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Review

Treatment of idiopathic inflammatory myopathies

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ABSTRACT

Adult idiopathic inflammatory myopathies (IIMs) are rare autoimmune disorders affecting multiple organs, making diagnosis and treatment challenging. Current management relies on immunosuppressants like corticosteroids, methotrexate, azathioprine, mycophenolate mofetil, rituximab, and intravenous immunoglobulin, though treatment responses vary across patients and subtypes. Despite substantial challenges in clinical research, such as patient recruitment, misdiagnoses from overlapping symptoms with other conditions, and inconsistencies in disease classification, the growing number of myositis-specific clinical trials provides optimism. Progress in targeted therapies has the potential to refine treatment approaches, support the development of more standardized, evidence-based guidelines, and ultimately enhance patient outcomes. In this paper, we aim to provide a review of the current therapeutic options based on IIM subtypes.

1. Introduction

Adult idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare chronic autoimmune disorders, with an incidence ranging from 1.19–10 per million individuals per year [1,2]. Based on clinical, serological and pathological findings, the main subtypes of myositis are dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), anti-synthetase syndrome (ASyS), overlap myositis and polymyositis (PM). Cases that would have been previously classified as PM are now increasingly classified as one of the other entities, with the term PM gradually tending to become obsolete [1,3,4].

Managing idiopathic IIMs is particularly challenging due to its systemic nature, with the disease affecting multiple organs and often coexisting with other connective tissue disorders [5]. The therapies currently in use were originally developed for other inflammatory diseases, meaning they primarily focus on symptom relief rather than directly addressing the root causes of myositis. Due to the complexities in the management of myositis, no standardized guidelines are available, and there are very few approved therapeutic options. The available treatment approaches for myositis are based on limited scientific evidence and largely depend on expert consensus and anecdotal data from case studies and series [6,7]. There is no uniform treatment protocol across different forms of the disease. However, leading regional and global organizations in rheumatology, dermatology, and neurology provide guidance, offering valuable support for both healthcare professionals and patients navigating treatment options. A recent paper reviewed and compared the most recent regional guidelines for adult myositis [5]: guidelines from the German Society of Neurology/German Society of Dermatology [8], the European Neuromuscular Centre (ENMC) [9], the Brazilian Society of Rheumatology [10], the Japan College of Rheumatology, Japanese Society of Neurology and Japanese Dermatological Association [11], and the British Society for Rheumatology (BSR) [12].

Herein we provide an updated review of the available therapeutic options for adult patients with DM, ASyS, IMNM and IBM.

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2. Dermatomyositis

Several factors influence the choice of treatment approach, including the extent of skin and muscle involvement, the presence of systemic manifestations, and any associated malignancy [13]. Muscle and skin manifestations in myositis often respond differently to treatment, with skin involvement often being more persistent and difficult to manage [14,15]. Symptoms such as pruritus, especially on the scalp, may continue even after muscle inflammation resolves. Despite the use of strong topical treatments in combination with systemic therapies, controlling skin symptoms remains a significant challenge [13].

Protecting the skin from ultraviolet exposure, such as by using broad-spectrum sunscreens and minimizing sun exposure during peak hours, is a crucial preventive measure [16]. While topical therapies are commonly used, they are generally inadequate for managing manifestations beyond mild skin lesions. Corticosteroids applied to the skin can help alleviate redness and itching, particularly in mild cases or when combined with systemic treatments. However, high-potency steroid solutions, frequently used for scalp itching, often yield unsatisfactory results. As an alternative, topical calcineurin inhibitors, like tacrolimus 0.1% and pimecrolimus 1%, may provide effects identical to those obtained with mid-potency corticosteroids, without the risk of skin thinning or changes in pigmentation associated with prolonged steroid use [13].

2.1. Contemporary treatment approaches in clinical practice

The initial treatment strategy for acute DM typically involves systemic glucocorticoids combined with a steroid-sparing immunosuppressive agent [17,18]. Glucocorticoid monotherapy is not generally recommended, as it has been linked to lower remission rates and a higher likelihood of disease flare-ups [18]. Hydroxychloroquine and other antimalarials have long been used to manage skin symptoms in DM. However, their therapeutic impact is considerably less pronounced than in systemic lupus erythematosus (SLE), with only a small proportion of patients, around 15%–25%, experiencing noticeable improvement [19].

Steroid-sparing immunosuppressive agents should be initiated alongside glucocorticoid therapy. Azathioprine (AZT), methotrexate (MTX), and mycophenolate mofetil (MMF) are commonly used as first-line options, with retrospective studies supporting their effectiveness [20–22]. Although MMF is sometimes categorized as a second-line therapy, its value is becoming more widely recognized, particularly in cases of severe skin involvement or concurrent lung disease, where multiple studies have suggested potential benefits [23,24].

For patients with progressive disease that does not respond to first-line treatment, second-line options may be considered. These include intravenous immunoglobulin (IVIG), combining multiple first-line immunosuppressive agents, or introducing calcineurin inhibitors (CNI). In more resistant cases, cyclophosphamide (CYC) and rituximab (RTX) may be utilized as an additional therapeutic approach.

IVIG has long been recognized for its immunomodulatory and anti-inflammatory properties, with its potential benefits in refractory DM first reported over two decades ago [25,26]. More recently, a landmark phase III clinical trial provided strong evidence of its effectiveness, showing that 79% of patients treated with IVIG experienced significant clinical improvement at 16 weeks, compared to 44% in the placebo group, based on a composite disease activity score [27]. Due to its proven effectiveness in managing both muscle and skin symptoms, IVIG has received FDA and EMA approval for adults with DM who do not respond well to standard treatments or are unable to tolerate traditional immunosuppressive therapies. While it is most commonly utilized as a second-line option, either alone or alongside other immunosuppressive medications, it may be chosen as an initial treatment in patients with severe disease manifestations, such as profound muscle weakness, dysphagia, or severe interstitial lung disease (ILD), where early intervention is critical [18].

Retrospective case series have reported that cyclosporine and tacrolimus may be beneficial in managing refractory DM, particularly in cases with persistent muscle or lung involvement [7,28]. The use of combined immunosuppressive agents, such as MTX and AZT, may also be explored, to enhance treatment effectiveness. However, this approach has certain drawbacks, including the gradual dose adjustment required and the necessity for careful monitoring to mitigate potential adverse effects.

Cyclophosphamide might be used in cases of severe, unresponsive disease. Due to its considerable toxicity risks, such as high infection susceptibility and potential malignancy, its use is typically restricted to patients with rapidly progressive ILD, systemic vasculitis, or those who have not improved with multiple prior treatment approaches [28,29].

Rituximab, a monoclonal antibody targeting CD20+ B-cells, has shown effectiveness in treating both muscle and skin manifestations of myositis. Various dosing strategies have been used, though the most common regimen consists of two 1-gram infusions administered two weeks apart [30]. In the largest clinical trial involving 195 patients with DM or PM, 83% experienced clinical improvement in both muscle and skin symptoms, along with a reduction in glucocorticoid use over one year [31]. Additionally, rituximab has demonstrated significant benefits in idiopathic inflammatory myopathy-associated interstitial lung disease (IIM-ILD) [32].

2.2. Emerging treatment strategies

2.2.1. Interferon pathways as a therapeutic target

Janus kinase inhibitors (JAK inhibitors) represent a promising new class of immunosuppressive therapies for DM [33,34]. Tofacitinib, along with ruxolitinib and baricitinib, functions as a broad-spectrum JAK inhibitor, disrupting various cytokine and growth factor signaling pathways.

Brepocitinib is a dual selective TYK2/JAK1 inhibitor. Dual inhibition of TYK2 and JAK1 may result in superior blockade of type I interferon, a key cytokine implicated in DM pathogenesis. A phase III multicenter, randomized, placebo-controlled, double-blind study to investigate its safety and efficacy in adults with DM is currently underway (NCT05437263).

Given the role of activated toll-like receptors (TLRs) 7 and 8 in promoting type I interferon production in dendritic cells and monocytes, a phase II clinical trial is currently underway to assess the safety and efficacy of enpatoran (M5049), a TLR7/8 inhibitor, in patients with DM and PM (NCT05650567).

Sifalimumab is a monoclonal antibody targeting IFN-α (a type I interferon). In 2013, a phase 1b randomized, double-blind, placebo-controlled multicenter trial evaluated its effects in 48 patients with IIM (including 27 with DM and 21 with PM). Sifalimumab reduced type I IFN expression by 66% in blood and 47% in muscle tissue [35].

2.2.2. Fragment crystallizable receptor (FcRn) inhibitors

Nipocalimab and efgartigimod are fully human IgG1 monoclonal antibodies engineered to selectively inhibit the neonatal Fc receptor (FcRn), leading to a reduction in circulating pathogenic IgG antibodies. A phase II clinical trial evaluating intravenous nipocalimab in patients with IIM was actively recruiting participants but screening was prematurely discontinued, with the study continuing according to the protocol in a reduced number of patients already enrolled (NCT05379634). Additionally, a phase II/III study is

in progress to investigate the efficacy of subcutaneous efgartigimod compared to placebo in individuals with IIM (NCT05523167).

2.2.3. Depletion of B cells

Chimeric antigen receptor (CAR)-T cell therapy targeting CD19-expressing B cells has recently emerged as a potential therapeutic approach. In a recent case series evaluating CD19 CAR-T therapy across various autoimmune diseases, all individuals with IIM demonstrated a major clinical response based on ACR–EULAR criteria. Notably, after a single infusion, patients maintained improvement over a median follow-up of 15 months, allowing for the complete discontinuation of immunosuppressive therapy [36]. Several CAR-T cell therapy trials are ongoing in IIM, namely antibody-positive DM, ASyS and IMNM [37].

2.2.4. Apremilast

Apremilast, a phosphodiesterase-4 (PDE-4) inhibitor, has shown potential as an adjunctive treatment for refractory cutaneous DM. Findings from an open-label phase IIa study indicated both safety and clinical benefit when administered at a dose of 30 mg twice daily [38].

3. Anti-synthetase syndrome

The clinical presentation of ASyS varies significantly, and many patients do not exhibit definitive skin manifestations or muscle involvement, making early and accurate diagnosis challenging. Although some studies report an ILD prevalence of up to 100%, it is the initial presentation in only 15–30% of cases, with symptoms often emerging as the disease progresses [39,40]. ILD remains the leading cause of morbidity and mortality, requiring immunosuppressive treatment to prevent irreversible parenchymal damage [28]. However, the lack of randomized controlled trials poses a challenge in determining the most effective therapeutic approach. All patients should be encouraged to incorporate daily aerobic exercise, participate in pulmonary rehabilitation when available, and focus on optimizing their overall health. This includes maintaining a healthy weight, preventing infections through vaccination, and, where applicable, smoking cessation [18].

3.1. Contemporary treatment approaches in clinical practice

The primary treatment strategy for ASyS involves systemic glucocorticoids alongside a steroid-sparing immunosuppressant. The selection of the steroid-sparing agent depends on the severity of lung involvement and other clinical manifestations of the disease [18]. MMF is often the preferred first-line treatment for patients with moderate to severe ILD [24]. AZT serves as an alternative option with established effectiveness [23]. Calcineurin inhibitors are also frequently utilized in ASyS-ILD, though some clinicians reserve them for cases that are progressive or resistant to other treatments. A small retrospective study reported that 13 out of 15 patients with ASyS experienced either stabilization or improvement in forced vital capacity (FVC) following CNI therapy [41].

IVIG has emerged as a potential treatment option for patients with severe disease. A retrospective study in ASyS patients found that adding IVIG to existing therapy helped maintain or improve lung function. These findings indicate that IVIG may serve as a valuable adjunct to standard immunosuppressive treatments [42].

For patients with progressive ILD, there are limited second-line treatment options. Rituximab is a potential alternative, having shown effectiveness in managing IIM-ILD [32]. Additionally, research has indicated that anti-Jo-1 positive patients receiving rituximab achieved better clinical outcomes compared to those treated with conventional immunosuppressive therapies [43]. A guideline issued by the American College of Rheumatology and American College of Chest Physicians conditionally recommended MMF, AZT, rituximab, CYC, JAKi, CNI, or short-term glucocorticoids as first-line treatment options for IIM-ILD [44].

CYC use is generally limited due to toxicity concerns. It is primarily considered for severe, refractory cases or those experiencing rapid disease progression. Some case series have reported positive outcomes in patients with IIM-ILD [45].

3.2. Emerging treatment strategies

3.2.1. Abatacept

Abatacept, which consists of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4/CD152) and an Fc portion of immunoglobulin G1, is a biological agent that inhibits T-cell activation. Although the pathophysiological role of T-cells as causative agents of myositis and pulmonary fibrosis is not fully understood [46] the potential of T-cell inhibition therapy in ASyS-ILD has been demonstrated [47]. A randomised pilot trial assessing the effect of abatacept in treating ASyS-ILD was recently published. In this trial, abatacept did not significantly improve the primary endpoint (change in % predicted forced vital capacity from baseline to week 24); however, trends at 48 weeks suggested potential benefits, which might support the need for a larger, long-term randomized controlled trial [48].

3.2.2. Anti-fibrotic agents

Nintendanib and pirfenidone are both anti-fibrotic agents, whose role in IIM-ILD remains to be defined. In the recent guideline issued by the American College of Rheumatology and American College of Chest Physicians, nintedanib received a conditional recommendation for use in patients whose IIM-ILD had progressed despite first-line treatment [44]. Two studies are currently recruiting to evaluate the efficacy of pirfenidone in combination with immunosuppressive therapies in patients with connective tissue disease-ILD (including IIM) (NCT05505409 and NCT04928586). Another pilot study is recruiting to evaluate the safety and tolerability of nintedanib among patients with IIM-ILD (NCT05335278) [49].

4. Immune-mediated necrotizing myopathy (IMNM)

Immune-mediated necrotizing myopathy is a distinct subgroup of IIM classically characterized by predominant myofiber necrosis with minimal inflammatory infiltrates on muscle biopsy. IMNM is also distinguished from other categories of IIM by highly elevated creatine kinase levels, paucity of extra-muscular involvement, and, occasionally, more severe disease that is difficult to fully control with immunosuppressive therapy [50]. Historically, these patients were most often diagnosed with ‘polymyositis’ due to the absence of skin involvement. The European Neuromuscular Centre (ENMC) criteria divide IMNM into three subtypes based on autoantibody positivity: anti-3hydroxy-3-methylglutaryl-CoA reductase (HMGCR) IMNM, anti-signal recognition particle (SRP) IMNM, and antibody-negative IMNM [9]. IMNM can also occur in association with malignancy or other connective tissue disorders such as scleroderma.

4.1. Contemporary treatment approaches in clinical practice

No therapies are approved specifically for IMNM. Treatment guidance is mainly based on observational studies and anecdotal evidence. Autoantibody status in IMNM has considerable correlation with clinical phenotype, prognosis, and recommended choice of immunosuppressive therapy [51].

4.1.1. Approach to treatment based on autoantibody

4.1.1.1. Anti-HMGCR. According ENMC guidelines [9], steroids are initiated as the first-line therapy for anti-HMGCR IMNM and seronegative IMNM patients, with the potential addition of MTX and/or IVIG within the first month. While corticosteroids are commonly used as first-line therapy, they are rarely sufficient as monotherapy, and additional immunomodulating agents are required, most commonly, MTX, MMF, AZA or IVIG [52]. IVIG monotherapy, even without steroids, may in fact be sufficient treatment for certain anti-HMGCR patients. In patients who are still refractory, rituximab might be started [51,52].

Statins should not be restarted or introduced in patients with anti-HMGCR IMNM, as they can provoke disease exacerbations [53]. Although rare, ezetimibe has been linked to toxic myopathy and should be administered with extreme caution, with prompt discontinuation if muscle symptoms worsen [54]. Alternatively, unlike statins, bempedoic acid does not carry a risk of myopathy, myositis, or myonecrosis. This is because its activation relies on the enzyme Very-long-chain Acyl-CoA Synthetase 1 (ACSVL1), which is absent in skeletal muscle. As a result, it is less likely to cause musculoskeletal side effects [55]. As another option, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors offer a safe alternative to statins without increasing the risk of disease recurrence [54].

4.1.1.2. Anti-SRP. Based on ENMC guidelines [9] for anti-SRP IMNM patients, oral or intravenous steroids are the preferred choice during the initial induction therapy, with the optional addition of MTX and/or rituximab within the first month. In a small longitudinal study, out of 17 patients with anti-SRP treated with rituximab, 13 exhibited marked clinical improvement. While some individuals maintained these positive effects for over two years, response rates differed, with certain patients requiring repeated or continuous treatment [56].

4.1.1.3. Seronegative IMNM. Definitive treatment protocols for seronegative IMNM are still lacking, similar to the challenges described in seropositive cases. However, since many patients eventually require more advanced therapies [57], a combination regimen that includes prednisone, an immunosuppressant—commonly MTX or MMF—and monthly IVIG might be preferred [52]. In cases where patients fail to show meaningful improvement within three months or present with particularly aggressive disease, rituximab can be introduced early in the treatment course.

4.2. Emerging treatment strategies

4.2.1. Plasma exchange

Plasma exchange is an alternative therapeutic approach for individuals with significant muscle involvement. A small retrospective study observed a notable drop in CK levels among six IMNM patients [58], highlighting the potential role of plasma exchange in treating seropositive IMNM, especially in those who do not respond adequately to standard immunosuppressive treatments.

4.2.2. Targeting FcRN

In contrast to other IIM, autoantibody levels have been shown to correspond closely with muscle function and CK levels. This association has generated interest in FcRN inhibitors (nipocalimab and efgartigimod) as a potential therapeutic approach. As mentioned in Section 2.2.2, there are ongoing trials investigating whether reducing pathogenic IgG antibodies through this mechanism could lead to significant clinical benefits.

4.2.3. Abatacept

A large, double-blind RCT of subcutaneous abatacept did not meet its primary or secondary endpoints in IIM. However, post-hoc analysis indicated a potential treatment benefit in patients with non-DM myositis subtypes (IMNM and PM) [59].

4.2.4. Complement inhibition

A phase 2, randomized, placebo-controlled trial investigated the efficacy of zilucoplan, a complement component 5 inhibitor, in HMGCR and SRP IMNM, based on the hypothesis that complement activation may underlie the pathogenesis of IMNM. Efficacy of zilucoplan over placebo was not observed [60].

5. Inclusion body myositis (IBM)

At present, no pharmacological treatments have been proven to halt disease progression in IBM. Management is primarily supportive and includes physical therapy, speech and language therapy, orthotic interventions and nutritional optimization. Patient education on fall prevention and the use of assistive devices also play important roles in maintaining mobility and independence [61].

5.1. Contemporary treatment approaches in clinical practice

In a recent systematic literature review (SLR) that aimed to identify the best evidence on the efficacy of treatment interventions for IBM [62], several pharmacological interventions were included: MTX alone, IVIG, interferon beta-1a and MTX, anti-T-lymphocyte immunoglobulin and MTX, AZT and MTX, oxandrolone, bimagrumab, arimoclomol and sirolimus. Overall, authors found that pharmacological interventions were not effective for most of the outcomes of interest and had no consistent effect on the progression of IBM [62].

Dysphagia is a common and potentially disabling symptom in patients with IBM [61]. Procedures such as cricopharyngeal myotomy or esophageal dilation, may offer temporary symptom relief for patients experiencing significant obstruction [63]. The efficacy and safety of botulinum toxin injections remain uncertain, with ongoing debate regarding their role [64]. While some anecdotal reports suggests that IVIG may improve dysphagia, the mainstay of management remains regular monitoring by speech and language/swallowing specialists [65]. Ongoing assessment supports tailored dietary modifications and helps mitigate aspiration-related complications.

5.2. Emerging treatment strategies

5.2.1. Sirolimus

Following the sirolimus (rapamycin) phase 2 clinical trial in IBM with some promising secondary outcome results [66], a phase 3 clinical trial with the same drug is ongoing (NCT04789070) as it is hypothesized that this will be effective in IBM to slow or stabilize disease progression.

5.2.2. Ulviprubart

A phase 2/3 trial (NCT05721573) is currently being conducted to investigate the potential of ABC008/Ulviprubart as a treatment for IBM. This monoclonal antibody is designed to target KLRG1, leading to the selective depletion of highly differentiated T cells. Initial results from a small pilot study involving three IBM patients showed a reduction in circulating KLRG1+CD8+ T cells and T-LGLs, while regulatory T cells remained unaffected [67]. Some patients also exhibited signs of functional improvement, indicating a possible therapeutic advantage.

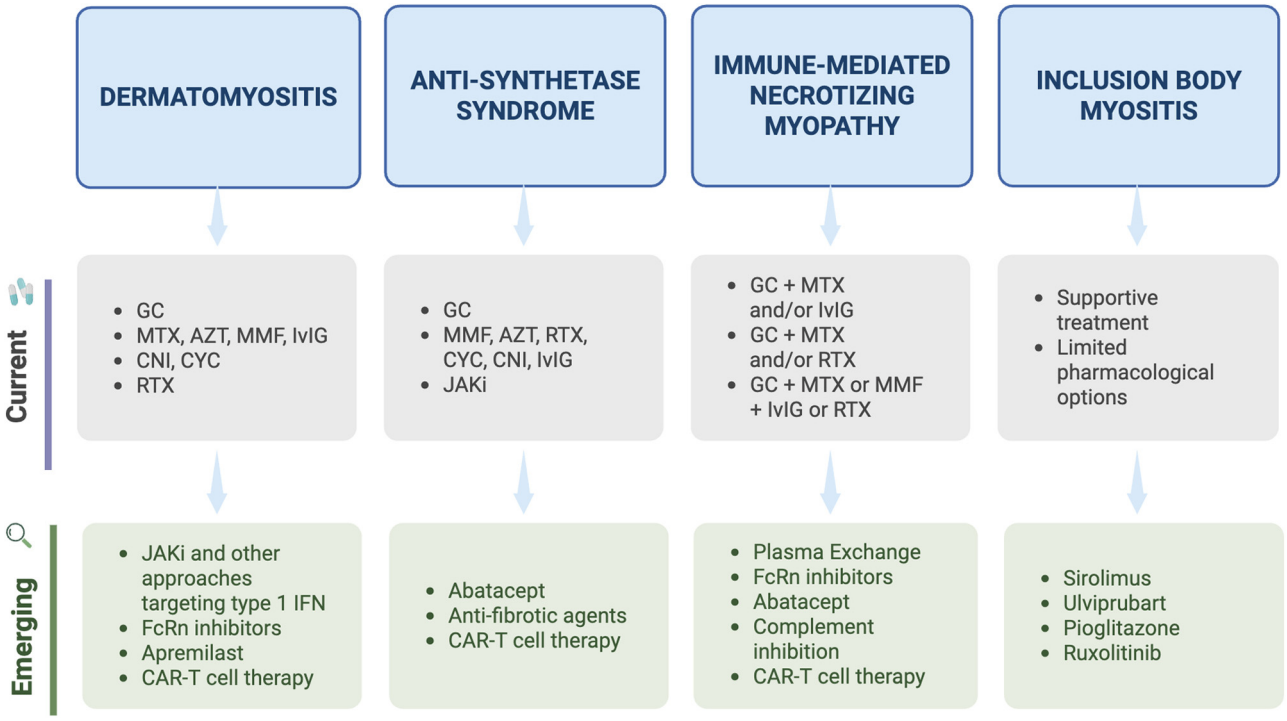

Fig. 1. Summary of current therapeutic options and emerging treatments for idiopathic inflammatory myopathies. AZT: azathioprine; CAR-T: chimeric antigen receptor T cell; CNI: calcineurin inhibitors; CYC: cyclophosphamide; FcRn: neonatal fragment crystallizable receptor; GC: glucocorticoids; IFN: interferon; IVIG: intravenous immunoglobulin; JAKi: Janus kinase inhibitors; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab.

5.2.3. Pioglitazone

In an open label phase 1 clinical trial in IBM, pioglitazone partially ameliorated some of the metabolic hallmarks of the disease [68]. The authors reported that a metabolic response in muscle may be associated with a more favorable clinical trajectory, suggesting that pioglitazone may warrant further investigation in IBM.

5.2.4. Ruxolitinib

Recent findings reveal that ruxolitinib, a JAK1/2 inhibitor already in clinical use, can reverse several IFNγ-induced effects linked to muscle degeneration. The authors showed that in IBM muscles, the levels of IFNγ transcripts were significantly elevated and correlated with myofibre atrophy [69]. In cell models of human muscle progenitor cells, ruxolitinib restored muscle stem cell function, prevented abnormal major histocompatibility complex-II expression, and lowered senescence indicators. When administered orally in vivo to myoinjured mice, it enhanced muscle fiber size and reduced signs of muscle wasting. These results highlight IFNγ's central role in driving muscle atrophy in IBM [69]. A phase II/III randomized, double-blind, placebo-controlled, multicenter clinical trial (NCT06536166) is set to initiate, representing a critical step toward evaluating the therapeutic potential and safety profile of ruxolitinib in patients with IBM.

6. Conclusion

The management of IIM continues to rely primarily on traditional immunosuppressive therapies, but emerging treatments are offering new possibilities as is summarized in Fig. 1. In clinical practice, therapeutic strategies for IIM are necessarily tailored to disease subtype, severity, and prior treatment history. In DM, first-line management typically involves systemic glucocorticoids in combination with steroid-sparing agents such as MTX, AZA or MMF, with IVIG considered in refractory or severe cases. ASyS often requires early and aggressive immunosuppression to control interstitial lung disease, with MMF, calcineurin inhibitors, and RTX as commonly used agents. In IMNM, treatment decisions are heavily influenced by autoantibody status, with IVIG showing promise, particularly in anti-HMGCR-positive patients. IBM remains largely treatment-resistant, and current strategies focus on supportive care, although novel targeted approaches are under investigation. The heterogeneity of IIM subtypes and variable disease trajectories underscore the importance of a personalised approach. Patients with milder disease and limited organ involvement may respond to less intensive regimens, while those with rapidly progressive features – especially involving the lungs or with severe muscle weakness – often require early initiation of combination therapy or escalation to biologic agents.

Ongoing randomized controlled trials are exploring new therapeutic molecules aimed at targeting specific disease mechanisms. However, clinical research in this area faces significant challenges. These include the complexity of multiple disease subtypes, difficulties with patient enrollment, frequent misdiagnoses due to overlapping symptoms with other inflammatory conditions, inconsistencies in disease classification, underrepresentation of rare subtypes, and insufficient data on patient-reported outcomes.

Alongside pharmacological interventions, non-pharmacological approaches, namely particularly tailored exercise programs, are increasingly recognized as essential components of comprehensive care, contributing to improved function, quality of life, and long-term outcomes.

Despite these hurdles, the growing number of myositis-focused trials offers hope for more effective treatments and the development of refined, subtype-specific therapeutic guidelines.

Disclosure of interest

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