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Updates in Treatment of Refractory Inflammatory Myositis

Kun Huang, MD, PhD, FRCPC, Aidan Pye, MD

Introduction

Idiopathic immune myopathies (IIM), also known as myositis, are a heterogeneous group of autoimmune diseases with varying phenotypes, prognoses, and treatment responses.[1] They are primarily characterized by muscle inflammation, however, many patients have extramuscular involvement including skin rash, arthritis, interstitial lung disease (ILD), cardiomyopathy, and gastrointestinal dysmotility. The discovery of myositis-specific autoantibodies (MSAs) has been a major advancement in the field of IIMs, shaping the new landscape of the clinical, phenotypical, histological, and serological correlations.[1] Based on this discovery, IIM can be more specifically classified into dermatomyositis (DM) (including amyopathic DM), antisynthetase syndrome (ASyS), immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM), and overlap myositis (OM).[1] An increasing number of histological studies have revealed a misdiagnosis of PM because many patients who were previously diagnosed with PM were later reclassified to other forms of IIM, including IBM, IMNM, ASyS, or DM without a rash.[2]

Treatment of IIMs is challenging owing to their rarity, heterogeneity, and variable organ involvement, with most of the evidence for treatment coming from retrospective cohort studies. Only intravenous immunoglobulin (IVIg), rituximab, and exercise have evidence from randomized controlled studies to guide treatment decisions.[3,4] Consequently, no

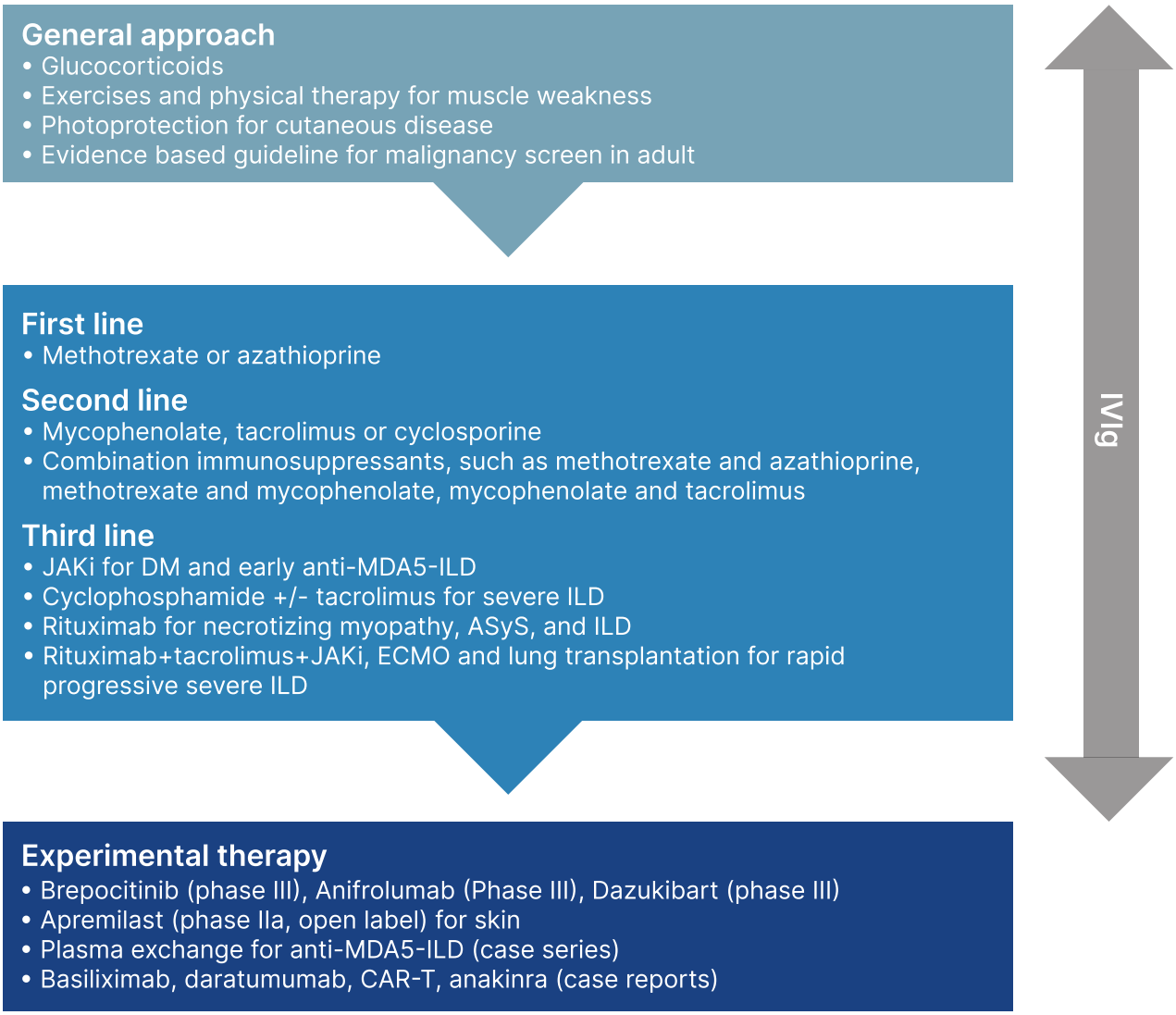

Figure 1. Common approach to IIM treatment (IBM excluded); courtesy of Kun Huang, MD, PhD, FRCPC and Aiden Pye, MD
Abbreviations: ASyS, antisynthetase syndrome; CAR-T, chimeric antigen receptor T cell therapy DM, dermatomyositis; ECMO: Extracorporeal Membrane Oxygenation; JAKi, Janus-kinase inhibitors; ILD, interstitial lung disease; MDA5-ILD, anti-melanoma differentiation-associated gene 5 dermatomyositis-interstitial lung disease

comprehensive consensus-driven guidelines exist for the treatment of IIMs.

The scope of this review is to summarize the general approach of myositis treatment with an emphasis on the management of refractory disease domains, including muscle, skin, and lung disease. As IBM does not respond to immunotherapy, and the mainstay treatment of IBM is exercise only, we will exclude IBM when referring to IIM or myositis in this review.

Current General Approach

The management of myositis includes non-pharmacological interventions, immunosuppressive therapies, and biologic agents, which are summarized in **Figure 1**. Adult-onset IIM is associated with an increased risk of cancer, particularly within the 3 years prior to and the 3 years after IIM onset. The International Myositis Assessment and Clinical Studies Group (IMACS) has recently developed an evidence - and consensus-based cancer screening guideline which stratifies cancer risk by age, myositis phenotypes, autoantibodies, and clinical features.[5]

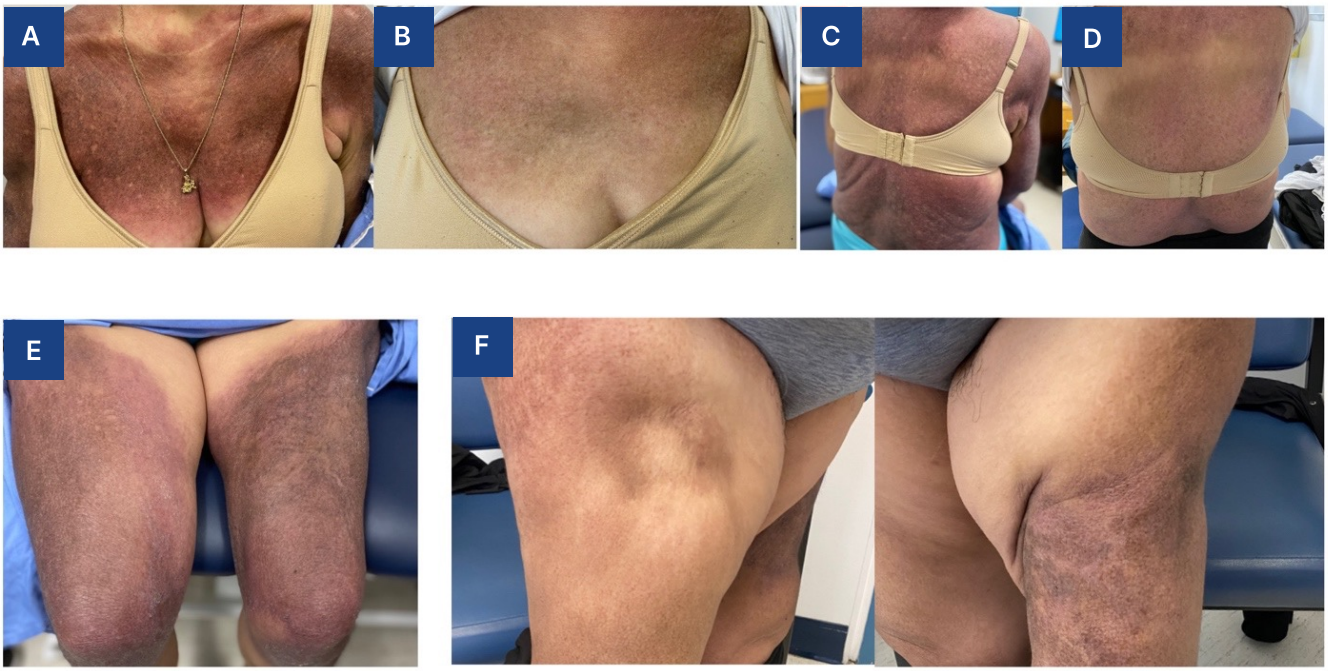

Figure 2. Improvement in cutaneous disease activity after a 2 month trial of tofacitinib
Photographs of a 64-year-old female with anti-SAE dermatomyositis for 6 years with severe myositis, dysphagia, widespread cutaneous rash, and subcutaneous panniculitis. Her myositis and dysphagia improved with high dose prednisone, IVIg, hydroxychloroquine, methotrexate, mycophenolate, cyclophosphamide, and rituximab; however, her cutaneous disease activity persisted . She was put on a trial regimen of tofacitinib 5 mg twice a day with IVIg. Pre-tofacitinib photographs are shown on panels **A, C** and **E**. After the 2 month trial regimen of tofacitinib, a significant improvement can be observed and is demonstrated in panels **B, D,** and **F**. Subcutaneous fat atrophy from panniculitis is also evident in panel **F**. Consent for the publication of the photographs was obtained from the patient; courtesy of Kun Huang, MD, PhD, FRCPC and Aidan Pye, MD
Abbreviations: IVIg, intravenous immunoglobulin; SAE, anti-small ubiquitin-like modifier activating enzyme

While many patients respond to first-line therapies and achieve a sustained remission, about 40% have relapsing/remitting or chronic refractory disease.[6] It is important to keep in mind that treatment for refractory cutaneous, muscular, and pulmonary diseases each follow a different treatment algorithm.

Refractory cutaneous disease

Most patients with cutaneous DM require systemic immunosuppression beyond antimalarials such as hydroxychloroquine.[7] Once a patient has failed to respond or has had a relapse of symptoms while taking steroid-sparing agents such as methotrexate with or without hydroxychloroquine, they are considered to have refractory disease. When assessing patients with persistent cutaneous disease, clinicians must review patients' compliance with strict photoprotection on a year-round basis, including the winter months. Daily use of broad-spectrum sunscreen (with a sun protective factor of at least 50), sun avoidance, wide-brimmed hats, and sun-protective clothing are strongly encouraged.[8]

If the area of affected skin is limited, further optimization with additional topical glucocorticoid and calcineurin inhibitors (CNIs), such as tacrolimus and pimecrolimus is reasonable.[8] Topical CNIs can be used on areas with thinner skin without the risk of atrophy.

However, refractory or severe cutaneous DM rash commonly requires an escalation of systemic treatment. Mycophenolate mofetil was shown to be an effective and well-tolerated agent for refractory cutaneous disease in case series and uncontrolled studies.[9] Typically, a higher dose of mycophenolate at 3 g daily is needed for clinical remission in cutaneous disease.[9] Furthermore, evidence suggests that Janus kinase (JAK) inhibitors are a viable treatment option for DM, especially in patients with refractory cutaneous DM[10,11] and calcinosis.[12,13] The most common choice of JAK inhibitor is tofacitinib at a dose of 5 mg or 10 mg twice a day. **Figure 2** illustrates an example of a dramatic cutaneous improvement after 2 months of tofacitinib at a dose of 5 mg twice a day in a 64-year-old female with anti-SAE DM who had previously failed therapy that included high-dose prednisone, IVIg, hydroxychloroquine,

methotrexate, mycophenolate, cyclophosphamide, and rituximab.

IVIg at a dose of 2 g/kg every 4 weeks is frequently used as a second-line or third-line treatment in combination with other immunosuppressive drugs. The efficacy of IVIg in cutaneous DM has been demonstrated in the large prospective randomized ProDERM study that included patients with the most severe skin manifestations.[14]

Calcinosis cutis is a particularly difficult skin manifestation to treat, and to date, there are no widely agreed upon effective pharmacotherapies. The consensus for treating ongoing cutaneous disease is to use immunosuppressants, while the addition of diltiazem (60-240 mg/day),[15] bisphosphonates (commonly pamindronate infusion at 1 mg/kg/day, for 3 days every 3 months),[16] and intravenous or intralesional sodium thiosulfate may be useful treatment options.[17] In many cases, surgical excision is the only treatment option.

Currently, there is conflicting evidence for the use of rituximab in cutaneous DM.[18,19] Therefore, rituximab is not primarily used for refractory skin disease; rather, it is reserved for refractory muscle and lung diseases. Other systemic treatment options for cutaneous disease, including tacrolimus, sirolimus, cyclophosphamide, azathioprine, dapsone, and cyclosporine have shown evidence that is limited to case studies and case series.

Refractory Muscle Disease

When treating refractory muscle disease, it is important to consider whether you have the correct diagnosis and if you have correctly discriminated between active disease, chronic disease damage, and deconditioning by further laboratory, imaging and electromyographic investigations.

For all IIM patients with muscle involvement, early initiation of physiotherapist-guided exercise regimens at the time of diagnosis should be considered as a standard adjunct intervention. Exercise programs are effective, well tolerated, and improve quality of life and muscle function.[20]

In general, myositis typically responds to treatment with glucocorticoids and traditional immunosuppressants. However, scleromyositis (OM) has a specific disease phenotype that includes a dropped head/bent spine due to neck and spine extensor muscle weakness; this phenotype is less likely to respond to immunosuppressants, and is associated with more severe myopathy and higher mortality.[21] Patients with dropped head often require neck collars for support.

When treating "PM" that is refractory to first-line therapies, start by revisiting the differential for an IIM, and ask whether this could be a PM mimic. Common conditions can mimic PM and could include PM with mitochondrial pathology (PM-mito), IBM, muscular dystrophy, or myositis related to drugs, infection, or cancer.

PM-mito is a rare and controversial form of inflammatory myopathy that shares many clinical and pathological features with IBM. The main pathological feature on muscle biopsy of PM-mito is endomysial inflammation with focal invasion of intact muscle fibres, and severe mitochondrial pathology; however, it lacks the characteristic rimmed vacuoles of IBM.[22] Similar to IBM, patients with PM-mito respond poorly to glucocorticoids. It is believed that PM-mito and IBM belong to a clinical continuum. One study has shown that a majority of patients with PM-mito had later developed clinically defined IBM.[22] In another study, 44% of patients who were initially diagnosed with PM-mito showed vacuoles typical of IBM on a repeat muscle biopsy.[23] We recommend that clinicians review the muscle biopsy with specialized muscle pathologists, keeping in mind that a repeat muscle biopsy may be warranted for diagnostic clarification. There is currently no pharmacologic cure for IBM. Current treatment strategies revolve around implementing supportive measures to address symptoms such as dysphagia, respiratory compromise, muscle weakness, and declining mobility.[24]

It is also important to distinguish the difference between disease activity (treatable inflammatory manifestations of the disease), disease damage (untreatable changes due to fatty replacement), muscle atrophy, steroid myopathy, and other comorbidities. Clinically, this may be challenging because muscle strength and functioning are not reliable methods of distinguishing active disease and damage. The most widely used laboratory measure is serum creatine kinase (CK), which unfortunately does not always correlate with disease activity. In fact, low or normal CK levels are well recognized in patients with active amyopathic DM. Conversely, persistent asymptomatic hyperCKemia in patients with treated IMNM is frequently observed despite normal muscle strength, magnetic resonance

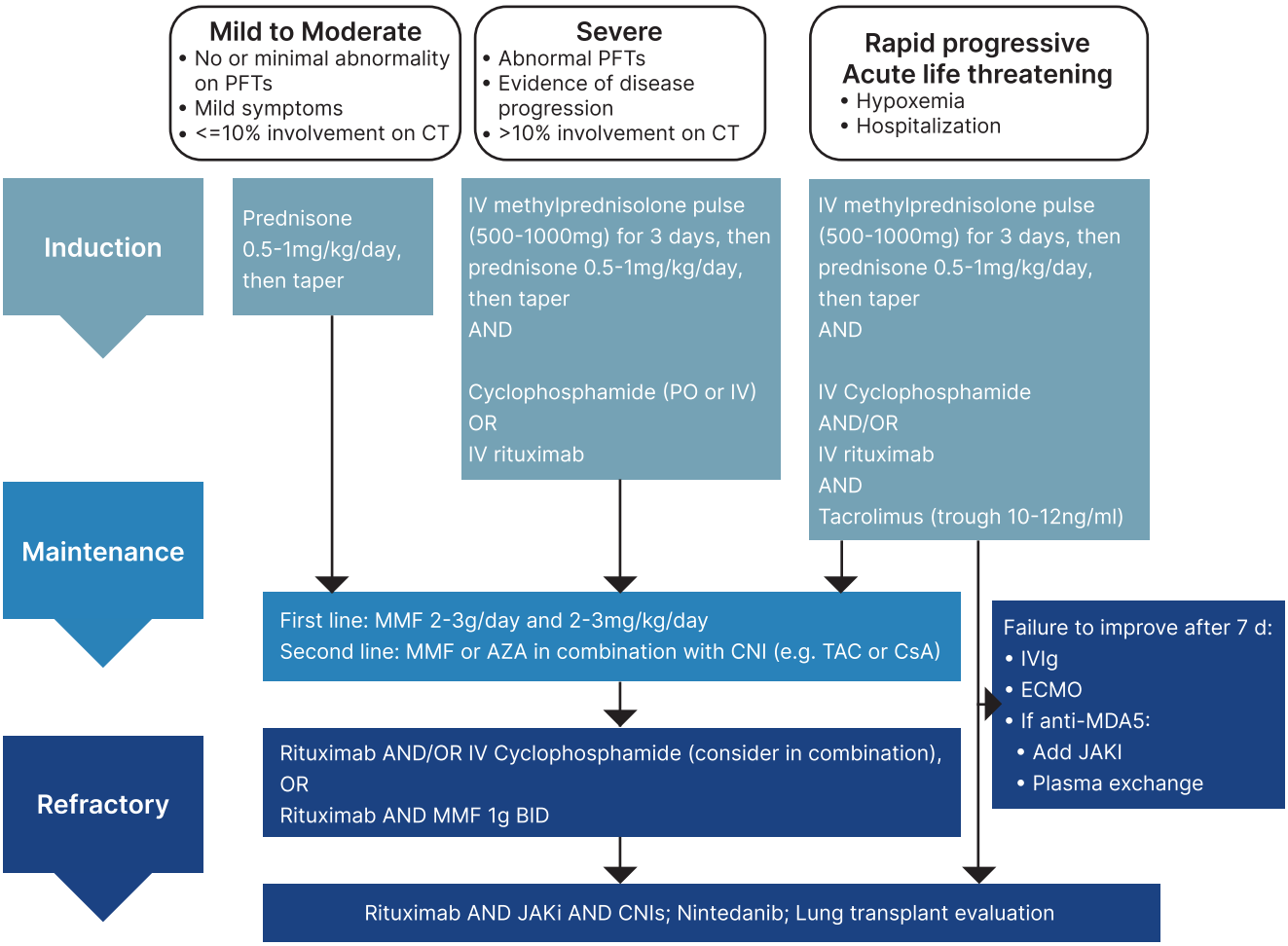

Figure 3. Diagram showing the treatment approach for myositis-associated interstitial lung disease; courtesy of Kun Huang, MD, PhD, FRCPC and Aidan Pye, MD

Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitors; CsA, cyclosporin A; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; IV, intravenous; IVIG, intravenous immunoglobulin; MDA5, anti-melanoma differentiation-associated gene 5 dermatomyositis; MMF, mycophenolate mofetil; PFTs, pulmonary function tests; PO, by mouth; TAC, tacrolimus

imaging (MRI), and electromyography (EMG). We recommend using MRI scans of the affected muscle groups to look for muscle edema suggesting active disease, or atrophy and fatty replacement suggesting chronic damage. Similar to MRI, EMG is useful in differentiating active myopathic processes from muscle atrophy and steroid myopathy. We do not routinely recommend repeat muscle biopsy to assess disease activity unless the underlying diagnosis is in question.

Refractory and Rapid Progressive ILD

ILD is a main driver of mortality and morbidity in IIMs, with a reported prevalence reaching 42.6%.[25] By far, the MSAs with the greatest pulmonary implications include anti-synthetase and anti-MDA5 autoantibodies. Anti-polymyositis-Scl (PM/Scl) and anti-Ku are two myositis-associated autoantibodies (MAAs) frequently associated with ILD, and are usually found in patients with OM.[26] Anti-Ro52/Tripartite motif containing-21 (TRIM21) is an MAA that is linked to more aggressive pulmonary and extrapulmonary disease in IIM.[27] The initial treatment should be determined by considering the severity of ILD (e.g., clinical symptoms, pulmonary functions, and chest high-resolution computed tomography findings) and poor prognostic factors (e.g. acute/subacute form, rapidly progressive ILD, anti-MDA5, older age, hypoxia, elevated ferritin, elevated C-reactive protein, and low forced vital capacity).[27]

In **Figure 3**, we outline the proposed treatment algorithm for myositis-associated ILD that is widely accepted by myositis and ILD experts and has been recently endorsed by the

2023 American College of Rheumatology (ACR) guidelines in Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease.[28] At our centre, this treatment algorithm is modified for some subgroups of myositis. In the setting of scleromyositis associated with stable ILD, there is no data to support starting high-dose glucocorticoid therapy for induction treatment. The benefits of glucocorticoids should be balanced with the potential side effects, as glucocorticoids have been associated with an increased risk of scleroderma renal crisis in systemic sclerosis. For stable usual interstitial pneumonia (UIP)-ILD without active extrapulmonary manifestations, the use of glucocorticoids may not be necessary. In both situations, initiation of steroid-sparing immunosuppressants alone without concurrent glucocorticoid therapy may be sufficient.

Outlook and Future Therapies

There have been tremendous advances in understanding the clinical, serological, and pathological phenotypes of IIM in the past decade; however, therapeutic interventions still lag behind those for other systemic autoimmune diseases. Traditional immunosuppressants have broad effects on the immune system, hence they often lead to frequent adverse effects. The need for new targeted therapies is urgent.

Results from clinical trials of targeted biologics such as tocilizumab (phase 2B), abatacept (phase 3), and ustekinumab (phase 3) have been disappointing[29,30]. Rituximab has been widely used in the treatment of refractory myositis including juvenile DM, IMNM, ASyS, and subtypes with ILD. The discovery of marked upregulation of Type I interferon-induced genes in DM has led to identification of new therapeutic targets. Type I IFNs and their downstream pathways can be targeted pharmacologically in several manners. One approach is to use monoclonal antibodies against IFNs (IFNB, such as with Darzukibart) or the IFN-receptors (IFNARs, such as with anifrolumab). Both Darzukibart and anifrolumab are undergoing phase 3 clinical trials for IIM. Another approach is to target the downstream signaling pathway of type I IFNs which lead to a wide usage of JAK inhibitors in the treatment of refractory DM including ruxolitinib, baricitinib, tofacitinib and upadacitinib.[10,11,31] Cytokines such as interleukin (IL)-4, IL-6, and IL-10 are significantly elevated in patients with myositis-associated ILD. These cytokines are mediated by JAK1, JAK3 and TYK2, which may be the basis for the use of tofacitinib in the treatment of anti-MDA5 DM patients with progressive ILD.[32] Clinical trials for the treatment of DM, including a phase 3 study of brepocitinib (a dual JAK1 and TYK2 inhibitor) and a phase 2 study of GLPG3667 (a TYK2 inhibitor) are currently underway.

Although rituximab, which targets CD20+ autoreactive naïve and memory B-cells, has been widely used in the treatment of refractory myositis, it has limited therapeutic efficacy in connective tissue disease and a delayed onset of action due to the persistence of autoreactive B cells in lymphatic organs and inflamed tissues.[33] In addition, long-lived plasma cells (CD20-, CD38+) can continue to circulate and secrete pathogenetic autoantibodies, resulting in refractory disease activity for months after initiation of rituximab. In our clinical experience, we commonly observe a delayed benefit of rituximab of several months after the first course, and occasionally observe a benefit only after the second course of rituximab. Daratumumab, an anti-CD38 human monoclonal antibody that depletes plasma cells, has recently been successful in cases of refractory lupus,[34] anti-SRP + IMNM,[35] anti-MDA5 DM ILD,[36] as well as other antibody mediated autoimmune diseases.[37] The addition of daratumumab to conventional immunosuppressants and rituximab may represent a new treatment paradigm for selected refractory and critically ill myositis patients.

Over the past two years, anti-CD19 chimeric antigen receptor (CAR) T cell therapy has gained traction in the treatment of refractory lupus, and there is evidence to suggest that it may be useful in the treatment of systemic sclerosis and myositis associated with ASyS.[38] Three case reports published in 2023 have shown the feasibility, tolerability, and efficacy of CAR T-cell therapy for the treatment of ASyS.[39-41] Remarkably, all three patients had failed rituximab, and one had failed both rituximab and ocrelizumab, both of which are anti-CD20 monoclonal antibodies. All three patients treated with CD19 CAR-T cell therapy had achieved a sustained drug-free remission.

The landscape of possible mechanisms now being explored to treat myositis has expanded remarkably in the past few years. Looking into the future of targeted myositis treatment, we are optimistic that 2024 will be an exciting year with several new therapies on the horizon. Planned clinical trials are expected to shed further light on the efficacy and safety of these promising therapies.

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