Idiopathic inflammatory myopathies: current insights and future frontiers

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Summary

Idiopathic inflammatory myopathies are a group of autoimmune diseases with a broad spectrum of clinical presentations, primarily characterised by immune-mediated muscle injury. Until recently, there was little insight into the pathogenesis of idiopathic inflammatory myopathies, which challenged the recognition of the breadth of heterogeneity of this group of diseases as well as the development of new therapeutics. However, the landscape of idiopathic inflammatory myopathies is evolving. In the past decade, advances in diagnostic tools have facilitated an enhanced understanding of the underlying disease mechanisms in idiopathic inflammatory myopathies, enabling the expansion of therapeutic trials. The fields of transcriptomics, proteomics, and machine learning offer the potential to gain greater insights into the underlying pathophysiology of idiopathic inflammatory myopathies. Harnessing insights gained from these sophisticated tools could contribute to the identification of differences at a molecular level among patients, accelerating the development of targeted, tailored therapies. Bolstered by the validation and standardisation of robust outcome measures, many promising therapies are in clinical trial development. Although challenges remain, there is great optimism in the field due to the progress in innovative diagnostics, outcome measures, and therapeutic approaches. In this Review, we discuss the expanding landscape of idiopathic inflammatory myopathies as the frontier of precision medicine becomes imminent.

Introduction

Idiopathic inflammatory myopathies are a group of rare autoimmune diseases with a broad spectrum of clinical manifestations (figure 1), most frequently sharing the feature of immune-mediated muscle injury.[1] Patients can be categorised as having dermatomyositis, immune-mediated necrotising myopathy, anti-synthetase syn-drome, inclusion body myositis, or polymyositis on the basis of characteristic clinical, serological, and pathological findings.[2]

A major barrier to advancements in the treatment of idiopathic inflammatory myopathies is the poor understanding of disease pathogenesis. Although clinical and histological differences between subgroups are well recognised, the exact pathological mechanisms driving immune-mediated injury remain poorly defined.3, 4 These limitations have hampered both the development of a more rigorous disease classification and the development of targeted therapies. Although the disease classification has evolved considerably since the criteria published by Bohan and Peter in 1975,[5] subgroups defined using current classification criteria for idiopathic inflammatory myopathies published by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) remain heterogeneous.[6]

Advances in diagnostics, most notably the advent of myositis-specific autoantibodies, have facilitated the recognition of homogenous subgroups within idiopathic inflammatory myopathies.[7] The recognition of these unique clinical phenotypes heralded the possibility of identifying specific pathological mechanisms specific to each disease associated with myositis-specific autoantibodies.[2] In the past 10 years, the fields of transcriptomics, proteomics, and machine learning technologies have offered hope of more comprehensive insights into the underlying pathophysiological mechanisms.[8]Harnessing these tools holds the potential for the development of a more rigorous disease classification, combining disease mechanisms with clinical, serological, and histological features. This more contemporary approach to classification could facilitate a paradigm shift towards precise, targeted therapies for patients with idiopathic inflammatory myopathies.

Although disease classification warrants a more refined approach, therapeutics for the treatment of patients with idiopathic inflammatory myopathies also require additional development. At present, treatment options are limited by the small number of available

therapies, as well as a reliance on eminence-based decision making as opposed to a rigorous evidence base. Furthermore, available therapies are broad and non-specific.[9]There are no validated tools to select treatments, nor biomarkers to predict treatment response. However, leveraging insights gained from myositis-specific autoantibodies has enabled the development of innovative trials to evaluate more refined, targeted therapies, which we discuss in the following sections.

Many challenges exist in the field of idiopathic inflammatory myopathies, including limited insights into disease pathogenesis and a dearth of available therapeutic options. However, propelled forward by the development of advanced tools that can recognise unique patient features at a molecular level, many novel diagnostic and therapeutic strategies are on the horizon. In this Review, we discuss current and future insights into the rapidly evolving landscape of idiopathic inflammatory myopathies in the context of diagnostics, outcome measures, and therapeutics as we face the exciting frontier of precision medicine.

Current insights into disease classification

By convention, the classification of idiopathic inflammatory myopathies was previously based on historical criteria published by Bohan and Peter.5 However, our expanding understanding of the spectrum of these disorders has broadened the diagnostic landscape to incorporate distinct clinical, serological, radiological, and pathological findings for the most precise diagnosis and classification of patients. Myositis-specific autoantibodies are increasingly relevant for diagnosing idiopathic inflammatory myopathies because of their ability to discern homogenous subgroups within idiopathic inflammatory myopathies.7,10 Although the EULAR and ACR criteria incorporate anti-Jo-1 myositis-specific autoantibody status, these criteria are limited by the number of patients with non-anti-Jo-1 myositis and other rare autoantibody subtypes included in the validation set.6

Current diagnostic tools

Serology

Myositis-specific autoantibodies are powerful tools that have facilitated the identification of homogenous subgroups with contrasting prognosis, clinical features, and organ involvement (figure 2A). Many patients with cancer-associated myositis are positive for anti-TIF1-γ antibodies, with cancer antedating or postdating myositis by up to 3–5 years in most instances.11 Anti-MDA5 dermatomyositis has a strong association with interstitial lung disease, which has been associated with poor prognosis, although several studies have shown the heterogeneity of the condition, with high variance across ethnicities.12,13 Anti-PM/Scl and anti-Ku antibodies are recognised as myositis-associated antibodies and are classically associated with overlap idiopathic inflammatory myopathies and systemic sclerosis.7,14 Most recently, three distinct clinical phenotypes were described from a cohort of patients with anti-PM/Scl antibody-positive disease, highlighting the potential for differential phenotypes even within specific subgroups of myositis-specific autoantibodies and myositis-associated antibodies.15

Many patients with polymyositis might be classifiable as having immune-mediated necrotising myopathy on the basis of myositis-specific autoantibodies, such as anti-SRP or anti-HMGCR antibodies; anti-synthetase syndrome on the basis of autoantibodies against aminoacyl-tRNA synthetases with or without other extramuscular features; or overlap idiopathic inflammatory myopathies (figure 2B). This clinical–serological syndromic approach to suspected idiopathic inflammatory myopathies has rendered the term polymyositis rather rudimentary.16,17

The diagnosis of inclusion body myositis relies mainly on clinical and histopathological findings; however, the presence of autoantibodies against cN1A can provide supportive evidence for the diagnosis.18

Imaging

MRI is an important diagnostic tool in the care of patients with idiopathic inflammatory myopathies, which can support the diagnosis and rule out other important differentials. MRI is very sensitive for identifying inflammatory changes in muscle, including intramuscular oedema, fascial oedema, fat replacement, and atrophy, as well as the evaluation of disease activity and severity, and determination of optimal muscle biopsy sites.19–21 The presence of extensive fat replacement and atrophy in pelvic, anterior, and medial thigh muscles can increase the probability of an underlying limb girdle muscular dystrophy, whereas fasciitis

can be an important clue towards anti-synthetase syndrome, anti-PM/Scl idiopathic inflammatory myopathies, and seronegative immune-mediated necrotising myopathy.22,23

Histopathology

Muscle biopsy findings are an important component of the diagnostic evaluation. In the absence of inflammatory infiltrates, myofiber necrosis is characteristic of immune-mediated necrotising myopathy, whereas rimmed vacuoles are characteristic of inclusion body myositis although absence of rimmed vacuoles does not exclude the diagnosis. MHC1 immunostaining is also useful for diagnosing myositis, with subtle differences in patterns: a focal pattern is associated with immune-mediated necrotising myopathy, a global pattern with inclusion body myositis, and a perifascicular pattern with dermatomyositis.24 In the past 20 years, research has resulted in an increased understanding of the granularity of muscle histopathology within the context of autoantibody subsets. Expression of various angiogenic molecules and greater endomysial capillary density was found to be linked to anti-HMGCR immune-mediated necrotising myopathy but not to anti-SRP-associated disease.25 Myofiber necrosis has also been identified in patients with dermatomyositis and anti-Jo-1 antibody-positive anti-synthetase syndrome, suggesting that biopsy might not always align with the clinical phenotype, calling for further exploration of stratified biopsy subsets of idiopathic inflammatory myopathies.26,27

Pathogenesis

In addition to the distinct features on clinical, radiological, serological, and histological investigations, pathophysiological mechanisms are considered distinct among subsets of idiopathic inflammatory myopathies. Interferon (IFN) pathways have been identified as major contributors to the pathogenesis of some subtypes of idiopathic inflammatory myopathies.28 IFNs are classified into three types: type 1 (IFN-α, IFN-β, IFN-κ, IFN-ε, and IFN-ω), type 2 (IFN-γ), and type 3 (IFN-λ).28 Type 1 and type 2 IFN pathways are differentially activated in different forms of idiopathic inflammatory myopathies.28–30 Dermatomyositis is associated with a prominent type 1 IFN signature,28 whereas small studies have described a type 2 IFN signature in patients with anti-synthetase syndrome and in those with inclusion body myositis,29,30 although additional larger studies are needed to further characterise these associations. Unique gene-expression patterns in muscle biopsies

from patients with different types of idiopathic inflammatory myopathies have been reported using a machine learning algorithm.31

Transcriptomic studies have shown that dermatomyositis is characterised by increased type 1 IFN-inducible genes in muscle, peripheral blood mononuclear cells, and skin, with type 1 IFN-inducible genes shown to correlate with disease activity.32,33 The expression of ISG15, a ubiquitin-like modifier conjugated to proteins in dermatomyositis, is characteristically upregulated in muscle samples from patients with dermatomyositis (panel 1).29,34,35 Elevated expression of type 2 IFN-inducible genes is also reported in patients with dermatomyositis.29 Although many genes are commonly upregulated in patients with dermatomyositis, differences between myositis-specific autoantibody-defined subsets are also observed, suggesting that different mechanisms might exist in each myositis-specific autoantibody subset within dermatomyositis;36 for example, muscle biopsies from patients with anti-Mi-2 autoantibodies show unique overexpression patterns of MADCAM1.31

The skin of patients with dermatomyositis also exhibits type 1 IFN signature.33 Type 1 IFN signature is expressed more strongly in the skin of patients with anti- MDA5 antibody-positive dermatomyositis than in those with anti-MDA5 antibody-negative dermatomyositis.37 Moreover, type 1 IFN score, using the expression levels of *IFI44* and *MX1* as type 1 IFN-stimulating genes, and the high numbers of circulating ISG15+ CD8+ T cells at baseline are associated with severity and poor prognosis in patients with anti-MDA5 antibody-positive disease.38,39

In patients with anti-synthetase syndrome, transcriptomic analyses have shown prominent type 2 IFN gene expression in muscle, blood, and lungs (panel 1).28– 30,40 High IFN-γ expression is consistent with MHC class II expression in the muscle of patients with anti-synthetase syndrome, which serves as a reliable histopathological marker in myofibres.30,41 Moreover, RNA processing-related genes are reported to be upregulated in the muscle of patients with anti-synthetase syndrome, possibly implying the pathogenic roles of tRNA synthetic pathways.36 Other uniquely expressed genes in patients with anti-synthetase syndrome include *CAMK1G*, *EGR4*, and *CXCL8*,31 which might be useful to distinguish anti-synthetase syndrome from dermatomyositis.

Inclusion body myositis is also associated with type 2 IFN signature, as well as enhanced expression of vasculogenesis-related pathways and the presence of plasma cells.29,31,36 In

contrast to dermatomyositis, anti-synthetase syndrome, and inclusion body myositis, the muscle in patients with immune-mediated necrotising myopathy shows low levels of IFN pathway activation.28 Thus, immune-mediated necrotising myopathy is characterised by the underexpression of those genes that are overexpressed in patients with other forms of myositis. Nonetheless, *APOA4*, a gene involved in cholesterol metabolism, is uniquely overexpressed in patients with anti-HMGCR antibody-positive immune-mediated necrotising myopathy, which can be triggered by statins.31 Because autoantibodies might have a dominant pathogenic role in patients with immune-mediated necrotising myopathy,42 alteration in gene expression in cellular infiltrate or muscle might not fully reflect the pathophysiological mechanisms. Collectively, these data indicate that distinct mechanistic pathways underlie disease pathogenesis in each type of myositis and help to identify specific targets that could be used to tailor therapies for each subset.

Emerging diagnostic tools

Serology

Although myositis-specific autoantibodies are powerful tools to identify subpopulations with distinct clinical phenotypes in idiopathic inflammatory myopathies, emerging data suggest that substantial heterogeneity within the same autoantibody group can exist.1 Using a proteomic approach, some studies have identified autoantibodies against CCAR1 and Sp4, both of which are strongly associated with the presence of anti-TIF1-γ antibody.43,44 These autoantibodies are associated with attenuated cancer risk in patients with anti-TIF1-γ antibody-positive dermatomyositis to levels similar to those in the general population.43,44 Additionally, the presence of a strong autoimmune signature evidenced by multiple autoantibodies was shown to be negatively associated with contemporaneous cancer in patients with anti-TIF1-γ-antibody-positive dermatomyositis.44,45 Furthermore, anti-Ro52 antibody, a myositis-associated antibody, is associated with severe interstitial lung disease and poor outcomes in patients with anti-MDA5 antibody-positive dermatomyositis and those with anti-synthetase syndrome.7 Thus, the combination of autoantibodies might provide a more precise classification. Notably, up to 30% of adults with idiopathic inflammatory myopathies might not have myositis-specific autoantibodies.7

Imaging

Muscle MRI remains the gold standard imaging modality in idiopathic inflammatory myopathies.19 There is increasing interest in the use of imaging biomarkers to enhance diagnostic and prognostic ability. Several studies have suggested distinct imaging and distribution patterns for each subset of idiopathic inflammatory myopathies.46,47 Assessment of muscle MRI using a deep-learning method has been attempted.46,48 MRI has the advantage of non-invasive and repeatable evaluation and is suitable for longitudinal monitoring; hence, in the past 10 years, it has been used as an objective outcome measure in clinical trials, such as the measurement of thigh muscle volume.49,50 Moreover, whole-body magnetic resonance has become an important imaging technique to investigate the global distribution of muscle involvement, including clinically silent involvement of some muscle compartments.51 Quantitative MRI has been regarded as an important modality because it provides objective measurements, such as fat fraction, T2 measurement, and diffuse tensor imaging, and can therefore provide information about tissue microstructure that might not be apparent on conventional MRI.52

Other related emerging technologies include magnetic resonance spectroscopy,53 which assesses metabolite concentrations, and magnetic resonance elastography,54 which evaluates stiffness, although their roles in evaluating myositis need to be clarified further. Similarly, ultrasound, including elastography, has been introduced to evaluate tissue elasticity and stiffness.55 PET might be useful for diagnosis and as a surrogate biomarker of therapeutic target engagement in patients with inclusion body myositis. Other novel tools being explored to distinguish healthy muscles from inflamed muscles include diffusion tensor imaging, based on water anisotropy, and magnetic resonance neurography to identify hypertrophy of the sciatic and tibial nerves in patients with inclusion body myositis.56,57

Regarding extramuscular involvement, high-resolution CT imaging is the optimal imaging modality for interstitial lung disease, whereas transthoracic echocardiogram can provide useful baseline information regarding cardiac involvement.

Outcome measures in patients with idiopathic inflammatory myopathies

Core set measures

Core set measures are tools created to specifically assess disease activity and quality of life in patients with idiopathic inflammatory myopathies. The expansion of new therapeutic trials in idiopathic inflammatory myopathies in the past 5 years can largely be attributed to the improved understanding of the pathogenesis of idiopathic inflammatory myopathies, as well as the validation and standardisation of more robust outcome measures for clinical studies and therapeutic trials in idiopathic inflammatory myopathies (panel 2).58 International organisations such as the International Myositis Assessment and Clinical Studies Group, the Paediatric Rheumatology International Trials Organisation, the ACR, and EULAR have had a crucial role in facilitating these advancements. Core set measures have been proposed, and they are the minimum set of measures that should be undertaken and reported in all myositis clinical studies and therapeutic trials (panel 2).59,60 Although applicable to all forms of myositis, these core set measures might not be suitable for inclusion body myositis, owing to distinct underlying pathophysiological mechanisms and clinical phenotype, for which a range of more suitable measures, including disease-specific measures, have been proposed and are currently being used in inclusion body myositis clinical studies and therapeutic trials.61–64 However, outcome measures for inclusion body myositis are largely inconsistent and there is an unmet need for core set measures specific to inclusion body myositis to facilitate research and clinical trials in this condition.62

Another major advance in outcome assessment in myositis was the development of the 2016 ACR–EULAR response criteria for adult patients with myositis and children with juvenile dermatomyositis (table).65,66 The 2016 criteria are now recommended for use as the primary outcome in myositis clinical trials. The criteria use six core set measures: (1) physician's global disease activity assessment, (2) patient's global disease activity assessment or parent's or carer's global disease activity assessment, (3) Manual Muscle Testing or Childhood Myositis Assessment Scale, (4) Health Assessment Questionnaire Disability Index or Childhood Health Assessment Questionnaire, (5) muscle enzyme activity (most elevated serum activity) or Child Health Questionnaire–Parent Form 50 Physical Summary Score, and (6) Extramuscular Global Activity Assessment or Disease Activity Score, combining the absolute percentage change in each core set measure with varying weights to obtain a total improvement score on a scale of 0 to 100. Different thresholds of

improvement have been set for minimal, moderate, and major response (table). Therefore, the criteria can be used either as a continuous outcome or as a 3-point categorical outcome. The publication of the 2016 response criteria followed the earlier publication of the less comprehensive and less validated preliminary definitions of improvement, which required an improvement of 20% or higher in a minimum of three of the six core set measures to establish that patients showed a minimal clinically meaningful improvement.67,68

For inclusion body myositis, the Inclusion Body Myositis Functional Rating Scale (IBMFRS) has gained popularity as the primary outcome in clinical trials. The IBMFRS was used as the primary outcome in the large arimoclomol randomised controlled trial69 and is currently being used in two other ongoing large randomised controlled trials (NCT04789070 and NCT05721573).

Other outcome measures have been used in myositis clinical trials and studies (panel 2), with the frequency of use and the level of validation and standardisation varying substantially between measures. Used sensibly and in a balanced way, taking feasibility into account, these additional measures can offer valuable information to health-care professionals and researchers regarding disease progression and the impact of treatments that might not be captured by core set measures alone. These outcome measures include measures of disease activity, damage, physical function, physical activity, mobility, endurance, work productivity, and health-related quality of life. Some of them are patient-reported outcomes, which can be particularly important to gain a deeper understanding of how myositis can influence the health, functioning, and abilities of patients. Ongoing future efforts must focus on further selection, validation, and standardisation of these additional measures.

Furthermore, because of the multisystem nature of myositis, measures to assess skin disease, the heart, lungs, and calcinosis need to be considered and might even be desirable as primary outcomes, if a trial is specifically designed at targeting one of these organs or systems (panel 2). A particular area of unmet need is swallowing-related outcome measures; the understanding of swallowing pathophysiology and optimal clinical management options for dysphagia is still unclear. The development and validation of these tools is essential to enhance dysphagia research efforts.70

Imaging tools for objective outcomes

There is an emerging appreciation of the role of imaging as an objective outcome measure in idiopathic inflammatory myopathies.71,72 Quantitative MRI has the greatest potential to be used as a primary or secondary outcome in early phase clinical trials, or as a secondary outcome measure in late phase clinical trials. Furthermore, the integration of segmentation algorithms based on artificial intelligence has substantially increased the potential of MRI as an outcome measure and holds the potential to revolutionise the field. By enabling the substitution of the laborious and time-consuming task of manual segmentation, quick automated segmentation could be used, streamlining the process, and saving valuable time. Other technologies, including ultrasound, electrical impedance myography, and PET, have shown promise in imaging of muscle tissues, and are also being studied in outcome assessment.71,72

Standardisation requirements

Training and standardisation in outcome assessment have a crucial role in improving the reproducibility and reliability of assessments. By ensuring consistent and detailed guidance, training helps minimise intraobserver and interobserver variability and enhances the accuracy of results, leading to more reliable and comparable data across different studies or clinical settings.

Therapeutic strategies

Current therapeutic approach

With the exception of inclusion body myositis, treatment of idiopathic inflammatory myopathies typically consists of one or more immunomodulatory agents. Systemic glucocorticoids are often combined with a steroid-sparing agent (eg, methotrexate, azathioprine, or mycophenolate mofetil) as initial therapy.17,73 Exercise and physical therapy are complementary cornerstones of immunomodulatory therapy.74 In 2022, the British Society for Rheumatology

published treatment recommendations for idiopathic inflammatory myopathies, to guide treatment decisions.75

However, in the absence of rigorous evidence-based or validated tools to inform treatment decisions, the choice of steroid-sparing agent is often determined by personal experience, disease severity, predominant disease manifestation, and patient comorbidities.9,76 Treatment course can be challenged by poor response, side-effects, and

difficulty in accessing therapies.9,17 Most agents are off-label; in 2021, the US Food and Drug Administration approved intravenous immunoglobulin for the treatment of dermatomyositis on the basis of the landmark ProDERM trial,77 representing only the second agent to be approved for the treatment of idiopathic inflammatory myopathies in the USA (the first one being Acthar gel, approved in 1952). Although this approval was greeted with universal

positivity, the supply and cost of intravenous immunoglobulin can be prohibitive in some regions. There is an

increasing focus on the development of therapies that target the most probable dominant pathogenic aberration, with several agents under development (figure 3).

Emerging therapies—immunomodulators

Given the positive results from the ProDERM study,77 a randomised, placebo-controlled, phase 2 trial evaluating upfront intravenous immunoglobulin is currently recruiting participants (NCT05832034). Recognising some of the cost and administration challenges of intravenous immunoglobulin formulation, a phase 3, randomised, placebo-controlled, double-blind study of subcutaneous immunoglobulin in adult patients with dermatomyositis is currently underway (NCT04044690). There is increased interest in the modulation of pathogenic IgG in idiopathic inflammatory myopathies. The neonatal fragment crystallisable (Fc) receptor (FcRn) functions as a recycling mechanism to prevent degradation of IgG, and FcRn inhibition reduces both pathogenic and non-pathogenic IgG, without affecting other components of the innate or adaptive immune systems.78 Thus, inhibition of FcRn has emerged as a potential mechanism to provide a targeted approach to IgG-mediated disease in patients with idiopathic

inflammatory myopathies. Currently, two clinical trials are underway evaluating the safety and efficacy of FcRn

inhibitors in patients with dermatomyositis, immunemediated necrotising myopathy, and anti-synthetase syndrome. Nipocalimab is being evaluated in a phase 2, randomised, double-blind, placebo-controlled, parallel group trial (NCT05379634), and efgartigimod is being evaluated in a phase 2/3, randomised, double-blind, placebo-controlled, parallel-group trial (NCT05523167).

Emerging therapies—targeting type 1 IFN

Given the substantial role of type 1-IFN inducible genes in the pathogenesis of dermatomyositis, several therapies

targeting type-1 IFN, such as inhibitors of the JAK–STAT pathway, are in development.28 JAK–STAT inhibitors have multiple effects, most notably suppression of multiple cytokine and pro-inflammatory responses.79 The first prospective, open-label, clinical trial of tofacitinib (ie, a pan-JAK and JAK–STAT inhibitor) in patients with refractory dermatomyositis showed clinical efficacy and reduction in type 1 IFN signature at 12 weeks,50 with sustained clinical efficacy at 96 weeks.80 Several clinical trials are underway investigating the efficacy of baricitinib, a selective JAK1 and JAK2 inhibitor, in patients with dermatomyositis (NCT04972760, NCT04208464, and NCT05361109). Research is also focusing on inhibition of the JAK–STAT pathway in patients with anti-MDA5 antibody-positive dermatomyositis: two retrospective studies showed clinical benefit of tofacitinib-based therapy in patients with anti-MDA5 antibody-positive disease,81,82 whereas a separate study showed that intensive therapy comprising rituximab, tofacitinib, and plasma exchange improved survival in 33 patients with anti-MDA5 antibody-positive disease accompanied by rapidly progressing interstitial lung disease.83 Currently, a single-arm, open-label, pilot study is enrolling patients with anti-MDA5 antibody-positive dermatomyositis to assess the efficacy of tofacitinib in this disease subgroup (NCT04966884).

Brepocitinib, a dual inhibitor of TYK2 and JAK1, is postulated to have a more potent blockade of type 1 IFN than tofacitinib, and is currently being evaluated in a phase 3, multicentre, randomised, placebo-controlled, double-blind study (NCT05437263).

Two other agents targeting type 1 IFN are also being evaluated in phase 2 studies. Results from a phase 2a study examining PF-06823859 (a humanised immunoglobulin neutralising antibody that reduces IFN β-mediated immunity) in patients with moderate-to-severe

dermatomyositis are currently pending (NCT03181893), whereas daxdilimab, a first-in-class, fully humanised monoclonal antibody targeting ILT7 on plasmacytoid dendritic cells is being evaluated in a phase 2, randomised, double-blind, placebo-controlled trial (NCT05669014).

Emerging therapies—IBM

Given the mounting evidence for a pathogenic role of T cells in inclusion body myositis,3,84 there has been increased interest in targeting T cells. KLRG1 is a surface marker of CD8+ T cells implicated in the pathology of inclusion body myositis, although KLGR1 expression is not restricted to T cells in inclusion body myositis. ABC008 is a humanised, afucosylated monoclonal antibody specific for KLRG1, which selectively depletes highly differentiated T cells while sparing other blood cell populations. A phase 2 trial is underway to investigate ABC008 in patients with inclusion body myositis (NCT05721573) after encouraging findings from a phase 1 study.85

Sirolimus is an mTOR inhibitor that inhibits T-cell activation and proliferation in response to antigenic and cytokine stimulation and prevents antibody production.

This inhibitor is hypothesised to be effective in patients with inclusion body myositis to slow or stabilise disease progression. A multicentre, phase 3, double-blind, randomised, controlled study of sirolimus has been launched (NCT04789070), after supportive phase 2 data.86

Emerging therapies—top down versus bottom-up approach

Traditionally, the approach to immunosuppressive therapy for idiopathic inflammatory myopathies has been a stepwise or bottom-up approach, where milder immunosuppressive agents are started first and escalated if necessary. However, this approach can delay disease control with resultant chronic damage and debility. A top-down approach, widely adopted in inflammatory bowel disease,87 refers to the use of more aggressive therapies upfront, to achieve rapid disease control, with the potential for reduced risk of disease progression and associated long-term debility. Although more aggressive upfront therapy is typically reserved for patients with severe disease manifestations (eg, dysphagia or rapidly progressive interstitial lung disease),17 two studies of patients with anti- MDA5 antibody-positive dermatomyositis have shown the efficacy of intensive upfront therapy, using either glucocorticoids, tacrolimus, and intravenous cyclophosphamide or rituximab, tofacitinib, and plasma exchange.83,88 Another study showed a benefit of upfront rituximab in combination

with mycophenolate among patients with interstitial lung disease,89 whereas a study evaluating the effect of early intravenous immunoglobulin is currently recruiting (NCT05832034). The utility of inducing early disease remission is a strategy that merits further investigation.

Emerging therapies—CAR-T cells

After successful reports of adoptive transfer of engineered T cells modified with chimeric antigen receptors (CAR) for CD19 target recognition in patients with refractory autoimmune rheumatic diseases, including systemic lupus erythematosus, systemic sclerosis, and anti-synthetase syndrome, trials using CAR T cells targeting CD19 or B cell maturation antigen in patients with idiopathic inflammatory myopathies are ongoing. Compared with existing B-cell depleting therapies, CAR T-cell therapy has the potential to induce a quicker and more profound therapeutic effect and facilitate drug-free remission.90,91

Emerging therapies—modulation of the microbiome

There is increasing interest in the role and potential for modulation of the microbiome in patients with idiopathic inflammatory myopathies, with this increase driven by advances in sequencing technologies and computational methods.92 A study reported that patients with dermatomyositis had lower microbial diversity and a distinct taxonomic composition compared with healthy controls.93 Another study found that dysbiosis of gut microbiota in patients with dermatomyositis was accompanied by changes in serum inflammatory factors and oxidative stress indexes.94 A post-hoc analysis found that low-dose IL-2 modified intestinal dysbiosis in patients with idiopathic inflammatory myopathies.95 Although it remains unclear whether microbial changes contribute to disease pathogenesis or are a consequence of the disease process itself, the role of the microbiome is a subject of great interest. Indeed, as the understanding of the intricacies of the pathogenesis of idiopathic inflammatory myopathies evolves, the modulation of the microbiome might bolster the therapeutic strategies in idiopathic inflammatory myopathies.

Patient perspectives and non-pharmacological approaches

The importance of ancillary approaches in idiopathic inflammatory myopathies cannot be over emphasised. The importance of graded resistance exercise in improving muscle strength in patients with idiopathic inflammatory myopathies is now well established.74 Besides

conventional physiotherapy, yoga has also been found to have positive benefits on muscle strength, flexibility, and mental wellbeing. One small study noted a positive impact of yoga on activities of daily living among patients with idiopathic inflammatory myopathies,96 although only a few specific studies of adequate statistical power have been undertaken in this regard.97

Increased digitalisation of health systems after the COVID-19 pandemic has increased the use of telecare by patients with poor mobility.98 Asynchronous texting, remote assessments of muscle strength using new patient-reported outcomes such as arm lift and walk distance, and audio-textual means of consultation were successful in bridging care for patients with idiopathic inflammatory myopathies during lockdowns.99,100

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Patients often resort to online information on drugs, disease, and supportive management. YouTube is a popular and valid source of information for myositis, particularly when linked to professional medical societies.101 Developing valid sources of online information can empower patients as equal stakeholders and improve self-management strategies, with patient support groups offering a collaborative approach to improving education and global outreach, fostering compliance, and enhancing social support for patients.102 However, physicians should be actively involved in the management of online resources to prevent undue stress or concerns that could be caused by misleading or invalid information online.

The future of digital myositis care offers several avenues including self-sampling, wide enrolment in research, virtual clinical trials, and improved tools for monitoring. Involvement of patient research partners can provide valuable insights into the challenges of such approaches and potential avenues for involving patients in self-care.103

Conclusions

The landscape of idiopathic inflammatory myopathies is evolving rapidly, driven by an enhanced understanding of underlying disease pathogenesis. The development of innovative therapeutic trials, coupled with the development of standardised outcome measures, holds

promise for expanding our therapeutic strategies. We stand at the forefront of a transformative frontier in idiopathic inflammatory myopathies, where sophisticated diagnostic and therapeutic approaches are poised to redefine patient care. The exciting opportunity to leverage advanced technologies to recognise patient-level disease mechanisms brings us closer to providing tailored treatments. By embracing these new technologies, we can strengthen clinical practices with innovative strategies and move towards a future of personalised therapies, leading to improved outcomes for patients with myositis.

Contributors

All authors contributed equally.

Declaration of interests

MF has received consulting or speaker fees from Sanofi, AbbVie, Eli Lilly, Taiho Pharmaceutical, Maruho, Janssen, Novartis, Sun Pharma, UCB, and Japan Blood Products Organization. PMM has received consulting or speaker fees from AbbVie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche, and UCB. JJP has received consulting fees from Alexion, Roivant, argenx, EMD Serono, Pfizer, Kezar Life Sciences, and Guidepoint; and clinical trial research support from Alexion, Pfizer, and Kezar Life Sciences. All other authors declare no competing interests.

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Panel 1: **Differentially upregulated genes reported in the muscles of patients with idiopathic inflammatory myopathies***

Dermatomyositis

ISG15, *IFI6*, *MX1*, *RSAD2*, *MX2*, *OAS1*, *IRF9*, *IFITM1*, *CMPK2*, and *OAS3*[31]

ISG15, *RSAD2*, *IFIT3*, *PSMB8*, *IFI44L*, *MX1*, *OAS1*, *IFI6*, *GBP1*, and *CXCL10*[35]

Anti-synthetase syndrome†

PSMB8, *ACTC1*, *GBP2*, *SAA1*, *SIK1*, *NNMT*, *MYH3*, *GADD45A*, *GBP1*, and *IFI30*

Inclusion body myositis

GBP2, *BIRC3*, *PSMB8*, *GBP1*, *CCL13*, *ITGAL*, *GBP5*, *HLA-DQA1*, *CD8A*, and *HLA-DOA*

Immune mediated-necrotising myopathy

SERPINA3, *ACTC1*, *CHRNA1*, *IFIITM10*, *TNC*, *KRT80*, *TNNT2*, *MYH3*, *ANKRD1*, and *DCLK1*

*The top **t**en genes are reported for each type of disease. †Includes only patients with anti-Jo-1 antibody-positive anti-synthetase syndrome.

Panel 2: **Outcome measures in idiopathic inflammatory myopathies***

Core set measures

Disease activity

Patient's global disease activity assessment or parent's or carer's global disease activity assessment by numerical rating scale or visual analogue scale†‡

Physician's global disease activity assessment by numerical rating scale or visual analogue scale†‡

Myositis Disease Activity Assessment Tool to assess extramuscular organs, including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac activity†

Manual Muscle Testing on a 0–10-point scale or on an expanded 0–5-point scale to evaluate eight muscle groups: one axial (neck flexors), five proximal (middle deltoid, biceps brachii, gluteus maximus, gluteus medius, and quadriceps), and two distal muscle groups (wrist extensors and ankle dorsiflexors)†‡

Disease Activity Score‡

Elevated serum activity of at least two muscle-associated enzymes among creatine kinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, or alanine aminotransferase†

Disease damage

Physician global disease damage assessment by Likert or visual analogue scale†‡

Myositis Damage Index†‡

Physical function

Health Assessment Questionnaire Disability Index†

Childhood Health Assessment Questionnaire†‡

Childhood Myositis Assessment Scale†‡

Health-related quality of life

36-Item Short Form Survey†

Child Health Questionnaire–Parent Form 50 Physical Summary Score‡

Growth and development

Height and weight, menses, and Tanner puberty stage†‡

Response or change measures

Total Improvement Score and respective thresholds of improvement

Physician's global impression and assessment of change

Patient's and parent's or carer's global impression and assessment of change

Inclusion body myositis specific measures

Inclusion Body Myositis Functional Rating Scale

Sporadic Inclusion Body Myositis Physical Functioning Assessment

Inclusion Body Myositis Weakness Composite Index

Patient Reported Impact of Symptoms in Inclusion Body Myositis

Other measures

Muscle strength assessment with dynamometry

Hand-held dynamometry

Quantitative muscle testing (fixed dynamometry)

Isokinetic dynamometry

Specific dynamometry

Physical function, mobility, endurance, and activity assessment

2-min and 6-min walking distance test

10-m walk or run

30-s chair stand test

Accelerometer-based wearable physical activity monitoring

Arm outstretched time

Arm lift test

Barthel Index for Activities of Daily Living

Functional Index-2 and Functional Index-3

Human Activity Profile

Lawton's Instrumental Activities of Daily Living Scale

MacMaster Toronto Arthritis Patients Preference Questionnaire

Myositis Activities Profile

Neuromuscular Symptom and Disability Functional Score

Nottingham Health Profile

One-repetition maximum leg and bench press

Pain Disability Index

Purdue Pegboard test

Short Physical Performance Battery

Sit to stand test

Stair climb test

Timed up-and-go test and modified timed up-and-go test

Health-related quality of life and work productivity

EQ-5D with three or five levels

Individual Neuromuscular Quality of Life Questionnaire

Paediatric Quality of Life Inventory

Work Productivity and Activity Impairment Questionnaire

Skin assessment

Adults' Dermatology Life Quality Index and Children's Dermatology Life Quality Index

Cutaneous Assessment Tool

Cutaneous Dermatomyositis Disease Area and Severity Index

Dermatomyositis Skin Severity Index

Investigator Global Assessment Scale of Skin Activity

Pruritus assessment by Likert or visual analogue scale

Skindex-29 and Skindex-16

Imaging biomarkers (semi-quantitative or quantitative assessments)

MRI of skeletal (whole-body or regional) or cardiac muscle

Ultrasound of skeletal or cardiac muscle

Lean body mass measured by dual-energy X-ray absorptiometry

Electrical impedance myography

PET

Dysphagia assessment

Deglutition Handicap Index

Dysphagia Handicap Index

Oesophageal manometry

Flexible endoscopic evaluation of swallowing

Inclusion Body Myositis Functional Rating Scale dysphagia item

Modified Sydney Swallowing Questionnaire

MRI and ultrasound assessment of bulbar muscles

Oropharyngeal scintigraphy

Reflux Symptom Index

Swallowing Quality of Life Questionnaire

Videofluoroscopic swallow studies (eg, timed water swallow, test of mastication, and swallowing solids)

Other assessments

Achievement of remission or inactive disease (consensus for adult myositis, defined by the Paediatric Rheumatology International Trials Organisation for juvenile dermatomyositis)

Achievement of complete clinical response (consensus, no data-driven definition)

Disease flare or worsening criteria (consensus, no data-driven definition)

Electromyography assessments

Fatigue assessment by numerical rating scale or visual analogue scale

Functional Assessment of Chronic Illness Therapy—Fatigue

Glucocorticoid use, cumulative dose, and discontinuation

Hospital Anxiety and Depression Scale

Incidence of falls

Liquid of tissue biomarkers (eg, antibodies, cytokines, histopathology, and gene regulators)

Low or ultra-low dose whole-body CT scanning for calcinosis assessment

Maximal and Submaximal Endurance Exercise Tests

Nailfold videocapillaroscopy (quantitative or qualitative)

Patient Acceptable Symptom State

Physician's global impression and assessment of severity

Patient's and parent's or carer's global impression and assessment of severity

Pain assessment by numerical rating scale or visual analogue scale

Patient-reported outcomes measurement information system (PROMIS) measures (eg, PROMIS-PF 20 and PROMIS 29+2)

Pulmonary Function Tests

*This comprehensive list of outcome measures is not necessarily an exhaustive and complete list; although the listed measures have all been used to some extent in myositis, the level of validation and standardisation varies substantially between measures. †Included in the International Myositis Assessment and Clinical Studies Group core set measures for juvenile dermatomyositis and adult idiopathic inflammatory myopathies. ‡Included in the Paediatric Rheumatology International Trials Organisation core set measures for juvenile dermatomyositis.

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