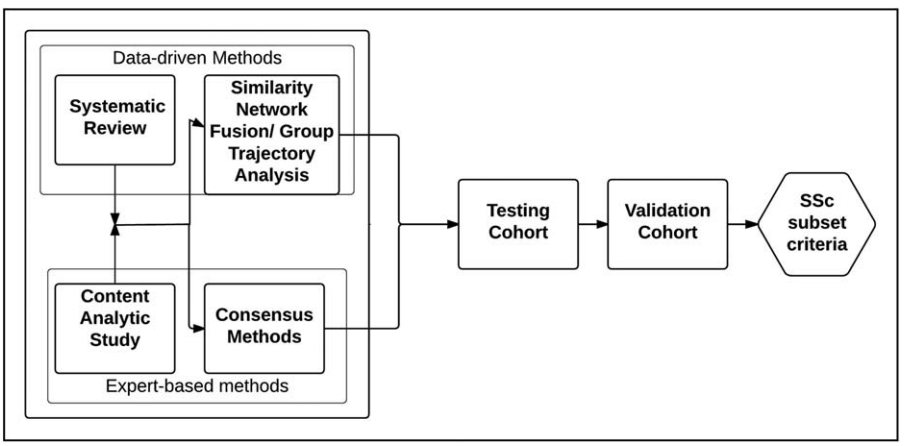

FIGURE 1. Overview of multiphase development and validation of new SSc subset criteria. SSc, systemic sclerosis.

Table 1. Summary of previous iterations of systemic sclerosis subset criteria

Reference	SSc subsets
Goetz [17]	Two subsets: acrosclerosis and diffuse: based on skin thickening limited to extremities or includes trunk
Tuffanelli and Winkelmann [18]	Two subsets: acrosclerosis: RP, acral skin involvement; diffuse SSc: no RP, skin involvement beginning centrally
Winterbauer [19]	CRST syndrome: calcinosis, RP, sclerodactyly, telangiectasia
Barnett and Coventry [20]	Three subsets: limited, moderate, extensive, based on skin involvement of the fingers only, limbs and face, and involvement of the trunk, respectively
Rodnan *et al.*[21]	Three subsets: classical disease involving skin of the trunk, face and proximal extremities, and early involvement of esophagus, intestine, heart, lung and kidney; CREST syndrome; and overlap syndromes including sclerodermatomyositis and mixed connective tissue disease
Giordano *et al.*[22]	Six subsets: I: sclerodactyly only; II: sclerodactyly and skin involvement of neck, lower eyelid or axillae; III: skin involvement of hands and forearms ± legs ± face; IV: group III and arm and/or thigh skin involvement; V: group III and thorax; VI: group III and/or IV and/or V and the abdomen
Giordano *et al.*[22]	Three subsets: limited: skin involvement of fingers, face, neck, axillae; intermediate: skin involvement proximal to fingers; diffuse: truncal skin involvement
Holzmann *et al.*[23]	Five subsets (types I–IV) based on the presence/absence of RP, sclerosis, extracutaneous manifestations, ANA
Masi [24]	Three subsets: digital: skin involvement of fingers or toes but not proximal extremity or trunk; proximal extremity: proximal extremities or face but not trunk; truncal: thorax or abdomen
LeRoy [11]	Two subsets: diffuse cutaneous SSc: onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse GI disease, myocardial involvement; absence of ACA, abnormal NC; limited cutaneous SSc: RP for years, skin involvement limited to hands, face, feet, forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of ACA, abnormal NC
Scussel-Lonzetti *et al.* [25]	Four subsets: normal skin, limited: skin involvement restricted to fingers, with RP, calcinosis, esophageal involvement and telangiectasia; intermediate: skin involvement of arms proximal to metacarpophalangeal joints, but not trunk; diffuse: skin involvement of the trunk
Ferri *et al.*[26]	Four subsets: sine scleroderma SSc: absence of cutaneous involvement with visceral involvement, NC changes and autoantibodies; limited cutaneous: skin involvement of fingers with or without involvement of neck, face and axillae; intermediate cutaneous: skin involvement of upper and lower limbs, neck and face without truncal involvement, diffuse cutaneous: distal and truncal skin involvement
Maricq *et al.*[27]	Six subsets: diffuse, intermediate, digital, scleroderma sine scleroderma, undifferentiated connective tissue disease with scleroderma, CREST syndrome

ACA, anticentromere antibody; ANA, antinuclear antibody; CREST, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia; CRST, calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasia; GI, gastrointestinal; ILD, interstitial lung disease; NC, nailfold capillaries; PAH, pulmonary arterial hypertension; RP, Raynaud's phenomenon; SSc, systemic sclerosis.
Adapted from Table 1 [10].

Winterbauer [19] described patients with CRST (calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasia) as a benign subset of SSc. Subsequent investigators have added 'E' (esophageal dysmotility). This description was intended for clinical practice and gained popularity, as it is easy to use. However, these criteria poorly discriminate between patients with mild, moderate and extensive skin involvement as all subtypes may have four or more Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia (CREST) manifestations [29].

Barnett and Coventry [20] developed a three-subset criteria set, based on the degree of skin involvement, to describe subsets of SSc in a clinical setting. These criteria have good divergent validity when compared to scleroderma-specific antibodies. Zero (0%), seven (31.8%) and five (55.5%) individuals with types I–III, respectively, were Scl-70 antibody-positive [30]. This criteria set has good predictive validity wherein type 1 disease has the longest survival, type 2 has intermediate survival and type 3 has the shortest survival [30].

Rodnan *et al.* [21] developed a three-subset criteria. However, the subsets were not mutually exclusive [31]. Thus, there may be confusion in their application, which may result in misclassification error [10].

Giordano *et al.* [22] proposed a three-subset (and a six-subset) criteria, based on the degree of skin involvement, for the classification of patients with SSc in the hospital setting. Both criteria sets have poor divergent validity with regard to scleroderma-specific antibodies, and poor predictive validity with regard to survival [22].

Masi [24] proposed a three-subset criteria set classifying patients based on skin involvement. The intent of this classification was to clarify terminology because of confusion between the three-subset criteria of Barnett *et al*. [29] and Giordano *et al*. [22].

Holzmann *et al.* [23] developed a five-subset criteria based on skin involvement, presence of Raynaud's phenomenon, internal organ involvement and the presence of antinuclear antibodies. This set of criteria was intended to be comprehensive as it includes subsets of patients without skin involvement, localized skin involvement and/or immune activation, thereby improving face validity.

LeRoy *et al.* [11] proposed a two-subset criteria to improve the nomenclature of SSc, identify patients at risk of visceral complications and classify homogeneous groups of patients for clinical research. Criteria development was based on the judgment of an expert panel. Diffuse SSc is frequently associated with tendon friction rubs, antitopoisomerase I and poor prognosis, whereas limited SSc is frequently associated with calcinosis, telangiectasia, antikinetochore antibody and pulmonary hypertension [31]. Human leukocyte antigen (HLA) DR1, DR5, DR6 and Bw35 occur more commonly in patients with limited SSc; however, only HLA-DR1 had statistical significance [32]. Patients classified as having diffuse SSc have often Scl-70 antibodies present and show nucleolar pattern on antinuclear antibody staining, and have anticentromere antibodies less frequently than patients classified as having limited SSc [22]. Although the feasibility of the criteria is limited to clinicians experienced in skin examination, auscultation of friction rubs and capillaroscopy, it has been successfully applied in multinational, tertiary-care settings [33]. Four studies demonstrated strong predictive validity for survival where patients with limited SSc have better survival than patients with diffuse SSc [22,26,31,34]. However, these criteria poorly predict lung involvement as restrictive lung disease occurs in 30% of patients with limited SSc and 50% of patients with diffuse SSc ($P = 0.16$) [35].

Scussel-Lonzetti *et al.* [25] developed a four-subset variation on the criteria of Barnett, Giordano and Ferri that classifies patients based on extent of skin involvement. The criteria have good predictive validity; the cumulative survival rates in the four subsets from normal to diffuse are 90.6, 79, 75.9 and 62.4% at 10 years, respectively [25]. Ferri *et al.* [26] also developed a four-subset criteria based on the extent of skin involvement. The purpose of the criteria is to identify subsets for an Italian descriptive and prognostic study. The criteria have good predictive validity, with 10-year survival rates in the limited, intermediate and diffuse subsets of 78.3, 65.5 and 52.2%, respectively [26]. Statistically significant differences between limited cutaneous SSc (lcSSc) versus intermediate cutaneous SSc and lcSSc versus diffuse cutaneous SSc (dcSSc) in the frequency of hypermelanosis, sicca syndrome, esophageal involvement and lung involvement have been demonstrated. However, no significant statistical differences were found in these disease manifestations when the lcSSc subset is compared to the dcSSc subset [26].

Maricq *et al.* [27] proposed the most comprehensive criteria set that classifies patients into six mutually exclusive subsets. The purpose of the criteria is to develop a comprehensive classification for all scleroderma spectrum disorders for use in clinical research. These criteria have incrementally improved face validity over other criteria sets as they incorporate subsets within the spectrum of SSc (scleroderma sine SSc, undifferentiated connective tissue disease with scleroderma) that have previously been excluded. The feasibility of applying these criteria is a concern; these criteria have been criticized for being 'too complicated' Wollheim [36] and thus feasible for use only by clinicians competent in SSc skin examination and capillaroscopy [10].

An updated literature search is underway to ensure that no other SSc subset systems have been missed.

UTILITY OF SYSTEMIC SCLEROSIS SUBSETS IN THE MODERN ERA

In an era of earlier diagnosis [37,38], antibody profiling [39,40], genetics [41], biomarkers [42] and personalized medicine [22], the construct of 'SSc subsets' may have evolved. As part of the development of new subset criteria, it is important to evaluate the construct underpinning the utility of SSc subsets, and the strengths and limitations of previous iterations of SSc subset criteria. The new criteria will build upon the strengths and attend to the limitations. For this reason, a content analytic study was undertaken to evaluate the construct of SSc subsets in the modern era [43▪].

Thirty experts from 13 countries underwent semistructured interviews. Using a content analytic approach, the interview transcripts underwent an iterative process with text deconstructed to single thought units until a saturated conceptual framework was developed. Three thematic clusters regarding the purpose of SSc subsetting were identified. Experts stated that SSc subsetting is important for facilitating research and communication; guiding patient management; and informing prognosis (prediction of internal organ involvement and survival).

The strength of the limited/diffuse system was its ease of use; however, 10% of participants stated that this system had marginal value. Shortcomings of the diffuse/limited classification were the risk of misclassification, predictions and generalizations did not always hold true, and that the elbow or knee threshold is arbitrary. Eighty-seven percentage of experts use more than two subsets including: antibody-determined subsets, speed of progression (rapid progressors versus slow progressors), age of onset (geriatric versus juvenile), scleroderma sine scleroderma and overlap conditions. In the modern era, a number of factors underlie the construct of SSc subsets. Considerations for the next phase of subset criteria development include rate of change and hierarchal clustering (e.g. limited/diffuse, then by antibodies).

DATA-DRIVEN SUBSET IDENTIFICATION

Factors that may affect SSc subsets include skin and organ involvement, antibodies, physiology, imaging and quality of life. Traditional analytic strategies evaluate only some of these data sources at a time, require preselection of data as a starting point (introducing bias) and exclude other important data. A novel, data-driven approach to utilize all sources of data is similarity network fusion (SNF) [44]. SNF is a methodology that facilitates integration of data that reflect the heterogeneity of biological processes and phenotypes leading to the identification of homogeneous subtypes [44]. This approach is completely data driven, thereby potential reducing the risk of bias(es) introduced by preconceived notions.

Contemporaneously, group-based trajectory analyses will be used as a method to identify SSc subsets. This novel approach identifies groups of patients who have a similar progression over time, and identifies disease characteristics that predict group membership. These approaches are currently underway, and the results will be compared.

FINAL PHASES OF SUBSET CRITERIA DEVELOPMENT

The draft system of subset criteria will then be presented to the SSc community. Using consensus methods, input on the draft system will be solicited and refinements made [45]. Using a derivation cohort of international SSc individuals, iterative changes to the draft system will be tested. The final subset classification system will be tested using a validation cohort of international SSc individuals. The sensitivity and specificity of the new system will be evaluated and compared against the LeRoy *et al.* [11] 1988 criteria.

In recent years, there has also been an improvement in our understanding of the molecular basis of SSc. This has led to consideration of SSc subsets based on diseased tissue molecular classification [14]. The recent evaluation of molecular targeting therapies (e.g. biologic response modifiers) adds to the value of molecular classification to assist recognition of those who may respond to therapy [46▪]. The next generation of subset classification criteria should consider integration of both molecular and clinical classification in the identification of subsets. Indeed, much can be learned from oncology in this regard.

CONCLUSION

Classification criteria are a critical component of rheumatic disease research. Previous iterations of SSc subset criteria have served the global community well; however, the time has come for a new iteration of SSc subset criteria, which reflect our understanding of the disease in the modern era. Using a combination of data-driven and expert-based innovative methodologies, a large international collaborative effort is underway. It is anticipated that this new system will shift the paradigm of how we study novel therapies in SSc.

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Conflicts of interest

There are no conflicts of interest.

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This article summarizes the current state of molecular and clinical classification in SSc.

Cardiac complications of systemic sclerosis and management: recent progress

Vibhav Rangarajan, Richard Matiasz, and Benjamin H. Freed

Purpose of review
Cardiac complications in systemic sclerosis (SSc) continue to be a leading cause of death in this patient population. Early recognition and treatment of the cardiac diseases commonly associated with SSc is essential.

Recent findings
Recent studies have confirmed the significant increase in mortality in SSc patients with cardiac involvement. Electrocardiography and echocardiography (2DE) continue to play a major role in screening and diagnosing cardiac manifestations such as arrhythmias or biventricular dysfunction, respectively. Novel techniques such as myocardial strain imaging on 2DE and T1 mapping on cardiovascular magnetic resonance are useful for detecting subclinical cardiac abnormalities, but the clinical relevance of these findings is still not known. An expert consensus was recently published to help establish best practice guidelines on management of cardiac complications in SSc, but data supporting these recommendations remain limited.

Summary
Recent studies continue to enhance our understanding of SSc cardiac disease. Although the results of these studies help lessen the ambiguity of managing and treating these patients, there is still much more research to be done.

Keywords
cardiovascular magnetic resonance, echocardiography, microvascular disease, myocardial fibrosis, systemic sclerosis

INTRODUCTION

Cardiac complications from systemic sclerosis (SSc) are thought to occur early in the disease course [1]. Cardiac complications can either be primary [microvascular coronary disease with resultant myocardial ischemia, myocardial fibrosis, myocarditis, left ventricular or right ventricular systolic and diastolic dysfunction, conduction abnormalities, pericardial disease] or secondary to other SSc complications [pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) [2▪▪] or kidney disease] [3]. Early detection and monitoring of myocardial involvement are integral to SSc management, as cardiovascular [4] involvement is known to be a poor prognostic indicator when present. Meta-analyses have reported that up to 29% of deaths in SSc patients were due to cardiac disease [5,6]. In addition, numerous studies have reported increased mortality related to individual types of cardiac involvement [6–8]. In this review, we discuss the most recent data regarding the epidemiology, diagnosis and management of cardiac complications of SSc (Table 1).

EPIDEMIOLOGY

The prevalence of cardiac involvement in SSc is difficult to estimate given the wide variety of cardiac complications that can occur, along with the variability in the techniques used to diagnose them. As a result, the rates of cardiac involvement depend on which cardiac manifestations are present, with

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KEY POINTS

- Cardiac involvement is common in scleroderma with an unclear overall prevalence due to significant heterogeneity in presentation.
- Left ventricular or right ventricular dysfunction may be due to myocardial fibrosis or overt myocarditis and evaluation should include echocardiography with tissue Doppler imaging, speckle tracking echocardiography, CMR with T1 mapping and extracellular volume evaluation, and natriuretic peptide measurements.
- Arrhythmias are common and are thought to be due to a combination of microvascular injury, fibrosis in the conduction system and myocardium, and autonomic dysfunction.
- Pericardial involvement is also common, but effusions should be managed conservatively and considered a sign of potentially worsening disease.
- Pulmonary arterial hypertension can present late but is highly morbid. Screening is required and new drugs may improve patient symptoms and even prolong life.

previous studies reporting a prevalence ranging between 7 and 44% [9▪▪,10▪]. The risk factors for developing cardiac involvement include diffuse cutaneous SSC, male sex, African–American ethnicity, older age at disease onset, presence of tendon friction rubs, peripheral myositis and worse quality-of-life scores. There are no new data concerning risk factors for cardiac complications in SSc.

LEFT VENTRICULAR DYSFUNCTION

Left ventricular dysfunction in SSc patients is the result of myocardial fibrosis or myocarditis and can manifest as diastolic dysfunction, systolic dysfunction or restrictive cardiomyopathy. Patients with SSc may be at an increased risk for atherosclerosis compared with the general population [11], though this may be related to microvascular disease rather than epicardial coronary artery disease (CAD) [12▪]. Accordingly, a consensus statement by the UK Systemic Sclerosis Study group has recommended that all SSc patients be assessed for the presence of both

Table 1. Prevalence, diagnosis and treatment of cardiac manifestations in systemic sclerosis

Cardiac manifestation	Prevalence	Evaluation	Therapy
LV systolic dysfunction	1.4–7%	Natriuretic peptides, 2DE, SPECT, PET, CMR	GDMT ± CRT, mechanical support devices, cardiac transplantation
LV diastolic dysfunction	17.7–51.9%	Natriuretic peptides, 2DE, TDI, STE, CMR	Symptomatic treatment (i.e. diuretics), adequate blood pressure control
Primary RV dysfunction	38%	2DE, TDI, STE, CMR	Symptomatic treatment (i.e. diuretics), Digoxin, invasive haemodynamic testing to rule out pulmonary arterial hypertension
Microvascular coronary artery disease	>60%	SPECT, PET, CMR	Vasodilators (Dihydropyridine calcium channel blockers, ACE inhibitors /angiotensin receptor blockers), statin, ranolazine for refractory angina, lifestyle modifications
Epicardial coronary artery disease	25%[a]	Coronary angiography, coronary calcium score and Coronary CT angiography for screening	Percutaneous or surgical coronary revascularization, aspirin, statin, lifestyle modifications
Myocarditis	Rare	2DE, CMR, endomyocardial biopsy	Corticosteroids, cyclophosphamide, mycophenolate mofetil, azathioprine, GDMT if LV systolic dysfunction
Pericardial effusion	15–72%	2DE with Doppler to look for echo evidence of cardiac tamponade	Treat only if symptomatic; rule our renal crisis; cautious diuretics in the setting of right heart failure; Pericardiocentesis if severely symptomatic/cardiac tamponade; pericardiocentesis contraindicated in patients with significant pulmonary arterial hypertension or RV dysfunction
Pericarditis	1.9–9%	CMR, cardiac CT, 2DE (with Doppler and TDI), simultaneous right and left heart catheterization	NSAIDs and colchicine; If constriction, then treat right heart failure symptoms with diuretics, sodium and fluid restriction; pericardial stripping surgery is contraindicated in most cases
Bradyarrhythmia	Rare	EKG, Holter and event monitor, ILR	Pacemaker according to standard guidelines
Tachyarrhythmia	17–28%	EKG, Holter and event monitor, ILR	Nondihydropyridine calcium channel blockers, avoid beta-blockers if Raynaud's present, cautious use of antiarrhythmics consider ablation or ICD in select patients

2DE, 2D echocardiography; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; PET, positron emission tomography; SPECT, single-photon emission computed tomography; STE, speckle tracking echocardiography; TDI, tissue Doppler imaging.
[a]Defined as coronary artery calcium score greater than 101.

Systemic Sclerosis related Cardiomyopathy (SSc-CM) and CAD [13▪▪].

Myocardial fibrosis is commonly associated with SSc and may present subclinically. Myocarditis, which can also present subclinically, has been occasionally reported and cellular inflammatory changes have been identified on endomyocardial biopsy [3,14]. Overt left ventricular systolic dysfunction is uncommon, and when present is usually the result of CAD [13▪▪,15]. Left ventricular diastolic dysfunction is more common [16], and is associated with increased disease duration and mortality [8,17].

Evaluation

There are several methods for evaluating left ventricular dysfunction. These include laboratory testing, 2D echocardiography (2DE), nuclear imaging and cardiac magnetic resonance (CMR).

Laboratory testing

Brain natriuretic peptide (BNP and NT-proBNP) levels may be elevated due to primary SSc-CM [18], but elevation of these markers is nonspecific and may also be increased secondary to other SSc-related complications or cardiac disease states unrelated to SSc. Troponin and Creatine Kinase-MB are not typically elevated in SSc-CM despite myocardial fibrosis, and, if elevated, they should raise suspicion for myopericarditis, acute coronary syndrome or pulmonary embolism [13▪▪].

Echocardiography

2DE along with tissue Doppler imaging is recommended in the evaluation and screening of all patients with SSc. This is particularly true in the setting of prestem cell transplantation cardiac assessment [19–21]. Meune *et al.* [22▪▪] compared 212 individuals with SSc to 50 controls and found reduced (but not abnormal) left ventricular ejection fraction, reduced E/A ratio (a sign of abnormal diastolic relaxation) and reduced tissue Doppler at the mitral annulus (a measure of the velocity of myocardial tissue as it relaxes and is associated with diastolic function) in patients with SSc. Furthermore, presence of SSc was shown to be associated with elevated left atrial pressures, as assessed by E/e' ratio, and increased left atrial size [23]. Speckle-tracking echocardiography (STE) for the measurement of left ventricular myocardial strain was shown to be associated with myocardial fibrosis in non-SSc studies and therefore may be of value in the assessment of subclinical SSc-CM [24,25].

Nuclear imaging

Nuclear imaging techniques such as thallium-201 single-photon emission computed tomography (SPECT) and PET are sensitive tools for the detection of abnormal myocardial perfusion and microvascular abnormalities [3]. Traditionally, these tests were commonly used for detection of myocardial perfusion abnormalities in SSc [26]. However, CMR is preferred where available due to the lack of radiation exposure and the additional information regarding chamber volumes and presence of myocardial fibrosis.

Cardiac magnetic resonance

CMR should be considered in patients considered to be high risk for or exhibiting signs or symptoms of SSc-CM [13▪▪,27▪▪]. CMR is also useful in cardiac assessment of SSc patients prior to stem cell transplantation to accurately determine left ventricular volumes and function [21,28]. Late gadolinium enhancement (LGE) is the gold standard for detecting focal myocardial fibrosis, which has been associated with poor cardiac reserve, increased risk for arrhythmia and left ventricular dysfunction [19,21,23]. A patchy, mid-wall, linear pattern of LGE involving the basal and mid left ventricular segments may be present in SSc [3,12▪,17,21,23,27▪▪,29], which is different from the typical regional subendocardial or transmural LGE pattern present in myocardial infarction. A study by Rodriguez-Reyna *et al.* [12▪] found that myocardial fibrosis was present in 45% of 62 patients with SSc, was more prevalent in dcSSc than lcSSc and was more frequently found in the basal septal segments of the left ventricle (LV). Furthermore, it was concluded that microvascular disease is common in SSc, as adenosine stress CMR showed circumferential subendocardial perfusion defects in 79% of patients [12▪].

T2-weighted imaging can detect myocardial oedema with mild sensitivity [30], with focal areas of oedema significantly increased in SSc patients compared with controls [23]. T1 mapping and extracellular volume (ECV) measurements are superior to LGE for detecting diffuse myocardial fibrosis [27▪▪,30–32]. SSc patients have higher average myocardial T1 values, larger areas of myocardial involvement as detected by native T1 mapping and an expanded ECV compared with controls [23,33,34▪] in the absence of significant left ventricular dysfunction. Therefore, T1 mapping and ECV may be useful in the detection of subclinical SSc-CM, perhaps as an early screening tool before the development of overt left ventricular systolic dysfunction [23,33,34▪] (Fig. 1).

CMR is very sensitive in the detection of regional perfusion and coronary flow reserve, which may limit its prognostic value by detecting clinically irrelevant abnormalities [19]. Markers of impaired diastolic function including impaired CMR-derived peak systolic circumferential strain, peak diastolic

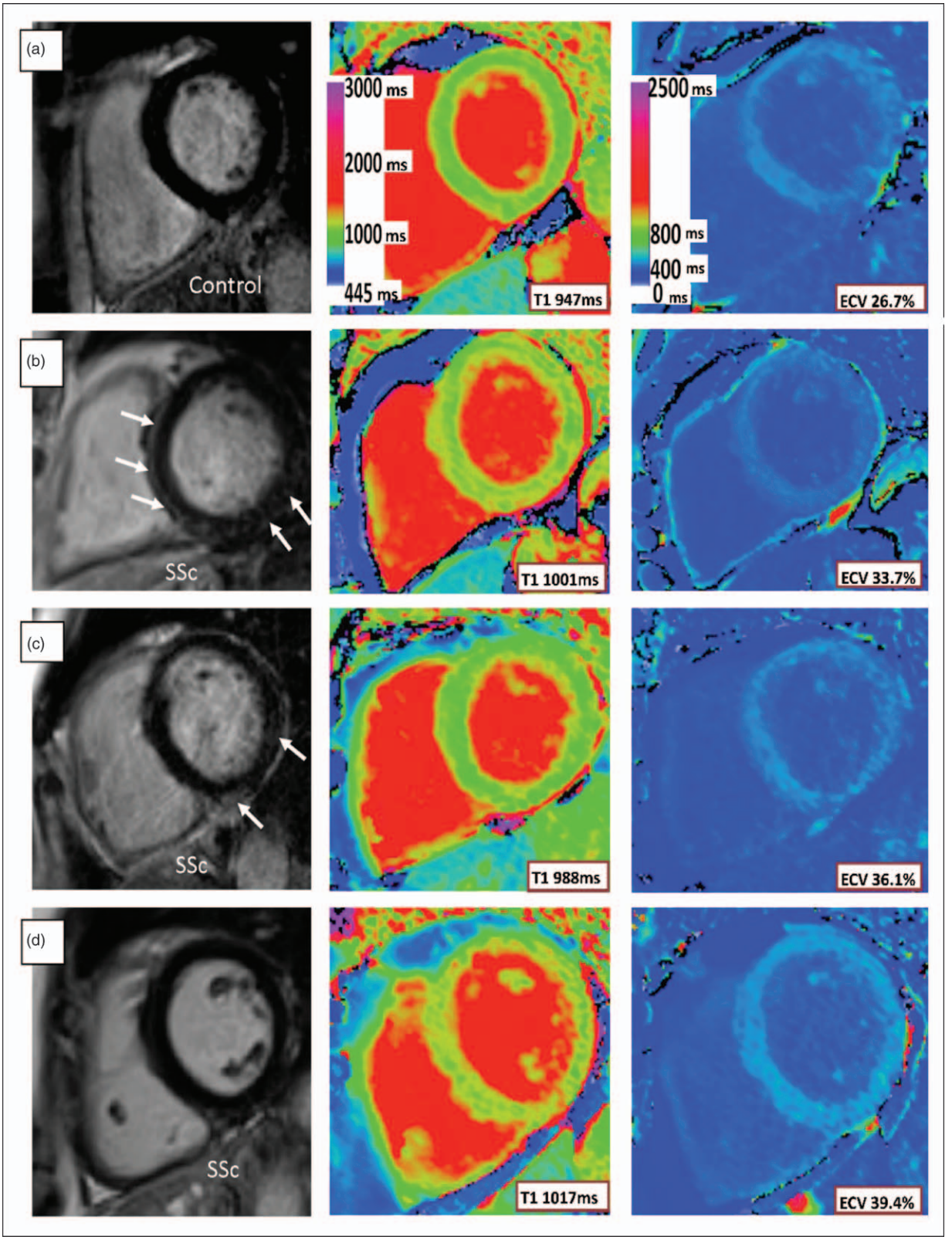

FIGURE 1. Representative examples of pre and postcontrast T1 maps with corresponding LGE in systemic sclerosis and controls. Top panel (a): normal control with no LGE, native T1 947 ms, postcontrast T1 514 ms, ECV 26.7%; Second panel (b): SSc patient with linear septal and patchy basal inferolateral LGE, native T1 1001 ms; postcontrast T1 453 ms; ECV 33.7%; Third panel (c): SSc patient with small areas of mid-wall inferior and lateral LGE, native T1 988 ms, postcontrast T1 439 ms, ECV 36.1%; Fourth panel (d): SSc patient with no LGE, native T1 1017 ms, postcontrast T1 421 ms, ECV 39.4%. Note the scale change between precontrast and postcontrast T1 maps. Source: Previously published with permission by authors from Ref. [23]. Publisher is BioMed Central.

strain rate and increased left atrial volumes, are more prevalent in SSc patients than controls [23,33].

Therapy

In SSc patients with evidence of myocardial fibrosis without heart failure, vasodilators such as dihydropyridine calcium channel blockers and ACE inhibitors (ACEI) remain a mainstay of therapy [3]. In SSc patients with evidence of myocarditis and heart failure symptoms, immunosuppressants (corticosteroids, cyclophosphamide, mycophenolate mofetil, azathioprine) led to clinical improvement, normalization of cardiac enzymes and improvement in CMR findings [13▪▪,14,35]. Steroids or immunosuppressive therapy can be considered in SSc patients with myocardial fibrosis if there is a progressive decline in function over time [13▪▪].

Standard guideline-directed medical therapy should be employed in patients with left ventricular systolic dysfunction (beta-blockers, ACEI, aldosterone antagonists); however there is less evidence for these therapies in left ventricular diastolic dysfunction. Of note, beta-blockers can exacerbate Raynaud's phenomena by acting as a peripheral vasoconstrictor and should be used with caution. Cardiac resynchronization devices, mechanical support devices and transplantation should be offered according to standard guidelines. CAD should be investigated and treated as in the general population [13▪▪].

RIGHT VENTRICULAR DYSFUNCTION

Right ventricular dysfunction in SSc may be the result of primary abnormalities of the right ventricle (RV), secondary to the effects of PAH, or due to mixed cause. There is evidence that the RV may be affected early in the course of the disease [36,37▪▪] and myocardial fibrosis may be responsible for diastolic and systolic right ventricular dysfunction [22▪▪,38▪]. This fibrosis can have a significant impact on the haemodynamics of the right heart, resulting in right ventricular dysfunction and elevated right atrial pressure in the setting of a relatively normal pulmonary artery (PA) pressure [38▪]. Accordingly, right ventricular dysfunction may contribute to the poorer outcomes that are observed in SSc-PAH compared with idiopathic PAH [39]. In addition, right ventricular dilatation and reduced right ventricular function have been shown to correlate with the onset of heart failure symptoms and mortality [5,26,28,38▪].

Evaluation

2DE and CMR are the most common imaging modalities used for evaluating right ventricular dysfunction.

Echocardiography

Evidence of right ventricular dysfunction on 2DE include right ventricular dilatation (Fig. 2a), flattening of the interventricular septum ('D-sign') suggesting right ventricular pressure or volume overload, and reduced semi-quantitative measures of right ventricular function [i.e. tricuspid annular systolic planar excursion (TAPSE) and fractional area change (FAC)]. Significant right ventricular dysfunction has been defined as TAPSE less than 1.8 cm and FAC less than 35% [21,28,37▪▪]. Meune *et al.* [22▪▪] showed reduced right ventricular systolic and diastolic function in SSc patients compared with controls. Right ventricular dysfunction was more common than left

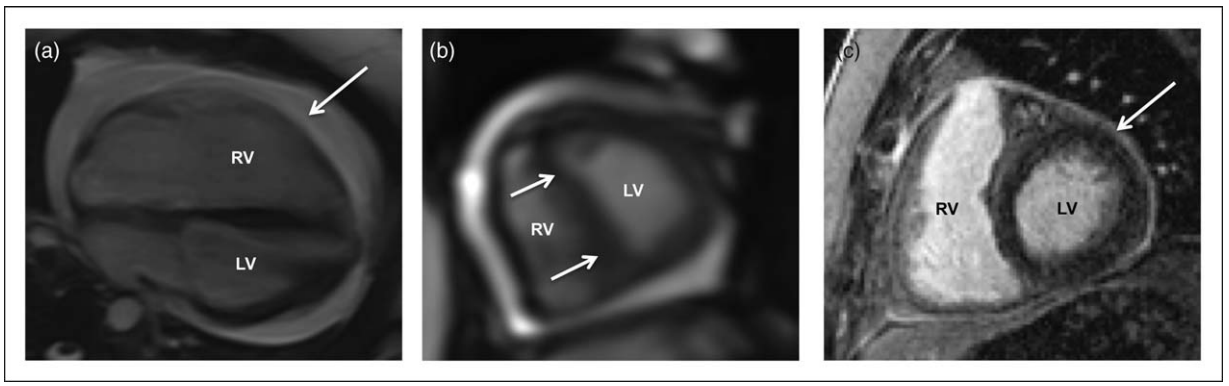

FIGURE 2. Cardiac manifestations of systemic sclerosis on cardiac magnetic resonance. (a) Four-chamber view of the heart with dilated right ventricle and small to moderate size pericardial effusion (arrow); (b) Short-axis real-time imaging of the heart showing dynamic interventricular septal flattening (arrow) with deep inspiration. Note decrease in spatial resolution with this sequence; and (c) Short-axis view of the heart with thickened and contrast-enhanced pericardium (arrow) consistent with pericarditis.

ventricular dysfunction in SSc patients and existed independently of the presence of PAH [22▪▪].

Most 2DE measures of right ventricular function are limited by the complex shape of the RV, load dependency and suboptimal reproducibility. STE avoids some of these pitfalls, and may be useful in the detection of subclinical right ventricular dysfunction [40]. Mukherjee *et al.* [37▪▪] investigated 138 patients with SSc compared with 40 control individuals and found that TAPSE was similar between the groups, while mean right ventricular FAC was statistically different between the groups. Both parameters were still within normal limits. Right ventricular free wall longitudinal strain, as measured by STE, was found to be significantly impaired in SSc patients, independent of PASP and SSc phenotype. Furthermore, a pattern of decreased strain magnitude in the apical and mid segments and increased strain magnitude in the basal segments was observed [37▪▪]. In small studies, 3D right ventricular strain has been shown to be an independent predictor of death [40,41].

Cardiac magnetic resonance

CMR does not require a suitable acoustic window for measuring right ventricular size, geometry and function, and, as a result, has excellent reproducibility for evaluation of the RV as compared with 2DE. CMR may be used to look for evidence of right atrial and right ventricular dilatation, right ventricular systolic dysfunction and interventricular septal flattening in SSc patients. Although CMR cine imaging provides excellent spatial resolution, free breathing sequences provide real-time physiologic assessment of the interventricular septal dynamics (Fig. 2B). These sequences are particularly helpful in understanding the ability of the RV to handle volume overload prior to undergoing stem cell transplantation. Whereas some interventricular septal flattening is expected during inspiration to accommodate the increased volume of blood, significant septal flattening is indicative of a vulnerable or dysfunctional RV. Evaluation of myocardial fibrosis with LGE is challenging due to the thin-walled RV. Therefore, high-resolution T1 mapping may be useful to detect diffuse right ventricular fibrosis in the absence of PAH [21,28,38▪].

Therapy

There are limited data on therapeutics in primary right ventricular dysfunction and SSc, and therefore treatment is empiric with digoxin and diuretics as needed [26]. Mineralocorticoid receptor antagonists such as spironolactone might be helpful due to their antifibrotic properties, but there are no substantial data to support this.

ARRHYTHMIAS

The mechanism for conduction system disease and arrhythmia formation in SSc is thought to be due to a combination of microvascular injury, fibrosis in the conduction system and myocardium, and autonomic dysfunction [13▪▪,42,43]. The prevalence of conduction defects in SSc as detected by electrocardiogram (EKG) and 24-h Holter has been reported anywhere between 4 and 51% [7,9▪▪]. The presence of right bundle branch block (RBBB) is an independent predictor of mortality [7].

Evaluation

Arrhythmias are assessed with EKG and cardiac monitoring if needed. 2DE and CMR can aid in the detection of cardiac structural or functional disease that may contribute to the arrhythmia detected.

Electrocardiogram

Twelve-lead EKG should be performed in all patients with SSc, even if asymptomatic, to screen for conduction system abnormalities [13▪▪]. The majority of SSc patients have a normal resting EKG; however, many patients develop arrhythmia with exercise [12▪,38▪]. In these patients, an exercise treadmill EKG may be helpful in identifying exertional arrhythmia [3]. The presence of myocardial fibrosis on CMR or suspicion of arrhythmia based on symptomatology should prompt more intensive screening with ambulatory ECG monitoring or implantable loop recorder [13▪▪,43].

Ambulatory electrocardiogram monitoring

Ambulatory EKG monitoring is more sensitive at detecting conduction defects and arrhythmias than 12-lead EKG [3]. De Luca *et al.* [44▪] studied 100 patients with SSc who underwent 24-h Holter monitoring. An abnormality was identified in 56% of patients, of whom 24% were found to have frequent premature ventricular complexes (PVCs). The PVC burden correlated with high-sensitivity troponin T levels and inversely correlated with left ventricular ejection fraction. In addition, seven patients in this study suffered sudden cardiac death (SCD) or required implantable cardiac defibrillator (ICD) placement, with a cutoff of more than 1190 PVCs in 24 h found to be 100% sensitive and 83% specific for these events [44▪]. Accordingly, ambulatory ECG monitoring may help identify SSc patients who

are at a high risk for developing SCD and therefore may benefit from ICD implantation.

Two-dimensional echocardiography and cardiac magnetic resonance

All SSc patients, regardless of the presence of arrhythmias, should undergo routine 2DE to evaluate cardiac structure and function. CMR may be further helpful in determining the risk for developing conduction system abnormalities and arrhythmias in SSc patients. Detection of focal myocardial fibrosis or scar by LGE is associated with an increased risk of arrhythmia [21,28].

Other diagnostic modalities

ECG abnormalities are also associated with septal or anteroseptal thallium perfusion defects and impaired strain on 2DE [43,45]. Invasive electrophysiological studies are generally performed in accordance with standard practice guidelines [13▪▪].

Therapy

Treatment of conduction system defects and arrhythmias in patients with SSc should follow the general cardiology guidelines for the management of arrhythmias [13▪▪]. Many antiarrhythmic therapies should be used with caution in SSc patients due to potential adverse reactions. Ablation therapy, ICD therapy and pacemakers should all be considered according to general cardiology practice guidelines. Bernardo *et al.* [47] reported a case series on 10 patients with SSc in whom ICDs were implanted. Thirty percent of these patients were noted to have ventricular arrhythmias that were successfully terminated by the device during a 36-month follow-up [46,47].

PERICARDIAL DISEASE

Pericardial involvement in SSc is common but not often symptomatic [48]. Pericardial complications include pericardial inflammation, effusion, tamponade, fibrinous pericarditis, pericardial adhesions and constrictive pericarditis (CP) [49]. The presence and size of a pericardial effusion conveys a significant risk but rarely do effusions progress to requiring drainage [50,51]. Many effusions occur in the setting of PAH [52]. Drainage of effusions or pericardial window creation can carry significant mortality [53]. Constrictive pericarditis can be challenging to diagnose in SSc. The clinical features of constriction (dyspnoea, right-sided heart failure, fatigue) overlap with complications of SSc including restrictive cardiomypathy. A degree of clinical suspicion combined with a multimodality approach is important for diagnosis [54].

Evaluation

Evaluation of pericardial disease includes a variety of tests including EKG, 2DE, computed tomographic (CT) imaging, CMR and possibly catheterization.

Electrocardiogram

The EKG will commonly reveal diffuse ST segment elevation and PR depression in pericarditis [55]. In pericardial effusions, low voltages or electrical alternans can sometimes be seen [56▪▪].

Two-dimensional echocardiography

In addition to visualization of pericardial effusion and pericardial thickening, 2DE is useful for haemodynamic assessment for tamponade physiology and ventricular interdependence. Abnormal ventricular septal motion exaggerated during inspiration is amongst the most obvious signs. Tissue Doppler imaging can assist with differentiating restrictive and constrictive cardiomyopathy, with e' velocity less than 7 cm/s supporting a restrictive diagnosis [55,56▪▪].

Computed tomography/cardiac magnetic resonance

CT is sensitive for pericardial fluid, and allows for a thorough anatomic assessment of fluid distribution, pericardial thickening or calcification and extracardiac manifestations/complications [56▪▪]. CMR allows for differentiation of cardiac restriction and constriction. Pericardial fusion without significant inflammation or effusion on CMR is useful in confirmation of CP, as is visceral-parietal adherence [57▪,58▪]. LGE of pericardium signals pericardial inflammation and potential recurrent pericarditis [59▪▪] (Fig. 2C). Similar to echo, CMR respiratory flow variation across the mitral valve exceeding 25% is a sensitive and specific sign for CP [60]. Assessment for myocardial involvement can assist in ruling out cardiomyopathies as a cause of symptoms [56▪▪]. CMR can also provide anatomic information for surgical planning.

Catheterization

Invasive haemodyanmic assessment with simultaneous right and left ventricular measurement is important in assessment of constriction. The equalization of pressures at end-diastole ('dip and plateau' sign) is not specific to constriction but can help confirm the diagnosis when combined with additional findings [56▪▪].

PULMONARY ARTERIAL HYPERTENSION

PAH is present in 12–29% of patients with SSc [61,62]. PAH is major risk factor and cause of death in those with SSc [6,61,63]. Three-year survival is estimated at 60% despite treatment [64], which is significantly worse than idiopathic PAH.

Evaluation

Current guidelines suggest screening all patients with SSc for PAH. Screening tests for PAH include EKG, 2DE, pulmonary function test and laboratory testing [65]. CT and CMR can be used for further evaluation. A right heart catheterization (RHC) is necessary to diagnose PAH.

Pulmonary function test

If the DLCO% is less than 60% or more than 3 years of disease duration, usage of the DETECT algorithm can improve detection of PAH [65]. DETECT uses clinical and test results to suggest echo or RHC, with a sensitivity of 96% and a very low false-negative rate [66].

Two-dimensional echocardiography

Echocardiography screening for SSc-PAH focuses on assessment of intracardiac pressures via the tricuspid regurgitant velocity or estimated pulmonary pressures [67▪▪]. Recommendations suggest referral for RHC if the tricuspid regurgitant velocity is more than 2.8 m/s or more than 2.5 m/s if signs and symptoms of PAH are present [65]. Additional echo findings suggestive of pulmonary hypertension (PH) should be monitored such as intraventricular septal flattening [67▪▪].

Computed tomography/cardiac magnetic resonance

Increased PA diameter (≥29 mm), septal flattening and RV-LV ratio suggest elevated pulmonary pressures [67▪▪]. High-resolution CT imaging is used to assess for ILD and for signs of pulmonary veno-

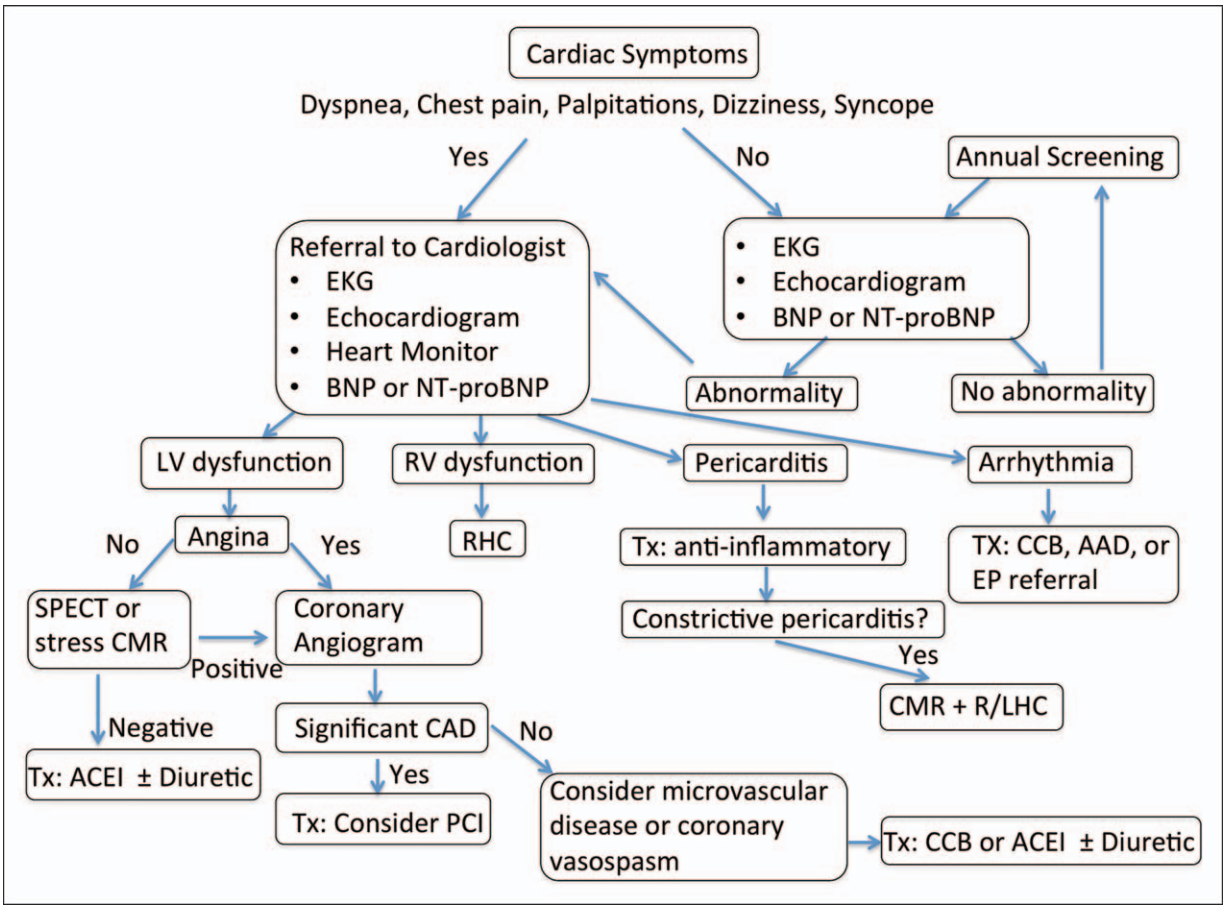

FIGURE 3. Clinical algorithm for screening and diagnosis of cardiac involvement in systemic sclerosis. AAD, antiarrhythmic drug; CCB, calcium channel blocker; EP, electrophysiology; PCI, percutaneous coronary intervention; R/LHC, right and left heart catheterization; RHC, right heart catheterization.

occlusive disease that can complicate both SSc-PAH diagnosis and therapy [68]. CMR allows for anatomic, functional and haemodynamic assessment in PAH such as right ventricular size and function [69].

Right heart catheterization

RHC remains the gold standard for haemodynamic assessment of PH. It is recommended for confirmation of diagnosis of elevated pulmonary pressures on 2DE, to rule out left-sided heart disease and to differentiate between the different causes of PH [67▪▪].

Therapy

Management of PAH due to SSc is treated similarly to idiopathic PAH. Supportive therapy generally begins with diuretics, digoxin and oxygen [67▪▪]. Long-term response to calcium-channel blocker is not seen, and routine usage is not recommended [70]. Phoshodiesterase-5 inhibitors (PDE5) such as sildenafil and tadalafil are effective in maintaining patient function [71–73]. Endothelin receptor-antagonist (ERA) ambrisentan improved function and survival out to 3 years [74▪▪]. Macitentan improved quality of life at 36 months [75]. Guanylate cyclase stimulator riociguat improved functional and haemodynamic parameters out to 2 years [76].

Prostacyclin analogues remain an effective therapy, but short half-life and chemical instability make epoprostenol and treprostinil difficult to administer [77▪▪,78]. Selexipag, an oral selective prostacyclin-receptor agonist with a long-lasting formulation, showed a reduced risk of death or PAH-related complication and improved function. [77▪▪,79▪]. Combination therapies can improve outcomes and recent trials have included patients already on one or more PAH therapies. Selexipag improved outcomes when added to ERA ± PDE5 inhibitors [79▪]. Ambrisentan/tadalafil combination therapy was shown to be more effective either agent alone [80▪▪]. Not all combinations are recommended as riociguat and sildenafil have safety concerns [71].

CONCLUSION

Cardiac involvement in SSc continues to be a significant source of morbidity and mortality. Screening techniques allow for earlier detection of complications, including myocardial fibrosis, conduction disease and PH. Modern imaging allows improved visualization of the RV, which is commonly involved and tied closely to significant morbidity. Figure 3 is a proposed clinical algorithm for screening and diagnosis of cardiac involvement in SSc based on expert opinion. Effective therapies for prevention of disease progression and reducing mortality are elusive and remain an important focus for research.

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Conflicts of interest

Gadolinium-based contrast agents are not FDA approved for cardiac imaging. This manuscript has been seen, reviewed and approved by all contributing authors.

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Treatment-naive patients received initial combination therapy and had improved outcomes over either monotherapy arm.

The roles of dermal white adipose tissue loss in scleroderma skin fibrosis

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Purpose of review
Dermal white adipose tissue (DWAT) is distinct from subcutaneous white adipose tissue and is lost in scleroderma skin fibrosis. The roles of DWAT loss in scleroderma skin fibrosis have not been well understood, and here we discuss recent findings that begin to provide insight into the multiple mechanisms involved.

Recent findings
The DWAT loss in part reflects the direct contribution of DWAT cells to the fibrotic tissue, with the reprogramming of adipocytes to myofibroblasts. The DWAT contains reparative adipose-derived stromal cells and expresses antifibrotic cytokines such as adiponectin, and the loss of these skin-protective mechanisms with DWAT loss further contributes to skin fibrosis and injury.

Summary
Potentially, halting or reversing the transdifferentiation of adipocytes to myofibroblasts along with improving survival of reparative adipose-derived stromal cells (ADSCs) and expression of antifibrotic cytokines may be effective therapeutic avenues.

Keywords
dermal white adipose tissue, mesenchymal stromal cells, myofibroblasts, scleroderma, skin fibrosis

INTRODUCTION: DERMAL-ASSOCIATED WHITE ADIPOSE TISSUE AND SCLERODERMA

Skin is associated with two types of white adipose tissue (WAT). There is subcutaneous WAT (SWAT) that is located beneath the skin that includes the adipose tissue removed by abdominal liposuction and the inguinal fat pads in mice. There is also a distinct dermis-associated WAT, recently termed dermal white adipose tissue (DWAT) [1]. DWAT is located directly under the reticular dermis. In rodents, but not in humans, SWAT and DWAT are separated by the muscle layer called panniculus carnosus (Fig. 1). In humans, DWAT is predominantly located around the pilosebaceous units forming cone geometry, which has a portion located in the dermis and the other traversing the dermis to infiltrate into the SWAT. DWAT has a developmental origin independent of the SWAT and shares a common precursor with dermal fibroblasts during embryogenesis [2]. Although DWAT can have insulating and energy-provision functions similar to SWAT [3▪,4▪], DWAT also contributes in multiple ways to skin biology by participating in hair follicle cycling [5], wound healing [6], and antibacterial defense [7].

There has been recent interest in the DWAT in scleroderma because the DWAT is partially lost with skin fibrosis [8]. Standard punch biopsies are unlikely to sample the entire depth of the dermis, and thus, quantifying the extent of DWAT loss is difficult. However, Fleischmajer *et al.* [9,10] performed excisional biopsies that allow sampling of skin to the muscle layer and observed that there was loss of DWAT in systemic scleroderma and most localized scleroderma patients. The DWAT loss is also observed in mouse models of dermal fibrosis [11–17], and time course studies show that DWAT loss precedes dermal thickening in the bleomycin

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KEY POINTS

- DWAT is lost in scleroderma skin fibrosis.
- The DWAT loss reflects direct contribution of adipocytes to fibrotic skin by reprogramming of adipocytes to myofibroblasts.
- The DWAT contains reparative ADSCs and expresses antifibrotic cytokines such as adiponectin, and the loss of these skin-protective mechanisms with DWAT loss further contributes to skin fibrosis and injury.
- Potentially, halting or reversing the transdifferentiation of adipocytes to myofibroblasts along with improving survival of reparative ADSCs and adiponectin expression may be effective therapeutic avenues.

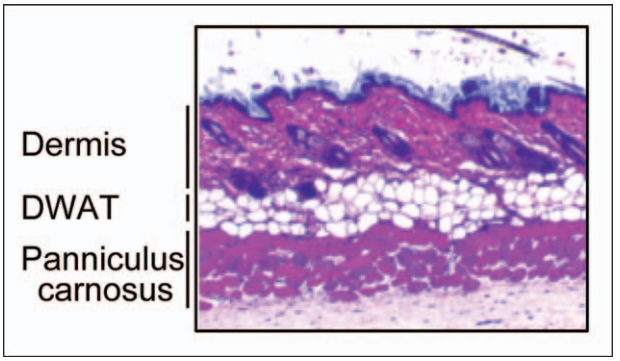

FIGURE 1. Skin anatomy and dermal white adipose tissue location. Hematoxylin and eosin stain of mouse skin shows the location of the dermal white adipose tissue under the reticular dermis and above the panniculus carnosus. The subcutaneous white adipose tissue is under the panniculus carnosus. Note that in humans, dermal white adipose tissue and subcutaneous white adipose tissue are contiguous, and the dermal white adipose tissue can partly infiltrate subcutaneous white adipose tissue in association with hair follicles and sebaceous glands.

model [18,19] and that a decrease in adipogenic gene expression precedes the increase in fibrinogenic gene expression [18]. These studies suggest that DWAT loss may either reflect a pathogenic process or play a pathogenic role in skin fibrosis. Here, we discuss recent findings that are beginning to unravel how the DWAT loss both reflects a direct pathogenic contribution of adipocytes to skin fibrosis and how the DWAT loss contributes to the skin fibrosis and injury.

DERMAL-ASSOCIATED WHITE ADIPOSE TISSUE LOSS REFLECTING DIRECT CONTRIBUTION OF ADIPOCYTES TO FIBROTIC SKIN

Recent studies have suggested transdifferentiation or, potentially, a fate switch between adipocytes and myofibroblasts in fibrosis. By using a transgenic mouse model, Marangoni *et al.* [18] showed that during fibrosis, cells that are restricted to DWAT and express the fat-specific marker adiponectin, which are presumed to be adipocytes, transdifferentiate into myofibroblasts in the bleomycin mouse model. *In vitro*, adipocyte-generating cultures can generate myofibroblasts with TGFβ signals [18]. Likewise, a switch in progenitor cell fate was suggested in a study whereby platelet-derived growth factor receptor α-positive (Pdgrα^{+}) progenitor cells expressing constitutively active ß-catenin showed suppression of adipogenesis and replacement of DWAT with fibrotic fibroblasts [20]. Conversely, during resolution of wound healing, myofibroblasts appear to transdifferentiate into adipocytes upon activation of the BMP-Zfp423 embryonic pathway [21▪▪]. Similar to these studies in skin, lineage-tracing approaches in lung showed that lipofibroblasts that resemble adipocytes transdifferentiate into myofibroblasts during bleomycin-induced lung fibrosis. During fibrosis resolution, myofibroblasts transitioned to a lipofibroblast-like phenotype [22▪]. Together, these studies strongly support the idea that adipocytes in DWAT may contribute directly to fibrosis by reprogramming to myofibroblasts. The extent to which the adipocyte–myofibroblast reprogramming involves direct transdifferentiation versus a fate switch of a progenitor cell type will need to be further determined, especially given the apparently protective functions of mesenchymal stromal cells discussed below.

DERMAL-ASSOCIATED WHITE ADIPOSE TISSUE LOSS AND LOSS OF REPARATIVE DERMAL-ASSOCIATED WHITE ADIPOSE TISSUE ADIPOCYTE-DERIVED STROMAL CELLS

The stromal-vascular fraction (i.e., the nonadipocyte fraction) of adipose tissue contains heterogenous assortment of mesenchymal stromal cells that include stem-like cells with multilineage differentiation potential as well as more differentiated adipocyte progenitors and preadipocytes that develop into adipocytes [23–25]. In addition to tissue regeneration potential, the adipose mesenchymal stromal cells, referred to as 'adipose-derived stromal cells' (ADSCs), have reparative properties. They are anti-inflammatory and immunosuppressive, showing efficacy n reducing graft-versus-host disease [26] and other autoimmune and inflammatory disease

models [27]. They express anti-inflammatory molecules such as nitric oxide, indoleamine-2,3-dioxygense, PGE2, and TGFβ. Although TGFβ can be profibrotic, these molecules can promote the development of regulatory T cells, and perhaps more relevant for scleroderma, macrophage polarization toward an anti-inflammatory and tissue-repair phenotype [28–31]. In addition, these cells can reduce oxidative stress [32] and be proangiogenic, either by differentiating into endothelial cells [33,34] or secreting proangiogenic factors [35,36], or by inducing myeloid cells to adopt a proangiogenic phenotype [28,31,37].

Injection of ADSCs or mesenchymal stromal cells from other sources is being tried as a potential beneficial therapy in localized and systemic scleroderma. In localized scleroderma, ADSCs cultured from SWAT or the SWAT ADSC-containing stromal-vascular fraction added to fat transfers may prolong the effectiveness of the fat grafts aimed at augmenting soft tissue volume [38,39]. Even without the fat grafts, injection of cultured ADSCs alone arrested progression and softened the skin in a small observational study [40]. In systemic scleroderma, stromal-vascular fraction cells injected into the base of fingers also showed promising effects on hand and vascular function at 12 months in an uncontrolled trial study [41▪]. Currently, the effectiveness of the finger injection on hand function is being assessed in a multicenter randomized double-blind controlled trial (Clinicaltrials.gov, trial NCT02396238). Systemic injection of mesenchymal stromal cells from bone marrow and umbilical cord has been reported anecdotally and in a small case series [42–44], and there is a Phase I/II study of allogeneic mesenchymal stromal cells in progress (Clinicaltrials.gov, trial NCT02213705). It is an exciting time for mesenchymal cell-based therapy in scleroderma.

The efficacy of local and systemic ADSC injection is replicated in mouse models of scleroderma, providing opportunities to understand how to optimize treatments and understand mechanisms. In a model induced by daily subcutaneous injection of hypochlorous acid (HOCl) into Balb/c mice, intravenous injection with healthy murine ADSCs from SWAT ameliorated skin fibrosis and also the lung fibrosis that occur in this model [45]. In the bleomycin model, we found that local injection of healthy murine DWAT ADSCs did not have appreciable effects on fibrosis, but improving the survival of the injected ADSCs was associated with amelioration of fibrosis [19]. Healthy human vascular-stromal fraction cells and adipose tissue injected locally into the lesions of bleomycin-treated nude mice ameliorated established skin fibrosis [46]. Although nude mice lack T cells [47], human mesenchymal stromal cells have been administered to immunocompetent mice in models of lupus, and rheumatoid arthritis without obvious immunogenic responses and with good therapeutic efficacy [48,49]. Indeed, healthy human ADSCs were as effective as murine ADSCs in ameliorating skin and lung fibrosis in the HOCl model [45]. Thus, preclinical models of scleroderma skin fibrosis can be useful for examining murine and human ADSCs as potential approach to therapy.

The clinical studies in scleroderma have used autologous cells, but it is unclear whether autologous cells are optimally effective. Bone marrow mesenchymal stromal cells from scleroderma patients were observed to be more senescent although they retained in-vitro immunosuppressive abilities [50] and were superior than healthy control mesenchymal stromal cells in having a greater proangiogenic activity [51,52]. ADSCs from scleroderma patients were less proliferative and migratory [53], but their cell surface phenotype, differentiation capacity, in-vitro immune suppressive, and proangiogenic effects were the same as those of healthy control ADSCs [53,54▪]. Whether there are differences in effectiveness between autologous and allogeneic cells from healthy donors, and also between freshly isolated ADSCs or stromal-vascular fraction cells and cultured cells in vivo will be important to understand to optimize therapy for scleroderma. In addition, although mesenchymal stromal cells are considered to be nonimmunogenic, they can stimulate a rejection response [55,56]; thus, understanding how to optimize autologous mesenchymal stromal cell therapy will be an important approach in the long term.

Endogenous DWAT ADSCs appear to have a protective role in scleroderma skin fibrosis models. We recently asked whether ADSCs are lost from the skin with DWAT loss and whether we could understand the mechanisms that maintain their numbers. In both the bleomycin and the graft-versus-host disease models, ADSCs were reduced by 80% when fibrosis was established and most of the ADSC loss was attributable to cell death [19]. This suggested the possibility that loss of reparative ADSCs due to DWAT loss may contribute to the incalcitrant nature of skin fibrosis. Lineage-tracing experiments by Driskell *et al.* [2] showed that an ADSC subpopulation gives rise to myofibroblasts during wound healing, adding to the idea that these are reparative cells. However, it raises the possibility that ADSCs could potentially contribute to the myofibroblast population in skin fibrosis as well. Although we could not rule out this possibility in the bleomycin model, we found by using dendritic cell depletion models that

dendritic cells maintained the survival of about 40% of the remaining ADSCs in fibrotic skin, and that dendritic cell depletion and loss of ADSCs was associated with worsened skin injury. Although fibrosis *per se* as reflected by collagen protein content was not worsened, the DWAT was further reduced, additional scleroderma-associated gene expression changes were observed, and wound healing that was compromised by bleomycin treatment was further affected [19]. These results suggested that ADSCs protect the skin state in fibrotic skin.

Our finding that dendritic cells could mediate DWAT ADSC survival in fibrotic skin suggested that provision of dendritic cell-derived signals could improve survival, and therefore, effectiveness of therapeutically delivered ADSCs. Mesenchymal stem cell therapy is felt to be limited in part by the survival span of the injected cells [57], and, indeed, most of the ADSCs that we injected into fibrotic lesions could not be found 2 weeks later. We found that dendritic cells maintained ADSC survival via expression of lymphotoxin $\alpha 1\beta 2$ and stimulation of LTβR, a tumor necrosis factor receptor family member, on ADSCs. Mimicking provision of LTβR signals with an LTβR agonist antibody improved the survival of the injected ADSCs and partly reversed established fibrosis. In addition to reduced collagen levels and dermal thickening, DWAT was increased, wound healing was improved, and some of the bleomycin-induced gene expression changes were reversed. These changes suggested that improving DWAT ADSC survival with LTβR stimulation had improved ADSC effectiveness. Potentially, stimulation of LTβR could improve effectiveness of human ADSC therapy in scleroderma.

DERMAL-ASSOCIATED WHITE ADIPOSE TISSUE LOSS AND LOSS OF DERMAL-ASSOCIATED WHITE ADIPOSE TISSUE-EXPRESSED PROTECTIVE CYTOKINES

Adipogenesis is regulated by the nuclear receptor Peroxisome proliferator-activated receptor-gamma (PPAR-γ), implicated in inflammation and fibrosis [58]. The antifibrotic effects of PPAR-γ are mediated by the adipose hormone adiponectin. In scleroderma, PPAR-γ expression is reduced in skin biopsies and adiponectin is reduced both in the serum and skin biopsies and is inversely correlated with the extension of skin fibrosis [59]. Among its multiple functions, adiponectin attenuates fibroblast activation and reverses the activated phenotype of scleroderma fibroblasts [60]. Transgenic mice overexpressing adiponectin are protected from skin and peritoneal fibrosis and from the loss of dermal adipose attrition [61]. Moreover, peptides targeting adiponectin receptors protect from skin fibrosis induced by bleomycin [61]. These findings implicate reduced adiponectin as a potent driver in fibrosis and target for therapy.

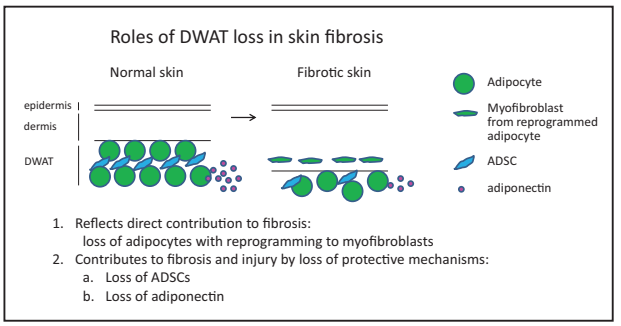

FIGURE 2. The roles of dermal white adipose tissue loss in scleroderma skin fibrosis. The dermal white adipose tissue loss in part reflects the direct contribution of dermal white adipose tissue cells to the fibrotic tissue, with the reprogramming of adipocytes to myofibroblasts. The dermal white adipose tissue contains reparative adipose-derived stromal cells and expresses antifibrotic cytokines such as adiponectin, and the loss of these skin-protective mechanisms with dermal white adipose tissue loss further contributes to skin fibrosis and injury.

CONCLUSION

The DWAT loss, then, both reflects a direct contribution of the DWAT to the skin fibrosis and contributes to fibrosis and injury by the loss of DWAT's skin protective mechanisms (Fig. 2). Potentially, halting or reversing the transdifferentiation of adipocytes to myofibroblasts along with improving survival of reparative ADSCs and expression of antifibrotic cytokines may be effective therapeutic avenues. The recent studies have begun to provide insight into the complex role of DWAT in fibrosis, and many questions remain. For example, in scleroderma, what are the drivers or what is the injury that initiates the reprogramming of adipocytes to myofibroblasts? Within the ADSCs, are there subpopulations that have different skin-protective capabilities? Along with mechanistic understanding, can the amount of DWAT loss in patients be used for early diagnosis or to measure outcome or perhaps identify those who would benefit from ADSC or adiponectin therapy? Further understanding of the DWAT in skin function and scleroderma holds promise for new therapies to reduce fibrosis and repair skin function in this severe disease.

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Conflicts of interest

There are no conflicts of interest.

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Novel insights of disability assessment in adult myositis

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Purpose of review
To review the novel development of standardized clinical outcome measures used in adult patients with idiopathic inflammatory myopathies (IIMs). A further aim was to determine what aspects of IIM are covered by these outcome measures according to the International Classification of Functioning, Disability and Health (ICF).

Recent findings
The sporadic inclusion body myositis functional assessment (sIFA) is the first diagnosis-specific patient-driven patient-reported outcome measure. The adult myositis assessment tool (AMAT) is a new outcome measure assessing physical performance. Also, new criteria to assess response to treatment have been presented for both adults and children with IIM. The ICF provides a standardized frame and structure to report outcome, including functional disability. Using this framework, it is evident that there is a lack of validated patient-reported outcome measures to assess disease aspects important to patient, and that no studies have evaluated life-style factors such as physical activity in these patients.

Summary
The sIFA will ensure patient-relevant patient-reported assessment of activity limitations in patients with inclusion body myositis. The AMAT is a partly validated tool that needs to be used in clinical trials for further validation. The response criteria will enhance assessment of individual response to different treatments.

Keywords
disability, functioning, impairment, myositis, outcome measures

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs), collectively known as myositis, are characterized clinically by muscle weakness, reduced muscle endurance and muscle inflammation. On the basis of different clinical and histopathologic features, three main subsets of adult myositis have been defined: polymyositis, dermatomyositis, immune-mediated necrotizing myopathy and inclusion body myositis (IBM) [1,2]. In all types of myositis, muscle performance and aerobic fitness are often reduced, affecting patients' activity performance and health-related quality of life [3]. During the progression of the disease, symptoms may occur in different organs at different times. A standardized, combined assessment of clinical outcomes, including patients' perspectives and objective measures, may help clinicians understand how disability develops through the diseases duration as well as impact of disability on patients' lives.

OUTCOME MEASUREMENT IN IDIOPATHIC INFLAMMATORY MYOPATHY

A critical part of evaluating a patient with myositis is to determine the degree of potentially reversible inflammation that may respond to immunosuppressive treatments (disease activity), and the degree of fibrosis or scarring resulting in nonreversible

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KEY POINTS

- Response criteria and a new patient-driven patient-reported tool have been developed recently.
- A large majority of clinical assessments in adult IIM are objective measures on ICF impairment.
- There are only a few PROMs on ICF activity limitation and participation restriction for adult IIM.
- ICF contextual factors, such as physical activity and other life style factors, have not been assessed in adult IIM.
- Symptoms important to patients, such as pain, fatigue and cognitive impact, are not included in recommended clinical assessment.

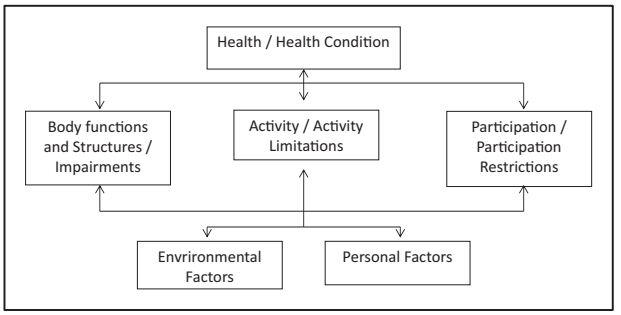

FIGURE 1. ICF was introduced by the World Health Organization (WHO) [6]. According to this framework, disability denotes the negative aspects of the interaction between a person's health conditions and his/her environment and refers to all impairments, activity limitations and participation restrictions [7]. Body functions refer to the physiological performance of body systems, whereas Body structure concerns all the anatomical parts of the body. Limitations in body functions and body structures are defined as impairment. Difficulties in executing an activity of daily life are defined as activity limitation, whereas participation restrictions are problems that an individual may experience in any life situation. Contextual factors, for example environmental factors reflect an individual's physical environment as well as social networks, whereas personal factors reflect an individual's personal resources, beliefs, perception of health – disability. ICF, International Classification of Functioning, Disability and Health.

tissue injury that will not respond to treatment (damage). The discrimination among these two aspects might be particularly difficult because in some cases, patients may exhibit an association between disease activity and damage if they have had a long-standing disease [4]. Until recent years, there has been a lack of disease-specific and validated assessment tools for patients with inflammatory myopathies, leading to extensive use of arthritis-specific or neurology-specific measures to assess these patients. So far, a few myositis-specific outcome measures have been developed and validated, and the properties of few outcome measures for adults and children with IIM have been presented [5,6]. The scope of this review focuses on novel standardized clinical outcome measures and their measurement properties used in adult patients with myositis. A further aim was to evaluate what aspects of IIM are covered by these outcome measures according to the International Classification of Functioning, Disability and Health (Fig. 1) [6,7].

BODY STRUCTURE AND BODY FUNCTION DISABILITY MEASUREMENT

In the last decade, an international, interdisciplinary network, the International Myositis Assessment and Clinical Studies Group (IMACS) created a core set of outcome measures. The six-item core set of disease activity measures included physicians' and patients' global activity assessment, muscle strength, functional disability, muscular enzymes and extra muscular disease activity [7]. This latter part of the core set represents a prominent aspect of myopathies disease activity as inflammation could be less remarkable in muscles, but more so in other organs. Extra muscular involvement encompasses mainly joints, lung, heart, skin and gastrointestinal systems. Lung computed tomography, pulmonary functional tests, echocardiography, heart MRI and esophageal motility assessment are important tools to approach extra muscular disease activity and damage [8]. Recently, the American College of Rheumatology board/European League Against Rheumatology committee endorsed the responder criteria of disease activity based on this core set and assigned categories for minimal, moderate and major clinical response (20, 40 and 60%, respectively) [9▪▪]. Two of the most important features of these criteria are that they assign weight for each item depending on the contribution to the final score and it is a continuous score which describes an absolute change for each patient. Nevertheless, one concern of these criteria is that 'worsening' and 'no change' receives the same score, because they are focused only on improvement. Further research is needed to address this limitation. The myositis damage index assesses the extent and severity of irreversible damage present for at least 6 months in 11 different organ systems (muscular, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral vascular, endocrine, ocular, infectious and malignancy) [8,10].

Muscle biopsies are essential to diagnose IIM, and the conchotome technique [11] has proven feasible for follow-up studies of inflammatory markers and gene expression. In these studies, correlation of biopsy findings with measures of clinical disease activity or disability has provided new knowledge of disease mechanisms and treatment response [12–16].

Muscle enzymes. Levels of creatinphosphokinase remain as one of the objective measures that discriminates active disease, which commonly demonstrates abnormally high levels of enzymes in the serum prior to treatment, from disease remission or disease damage, which is indicated by normal or subnormal enzyme levels [17,18]. Lactate levels have been investigated in both muscle tissue and serum in patients with established polymyositis and dermatomyositis. Lactate levels in the extra-cellular matrix were examined by a microdyalisis technique after incremental activity on a stationary cycle until exhaustion in patients and healthy controls [13]. The lactate levels were significantly reduced on a follow-up stationary cycle test on the same intensity after 12 weeks of endurance training. When investigating lactate levels in serum after a treadmill workout to exhaustion, there was a significant difference between patients and controls; nevertheless, after a 6-week program of aerobic exercise, lactate levels decreased and an improvement of physical performance was observed [19]. Even so, standardized techniques that correlate lactate levels and physical endurance are still lacking.

MRI is one of the few tools that can discriminate between disease activity and damage in a patient with inflammatory myositis [20▪]. It has performed as a valuable implement in clinical monitoring of responses to therapy because of its good correlation with other clinical measures of myositis activity, including physician global activity, strength testing and muscle histopathology [21]. A distinctive advantage of MRI is its capacity to distinguish between myositis subtypes, including amyopathic and myopathic myositis [22], and polymyositis/dermatomyositis and IBM.

Impaired muscle function is the most prominent clinical feature of the inflammatory myopathies and is related to both muscle weakness and decreased endurance with more easily fatigued muscle, predominantly in proximal and axial muscle groups [23]. The purpose of the manual muscle test (MMT) is to measure isometric muscle strength as part of physical examination. The most recent version is derived from the total score measured in eight muscle groups (including neck flexors, deltoids, biceps, wrist extensors, gluteus medius and maximus, quadriceps and dorsi-flexors of the ankle, MMT8); each muscle is rated in a 0–10 with higher scores for higher strength to a maximum of 80 [24]. Isokinetic muscle strength, defined as muscle action performed in the same pace throughout the whole range of motion in degrees/second, has also been used to assess muscle strength [25]. Although this system has the potential to quantify torque during muscle contraction and is useful for measuring muscle power (work velocity), fatigue and endurance, its use is limited, as it is costly and requires well-trained personnel for operation. Another way of assessing muscle strength is the voluntary repetition maximum (VRM) procedure. A 1 VRM equals the weight that the patient can lift once but not in a second chance, which is often used in healthy populations. Five VRM and 10–15 VRM have been used to assess muscle strength in two exercise studies in polymyositis/dermatomyositis patients [13,26]. Both the 5 and 10–15 VRM were sensitive to detect significant improvements in muscle strength. However, there are no data on the reliability of these tests in myositis patients. Grip strength has been assessed in adults with IIM using the Grippit instrument [27], and it was recently shown that myositis patients have reduced grip force compared with controls and this might also affect quality of life [28].

The functional index was the first specific assessment tool to evaluate muscle endurance in patients with myositis. This score was further developed into the functional index-2 [29], wherein the number of maximal repetitions for each muscle group was increased. Furthermore, a given pace measured by a metronome was introduced to further standardize the test. With very high correlations between right and left sides, only one side of the body needs to be assessed, making the measure less time consuming and better tolerated by patients feasible to perform it in clinical practice. Another functional evaluation recently used in myositis is the walking test. This test measures the distance that can be walked within a standardized period of 2 or 6 min (2-MWT or 6-MWT, respectively). Both tests correlate moderately with each other; thus, 2MWT is more feasible in clinical care and research with less patient burden [30]. The maximal oxygen uptake test by cycle ergometry is a sensitive method to investigate maximal aerobic capacity in patients with adult IIM. In this functional test, aerobic exercise limitation, including peak oxygen uptake and work, correlates well with disease duration, global disease activity and damage as well as self-reported physical function [31,32].

ACTIVITY LIMITATION/PARTICIPATION RESTRICTION

From a patient perspective, activity limitation and participation restriction may be even more

important measures, as they serve to identify individual disease-related disabilities. Recently, an international collaboration in the field of rheumatology (OMERACT) has identified the need to include valid patient-driven and PROM in clinical trials [3]. According to an extensive literature review, six scales were identified: two specifically created for myositis patients; four of these scales, though not specifically for myositis, have been validated in these patients and additionally, two mental health tests were added as a new perspective for integral evaluation.

The sporadic inclusion body myositis physical functioning assessment (sIFA) was recently developed and validated, specifically for patients with IBM [33▪▪]. To ensure content validity, the questionnaire was based on a literature review, interviews with expert clinicians and on individual interviews with patients. Data were analyzed qualitatively and patients were then included to discuss the questionnaire's content, wording and scaling. The sIFA consists of 10 items divided in three subscales: lower body functioning (standing up from sitting, getting on and off a toilet, walking on flat ground, walking on uneven or sloping ground, climbing five steps, stepping up and down a sidewalk curb), upper body functioning (carrying a five-pound object, gripping small objects like a key in a lock or tying shoes) and general functioning (getting off the floor or ground, swallowing). Each item is scored on a numerical scale from 0 to 10, with a total score ranging from 0 to 100, where 100 indicates severe limitations. The sIFA had good internal consistency and moderate-to-strong interitem correlations. Good test-retest reliability was demonstrated, with an intraclass correlation of 0.91. Correlation between the sIFA and the health assessment questionnaire (HAQ) test was good, whereas correlation with impairment measures was lower. A small effect size was evident from noninterventional studies [34]. The sIFA is the first PROM developed based on patients' own experience of myositis, specifically IBM which could ensure patient-relevance of items.

The adult myopathy assessment tool (AMAT) scale is a recently developed 13-item physical performance test that encompasses two subscales: a functional (range 0–21) and endurance (range 0–24) scale for a total score ranging from 0 to 45. It does not require any specialized equipment, and it may be completed within 20–30 min. The two domains reflect the contribution of impaired muscle force on functional limitations and incorporate the fact that excessive fatigue may interfere with physical performance and activities of daily life. The AMAT tool has been tested in healthy individuals and a small group of myositis patients, finding neither ceiling nor floor effect. The scale has acceptable intrarater agreement and is easy to apply. However, the tool as to minimally clinically important difference, responsiveness and test-retest reliability in larger groups of myositis patients [35▪].

The HAQ-DI [36] has been in use for many years to assess patients with adult inflammatory myopathies. Even though it is included in the IMACS core set, it has not been validated for these patients. To fill the HAQ gaps, the myositis activities profile was developed [37]. With this tool, patients with adult polymyositis and dermatomyositis are asked to rate the difficulty and the importance of 31 activities covering a wider range of International Classification of Functioning, Disability and Health domains compared to HAQ [38].

The McMaster Toronto arthritis patient preference questionnaire (MACTAR) was originally developed as an arthritis-specific questionnaire and modified later into a semistructured interview [39]. The MACTAR Baseline and Follow-up consist of questions divided into six different categories, including general health, quality of life, physical function and social function, as well as the most important daily activities requiring improvement, where patients are encouraged to spontaneously identify at least five activities that they want to improve. The MACTAR has been validated for patients with adult polymyositis/dermatomyositis and can detect significant improvement in patient-preference activity limitation following 12 weeks of exercise [13].

The inclusion body myositis functional rating scale [40] is the first functional scale developed exclusively for IBM clinical trials and should be performed as an interview and not as a self-reported questionnaire. It can be administered in less than 10 min and is sensitive to change over time. The disability of the arm, shoulder and hand (DASH) is not a new measure, but has not been used in myositis until recently. The DASH is a 30-item, patient-reported outcome to assess activity limitation and participation restriction in relation to upper extremity function in individuals with musculoskeletal disorders [41]. This instrument has been used in a hand-exercise study in adults with polymyositis and dermatomyositis [28]. It is an easily administered questionnaire with available population-based reference values.

The generic short form-36 (SF-36) questionnaire [42] is a generic PROM proven to be sensitive for the assessment of perceived health in patients with inflammatory myopathies and has been endorsed by the IMACS. Several studies of patients with adult myositis and adults with juvenile-onset disease were rated as having significantly poorer health in all eight domains compared to the normal population

and were related to disability and poor survival rate [43–46]. In two different cohorts, the SF-36 was able to detect significant improvement in several domains following a 12-week exercise programmes in patients with chronic as well as recent-onset disease [47,48]. Other studies using nonspecific measurement scores like the WHOQOL-BREF score have been used to evaluate this aspect of participation restriction, and these findings are similar to SF-36 performance [49].

DISCUSSION

Most outcome measures assess impairment (limitations in body function and structures), whereas fewer outcome measures focus on activity limitation and participation restriction. No studies so far have measured contextual factors such as physical activity levels, barriers and support for physical activity, self-locus of control or environmental factors (Fig. 2). Most assessments are objective, but the importance of also using patient-reported outcome measures is recognized. The first patient-reported, diagnosis-specific outcome measure based on patients' experience derived from qualitative methodology was recently published for patients with IBM, the sIFA. The functional index-2 and another newly developed measure of impairment, the AMAT, are the only myositis-specific measures of impairment created for adults with myositis.

Few of the objective and patient-reported outcome measures used in adults with IIM are thoroughly validated for this group of patients. The AMAT and the functional index-2 are functional assessments of impairment, initially developed and validated for patients with adult polymyositis and dermatomyositis; however, little is known of these tools' responsiveness, as their use in clinical trials is limited. The MMT-8 muscle group was partly validated in terms of interrater and intrarater reliability, but there may be a risk of ceiling effects for patients with polymyositis and dermatomyositis. It may be argued that the MMT, hand-held myometers and VRM-tests could be generic; however, it is valuable to know their measurement properties for various diseases and how responsive these tests are to medical and nonmedical treatments. A limitation of functional impairment measures is the lack of reference values. A small study concluded that 17 patients had significantly lower muscle endurance assessed by the functional index-2 in measures of lower limbs compared to healthy controls, but not in neck flexion or shoulder flexion/shoulder abduction [50]. Although there are more reference values for standard protocols of muscle strength and muscle endurance in the Biodex system, its limitations lie in its costliness and necessity of trained personnel. Further, a Biodex assessment should be combined with a functional objective and/or patient-reported measures to gain knowledge of the impact of muscle impairment on patients' lives and improve clinical relevance.

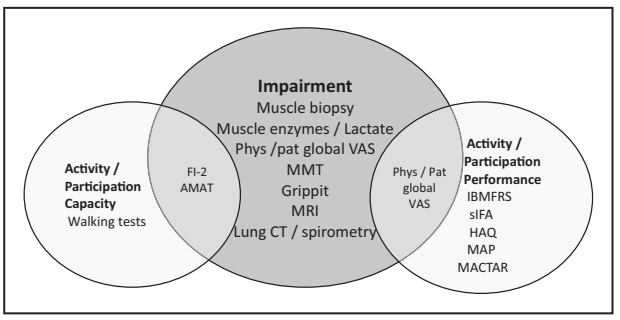

FIGURE 2. Outcome measures used in myositis according to the ICF. Phy/pat global HAQ, health assessment questionnaire disability index; IBMFRS, inclusion body myositis functional rating scale; Lung CT, lung computed tomography; MACTAR, McMaster Toronto arthritis patient preference questionnaire; MAP, myositis activities profile; MMT, manual muscle test; MRI, magnetic resonance imaging; SF-36, short form-36; sIFA, sporadic inclusion body myositis physical functioning assessment; VAS, physician and patient global assessment visual analogue scale.

The Food and Drug Administration and other authorities have stressed the need for valid and responsive patient-reported outcome measures used in clinical trials (FDA 2009). Further, these patient-reported outcomes need to be patient-relevant. The international collaboration OMERACT is focusing on evaluating patients' experience of their disease and what symptoms or life areas patients consider important to measure in clinical trials. Since 2011, the OMERACT Myositis Working Group consisting of physicians, health professionals and patient research partners from four continents (Australia, Europe, Asia and North America) is focusing on identifying a core set of PROMs to be used in all clinical trials and identifying or developing PROMS assessing these core domains. There was a discrepancy between domains identified as important to assess in patients and domains that were designated as important to include in clinical trials [51▪]. According to patients, fatigue, pain and sleep were among the most important domains to assess in polymyositis and dermatomyositis. Focus groups of adults with polymyositis and dermatomyositis have identified the symptoms that are important to patients, such as fatigue, pain and cognitive impact, which are not well described in the literature. Ongoing online Delphi surveys with patients, health professionals and pharmaceuticals

will outline what should be included in minimal and additional core sets of PROMs in adult polymyositis and dermatomyositis during the next couple of years. There are several PROMs assessing different aspects of fatigue, pain and cognitive function; however, the optimal PROM for use in myositis is not known. A close collaboration between the IMACS and the OMERACT Myositis Working Group will lead to further improved clinical assessment and foster the use of uniform core sets in clinical care and clinical trials worldwide. International collaborations can also enhance cross-cultural validation of core PROMs.

So far, contextual factors, either personal or environmental, have not been assessed in adult myositis. Factors such as smoking habits are often assessed in clinical trials concerning rheumatic diseases, as these factors have been found to impact prognosis and responsiveness to treatment [52]. However, research has so far not focused on factors such as physical activity level, work environment or residential environment. There are many challenges in assessing lifestyle habits such as physical activity. Although many patient-reported outcome measures are available and most of them are defined as generic [53], there is a risk of over rating or underrating physical activity. So far, there are no studies published evaluating physical activity levels in myositis, although there are a few ongoing efforts evaluating physical activity using accelometers. Many small studies and a few larger RCTs evaluating different well-defined exercise programmes for adults with IIM generate evidence that supports the benefits of exercise [54]. However, no study has explored the effects of everyday physical activity in IIM. Improved objective and patient-reported outcome measures would enhance this area.

CONCLUSION

Recent developments with responder criteria and a patient-driven patient-reported outcome will contribute to improved assessment and understanding of myositis. However, despite receipt of adequate medical treatment, inflammatory myositis causes significant disabilities. Nowadays, health professionals count on several tools to approach these patients and objectively quantify the impact of interventions. Objective measurements to assess all aspects of disability have been well analyzed and described, although some of them still require validation for certain populations. Although qualitative research has revealed that fatigue, pain, cognitive impairment and emotional factors are highly important disease consequences, these symptoms are rarely described in the literature. These symptoms are multidimensional and further research is needed to develop specific outcome measures for these disease aspects. No studies have explored the impact of contextual factors (such as physical activity, compliance to treatment and side-effects of medical treatment) on treatment response. Further research must be supported to expand the knowledge of how disability continues to impact myositis patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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Cardiovascular involvement in myositis

Louise P. Diederichsen

Purpose of review
The purpose of this review is to provide an update on cardiovascular involvement in idiopathic inflammatory myopathy (IIM). Studies from the past 18 months are identified and reviewed. Finally, the clinical impact of these findings is discussed.

Recent findings
Epidemiological studies have revealed an increased risk of myocardial infraction and venous thromboembolism (VTE) – including deep venous thrombosis and pulmonary embolism – in adults with polymyositis or dermatomyositis compared to the general population, even after adjustment for potential confounders. This increased risk applies particularly within the initial year of diagnosis. In addition, cross-sectional studies have shown subclinical cardiac involvement in IIM effecting both heart function and rhythm, and conduction abnormalities, which in part might be because of myocarditis. The International Consensus Group on cardiac magnetic resonance (CMR) imaging suggests that CMR should be considered as a potentially viable diagnostic tool to evaluate the possibility of silent myocardial inflammation in IIM with normal routine noninvasive evaluation.

Summary
Updated literature on cardiovascular involvement in IIM has identified an increased risk for subclinical and clinical cardiovascular disease in these rare inflammatory muscle diseases.

Keywords
cardiovascular disease, myocarditis, myositis, venous thromboembolism

INTRODUCTION

It has long been known that idiopathic inflammatory myopathies (IIM) may effect other organ systems – including the heart – other than the skeletal muscles. Furthermore, IIM is associated with increased morbidity and mortality and cardiovascular comorbidity represents a major contributing factor. Still, limited data are available on cardiac and especially vascular involvement in IIM.

The main processes affecting the heart in IIM include disease-specific inflammation of the myocardium and accelerated coronary atherosclerosis secondary to IIM (Fig. 1) [1▪]. Other pathophysiologic processes might be involved as well, although their role is uncertain and poorly elucidated. Regardless of the underlying cause, structural changes within the heart may cause changes in heart function and/or arrhythmia and conduction disturbances, which might be fatal but most often are subclinical.

The present review summarizes current knowledge on cardiovascular involvement in IIM. Given the limited studies on peripheral vascular complications in IIM the main focus of this review will be the heart and adjacent vessels.

MYOCARDIAL INFARCTION

Limited data are available on the risk of cardiovascular disease in IIM. Sharan *et al.* [2] investigated the risk of incident myocardial infraction and ischaemic stroke in adults with polymyositis and dermatomyositis in British Columbia at a general population level. They retrospectively assembled a cohort of adults with polymyositis/dermatomyositis ($n = 774$) matched with adults randomly selected from the general population ($n = 7923$). A total of 15 years of follow-up was examined and all cases with prior myocardial infraction or stroke were excluded from both groups. The primary events were the first-ever myocardial infraction or stroke event during the follow-up period. They demonstrated an increased risk of myocardial infraction but not of stroke in patients with polymyositis/

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KEY POINTS

- There is an increased risk of myocardial infraction and venous thromboembolism – including deep venous thrombosis and pulmonary embolism – in patients with IIM compared to the general population.
- Subclinical cardiac involvement is pronounced in long-term IIM and may effect heart function and cause rhythm and conduction abnormalities.
- Cardiac magnetic resonance imaging should be considered as a potentially viable diagnostic tool to evaluate the possibility of silent myocardial inflammation in IIM with normal routine noninvasive evaluation.

dermatomyositis compared to controls. The incidence rate per 1000 person-years for myocardial infraction in polymyositis and dermatomyositis was 22.52 versus 5.50, respectively (Table 1). The adjusted hazard ratios (HRs) [95% confidence interval (CI)] for myocardial infraction in polymyositis and dermatomyositis compared to controls was 3.89 (2.28–6.65) versus 2.92 (1.48–5.78), respectively, and highest in the first year after the IIM diagnosis.

MYOCARDITIS

Myocarditis is a well known but rare manifestation of IIM. Although a definitive diagnosis of inflammation of the myocardium still relies on

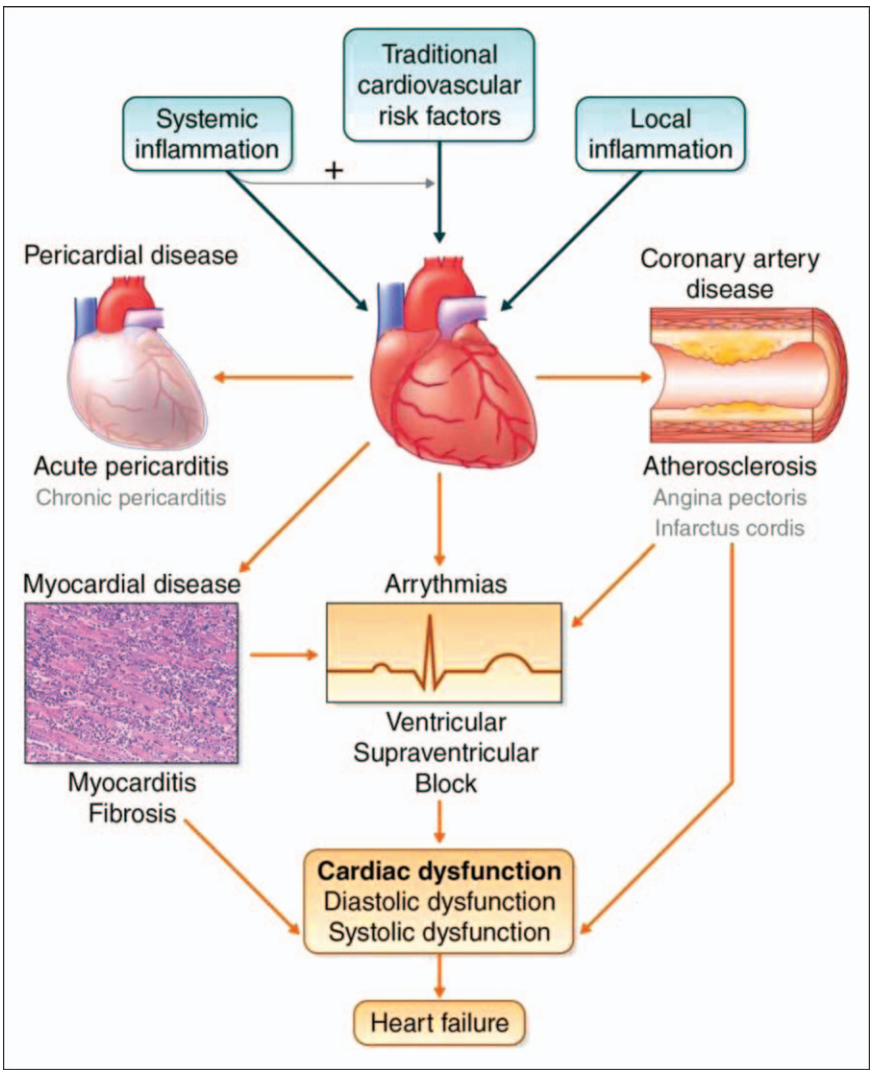

FIGURE 1. Traditional cardiovascular risk factors can cause cardiac disease in patients with IIM. Systemic and local inflammation may either have a direct effect on the myocardium or make the heart more susceptible to traditional risk factors. In the heart, disease can occur in the pericardium, coronary arteries, or the myocardium, and arrhythmias can appear. Myocardial disease can result in diastolic or systolic dysfunction, and when clinical symptoms arise, the patient has developed heart failure. Myocardial disease may result in arrhythmias, or they can occur as a result of inflammation directly influencing cardiomyocyte function. Both arrhythmias and coronary artery disease, such as myocardial infarction, can directly result in heart failure.

Table 1. Relative risk of incident myocardial infarction according to polymyositis/dermatomyositis status

Myocardial infarction	Polymyositis (*n* = 431)	Non-polymyositis (*n* = 4496)	Dermatomyositis (*n* = 352)	Non-dermatomyositis (*n* = 3528)
Events, *n*	29	108	13	74
Total follow-up time	1287	19650	1035	15764
Incidence rate per 1000 person-years	22.52	5.50	12.56	4.69
Age-, sex-, and entry time–matched cox HR (95% CI)	5.20 (3.31, 8.17)	1.0	3.51 (1.88, 6.54)	1.0
Fully-adjusted age-, sex-, and entry time–matched cox HR (95% CI)	3.89 (2.28, 6.65)	1.0	2.92 (1.48, 5.78)	1.0

Fully adjusted models include the following covariates: polymyositis: number of outpatient visits, glucocorticoids and angina; dermatomyositis: number of outpatient visits, NSAIDs, and cardiovascular drugs.

endomyocardial biopsy, myocarditis can be visualized by cardiac magnetic resonance (CMR) imaging (Fig. 2) [3]. At least two of three CMR abnormalities are required to diagnose myocarditis: myocardial edema on T2-weighted sequences, capillary leak, and fibrosis, the latter is assessed on gadolinium enhancement sequences [4]. In 2012, The International Consensus Group on CMR was formed aiming to achieve consensus among CMR and rheumatology experts in developing initial recommendations on the current state-of-art use of CMR in connective tissue diseases including myositis [3]. It was suggested among others that that CMR should be considered as a potentially viable diagnostic tool to evaluate the possibility of silent myocardial inflammation in IIM with normal routine noninvasive evaluation.

CMR abnormalities because of myocarditis have been linked to different subsets of IIM. Yanagi *et al.* [5] described a case of PM with accompanying myocarditis. At hospital admission, the 42-year-old patient had clinical signs of both heart and skeletal muscle disease. Echocardiography (ECHO) revealed left ventricular ejection fraction of 40%. Serum cardiac troponin T level was elevated but no significant stenosis was observed on coronary angiography. Subsequently, myocarditis was diagnosed in view of cardiac MRI, myocardial perfusion scintigraphy, and endomyocardial biopsy.

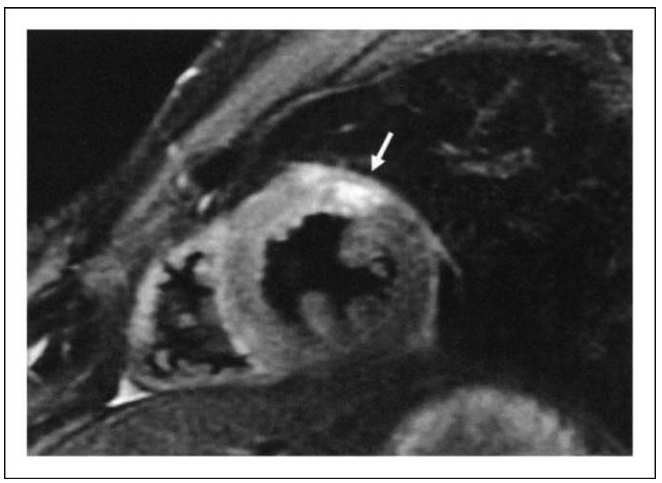

FIGURE 2. Evidence of local edema in the anterolateral wall of LV (arrow) can be detected by STIR T2 imaging during myocarditis.

Sado *et al.* [6] reported a case of myocardial edema in antisynthetase syndrome. A 56-year-old patient presented with 7 months of lung, skin, and muscle symptoms. Computed tomography revealed interstitial lung disease, clinical examination showed mechanic's hands, and ASS was confirmed by presence of anti-PL12. ECG and ECHO were normal; however, CMR showed small pericardial effusion and global myocardial edema. Endomyocardial biopsy confirmed inflammation. CMR was repeated after 2 months on steroid therapy and was returned to normal.

Heart function

Myocarditis has been proposed as one of the possible mechanisms causing systolic heart failure with reduced ejection fraction in IIM whereas fibrosis and stiffness of the left ventricle because of the underlying inflammatory process could lead to heart failure with preserved ejection fraction – diastolic heart failure.

We recently showed normal left ventricular systolic heart function but left ventricular diastolic dysfunction in a cohort of patients with polymyositis or dermatomyositis [7▪]. In a cross-sectional study, 76 patients with polymyositis/dermatomyositis and 48 age and sex matched healthy controls were assessed by ECHO in addition to a number of other noninvasive cardiac measurements. Diastolic dysfunction was associated with increasing age, as known from the general population. However, the occurrence of diastolic dysfunction was more pronounced in the patient group compared to the controls. The diastolic dysfunction was correlated

to high cardiac tracer uptake on scintigraphy, the latter supporting the notion of myocardial inflammation as the underlying pathology. Furthermore, cardiac dysfunction was associated with the presence of myositis-specific and myositis-associated autoantibodies, although a relationship to a specific autoantibody was not observed, probably because of low number of patients with each autoantibody specificity. Previously, anti-SRP has been linked to cardiac involvement in a small cohort of patients with anti-SRP positive IIM [8]. These findings have not been confirmed in larger cohort studies and Picard *et al.* [9] retrospectively observed myocarditis in only two patients from a cohort of 36 patients with anti-SRP positive IIM (8%).

In the general population, manifest diastolic dysfunction is associated with an increased mortality and decrease quality of life, but the specific effects in IIM are yet to be examined. Berntsen *et al.* [10] found reduced submaximal exercise capacity in patients with juvenile dermatomyositis (JDM). The same patient group has previously been shown to have reduced, but subclinical, systolic and diastolic dysfunction. However, the authors opined that the reduction in exercise capacity was due to skeletal muscle and lung dysfunction and not with the cardiac findings.

Arrhythmia and conduction disturbances

Rhythm and conduction abnormalities are the most frequently reported cardiac abnormalities in patients with IIM probably in part due to high ECG availability, portability and low cost. The abnormal findings include atrial and ventricular arrhythmias, atrial and ventricular premature beats, nonspecific ST-T wave changes, conduction abnormalities such as right and left bundle branch blocks, fascicular blocks and atrioventricular blocks.

Baek *et al.* [11▪] retrospectively investigated the prevalence and clinical outcome of atrial fibrillation in 20 772 patients with various autoimmune rheumatic diseases (ARD), including 317 patients with IIM. Atrial fibrillation was observed in 235 (1.1%) of the patients with ARD overall. The atrial fibrillation prevalence was higher in IIM patients (3.5%) compared to those with other rheumatic diseases ($P < 0.05$) and in the adjusted model the HR for development of atrial fibrillation was 3.29 (95% CI, 1.94–5.58; $P < 0.001$) in IIM. As in the general population, patients with ARD (including those with IIM) with atrial fibrillation had a higher all-cause death and stroke event rate compared to patients with ARD without atrial fibrillation.

Deveza *et al.* [12] compared ECG of 112 patients with polymyositis or dermatomyositis with 86 controls without rheumatic diseases. All participants had no history of heart disease. They found similar ECG abnormalities between the two groups, except a higher frequency of left ventricular hypertrophy in the patient group compared to the controls (10.7 vs. 1.2%, $P = 0.008$). The specific ECG changes indicating ventricular hypertrophy were not described. No further analysis of the ECG changes and potential associations with demographic, clinical data, or comorbidities was made.

Our group investigated ECG changes in the previously mentioned cross-sectional study on patients with polymyositis/dermatomyositis compared to controls [7▪]. Using international standard criteria for ECG interpretation, we found that patients had longer median QTc intervals, which is an independent risk factor of ventricular arrhythmias and sudden death in the general population. One patient had formerly unrecognized ventricular arrhythmia combined with decreased systolic function. A β-blocker was prescribed leading to resolution of the disturbance and normalization of systolic function.

Heart rate variability (HRV) gives information on variability in time between the QRS complexes and is analysed from Holter ECG monitoring. HRV is reported to reflect the autonomic nervous control of the heart rhythm, although the clinical significance is controversial. Barth *et al.* [13] investigated HRV in 55 patients with JDM compared with matched controls. Patients with JDM had reduced HRV, which was associated with elevated inflammatory markers, active disease and reduced systolic and diastolic function. These findings suggest reduced vagal control of the heart in the patients with JDM. Associations to cardiac morbidity and mortality still need to be determined, as acknowledged by the authors.

Pulmonary arterial hypertension

Pulmonary hypertension is a potentially life-threatening disorder, which might lead to death through right ventricular failure. ECHO is currently the most effective screening tool for pulmonary hypertension. Pulmonary arterial hypertension (PAH) is a subgroup of pulmonary hypertension associated with connective tissue disorders and is diagnosed by right-heart catheterization. PAH associated with IIM is rare but exists. Sanges *et al.* [14] looked into PAH in IIM by retrieving all cases of IIM-PH ($n = 34$) from the French Pulmonary Hypertension Registry ($n = 5223$) of which three had IIM-PAH. These three cases were pooled with six cases previously reported and compared with 35 patients with IIM without PAH. IIM-PAH seemed associated with dermatomyositis and anti-Sjögren's-syndrome-related antigen

Table 2. Multivariable analysis of the risk of VTE, DVT, and pulmonary embolism in individuals with polymyositis/dermatomyositis

	Polymyositis, *n* = 443	Non-polymyositis, *n* = 4603	Dermatomyositis, *n* = 355	Non-dermatomyositis, *n* = 3577
VTE				
Multivariable HR (95% CI)	7.0 (3.34–14.64)	1.0	8.39 (3.04–23.14)	1.0
DVT				
Multivariable HR (95% CI)	6.16 (2.07–18.35)	1.0	9.40 (2.88–30.68)	1.0
Pulmonary embolism				
Multivariable HR (95% CI)	7.23 (2.86–18.29)	1.0	4.70 (0.85–25.98)	1.0

DVT, deep vein thrombosis; VTE, venous thromboembolism.

A positivity, but the findings should be interpreted with caution due to the low number of patients.

Venous thromboembolism

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary embolism. Although an increased risk of VTE has been shown in other connective tissue diseases, including systemic sclerosis and systemic lupus erythematosus, data on VTE are scarce in patients with IIM. Carruthers *et al.* [15▪▪] investigated the risk of VTE, DVT, and pulmonary embolism in IIM. They assembled a retrospective cohort of all patients with incident PM/DM ($n = 752$) in British Colombia and a corresponding comparison cohort of matched individuals from the general population ($n = 8180$). Both polymyositis and dermatomyositis were associated with increased risk of VTE compared to controls; the incidence rate per 1000 person-years for VTE in polymyositis and dermatomyositis was 16.49 and 12.42, respectively. After adjustment for relevant risk factors, the corresponding multivariate HRs (95% CI) for development of VTE in polymyositis and dermatomyositis were 7.0 (3.34–14.6) and 8.39 (3.04–23.14), respectively (Table 2) [15▪▪].

CONCLUSION

In summary, the recent literature on cardiovascular involvement has yielded important information on an increased risk of myocardial infraction and VTE – including deep venous thrombosis and pulmonary embolism – in adults with polymyositis or dermatomyositis compared to the general population. This applies particularly within the initial year of diagnosis, which calls for vigilance in cardiovascular monitoring especially in newly diagnosed patients with IIM. In addition, subclinical cardiac involvement is pronounced in long-term IIM with affection of the heart function and rhythm and conduction abnormalities. However, the impact of these subclinical cardiac findings on morbidity and mortality in IIM still needs to be determined. In addition, the potential cardio-predictive role of autoantibodies is unclarified and there is an unmet need to identify biomarkers for cardiac involvement in IIM. Therefore, longitudinal follow-up of these rare diseases including organ-specific outcome is needed internationally using standardized outcome measures. The EuroMyositis Registry (https://euromyositis.eu) may be used to facilitate this.

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Conflicts of interest

The author has received coverage for travel and accommodation expenses (European Congress of Rheumatology 2016) from UCB Nordic A/S.

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- ▪ of special interest
- ▪▪ of outstanding interest

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Many studies have shown an increased risk of VTE in other connective tissue diseases. This study is unique in beeing the first study to show an increased risk of VTE in patients with myositis.

Immune-mediated necrotizing myopathy associated with statins: history and recent developments

Eleni Tiniakou and Lisa Christopher-Stine

Purpose of review
The use of statins has increased exponentially over the last 2 decades. Consequently, side effects have also increased, with muscle-related side effects commonly reported.

Recent findings
Although once thought to be only associated with self-limited direct myotoxicity, statins have recently been described in association with an autoimmune myopathy in association with antibodies directed against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate limiting enzyme in cholesterol synthesis and the pharmacologic target of statins. Since this discovery, various cohorts have been identified worldwide and highlight both similarities and differences among them.

Summary
Recent studies from different fields have revealed diverse aspects of anti-HMGCR-associated immune-mediated necrotizing myopathy (IMNM). HMGCR IMNM is a unique autoimmune disease characterized by a well defined environmental trigger (statins) and a strong association with a genetic risk factor (Human leukocyte antigen D related B 1*11 : 01). New diagnostic modalities have been established to confirm the presence of anti-HMGCR antibody and confirm the diagnosis of HMGCR IMNM. Clinical studies have shown that disease severity, as measured by muscle strength, as well as the rate of response to treatment have been associated with age at disease onset. Furthermore, a case series supported that intravenous immunoglobulin administration, perhaps even as monotherapy, may be a beneficial therapeutic intervention for selected patients.

Keywords
anti-3-hydroxy-3-methylglutaryl-CoA reductase, myopathy, stains, statin myopathy, statin toxicity

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) are a diverse group of autoimmune disorders affecting mainly the skeletal muscles. Typically, patients with IIM experience progressively worsening proximal muscle weakness, and present with elevated muscle enzymes, distinctive electromyography (EMG) abnormalities, characteristic muscle biopsy findings and myositis-specific antibodies. Since 1975, many classification criteria for diagnosis of IIM have been proposed, but the Bohan and Peter [1,2] criteria still remain the most commonly used in clinical practice and research. Nevertheless, emerging data, including the identification of novel myositis-specific antibodies [3], advancement in immunopathologic fields and new insights into the immune-mediated mechanisms involved in the autoimmune processes, emphasize the need to introduce new classification criteria for this heterogeneous group of autoimmune muscle diseases.

In 2004, the Muscle Study Group/European Neuro Muscular Centre (ENMC) classified the IIMs, based predominately on muscle biopsy features, into polymyositis, dermatomyositis, inclusion body myositis, nonspecific myositis and immune-mediated necrotizing myopathy (IMNM) [4]. IMNM was defined by the presence of muscle cell necrosis and degeneration along with a lack of significant inflammatory infiltrates (Table 1). The ENMC criteria introduced a new comprehensive list of exclusion criteria, such as indications of muscular dystrophy

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KEY POINTS

- Anti-HMGCR-associated IMNM. HMGCR IMNM is a distinct autoimmune muscle disease characterized by a well defined environmental trigger (statins) and a strong genetic association (HLA DRB1*11 : 01).
- New diagnostic modalities have been developed to confirm the presence of anti-HMGCR antibody and establish the diagnosis of HMGCR IMNM. Some are now commercially available.
- Whether anti-HMGCR antibodies play a pathogenic role in the disease process is still unclear.
- Disease severity, as measured by muscle strength, as well as the rate of response to treatment have been associated with age at disease onset.
- There are no guidelines for therapy; however, at least some small studies suggest that intravenous immunoglobulin may be beneficial, even as monotherapy.

or perifascicular atrophy, to better differentiate and subclassify patients with this type of myositis. In this review, we intend to summarize and present the recent data regarding the clinical picture, immunopathology and therapeutic options in the field of the statin-associated IMNM.

STATINS

In early 1970s, clinical studies were starting to convey the contribution of cholesterol to atherosclerosis and, therefore, led to the need of new drug development. In 1976, Japanese biochemist Akira Endo was able to isolate three compounds from the fungus species *Penicillium citrinum*, which were able to impede cholesterol synthesis in a mouse liver enzyme system by blocking the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) enzyme [5]. Two years later, the first medication in its class of statins, Mevacor (Lovastatin; Merck, Rockville, MD, USA), was marketed, which was isolated from *Aspergillus terreus*. As of today, seven different statins are available in the US market, and they have proved to be some of the most widely used and profitable medications in recent years.

The use of statins has increased exponentially over the last 2 decades. In 2013, the American College of Cardiology and the American Heart Association published new guidelines for the management of cholesterol [6] based on elevated LDL cholesterol level, the presence of diabetes or the predicted risk of a cardiovascular event. When these guidelines are used to estimate the number of persons in the United States who would be eligible for statin therapy, the number reaches 56 million Americans between the ages of 40 and 75 years [7], accounting for almost one-fifth of the population. Particularly amongst adults between 60 and 75 years, 87.4% of men and 53.6% of women are now advised to be on cholesterol-lowering medications. Consequently, we expect to see a substantial increase in the consumption of statins and their side effects thereof.

STATIN TOXICITY

At least half of the documented statin-associated side effects are related to muscle complaints [8,9]. Various studies have reported that 7–29% of people on statins can develop nonspecific myalgias and weakness [10,11]. As defined by the European Atherosclerosis Consensus Panel, the spectrum of muscle-related events includes a broad range of manifestations, encompassing asymptomatic elevation of creatine kinase, myalgias, rhabdomyolysis, up to myositis or myopathy [12].

There have been many attempts to explain the multitude of myotoxic effects of statins. Inhibition of HMGCR not only decreases the synthesis of cholesterol, which is essential for the maintenance of the cell membrane, but can also have effects on other metabolic pathways, like Coenzyme Q_{10} production and mitochondrial function. Other theories evoked include also individual variations in hepatic uptake of drugs, deficiencies in cell membrane repair or impaired sarcoplasmic reticulum calcium cycling [13,14].

PROTOTYPIC PATIENT

A 59-year-old woman, with history of longstanding diabetes, hypertension and hypercholesterolemia, was started on high-intensity statin (atorvastatin 80 mg) in fashion with the appropriate guidelines. A month later, she noticed that she required help to get out of the car and progressively could not even get up from a chair. When her creatine phosphokinase was checked 8 months later, it was above 17 000. She was diagnosed with statin-induced rhabdomyolysis, and the presumed offender was stopped. Six months later, she continued to complain of muscle weakness. Her EMG was consistent with irritable myopathy, and her muscle biopsy showed necrotizing myopathy with lack of inflammatory infiltrate. Examples like the aforementioned patient, although rare, cultivated the impression that statins were potentially associated with the development of autoimmune muscle disease.

Table 1. European Neuro Muscular Centre diagnostic criteria for immune-mediated necrotizing myopathy [4]

Clinical criteria	
	Inclusion
	Onset over 18 years
	Subacute or insidious onset
	Pattern of weakness
	Symmetric proximal > distal
	Neck flexor > neck extensor
	Exclusion
	Clinical features of IBM
	Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness
	Toxic myopathy, active endocrinopathy, amyloidosis, family history of muscular dystrophy or proximal motor neuropathies
Elevated CK	
Other laboratory criteria (1 of 3)	
	Electromyography (EMG)
	MRI
	Myositis-specific antibodies
Muscle biopsy criteria	
	Inclusion
	Many necrotic muscle fibers as the predominant abnormal histological feature
	Inflammatory cells are sparse or only slight perivascular
	Perimysial infiltrate is not evident
	MAC deposition on small blood vessels or pipestem capillaries on EM may be seen
	Tubuloreticular inclusions in endothelial cells are uncommon or not evident
	Exclusion
	Endomysial inflammatory cell infiltrate (T cells) surrounding and invading nonnecrotic muscle fibers
	Endomysial CD8+ T cells surrounding, but not definitely invading nonnecrotic muscle fibers, or ubiquitous MHC-1 expression
	Perifascicular atrophy
	MAC depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells on EM, or MHC-1 expression of perifascicular fibers
	Perivascular, perimysial inflammatory cell infiltrate
	Scattered endomysial CD8 þ T cells infiltrate that does not clearly surround or invade muscle fibers
	Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers that would suggest IBM
	MAC deposition on the sarcolemma of nonnecrotic fibers and other indications of muscular dystrophies with immunopathology

CK, creatine kinase; EM, electron microscopy; IBM, inclusion body myositis; MAC, membrane attack complex; MHC, major histocompatibility complex.

ANTI-3-HYDROXY-3-METHYLGLUTARYL-COA REDUCTASE AUTOANTIBODY

The muscle-related adverse effects of statins usually resolve within weeks to months after cessation of statins, as they are thought to be due to a noninflammatory, toxic effect [15]. However, some patients would develop persistent myositis and eventually meet the diagnosis of polymyositis, as per Bohan and Peter criteria [16,17]. In the late 2000s, the hypothesis of statins triggering an autoimmune reaction was emerging, quite revolutionary in the concept that a medication can lead to a pure autoimmune development [18].

Still, it was not until 2010, when a new antibody targeted against HMGCR, the pharmacologic target of statins, was described and was able to explain the persistent muscle symptoms [19]. Out of 454 patients of the Johns Hopkins Cohort who were screened, 26 patients were found to have predominant necrosis on muscle biopsy and no known antibody. Sixteen of those were able to immunoprecipitate 200/100 kDa proteins when their sera were assessed using HeLa lysates. These patients had proximal muscle weakness, muscle edema on MRI, irritable myopathy on EMG and elevated creatine kinase levels (mean 10 333 IU/l; range 3052–24 714). When the clinical characteristics of these patients were analyzed, it was detected that 83.3% of those above the age of 50 years old were on a statin, compared with 25% in dermatomyositis and 36.8% in polymyositis. That observation led to further investigation of a potential relationship between drug exposure and this newly found autoantibody. Initially, it was established that statins were able to upregulate the expression of the 200/100-kDa autoantigen in muscle fiber cultures [20]. That could mean that the target autoantigen could be any of the 19 enzymes involved in the mevalonate pathway. As HMGCR is a 97-kDa protein, it stood to reason that it would be the first one to screen. Indeed, the recognition that the novel autoantibody recognized the HMGCR, led to the formation of a new subgroup of IIM known as anti-HMGCR associated IMNM. The 200-kDa protein has not been identified to date but thought to potentially be a dimer.

To test the diagnostic utility of this new antibody, 1966 participants of a community-based Atherosclerosis Risk in Communities Study and 98 French Canadian patients with familial hypercholesterolemia were screened for the presence of anti-HMGCR antibodies. None of those patients were found to be positive for these autoantibodies, although a significant portion of those were exposed to a statin. Therefore, anti-HMGCR could be used as a discriminating factor between self-resolved toxic myopathy and IMNM, which requires immunosuppressive treatment [21]. This was also verified at a consequent study amongst 101 patients with severe self-limited statin intolerance and proved that self-limiting symptoms are not associated with autoantibody formation [22]. In addition, when 47 patients with an inherited muscle disease were screened, none of those were found to be positive for anti-HMGCR, suggesting once again that these antibodies are highly specific [23]. Contrariwise, when eight refractory patients had whole exome sequencing of their DNA, no pathogenic mutations in dystrophy genes were discovered [24▪].

IMMUNOFLUORESCENCE PATTERN

The commonly used diagnostic method for anti-HMGCR antibodies has been an ELISA, which sensitivity has been verified when compared with the gold standard procedure of immunoprecipitation assay. A new screening method based on immunofluorescence pattern has recently been suggested, in which the antibodies create a centrolobular distribution amongst stained rat hepatocytes [25▪]. This observed pattern was unique for anti-HMGCR antibodies and can be used as an initial screening test, as it is relatively inexpensive.

MUSCLE BIOPSY FINDINGS

As mentioned previously, the anti-HMGCR autoantibody was discovered on the basis of observations based on patients with IMNM. All consecutive patients of the Johns Hopkins Cohort were screened for anti-HMGCR, and muscle biopsies from 18 patients were available for review [26]. The majority of those patients were exposed to statins (16/18 or 88.9%). The data confirmed the predominance of myofiber degeneration and infiltrating macrophages of the M2 phenotype, known to contribute to muscle regeneration and repair. Major histocompatibility complex class I was found to be upregulated in the majority of the biopsies, consistent with IIM. However, 20–30% of them had also collections of inflammatory cells, 50% of which were identified as scattered T cells (CD4+ and CD8+). The above results were also confirmed at a European and another US cohort, with the only difference that the exposure to statins was significantly lower [27,28].

Given the rarity of infiltrating T cells, the presence of membrane attack complex depositions on nonnecrotic muscle fibers and association of antibody titers with disease severity, the authors hypothesized on the interaction of autoantibodies and complement cascade as the main pathogenetic

pathway for anti-HMGCR IMNM [26]. Concurring to the idea aforementioned, culture of muscle fibers with anti-HMGCR antibodies in an in-vitro system induced muscle fiber atrophy and decreased myofiber fusion [29▪▪]. The above outcome implicates the autoantibodies as being pathogenic, rather than an epiphenomenon of an autoimmune process. However, further studies need to be conducted to confirm the results *in vivo* as well.

CLINICAL CHARACTERISTICS/STATIN EXPOSURE

The typical clinical picture of anti-HMGCR IMNM involves a patient with proximal muscle weakness and significantly elevated creatine kinase levels. Although proximal muscle weakness is commonly uniform between the patients with anti-HMGCR+ IMNM, extramuscular manifestations are relatively rare. These can include dysphagia, skin or lung involvement [19,24▪,27,30,31].

However, there are differences depending on the origin of the described cohort. Many anti-HMGCR myositis cohorts have been reported worldwide (Table 2). The Johns Hopkins cohort reported mean age of patients 55 years (52.4–57.6), with female (59%) and white (72%) predominance, and elevated creatine kinase of 2812 IU/l (1399–6821 IU/l). The majority of those had a prior history of statin exposure (75%) [24▪]. In juxtaposition, a cohort from central United States described anti-HMGCR IMNM in patients with mean age 50 years old, 67% women, 76% whites and only 38% reported use of statins (18/47) [28]. In a study from Australia, the mean age of the typical patient was 70 years old (55–89 years), male (61%) and 84% exposed to statins (16 out of 19) [32]. When assessing a single-center cohort from the Czech Republic, 36% of them were men, mean age of 55 years old, and all of them admitted use of statins (15 out of 15, 100%) [33]. Similarly, eight patients were described in New Zealand with mean age 67.8 years and 75% exposure to statins [34]. At the same time, France, China and Japan documented to have a much lower statin exposure. The French Myositis Network reported 45 anti-HMGCR+ patients, of whom 73% were women, with a mean age of 48.9, and only in 44%, there was an association with statins [27]. The study from China identified only 15% prevalence of statin exposure in anti-HMGCR positive patients. However, only five out of the 22 patients were over the age of 50 years old [30]. In Japan, the mean age of anti-HMGCR+ patients was 56.4 and only 18% (eight out of 48) had ever been on a statin [31].

Lastly, collaborative work comprising nine different countries, including China and France, reported a mean age of 62.5 (58.0–67.0) with a statistically significant ratio of increased statin users amongst the patients with anti-HMGCR myopathy (52 out of 91) [39▪]. The difference in statin exposure is probably associated with the mean age of the relevant cohort, as statin prevalence is associated with increasing age.

GENETIC RISK FACTORS

HMGCR INMN is additionally unique, as it has one of the strongest associations between an immunogenetic risk factor and autoimmune disease. The class II human leukocyte antigen (HLA) allele D related B (DRB)1*11 : 01 has an odds ratio (OR) of 24.5 in whites and 56.5 in blacks [44]. The above finding has been verified in different cohorts from Australia and Japan as well [32,45]. Interestingly enough, a recent study based on a pediatric cohort from the United States showed an association with DRB1*07 : 01 [41▪]. That implies that there is probably a different mechanism causing autoimmunity between children and adults that does not involve statin exposure and most likely involve different epitope recognition.

TITERS AND STRENGTH AND AGE

At an initial study in 2012, the titer of anti-HMGCR antibodies was associated with creatine kinase and inversely correlated with muscle strength but only for statin exposed patients. Although autoantibody titers and creatine kinase levels decreased over time with treatment in statin exposed patients, on the other hand, statin naïve patients were quite resistant, implying reasonably a different pathogenetic process [35]. However, a follow-up analysis of the same cohort showed that a history of statin exposure was not independently associated with the severity and the improvement rate, as measured by increase in muscle strength. Instead, age at disease onset associated with severity; interestingly and somewhat counterintuitively, patients who were older at disease onset were usually stronger and were found to improve faster than younger patients [24▪].

DIABETES

Type 2 diabetes mellitus has been associated with anti-HMGCR myopathy at the Johns Hopkins cohort (OR: 15.6, $P = 0.006$) [46▪], although this relationship was not maintained in the Australian cohort, when controlling for sex and statin use [32].

Table 2. Clinical and laboratory characteristics of HMGCR+patients across different study populations

Reference	Country	No of HMGCR+ patients	No of screened patients	Statin exposed patients [% (no)]	Mean age at disease onset in years (range)	Females [% (no)]	Screening/ verification of anti-HMGCR antibodies	Mean CPK [IU/l (range)]	Dysphagia [% (no)]	Myalgia [% (no)]	Cancer [% (no)]	Skin rash [% (no)]	ILD [% (no)]	Arthralgia [% (no)]	IMNM [% (no)]	DRB 1*11:01 [% (no)]
Christopher-Stine *et al.* [19]	USA	16	26	63% (11/16)	54	63% (10/16)	ELISA/IP	10 333 (3052–24 714)	63% (11/16)	75% (12/16)	13% (3/16)	44% (7/16)	0% (0/16)	50% (8/16)	–	–
Mammen *et al.* [20]	USA	45	750	66.6% (30/45)	52 ± 16	57.8% (26/45)	ELISA/IP	9718 ± 7383	–	–	–	–	–	–	100% (40/40)	–
Werner *et al.* [35]	USA	55	1006	72.7% (40/55)	–		ELISA/IP	10 104 ± 6973	–	–	–	–	–	–	71.7% (38/53)	–
Allenbach *et al.* [27]	France	45	206	44% (20/45)	48.9 ± 21.9	73.3% (33/45)	ALBIA	6941 ± 8802	26.7% (12/45)	53.3% (24/45)	–	–	2.2% (1/45)	11.1% (5/45)	97.6% (42/43)	–
Ramanathan *et al.* [36]	Australia	6	–	100% (6/6)	70 (60–77)	50% (3/6)	ELISA	6126 (2700–16 200)	–	–	–	–	–	–	100% (6/6)	–
Limaye *et al.* [32]	Australia	19	207	94% (16/17)	70 (55–89)	42% (8/19)	ELISA/ immunoblot	–	–	–	26% (5/19)	–	–	–	9% (2/19)	90% (10/11)
Klein *et al.* [33]	Czech Republic	15	217	100% (15/15)	67 (55–76)[a]	64% (7/11)	ELISA	–	–	36% (4/11)	–	–	–	–	73% (11/15)	–
Ge *et al.* [30]	China	22	405	15% (3/20)	–	73% (16/22)	ELISA	2538.7 ± 3047.6	50% (10/20)	70% (14/20)	–	–	15% (3/20)	25% (5/20)	67% (8/12)	–
Watanabe *et al.* [37]	Japan	8	460	37.5% (3/8)	65.5 (49–79)	37.5% (3/8)	ELISA/IP	7737 (3028–10 452)	0% (0/8)	37.5% (3/8)	–	–	–	–	–	–
Alvarado-Cardenas *et al.* [25▪]	Spain	23	0	14 (6 patients missing data)	63 (52–82)		ELISA/i mmunoblot	6941 (2270–18 417) 50% (7/14)	–	50% (7/14)	–	–	–	–	–	83% (5/6)
Kennedy *et al.* [34]	New Zealand	8	425	75% (2/8)	67.8 (56–81)	50% (4/8)	ELISA	10 500 (4200–21 800)	–	–	–	–	–	–	–	–
Kadoya *et al.* [38▪]	Japan	33	621	21% (7/33)	59 ± 15	70% (23/33)	ELISA/ Western Blot	9767 ± 8131	24% (8/33)	42% (14/33)	36% (12/33)	15% (5/33)	3% (1/33)	6% (2/33)	–	–
Musset *et al.* [39▪]	Belgium, Canada, China, Chech Republic, France, Hungary, Italy, Japan, Mexico				62	1906	52% (31/60)	62.5 (58.0–67.0)	–	ELISA	–	–	–	–	–	–
–	74% (32/44)	–														
Watanabe *et al.* [31]	Japan	46	460	18% (8/45)	56.4 ± 16.1	69% (31/45)	ELISA/IP	6436 ± 4403	44% (20/45)	22% (10/45)	4% (2/45)	4% (2/45)	7% (3/45)	0% (0/45)	100% (45/45)	–
Allenbach *et al.* [40▪]	France	52	–	46.1% (24/52)	50 ± 22	73.1% (38/52)	ALBIA	7012 ± 5944	–	–	17% (9/52)	0% (0/52)	–	–	–	–
Tiniakou *et al.* [24▪]	USA	104	1947	75% (78/104)	55.0 (52.4, 57.6)	59% (61/104)	ELISA/IP	2812 (1399–6821)	27% (29/104)	–	6% (6/104)	5% (5/104)	4% (4/104)	–	77% (80/104)	–
Kishi *et al.* [41▪]	USA	5	440	0% (0/5)	8.1 (7.1–12.0)	60% (3/5)	ELISA/IP	–	60% (3/5)	40% (2/5)	–	60% (3/5)	0% (0/5)	100% (5/5)	40% (2/5)	0% (0/5)
Liang *et al.* [42]	Japan	9	62	0% (0/9)	7.2 (0.8–13)	56% (5/9)	ELISA	6553 (352–10 891)	–	22% (2/9)	–	22% (2/9)	0% (0/9)	–	100% (9/9)	–
Tansley *et al.* [43]	UK	4	381	0% (0/4)	9.25 (4–13)	75% (3/4)	ELISA/ Western Blot	15 500 (12 180–44 002)	–	–	–	50% (2/4)	–	–	0% (0/4)	–

CPK, creatine phosphokinase; DRB, D related B; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy.
[a]Octapharm for LCS disclosures.

CANCER

The association between inflammatory myopathy and cancer was initially described at the beginning of the twentieth century and has since been established in different cohorts [47]. Similarly, an association was investigated by Limaye *et al.* [32] but was not statistically significant. However, in the French cohort, anti-HMGCR-positive myositis patients were indeed found to have a modestly increased risk of malignancy (17.3%), with a mean age at the age of diagnosis of cancer of 67 ± 15 years, whereas the mean age at the diagnosis of myopathy was 50 ± 22 years [40▪]. That implies that the older the patient develops myopathy, the more likely it is to be diagnosed with myositis associated malignancy. Comparably, 36% of anti-HMGCR+ Japanese patients were identified to have synchronous cancer (92% within 1 year of the myositis diagnosis) and 33% of them had history of statins (four out of 12) [38▪]. The authors concluded that malignancy itself could be a trigger, rather than exclusively the statin, which could lead to the development of HMGCR+ myopathy. At the opposite end of the spectrum, no association with malignancy was found at the Johns Hopkins cohort, which comprises patients of older age and with a higher prevalence of statin use [24▪].

THERAPY

Self-limited statin-induced toxic myopathy generally resolves within few weeks to months after cessation of the medication. In the case of anti-HMGCR IMNM, however, statins are thought to trigger a perpetual autoimmune process. On rare occasions, patients have been reported to improve without the use of immunosuppression [24▪,27], but the majority of anti-HMGCR-positive patients require intensive treatment for control of their disease. Previous reports have indicated that patients often require at least two agents for remission of the disease, as established by improvement of the muscle strength [24▪,27,31], but one case series suggested that intravenous immunoglobulin (IVIG) monotherapy could be adequate for a specific subset of patients [48]. Given the recent association of severity of disease with age at disease onset [24▪], we would suggest tailoring the intensity of the treatment to the age of the patient.

CONCLUSION

Recent studies from different fields have revealed diverse aspects of the anti-HMGCR associated IMNM. HMGCR IMNM is a unique autoimmune disease characterized by a well defined environmental trigger (statins) and a strong association with a genetic risk factor (HLA DRB1*11 : 01). New diagnostic modalities have been developed to confirm the presence of anti-HMGCR antibody and establish the diagnosis of HMGCR IMNM. Whether anti-HMGCR antibodies play a pathogenic role in the disease process remains to be addressed. Clinical studies have shown that disease severity, as measured by muscle strength, as well as the rate of response to treatment have been associated with age at disease onset. Furthermore, a case series supported that IVIG administration may be a beneficial therapeutic intervention for selected patients.

Given the rarity of the disease, multicenter studies are required to recruit sufficient number of patients to study the clinical spectrum of the disease, to understand the immunopathologic mechanisms involved in disease pathogenesis, and to test additional therapeutic choices. The discovery of key molecular and biological pathways involved in the disease process could offer the opportunity to identify potential diagnostic and prognostic biomarkers and thus lead to innovative therapeutic targets.

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Conflicts of interest

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Clinical spectrum of anti-Jo-1-associated disease

Sara Monti, Carlomaurizio Montecucco, and Lorenzo Cavagna

Purpose of review
To provide the most recent evidence on anti-Jo-1 syndrome.

Recent findings
Several new evidences on anti-Jo-1 syndrome have recently emerged. It has been clearly established that, at disease onset, the classic clinical triad (arthritis, myositis and interstitial lung disease – ILD) is only rarely observed. Indeed, disease onset with an isolated arthritis is common. Patients presenting with an isolated manifestation are at high risk for the subsequent occurrence of initially lacking triad findings. Moreover, the ex-novo occurrence of accompanying features such as Raynaud's phenomenon, mechanic's hands and fever during follow-up is a strong risk factor for the occurrence of overt antisynthetase syndrome (ASSD) with further triad manifestations. Several contributions on ILD involvement and prognosis have been published, as well as the distinctive muscle MRI characteristics compared with healthy controls, and a novel definition of a rare skin manifestation (hiker's feet).

Summary
Recent evidence has shed a light on the need for a better understanding of the clinical course, imaging modalities and prognosis of anti-Jo-1 syndrome, providing some relevant elements to allow early diagnosis of this often unrecognized disease.

Keywords
anti-Jo-1 syndrome, antisynthetase syndrome, arthritis, interstitial lung disease, myositis

INTRODUCTION

Increasing interest has been recently directed toward a better understanding of antisynthetase syndrome (ASSD) and, particularly, of anti-Jo-1-positive patients. Anti-Jo-1-associated disease represents the most common form of ASSD, a connective tissue disease included in the spectrum of idiopathic inflammatory myopathies (IIMs), characterized by the presence of antiaminoacyl-tRNA synthetase (ARS) antibodies and leading to systemic, multiorgan clinical manifestations, not limited to muscle involvement. Very large multicentric cohorts have been developed [1,2▪▪,3▪▪,4▪,5▪▪,6▪▪,7▪], allowing to focus on clinical and laboratory aspects of anti-Jo-1 syndrome, leading to the identification of previously unrecognized aspects.

The aim of this review is to provide the most relevant evidences regarding anti-Jo-1 syndrome published in 2016 and 2017.

CLINICAL SPECTRUM TIME-COURSE OF ANTI-JO-1 SYNDROME

Anti-Jo-1 syndrome is typically associated with the classical clinical triad: arthritis, myositis and interstitial lung disease (ILD), reported in up to 90% of cases [1]. Raynaud's phenomenon, mechanic's hands and fever are other typical, but less commonly observed, features defined as 'accompanying findings' for practical purposes. Nevertheless, a relevant proportion of patients do not present with the complete triad, but experience an 'incomplete' disease pattern [1,2▪▪,3▪▪]. This often represents the main reason for unrecognized or delayed diagnosis. In 2015, the American, European NEtwork of Antisynthetase Syndrome (AENEAS) collaborative group demonstrated that patients with anti-Jo-1 syndrome presenting with an incomplete disease experience a significant trend toward the ex-novo occurrence of classical triad findings during follow-up, particularly when disease onset is characterized by a single triad manifestation [1]. Similar results have been confirmed in 2016 by another study performed on a large series of anti-Jo-1-positive Spanish patients

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KEY POINTS

- At disease onset, anti-Jo-1 syndrome often presents with isolated symptoms or incomplete clinical forms that require a high level of suspicion at a multidisciplinary level to ensure prompt recognition, even when different diagnoses may seem likely.
- The occurrence of accompanying features (mechanic's hands, Raynaud's phenomenon and fever) carries a four-fold risk of development of classical clinical triad (arthritis, myositis and ILD).
- Anti-Ro antibodies, mainly anti-Ro52 kDa, are detected in about 50% of anti-Jo-1-positive patients, whereas cytoplasmic positivity of antinuclear antibody test is a strong clue for an underlying ASSD.
- Promising evidence is emerging on the role of anti-Jo-1 antibodies titers as a useful monitoring tool for the evaluation of lung and muscle treatment response.
- There is an increased need to develop shared and internationally recognized ASSD classification criteria.

[2▪▪]. The multicenter Spanish IIM and Autoimmune Diseases Study Group investigated the clinical manifestations and long-term outcome of 148 patients affected by anti-Jo-1 syndrome. The majority of patients presented with an incomplete form: isolated ILD 47 (32.4%) patients, isolated myositis 39 (26.9%) patients and isolated polyarthritis 26 (17.9%) patients. Only a minority had a stable disease at the end of follow-up with isolated ILD still reported in 21 (14.5%) of patients, isolated myositis in 23 (15.9%) and isolated polyarthritis in three (2.1%) patients. Median follow-up was 78.3 months, estimated survival rates were 87.7% at 5 years and 75.4% at 10 years, with a four-fold higher mortality rate compared with the general population, mainly due to pulmonary complications and cancer.

It has also been shown that anti-Jo-1-positive patients, without a complete triad, but with ex-novo occurrence of accompanying features during follow-up (e.g. Raynaud's phenomenon, fever or mechanic's hands) have nearly a four-fold increased risk of short-time classic triad occurrence and should be carefully monitored for this possibility [6▪▪]. Of notice, disease progression often occurs despite immunosuppressive treatment. An overview of the most recent evidence on the evolving spectrum of ASSD is presented in Table 1.

UPDATES ON PULMONARY INVOLVEMENT IN ANTI-JO-1 SYNDROME

Waseda *et al.* [8] cross-sectionally analyzed pulmonary high-resolution computed tomography findings in 64 patients with ARS-associated ILD, of whom 16 (25%) were positive for anti-Jo-1 antibodies. Ground-glass attenuation was the most commonly observed lesion (98.4% of patients), followed by interlobular septal thickening (76.6%), reticulation (67.2%) and air space consolidation (48.4%), whereas honeycombing was a rare finding (3.1%). A nonspecific interstitial pneumonia (NSIP) pattern was reported in 55% of cases, organizing pneumonia, with or without fibrosis, in 41% of cases, whereas only one patient had evidence of usual interstitial pneumonia (UIP). Significantly, the majority of patients were diagnosed with idiopathic pulmonary fibrosis (IPF) and a diagnosis of ASSD was not recognized in any of the assessed cases. However, given the pneumological setting of patients described by Waseda *et al.*, a referral bias between pulmonary and rheumatologic centers should be considered when interpreting these results. The higher frequency of ASSD-associated NSIP pattern, followed by organizing pneumonia has been confirmed in another large cohort of anti-Jo-1-positive patients described by Zamora *et al.* [9]. The 10-year survival rate of patients with ILD in this cohort was particularly high (68%), thus suggesting that ARS-associated ILD, especially if related to anti-Jo-1 antibodies, has a better prognosis compared with other lung fibrosing conditions. Aggarwal *et al.* [10▪] showed that patients with IIMs–UIP, including those with anti-Jo-1 antibodies, had a better cumulative and event-free pulmonary survival time compared with their idiopathic counterparts (5.25/1.8 years versus 16.2/10.8 years). Similarly, Tanizawa *et al.* [11▪] confirmed a better prognosis of ARS-ILD compared with IPF on a large cohort of patients (36 anti-Jo-1, 100 IIP and seven NSIP negative for ARS). On the other hand, no significant survival differences were observed between ARS-positive ILD and ARS-negative NSIP (log-rank test, $P = 0.59$).

Nevertheless, some negative prognostic factors have been recently identified in ASSD. Black American ethnicity has been described as an independent prognostic factor associated with increased lung involvement severity [4▪], whereas male sex and reduced diffusion capacity of the lung for carbon monoxide at ILD presentation with reduced survival [9].

From a therapeutic point of view, Bauhammer *et al.* [12▪▪] confirmed the effectiveness of rituximab in anti-Jo-1 syndrome patients with refractory ILD, in particular in cases of concomitant high titers of anti-Ro52-kDa antibodies.

UPDATES ON MYOSITIS IN ANTI-JO-1 SYNDROME

In 2017, Andersson *et al.* [13▪▪] published a cross-sectional muscle MRI analysis including 68 ASSD patients (men/women: 23/45, of whom 57 were

Table 1. Disease pattern change over follow-up of patients with antisynthetase syndrome: overview of the most recent evidence

Study	Cavagna *et al.* on behalf of AENEAS 2015 [1]	Trallero-Araguás *et al.* on behalf of GEAS 2016 [2▪▪]	Cavagna *et al.* on behalf of AENEAS 2017 [3▪▪]	Pinal-Fernandez *et al.* 2017 [4▪]	Bartoloni *et al.* 2017 [6▪▪]
Design	International, multicenter, retrospective	National, multicenter, retrospective	International, multicenter, retrospective	Monocentric, longitudinal cohort	International, multicenter, retrospective
Patients number	225 (M/F: 58/167)	148 (M/F: 58/90)	58 (M/F: 45/13)	169 (M/F: 46/123)	165 (M/F: 42/123)
ARS-antibodies	Anti-Jo-1 (100%)	Anti-Jo-1 (100%)	Anti-Jo-1 (100%) with isolated arthritis at onset	-124 (73.4%) anti-Jo-1; 23 (13.6%) anti-PL12; 16 (9.5%) anti-PL7; 3(1.8%) anti-EJ and anti-OJ	Anti-Jo-1 (100%) with incomplete onset
Other antibodies	-Anti-Ro52 (54%); -ACPA/RF (13.5%/31.5% of arthritis)	-Anti-Ro52 (65%); -ACPA/RF (15% of arthritis)	-Anti-Ro52 (47%); -ACPA/RF (39%/28% of arthritis)	-Anti-Ro52 (66%)	-
Age (year) (median; IQR or mean ± SD)	53.5 (46.5–62.0)	50.8 ± 16	54 (43–62)	47.4 ± 13.5	53 (42–64)
Follow-up months (median; IQR or mean ± SD)	82 (40–147)	78.3 (38.1–140)	84 (58–151)	49 ± 40	94 (49–156)
Clinical presentation at disease onset					
Complete triad	44 (19.5%)	–	–	–	99 (60%)
Myositis + ILD	25 (35.5%)	33 (22.8%)		Anti-Jo-1: 43(35%); Anti-PL12: 2(9%); Anti-PL7: 5(31%)	25 (15%)
Isolated arthritis	54 (49%)	26 (17.9%)	58 (100%) as per study design	Anti-Jo-1: 13(10%); Anti-PL12: 5(22%); Anti-PL7: 0(0%)	48 (29%)
Isolated myositis	28 (25.5%)	39 (26.9%)		Anti-Jo-1: 32(26%); Anti-PL12: 0(0%); Anti-PL7: (12%)	27 (16%)
Isolated ILD	28 (25.5%)	47 (32.4%)		Anti-Jo-1: 32(26%); Anti-PL12: 15(65%); Anti-PL7: 9(56%)	24 (15%)
End of follow-up					
Disease progression	107 (59%)	134 (90%)	53 (91%)	>60%	95 (57.5%)
Time to progression, months (median, IQR)	12 (6–40.8)	Range 16.9–33.6 (6–72)	14 (8–42)	–	15 (9–51)
Complete triad	113 (50%)	–	33 (57%)	–	64 (39%)
Myositis + ILD	33 (30%)	98 (67.6%)	–	Anti-Jo-1: 74(60%); Anti-PL12: 15(65%); Anti-PL7: 13(81%)	30 (18%)
Isolated arthritis	5 (4.5%)	3 (2.1%)	–	Anti-Jo-1: 4(3%); Anti-PL12: 0(0%); Anti-PL7: 0(0%)	5 (3%)
Isolated myositis	5 (4.5%)	23 (15.9%)	Developed myositis 38 (65.5%)	Anti-Jo-1: 32(26%); Anti-PL12: 1(4%); Anti-PL7: 0(0%)	6 (3.5%)
Isolated ILD	15 (13%)	21 (14.5%)	Developed ILD 48 (83%)	Anti-Jo-1: 13(10%); Anti-PL12: 7(30%); Anti-PL7: 3(19%)	15 (9%)
Risk factors for progression	Single main feature onset	Younger age at onset → ILD + myositis	–	Anti-Ro52: earlier arthritis, mechanic's hands and skin changes; anti-PL7, anti-PL12: GERD	Occurrence of new accompanying findings (RF, mechanic's hands, fever)

ACPA, anti-cyclic citrullinated peptide antibodies; AENEAS, American and European Network of Antisynthetase syndrome; ARS antibodies, anti-aminoacyl-tRNA synthetase antibodies; FR, Raynaud's phenomenon; FVC, forced vital capacity; GEAS, idiopathic inflammatory myositis-Autoimmune diseases Study Group; GERD, gastro-esophageal reflux disease; ILD, interstitial lung disease; RF, rheumatoid factor.

positive for anti-Jo-1 antibodies) and 67 matched controls. In ASSD patients, thigh muscle MRI changes were more frequently detected in the posterior compartment, followed by the anterior and medial compartments, with muscle edema and fatty replacement, respectively, predominant in the anterior and in the posterior compartments. Furthermore, the extent of total muscle edema on MRI correlated with creatine kinase levels and with anti-Ro52 kDa positivity, but not with muscle strength and endurance, which conversely correlated with MRI damage extent, indicated by the degree of fatty replacement and muscle volume reduction.

Even if the results of this study are interesting, the important issue of the lack of a clear definition of normal muscle volumes was raised, making muscle atrophy often difficult to assess as possibly influenced by sex, age and physical activity. Finally, muscle MRI alterations such as edema, damage, fatty replacement and volume reduction were also observed in healthy controls, even if in a milder form, and with very rare concomitant signs of muscle edema and damage. Further prospective studies will be useful to clarify the progression of MRI signs of disease activity and damage; nevertheless, the significance and specificity of MRI findings certainly need to be further addressed.

In a recent detailed review, Meyer *et al.* [14] reported on the distinguishing histologic changes characterized by the presence of perifascicular necrotic fibers expressing both human leukocyte antigen (HLA-I) and HLA-II, and carrying C5b-9 membrane attack complex deposits that may differentiate ASSD from dermatomyositis.

Finally, in a cohort of 28 patients, Aggarwal *et al.* [15▪▪] showed that anti-Jo-1 levels decreased after rituximab treatment and strongly correlated with myositis core-set measures, such as creatine kinase levels, the manual muscle test, physician and patient global disease activity, health assessment questionnaire and extramuscular disease activity. This strong association between anti-Jo-1 levels and clinical outcomes supports an innovative role for anti-Jo-1 autoantibodies as effective biomarkers in the assessment of ASSD activity and suggests a pathogenic role of anti-Jo-1 antibodies.

UPDATES ON ARTICULAR INVOLVEMENT IN ANTI-JO-1 SYNDROME

Arthritis related to ASSD is a relevant issue that has been analyzed in recent years by the *French Club Rhumatisme et Inflammation* [16,17] showing that anticyclic citrullinated peptide antibodies (ACPA) positivity is associated with severe and erosive arthritis, and that a seronegative polyarthritis may be the presenting finding of ASSD, particularly in patients with concomitant Raynaud's phenomenon.

The AENEAS collaborative group recently reported data on 243 anti-Jo-1-positive patients and demonstrated that isolated arthritis was the presenting finding of ASSD in 58 cases (24%) [3▪▪]. Differential diagnosis in patients with ASSD arthritis can be particularly challenging, especially when polyarticular involvement is associated with rheumatoid factor and/or ACPA positivity, possibly with erosive findings on radiographs. Indeed, in this cohort, arthritis was polyarticular in 41 cases (71%), oligoarticular/asymmetrical in 17 (29%), IgM-rheumatoid factor was positive in 22 out 57 patients (39%) and ACPA in 13 out of 47 cases (28%). Anti-Ro antibodies were positive in 27 patients (47%). Significantly, despite having ASSD, all patients with symmetrical polyarthritis fulfilled the 1987 revised ACR classification criteria for rheumatoid arthritis (RA) [18]. Furthermore, the development of classic triad findings lacking at disease onset was really common, being observed in 49 cases (91% of cases). Myositis was developed by 38 patients (65.5%), whereas ILD occurred in 48 patients (83%) after a median time from arthritis onset of 17 and 14 months, respectively. The complete triad was eventually reported in 33 patients (57%) after a variable period of time, ranging from a few months to several years. Most patients progressed despite immunosuppressive treatment, often having been prescribed for suspected RA. These findings highlight the need for anti-Jo-1 antibodies screening in patients presenting with isolated arthritis. This aspect is particularly relevant as some cases of anti-TNF-alpha-induced anti-Jo-1-positive myositis or ILD reported in the setting of RA [19] may be related to the natural history of an unrecognized ASSD disease rather than to anti-TNF-alpha agents.

UPDATES ON CUTANEOUS INVOLVEMENT AND OTHER LESS FREQUENTLY REPORTED MANIFESTATIONS OF ANTI-JO-1 SYNDROME

Recently, a novel cutaneous finding in IIMs has been described as 'hiker's feet' [20▪▪], the correspondent of mechanic's hands at the level of toes and plantar surface and traditionally defined as mechanic's feet. Although rare (0.4% in a cohort of 2145 patients with IIMs), and often occurring together with hands involvement, this manifestation should be kept in mind, particularly when assessing patients for suspected ASSD. In this cohort, 67% of patients with hiker's feet presented with anti-Jo-1 antibodies.

Anecdotal reports over the last 12 months focused on the potential cardiac involvement due to ASSD in

the form of global myocardial edema, only detected with dedicated magnetic resonance mapping techniques [21]. Finally, Casal-Dominguez *et al.* [22] observed a decreased pressure of lower esophageal sphincter and a higher proportion of hypotonic lower esophageal sphincter in ASSD, including anti-Jo-1-positive patients, compared with other myositis patients. On this basis, the authors suggested that esophageal involvement in ASSD affects smooth muscle of the esophageal body and of the lower esophageal sphincter, as observed in other connective tissue diseases, namely systemic sclerosis [23].

UPDATE ON LABORATORY TESTS IN ANTI-JO-1 SYNDROME

Recent evidence regarding diagnostic tools and laboratory tests for ASSD confirmed that in patients with anti-Jo-1 syndrome presenting with an isolated arthritis, anti-Ro antibodies cooccur in about 50% of cases [3▪▪]. Another relevant and recently confirmed concept is that a negative antinuclear antibody (ANA) test does not exclude a diagnosis of ASSD considered as a whole, or, more specifically of anti-Jo-1 syndrome. Aggarwal *et al.* [5▪▪] tested sera for ANA and cytoplasmic staining on indirect immunofluorescence on a very large single center cohort of ASSD (122 anti-Jo-1 and 80 non-anti-Jo-1-positive patients). ANA test was positive in 50% of cases, whereas a cytoplasmic positivity was reported in 72%. Indeed, cytoplasmic positivity showed high sensitivity (72%), specificity (89%), negative predictive value (95%) and accuracy (86%), but only modest positive predictive value (54%) for ARS antibodies, with a better performance in detecting ASSD compared with ANA positivity.

Therefore, cytoplasmic staining may represent a useful tool for the early suspicion of ASSD in clinical practice.

THE RELATIONSHIP BETWEEN INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES AND ANTI-JO-1 SYNDROME: THE LACK OF SHARED CLASSIFICATION CRITERIA

Despite the increasing interest observed in recent years, there has never been a unified effort to develop data and consensus-driven classification criteria for ASSD that can be accepted and validated as useful to clinicians and researchers around the world. This represents a limit for further advances in terms of clinical, therapeutic and laboratory research on the topic of ASSD. Shared and accepted criteria are pivotal in the design of future clinical trials and prospective investigative studies addressing ASSD. Noteworthy, in such context of general lack of standardization, the rheumatology community recently dealt with the issue of European Respiratory Society/American Thoracic Society-endorsed classification criteria for interstitial pneumonia with autoimmune features (IPAF) [24]. According to these criteria, anti-Jo-1-positive ILD patients with oligoarthritis, Raynaud's phenomenon and mechanic's hands can be classified as IPAF whereas they would most certainly be classified as ASSD by the majority of rheumatologists. This is not a secondary issue as ARS-antibody-positive patients are often first referred to pneumology centers rather than rheumatology clinics.

Recently, to highlight the potential problems related to the lack of classification criteria for ASSD, the AENEAS collaborative demonstrated that 146 (21%) out of the 684 enrolled patients with an established diagnosis of ASSD formulated in a rheumatologic setting would have been classified as IPAF [7▪,24]. At the end of follow-up, 85 (58%) patients would have still been classified as IPAF. The remaining 61 (42%) developed further manifestations that would have met classification criteria for diseases other than ASSD (e.g. RA, IIMs). The problem of the possible misclassification related to the lack of established classification criteria for ASSD has been also recently highlighted by other authors. Chartrand *et al.* [25▪▪] described a cohort of 33 patients with IPAF, including 27 ARS-antibody-positive patients, the majority of whom (44%) were anti-Jo-1-positive. Mejía *et al.* [26▪▪] applied IPAF and Bohan and Peter's criteria (BPC) for IIMs in a cohort of 68 patients with ILD and myositis-specific or associated antibodies, represented by anti-Jo-1 in 65% of cases. Also in this case, IPAF criteria performed well in classifying all patients not fulfilling BPC criteria, which would have effectively classified only 50% of the cohort, underlying the importance of future efforts for the development of dedicated classification criteria.

Nonetheless, despite the criticisms, we should recognize that IPAF classification criteria allow the identification of a critical area of unmet needs for the entire rheumatology community.

CONCLUSION

Recent evidences on the clinical spectrum of anti-Jo-1 syndrome focused on the need of improving our knowledge of the disease course to ensure early diagnosis and prevent damage. The increasingly reported disease onset with single or incomplete clinical features highlights the need to keep a high level of suspicion for ASSD in patients presenting with isolated arthritis or ILD. The implementation of international multidisciplinary collaborative groups enrolling large cohorts of patients represents the only effective way to improve our understanding and management of this

rare, but still not fully acknowledged disease. Future efforts should be aimed at developing internationally recognized classification criteria to overcome the problem of heterogeneity between studies and allow better standardized future research.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Cavagna L, Nuño L, Scirè CA, *et al.* Clinical spectrum time course in anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. Medicine (Baltimore) 2015; 94:e1144.
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This study confirmed the recent finding that most patients with antisynthetase syndrome (ASSD) present with an incomplete form that warrants a high level of suspicion given the four-fold increased mortality risk.

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This study highlighted the frequency (up to 24%) of patients with isolated arthritis at ASSD onset, discussing the relevant risk of misdiagnosis, particularly of rheumatoid arthritis. This evidence is relevant to improve our knowledge of the disease course and allow for early diagnosis.

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This study identified black ethnicity as a strong independent risk factor for pulmonary involvement severity, together with the already known association with antiaminoacyl-tRNA synthetase specificity.

5. ■■ Aggarwal R, Dhillon N, Fertig N, *et al.* A negative antinuclear antibody does not indicate autoantibody negativity in myositis: role of anticytoplasmic antibody as a screening test for antisynthetase syndrome. J Rheumatol 2017; 44:223–229.

This study confirms the important concept that antinuclear antibody (ANA) test is not sufficient to exclude autoantibody positivity in inflammatory myositis. The presence of anticytoplasmic staining is fundamental as this identifies a significant higher proportion of patients (72 compared with 50% with ANA positivity).

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This study showed for the first time that the development of accompanying symptoms (fever, mechanic's hands and Raynaud's phenomenon) are strong predictors of classical synthomatologic triad development. These data add relevant information that can guide the clinicians on a multidisciplinary level.

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This article analyzed the percentage of patients with ASSD who would have been classified as having interstitial pneumonia with autoimmune features (IPAF), identifying 21% out of 684 patients; 55% of them with anti-Jo-1 positivity. The authors concluded that there the development of dedicated ASSD criteria are pivotal to avoid misclassification of these patients.

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This study showed a significantly better survival of ASSD-ILD compared with the idiopathic counterparts.

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This study identified an important measurable marker for acute-onset ILD severity and nonresponse to traditional immunosuppressants. Rituximab was equally effective in patients with anti-Jo-1 syndrome and anti-Ro52 positivity.

13. ■■ Andersson H, Kirkhus E, Garen T, *et al.* Comparative analyses of muscle MRI and muscular function in antisynthetase syndrome patients and matched controls: a cross-sectional study. Arthritis Res Ther 2017; 19:17.

This was an interesting study comparing for the first time the thigh MRI findings of ASSD patients and healthy controls. Significantly, disease-specific MRI findings were not identifying, with some degrees of edema and signs of damage being possibly identified also in healthy individuals. Nevertheless, the extent and frequency of these findings in the healthy were much rarer. Another important issue raised is the difficult assessment of muscle atrophy that can be significantly influenced by age, sex and physical activity.

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This study introduced the important information that anti-Jo-1 antibodies titers correlated with clinical response to rituximab. This has significant clinical implications and should be further explored on larger cohorts of patients. This study included 28 patients.

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This study highlights the potential misclassification of ASSD patients in the new entity recognized as IPAF. In a cohort of 33 patients classified as IPAF, 44% were anti-Jo-1-positive. This underscores the importance of developing dedicated classification criteria for ASSD to ensure diagnostic recognition outside the rheumatologic settings.

26. ■■ Mejía M, Herrera-Bringas D, Pérez-Román DI, *et al.* Interstitial lung disease and myositis-specific and associated autoantibodies: clinical manifestations, survival and the performance of the new ATS/ERS criteria for interstitial pneumonia with autoimmune features (IPAF). Respir Med 2017; 123:79–86.

Similar to the study above, the authors demonstrated that IPAF criteria effectively classify patients who would not fulfill classical idiopathic inflammatory myositis criteria. These patients were anti-Jo-1-positive in 65% of cases, again highlighting the gap left by the lack of dedicated classification criteria.

Which nonautoimmune myopathies are most frequently misdiagnosed as myositis?

Andrew L. Mammen

Purpose of review
To discuss the spectrum of nonautoimmune myopathies that may be misdiagnosed as autoimmune myopathy.

Recent findings
Inherited myopathies, such as dysferlinopathy, calpainopathy, and facioscapulohumeral dystrophy may be misdiagnosed as autoimmune myopathy, especially when they have inflammatory muscle biopsies. Inclusion body myositis is frequently misdiagnosed as polymyositis when rimmed vacuoles are absent on muscle biopsy, and a careful neuromuscular evaluation is not performed. Hypothyroid myopathy can be misdiagnosed as immune-mediated necrotizing myopathy if thyroid function tests, including a T4 level, are not obtained. Self-limited statin myopathy can be distinguished from statin-associated autoimmune myopathy because patients with the former do not have autoantibodies recognizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

Summary
Autoimmune myopathies can usually be distinguished from nonautoimmune myopathies based on a combination of the patient history, neuromuscular exam, laboratory findings, and/or muscle biopsy features.

Keywords
autoimmune myopathy, endocrine myopathy, inclusion body myositis, muscular dystrophy, polymyositis

INTRODUCTION

The autoimmune myopathies include dermatomyositis, polymyositis, and immune-mediated necrotizing myopathy (IMNM) [1]. In contrast, nonautoimmune myopathies include inherited, endocrine, and toxic myopathies. Distinguishing autoimmune from nonautoimmune myopathies is essential because, in general, only the former respond to immunosuppressive therapy. This review will focus on those nonautoimmune myopathies that are frequently misdiagnosed as an autoimmune myopathy. Of note, although emerging evidence suggests that sporadic inclusion body myositis (IBM) may have a significant autoimmune component [2], this disease will be treated as a nonautoimmune myopathy given that it rarely, if ever, improves with existing immunosuppressive therapies.

INHERITED MYOPATHIES

The inherited myopathies can be divided into two main groups, metabolic myopathies and muscular dystrophies. The metabolic myopathies include disorders of glycogen storage and fatty acid oxidation. Patients with either of these can experience episodic muscle weakness, muscle pain, and elevated serum muscle enzyme levels. Such episodes are typically triggered by exercise, fasting, or illness. In addition, patients with glycogen storage disorders may have proximal weakness and elevated muscle enzyme levels between episodes of more severe muscle symptoms; these patients are occasionally misdiagnosed as having an autoimmune myopathy. However, as disorders of fatty acid oxidation are only rarely accompanied by fixed weakness and/or elevated creatine kinase levels, they are not discussed further here.

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KEY POINTS

- Facial weakness, asymmetric weakness, scapular winging, and/or prominent distal weakness are uncommon features of autoimmune myopathies and suggest the possibility of inclusion body myositis or a muscular dystrophy.
- Exercise-induced muscle cramping and/or creatine kinase elevations should prompt an evaluation for metabolic myopathies.
- A careful review of medications is required to exclude the possibility of a toxic myopathy caused by statins, colchicine, hydroxychloroquine, and others.
- A nonautoimmune cause should be suspected in patients with muscle disease who do not have extramuscular manifestations or a myositis autoantibody.

Although more than a dozen different glycogen storage disorders have been identified, myophosphorylase deficiency (i.e., McArdle's disease) and adult-onset acid maltase deficiency (i.e., Pompe disease) are the most common and most likely to be misdiagnosed as autoimmune myopathy. Myophosphorylase deficiency is an autosomal recessive disorder caused by mutations in *PYGM*, a gene that encodes a muscle-specific glycogen phosphorylase [3]. Affected patients are unable to utilize glycogen stores for energy and present in childhood or early adulthood with exercise-induced cramping, markedly elevated creatine kinase levels (often over 10 000 IU/l), and myoglobinuria. Interestingly, after ~10 min of exercise, these symptoms may spontaneously improve or resolve. This unique characteristic of myophosphorylase deficiency, known as the 'second wind phenomenon', distinguishes it from other metabolic myopathies. Although younger patients with myophosphorylase deficiency are usually strong between episodes, they may have moderately elevated creatine kinase levels even when resting. In addition, older patients can develop progressive proximal muscle weakness that, in association with elevated muscle enzyme levels, may lead to a misdiagnosis of autoimmune myopathy. This diagnostic error can usually be avoided by eliciting a history of exercise-induced cramping with the second wind phenomenon. In patients with this unique feature, a diagnosis of myophosphorylase deficiency can be confirmed directly by sequencing the *PGYM* gene. The diagnosis should also be suspected in patients who have muscle biopsies that reveal subsarcolemmal glycogen deposits best seen with periodic acid-Schiff (PAS) staining. In these cases, the diagnosis can be confirmed by demonstrating the absence of myophosphorylase activity on frozen muscle sections. Unfortunately, effective therapies for myophosphorylase deficiency are not yet available.

Acid maltase deficiency is an autosomal recessive disease caused by mutations in *GAA*, the gene encoding the lysosomal enzyme acid alpha-glucosidase. Individuals with *GAA* mutations resulting in severe reductions in enzymatic activity (<1% of normal), typically present as infants with hypotonia, diaphragmatic weakness, and cardiac involvement; these infants may die within 1 year of birth. Patients with 1–6% of normal enzymatic activity may not present until childhood, but still develop severe proximal muscle weakness and may die from respiratory failure within 5–20 years. In contrast, patients with 1–29% of normal acid alpha-glucosidase activity maybe asymptomatic until middle age and only then develop gradually progressive proximal muscle weakness [4,5]. While these patients may be misdiagnosed as having an autoimmune myopathy, several clues may suggest the possibility of adult-onset acid maltase deficiency instead. First, myotonic discharges on electromyography can be seen in acid maltase deficiency but are rare in patients with autoimmune myopathy. Second, as the diaphragm tends to be more severely involved than other skeletal muscles, a low forced vital capacity on pulmonary function testing should raise a suspicion for acid maltase deficiency. And finally, muscle biopsies from patients with acid maltase deficiency usually reveal PAS-positive vacuoles and do not have inflammatory infiltrates as seen in those with autoimmune myopathy. The diagnosis of acid maltase deficiency can be confirmed using an enzyme activity assay and the precise mutations subsequently identified by gene sequencing. Because a Food and Drug Administration-approved enzyme replacement therapy is now approved for this condition, making the correct diagnosis is especially important.

Muscular dystrophies represent the second main group of inherited conditions that may be confused with autoimmune myopathy. While there are more than a hundred different types of muscular dystrophy, this review will focus on a few that are most often misdiagnosed as autoimmune myopathy, because they can present with proximal muscle weakness, elevated serum muscle enzyme levels, muscle biopsies, including prominent collections of inflammatory cells, and/or no family history due to an autosomal recessive inheritance pattern. These include dysferlinopathy, calpainopathy, and facioscapulohumeral dystrophy.

Dysferlinopathy patients have pathogenic mutations on both copies of their *DYSF* gene, resulting in a defective protein unable to participate in its

usual role in muscle membrane repair. Such patients most often present in their teens or early 20s with slowly progressive proximal muscle weakness and creatine kinase levels over 10 000 IU/l. A subset of dysferlinopathy patients presenting with distal weakness are rarely misdiagnosed as autoimmune myopathy. The majority of dysferlinopathy patients have muscle biopsies that include cellular infiltrates and upregulation of major histocompatibility complex class I molecules [6] as frequently described in autoimmune myopathies; these patients are most vulnerable to misdiagnosis. Indeed, one study revealed that 10 out of 40 dysferlinopathy patients were initially treated with corticosteroids and other immunosuppressive agents because they were misdiagnosed with polymyositis [7]. Such therapeutic misadventures can be avoided by immunostaining muscle biopsies for dysferlin protein, which is absent in patients with dysferlinopathy. Alternatively, genetic testing revealing pathogenic mutations in each *DYSF* gene can also confirm the diagnosis of dysferlinopathy.

The *CAPN3* gene encodes calpain-3, a calcium-dependent protease, which plays a role in cytoskeletal remodeling and membrane repair. Patients with homozygous pathogenic *CAPN3* mutations have calpainopathy and typically present in childhood with progressive proximal muscle weakness and mildly to moderately elevated creatine kinase levels. Individuals with calpainopathy also often have scapular winging, which is only rarely present in patients with autoimmune myopathy. However, as muscle biopsies may reveal infiltrates consisting of eosinophils [8] or macrophages and lymphocytes [9], this occasionally leads to an erroneous diagnosis of autoimmune myopathy. This error can be avoided by immunohistochemical staining for calpain-3 on muscle biopsy (staining is reduced in those with calpainopathy) or by *CAPN3* gene sequencing.

Facioscapulohumeral dystrophy typically presents in young adults who complain of arm weakness. This weakness is often asymmetric and the forearm muscles may be dramatically atrophied despite relatively normal deltoid muscles, resulting in characteristic 'Popeye' arms. In addition, weakness of the shoulder girdle muscles often results in scapular winging. Finally, facial weakness is usually present on examination even if it is not noted by the patient. Although asymmetric weakness, sparing of deltoid muscles, scapular winging, and facial weakness would all be atypical in a patient with autoimmune myopathy, one-third of facioscapulohumeral dystrophy patients have inflammatory muscle biopsies with CD4+ and CD8+ T-cells [10,11]; these patients are occasionally diagnosed as having polymyositis. The correct diagnosis can be confirmed by genetic testing. In contrast to dysferlinopathy or calpainopathy, facioscapulohumeral dystrophy is most often inherited in an autosomal dominant fashion because of deletions in the D4Z4 repeat sequence in chromosome 4. However, as several genetically distinct forms of facioscapulohumeral dystrophy have been identified, additional genetic tests may be utilized to confirm the diagnosis.

INCLUSION BODY MYOSITIS

Sporadic IBM is the most common myopathy presenting in older adults and probably the muscle disease most frequently misdiagnosed as a treatable autoimmune myopathy. In one study, up to 50% of IBM patients were initially diagnosed as having polymyositis or another muscle disease [12]. In most cases, the typical features of IBM should help clinicians who perform a detailed neuromuscular exam distinguish IBM from polymyositis and other forms of autoimmune muscle disease. First, IBM patients have a unique pattern of muscle involvement including not only proximal muscle weakness, but also weakness of the deep finger flexors, wrist flexors, and ankle dorsiflexors. In many cases, the quadriceps are weaker than the hip flexors, which would be highly unusual in patients with autoimmune muscle disease. Also, many IBM patients have orbicularis oculi weakness which is rare in patients with autoimmune myopathies. Finally, while symmetric muscle involvement is the rule in patients with autoimmune myopathy, asymmetric muscle weakness is often noted in IBM patients. Importantly, about half of IBM patients have dysphagia. However, as this can also be present in patients with autoimmune myopathy, it may not be less helpful in distinguishing between the two conditions.

The typical muscle biopsy features of inclusion body myositis include not only invasion of healthy myofibers by cytotoxic CD8+ T cells, as described in polymyositis, but also rimmed vacuoles and evidence of mitochondrial dysfunction. When present, this combination of features should strongly suggest the diagnosis of IBM. However, approximately 20% of patients with otherwise typical clinical features of IBM have inflammation but no rimmed vacuoles on muscle biopsy [13]. These patients can easily be misdiagnosed as having polymyositis if asymmetric weakness, distal weakness, and/or orbicularis oculi weakness are not revealed by a careful neuromuscular exam.

It has been noted that some patients initially presenting with symmetric proximal muscle weakness, high serum creatine kinase levels, inflammatory muscle biopsies, and responsiveness to immunosuppressive therapy eventually evolve into

a typical IBM phenotype. For example, we recently described five patients with myositis in the context of HIV infection who presented with both proximal and distal weakness, and who had improved proximal muscle strength following immunosuppressive therapy. However, each of these patients went on to develop weakness primarily affecting wrist flexors, finger flexors, knee extensors, and/or ankle dorsiflexors as commonly seen in IBM [14▪]. Thus, even patients with an established diagnosis of treatment-responsive polymyositis should be carefully monitored over time for the development of weakness in an IBM pattern. Whether such patients should continue to be treated with immunosuppressive agents remains unknown and may require an empiric trial of drug tapering.

ENDOCRINE MYOPATHIES

While mild hypothyroidism may be associated with fatigue, muscle pain, and cramping, patients with severe hypothyroidism can have proximal muscle weakness, markedly elevated creatine kinase levels, and a necrotizing muscle biopsy [15]. Such patients can easily be misdiagnosed as having IMNM if thyroid function tests are not ordered. Importantly, patients with central hypothyroidism may have a necrotizing myopathy even the context of a normal thyroid-stimulating hormone level [16]. In these cases, low or absent circulating T4 levels should suggest the correct diagnosis. While hyperthyroidism is less frequently a cause of myopathy, this should also be considered. Finally, hyperadrenocorticism associated with Cushing syndrome can cause a myopathy with proximal muscle weakness. However, other features of Cushing syndrome, such as abdominal stria and moon facies, should alert clinicians to this condition. Moreover, since patients with myopathy caused by Cushing syndrome have normal creatine kinase levels and noninflammatory muscle biopsies, they should only rarely be misdiagnosed with an autoimmune myopathy.

TOXIC MYOPATHIES

More than 39 million adults in the United States currently prescribed a statin [17], mostly well tolerated. However, muscle symptoms may occur in as many as 10% of patients and this is a common reason for stopping statin therapy [18]. Given that the overwhelming majority of those with statin-related muscle symptoms do not have weakness or elevated creatine kinase levels, these individuals are not typically misdiagnosed with autoimmune myopathy. However, rare patients will experience more severe statin toxicity with elevated creatine kinase levels and proximal muscle weakness. This more severe statin-related toxicity, which some evidence suggests may result from mitochondrial dysfunction [19▪], occurs at an estimated rate of 0.4 per 10 000 person years of statin treatment [20]. Fortunately, most patients with this form of self-limited statin myopathy will recover spontaneously after stopping the statin. However, especially since the discovery of statin-associated autoimmune myopathy [21], some patients with self-limited statin toxicity may be misdiagnosed as having an autoimmune process and treated inappropriately with corticosteroids and/or other immunosuppressive treatments. Distinguishing patients with statin-associated autoimmune myopathy from those with either mild or severe self-limited statin toxicity can be accomplished by testing for autoantibodies recognizing 3-Hydroxy-3-Methylglutaryl-coenzyme A (HMG-CoA) reductase, because only the former patients have these autoantibodies [22,23,24▪].

In addition to statins, several other drugs are known to cause myopathy; in rare cases these individuals might be suspected of having an autoimmune myopathy. For example, colchicine can cause a myopathy characterized by vacuolization on biopsy [25]. Because the potential for toxicity is related to circulating levels of colchicine and this drug is excreted by the kidneys, renal dysfunction may precipitate toxicity in individuals who have been taking colchicine without difficulty for years.

Amphiphilic drugs, such as chloroquine, hydroxychloroquine, amiodarone, procainamide, and doxorubicin may cause myopathy by disrupting the muscle cell membrane. Particularly in patients taking hydroxychloroquine for lupus, the possibility of coexisting autoimmune myopathy may be considered when weakness develops. If discontinuing the medication does not lead to resolution of weakness within a few weeks or weakness progresses despite drug cessation, then a muscle biopsy may be considered. In patients with drug-induced myopathy, the biopsy should show vacuoles that stain positively for lipids and acid phosphatase rather than inflammation.

Although in the developed world zidovudine is rarely used to treat HIV infection, its low cost makes it an attractive treatment in poorer countries. Myopathy is a well described adverse effect of zidovudine and can present with high creatine kinase levels and proximal weakness. Because HIV-infected patients may also develop autoimmune myositis, it may be difficult to distinguish drug toxicity from an autoimmune process. In these cases, muscle biopsies showing ragged red fibers and numerous cytochrome oxidase-negative fibers reflecting mitochondrial dysfunction should suggest zidovudine toxicity. In contrast, an inflammatory muscle

biopsy would be more consistent with an autoimmune process.

CONCLUSION

A variety of different disease processes can mimic an autoimmune myopathy. However, the history and expert neuromuscular examination can usually help distinguish these. For example, a careful drug history can suggest the possibility of a toxic myopathy. Similarly, a history of muscle cramping with exercise should prompt an evaluation for metabolic myopathies. The presence of facial weakness, asymmetric weakness, scapular winging, or distal weakness out of proportion to proximal weakness should suggest the possibility of inclusion body myositis or a muscular dystrophy. Laboratory testing may also be helpful in excluding endocrine myopathies. It is also helpful to remember that most patients with autoimmune myopathy have multisystem disease with skin, joint, or lung involvement, whereas those with nonautoimmune myopathy do not. Therefore, the absence of extramuscular symptoms should always prompt a search for a nonautoimmune cause of the myopathy. An exception to this rule would be patients with IMNM, who rarely have extramuscular manifestations [26,27]. However, these patients can usually be identified based on the presence of autoantibodies recognizing the signal recognition particle or HMG-CoA reductase. Finally, when a patient with a diagnosis of autoimmune myopathy worsens or does not improve despite aggressive immunosuppressive therapy, the possibility of a different or coexisting nonautoimmune condition should be considered.

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Conflicts of interest

Until 2014, A.L.M. received royalties from INOVA Diagnostics for a patent on anti-HMGCR autoantibody testing entitled 'Compositions and Methods for Characterizing a Myopathy'.

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MRI scoring methods used in evaluation of muscle involvement in patients with idiopathic inflammatory myopathies

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Purpose of review
MRI is a promising imaging method commonly used to assess muscle involvement in patients with idiopathic inflammatory myopathies (IIM). MRI enables evaluation of both activity and damage and is therefore an ideal noninvasive diagnostic and monitoring tool. Despite its widespread use, there is no universally accepted method for scoring and reporting of MRI findings. The aim of this review is to provide an overview of systems used in the evaluation of MR images in patients with IIM.

Recent findings
A number of semi-quantitative and quantitative methods have been used to evaluate and record the severity of myopathy on MRI. These scoring systems differ in the number and type of parameters assessed and in their complexity; furthermore, they were evaluated in different patient populations, all of which make comparisons between them difficult.

Summary
There is a need to create a standardized and validated protocol for evaluation of pathological changes in muscle MRI in IIM. The most appropriate number and distribution of muscle groups as well as evaluated pathological features need to be determined. Based on this literature search, the future scoring system should include assessment of muscle oedema, fatty infiltration, muscle atrophy and possibly the presence of fascial and subcutaneous inflammation. Whether the quantitative methods provide more reliable information regarding disease activity remains unclear.

Keywords
evaluation, idiopathic inflammatory myopathy, MRI, scoring system

INTRODUCTION

MRI is currently a key imaging method for assessing muscle involvement in patients with idiopathic inflammatory myopathies (IIM) [1]. In patients with muscle weakness MRI can distinguish between active muscle inflammation and chronic muscle damage. MRI helps in the diagnostic process by providing detailed imaging of large muscle volume, which can be used for selecting an optimal biopsy site [2], or to provide evidence of morphological changes localized in areas of muscle, which were not sampled in patients with negative biopsy results [3]. In addition, MRI can detect the presence of muscle inflammation in patients with typical complaints but preserved strength and normal creatine kinase levels [4].

There is still no universally accepted and validated scoring protocol for the evaluation and grading of muscle MRI pathology in patients with IIM.

PATHOLOGICAL MRI FINDINGS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

The normal, healthy muscle generates on T1-weighted sequences (T1W) an intermediate signal intensity – slightly higher than that of water and bone, but lower than the intensity of bone marrow. On T2-weighted sequences, healthy muscle tissue generates much lower signal compared with both fat and water [5]. The areas affected by muscle inflammation generate bright, hyperintense signal due to

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KEY POINTS

- There is no standardized protocol for evaluation of MRI in patients with myositis.
- Several different semi-quantitative or quantitative assessment methods have been used in previous studies.
- There is a need to define the exact parameters, anatomical localizations and MR imaging techniques to be used in the future scoring system.

increased (intracellular or extracellular) water content. Fluid sensitive techniques such as fat suppressed T2-weighted or short-tau inversion recovery (STIR) sequences are therefore appropriate for evaluation of muscle oedema [6▪]. Hyperintense signal of fascia is considered to be a marker of fasciitis; analogically subcutaneous soft-tissue oedema can be seen in patients with skin involvement of dermatomyositis. Fatty replacement and atrophy can be assessed on T1-weighted sequences [7].

SYSTEMS USED FOR EVALUATION OF MRI

We have identified several studies that have used an MRI scoring system in order to evaluate and record the degree and severity of pathological alterations in muscles of patients with IIM. Some of those systems were based on visual assessment by one or more evaluators only; others used a quantitative method for measuring different MRI signal parameters.

Semi-quantitative scoring systems

In semi-quantitative scoring systems, the evaluator uses a numerically defined grade on an analogue scale to describe the severity of involvement based on a visual assessment. This evaluation technique has the advantage of being relatively easy to implement, but the final outcome is influenced by the individual experience of the evaluator. In the past years, various scoring systems with a large variability in the number and localization of assessed muscles as well as evaluated parameters were established (Table 1).

First studies using a semi-quantitative evaluation system to correlate muscle involvement on MRI with clinical and laboratory parameters appeared more than 10 years ago. An approach based on evaluation of extent of inflammatory oedema (EMRI), intensity of the signal in affected area (IMRI) and total MRI affection (TMRI) was reported in 2007 [8]. All MRI parameters were assessed on axial STIR sequences of both thighs using a 10 cm visual analogue scale in 29 patients (9 with polymyositis, 20 with dermatomyositis). In a subgroup of 10 patients, second MRI examination was done after 2–6 months enabling longitudinal comparison of these MRI parameters after treatment. Results showed association of the initial intensity of oedema (IMRI) with clinical activity and this parameter also improved significantly in response to treatment. Levels of creatine kinase correlated with the total MRI score (TMRI). During the second examination after a period of treatment, clinical muscle activity correlated both with the EMRI and TMRI, but there was no correlation of any of the assessed MRI parameters with global clinical activity (assessed on 10 cm visual analogue scale) or with creatine kinase levels, with no statistically significant difference between polymyositis and dermatomyositis patients.

All other studies published so far also considered the muscle oedema as the main MRI feature, even though the grading methods varied in their complexity. In the study of Malattia *et al.* [9] muscle inflammation was scored using a 0–2-point scale (0, no muscle signal abnormalities; 1, mild-to-moderate signal abnormalities; 2, high degree of signal abnormalities). In patients with juvenile dermatomyositis (JDM), the evaluation was made considering both the degrees of signal intensity abnormality and its extent (with score of 2 corresponding to involvement of more than 50% of the muscle area). The symmetrical muscles were scored separately and the final score was obtained as an arithmetical sum of all acquired scores performed in total 42 muscular groups on coronal whole-body STIR MRI sequences. In addition to muscle oedema, perifascicular and subcutaneous tissue inflammation was evaluated using a binary scale (0, absent; 1, increased signal intensity). Thus, designed scoring system showed moderate-to-excellent correlation with clinical indicators of disease activity (Manual Muscle Test, Childhood Myositis Assessment Scale), whereas the whole body MR subcutaneous and myofascial scores are highly correlated with Physician's Global Assessment of disease activity and Childhood Health Assessment Questionnaire.

Davis *et al.* [10] used a 4-point scale for assessing of acute inflammatory changes in patients with JDM (0, none; 1, mild; 2, moderate; 3, severe changes), and dichotomous evaluation of the presence of soft-tissue oedema and perifascicular oedema (1, present; 0, absent). This study described fair-to-moderate agreement between two experienced musculoskeletal paediatric radiologists whenever evaluating the suggested parameters. Grading was performed in

Table 1. Semi-quantitative MRI scoring systems

Study, year	Evaluated parameters				
	Muscle oedema	**Fatty infiltration**	**Sequences**	**Evaluated muscle groups**	**Other evaluated features**
Studynkova *et al.* [8], 2007	Signal intensity, oedema extent, total MRI affection; *VAS 0–10*	–	STIR	Thigh muscles, not specified	–
Malattia *et al.* [9], 2014	0–2 0, No signal abnormalities 1, Mild-to-moderate in less than 50% *2, High degree of visual signal abnormalities in more than 50%*	–	STIR	Forty-two muscular groups (whole body MRI)	Perifascicular and subcutaneous tissue inflammation
Davis *et al.* [10], 2011	0–3 0, Absent 1, Mild 2, Moderate *3, Severe*	–	STIR	Four muscle groups of the thigh bilateral	Soft-tissue oedema + perifascicular oedema
Zheng *et al.* [11], 2015	0–5 Modified Stramare score [12] 0, Absent 1, Mild, interfascicular 2, Mild, intrafascicular 3, Mild, intrafascicular, segmented 4, Moderate, intrafascicular, segmented *5, Moderate, intrafascicular, global*	0–5 Modified Mercuri score [13] 1, Normal appearance 2, Mild involvement less than 30% of the volume 3, moderate involvement Fatty replacement 30–60% 4, Severe involvement greater than 60% *5, End-stage: muscle replaced by fat*	T1W STIR	Forearm, scapular muscles, skeletal muscles of the both limbs, not specified	–
Cox *et al.* [14], 2011	0–1 1, Present *0, Absent*	0–3 0, No infiltration 1, Mildly abnormal, <30% of fat 2, Moderately abnormal, 30–60% of fat *3, Severely abnormal, greater than 60% of fat*	T1W STIR	Sixty-eight muscles: shoulder region, upper arm, forearm, pelvis, upper and lower leg	muscle atrophy

Table 1 (*Continued*)

Study, year	Evaluated parameters				
	Muscle oedema	**Fatty infiltration**	**Sequences**	**Evaluated muscle groups**	**Other evaluated features**
Andersson *et al.* [15▪▪], 2017	Extent 0–3	0–*5*	T1W	Muscles involved in hip flexion, abduction and knee locomotion	Fascial oedema
	0, No oedema	Goutallier *et al.*[16] grading:	STIR		
	1, Minor extent < 33.3%	0, No fat			
	2, 33.3–66.6%	1, Fatty streaks			
	3, Major extent > 66,6% of muscle area	2, Muscle greater to fat			
	signal intensity 0–3	3, Muscle equal to fat			
	0, Normal intensity	4, muscle less to fat			
	1, Low intensity	*5, Muscle totally replaced by fat*			
	2, Moderate				
	3, High signal intensity				
Pipitone *et al.* [17], 2016	0–1	–	STIR	Seventeen muscles bilateral, not specified	–
	1, Present				
	0, Absent				
Barsotti *et al.* [18], 2016	0 –3	0–1	STIR 2D gradient echo DWI	–	Apparent Diffusion Coefficient
	0, No oedema	1, Present			
	1, Mild oedema	*0, Absent*			
	2, Moderate				
	3, Severe oedema				
Pinal-Fernandez *et al.* [19], 2017	0–1	0–1	T1W	Fifteen muscles of thighs bilateral	Muscle atrophy fascial oedema
	1, Present	1, Present	STIR		
	0, Absent	*0, Absent*			

DWI, Diffusion-weighted imaging; STIR, T2-weighted or short-tau inversion recovery sequences; T1W, T1-weighted sequences.

each of the four muscle groups: gluteal muscles, hamstrings, quadriceps femoris and adductors. There was no difference in reached total scores (maximum 20 points) for each side, reflecting the symmetry of muscle involvement in JDM.

A complex evaluation system of muscle oedema in patients with non-inflammatory myopathies was suggested by Stramare *et al.* [12]. The proposed grading system divided muscle oedema into six grades (0–5), considering the severity and localization of the inflammation (Table 1). Zheng *et al.* [11] adopted this scoring system in a study in patients with anti-SRP-positive myopathy. According to the results, the degree of oedema did not correlate with creatine kinase levels or myositis disease activity assessment. Fatty infiltration as a marker of chronic muscle damage was evaluated using the Mercuri scale, developed originally for the assessment of inherited neuromuscular disorders [13]. The scale consists of 6 grades (0–5) from normal appearance to a complete fatty infiltration (Table 1). The simpler classification of fatty infiltration degree was used in a study with sporadic inclusion body myositis patients by Cox *et al.* [14]. Muscle damage in this study was graded 0–3 based on the extent of fatty replacement.

Recent comparative analysis of MRI findings in patients with antisynthetase syndrome and matched controls [15▪▪] used a detailed scoring model. Muscle oedema was assessed in terms of extent (0, no oedema; 1, minor extent less than 33.3%; 3, major extent greater than 66,6% of muscle area) as well as signal intensity (0, normal intensity; 1, low; 2, moderate; 3, high signal intensity). The highest possible score for muscle oedema was 36 points (18 for each side, evaluated were the muscles involved in hip flexion, abduction and knee locomotion in anterior, posterior and medial compartment, using a grading scale 0–3 for both parameters). Fatty replacement was assessed according to a grading system developed by *Goutallier et al.* [16], where a Goutallier score of at least 2 in at least one compartment was considered pathological (Table 1). Fascial oedema (defined as an abnormal thick deep fascial layer with increased STIR signal) was binarily scored as 1, present; 0, not present. Based on this assessment, two summary scores were calculated: a total oedema score (42), including three components: oedema extent (18), oedema intensity (18) and presence of fascial oedema (6); and a total damage score (36), consisting of the score for fatty replacement (30) and presence of muscle volume reduction (6). A summation of total oedema score and total damage score created a TMRI score (maximum 78). According to the results, plasma creatine kinase levels did not correlate with total oedema or damage score, but significant correlations were observed between both scores and Manual Muscle Test and Functional Index Test.

The uncomplicated binary system of oedema evaluation (1, present; 0, absent) was also used in an Italian study [17], that compared the distribution of muscle involvement between dermatomyositis and polymyositis patients. Muscle oedema was assessed bilaterally in 17 pelvic floor and thigh muscles by two independent radiologists, MRI oedema score was then calculated by adding the separate scores for each side and dividing them by two. The intraclass correlation coefficient between the evaluators was 0.78. This study showed higher incidence of oedema in patients with dermatomyositis in comparison to those with polymyositis in all localizations except of posterior thigh muscles.

Barsotti *et al.* [18] combined binary assessment system with a more detailed grading of muscle oedema on STIR sequences (a 4-level scale: 0, no oedema; 1, mild; 2, moderate; 3, severe oedema). Oedema score was calculated as the mean of the values in 10 muscles on both sides. Fatty muscle infiltrates were evaluated as present or absent. MRI results were compared with the IMACS disease activity score set (physician assessment, enzyme levels, and Manual Muscle Test). There was a good correlation between creatine kinase levels and oedema score, especially for higher oedema scores. In addition, the study introduced a Diffusion-weighted Imaging (DWI) technique with a measurable diffuse coefficient as a contributing value for quantification of the disease progression.

Recently published extensive study from the Johns Hopkins University group [19], comparing immune-mediated necrotising myopathy patients with other IIM subgroups, used this dichotomous evaluation system in order to increase the reproducibility and to simplify the methodology. The presence of oedema, fatty replacement, atrophy and fascial oedema was evaluated in 15 muscles of both thighs and the severity of the findings was represented by the percentage of muscles showing that concrete MRI feature. The results revealed more severe muscle involvement in anti-SRP-positive compared with anti-HMGCR-positive patients.

Quantitative evaluation systems

Hand-in-hand with innovations in MRI imaging and availability of postprocessing techniques, several studies aimed to develop a quantitative system (qMRI), describing more precisely the degree of muscle impairment. Some studies presented methods based on computer analysis of pixel intensity values.

Forty-four patients with IIM underwent MRI examination in the study by Yao *et al.* [20], who used image postprocessing technique implemented in ImageJ open platform. This postprocessing modality creates T2 maps and T2 maps corrected for muscle fat content, calculated from the in-of-phase and out-of-phase gradient echo images based on a Dixon formulation [21]. Affected regions were defined using a semi-automated, adaptive, moving-window intensity-based segmentation algorithm [22]. Results of this quantitative measurement were comparable with results from assessment of conventional STIR sequences using visual scoring system (Table 2), performed by an experienced musculoskeletal radiologist [23]. These results support the potential usefulness of this semi-automated quantitative MRI evaluation.

Dixon method acquires proton-density weighted gradient echo images with two, three, or more different echo times. As the resonant frequency of water and fat differs, the images at different echo times contain different combinations of fat and water signals. It is possible to create a mathematical model, that calculates the fat and water components of the image with subsequent correction of image inhomogeneities. At the endpoint stands the calculation of fat-fraction with every pixel containing the percentage fat in the MR signal (0–100%).

This principle was successfully used in a cohort of limb–girdle muscular dystrophy patients [24] and the results were compared with values obtained from visual scoring (Table 2). Patients were followed over 12-months period. Compared with an optical scoring performed by a consultant neurologist, the outcome of quantitative fat fraction calculation detected a significant rise in 9 out of the 14 muscles, whereas visual grading analysis showed no progression over the 12 months. This work suggested that visual scoring of T1 weighted images was not discriminating enough to detect progression of muscle pathology in patients with slowly progressing disease. After all, the higher sensitivity of qMRI has actually been already described in publications dealing with facioscapular muscular dystrophy type I [27] and Duchenne muscular dystrophy patients [28]. In these dystrophic patients, Wokke *et al.* [29] documented that the visual scores related to the muscle fat fraction were generally higher than the corresponding quantitative values. This could point out the lower accuracy of the visual scores compared with the qMRI values.

T2 mapping of fatty infiltration and oedema was applied in patients with various muscle diseases in a study by Elessawy *et al.* [25]. This study included four groups of patients, where nine patients had a diagnosis of idiopathic inflammatory myopathy. Results of the quantitative measurement were compared with visual assessment (Table 2). Quantitative T2-histogram analysis showed a significant correlation with semi-quantitative MRI imaging score of fatty infiltration and the clinical grade of muscle power. Used grading system for muscle oedema (Carlo Borsato scaling [26], Table 2) was replaced by protocol suggested by Quijano-Roy *et al.* [30] in Elessawy *et al.*'s [31] study published in 2016. The study described extent and distribution of muscle involvement in the whole-body MRI, performed in 15 patients with IIM. The authors advocate the use of whole-body MRI because they observed time-in-disease-course dependent distribution of oedema between upper and lower extremities and also frequent involvement of proximal calf muscles.

Maillard *et al.* [32] conducted a study, that aimed to examine validity and reliability of a quantitative measure of increased T2 relaxation times as marker of inflammation on MRI in children with JDM. Eight image slices throughout the left thigh were gained at each scan (the first slice at the level of the base of the greater trochanter, final slice at the level of superior aspect of condyles, the six slices were automatically equidistantly positioned between these two). Data from two consecutive slices at the positions of the fourth and fifth slices were measured. The results showed significantly higher values in children with active JDM compared with patients with inactive disease and the healthy controls. There was not a significant difference between inactive JDM group and healthy individuals. Scores in active patients reached good correlations with Patient Global Assessment, Childhood Myositis Assessment Scale and Childhood Health Assessment Questionnaire. The authors conclude that MRI T2 relaxation time could be a reliable parameter of disease activity.

According to the published results, quantitative methods have performed at least as well as visual assessment. They can distinguish healthy individuals from participants with active disease and provide a statistically clearly defined outcome. Software compatibility has to be tested on larger cohort, using different MRI scanners and with more evaluators in order to prove the reliability of obtained data.

CONCLUSION

MRI has become an important tool for visualization of muscle pathology in idiopathic inflammatory myopathies. It plays an essential role in the assessment of ongoing inflammation activity [33]. This literature overview demonstrates a large variability of scoring approaches used across differently designed studies. None of the above-mentioned systems has been fully validated and the results

Table 2. Semi-quantitative systems used in patients with IIM in comparison with quantitative methods

	Evaluated parameters				
Study, year	**Muscle oedema**	**Fatty infiltration**	**Sequences**	**Evaluated muscle groups**	**Quantitative method**
Yao and Gai [23], 2012	0–4	0–5	STIR	Medial, anterior, posterior compartment bilateral	T2 maps
	0, Normal	0, Normal	T1W		
	1, Possible disease	1, Possible fatty replacement			
	2, Definite disease less than 25% of compartment involved without marked STIR hyperintensity	2, Definite fatty replacement, less than 25% of compartment involved			
	3, Definite disease greater than 25% but < 50% of compartment involved or marked STIR hyperintensity and less than 25% of compartment involved	3, Definite fatty replacement, greater than 25% but less than 50% of compartment involved			
	4, Definite disease, greater than 50% but less than 75% of compartment involved or marked STIR hyperintensity and greater than 25% but less than 50% of compartment involved	4, Definite fatty replacement, greater than 50% but less than 75% of compartment involved			
	5, Definite disease, greater than 75% of compartment involved or marked STIR hyperintensity and greater than 50% of compartment involved	5, Definite fatty replacement, greater than 75% of compartment involved			
Willis *et al.* [24], 2013	–	Mercuri score [13]:	T1W	Mid-lower leg, mid-thigh	Fat fraction maps
		0, Normal appearance			
		1, Early moth-eaten appearance, with scattered small areas of increased			
		2a, Late moth-eaten appearance, with numerous discrete areas of increased density with beginning confluence, comprising less than 30% of the volume			
		2b, Late moth-eaten appearance, with numerous discrete areas of increased density with beginning confluence, 30–60% of the volume			
		3, Washed-out appearance, fuzzy appearance due to confluent areas of increased density with muscle still present at the periphery			
		4, End-stage appearance, muscle replaced by increased density connective tissue and fat, with only a rim of fascia and neurovascular structures distinguishable			

Table 2 (*Continued*)

Study, year	Evaluated parameters				
	Muscle oedema	Fatty infiltration	Sequences	Evaluated muscle groups	Quantitative method
Elessawy *et al.* [25], 2013	Borsato *et al.* [26] scale: 0–3 0, No oedema 1, Slight interfascicular oedema 2, Slight interfascicular and intrafascicular segmental or global oedema 3, Moderate interfascicular and intrafascicular segmental or global oedema	modified Mercuri score [13]: 0–4 0, No fatty infiltration 1, Minimal scattered fatty infiltration 2, Mild fatty infiltration with additional patchy areas of intramuscular high T1 signal intensity less than 30% of the muscle volume 3, Moderate fatty infiltration, 30–60% of volume, but with preserved differentiation Between muscle and subcutaneous fat 4, Severe fatty infiltration greater than 60% of volume with loss of demarcation *between muscle and subcutaneous fat*	STIR FLAIR T1W	Gluteal, thigh and calf muscles	T2 maps

FLAIR, fluid attenuation inversion recovery; STIR, T2-weighted or short-tau inversion recovery sequences; T1W, T1-weighted sequences.

are not comparable due to a diversity of examined study participants and parameters. Some of the proposed scoring methods seem to be too complicated and time-consuming for daily clinical practice use. Furthermore, semi-quantitative systems are limited by their subjectivity. Several studies were conducted in paediatric cohorts; no studies have reported data on the long-term follow-up of adult IIM patients. Qualitative methods partially use the approximation of adjacent points, the automatic choice of region of interest can be imprecise and requiring manual correction. The use of specialized postprocessing procedure needs advanced skills with MRI software, that makes the method generally difficult to implement.

In order to facilitate MRI use for the diagnosis and monitoring of IIM patients, a standardized scoring should be developed and validated. In view of published results this protocol should evaluate muscle oedema, fatty infiltration and atrophy, perifascicular oedema or fascial oedema and subcutaneous tissue inflammation. An international collaboration of experienced specialists forming a task force seems to be the best way to develop the new recommendations.

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Conflicts of interest

There are no conflicts of interest.

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Inclusion body myositis: advancements in diagnosis, pathomechanisms, and treatment

Karsten Schmidt and Jens Schmidt

Purpose of review
To review new advances in inclusion body myositis (IBM) and discuss them in light of current knowledge on diagnosis, pathomechanisms, and treatment perspectives.

Recent findings
IBM is a treatment refractory inflammatory myopathy in middle-aged patients that leads to a slow, relentlessly progressive muscle weakness, and atrophy. Recent data collections suggest that mortality in IBM patients is somewhat elevated compared with the general population. One major risk factor for death is severe dysphagia, which can now be determined by a novel real-time MRI technique. Recently, proposed diagnostic criteria with a combination of clinical and histopathological features have improved sensitivity and specificity. cytosolic 5′-nucleotidase 1A antibodies have been characterized in IBM patients and their pathophysiologic role has recently been studied. New inflammatory pathomechanisms have been identified in IBM muscle and may help to design novel treatment strategies. A broad spectrum of immunosuppressive and immunomodulatory trials have been conducted, but – so far– no effective treatment is available. Current therapeutic attempts aim to block the myostatin pathway or restore the protein homeostasis.

Summary
The expanding knowledge of the complex disease, the refinement of diagnostic criteria, and developments in diagnostic procedures are expected to foster the much needed design of new treatment approaches for future clinical trials.

Keywords
cN1A autoantibodies, diagnostic criteria, dysphagia, immunoglobulin G, inclusion body myositis

INTRODUCTION

Inclusion body myositis (IBM) belongs to the group of inflammatory myopathies, which also includes dermatomyositis (DM), polymyositis (PM), necrotizing myopathy, and overlap myositis. IBM patients are mostly beyond 50 years of age at initial presentation. IBM can be distinguished from the other inflammatory myopathies by its unique clinical presentation with asymmetrical muscular weakness and atrophy, predominantly affecting long finger flexors and the quadriceps muscles. The histopathological hallmarks of the disease include a T-cell-dominated immune infiltration and myodegenerative features like multiple protein aggregates inside muscle fibers. IBM usually does not respond to standard immunosuppression such as by glucocorticosteroids, methotrexate, or azathioprin.

EPIDEMIOLOGY AND LIFE EXPECTANCY

The prevalence of IBM is highest in Whites in Northern Europe, North America, and Australia, ranging from 4.9 to 33 per million and even 51.3 per million people for the group of patients above 50 years of age [1–3]. In a recently published meta-analysis of nine publications, the metaprevalence was 24.8 per million in total [4▪]. It is thought that the prevalence of IBM is underestimated, for example, because of a wrong diagnosis as PM. In recent studies, there is an increase in prevalence, which could be explained with growing disease awareness and improved diagnostic tools. Men are about two-fold more often affected than women [5,6].

The disease course is typically slowly progressive over decades and leads to increasing impairment of

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KEY POINTS

- The diagnosis depends on clinical, histological, and serological parameters.
- Dysphagia is a common, relevant, and sometimes initial symptom that often requires special attention.
- Standard immunosuppression is usually not justified and IVIG may be suitable for selected patients, particularly in case of severe dysphagia.
- Novel effective treatment strategies will depend on a better understanding of the pathomechanisms.

daily activities, particularly those involving hand and finger muscles such as writing, using knife and fork, getting dressed, and so on. Mobility is increasingly limited, leading to walking sticks or walker dependence after 5–10 years. The rate of yearly progression in weakness is about 5% [5,6]. The mortality has recently been shown to be somewhat increased as reflected by an international questionnaire of 'IBM experts' [3,7▪]. There is no evidence of increased risk of malignancy in IBM patients [8].

CLINICAL SYMPTOMS

Patients with IBM usually display a typical pattern of involved muscles. In general, the quadriceps femoris and the long finger flexors are mainly affected. Other muscle groups that are commonly affected include the biceps and the foot dorsiflexors. With progression of the disease, all affected muscle become atrophic. An affection of paraspinal muscles can cause camptocormia or a dropped head syndrome in IBM patients [9].

An important symptom of the disease is dysphagia which is noted in 40–80% of IBM patients [10▪,11,12]. Patients typically report that food gets stuck in their throat and that they need to swallow repeatedly for clearance. In some cases, dysphagia is the initial, presenting symptom [13,14]. Assessment of swallowing is usually performed by videofluoroscopy [11]. A recent study demonstrates that real-time MRI is comparably reliable for detection of an impaired food passage in patients with dysphagia because of IBM [10▪]. Compared with videofluoroscopy, this novel tool has the advantage that it does not rely on X-rays and it can visualize soft tissue such as muscle. Thus, real-time MRI may be an ideal tool for assessing and monitoring dysphagia as part of clinical care as well as in clinical studies of IBM. Patients with only a mild swallowing impairment usually do not report this as part of the history [12]. Therefore, the use of formal swallowing questionnaires appears to be advisable not to overlook a relevant dysphagia in IBM patients: Such questionnaires include the swallowing-related quality of life questionnaire as well as the Sydney swallowing questionnaire [15]. The swallowing scales correlated well with the flexible endoscopic evaluation of swallowing and real-time MRI. Both questionnaires have been used in detecting swallowing problems in different neurological and nonneurological diseases such as Parkinson's disease or amyotrophic lateral sclerosis [16–18].

DIAGNOSTIC CRITERIA

Diagnosis of IBM is often delayed by an average of 5 years from symptom onset and is usually made by a combination of clinical, electrodiagnostic, and pathological assessment [9]. There have been different diagnostic criteria used for research and daily practice issues. Griggs *et al.* [19] defined in 1995 the diagnostic criteria for IBM: they are much focused on histopathological features so that the diagnosis of a definite IBM can only be made if all pathological features are present, that is, mononuclear cell invasion of nonnecrotic fibers, vacuolated muscle fibers, and evidence of protein accumulation. It has been shown that an overweight of histopathological changes vs. clinical symptoms will likely lead to an underdiagnosis of IBM and overdiagnosis of PM [20]. The inherent problems of overemphasizing histopathological diagnosis of definite IBM is the fact that one or more of the required features will often be absent. In a retrospective study, enhanced specificity and sensitivity could be found when tissue sections were examined looking for rimmed vacuoles in combination with the respective distribution of p62 and inflammatory changes [21]. In tissue sections lacking rimmed vacuoles, the estimation of inflammatory changes appearing simultaneously with mitochondrial malformation resulted in higher sensitivity and good specificity. The European Neuromuscular Centre (ENMC) criteria for IBM took into account the typical clinical phenotype and performed more inclusive compared with Griggs' criteria [1]. In 2013, revised ENMC criteria for IBM were published and used an approach of combining clinical, laboratory, and pathological observations [22]: a distinction between clinico-pathologically defined IBM, clinically defined IBM, and probable IBM was suggested (Table 1). A recent study evaluated different sets of diagnostic criteria from various previous publications and most of them – including the revised ENMC criteria – showed poor sensitivity: Using machine learning techniques in an approach

Table 1. ENMC diagnostic criteria of inclusion body myositis

	Clinico-pathologically defined IBM	Clinically defined IBM	Probable IBM
Clincal and laboratory criteria	Duration >12 months Age at onset >45 years sCK no greater than 15 ULN Knee extension weakness at least hip flexion weakness and/or Finger flexion weakness more than shoulder abduction weakness	Duration >12 months Age at onset >45 years sCK no greater than 15 ULN Knee extension weakness at least hip flexion weakness and Finger flexion weakness more than shoulder abduction weakness	Duration >12 months Age at onset >45 years sCK no greater than 15 ULN Knee extension weakness at least hip flexion weakness or Finger flexion weakness more than shoulder abduction weakness
Pathologic criteria	All of the following: Endomysial inflammatory infiltrate Rimmed vacuoles Protein accumulation[a] or 15–18-nm filaments	One or more of: Endomysial inflammatory infiltrate Up-regulation of MHC class I Rimmed vacuoles Protein accumulation[a] or 15–18-nm filaments	One or more of: Endomysial inflammatory infiltrate Up-regulation of MHC class I Rimmed vacuoles Protein accumulation[a] or 15–18-nm filaments

The table provides clinical, laboratory, and pathological criteria for diagnosis of clinico-pathologically defined, clinically defined, and probable IBM as proposed by the ENMC workshop 2011.
ENMC, european neuromuscular center; IBM, inclusion body myositis; MHC, major histocompatibility complex; sCK, serum creatine kinase; TDP, transactive response dna binding protein; ULN, upper limit of normal.
[a]Demonstration of amyloid or other protein accumulation by established methods (e.g., congo red, crystal violet, thioflavin T/S, or immunostaining for p62, SMI-31, and TDP-43).
Adapted with permission [22].

including 371 patients, best specificity and sensitivity was identified by combining finger flexor or quadriceps weakness with endomysial inflammation and either invasion of nonnecrotic fibers or rimmed vacuoles [23]. The international standard of care in IBM has been discussed at an ENMC workshop in 2011 [22] and an IBM guideline development group has been formally established. This group has assessed the best practice for diagnosis and treatment of IBM [24] by a Delphi method and a live meeting for all participants of the group Publication of the results is expected soon.

CN1A ANTIBODIES

The reliability of the diagnosis is hampered by the fact that the clinical presentation as well as the histological picture can be very variable and until today no precise biomarker is available. In 2011, a circulating antibody against a 43 kDa muscle protein was described in blood samples from IBM patients [25]. This antibody was later characterized being reactive against the cytosolic 5'nucleotidase 1A [26,27]. However, despite initial enthusiasm about this antibody as a potential new biomarker for IBM, recent data demonstrate that IBM patients are positive in a range of not more than 33–61% [28▪–31▪]. Moreover, other autoimmune disorders such as PM (5%), DM (15%), systemic lupus erythematodes (14–20%), and especially Sjögren's syndrome (23–36%) show a high rate of cytosolic 5'-nucleotidase 1A (cN1A) antibodies [28▪,29▪].

So far, it is unclear if the autoantibody status is useful to distinguish different IBM subtypes, for example, a more severe phenotype. Some authors describe a higher adjusted mortality risk in patients with cN1A antibody positivity [30▪], whereas others did not identify a relevant difference between these two groups of IBM patients [28▪,31▪]. The response rate to immunosuppressive treatment did also not differ significantly between antibody-positive and negative patients [31▪].

Histopathologically, antibody-positive patients tend to have increased cyclooxygenase-deficient muscle fibers [30▪] and a lower frequency of rimmed vacuoles [28▪]. In-vitro and in-vivo exposure to immunoglobulin G from cN1A-positive patients led to p62-aggregates in rhabdomyosarcoma cells and in muscle fibers of injected mice [31▪].

Testing for antibody status in suspected IBM can be of diagnostic value, as demonstrated in suggested diagnostic algorithms [32]. Despite some implication for diagnosis, the pathogenic relevance of cN1A antibodies in IBM remains open and is currently studied by several groups.

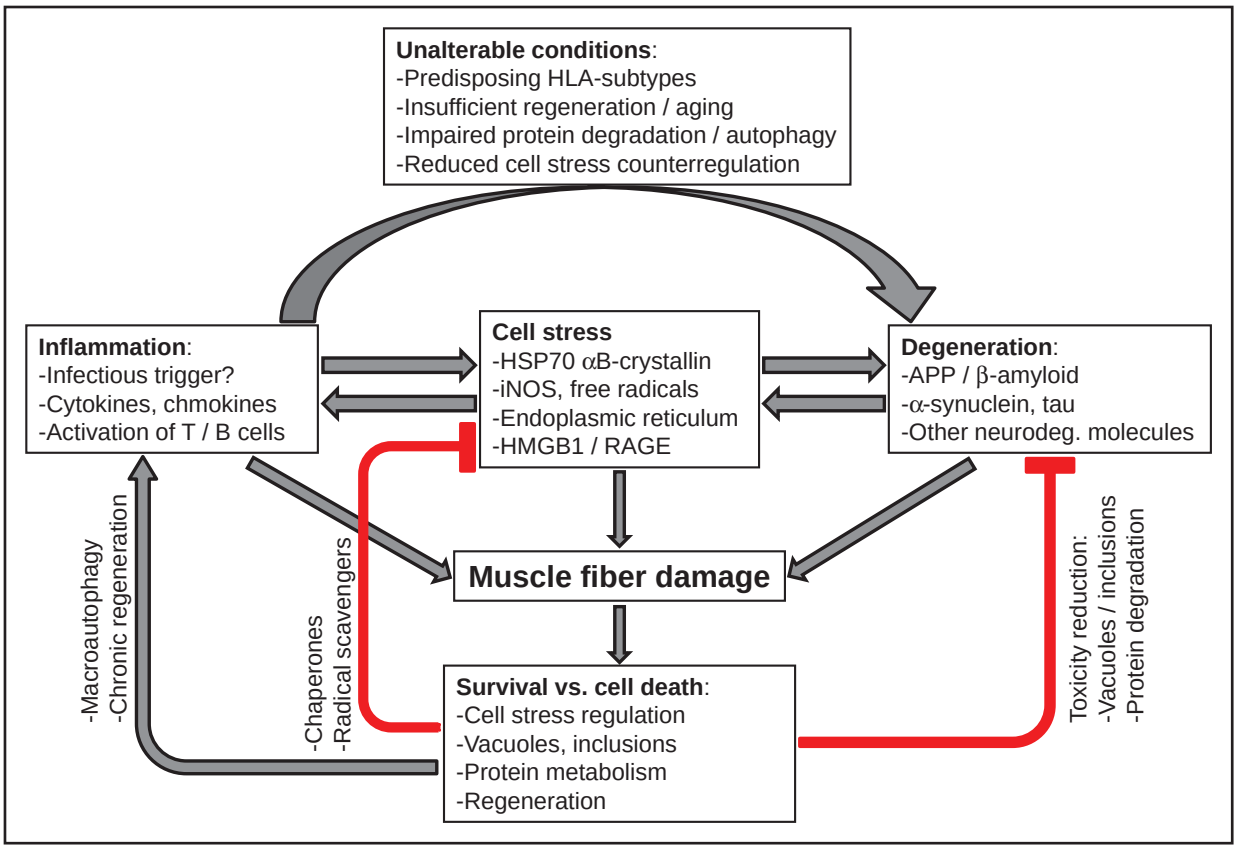

FIGURE 1. Model of IBM pathogenesis, initial damage to the muscle because of a potential infection or other inflammatory stimulus may, in case of a distinct genetic predisposition, cause chronic inflammation and subsequent protein dyshomeostasis in the skeletal muscle. Protein accumulation and inflammation are interlinked by cell stress mechanisms, which can fuel a vicious cycle with an ultimately irreversible degeneration of the muscle. Endogenous regulators of chaperons or formation of vacuoles may alleviate the cell stress. By contrast, upon autophagic processing, endogenous antigens presented via MHC class II may augment the inflammatory cell stress. Adapted with permission [39]. APP, amyloid precursor protein; HMGB, high mobility group box; HSP, heat shock protein; MHC, major histocompatibility complex; RAGE, receptor for advanced glycation end products.

PATHOMECHANISMS

The coexistence of two very different hallmarks, inflammation and myodegeneration, explains the complexity of the pathogenesis of IBM. Inflammation with autoaggressive T cells attacking nonnecrotic fibers, upregulation of major histocompatibility complex (MHC) class I antigens, and an upregulation of inflammatory mediators is accompanied by a myodegenerative disease with protein accumulation, vacuolization, and mitochondrial changes [33–35,36▪▪]. There are several links between inflammatory and degenerative pathomechanisms, such as intracellular nitric oxide or impaired autophagy [37,38] (Fig. 1). However, the precise interplay of degenerative and inflammatory mechanisms has so far remained elusive.

Since the initial description of virus-like inclusions in IBM four decades ago, it has been speculated that viruses might play a role in the pathogenesis of IBM. In general, it is conceivable that antiviral response mechanisms will affect self-tolerance, autoantigen recognition, and/or chronic stimulation of low affinity, autoaggressive effector cells such as cluster of differentiation (CD)8^+ T cells. Despite manifold efforts, no study so far provides sufficient evidence of a direct attack in IBM affected muscle fibers [40]. However, an increased incidence of IBM in Hepatitis C virus-infected patients was recently described [41]. Presence of human leukocyte antigen (HLA)-A∗ 0201-HIV-gag-positive endomysial T cells has been demonstrated in IBM muscle samples [42]; However, the HIV gag antigen was found only in macrophages, but not in muscle fibers. A recent study on HIV-positive patients with myositis demonstrated typical features of IBM-like rimmed vacuoles and finger flexor weakness [43]. Interestingly, the cN1A autoantibody was present in 64% of the HIV patients with myositis. Taken together, a pathogenic role of a putative viral trigger of autoimmunity in IBM cannot be ruled out, but more conclusive data are warranted.

The autophagic machinery in skeletal muscle is capable of removing misfolded proteins. In IBM, it could be demonstrated that accumulated amyloid precursor protein (APP) and Aβ are targeted for lysosomal degradation via macroautophagy [44]. Furthermore, the proinflammatory cytokines tumor necrosis factor-α, and interleukin-β in combination with interferon (IFN)-γ have been shown to cause an upregulation of the autophagic activity in cultured myoblasts [38,45]. Antigen presentation via MHC II has been shown to be regulated by the autophagic machinery, serving as an interesting link between inflammation and degeneration in IBM disease [46]. In a recent study, proteomic analysis revealed accumulation of FYVE and coiled-coil protein (FYCO)1 in rimmed vacuoles [47]. Further analysis showed overexpression of rare missense variants of FYCO1 in IBM patients, leading to an impaired autophagic function. In another approach to identify genetic risk factors for IBM, missense pathogenic variants of the valosin containing protein and p62/SQSTM1 have been found by whole-exome sequencing in 181 IBM patients [48]. Both molecules are involved in autophagosome maturation and degradation. These genetic data support the hypothesis of an underlying defect of autophagosome function in IBM, which could be a crucial prerequisite in IBM pathogenesis in that an inflammatory stimulus can trigger a chronic cell stress response which drives a vicious cycle with upregulation and overloading of the autophagic machinery. Such predisposing factors could act together with HLA alleles such as DRB1∗0301, which has been demonstrated to be associated with a more severe disease course of IBM [32].

TREATMENT

Despite the pronounced inflammatory features on muscle biopsy, immunosuppressive or immunomodulatory drugs such as glucocorticosteroids, azathioprin, methotrexate, or IFN-β are not effective in IBM and studies with etanercept and anakinra failed to demonstrate an improvement [5,49–54]. Alemtuzumab, a lymphocyte-depleting antibody against CD52, led to a transient improvement in some patients in an unblined proof of concept study [55]. In a subsequent post hoc analysis, a downregulation of inflammatory markers was noted without an effect on degenerative molecules, which could possibly explain the insufficient long-term effect of this drug [56]. In view of the small sample size and open-label design of this study, the results need to be interpreted with care. Comparable results were obtained in a post hoc analysis of biopsies from a placebo-controlled trial with intravenous immunoglobulin G (IVIG) and prednisolone, which down-modulated inflammatory mediators, but failed to block nitric oxide stress in the muscle and in a corresponding in-vitro model [57]. As immunosuppression generally fails in IBM, treatment with glucocorticosteroids or other immunosuppressants is not recommended, particularly in view of the potential side-effects. Treatment with immunoglobulin G – either intravenously or subcutaneously – can be associated with a stabilization or even transient, mild improvement of muscle strength and particularly an improved dysphagia in several IBM patients [58,59] and own observations (unpublished data). Therefore, particularly in patients with relevant dysphagia, a probatory treatment with IVIG can be justifiable in selected patients [60] (see below for details).

Aside from immunosuppressive or immunomodulatory strategies, drugs with alternate mechanisms of actions have failed in small clinical studies including oxandrolone, an anabolic steroid [61], and simvastatin, a cholesterol lowering agent [62]. Lithium as a drug that reduces phosphorylation of APP, increases proteasome activity and inhibits glycogen synthase kinase 3β in APP – overexpressing cultured human muscle fibers is currently tested in a clinical trial. Arimoclomol, a drug already tested in amyotrophic lateral sclerosis [63], ameliorated the disease course and improved muscle strength in mutant valosin-containing protein mice, which develop an inclusion body myopathy [64▪]. Within the same report, the drug appeared to be well tolerated in a clinical concept study in IBM patients. A large placebo-controlled study is currently underway. For the future, it may be of interest to design studies that target inflammation and degeneration at the same time [60,65,66]. For this reason, it is imminent to better understand the unique interplay between inflammation, cell stress pathways, and accumulation of aberrant proteins in the disorder (see above).

Targeting the impaired regeneration potential in IBM has been put into focus by blocking the binding of myostatin to its receptor activin RII. Activation of this pathway leads to inhibition of muscle growth with phosphorylation and activation of downstream effectors of the activin RII receptor [67]. In a proof of concept trial with 14 IBM patients, an increased thigh muscle volume on MRI and improvement in the 6-min walking test was observed [68]. However, the subsequent double blind placebo-controlled trial did not meet its primary endpoint (data not published yet).

Another potent inhibitor of myostatin is follistatin, delivered by an adenovirus-mediated gene therapy. In a proof of concept trial with six IBM patients, this vector was directly injected into the

quadriceps muscle. All of the treated patients improved in 6-min walking test compared with an untreated control group [69▪]. A placebo-controlled trial would be required to determine the efficacy.

TREATMENT OF DYSPHAGIA

Dysphagia in IBM is thought to be caused by an upper esophageal sphincter dysfunction due to an impairment of suprahyaloidual muscles [10▪,12]. Treatment with cricopharyngeal myotomy or pharyngoesophageal balloon dilatation showed a reasonable benefit in a small group of patients [70,71]. A more recently published study revealed that most of the patients have an abnormal hyolaryngeal excursion and would, therefore, not benefit from this procedure [72]. In several case series, local injection of botulinum toxin into the upper esophageal sphincter was effective in improving dysphagia [70,73]. IVIG led to a relevant improvement of dysphagia in clinical trial settings [50,74]. Based upon our own observations, selected patients may respond surprisingly well and may display an improvement of dysphagia for several months to years. Treatment approaches for dysphagia in muscle disorders have recently been evaluated in a Cochrane review [75].

CONCLUSION

In recent years, a range of new aspects have been addressed in the field of IBM with respect to epidemiology, diagnostic criteria, pathomechanisms, and novel treatment approaches. So far, no effective pharmacological therapy has been identified. A better understanding of the complex disease and possible predisposing genetic factors will be crucial to develop successful treatment strategies. The development and evaluation of reliable diagnostic criteria will help to identify suitable patients for future clinical trials.

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Conflicts of interest

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REVIEW

OPEN

Genetics in inclusion body myositis

Simon Rothwell[a], *James B. Lilleker*[a,b], *and Janine A. Lamb*[c]

Purpose of review
To review the advances in our understanding of the genetics of inclusion body myositis (IBM) in the past year.

Recent findings
One large genetic association study focusing on immune-related genes in IBM has refined the association within the human leukocyte antigen (HLA) region to *HLA-DRB1* alleles, and identified certain amino acid positions in HLA-DRB1 that may explain this risk. A suggestive association with *CCR5* may indicate genetic overlap with other autoimmune diseases. Sequencing studies of candidate genes involved in related neuromuscular or neurodegenerative diseases have identified rare variants in *VCP* and *SQSTM1*. Proteomic studies of rimmed vacuoles in IBM and subsequent genetic analyses of candidate genes identified rare missense variants in *FYCO1*. Complex, large-scale mitochondrial deletions in cytochrome c oxidase-deficient muscle fibres expand our understanding of mitochondrial abnormalities in IBM.

Summary
The pathogenesis of IBM is likely multifactorial, including inflammatory and degenerative changes, and mitochondrial abnormalities. There has been considerable progress in our understanding of the genetic architecture of IBM, using complementary genetic approaches to investigate these different pathways.

Keywords
degeneration, genetic association study, genetics, inclusion body myositis, mitochondria, sequencing

INTRODUCTION

Sporadic inclusion body myositis (IBM) is the most common acquired muscle disease presenting in people over 50 years of age. Clinically, it is characterized by slowly progressive weakness and muscle wasting predominantly of the quadriceps and long finger flexor muscles.

In IBM, inflammatory features in muscle biopsy specimens suggest an immune-mediated component to disease pathogenesis. In addition, circulating anti-Ro autoantibodies may be found in around 20% of patients and recent work has identified cytosolic 5′-nucleotidase 1A (anticN-1A) autoantibodies in around one-third of patients. However, unlike other idiopathic inflammatory myopathies (IIMs), such as polymyositis and dermatomyositis, IBM is unresponsive to conventional immunosuppressive treatments. This lack of response may be explained by evidence of impaired autophagic processes, including rimmed vacuole formation and the accumulation of misfolded proteins. Whether these degenerative processes represent a primary or secondary involvement is unclear.

Some hereditary diseases may mimic clinical features of IBM. These diseases may also exhibit similar pathological features, such as rimmed vacuoles and protein accumulations [1,2]. These disorders are sometimes referred to as hereditary IBM (hIBM), but are better described using the associated genetic abnormality. Genes involved with these 'rimmed vacuolar myopathies' will not be discussed here, but have been reviewed previously [3,4].

Although the primary cause of IBM remains unknown, genetic factors likely influence disease

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KEY POINTS

- There is evidence that the pathogenesis of IBM is multifactorial, including inflammatory and degenerative changes, and mitochondrial abnormalities.
- The strongest genetic risk lies within the HLA region, and there is evidence that other immune-related genes are associated with IBM.
- Candidate gene sequencing studies have identified rare variants in VCP, SQSTM1 and FYCO1 suggesting impaired autophagy as a mechanism in IBM pathogenesis.
- Mitochondrial DNA deletions in COX-deficient muscle fibres correlate with T-lymphocyte infiltration and muscle fibre atrophy, suggesting a mechanistic link between these inflammatory and degenerative disease processes.

susceptibility. This article reviews advances that have been made in the past year in our understanding of the genetic component of IBM and potential future approaches for research in this rare disease.

APPROACHES IN GENETIC STUDIES

There has been considerable progress in our understanding of the genetic basis of IBM. Two different approaches have been used recently in IBM; large genetic association studies and smaller targeted sequencing studies.

The study design of genome-wide association studies (GWAS) and contemporary genetic association studies frequently test hundreds of thousands, if not millions, of single nucleotide polymorphisms (SNPs) across the genome. Results from GWAS in autoimmune diseases suggest that most associated variants reside in regulatory regions, exerting their low effect sizes (odds ratio <1.1) on the expression of immune-mediated genes [5,6]. The combination of the burden of multiple testing and modest effect sizes of associated SNPs means that studies in rare diseases are hampered by low power because of small sample size. Success will depend on the presence of common variants of modest effect sizes (Fig. 1).

Other approaches to investigate the genetic component of IBM have relied on detecting rarer variants through sequencing studies that commonly involve fewer individuals than GWAS. To date, these have focused on candidate genes taken from related neuromuscular or neurodegenerative diseases. However, novel approaches are also being used, including targeting of genes identified in proteomic studies. Variants discovered through these studies likely will be rarer, with a larger effect size than those discovered by GWAS. Therefore, GWAS and sequencing approaches test complementary hypotheses to investigate the genetic architecture of IBM.

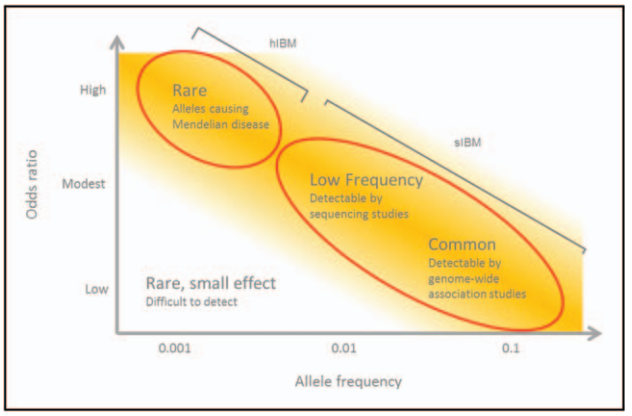

FIGURE 1. Strategies for identifying genetic variants in IBM. Rare causal variants of high effect size are expected in Mendelian diseases such as hIBM. Genetic variants contributing to IBM susceptibility are expected to have a more modest effect size. Low-frequency variants of intermediate effect sizes will likely be found using sequencing studies. Common variants of low effect size will be detectable by well-powered genetic association studies. hIBM, hereditary IBM; IBM, body myositis.

IMMUNE-RELATED GENES IN INCLUSION BODY MYOSITIS

There are multiple lines of evidence for inflammation as a key pathway in the pathogenesis of IBM. These include the presence of $CD8^+$ cytotoxic T cells surrounding major histocompatibility complex (MHC) class I-expressing fibres [7], the presence of plasma cells within affected muscle [8], IBM specific and nonspecific autoantibodies [9,10] and a strong genetic association with the human leukocyte antigen (HLA) region [11–13]. Recent studies suggest that several autoimmune diseases, including the IIMs, share genetic overlap for susceptibility to disease [14,15]. In line with this evidence, a recent study hypothesized that there may be shared immune loci associated with IBM [16▪▪].

Through the international Myositis Genetics Consortium (MYOGEN), 252 patients with IBM were recruited and genotyped on the Illumina Immunochip array. This SNP array contains coverage of 186 established autoimmune susceptibility loci and extended coverage across the MHC. The strongest associations with IBM were seen within the MHC, therefore imputation was used specifically to investigate classical class I and class II HLA alleles that may be explaining the risk in this region. Three

HLA-DRB1 alleles were found to be independently associated with IBM; HLA-DRB1*03:01, HLA-DRB1*01:01 and HLA-DRB1*13:01. Although HLA-DRB1*03:01 is known to be associated with polymyositis and dermatomyositis, the association with HLA-DRB1*01:01 and HLA-DRB1*13:01 is unique to IBM within the IIMs. Unlike many other diseases [14,17,18], it is interesting to note that the association of IBM with HLA is localized to HLA-DRB1. Although this may be due to low power to detect other HLA genes, it is in keeping with previous studies in IBM [12,19]. One potential explanation for risk shared across multiple HLA alleles is an amino acid 'signature' that may confer risk. When analyzing amino acid positions within HLA-DRB1, positions 26 and 11, located within the peptide binding groove, were associated with IBM. The strongest associations were with amino acids present on classical risk haplotypes, such as a tyrosine at position 26, predominantly carried on HLA-DR3 alleles. Functional research is needed to elucidate whether the association within this gene can be explained by these amino acids. Other candidate genes within the MHC were not investigated in this study, for example *NF-kB* genes, *TNFA* and *NOTCH4* [20–22]. *NOTCH4* has been associated previously with IBM, although because of the strong linkage in this region, it is not clear whether it is directly involved in disease or associated because of carriage on classical HLA-risk haplotypes.

Potential genetic associations within the HLA region were also investigated for the development of anticN-1A (NT5c1A) antibodies, a recently described autoantibody common in IBM. A significant association was seen with HLA-DRB1*03:01 when compared to healthy controls; however, there was no difference when 35 anticN-1A positive patients were compared to 68 anticN-1A negative IBM patients [16▪▪]. This suggests that there is no strong HLA association with the antibody over and above the general association with HLA-DRB1*03:01 in IBM. Similarly, a study in 24 anticN-1A positive IBM patients did not detect a unique HLA class II association independent of HLA-DR3 [23].

In the total IBM analysis, no loci outside the MHC reached genome wide significance [16▪▪]. However, three other loci reached a suggestive level of significance, one of which was assigned to the *CCR5* gene. The authors hypothesize that the protective effect of this association may be due to a frameshift mutation in *CCR5* which inhibits its function as a chemokine receptor involved in T-cell migration. *CCR5* previously has been associated with other autoimmune diseases lending support to the hypothesis of an immune-mediated component to IBM [24].

SEQUENCING STUDIES IN INCLUSION BODY MYOSITIS

Evidence for a degenerative component of IBM pathogenesis includes the formation of rimmed vacuoles and accumulation of misfolded proteins such as β-amyloid, p62, TDP43 and phosphorylated tau. To date, candidate gene studies mostly have focused on genes known to be associated with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS). Genes investigated include amyloid β precursor protein, microtubule-associated protein tau, α-1-antichymotrypsin (*SERPINA3*), prion protein and *C9orf72*. However, these studies have failed to find significant associations [4]. A well-studied locus is Apolipoprotein E (*APOE*) -'translocase of outer mitochondrial membrane 40' (*TOMM40*) [25–27], and although a recent study showed no significant associations with risk of developing IBM, a potential association with later onset of symptoms was reported [28]. Another negative study investigated genetic variants within autoantibody targets such as *cN1A* or *cN1B* [29]. One large candidate gene sequencing study reported, among others, two rare variants in the valosin-containing protein gene (*VCP*) [30]. Variants in *VCP* cause IBM associated with Paget's disease of the bone (PDB) and frontotemporal dementia (FTD); however, neither patient in this study manifested other symptoms reported with VCP mutations and both fulfilled the diagnostic criteria for IBM.

A recent study used whole exome sequencing (WES) in 181 IBM patients focusing on p62, also named sequestosome 1 (SQSTM1), and *VCP* genes, both of which are known to harbour genetic variants associated with ALS, PDB and FTD [31▪▪]. They report four rare missense variants in *SQSTM1* and three variants in *VCP*. This represented 4.0% of the cohort, and is the first time potential pathogenic variants in *SQSTM1* have been observed in IBM patients. As these variants may cause diseases that mimic IBM, it was confirmed that none of these patients had developed symptoms of PDB, FTD or ALS and all fulfilled diagnostic criteria for IBM. As *SQSTM1* is involved in the autophagy pathway, and *VCP* is involved in proteasomal degradation of misfolded proteins, this further supports the role of autophagic alterations and aggregation of proteins in the pathogenesis of IBM. These studies suggest that there is merit in the targeted sequencing of genes previously associated with hIBM and other inherited muscle disorders.

Rather than using related diseases, a novel way of identifying candidate genes is using proteomic analysis. We know that p62/SQSTM1 accumulates in inclusions of IBM muscle fibres [32]. A recent study

sought to identify other proteins present in the rimmed vacuoles in skeletal muscle of IBM patients by mass spectrometry [33▪▪]. Two hundred and thirteen proteins showed a statistically significant overrepresentation in rimmed vacuole samples compared to controls. Many proteins already known to be involved in IBM or other protein aggregate myopathies overlap with the proteins identified, validating this approach. The 173 novel proteins not described before in IBM warrant further investigation. Proteins that were present in at least 50% of rimmed vacuole samples (131 genes) were taken forward for genetic analysis using WES data from 62 patients with IBM. Hundred missense or loss of function variants were identified in 52 genes. Genetic data from ALS patients were then used to identify variants statistically enriched that are specific to IBM. Rare missense or loss of function variants in *FYCO1* were enriched in IBM patients (11.3%) compared to ALS patients (2.6%, $P = 0.003$) or healthy controls (3.4%, $P = 0.01$). *FYCO1* is involved in autophagosome/endosome trafficking. Along with the *VCP* and *SQSTM1* associations described above, this provides further evidence for autophagosome processing as a basis for future mechanistic studies. Novel treatments targeting protein dyshomeostasis are currently in development [34].

In contrast to the studies outlined above, a smaller sequencing study from Finland did not find any rare missense genetic variants [35]. This study sequenced the exomes of 30 patients from Finland and a replication cohort of 12 patients from Italy, with the hypothesis that the genetically more homogeneous Finnish population would be conducive to identifying genetic risk variants. Initially, a candidate gene approach on WES data was taken, focusing on 180 genes including those known to cause hereditary primary myopathies as well as 42 novel candidate genes [36]. No rare missense variants in *SQSTM1* and *VCP* were found, or in genes that would explain the observed clinical phenotype. A subsequent case–control association analysis identified seven SNPs enriched in the Finnish IBM population with $P < 0.005$. Reassuringly, two of these were within the HLA region; however, the other associations were in novel genes; *STARD3*, *SGPL1* and *SETD4*. Results from a small association study are to be treated with caution, and will need to be replicated.

As discussed above, associations with *VCP*, *SQSTM1* and *FYCO1* validate the use of a sequencing approach, and have given us greater mechanistic insight in to IBM cause. It is worth noting, however, that in all of these cases, patients lacked a family history of IBM or weakness, indicating that these inherited variants alone are not sufficient for disease pathogenesis. There are likely many more variants that predispose to IBM. Identification of novel genes will come from WES and whole genome sequencing (WGS) studies that detect rarer coding variants with potentially larger effect size. Additional WES studies in IBM are currently being undertaken [37]. Future studies will employ WGS, which comprehensively covers the genome including regulatory regions, intronic regions and structural variations that may be missed by WES. WGS studies, however, are still expensive, with the huge amount of data produced being complex, and computationally expensive to analyse and store.

MITOCHONDRIAL DNA DELETIONS

Cytochrome c oxidase (COX)-deficient muscle fibres are a common histopathological feature of IBM, and there is increasing evidence that mitochondrial abnormalities may play a role in the cause of this disease. Recent research has shown increased mitochondrial DNA (mtDNA) deletions in COX-deficient muscle fibres, and that the proportion of these deficient fibres correlates with severity of T-lymphocyte infiltration and muscle fibre atrophy suggesting a mechanistic link between these disease processes [38,34]. In addition, a recent study in IBM has implicated a number of nuclear DNA genes that are associated with transcription, replication and maintenance of mtDNA [39].

Myofibres may harbour clonally expanded large-scale mtDNA deletions responsible for respiratory chain deficiency that is thought to be central to IBM pathogenesis [40,41]. Previous works reporting mtDNA deletions have been based on a small number of mtDNA genes, and were focused on single major arc deletions. A recent study sought to characterize mtDNA deletions in more detail in patients with IBM [42▪]. mtDNA rearrangements were investigated in single muscle fibres from patients with IBM using complementary techniques. The authors confirmed the presence of mtDNA deletions in 78 out of 92 (~85%) COX-deficient cells, but demonstrated that mtDNA rearrangements in IBM are more complex than previously assumed. The authors showed for the first time that 20% of COX-deficient cells harboured two or more mtDNA deletions. In addition, some unusually large deletions were detected that extended into the origin of light strand replication.

Further evidence for mitochondrial dysfunction in IBM is provided by research that sought to characterize mitochondrial phenotype at a genetic, molecular and functional level in 30 IBM patients [43▪]. The authors also compared mitochondrial

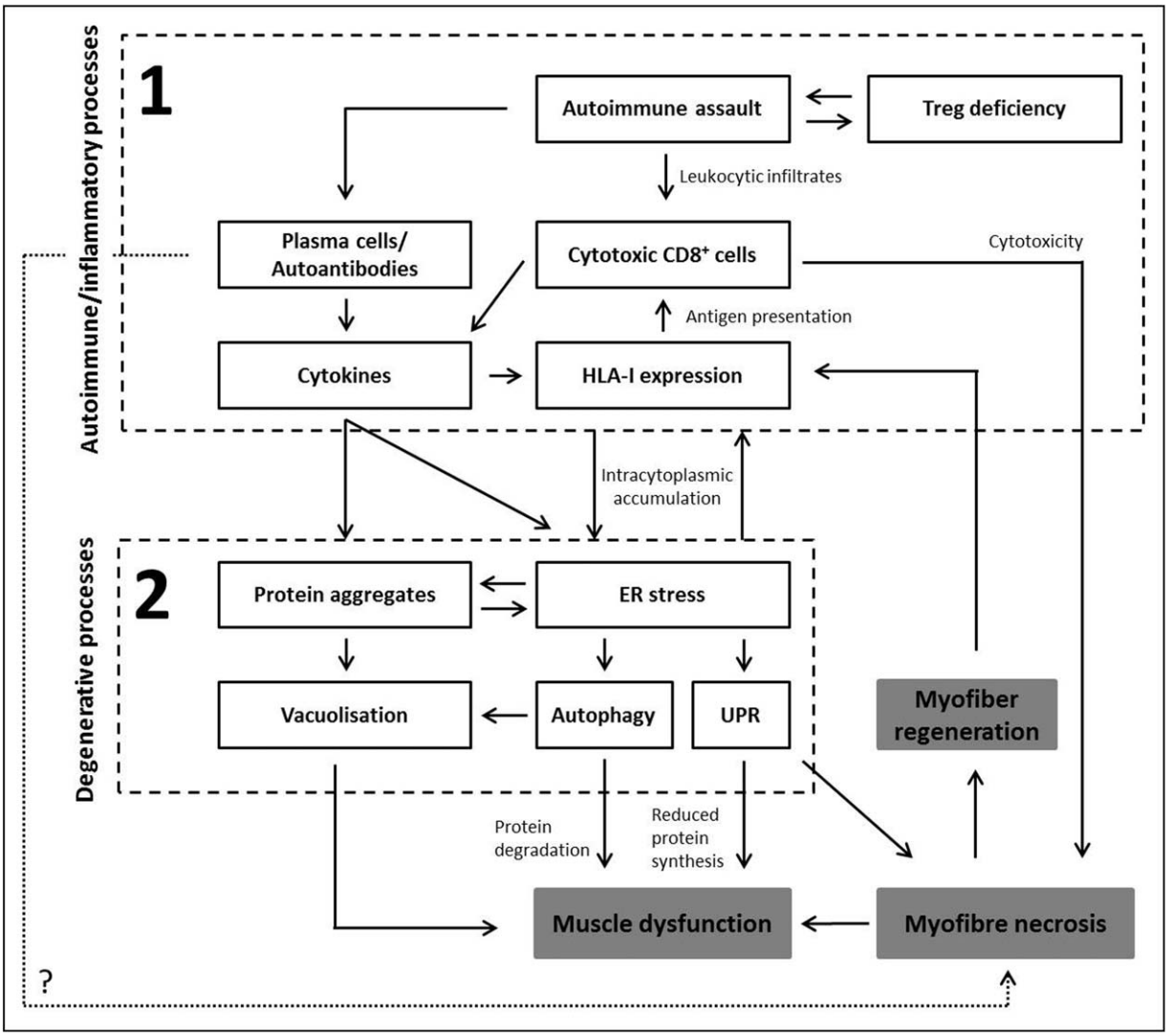

FIGURE 2. A proposed model for the pathogenesis of IBM. Inflammation within muscle (Box 1) may induce fibre injury and HLA-I overexpression. Overloaded protein degradation systems (Box 2) induce misfolded protein deposits in muscle fibres. ER, endoplasmic reticulum; UPR, unfolded protein response. Figure adapted from [44].

differences between muscle and peripheral blood mononuclear cells (PBMCs) in IBM cases and controls to assess whether these alterations could be used as biomarkers in a less invasive tissue. Multiple mtDNA deletions were found in the muscle of 57% patients, and while there was a significant decrease in total mtDNA in muscle, the decrease was less pronounced in PBMCs. This may be attributed to shorter lifespan of PBMCs and thus reduced accumulation of mitochondrial deficiencies. The authors found that mitochondrial COX activity was decreased in both muscle and PBMCs suggesting that mitochondrial dysfunction may not be confined to the target tissue of the disease.

CONCLUSION

There has been considerable progress in our understanding of the genetic architecture of IBM. Evidence suggests a complex interplay between inflammatory and degenerative processes and mitochondrial abnormalities. A model starting with inflammation within muscle and subsequent deposition of amyloid and other proteins because of overloaded protein degradation systems has been proposed by Benveniste *et al.* in Fig. 2 [44]. Complementary approaches to investigate these hypotheses have been used successfully in IBM. Investigating the effect of common variants on disease susceptibility in rare diseases will rely in part on continuing sample collection by coordinated international collaborations, including different ethnicities that will facilitate larger studies. In addition, novel statistical methods are being developed that leverage the power from larger datasets in related diseases because of the similarities in genetic susceptibility [45]. WES and WGS studies will identify novel variants across

the genome and may uncover previously overlooked biological processes to further expand our knowledge of the genetic component of IBM.

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Conflicts of interest

There are no conflicts of interest.

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Biologics for idiopathic inflammatory myopathies

Siamak Moghadam-Kia[a,b], *Rohit Aggarwal*[a], *and Chester V. Oddis*[a]

Purpose of review
As treatment of refractory cases of idiopathic inflammatory myopathies (IIMs) has been challenging, there is growing interest in assessing novel biologics that target various pathways implicated in the pathogenesis of IIM.

Recent findings
In the largest clinical trial in adult and juvenile IIM assessing the effectiveness of rituximab, the primary outcome was not met but 83% of this refractory group of IIM patients met a predefined definition of improvement and rituximab demonstrated a significant glucocorticoid-sparing effect. Antitumor necrosis factor utility in IIM is generally limited by uncertain efficacy data along with recent reports suggesting their potential for inducing systemic autoimmune disease including IIM.

Summary
Further research is required to evaluate the role of newer therapies such as tocilizumab (anti-interleukin-6), abatacept (inhibition of T-cell costimulation), sifalimumab (anti-interferonα) and ruxolitinib, (Janus kinase inhibitor) given their biological plausibility and encouraging recent small case series results. Future clinical trials should consider the targeting of biomarkers implicated in the etiopathogenesis of IIM, predictive factors of treatment response, recent revisions in IIM classification criteria, as well as newly developed data-driven response criteria which employ validated core set measures.

Keywords
biologic agents, dermatomyositis, idiopathic inflammatory myopathy, myositis, polymyositis, treatment

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic autoimmune rheumatic diseases that include adult polymyositis, adult dermatomyositis, myositis associated with other systemic autoimmune rheumatic diseases or malignancy, juvenile myositis [Juvenile Dermatomyositis (JDM) and juvenile polymyositis], inclusion body myositis and necrotizing myopathy.

The treatment of IIM has been very challenging. The reasons include low incidence and prevalence of IIMs, their variable and heterogeneous clinical phenotypes and the small number of randomized, double-blind controlled clinical trials [1–4]. Traditional treatment approaches include glucocorticoids and conventional immunosuppressive or immunomodulatory agents such as methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine and intravenous immunoglobulin (IVIg). Some patients experience disease recurrences during or after conventional therapy and some do not have complete response which may present therapeutic challenges. Therefore, there has been growing interest in assessing novel and targeted therapies such as biologics that target various pathways involved in the etiopathogenesis of IIM. Biomarkers implicated in the pathogenesis of IIM have been explored using a variety of techniques including cytokine/chemokine analyses, advanced immunohistochemistry and flow cytometry, microarrays and RNA-sequencing analysis. In addition, novel classification schemes for IIM based on serologic and histopathologic features will improve the design of clinical trials and facilitate human enrollment [5,6].

Over the past several years, data-driven and consensus core set measures (CSMs) have replaced nonstandardized muscle strength and functional assessments for evaluation of IIM disease activity

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KEY POINTS

- The treatment of refractory IIMs can be challenging and efficacy data on biologic agents remain limited.
- In the largest randomized, double-blind, controlled clinical trial in IIM [the RIM trial), the DOI was met by 83% of refractory IIM patients.
- The efficacy data of rituximab therapy specific to IIM-ILD are limited to uncontrolled studies, but recent case series have reported promising results.
- Additional well-designed controlled trials are required to develop an evidence-based approach to the treatment of IIM and IIM-ILD using novel biologics including tocilizumab (anti-IL6), abatacept (inhibition of T-cell costimulation), sifalimumab (anti-IFNα) and ruxolitinib (Janus kinase inhibitor).

and damage. In particular, two international groups, the International Myositis Assessment and Clinical Studies (IMACS) Group and the Pediatric Rheumatology International Trials Organization (PRINTO), have defined and validated consensus CSMs for adult and pediatric populations [7–9]. These CSMs along with active international initiatives to develop both data-driven and consensus-driven response criteria will assist in studying novel therapies in a more systematic fashion [10].

In this article, we review the novel biologics used for treating polymyositis and dermatomyositis, necrotizing myopathy or overlap myositis syndromes and IIM-associated interstitial lung disease (ILD).

RITUXIMAB

Rituximab, a B-cell depleting agent, is a monoclonal antibody against the CD20 antigen on B lymphocytes. The efficacy of rituximab in refractory IIM has been suggested in several small case reports and case series [11–15]. In a small, open-label, uncontrolled, pilot trial of rituximab therapy (4 weekly IV doses) in six treatment-resistant dermatomyositis patients, all individuals had major clinical improvement in muscle strength and rash [16]. In another small open-label trial of rituximab in four patients with refractory polymyositis, all patients demonstrated return of full muscle strength and significant decline in serum total creatine kinase (CK) levels [17]. However, in another open-label trial of rituximab in eight patients with dermatomyositis, cutaneous disease (skin scores based on Dermatomyositis Skin Severity Index) and total CK levels did not significantly change from those at baseline and only three patients demonstrated modest improvement in muscle strength [18].

In the largest randomized, double-blind, controlled clinical trial in IIM [the Rituximab in Myositis (RIM) trial], 195 patients (75 with polymyositis, 72 with dermatomyositis and 48 with JDM; all refractory to glucocorticoid therapy and at least one immunosuppressive drug) were randomized to receive two 1 g rituximab infusions either at baseline or 8 weeks later [1]. Entry criteria included fairly significant muscle weakness (not required in the JDM patients) and at least two additional abnormal CSMs for adults and at least three abnormal CSMs with or without muscle weakness for the pediatric individuals. Glucocorticoid and/or immunosuppressive therapy were allowed at study entry. The primary end point was the time to achieve the IMACS definition of improvement (DOI) which was compared between the rituximab early and rituximab late groups. Secondary end points included the time to achieve at least 20% improvement in muscle strength and the proportions of patients in the early and late rituximab groups achieving the DOI at week 8 (the time-point at which one-half of the individuals had received B-cell depleting therapy 8 weeks earlier, whereas the other one-half of individuals received placebo). Although the early rituximab group demonstrated no faster response to therapy than the group receiving rituximab later (failing to meet the primary outcome), the DOI was met by 83% of this refractory group of IIM patients with a median time to achieving the DOI of 20 weeks. Rituximab was also associated with a significant steroid-sparing effect as the mean prednisone dose decreased from 20.8 mg at baseline to 14.4 mg daily at the end of the clinical trial. In addition, patients who initially met the DOI and who were subsequently retreated with rituximab after a disease flare responded to rituximab retreatment. Rituximab therapy was generally well tolerated and the most common adverse effects were infections. Additional studies derived from the RIM trial data demonstrated that the presence of antisynthetase and anti-Mi-2 autoantibodies along with the JDM subset, and lower disease damage were strong predictors of clinical improvement and response to B-cell depletion therapy with rituximab [19]. In a more recent analysis of the RIM trial data, significant improvements were noted in cutaneous disease activity after the addition of rituximab to the standard therapy in adult dermatomyositis and JDM individuals [20▪▪]. The cutaneous visual analog scale activity improved in adult dermatomyositis (3.22–1.72, $P = 0.0002$) and JDM (3.26–1.56, $P < 0.0001$), with erythroderma, erythematous rashes (without secondary changes of ulceration or necrosis), heliotrope, Gottron sign and papules improving most prominently.

The efficacy data of rituximab therapy specific to IIM-ILD are limited to uncontrolled studies [13,14]. In a recent retrospective study of 50 patients with severe, progressive ILD (10 with IIM-ILD), rituximab therapy was associated with a median improvement in forced vital capacity (FVC) of 6.7% ($P < 0.01$) and stability of the diffusing capacity of the lungs for carbon monoxide [(DLCO); 0% change; $P < 0.01$] in the 6–12-month period after rituximab use [21]. Among the systemic autoimmune rheumatic disease (SARD)-ILD patients included in this study, the best results were observed in patients with IIM-ILD as five of the 10 (50%) patients demonstrated an increase in their FVC more than 10% and/or an increase in their DLCO more than 15%, as compared to four out of 22 (18.2%) patients with other SARD-ILDs ($P = 0.096$). In a more recent retrospective study from Norway, 24 patients with antisynthetase syndrome and severe ILD with more than 12 months follow-up (median 52 months) postrituximab therapy were identified [22]. The median percentage of predicted FVC, forced expiratory volume in 1 s (FEV1) and DLCO increased by 24, 22 and 17%, respectively, postrituximab. The best outcome (>30% improvement in all three pulmonary function testing parameters) was observed in seven patients with a disease duration less than 12 months and/or an acute onset/exacerbation of ILD. High-resolution CT (HRCT) findings (extent of ILD prerituximab and postrituximab was scored and expressed as a percentage of total lung volume) demonstrated a median 34% reduction in ILD extent postrituximab. Manual muscle testing (MMT8 score) also increased postrituximab therapy and the total CK significantly declined as well. All individuals demonstrated a decrease in their anti-Jo-1 levels by a median of 33% ($P < 0.008$). One limitation of the study was combined therapy with another immunosuppressive agent as 10 of the 12 patients also received cyclophosphamide making it difficult to attribute the response to rituximab therapy alone. There were seven deaths among the 34 rituximab-treated patients (mortality rate comparable to that of the remaining antisynthetase cohort), six with infections (including three with *Pneumocystis jirovecii* pneumonia). In a recent multicenter, open-label, phase II trial, 10 antisynthetase antibody-positive patients with IIM and ILD refractory to traditional treatments (prednisone and at least two immunosuppressive agents) received 1 g of rituximab at day 0, day 15 and after 6 months [23]. Seven patients demonstrated an increase of at least four points on MMT10 and the total CK level declined from 399 IU/l (range, 48–11 718) to 74.5 IU/l (range, 40–47 857). Rituximab therapy was associated with a significant steroid-sparing effect as the mean prednisone dose decreased from 52.5 mg/day (range, 10–70) at baseline to 9 mg/day (range, 7–65) along with a concomitant decrease in the associated immunosuppressive therapy. ILD improved in five and stabilized in four based on FVC and/or DLCO, and decrease in the burden of the associated immunosuppressive therapy. In another recent retrospective study of anti-Jo-1 antibody-positive patients, 17 received rituximab and 30 patients were treated with conventional immunosuppressive agents and followed for a mean of 35 and 84 months, respectively [24▪]. Sixteen of the 17 receiving rituximab demonstrated a more rapid and marked response. In contrast to conventional immunosuppressive agents, response to rituximab was independent of the anti-Ro52 antibody status.

ANTITUMOR NECROSIS FACTOR AGENTS

In a series of five patients with dermatomyositis refractory to glucocorticoid and cytotoxic therapy, etanercept (25 mg subcutaneously twice a week for at least 3 months) was associated with exacerbation of muscle weakness, elevation of muscle enzyme levels and unchanged dermatomyositis rash in all patients [25]. In contrast, in a more recent randomized, double-blind, controlled trial of etanercept (50 mg subcutaneously weekly for 52 weeks) in 16 dermatomyositis patients, etanercept therapy was associated with a significantly longer median time to treatment failure (358 vs. 148 days; $P = 0.0002$) and a significantly lower average prednisone dose after week 24 (1.2 vs. 29.2 mg/day; $P = 0.02$) [26].

A few anecdotal reports suggested the efficacy for infliximab in IIM [27–29]. However, two patients who initially appeared to respond to infliximab had an exacerbation of their myositis and resuming infliximab was associated with anaphylaxis and the development of antidsDNA antibodies [30]. In a larger retrospective series of eight patients with refractory dermatomyositis or polymyositis, infliximab use was associated with improved muscle strength and fatigue but only a partial drop in serum CK levels [31]. In a more recent pilot study of 13 patients with refractory IIM, infliximab therapy (four infusions of 5 mg/kg body weight over 14 ‘weeks) was ineffective [32]. An unpublished randomized controlled trial of infliximab in IIM also failed to demonstrate efficacy [33]. A multicenter, open-label, controlled trial of infliximab in combination with weekly methotrexate in patients with polymyositis or dermatomyositis was terminated prematurely because of a low inclusion rate and high drop-out because of disease progression and infusion reactions [34].

In general, anti-TNF therapy is not routinely used in IIM in view of its unclear efficacy as

well as the recent reports suggesting the potential for inducing polymyositis and dermatomyositis [35–38]. Anecdotally, anti-TNF agents may be helpful for the management of inflammatory arthropathy in IIM patients.

TOCILIZUMAB

Since the approval of tocilizumab, an antagonist of the interleukin-6 (IL-6) receptor, for the treatment of rheumatoid arthritis, there has been growing interest in evaluating its potential efficacy in other systemic autoimmune rheumatic diseases including myositis.

In the first report of tocilizumab use in IIM, two patients with refractory polymyositis demonstrated improvement in the total CK level and MRI of their thigh muscles [39]. In another report, a 32-year-old Japanese patient with an overlap syndrome, including features of dermatomyositis (proximal muscle weakness, heliotrope rash and Gottron sign) and systemic sclerosis, inflammatory arthropathy and CCP positivity (refractory to cyclosporine, IV cyclophosphamide, IVIg, tacrolimus and combination methotrexate and adalimumab) were treated with tocilizumab which resulted in resolution of the dermatomyositis rash and arthritis with gradual improvement in the muscle weakness and CK elevation allowing glucocorticoid tapering [40].

An investigator-initiated (University of Pittsburgh) multicenter, randomized, double-blind, controlled trial is ongoing to assess the efficacy of tocilizumab in refractory adult polymyositis and dermatomyositis (clinicaltrials.gov, NCT02043548).

ABATACEPT

CD28 and CTLA-4, costimulatory molecules, have been reported to be upregulated in the muscles of polymyositis and dermatomyositis patients [41,42].

Abatacept, which targets CD80 and CD86 on antigen-presenting cells, was reported to be successful in a patient with refractory polymyositis [43]. A child with severe recalcitrant JDM with ulcerative cutaneous disease and progressive calcinosis also demonstrated a favorable response to combination therapy with abatacept and sodium thiosulfate [44]. In another case report from Japan, abatacept therapy was associated with a favorable outcome in an antisignal recognition particle-positive patient with refractory IIM [45]. In a more recent report from Europe, a patient with severe IIM in overlap with rheumatoid arthritis, peripheral vasculitis and ILD, refractory to several traditional and biologic therapies, responded well to abatacept with good control of myositis [46].

An ongoing clinical trial (ARTEMIS) is currently underway to assess the efficacy and potential role of abatacept in refractory IIM and another multicenter study is being planned.

SIFALIMUMAB

There is growing evidence that type I interferon (IFN α/β)-mediated innate immunity may be implicated in the pathogenesis of IIM.[47–49] In a study of 56 patients with adult or JDM (using peripheral blood samples and clinical data), the type I IFN gene and chemokine signature and serum levels of IL-6 correlated with each other and with IIM disease activity [50].

A recent phase 1b multicenter, randomized, double-blinded, controlled, clinical trial assessed sifalimumab, an anti-IFNa monoclonal antibody, in polymyositis and dermatomyositis [51] and demonstrated the suppression of the IFN signature in peripheral blood and muscle tissue (66 and 47%, respectively) which correlated with clinical improvement in patients received safalimumab. The patients with at least 15% improvement in the MMT had greater neutralization of IFN signature in both peripheral blood and muscle than those with less than 15% improvement.

RUXOLITINIB

Ruxolitinib, a Janus kinase inhibitor, was recently reported in a case report to be effective for the treatment of refractory dermatomyositis [52]. A 72-year-old woman refractory/partial responsive to glucocorticoids, azathioprine, IVIg and mycophenolate mofetil received ruxolitinib after being diagnosed with a JAK2 mutation-associated myeloproliferative neoplasm. Ruxolitinib monotherapy led to rapid and significant improvement of dermatomyositis symptoms as the dermatomyositis was in remission by 12 months.

CONCLUSION

Treatment of IIM and IIM-ILD patients who experience disease recurrences during or after conventional therapy or those who do not have complete response can be challenging. Over the past decade, there have been several small series and a limited number of clinical trials assessing the potential use of novel biologic agents in IIMs. Although the efficacy data are limited at this time, given the biological plausibility and encouraging small case series/clinical trial results, further research is required to assess the role of biologics such as tocilizumab (anti-IL6), abatacept (inhibition of T-cell costimulation),

Table 1. Results from the most recent and important publications in idiopathic inflammatory myopath

	Study	Results
Rituximab	Rituximab in Myositis (RIM) trial: randomized, double-blind, placebo-controlled: 195 patients (75 with PM, 72 with DM and 48 with JDM; all refractory to glucocorticoid therapy and at least one immunosuppressive drug) [1]	Definition of improvement met by 83% of these refractory IIM patients Rituximab had a statistically significant steroid-sparing effect Rituximab generally well tolerated and the most common adverse effects were infections
	Additional studies derived from the RIM trial [19,20▪▪]	Presence of antisynthetase and anti-Mi-2 autoantibodies along with the juvenile DM subset, and lower disease damage were strong predictors of clinical improvement and response to rituximab Significant improvements noted in cutaneous disease activity after the addition of rituximab to standard therapy in adult DM and JDM individuals
	Retrospective study of 24 patients with antisynthetase syndrome and severe ILD with more than 12 months follow-up postrituximab therapy (10 of the 12 patients also received cyclophosphamide) [22]	FVC, FEV-1 and DLCO increased by 24, 22 and 17%, respectively, postrituximab HRCT findings (expressed as a percentage of total lung volume) demonstrated a median 34% reduction in ILD extent postrituximab
	Multicenter, open-label, phase II trial, 10 antisynthetase antibody-positive patients with IIM and ILD refractory to traditional treatments (prednisone and at least two immunosuppressive agents), received 1 g of rituximab at day 0, day 15 and after 6 months [23]	ILD improved in five and stabilized in four based on FVC and/or DLCO; decrease in the burden of the associated immunosuppressive therapy Seven patients demonstrated an increase of at least four points on MMT-10 and the total CK level declined from 399 IU/l
	Retrospective study of anti-Jo-1 antibody-positive patients: 17 received rituximab and 30 patients were treated with conventional immunosuppressive agents and followed for a mean of 35 and 84 months, respectively [24▪]	Sixteen of the 17 receiving rituximab demonstrated a more rapid and marked response (response was independent of the anti-Ro52 antibody status)
Tocilizumab	32-year-old Japanese patient with an overlap syndrome, including DM and systemic sclerosis features, inflammatory arthropathy and CCP positivity (refractory to cyclosporine, IV cyclophosphamide, IVIg, tacrolimus and combination methotrexate and adalimumab) [40]	Tocilizumab led to the resolution of DM rash and arthritis with gradual improvement in the muscle weakness and CK allowing glucocorticoid tapering
Abatacept	Case report from Japan: anti-SRP positive patient with refractory IIM [45]	Abatacept therapy led to favorable outcome
	Case report from Europe: severe IIM in overlap with rheumatoid arthritis, peripheral vasculitis and ILD, refractory to several traditional and biologic therapies [46]	Abatacept therapy led to control of myositis
Sifalimumab	Phase 1b multicenter, randomized, double-blinded, controlled, clinical trial assessed sifalimumab, an anti-IFNa monoclonal antibody, in PM and DM [51]	Suppression of the IFN signature in peripheral blood and muscle tissue (66 and 47%, respectively) correlated with clinical improvement
Ruxolitinib	72-year-old woman with refractory DM and partial response to glucocorticoids, azathioprine, IVIg and mycophenolate mofetil (also diagnosed with a JAK2 mutation-associated myeloproliferative neoplasm) [52]	Ruxolitinib monotherapy led to rapid and significant improvement of DM with remission by 12 months

CK, creatine kinase; DM, dermatomyositis; IFN, interferon; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IVIg, intravenous immunoglobulin; JAK2, Janus kinase2; JDM, juvenile dermatomyositis; PM, polymyositis.

sifalimumab (anti-IFNα) and ruxolitinib (JAK inhibitor) Table 1 [1,19,20▪▪,22,23,24▪,40,45,46,51,52].

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There are no conflicts of interest.

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Recent clinical trials in idiopathic inflammatory myopathies

Valérie Leclair and Ingrid E. Lundberg

Purpose of review
Idiopathic inflammatory myopathies (IIMs) are complex multisystemic autoimmune diseases. Glucocorticoids remain the cornerstone of treatment in IIM, and the benefit of additional immunosuppressors is still debated. A limited number of controlled clinical trials have been available to support treatment guidelines, but in the last year, several clinical trials have been published. In this review, the highlights of recently published and on-going clinical trials in IIM will be summarized and discussed.

Recent findings
Post hoc analyses of a large randomized controlled trial (RCT) suggested new predictive factors of response to rituximab in refractory IIM individuals. An international collaboration enabled the completion of a large RCT in early juvenile dermatomyositis that will orient first-line treatment in that population. New approaches are showing encouraging results in inclusion body myositis.

Summary
Recent advances in molecular mechanisms underlying IIM pathogenesis and the development of novel targeted therapies have influenced recent and on-going clinical research.

Keywords
clinical trials, dermatomyositis, inclusion body myositis, inflammatory muscle diseases, treatment

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are autoimmune multisystemic diseases. The major subsets of IIM studied in clinical trials are dermatomyositis, polymyositis, juvenile dermatomyositis (JDM) and sporadic inclusion body myositis (sIBM). For decades, clinicians relied mainly on glucocorticoids often combined with immunosuppressors such as azathioprine, methotrexate, cyclosporine and mycophenolate mofetil to treat those chronic diseases. A Cochrane review on treatment of dermatomyositis and polymyositis failed to confirm the benefit of those additional immunosuppressors, because of the lack of evidence from randomized controlled trials (RCTs) [1]. In practice, these options are often not sufficient to induce prolonged clinical remission and long-term steroid exposition leads to unacceptable side-effects. Morbidity and mortality remain significant especially with specific extra-muscular organ involvement such as dysphagia or interstitial lung disease (ILD) [2,3].

In the last decades, successes of targeted therapies in various rheumatologic conditions and advances in understanding of pathophysiology have slowly modified the therapeutic landscape in IIM Figure 1. This review will present recently published as well as on-going clinical trials in IIM.

ADULT IDIOPATHIC INFLAMMATORY MYOPATHY

Traditional approach with conventional immunosuppressive treatment and intravenous immunoglobulin

Several published and on-going clinical trials in IIM focus mainly on refractory cases. A recent placebo-controlled factorial trial looked at the efficacy of

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KEY POINTS

- High interferon type 1 expression in skeletal muscle and serum at baseline, JDM subset, lower disease damage and certain autoantibody profiles such as anti-Jo1 were found to predict rituximab response in IIM.
- The results of a large RCT in JDM support the use of glucocorticoids in combination with methotrexate as the first-line treatment in that population.
- Alemtuzumab and follistatin gene therapy have shown some clinical benefit in sIBM.
- JAK inhibitors are under investigation in refractory dermatomyositis following positive results in case reports.

second-line immunosuppression in refractory IIM [4]. Fifty-eight individuals were randomized in four different groups: steroid alone, steroid and ciclosporine, steroid and methotrexate or a combination of steroids, ciclosporine and methotrexate. No added beneficial effect was found of combination therapy over glucocorticoid treatment alone. However, the number of patients in each arm was small and the IIM subsets were poorly defined in terms of autoantibody status or extra-muscular organ involvement. The PROMETHEUS trial, a randomized open-label assessor-blinded study, compared the efficacy and safety of a methotrexate and steroid combination to steroid alone in early dermatomyositis/polymyositis (NCT00651040). Their preliminary results on 31 individuals also showed no benefit of methotrexate combination therapy over glucocorticoids alone after 48 weeks of treatment [5]. These results further support the efficacy of glucocorticoids in IIM treatment, but controversy remains on the most appropriate glucocorticoid regimen to use. As an alternative to traditional glucocorticoids protocols and based on case report results [6], an open-label trial looked at the efficacy, safety and tolerability of adrenocorticotropic hormone gel (ACTH) 80 mg subcutaneously twice weekly for 6 months for treatment of active refractory dermatomyositis/polymyositis individuals (NCT01906372). At the time of writing, this trial was completed but no results were available. Intravenous immunoglobulins (IVIg) in refractory IIM are also a matter of debate among experts and important geographical variations exist in their use. There is evidence supporting IVIg efficacy in JDM, 3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody-associated myopathy and for specific organ involvement such as dysphagia [7▪▪]. Subcutaneous immunoglobulins (SCIg) are an interesting and safe alternative that showed some efficacy in case reports [8] and retrospective [9▪] studies. An open-label

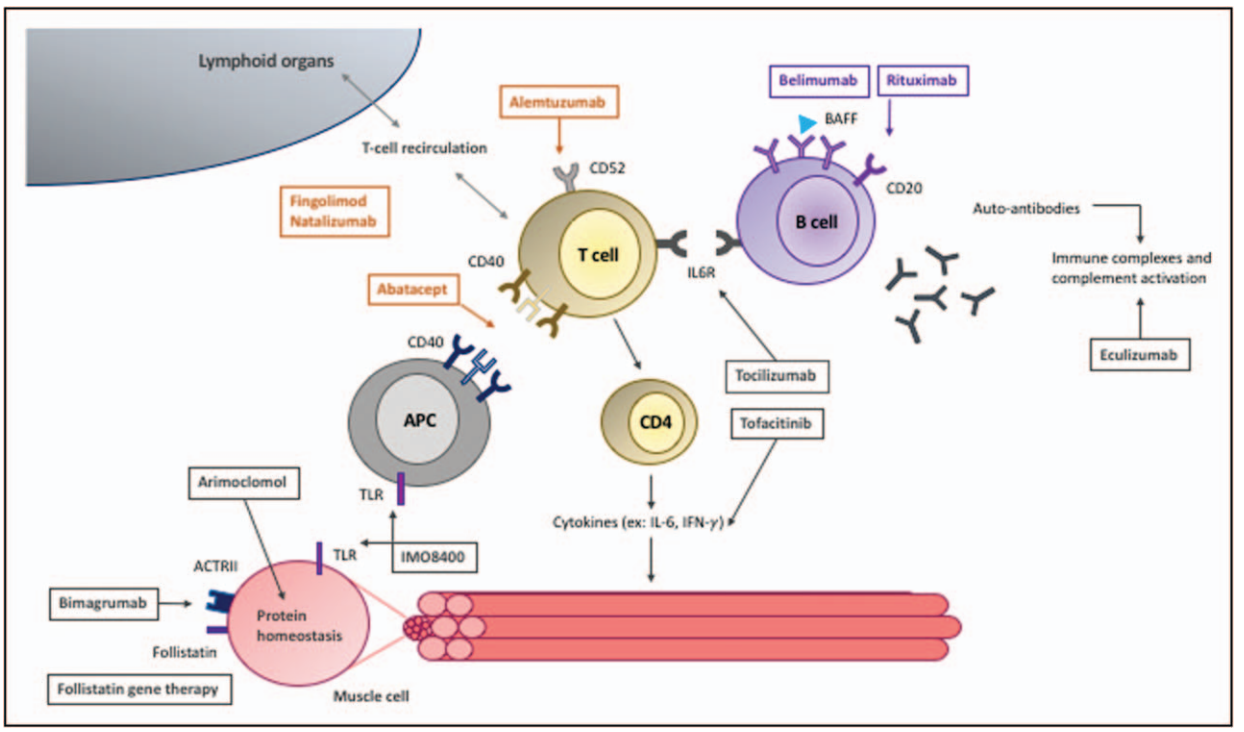

FIGURE 1. Overview of molecular mechanisms of action of different treatments studied in recent or on-going clinical trials in patients with idiopathic inflammatory myopathies. ACTRII, activin receptor; APC, antigen presenting cell; BAFF, B-cell activating factor; TLR, toll-like receptor.

study on SCIg efficacy in dermatomyositis is currently on-going (NCT02271165).

B-cell blockade

The largest RCT to date in IIM, the rituximab in myositis (RIM) trial, included 200 juvenile (JDM) and adult refractory polymyositis and dermatomyositis cases who were randomized in an early (weeks 0 and 1) or late rituximab treatment arm (weeks 8 and 9) [10]. The primary endpoint was comparison of time to achieve the International Myositis Assessment and Clinical Studies (IMACS) group definition of improvement (DOI) (Table 1) [11] and a secondary endpoint was comparison of response rates between the two groups at 8 weeks. Even if those endpoints were not achieved, 83% of the randomized individuals met the DOI by week 44 and a significant steroid-sparing effect was found. A post hoc analysis looked at cutaneous activity and damage scores of 120 patients included in the RIM trial to assess the efficacy of rituximab at improving refractory dermatomyositis rashes [12▪]. In adult individuals, there was a significant decreased frequency of any rash at week 36 (89–76%, $P = 0.047$), but no significant difference for more severe rashes (cutaneous ulceration, panniculitis or erythematous rashes with secondary changes). Interestingly, there was a significant decrease in the mean damage score. Similar declines were seen in JDM, but improvement in treatment-resistant cutaneous ulcerations was noted in this group. The clinical data of the RIM trial were also studied to identify possible predictors of treatment response. High interferon type 1 expression in skeletal muscle and serum at baseline, JDM subset, lower disease damage and certain autoantibody profiles (anti-Jo1, anti-TIF1γ and anti-Mi2) [13,14▪▪,15▪▪,16] were found to predict rituximab response. In line with those results, an open-label trial on rituximab efficacy in refractory antisynthetase syndrome reported increased muscle strength, decreased creatinine kinase levels and a steroid- sparing effect on 10 patients who completed the 12-month study [17]. Half of their individuals also showed ILD improvement on pulmonary function testing. Despite its small sample, this study remains one of the rare to focus on an autoantibody-defined IIM subset in a clinical trial. Another B-cell depleting agent, belimumab, is currently under study in refractory IIM (NCT02347891). This recombinant monoclonal antibody against B lymphocyte stimulator impairs B lymphocytes survival and is currently approved for systemic lupus erythematosus treatment.

Antifibrotic agents

ILD is an important cause of morbidity and mortality in antisynthetase syndrome and in clinically amyopathic dermatomyositis (CADM). When presenting with rapidly progressive ILD (RPILD) and antibodies against antimelanoma differentiation-associated gene 5, CADM individuals have a particularly high mortality rate [18]. A Chinese group administered pirfenidone, an antifibrotic agent recently approved for idiopathic pulmonary fibrosis, to 30 individuals with CADM and RPILD. This single center open-label trial with retrospective controls found decreased mortality in their subacute ILD subgroup ($n = 10$) at 1 year [19]. This might indicate a role for antifibrotic agents in slowing the progression of ILD in CADM with subacute ILD onset.

Table 1. Consensus on the minimum percentage change in the myositis core set of measures to classify a patient as clinically improved

Core set domain	Validated method of assessment	Percentage change, median (25th percentile, 75th percentile)	
		Adult specialists	Pediatric specialists
Physician's global activity assessment	Horizontal 10-cm VAS	20 (20,25)	20 (15,20)
Patient's/parent's global activity assessment	Horizontal 10-cm VAS	20 (20,25)	20 (15–24)
Muscle strength	MMT	15 (10,20)	18 (11,20)
Physical function	HAQ/C-HAQ; CMAS	15 (10,20)	15 (10,20)
Muscle-associated enzymes	At least two of CK, LDH, AST, ALT or aldolase	30† (20,50)	30† (20,30)
Extramuscular activity assessment	Extramuscular portion of the MDAAT	20 (20, 28)	20 (15,20)

Adapted from [11]. In the RIM trial, DOI was defined as three of any six core set measures improved by 20%, with no more than two worse by 25% which could not be MMT8.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-HAQ, Childhood HAQ; CK, creatinine kinase; CMAS, Childhood Myositis Assessment Scale; HAQ, Health Assessment Questionnaire; LDH, lactate dehydrogenase; MDAAT, myositis disease activity assessment tool; MMT, manual muscle testing; VAS, visual analog scale.

†In adult specialists, the median change was 25% for LDH. In pediatric specialists, the median change was 25% for aldolase.

T-cell blockade

T cells and their costimulatory molecules cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and CD28 are playing an important role in IIM pathogenesis [20]. This explains T-cell blockade introduction as a possible new therapeutic approach in IIM. Abatacept, a CTLA-4 analog, blocks the interaction between antigen presenting cell and T cell, preventing costimulation. After positive results in case reports [21–24], the ARTEMIS trial, an open-label trial with delayed start design, was conducted in refractory dermatomyositis/polymyositis (NCT02971683). Preliminary results of this pilot study suggest improved muscle performance and health-related quality of life in refractory IIM cases treated with abatacept [25]. Fingolimod, a sphingosine 1-phosphate receptor modulator leading to T-cell trapping in lymphoid organs, has shown anti-inflammatory and possible neuroprotective effects in multiple sclerosis [26]. A trial of fingolimod in refractory dermatomyositis/polymyositis was completed (NCT02029274) with inconclusive preliminary results despite effective decrease (>75%) of absolute T lymphocytes counts as reported in an abstract [27].

JUVENILE DERMATOMYOSITIS

Traditional approach

In 2016, the first RCT on first-line treatment in early JDM was published [28▪▪]. The authors randomized 139 newly diagnosed untreated JDM patients to either prednisone monotherapy or combination treatment with either methotrexate or ciclosporine. Combination therapy, particularly methotrexate, showed shorter time to clinical remission, longer time to treatment failure, decreased treatment failure and a steroid-sparing effect. The methotrexate treated group also showed a better side effect profile. These results support the use of glucocorticoids in combination with methotrexate as the first-line treatment in JDM.

Exercise and creatine supplementation

Exercise has proven to be both safe and effective in the adult IIM population, but had never been studied in an RCT in the pediatric population [29▪▪]. Twenty-six JDM individuals were randomized to a 12-week home-based exercise programme ($n = 14$) or to a waiting control group ($n = 12$) starting the same exercise programme at week 12. Seventy-five percent of the participants completed the intervention without relapse or hospitalization. The intervention group showed increased muscle function and functional ability, which parallels the adult experience. The JDM individuals included in this study were clinically stable. The same intervention in an active population could generate different results, with possibly increased efficacy. Creatine supplementation was tested on 15 JDM patients, both with active and inactive disease, for 12 weeks [30▪]. The treatment was well tolerated, but the authors found no therapeutic effect. These results are contrasting with the improved functional performance found in an RCT on 37 IIM adult individuals [31]. The authors noted the lack of increase in intramuscular phosphocreatine content in their pediatric population, possibly explaining the lack of benefit observed in their study.

Sporadic inclusion body myositis

sIBM patients usually demonstrate a poor response to conventional treatment with consequent significant long-term impairment. There is still controversy on the pathogenesis of this disorder that displays both inflammatory and degenerative components.

Alemtuzumab

T-cell blockade has been tried with moderate success in sIBM in the uncontrolled proof-of-concept study CAMPATH-1 [32]. Thirteen sIBM individuals received alemtuzumab, a humanized monoclonal anti-CD52 antibody inducing a profound depletion of mature T cell and monocytes, at a dose of 0,3 mg/kg/day for 4 days. A slower muscle strength decline was noted 6 months after the treatment, but only five patients reported definite functional improvement. The biopsies before and after treatment were recently analyzed for inflammatory and degenerative markers [33▪]. A trend toward downregulation of the expression of certain inflammatory molecules was noted especially in responders. However, this trend was not seen for crucial markers of cell-stress and degeneration as B-amyloid or ubiquitin. Those results, even if modest, are still encouraging in a condition as refractory to treatment as sIBM.

Arimoclomol

Amplification of heat shock protein (HSP) expression was proposed as a novel treatment in sIBM. The HSPs form a family of ubiquitously expressed protein chaperones that prevents aberrant protein–protein interaction and promotes adequate protein folding. Arimoclomol is a drug that prolongs heat shock factor 1, the main transcription factor of HSP. An RCT proof-of-concept trial on 24 sIBM patients was well tolerated, but failed to show significant benefits in the treated group ($n = 16$) compared with

placebo ($n = 8$) [34]. The authors are now recruiting individuals for a larger RCT (NCT02753530).

Bimagrumab

Another approach proposed to address the degenerative aspect of sIBM was to block the myostatin pathway. Myostatin binds the activin receptors (ActRII) which, when activated, inhibit skeletal muscle differentiation and growth. Bimagrumab, a human monoclonal antibody against ActRII, was tested in an RCT on 14 sIBM individuals. Eleven individuals received one single intravenous infusion of bimagrumab and three individuals a placebo dose [35]. Even if this proof-of-concept study showed some increase in the thigh volume at 8 weeks correlating with improvement on the 6-min walk test (6MWT), a phase IIb/III (NCT01925209) failed to meet its primary endpoint (Novartis April 21, 2016).

Follistatin gene therapy

A novel therapeutic approach to myostatin inhibition is through follistatin gene therapy [36▪▪]. On the basis of mouse models and positive results in Becker muscular dystrophy [37], six sIBM patients received follistatin gene transfer in the quadriceps muscles of both legs. To prevent immune response to the gene delivery, they also received high-dose prednisone for at least 2 months and were encouraged to exercise. The treatment was well tolerated and treated individuals ($n = 6$) improved their 6MWT by 56 m/year, whereas untreated patients ($n = 8$) decreased their walking distance by 25,8 m/year. On comparison of muscle biopsies obtained at baseline and 6 months after gene transfer, treated patients showed decreased fibrosis and improved regeneration. These positive results are encouraging and future studies will show if those benefits can be maintained and reproduced in a larger trial.

New perspectives

The aim of this review was to present the findings of recent clinical trials. However, novel therapies currently under study are listed in Table 2 [25,27,5,38] and some will be reviewed in this section.

Janus kinase inhibitors

Janus kinase (JAK) inhibitors, recently approved for the treatment of rheumatoid arthritis, showed

Table 2. Completed, on-going or terminated clinical trials in idiopathic inflammatory myopathy

Drug	Mechanism of action	Population
Completed but not yet published		
Abatacept [25], NCT02971683	T-cell activation inhibitor	Refractory DM/PM
ACTH, NCT01906372	Adrenocorticotropic hormone	Refractory DM/PM
Eculizumab, NCT00005571	Anti-C5 antibody	Refractory DM
Fingolimod [27], NCT02029274	Sphingosine 1-phosphate modulator	Refractory DM/PM
GC vs. GC + MTX [5], NCT00651040	Antifolate agent	Early DM/PM
On-going		
Arimoclomol, NCT02753530	Amplification of HSP expression	sIBM
Belimumab, NCT02347891	B-cell activation inhibitor	Refractory IIM
Hizentra, NCT02271165	Subcutaneous immunoglobulins	DM
Natalizumab [38], NCT02483845	Anti-α-4 integrin	sIBM
Rapamycin, NCT02481453	mTOR complex 1 inhibitor	sIBM
RTX vs. CYC, NCT01862926	Chimeric anti-CD20 antibody	Scleroderma, IIM and MCTD
Tocilizumab, NCT02043548	Anti-IL6 receptor antibody	Refractory DM/PM
Tofacitinib, NCT03002649	JAK1/3 inhibitor	Refractory DM
IMO8400, NCT02612857	Anti-TLR	Refractory DM
Terminated		
Autologous stem-cell transplant (NCT00278564)		
Fingolimod (NCT01148810, NCT01801917)		
Gevokizumab (EudraCT 2012–005772–34)		

ACTH, adrenocorticotropic hormone; CYCs, cyclophosphamide; DM, dermatomyositis; GCs, glucocorticoids; HSP, heat shock protein; IIM, idiopathic inflammatory myopathy; IL6, interleukin 6; JAK, janus kinase; MCTD, mixed connective tissue disease; mTOR, mammalian target of rapamycin; MTX, methotrexate; PM, polymyositis; RTX, rituximab; sIBM, sporadic inclusion body myositis; TLR, toll-like receptor.
Data compiled from ClinicalTrials.gov and other sources.

their efficacy at treating different inflammatory conditions including skin autoimmune diseases. The first generation of JAK inhibitors, including tofacitinib, ruxolitinib and baricitinib, are blocking more than one of the four JAKs (JAK1, JAK2, JAK3 and TYK2). These molecules have a suppressing effect on interferon signaling, which is suggested to be dysregulated in IIM [39]. The first case published of JAK inhibition in IIM presented the case of a patient with post–polycythemia vera myelofibrosis treated with ruloxitinib that improved both her hematological condition and dermatomyositis rash [40]. This was followed by a case series of refractory dermatomyositis reporting clinical improvement in three patients treated for 4 weeks with tofacitinib, mainly a JAK1 and JAK3 inhibitor [41▪▪]. These results suggest some efficacy of JAK inhibition in treating refractory dermatomyositis cutaneous manifestations, and a clinical trial on tofacitinib is currently recruiting refractory dermatomyositis individuals (NCT03002649).

Inhibitors of toll-like receptors

Evidence is suggesting that toll-like receptors (TLRs) are involved in IIM pathogenesis. These transmembrane receptors are expressed on a variety of immune and nonimmune cells and are known as key players of the innate arm of the immune system. They recognize certain molecular patterns displayed by invading organisms or damage-associated molecules. Upon recognition, they trigger an immune response and the release of cytokines. Muscle biopsies of IIM individuals have shown increased expression of TLR-2, TLR-3, TLR-4 and TLR-9 [39]. The protein histidyl-tRNA-synthetase, the antigen against which certain IIM patients produce a myositis-specific autoantibody (anti-Jo1), and the high-motility group box protein 1 have been proposed as certain damage-associated molecular patterns in IIM. TLR antagonism was previously studied in a small RCT in psoriasis with modest results, but overall good tolerance [42]. On the basis of this evidence, a double-blind, placebo-controlled trial with an investigational oligonucleotide-based antagonist of TLR-7, 8 and 9 has been initiated in dermatomyositis (NCT02612857) [43].

Stem-cell transplantation

Another therapy gaining attention in severe refractory IIM is stem-cell transplantation. The rationale of this treatment is to administer lymphotoxic chemotherapy (e.g. cyclophosphamide and antithymocyte globulins) with subsequent restauration of immunological tolerance. Autologous hematopoietic stem-cell transplantation has been used for two decades for the treatment of severe cases of various autoimmune diseases. To date, only a few case reports have been published on dermatomyositis, JDM and polymyositis cases [44–46]. The largest case series of 10 dermatomyositis/polymyositis patients treated with allogeneic mesenchymal stem-cell transplantation showed improved creatinine kinase levels, patient assessment scores and muscle strength [45]. Of note, some of these patients even had ILD improvement. A positive clinical response in two JDM patients was also reported in another recent case series [46]. These encouraging results led to an open-label trial of autologous stem-cell transplantation in refractory dermatomyositis and polymyositis that was, however, terminated because of the high-relapse rate in treated individuals (NCT00278564).

CONCLUSION

Conducting clinical trials in IIM is challenging. Recruiting large numbers of patients requires international multicenter collaboration as shown in the largest trials reviewed in this article [10,28▪▪]. This will become critical as we are now approaching subsetting based on clinical, pathological and, more importantly, autoantibody status. An individualized approach in IIM calls for well-defined subsets and a clear understanding of underlying pathologic mechanisms. In this regard, using to its full extent the material gathered in clinical trials is essential in understanding response predictors and molecular mechanisms. With the advent of targeted therapies and improved outcomes in IIM, also comes the question of 'treating to target'. In a population as heterogeneous as IIM, this is not straightforward. The meaning of satisfactory treatment response might differ depending on individual perspective, clinical phenotypes and underlying comorbidities. New clinical response criteria from IMACS and paediatric rheumatology international trials organisation, endorsed by the american college of rheumatology/european league against rheumatism, were recently published and address some of these issues [47,48]. Clinicians might, however, find these criteria difficult to transpose on an individual level particularly when extra-muscular features are dominating the clinical picture. Yet, we believe that international multidisciplinary collaboration is a key to future success in the development of new therapies for patients with IIM.

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Conflicts of interest

There are no conflicts of interest.

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