MYOSITIS

CHI Formulary Development Project

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Table of Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndication

List of Tables

List of Figures

Abbreviations

ACR	American College of Rheumatology
ADM	Amyopathic Dermatomyositis
AGREE	Appraisal of Guidelines for Research and Evaluation
AZA	Azathioprine
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
CARRA	Children's Arthritis and Rheumatology Research Alliance
CHI	Council of Health Insurance
CK	Creatine Kinase
CPG	Clinical Practice Guideline
CRP	C-Reactive Protein
CsA	Cyclosporin A
CTP	Consensus Clinical Treatment Plan
DM	Dermatomyositis
DMARD	Disease-Modifying Anti-Rheumatic Drug
ECG	Electrocardiogram
EMA	European Medicines Agency
EMG	Electromyography
EULAR	European League Against Rheumatism
FAI^{2}R	Rare Autoimmune and Autoinflammatory Diseases Network (French)
FDA	Food and Drug Administration
GC	Glucocorticosteroids
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment

IBM	Inclusion Body Myositis
IDF	Insurance Drug Formulary
IIM	Idiopathic Inflammatory Myopathy
ILD	Interstitial Lung Disease
IQWIG	Institute for Quality and Efficiency in Health Care (German)
IVig	Intravenous immunoglobulin
JDM	Juvenile Dermatomyositis
LDH	Lactate Dehydrogenase
MMF	Mycophenolate Mofetil
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NHP	National Health Protocol
NICE	National Institute for Health and Care Excellence
NM	Necrotizing Myopathy
OM	Overlap syndrome with Myositis
PBAC	Pharmaceutical Benefits Advisory Committee
PM	Polymyositis
RAISE	French national reference center for inflammatory rheumatism and rare systemic autoimmune diseases in children
RCT	Randomized Controlled Trial
RP-ILD	Rapidly Progressive Interstitial Lung Disease
SFDA	Saudi Food and Drug Authority
Tac	Tacrolimus

Executive Summary

Idiopathic inflammatory myopathies (IIMs) are a diverse group of chronic systemic autoimmune diseases, with an annual occurrence of two to five cases per million individuals, characterized by muscle inflammation and a gradual weakening of muscle strength. Among this category, the three main diseases are dermatomyositis (DM), which includes a separate juvenile subtype (JDM), polymyositis (PM), and inclusion body myositis (IBM).

DM is an autoimmune disease that affects individuals of all ages, including both children (JDM) and adults. It is clinically characterized by progressive symmetrical weakness in the proximal muscles, as well as distinct skin manifestations such as Gottron's papules, heliotrope rash, and macular erythema. The onset of skin symptoms may precede the development of myositis by months or even years and can be exacerbated by exposure to sunlight. Notable differences between juvenile and adult DM include the presence of subcutaneous calcinosis, which can affect the elbows and knees, sometimes leading to ulceration in juvenile cases. Additionally, other manifestations may include joint pain (arthralgia), difficulty swallowing (dysphagia), Raynaud's phenomenon, and respiratory symptoms. In approximately 20 to 25% of cases, DM may be associated with an underlying malignancy, particularly in the lungs, ovaries, gastrointestinal tract, or in conjunction with other connective tissue diseases[1].

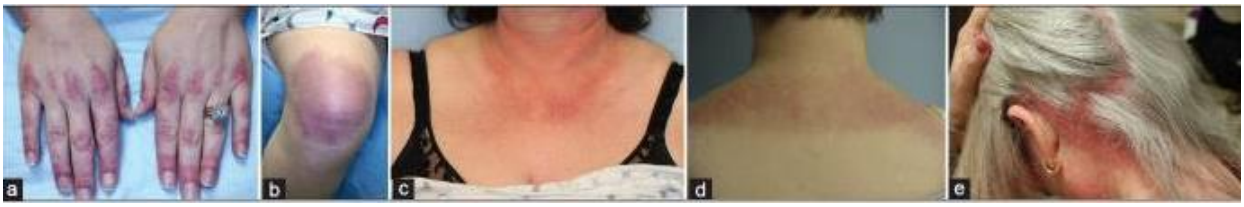

Figure 1. *(a) Gottron's papules: Violaceous, scaling papules on the skin overlying the joints and proximal nailfolds. (b) Gottron's sign: Violaceous patches overlying the knees. (c) "V neck" sign: Erythematous and hyperpigmented macules on the chest. (d) Shawl*

PM is an immune-mediated syndrome associated with compromised cellular immunity, often co-occurring with other systemic autoimmune conditions. It primarily affects individuals between 30 and 60 years old, rarely occurring in those under 20. The onset of muscle weakness, primarily in the proximal areas, develops gradually over weeks to months, displaying symmetric weakness in the upper and lower limbs, particularly in the neck flexors. While distal muscles may also be affected, it is typically to a lesser extent. Additional symptoms may include dysphagia, constitutional symptoms like fever and fatigue, arthritis-like symptoms, severe interstitial lung disease, and, though less common, various cardiac manifestations[2].

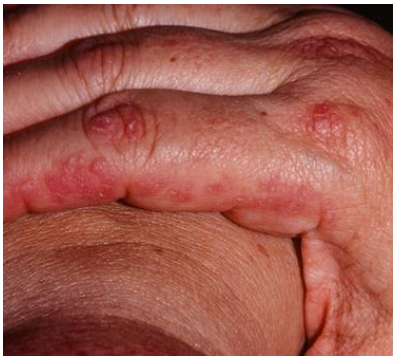

Figure 2. *Polymyositis (PM) mechanic's hands*

IBM is predominantly observed in individuals aged 50 and above, with a higher incidence in men. Its onset is gradual, and it may take several months to years from the initial appearance of symptoms to receive a diagnosis. This condition typically affects both proximal and distal muscles, with frequent falls being a common symptom. Muscle atrophy and difficulties with swallowing are also prevalent in IBM. In terms of pathological features, IBM shares similarities with polymyositis but also exhibits lined vacuoles and the presence of beta-amyloid and ubiquitin deposits. Additionally, about 15% of IBM patients are associated with other connective tissue diseases. Approximately 30% of patients may have specific antibodies related to myositis, and serum creatine kinase (CK) levels are only slightly elevated in most cases. Electromyography (EMG) may reveal neurogenic changes or a combination of neurogenic and myopathic alterations[3].

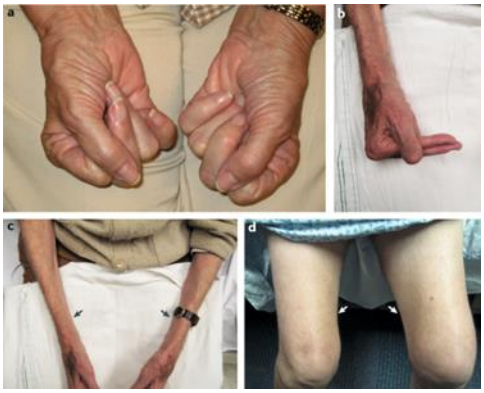

Figure 3. *Inclusion body myositis (IBM) clinical features*

The prevalence of IIMs in Middle Eastern countries, including Saudi Arabia, has not been extensively studied. To address this gap, a retrospective study in 5 medical tertiary centers in Saudi Arabia was conducted to describe the demographics, evaluate clinical features, organ involvement, investigations, treatment strategies, and to assess factors affecting remission in IIM patients[4].

The treatment of IIMs varies depending on the specific type. For DM, the primary approach involves the administration of high-dose corticosteroids, such as

prednisolone, to suppress inflammation. In more severe cases, immunosuppressive agents like methotrexate or mycophenolate mofetil may be prescribed in combination with corticosteroids. Additionally, topical treatments are utilized to address skin manifestations, and physical therapy is employed to maintain muscle strength and mobility.

In the case of PM, similar treatment strategies are applied, with high-dose corticosteroids being the cornerstone of therapy. Immunosuppressive agents like methotrexate or mycophenolate mofetil may be added to augment the treatment regimen. Physical therapy is crucial in PM to preserve muscle function and prevent contractures.

In contrast, IBM presents unique challenges in treatment, as it is generally less responsive to interventions. Physical therapy remains a central component, focusing on the preservation of mobility and function. While experimental therapies are being explored, no established standard treatment protocol for IBM currently exists. Regular monitoring and consultation with a specialized healthcare provider are essential for adjusting treatment plans based on individual patient needs and disease progression.

This report compiles all clinical and economic evidence related to IIMs according to the relevant sources. The ultimate objective of issuing IIM guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to IIM patients in Saudi Arabia. The focus of the review was on Saudi, American, European, and international guidelines issued within the last five years.

Several classes and drugs can be used for the management of IIMs and are summarized in the table below.

Table 1. Summary of SFDA-Registered Drugs for the Management of Idiopathic Inflammatory Myopathies

Drug	Indication	Dose	Level of evidence and HTA recommendation
CORTICOSTEROIDS			
Prednisolone	First line therapy in PM and DM.	Oral: 1mg/kg/day as a single daily dose for 4 to 6weeks.	Level 1, Grade B, 100%. No HTA recommendations for prednisolone.
Methylprednisolone	The use of intravenous methylprednisolone should be considered, especially when there are concerns about gastrointestinal absorption.	IV: 30 mg/kg/day for 3 to 5 days.	Level 1, B, 100%. No HTA recommendations for prednisolone.
DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)			
Hydroxychloroquine	Recommended for DM as an off-label use in combination with antipruritic medications and topical therapy. Indicated for juvenile DM, especially when there is skin involvement.	Oral: 5mg/kg/day (maximum 400 mg/day)	No HTA recommendations for hydroxychloroquine.
IMMUNE GLOBULIN			
Immune Globulin	In severe, refractory, or life-threatening PM and DM, as	IV: 1g/kg per day on 2 consecutive days every	Level 1, B, 100%.

	an adjunct to corticosteroids or other immunosuppressive agents.	4weeks or 2g/kg as a single dose every 4weeks.	HAS and CADTH: positive recommendations. IQWIG, PBAC, NICE: N/A
IMMUNOSUPRESSIVE AGENTS			
Azathioprine	Adjunctive therapy with GC in patients with PM and DM.	50mg once daily. May increase daily dose by 50mg/week to 1.5mg/kg/day. (250mg/day max)	Level 1, B, 100%. CADTH, HAS: positive recommendations
Methotrexate	Adjunct to GC or as an alternative initial therapy in patients with PM or DM who cannot receive GC.	Oral: 7.5 to 15mg once weekly.	Evidence level V, Grade B CADTH: positive recommendation
Tacrolimus	As monotherapy or in combination with GC in patients with GC-resistant diseases.	Oral: 3 to 5mg/day or 0.1mg/kg/day in 1 or 2 divided doses.	Evidence level V, Grade B CADTH: positive recommendation
Mycophenolate mofetil	In refractory DM.	Oral: 500mg twice daily for 2weeks then 1g twice daily (1.5g twice daily max).	Level 2, C, 100%. CADTH: positive recommendation. Other: N/A
Rituximab	Treatment PM and DM refractory to GC/DMARDs-based immunosuppression.	IV: 1g every 2weeks for 2 doses.	No recommendation Grade. CADTH: positive recommendation.

Cyclophosphamide	In severe, refractory, or life-threatening PM and DM, as an adjunct to corticosteroids or other immunosuppressive agents.	IV: 500 to 750 mg/m2 (1200mg/dose max) every 4 weeks up to 6 months. Oral: 1,5 to 2mg/kg/day (200mg/day max) up to 6 months.	Level 1, B, 100%. CADTH and HAS: positive recommendations, Other: N/A
Cyclosporine	For patients with GC-resistant disease. In cases of interstitial lung disease (ILD), cyclosporine is recommended as part of the induction therapy, especially in the early stages, and should be combined with steroids.	**Oral:** 2.5 mg/kg/day in 2 divided doses given every 12 hours (maximum of 5 mg/kg/day).	Level 1, B, 100%. CADTH: positive recommendations

Abatacept

Abatacept has been investigated as a potential treatment for certain forms of IIMs, particularly DM. Abatacept is a biologic medication that works by inhibiting T-cell activation. T-cells play a role in the immune response and can be involved in autoimmune conditions like IIMs.

Research on the use of Abatacept in IIMs, however, is still considered experimental and is **not yet considered standard therapy**. Clinical trials and studies are ongoing to assess its safety and effectiveness.

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of IIMs, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

1.1.1 Inflammatory Muscle Disease, 15-Year Experience at Tertiary Centers (*Intern Med*, 2016)

IIMs are a group of inflammatory muscle diseases with limited data and literature in Saudi Arabia, and to date, there are no clinical guidelines published for the management of IIMs. The objective of the study published by attar et al. in 2016 was to outline the demographics, assess clinical characteristics, organ involvement, investigations, treatment approaches, and examine factors influencing remission in individuals with IIMs. Patients records from 1999 to 2014 at five prominent medical centers in Saudi Arabia were examined[4].

a. Characteristics of IIMs

IIMs are systemic connective tissue disorders characterized by symmetrical, proximal muscle weakness and chronic muscle tissue inflammation. They can be categorized into:

- JDM
- DM
- PM
- IBM

based on distinct clinical and histopathological traits. Additionally, these conditions often affect other systems, with interstitial lung disease, esophageal dysmotility, and heart failure being among the most prevalent manifestations.

b. Demographic and clinical characteristics in patients with IIMs

This study included 28 patients with IIMs, 9 patients had PM, 6 had DM, 3 had JDM, and 10 patients had IIM mixed with connective tissue diseases. The majority were female Saudis, with a mean age of 37.7 years and an average disease duration of 7.09 years. The most common presenting symptoms were muscular weakness, arthralgia/arthritis, rash, and facial rash. Musculoskeletal involvement was predominant, followed by gastrointestinal and respiratory system involvement. Cardiovascular system involvement was less common. Three patients developed malignancies. Laboratory findings indicated elevated levels of CK, hepatic enzymes

and Lactate Dehydrogenase (LDH). Inflammatory markers like C-Reactive Protein (CRP) were notably elevated, and various autoimmune markers were positive. EMG and muscle biopsy results supported the diagnosis of inflammatory myopathies in most patients.

c. Treatment of IIMs

Oral corticosteroid (prednisolone) was administered to 27 patients (96%), leading to normalization of CK enzymes in 57.1% of cases and improved muscle power in 71.4%. Patients who received steroids exhibited an impressive improvement in their symptoms (p=0.023) reinforcing the most favorable outcome achieved with steroid treatment.

Additional therapeutic approaches included **methotrexate** and **hydroxychloroquine** for 57.1% of patients, **intravenous immunoglobulin** (IVig) in the emergency room for 42.9%, **rituximab** for 28.6%, and **cyclophosphamide** for 7.1%. Notably, no resistance to treatment was observed in any of the patients. Total remission was achieved in 60.7% of cases, while 39.3% experienced relapse.

There were no significant differences in medical complaints recorded at the time of diagnosis for remissions and relapsing patients; however, patients in remission had lower presentation of proximal muscle myopathy (23.1%), fever (11.5%), dysphagia (7.7%), arthralgia/ arthritis (19.2%), and skin manifestations (38.5%).

1.2 European Guidelines

1.2.1 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups (2017)

The objective of this guideline published jointly by EURLAR and ACR is to develop and validate new classification criteria for adult and juvenile IIMs and their major subgroups. Candidate variables were assembled from published criteria and expert opinion using consensus methodology. Data were collected from 47 rheumatology, dermatology, neurology, and pediatric clinics worldwide. The classification that ensued employs easily accessible and operationally defined elements and has been partially validated. It allows classification of "**definite**", "**probable**", and "**possible**" IIM, in addition to the major subgroups of IIM, including juvenile IIM. They generally perform better than existing criteria. The EULAR/ACR classification criteria for IIM have been endorsed by international rheumatology, dermatology, neurology, and pediatric groups[5].

Patients with pathognomonic skin rashes (heliotrope rash, Gottron's papules and/or Gottron's sign) of JDM or DM are accurately classified with the EULAR/ACR

classification criteria without including muscle biopsy data. For patients without these skin manifestations muscle biopsy is recommended. For DM patients without muscle involvement a skin biopsy is recommended.

The EULAR/ACR classification criteria provide a score and a corresponding probability of having IIM. Each probability displays a unique sensitivity and specificity. The best balance between sensitivity and specificity can be found for a probability of 55-60% (total aggregated score of ≥5.5 and ≤ 5.7) for the criteria not including muscle biopsy data, and 55-75% (total aggregated score ≥6.7 and ≤ 7.6) when including muscle biopsies. These cases are designated "probable IIM". The recommended cutoff needed for classifying a patient as IIM is ≥ 55%.

"Definite IIM" corresponds to a probability of ≥ 90% or a total aggregate score of 7.5 or more without muscle biopsy and 8.7 with muscle biopsy and is recommended in studies where a high specificity is required.

A patient is termed "possible IIM" if the probability is ≥ 50% and < 55% (a minimum score of 5.3 without biopsies and 6.5 with biopsies).

1.2.2 British Society for Rheumatology (BSR) Guideline on Management of Pediatric, Adolescent and Adult Patients with Idiopathic Inflammatory Myopathy (2022)

IIMs is an autoimmune condition that affects multiple systems, characterized by muscle inflammation (myositis), skin manifestations and interstitial lung disease (ILD). It occurs at a rate of up to 19 cases per 1,000,000 person-years in adults and up to 4 cases per 1,000,000 person-years in children. This guideline was developed in line with the BSR Creating Clinical Guidelines Protocol using AGREEII (Appraisal of Guidelines for Research and Evaluation II) methodology, and the quality of body of evidence was summarized for each recommendation as high (A), moderate (B), low (C), or very low (D) according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology[6].

Treatment of skeletal muscle inflammation (myositis)

Testing for myositis autoantibodies is recommended (1, B, 100%). Myositis-specific antibodies and myositis-associated autoantibodies play a valuable role in aiding diagnosis, providing insights into disease characteristics and long-term outlook, and can assist in tailoring treatment options. However, autoantibody levels should not be solely relied upon to monitor disease activity.

1. In the initial stages of treatment, high doses of glucocorticosteroids (GC) should be administered to treat active muscle inflammation (1, Grade B, 100%).

- For adults, it is recommended to use oral prednisolone at a dosage ranging from 0.5 to 1 mg/kg/day, typically 40 to 60 mg per day (1, B, 100%).
- Oral prednisolone should be gradually reduced once substantial improvement in disease activity, across all domains, is observed, typically after approximately 6 weeks of treatment initiation (1, B, 100%).
- **Pediatric specific:** It is recommended to use oral prednisolone at a dosage of 1 to 2 mg/kg/day, or alternatively, administer intravenous methylprednisolone pulses at a dosage of 30 mg/kg/day, with a maximum daily intravenous dose of 1 g (1, B, 100%). The use of intravenous methylprednisolone should be considered, especially when there are concerns about gastrointestinal absorption. Administering methylprednisolone intravenously may lead to a heightened therapeutic effect with reduced potential for toxicity compared to oral glucocorticoids (2, B, 96%).

2. Disease-modifying anti-rheumatic drugs (DMARDs) should be used to diminish muscle inflammation, achieve clinical remission, and reduce the reliance on steroids (1, C, 100%).
    - It is crucial to address muscle weakness and inflammation promptly and comprehensively in juvenile-onset IIM to enhance outcomes and reduce disease-related complications (1, B, 100%).
    - For adult cases, methotrexate, azathioprine, tacrolimus, ciclosporin, and mycophenolate mofetil should be taken into consideration for both the treatment of active myositis and the long-term maintenance of disease remission (2, C, 96%).
    - **Pediatric specific:** A combination of high-dose GC and methotrexate is recommended as the primary treatment in most instances (1, B, 100%). A combination of prednisolone and methotrexate, rather than prednisolone and ciclosporin, is preferred due to its more favorable side effect profile (1, B, 100%). Mycophenolate mofetil can be beneficial in improving skin and muscle disease (2, C, 100%).
3. The management of IIMs should include a safe exercise program overseen and supervised by a specialist physiotherapist and/or a specialist occupational therapist, aiming to enhance quality of life and function (1, B, 100%).
4. Rituximab is to be considered as a treatment choice for refractory myositis, particularly demonstrating potential effectiveness in (2, A, 100%):
    - Juvenile-onset disease,
    - Patients with a positive myositis autoantibody profile,
    - Patients with a lower burden of disease damage.

5. Cyclophosphamide (1, B, 100%), intravenous immunoglobulin (1, B, 100%) and Abatacept (2, B, 100%) should be considered as a treatment option for severe and/or refractory IIMs, despite GC and DMARDs therapy.

Treatment of IIMs-related skin manifestations

- Rituximab is to be considered for the treatment of skin disease refractory to GC/DMARDs-based immunosuppression (2, B, 100%).
- IVig may be a viable option for treating skin disease that proves resistant to immunosuppression based on GC or DMARDs (1, B, 100%).
- It is advisable to consider strategies such as sun avoidance and the regular application of high-factor broad-spectrum sun cream to lower the likelihood of a disease flare affecting the skin or muscles (2, C, 100%).
- **Pediatric specific:** It is recommended to contemplate the use of systemic immunosuppressive drugs in cases of ongoing skin disease activity, which may also involve reduced nailfold capillary density (2, C, 100%).

Treatment of IIMs-related ILD

- ILD should be screened for in high-risk patients (1, B, 100%). ILD screening methods include plain chest X-ray radiography, pulmonary function tests, and where indicated, high resolution CT scanning.
- When addressing Rapidly Progressive ILD (RP-ILD):
    - It is advisable to contemplate induction therapy with high-dose steroids (2, C, 96% consensus).
    - The consideration of using ciclosporin or tacrolimus in conjunction with steroids is recommended for patients with RP-ILD (2, C, 96% consensus).
    - Early consideration of cyclophosphamide or rituximab therapy, potentially as part of the induction regimen, is suggested (2, C, 96% consensus).
- In the treatment of chronic IIMs-associated ILD:
    - Consider immunosuppression using steroids with or without a single DMARD (azathioprine, ciclosporin, tacrolimus, mycophenolate) (2, C, 100%).
    - Consider the use of rituximab or cyclophosphamide in patients who do not respond to initial treatment (2, C, 100%).

- **Pediatric specific:** Regular evaluation of pulmonary function, including the measurement of diffusing capacity or transfer factor of the lung for carbon monoxide, should be conducted in cases of juvenile-onset IIMs. This is important as pulmonary function abnormalities are common and may not always present with noticeable symptoms (1, B, 100%).

Management steps to reduce fracture risk in people with IIMs

Given the use of GC, the higher incidence in females, and the average age of onset for adult disease, it is crucial to consider the risk of fractures in IIMs. It is recommended to assess the risk of fragility fractures following NICE guidelines at the time of diagnosis and whenever risk factors change. Gradual tapering of glucocorticoid dosage, once remission is achieved, may help reduce the risk of fragility fractures (1, B, 100%).

Management steps in children with IIMs

- Juvenile-onset IIMs necessitates management by pediatric specialists due to notable distinctions from adult-onset IIM (higher incidence of subcutaneous calcification, less overall disease damage, no apparent association with cancer, an elevated risk of vasculitis, and varying autoantibody profiles) (1, C, 95%).
- It is crucial to aim for a prompt diagnosis, as it correlates with improved disease outcomes. Consequently, early referral to a specialized service is recommended (2, C, 100%).
- When employing tools to assess muscle strength, function, and quality of life in pediatric cases, it is imperative to consider age-specific factors (1, B, 100%).

Management of IIMs related diseases

- The risk of cancer should be considered in all patients and screening should be particularly considered in those with the following risk factors (1, B,100%).
- Patients should undergo a regular cardiovascular risk assessment (1, C, 100%). Micro-vasculopathy and GC treatment are considered responsible for the hypertension observed in25–50% of patients with IIM.
- Patients should undergo screening for cardiac involvement; serum cardiac damage markers like Troponin I, electrocardiogram (ECG), echocardiography, and cardiac magnetic resonance imaging (MRI) are to be considered (2, B, 100%).
- Routine assessment of dysphagia is to be considered in all patients (2, C, 92%). Swallowing assessment and involvement of speech and language therapist/gastroenterology teams is to be considered in those with dysphagia

(2, C, 100%).3-IVIG therapy for active disease and dysphagia resistant to other treatments is to be considered (2, C, 100%).

- Psychological wellbeing and psychiatric comorbidities should be assessed (1, C, 92%).

1.2.3 French Expert Opinion for the Management of Juvenile Dermatomyositis (2018)

The reference center for childhood inflammatory rheumatism and rare systemic diseases (RAISE), on behalf of FAI²R (rare autoimmune and autoinflammatory diseases network) and Filnemus (rare neuromuscular diseases) referral centers, has drawn up a national health protocol (NHP). The objective was to detail the current optimal management of a child with juvenile dermatomyositis (JDM) for healthcare professionals[7].

The treatment of JDM is essentially based on systemic corticosteroid therapy, associated with an immunosuppressant to limit cortisone use. Rehabilitation is essential. All patients suspected of inflammatory myopathies should be referred to a specialized center.

The following signs of severity require urgent care:

1. severe impairment leading to bed confinement
2. CMAS score < 15 or MMT8 score < 30
3. severe interstitial parenchymatous pulmonary disease
4. digestive vasculitis (determined by imaging or the presence of melena/rectorrhagia)
5. hospitalization in an intensive care unit
6. swallowing disorders leading to dysphagia or requiring aspiration or a nasogastric tube
7. severe cutaneous ulcerations
8. myocarditis
9. age < 1 year.

The **first-line** treatment recommended at the diagnosis of JDM involves high-dose **corticosteroids** (oral or intravenous) and **methotrexate**.

In cases of resistance to treatment in a newly diagnosed patient, therapeutic intensification should be considered within 12 weeks. **Mycophenolate** should be considered as a second-line approach. **Intravenous immunoglobulins** (IVIG) can be

proposed as an adjuvant treatment in cases of corticosteroid dependence or corticosteroid resistance, particularly for persistent skin disorders.

Various third-line treatments can be proposed in cases of intolerance or ineffectiveness of previous treatments. The evidence of their efficacy is mostly only from small uncontrolled series: cyclosporine A, azathioprine, cyclophosphamide, and tacrolimus.

1.3 North American Guidelines

1.3.1 Childhood Arthritis and Rheumatology Research Alliance Consensus Clinical Treatment Plans for Juvenile Dermatomyositis with Persistent Skin Rash (2017)

JDM is the most prevalent type of IIMs in children. Some children have JDM rash without substantial muscle weakness, and the most effective treatments for them are unknown. The study aims to outline the development of Consensus Clinical Treatment Plans (CTPs) for children with JDM who exhibit active skin rashes but lack significant muscle involvement, referred to as "skin predominant JDM". The Children's Arthritis and Rheumatology Research Alliance (CARRA) is a North American consortium of pediatric rheumatology healthcare providers. CARRA members collaborated to establish a consensus on standard treatments for JDM patients with skin symptoms and no significant weakness. The development of these CTPs involved a combination of Delphi surveys and nominal group consensus meetings. Existing treatment approaches for JDM and skin predominant JDM vary widely, with recommendations for both topical and systemic therapies, but lacking trial data or case experiences to support them[8].

These patients are children who have displayed cutaneous symptoms of JDM skin disease for at least 6 weeks, and there is no observed weakness reported by the patient, parent, or clinician. All patients included in this CTP must exhibit one of the distinctive rashes associated with JDM, such as Gottron's papules or heliotrope rash, with or without other skin manifestations (e.g., Shawl sign, V-sign, malar rash, periungual erythema, vasculopathic changes in nail bed capillaries, etc.). Patients may have mild calcinosis as determined by the treating clinician, but they should not have lipodystrophy or skin ulceration since such findings indicate greater disease severity beyond the scope of this CTP. In addition, patients should not exhibit systemic involvement or signs of major organ involvement, including parenchymal lung disease, dysphagia, aspiration, intestinal vasculitis, or myocarditis, as determined by the treating clinician.

All treatment plans include **hydroxychloroquine** at 5 mg/kg/day (maximum 400mg). In treatment option A, this is administered as monotherapy. Treatment option B

involves the additional use of **methotrexate**, given parenterally (preferred), at a dose of 15 mg/m^2 or 1 mg/kg (maximum 40 mg) once weekly. Treatment option C combines **oral corticosteroids** (prednisone at 1–2 mg/kg/day, maximum 60 mg) with weekly methotrexate and daily oral hydroxychloroquine at the same doses as in Treatment Plan B. In all CTPs, it was advised that patients should practice sun avoidance and make the most of sunscreen usage, with a preference for broad-spectrum products having SPF ≥ 30. Specific recommendations were to be tailored to each patient by the treating clinician.

1.4 International Guidelines

1.4.1 Japanese Society of Neurology/Japanese Dermatological Association/Japan College of Rheumatology Treatment Consensus for Management of Polymyositis and Dermatomyositis Among Rheumatologists, Neurologists, and Dermatologists (2018)

A multidisciplinary treatment consensus for PM and DM was established to standardize patient care among rheumatologists, neurologists, and dermatologists. Twenty-three clinical questions were raised to determine the most appropriate treatment methods based on expert opinion. A comprehensive literature search was conducted using PubMed to evaluate qualified studies published until 2014. The nominal group technique was employed to assess and discuss study results for consensus. The levels of evidence and recommendation grades were defined to guide clinical practice. The recommendations are summarized below[9].

Prognosis and therapeutic response

- Some clinical symptoms and laboratory tests can be used to predict both the prognosis and responsiveness to treatment, with a recommendation grade of C1.
- Although it's challenging to precisely predict the prognosis and therapeutic response in myositis patients, there are empirically known factors that correlate with these outcomes.
- Risk factors for life prognosis include old age, male sex, non-Caucasian race, the time interval from symptom onset to treatment initiation, clinical subsets such as cancer-associated myositis and clinically amyopathic DM, skin ulcer, dysphagia, respiratory complications like respiratory muscle weakness or interstitial pneumonia, and cardiac involvement (evidence level III-IV).
- In cases of cancer-associated myositis, therapeutic response is commonly reported as suboptimal. In rare instances, surgical removal of the malignancy has shown to be effective in improving the condition.

- There is no consensus regarding the relationship between serum CK levels and the patient's response to treatment. High CK levels might suggest a poorer response to treatment, though this could be due to the time required for CK levels to normalize.
- Reports indicate that therapeutic response tends to be unsatisfactory when muscle biopsies reveal severe muscle fiber necrosis and limited inflammatory cell infiltration.

Glucocorticosteroids

- For patients with interstitial pneumonitis and those with malignancy, the first-line treatment for PM/DM is the administration of GC. (recommendation grade B).
- **Prednisolone** is commonly recommended as the first-line treatment for myositis in clinical practice. While empirical data support its use in most cases, it's worth noting that this recommendation lacks the backing of prospective or randomized controlled trials (RCTs) assessing its efficacy (evidence level VI).
- Several GC options are available in Japan for oral and intravenous administration, and although their potential differences in efficacy have not been studied, **methylprednisolone** is commonly used for steroid pulse therapy.
- Factors that can influence the effectiveness of GC include advanced age, the presence of organ failures beyond the muscles (such as interstitial pneumonia and malignant tumor complications), as supported by evidence at level VI.
- Prednisolone at a dose of 0.75-1 mg/kg per day is commonly used to induce remission in PM and DM (recommendation grade C1).
- There is no specific evidence regarding when to begin tapering GC. Conventionally, the initial dose is maintained for 2-4 weeks and is then tapered by 5-10 mg per week based on disease improvement, primarily to prevent steroid myopathy. Tapering GC is generally easier when initiated concurrently with immunosuppressants.
- GCs are typically administered daily in three divided doses, but they can also be given on alternate days or once every morning to minimize adrenal suppression. However, even with such regimens, it's challenging to entirely avoid adrenal suppression when using moderate or high GC doses. The therapeutic effect is slightly reduced compared to daily divided doses, making the once-every-morning or alternate-day regimen more suitable as GC doses are tapered to lower levels.

- Generally, reported remission rates fall within the range of 40% to 60%, indicating that discontinuing GC may be possible for some patients. The decision to continue or discontinue GC therapy should be based on individual patient clinical outcomes, as it is currently challenging to classify myositis types that require maintenance GC therapy.
- Historically, high-dose GC has been the standard treatment for myositis since the 1950s, but not all patients respond to GC alone. Some experience relapse after tapering GC doses. A study by van de Vlekkert et al. in 2010 showed that approximately 45% of patients treated with GC alone experienced recurrence[10] (evidence level II).
- While many patients initially respond to high-dose GC and achieve remission, relapses can occur during GC tapering. In such cases, combination therapy with immunosuppressants is recommended.
- A retrospective study comparing high-dose (typically >0.5 mg/kg per day) prednisolone with low-dose (≤0.5 mg/kg per day) prednisolone and immunosuppressants showed similar muscle enzyme and muscle function outcomes after treatment. The low-dose group experienced fewer vertebral fractures, suggesting that prednisolone less than 0.5 mg/kg per day may be sufficient for PM/DM treatment when used with immunosuppressants.
- A study by Bunch et al. provides strong evidence. This trial compared the effects of prednisone plus AZA with prednisone alone in 16 patients. After 3 years, patients treated with the combination therapy required lower maintenance prednisone doses (1.6 mg/day vs. 8.7 mg/day) and showed improved functional outcomes[11] (evidence level II).
- Potential long-term side effects of steroids include osteoporosis, cataracts, skin atrophy, diabetes mellitus, hypertension, mood swings, weight gain, and an increased risk of infections. Patients on long-term steroid treatment should receive daily 1000 mg calcium and 500 IU vitamin D to avoid osteoporosis and other bone related complication with the long-term use.

Immunosuppressants

- Patients with PM and DM resistant to GC therapy should receive immunosuppressants (recommendation grade: B).
- First-line therapy for PM and DM patients can include **methotrexate**, **azathioprine**, **tacrolimus**, and **cyclosporin A** (CsA) in combination with GC (recommendation grade: B).
- Adding immunosuppressants is beneficial for the early tapering of GC doses (recommendation grade: C1).

- In the case of juvenile DM, early treatment involving a combination GC and methotrexate is effective in reducing corticosteroid use early on (evidence level V). Moreover, a combination of methylprednisolone pulse therapy with oral GC has been associated with a higher improvement rate and a significantly shorter time to normalize CK levels compared to oral GC alone (evidence level III).
- In juvenile DM patients unresponsive to GC and other immunosuppressants, treatment with cyclosporin resulted in muscle strength recovery and GC reduction (evidence level V).
- Tacrolimus treatment in anti-synthetase syndrome and ILD patients improved muscle or lung involvement and reduced prednisone doses by 67% (evidence level V).
- **Mycophenolate mofetil** (MMF) treatment in juvenile DM patients led to decreased skin and muscle disease activity and lower GC doses after 12 months of therapy (evidence level V).
- In patients with skin lesions resistant to traditional therapies or experiencing toxic effects from them, MMF decreased GC doses by 93% (evidence level V).
- Azathioprine, methotrexate, tacrolimus, cyclosporin, MMF, or cyclophosphamide can be effective in the treatment of myositis (recommendation grade: B).
- AZA: Combination therapy with GC was reported to be effective around 1980. Azathioprine can improve survival rates in JDM and is considered an option for myositis relapse. Recommended dosage is 50-100 mg/day, administered once or twice daily.
- MTX: Methotrexate has shown efficacy in myositis relapse, despite not being officially covered by health insurance in Japan. The recommended dose is 7.5-15 mg/week.
- Tac: Tacrolimus has been reported as effective in myositis relapse. Patients receiving GC and tacrolimus combination therapy showed significant improvements in CK levels, aldolase levels, and MMT scores compared to those receiving GC alone. It is also effective for ILD in PM and DM patients and myositis unresponsive to cyclosporin. Tacrolimus is covered by Japanese medical insurance for ILD treatment associated with PM and DM. Recommended dosing is twice daily to achieve an optimal trough concentration of 5-10 ng/mL.
- CsA: An RCT has shown cyclosporin effectiveness in early GC tapering. It is an option for myositis relapse and is particularly effective for PM and DM patients with associated ILD. The recommended dosing is twice daily to reach the

optimal trough concentration of 100-150 ng/mL, or once daily for a concentration of 1000 ng/mL 2 hours after administration.

- MMF: MMF's efficacy has been reported for myositis relapse. In a cohort of 50 patients with juvenile DM, it significantly improved the activity index of dermatitis and myositis. Therefore, MMF is considered an option for myositis relapse. The recommended dose is 1-3 g/day, administered twice daily.
- CPA: While Cyclophosphamide is less commonly administered for PM and DM compared to other connective tissue diseases, it has been reported as effective in the treatment of recurrent myositis and ILD in PM and DM. It can be used for refractory myositis and myositis relapse. Recommended dosing is 50-100 mg/day once or twice daily, or intravenous infusion of 500 mg/m2 body surface area with 4-week intervals.

Intravenous immunoglobulin (IVIg)

- IVIg treatment can be initiated in steroid-resistant DM (recommendation grade: B) and PM (recommendation grade: C1) patients.
- Evidence from two RCT:
    - Dalakas et al.: IVIg significantly improved muscle strength and neuromuscular symptoms in DM patients resistant to treatment[12].
    - Miyasaka et al.: In steroid-refractory patients with PM and DM, IVIg showed significant improvement in muscle strength and other markers, although there was no significant difference compared to the placebo group[13].
- According to an evidence-based guideline from the American Academy of Neurology, IVIg treatment for non-responsive DM in adults may be considered (evidence level VI).

Relapse of myositis

Consider the following options based on evidence and recommendations:

- **Increase of GC (recommendation grade: B):** In cases of disease flare, dose escalation of GC to 0.5–1.0 mg prednisolone/kg is recommended, although specific dosing may vary. Consider concomitant use of immunosuppressive agents for patients who cannot tolerate the adverse effects of increased GC doses.
- **Immunosuppressants (recommendation grade: B)**
- **IVIg (recommendation grade: B):** IVIg has been shown to be effective for relapse of PM/DM and refractory diseases. It can reduce the frequency of relapses and improve long-term prognosis, particularly for patients with

dysphagia or ILD. Repeated treatments may be required for long-term benefits.

- **Tocilizumab (recommendation grade: C1):** Some patients with refractory PM have responded well to tocilizumab, indicating potential efficacy in relapse cases. The role of interleukin (IL)-6 in the pathogenesis of PM/DM is under investigation.
- **Rituximab (no recommendation grade):** While case reports and uncontrolled trials have suggested the efficacy of rituximab in PM/DM, a recent RCT did not demonstrate its effectiveness for refractory disease.
- **TNF inhibitors (recommendation grade: C2):** Some patients with refractory PM/DM have shown a favorable response to TNF inhibitors, but subsequent trials failed to confirm their efficacy. There have been rare reports of TNF inhibitor-induced PM/DM.
- **Plasmapheresis (recommendation grade: C2):** Some case reports have reported positive outcomes after plasmapheresis for myositis relapse, but a double-blind, placebo-controlled trial did not demonstrate its effectiveness in chronic refractory PM/DM.

Opportunistic infections

When high-dose GC and/or immunosuppressants are administered to myositis patients with ILD, measures should be taken to prevent opportunistic infections, such as pneumocystis pneumonia (recommendation grade: A).

- Opportunistic infections have been observed in myositis patients, with fungi, including *Candida albicans* and *Pneumocystis jiroveci*, being common pathogens.
- Prophylactic use of sulfamethoxazole-trimethoprim combination is recommended for patients taking prednisone more than 20 mg/day for more than a month, particularly when combined with immunosuppressants, to prevent pneumocystis pneumonia.
- To prevent pulmonary tuberculosis, prophylactic measures similar to those for HIV-infected patients should be considered, such as isoniazid administration for patients with old pulmonary tuberculosis lesions.

Dysphagia Treatment

- **IVIg is recommended for steroid-resistant dysphagia (recommendation grade: C1):** IVIg is a recommended therapeutic option for patients with myositis who do not respond to steroids.

- Other treatment options include cricopharyngeal myotomy, dilation, reflux treatment, cyclosporin, intravenous cyclophosphamide, and endoscopic balloon dilatation.

Interstitial Lung Disease Treatment

- **High-dose GC (prednisolone 1 mg/kg) is recommended:** High-dose GC therapy is recommended for ILD in PM/DM, but the choice of target (myositis or ILD) is case-dependent.
- **Immunosuppressants with GC:** In rapidly progressive ILD or high-risk cases, immunosuppressants should be combined with GC, especially in CADM patients who are resistant to conventional treatments.
- **Initial treatment:** High-dose GC with or without methylprednisolone pulse therapy can be initiated. If respiratory symptoms worsen within weeks or months, GC therapy should be combined with a calcineurin inhibitor, such as cyclosporin or tacrolimus. Intermittent intravenous cyclophosphamide and IVIg can be considered for serious or intractable cases.

Cardiac Involvement Treatment

- **Consider high-dose GC with immunosuppressants:** In patients with symptomatic cardiac complications (PM/DM), high-dose GC therapy, including three consecutive pulses of intravenous methylprednisolone, should be considered. Early control of disease activity is important.
- **Concomitant use of immunosuppressants:** Immunomodulatory agents are recommended in addition to high-dose GC, especially for better prognosis.
- **Alternative treatments:** Patients have received IVIg and plasma exchange as alternative treatments, but further research is needed to confirm their efficacy.

DM Patients with Skin Manifestations Alone

- For DM patients with cutaneous manifestations alone, observation or topical corticosteroid therapy is recommended (recommendation grade: C1).
- Patients with amyopathic dermatomyositis (ADM) may eventually develop muscle diseases and/or ILD, so regular follow-up is required.
- ADM patients also have a high frequency of malignancies and should be examined for malignancies.
- GCs are commonly used for topical therapy, with mild-class GC applied to facial lesions and very strong-class or upper-class GC needed for trunk and extremity lesions.

- Other topical therapies, such as Tac ointment, may be considered based on their reported effectiveness.
- Systemic administration of GC or immunosuppressants is not recommended.

Non-pharmacological treatment

For the treatment of PM and DM the following points regarding rehabilitation are provided:

- **Beginning rehabilitation early in the treatment:** Starting rehabilitation in the early stage of treatment has been reported as effective for muscle strength recovery. There is no evidence suggesting harm in implementing rehabilitation. However, the definitive prognosis for functional improvement remains uncertain. The appropriate load for rehabilitation has not been determined (recommendation grade: C1).
- **Rehabilitation in the chronic stage** is likely effective in recovering muscle strength without exacerbating inflammation and is recommended (recommendation grade: B).

1.5 Systematic Reviews & Meta Analyses

1.5.1 Idiopathic Inflammatory Myopathies: State of the Art on Clinical Practice Guidelines

IIMs encompass a wide range of conditions with diverse manifestations, extending beyond just muscle involvement, which leads to varying patient needs. Diagnosis can also be difficult, leaving patients with numerous uncertainties and questions about their condition and its future implications. Unfortunately, these questions may not always have clear answers in the case of IIMs or may receive different responses from different specialists. Patients face a lack of consistency in medical approaches and minimal participation in the development of a shared treatment path.

Currently, there are no Clinical Practice Guidelines (CPGs) available for the diagnosis of IIMs. Early intervention is crucial for better outcomes, but IIMs are often misdiagnosed as various other conditions, including non-inflammatory myopathies and other inflammatory diseases. Current CPGs inadequately address the management of extramuscular organ involvement beyond the skin. Lung disease, a common manifestation in IIMs and a significant cause of mortality, is only addressed by one CPG. No CPGs currently cover heart, joint, and gastroenterological manifestations, despite their potential impact on patients' quality of life and mortality. IIMs encompass a diverse group of diseases, and CPGs do not specifically cater to distinct subgroups based on clinical manifestations, autoantibody profiles, or muscle histology. Precise monitoring of muscle inflammatory activity and

damage is vital, yet only one CPG addresses this challenge. Life-threatening complications in IIMs patients, such as severe rapidly progressive ILD, myocarditis, and others, require rapid diagnosis and management, yet no CPGs currently address these concerns.

The research was conducted in collaboration with the European Reference Network on rare and complex connective tissue and musculoskeletal diseases (ReCONNET), supported by the European Union's Health Programme. Fourteen original CPGs were found, however, only half of these CPGs were evidence-based. Recommendations of available CPGs notably stated that:

i. Evaluation of extra-muscular involvement.

ii. Use of GC, methotrexate, or azathioprine as first-line treatments for IIMs.

iii. Consideration of IVig for treatment-resistant DM and other resistant IIMs.

iv. Incorporation of physical therapy and sun protection (for DM patients) as part of the treatment.

v. Tumor screening for DM patients, including chest, abdomen, pelvis, and breast (for women), and colonoscopy (for patients over 50).

vi. Monitoring disease activity and damage using standardized and validated tools[14].

Hengstman, 2009[15]

- The first-line treatment for IIMs consists of prednisone at a dosage of 1 mg per kilogram of body weight, along with either azathioprine or methotrexate.
- In cases with severe pulmonary involvement as a second-line option, treatment may involve cyclosporin, tacrolimus, or cyclophosphamide.
- For patients without severe pulmonary involvement as a second-line treatment, IVig is recommended.
- The third-line treatment options include rituximab, tacrolimus, MMF, cyclosporin, or cyclophosphamide.

Sunderkotter (2016)[16]

- All IIMs patients should undergo a pulmonary function test, and if abnormal results are observed, they should receive further evaluation by a pulmonologist.
- For DM patients with anti-TIF1-γ, tumor screening is recommended, involving 18-fluoro-deoxyglucose-positron emission tomography/CT or CT of the thorax

and abdomen, along with a gynecological/urological examination. However, there is no recommended strategy for other cases in the CPGs.

- The treatment for IIMs includes the following:
    - Corticosteroids, intravenous for severe cases and oral for milder cases.
    - Azathioprine for adults and methotrexate for children when:
        1. The IIM is severe.
        2. It is not possible to reduce corticosteroids dosage below the 'Cushing threshold' after three months.
    - IVig is recommended for patients who do not respond to corticosteroids and azathioprine.
    - Non-pharmacological measures, such as regular physical therapy and sun protection, are advised for DM patients.

Enk (2016)[17]

Indication of IVIG in Severe Forms of DM, PM, and IBM:

- Severe forms of DM, PM, and IBM are considered by the authors as indications for IVig.
- IVig can be used as a first-line treatment in cases of fulminant course, severe myolysis, or paralysis, and as a second-line treatment in other scenarios while continuing immunosuppressive therapy.

Pregnancy in Patients with IIMs:

- Patients with IIMs should receive accurate information about the risks associated with pregnancy.
- Pregnancy should ideally be planned when IIMs is in a state of remission.
- Pregnant patients with IIMs should undergo regular monitoring by a multidisciplinary team during gestation and the postpartum period.
- In case of disease relapse during pregnancy, treatment should be initiated as soon as possible.
- Treatment for IIMs in pregnant patients includes corticosteroids (1 mg/kg/day until serum CK levels normalize). If there is an inadequate response, other options may include cyclosporin, azathioprine, plasma exchange, or IVig.

Fujimoto (2016)[18]

Calcinosis in IIMs:

- Options recommended for calcinosis in IIMs include:
    - Low-dose warfarin.
    - Aluminum hydroxide gel.
    - Diltiazem hydrochloride.
    - Probenecid.
    - Bisphosphonate.
- Surgical treatment is also suggested as an option.

Panniculitis in IIMs:

- The recommended treatment for panniculitis in IIMs is corticosteroids.
- If there is no response to corticosteroids alternative options include: Cyclosporin, methotrexate and azathioprine.

Morrisset (2016)[19]

In Acute or Severe IIMs with ILD:

- The recommended treatment for acute or severe cases of IIMs with ILD includes:
    - High-dose steroids.
    - A choice of treatments like cyclophosphamide, rituximab, cyclosporin, or tacrolimus.

In Chronic or Mild to Moderate IIMs with ILD:

- For chronic or mild to moderate IIMs with ILD::
    - Steroids.
    - Options such as MMF or azathioprine.

In Case of Treatment Failure:

- If the initial treatment fails, it is recommended to consider the following options:
    - Switching to a different agent.
    - Considering a combination of agents.
    - Exploring IVig.
    - Referring for transplantation evaluation.

Enders (2017)[20]

- All children suspected of having IIMs should be referred to a specialized center. High-risk patients should receive immediate or urgent referral.
- It is recommended that all children with IIMs undergo an assessment to evaluate organ involvement (muscles, skin, lung, heart), calcinosis, and specific antibodies, as detailed in the CPG.
- Monitoring of disease activity, damage, and overall health status should be conducted in a standardized manner.
- The treatment approach for juvenile IIMs includes:
    - Sun protection and participation in an exercise program.
    - As the first-line treatment: high-dose corticosteroids and methotrexate.
    - If there is treatment failure (within the first 12 weeks), the following options should be considered:
        - Topical tacrolimus/Corticosteroids (for localized skin disease).
        - Cyclosporin or MMF (if there is intolerance to methotrexate).
        - IVig as an adjunct.
        - Rituximab as an adjunct.
        - Cyclophosphamide or antitumor necrosis factor therapies (in cases of resistance).

Jens Schmidt (2018)[21]

Glucocorticoids

- Glucocorticosteroids are the primary treatment for PM, DM, Necrotizing Myopathy (NM), Overlap syndrome with Myositis (OM).
- Prednisolone is typically administered orally at a dose of 0.5–1.0 mg/kg per day. In acute and severe cases, initiation with intravenous high-dose pulses (250–1000 mg/day for 3–5 days) may be considered.
- Continued steroid use for 4–12 weeks is recommended, with tapering based on clinical improvement in muscle strength or assessment scales.
- Tapering should be slow, reducing by 10 mg every 1 or 2 weeks until 20 mg/day is reached. Subsequent tapering can be done in 2.5–5.0 mg steps every 1 or 2 weeks, depending on the disease course.
- Maintenance doses of around 5 mg prednisolone per day may be necessary, at least for an interim or long-term phase.

- Alternating-day treatment with glucocorticosteroids is a potential alternative, offering reduced long-term side effects and potentially higher efficacy simultaneously. Alternate-day steroid application shows a higher long-term survival rate compared to daily use.
- A third option involves monthly oral pulse treatment with 4 days of 40 mg/day dexamethasone, demonstrating similar efficacy with fewer side effects.

Immunosuppression Treatment

- Long-term immunosuppression should be initiated concurrently with steroids unless the disease course is very moderate.
- Immunosuppressants include methotrexate, azathioprine, or mycophenolate mofetil.
- A Cochrane analysis found no significant efficacy differences among these agents in myositis.
- Dose increases should be performed in biweekly intervals with regular monitoring of blood parameters, including full blood count, liver, and renal function tests.
- Most immunosuppressants have the potential for embryotoxicity or gonadotoxicity. MTX, MMF, and cyclophosphamide, in particular, should be avoided during pregnancy. AZA and CsA are considered less toxic, and reports suggest normal child development, but it's advisable to avoid any immunosuppressive drugs months before conception (for both females and males) and during pregnancy.

Alternative Options

- If the standard regimen with steroids and immunosuppressants is intolerable or ineffective, two alternatives are available: Oral ciclosporin IVig.
- Ciclosporin, effective as an immunosuppressant, can be used alone or in combination with other drugs, with potential side effects including gastrointestinal symptoms, hypertension, kidney disease, and malignancy.

Alternative/Add-On Treatment with IVig

- IVIG is a well-established alternative or add-on treatment for myositis.
- Efficacious in DM and NM based on clinical studies and case series.
- Individual patient dosing is determined over several treatment cycles.
- Potential side effects include allergic reactions, headache, fever, thrombosis, and hemolysis, often dose and infusion rate related.
- Therapeutic effect expected to be similar across different IVig products.

- If standard immunosuppression and IVig are insufficient: Consider treatment escalation to rituximab or cyclophosphamide.

Specific Considerations for Myositis Subcategories

Skin Involvement

- Protect from sunlight/UV exposure.
- Consider add-on treatment with topical glucocorticosteroids.
- IVig effective for skin lesions in DM.
- Anti-malaria drugs (hydrochloroquine) can be useful in juvenile DM.

ILD

- Requires interdisciplinary management with a pulmonologist.
- More aggressive treatment may be needed, combining high dose glucocorticosteroids with an immunosuppressant (AZA plus either rituximab or Cyclophosphamide).
- CsA may be sufficient for milder forms.
- Use caution with MTX, as it may induce pneumonitis.
- IVig may be a temporary option during infection or an alternative/add-on treatment in patients with ILD and contraindications for immunosuppressive escalation therapy.

Section 2.0 Drug Therapy

2.1 Glucocorticosteroids

2.1.1 Prednisolone

Information on Prednisolone is detailed in the table below[22].

Table 2. Prednisolone Drug Information

SCIENTIFIC NAME PREDNISOLONE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	M33
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB04
Pharmacological Class (ASHP)	Glucocorticoids
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]	1mg/kg/day as a single daily dose until improvement (usually for 4 to 6 weeks); then gradually tapered (total duration usually 9 to 12 months).
Maximum Daily Dose Adults	80 mg/day
Dose (pediatrics)	1 to 2 mg/kg/day; continue for 4 weeks then if adequate patient response, begin taper; taper dose by 0.5 mg/kg increments every 2 weeks based on response until dose is 0.5 mg/kg/day, then taper every 4 weeks as tolerated.

Maximum Daily Dose Pediatrics	60 to 80 mg/day have been reported.
Adjustment	N/A
Prescribing edits	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Adjunctive therapies like DMARDs or other immunosuppressive agents may be used with Prednisolone if prednisolone alone is not providing sufficient relief, or if there are concerns about potential side effects associated with long-term prednisolone use.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, Cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effect (glaucoma).
Drug Interactions	**Category X:** • Aldesleukin • Brivudine • Brivudine • Cladribine • Desmopressin • Disulfiram • Mifamurtide • Natalizumab • Pimecrolimus • Ruxolitinib • Tacrolimus

	• Tertomotide • Vaccines like Mumps- Rubella- or Varicella-Containing Live Vaccines
Special Population	Pediatric, older patients.
Contraindications	Hypersensitivity to prednisolone, administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose • Growth in pediatric • Bone mineral density
Precautions	Hepatic and renal impairments, Myasthenia gravis, perforation risk in patients with GI diseases.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for prednisolone in IIM. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Prednisolone

Prednisolone is a synthetic GC derived from cortisone, used to treat various diseases with anti-inflammatory or immunosuppressive effects. It is considered as first line therapy for IIMs, particularly in cases where symptoms are severe or rapidly progressive. It helps control inflammation and alleviate symptoms such as muscle weakness and skin rashes. However, the specific dosage and duration of prednisolone treatment may vary depending on the type and severity of the IIMs. It is typically prescribed at a dosage of 1 mg/kg as a single daily dose until improvement (usually for 4 to 6 weeks), then gradually tapered (total duration usually 9 to 12 months). In some cases, additional treatments may be considered if prednisolone alone is not providing sufficient relief, or if there are concerns about potential side effects associated with long-term prednisolone use. It's crucial to note that the use of prednisolone should be carefully monitored by a healthcare professional, as corticosteroids can have potential side effects, particularly when

used over an extended period or at high doses. There are no recommendations issued by the HTA bodies for prednisolone.

2.1.2 Methylprednisolone

Information on Methylprednisolone is detailed in the table below[22].

Table 3. Methylprednisolone Drug Information

SCIENTIFIC NAME METHYLPREDNISOLONE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	M33
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB04
Pharmacological Class (ASHP)	Glucocorticoids
DRUG INFORMATION	
Dosage Form	Powder with solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	1 g daily for 3 to 5 days, followed by oral prednisolone.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	N/A
Prescribing edits*	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Intravenous methylprednisolone should be given for 3 to 5 days, followed by oral prednisone or prednisolone.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A

PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, Cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effect (glaucoma).
Drug Interactions	**Category X:** • Aldesleukin • Brivudine • Brivudine • Cladribine • Desmopressin • Disulfiram • Mifamurtide • Natalizumab • Pimecrolimus • Ruxolitinib • Tacrolimus • Tertomotide • Vaccines like Mumps- Rubella- or Varicella-Containing Live Vaccines
Special Population	Pediatric, older patients.
Contraindications	Hypersensitivity to methylprednisolone, administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose • Growth in pediatric • Bone mineral density

Precautions	Hepatic and renal impairments, Myasthenia gravis, perforation risk in patients with GI diseases.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies didn't yield any guidance for methylprednisolone in IIMs. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Methylprednisolone

Methylprednisolone is a GC used to treat various diseases with anti-inflammatory or immunosuppressive effects. The use of intravenous methylprednisolone should be considered, especially in patients with severe and profound weakness or there are concerns about gastrointestinal absorption of methylprednisone. Administering methylprednisolone intravenously may lead to a heightened therapeutic effect with reduced potential for toxicity compared to oral GC. It is typically prescribed at a dosage of 1g daily dose for 5 days, followed by oral prednisone or prednisolone. It's crucial to note that the use of methylprednisolone should be carefully monitored by a healthcare professional, as corticosteroids can have potential side effects, particularly when used over an extended period or at high doses. There are no recommendations issued by the HTA bodies for methylprednisolone.

2.2 Immunosuppressive Agents

2.2.1 Azathioprine

Information on Azathioprine is detailed in the table below[23].

Table 4. Azathioprine Drug Information

SCIENTIFIC NAME AZATHIOPRINE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMEA	N/A

MHRA	N/A
PMDA	N/A
Indication (ICD-10)	M33
Drug Class	Immunosuppressant Agent
Drug Sub-class	Purine Analogues
ATC Code	L04AX01
Pharmacological Class (ASHP)	Immunosuppressant Agent
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]	**DM/PM (adjunctive agent) (off-label use):** **Oral: Initial:** 50 mg once daily in combination with a GC; increase daily dose by 50 mg/week to 1.5 mg/kg/day; if inadequate response at 3 months, may increase up to 2.5 mg/kg/day. Once remission is achieved and glucocorticoids have been tapered, may consider slow taper at monthly intervals with planned cessation of therapy over ~6 months.
Maximum Daily Dose Adults	Do not exceed 250 mg/day.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Kidney impairment:** CrCl 10 to <30 mL/minute: Initial: Administer 75% to 100% of the usual indication-specific dose. Cl <10 mL/minute: Initial: Administer 50% to 100% of the usual indication-specific dose. **Hemodialysis:** dialyzable, administer 50-100% of the dose. Administer after hemodialysis if need to administer on dialysis day. If not, provide a 50% supplemental dose. **Peritoneal dialysis:** Initial: Administer 50% to 100% of the dose.

	CRRT and sustained, low efficiency diafiltration with PIRRT: Administer 75% to 100% of the dose.
Prescribing edits	CU, MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Azathioprine is generally given in combination with a GC.
G (Gender Edit): N/A	N/A
MD (Physician Specialty Edit):	Should be prescribed by a specialist.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	AZA is an option for managing refractory IIMs after an initial treatment with GC.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: Nausea, vomiting, leukopenia, infection **Most serious**: GI effects, Hematologic toxicity, Infections, Liver dysfunction, Malignancy, Pancreatitis
Drug Interactions	**Category X:** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine [INT] • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Febuxostat • Fexinidazole • Filgotinib

	• Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mercaptopurine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)
Special Population	Consider testing for thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (nucleotide diphosphatase; NUDT15) deficiency in patients who develop severe bone marrow toxicities (may require dose reduction or discontinuation). Dosage reduction or selection of alternative therapy is recommended in patients with TPMT and/or NUDT15 deficiency.
Pregnancy	Azathioprine crosses the placenta. Available guidelines suggest that use of

	azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy.
Lactation	The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk. Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. Patients who are concerned with the theoretical risks of immunosuppression may consider pumping and discarding breast milk for the first 4 hours after an azathioprine dose to decrease potential exposure to the breastfed infant.
Contraindications	Hypersensitivity to azathioprine or any component of the formulation; pregnancy (in patients with rheumatoid arthritis, patients with rheumatoid arthritis and a history of treatment with alkylating agents (e.g., cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk of malignancy with azathioprine treatment.
Monitoring Requirements	Obtain CBC with differential and platelets, total bilirubin, liver function tests, and creatinine clearance. Consider testing for thiopurine S-methyltransferase (TPMT) deficiency particularly in patients with abnormally low CBC unresponsive to dose reduction. Assess for signs of photosensitivity reactions. Consider timing and types of vaccines. Assess for signs/symptoms of infection and malignancy (e.g., splenomegaly, hepatomegaly, abdominal pain,

	persistent fever, night sweats, weight loss). Dosage adjustment may be needed if patient is taking allopurinol.
Precautions	Use with caution in patients with hepatic or renal impairment. Mercaptopurine: Azathioprine is metabolized to mercaptopurine; concomitant use may result in profound myelosuppression and should be avoided. Vaccines: Immune response to vaccines may be diminished. Toxicity or adverse reactions to live vaccines may be enhanced (depending on the azathioprine dose). Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis.
Black Box Warning	**Malignancy:** include post-transplant lymphoma and hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIMs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Azathioprine.**

Table 5. Azathioprine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Azathioprine	NICE	N/A
	CADTH[24]	**June 2023** Other immunosuppressants, including AZA, MMF and Tac have also been explored for their role in the treatment of refractory IIMs. Steroid-sparing therapy using AZA, MMF, or MTX may be considered in mild or moderate IIMs after initial treatment with GC.
	HAS[25]	**October 2015** The Commission gives a favorable opinion on the continued inclusion in the list of specialties reimbursable by social security for the indications specified in the AMM, including PM and DM. Proposed reimbursement rate: 100%.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Azathioprine

Azathioprine is used for its potential role in managing refractory IIMs and for cases of mild to moderate IIMs, after the initial treatment with GC, as a steroid-sparing therapy. Azathioprine can cross the placenta and is considered acceptable for managing musculoskeletal diseases during pregnancy according to guidelines. While the metabolite 6-mercaptopurine is found in breast milk, recommendations regarding breastfeeding during azathioprine therapy vary, with the manufacturer advising against it due to potential risks to the infant. Patients concerned about immunosuppression risks can consider pumping and discarding breast milk for the first 4 hours after taking azathioprine to minimize exposure to the breastfed infant. Limitations for the use of Azathioprine include malignancy. Do not exceed 250 mg/day.

2.2.2 Tacrolimus and Cyclosporine

Information on Tacrolimus[26] and Cyclosporine[27] are detailed in the table below.

Table 6. Tacrolimus and Cyclosporine Drug Information

SCIENTIFIC NAME		
	TACROLIMUS	**CYCLOSPORINE**
SFDA Classification	Prescription	Prescription
SFDA	Yes	Yes
US FDA	N/A	N/A
EMEA	N/A	N/A
MHRA	N/A	N/A
PMDA	N/A	N/A
Indication (ICD-10)	M33	M33
Drug Class	Immunosuppressant Agent	Immunosuppressant Agent
Drug Sub-class	Calcineurin Inhibitor	Calcineurin Inhibitor
ATC Code	L04AD02	L04AD01
Pharmacological Class (ASHP)	Immunosuppressant Agent	Immunosuppressant Agent
DRUG INFORMATION		
Dosage Form	Capsule, hard capsule, prolonged release capsule, ointment	Concentrate for solution for infusion, capsule, oral solution
Route of Administration	Oral use, topical	IV Use, Oral Use
Dose (Adult) [DDD]	**Chronic immunosuppressive therapy (alternative agent) (off-label use):** For use as monotherapy or in combination with GC in patients with GC-resistant or GC-dependent disease.	**Chronic immunosuppressive therapy (alternative agent) (off-label use):** For use as monotherapy or in combination with GC in patients with GC-resistant or GC-dependent disease.

	Immediate release: **Oral:** Initial: 3 to 5 mg/day **or** 0.1 mg/**kg**/day, in 1 or 2 divided doses; titrate to achieve target trough concentrations.	**Oral:** Initial: 2.5 mg/kg/day in 2 divided doses given every 12 hours; may increase total daily dose in increments of 0.5 mg/kg/day every 4 to 8 weeks to a maximum of 5 mg/kg/day based on tolerance, efficacy, and target trough concentration.
Maximum Daily Dose Adults	N/A	N/A
Dose (pediatrics)	Oral: Immediate release: Initial: 0.1 mg/kg/day divided every 12 hours; adjust to target serum concentration; the reported dose range (regardless of target serum concentration) is 0.06 to 0.19 mg/kg/day in divided doses every 12 hours.	N/A
Maximum Daily Dose Pediatrics	N/A	N/A
Adjustment	**Altered kidney function:** Dose adjustments should be guided by therapeutic drug monitoring. **Severe hepatic impairment (Child-Pugh class C):** Lower initial doses may be required; closely monitor blood concentrations.	**Severe hepatic impairment:** There are no dosage adjustments provided in the manufacturer's labeling; however, metabolism is extensively hepatic (exposure is increased). Monitor blood concentrations; may require dose reduction. **Kidney impairment prior to treatment initiation:** No adjustment necessary. During treatment: Nontransplant indications: If

		serum creatinine increases 25% to 30% above baseline (measured on 2 separate occasions at least 2 weeks apart), or by ≥50% at any time during therapy, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, discontinue cyclosporine. For patients receiving renal replacement: Consider temporary interruption of therapy or switching to an alternative agent to help promote renal recovery and preserve residual kidney function if other factors contributing to decreased kidney function cannot be mitigated. Continued use should only be considered if benefits outweigh risks of further kidney injury.
Prescribing edits	CU, MD, ST	CU, MD, ST
AGE (Age Edit):	N/A	N/A
CU (Concurrent Use Edit):	To be given concurrently with glucocorticosteroids	To be given concurrently with glucocorticosteroids
G (Gender Edit):	N/A	N/A

MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy should prescribe Tacrolimus.	Only physicians experienced in immunosuppressive therapy should prescribe Cyclosporine.
PA (Prior Authorization):	N/A	N/A
QL (Quantity Limit):	N/A	N/A
ST (Step Therapy):	Tac is an option for managing refractory IIMs after an initial treatment with GC.	CsA is an option for managing refractory IIMs after an initial treatment with GC.
EU (Emergency Use Only):	N/A	N/A
PE (Protocol Edit):	N/A	N/A
SAFETY		
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Cardiovascular, skin discoloration and photosensitivity, acidosis, abdominal pain and distention, anemia, cholestatic jaundice, hypersensitivity reaction **Most serious:** Diabetes mellitus, Drug-induced thrombotic microangiopathy, Hyperkalemia, Hypersensitivity reactions (immediate and delayed), Hypertension, Infection, Malignancy, nephrotoxicity, neurotoxicity, Pure red cell aplasia	**Most common:** Hypertension, Hirsutism, Urinary tract infection, Tremor **Most serious:** • Diabetes mellitus • Drug-induced gingival overgrowth • Drug-induced thrombotic microangiopathy • Hepatotoxicity • Hyperkalemia • Hypertension • Infections • Malignancy

		• Nephrotoxicity • Neurotoxicity
Drug Interactions	**<u>Category X:</u>** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Baricitinib • BCG Intravesical • BCG Vaccine (Immunization) • Brivudine [INT] • Cholera Vaccine • Cladribine • CycloSPORINE (Systemic) • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Erdafitinib • Fexinidazole • Filgotinib • Foscarnet • Fusidic Acid (Systemic) • Grapefruit Juice • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated)	**<u>Category X:</u>** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Aliskiren • AMILoride • Asunaprevir • Atorvastatin Depends on International labeling • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Bilastine Depends on Renal Function • Bosentan • Brivudine [INT] • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Disulfiram Depends on Dosage Form • DOXOrubicin Conventional • Dronedarone • Ebola Zaire Vaccine (Live) • Elagolix • Elagolix, Estradiol, and Norethindrone

	• Lasmiditan • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mifamurtide • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Ombitasvir, Paritaprevir, and Ritonavir • Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir • Pacritinib • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Saquinavir • Sirolimus (Conventional) • Sirolimus (Protein Bound) • Smallpox Vaccine Live • Sparsentan • Tacrolimus (Topical)	• Elbasvir and Grazoprevir • Eplerenone • Erdafitinib • Fexinidazole • Filgotinib • Foscarnet • Fusidic Acid (Systemic) • Grapefruit Juice Depends on Route • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Lasmiditan • Lercanidipine • Lovastatin • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Methotrimeprazine Depends on Dosage Form • Mifamurtide • MiFEPRIStone Depends on Indication • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab

	• Talimogene Laherparepvec • Taurursodiol • Temsirolimus • Tertomotide • Tofacitinib • Treosulfan • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine Zoster Vaccine (Live/Attenuated)	• Ornidazole Depends on Dosage Form and International labeling • Pacritinib • PAZOPanib • Pimecrolimus • Pimozide • Pitavastatin • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Red Yeast Rice • Revefenacin • Rotavirus Vaccine • Ruxolitinib (Topical) • Secnidazole Depends on Dosage Form • Simeprevir • Simvastatin • Sirolimus (Protein Bound) • Smallpox Vaccine Live • Sparsentan • XSpironolactone • Tacrolimus (Systemic) • Tacrolimus (Topical) • Talimogene Laherparepvec • Taurursodiol • Tertomotide • Tofacitinib

		• Topotecan Depends on Route • Treosulfan • Triamterene • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • VinCRIStine (Liposomal) • Voxilaprevir • Yellow Fever Vaccine • Zavegepant • Zoster Vaccine (Live/Attenuated)
Special Population	Younger children generally require higher maintenance doses on a mg/kg basis than older children, adolescents, or adults.	Older Adult Considerations Cyclosporine may be used in combination therapy for the treatment of severe rheumatoid arthritis. Monitor renal function closely during therapy and decrease dose as needed.
Pregnancy	Tacrolimus crosses the human placenta and is measurable in the cord blood, amniotic fluid, and newborn serum. Tacrolimus also accumulates in the placenta in concentrations that may be higher than the maternal serum. Based on limited data, tacrolimus may be used in pregnant patients with rheumatic and	Cyclosporine crosses the placenta. Cyclosporine can be used during pregnancy for refractory cases of lupus nephritis and other rheumatic and musculoskeletal diseases in patients who are not able to use alternative therapies; however, close monitoring of blood pressure is recommended.

	musculoskeletal diseases who are not able to use alternative therapies; however, close monitoring of blood pressure is recommended.	
Lactation	Tacrolimus is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the breastfeeding patient.	Cyclosporine is present in breast milk. Due to the potential for serious adverse in the breastfeeding infant, the manufacturer recommends a decision be made to discontinue cyclosporine or to discontinue breastfeeding, considering the importance of treatment to the mother.
Contraindications	Hypersensitivity to tacrolimus, polyoxyl 60 hydrogenated castor oil (HCO-60), or any other component of the formulation.	Hypersensitivity to cyclosporine or any component of the formulation. IV cyclosporine is contraindicated in hypersensitivity to polyoxyethylated castor oil. Additional contraindications (not in the US labeling): Concurrent use with bosentan; rheumatoid arthritis and psoriasis patients with primary or secondary immunodeficiency excluding autoimmune disease, uncontrolled infection, or malignancy (excluding non-melanoma skin cancer).
Monitoring Requirements	Obtain renal function tests, liver function tests, serum electrolytes (magnesium, phosphorus, potassium), and glucose. Monitor blood pressure frequently. Assess for signs of	Obtain plasma concentrations, renal function tests, liver function tests, and serum glucose. Monitor blood pressure periodically and with addition, modification, or deletion of other medications. Assessing for

	hypersensitivity during first 30 minutes of infusion. Patients should be advised to monitor glucose levels closely (this medication may alter glucose levels). Monitor for signs of opportunistic infection. Monitor mental status for signs and symptoms of neurotoxicity. May cause QT prolongation; consider ECG and electrolyte monitoring in patients at risk periodically during therapy. Monitor weight due to significant GI disturbances. Obtain vaccine history prior to prescribing.	hypersensitivity reactions with IV use. Assess for signs and symptoms of liver toxicity, secondary malignancy, diabetes, and infection. Assess for progressive cognitive or motor deficits. Consider MRI if posterior reversible encephalopathy syndrome is suspected. Assess other medications patient is taking; alternative therapy or dosage adjustment may be needed. When transferring patients with previously poor absorption of cyclosporine (non-modified), monitor trough levels at least twice weekly. For myasthenia gravis patients, abrupt cessation of cyclosporine may cause rapid deterioration of myasthenic symptoms and myasthenic crisis.
Precautions	• Cardiovascular: Myocardial hypertrophy; may be reversible with dose reduction or discontinuation. Prolongation of the QT/QTc and torsade de pointes may occur; avoid use in patients with congenital long QT syndrome. • Gastrointestinal perforation: may occur. • Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid	Product may contain corn oil or ethanol or polyoxyethylated castor oil or propylene glycol. Discontinuation of therapy: Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis. Vaccines: Live, attenuated vaccines may be less effective; vaccination should be avoided.

	deterioration of myasthenic symptoms and possibly myasthenic crisis. • IR and ER capsules are NOT interchangeable or substitutable. Patients should be brought up to date with all immunizations before initiating therapy.	
Black Box Warning	Malignancies and serious infection.	• Only health care providers experienced in the management of systemic immunosuppressive therapy for the indicated disease should prescribe cyclosporine. • Immunosuppression • Erratic absorption and bioavailability • Psoriasis patients previously treated with psoralens plus ultraviolet A (PUVA) and, to a lesser extent, MTX or other immunosuppressive agents, ultraviolet B (UVB), coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking cyclosporine. • Hypertension/nephrotoxicity
REMS	N/A	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIMs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for tacrolimus (table 7) and cyclosporine (table 8).**

Table 7. Tacrolimus HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tacrolimus	NICE	N/A
	CADTH[24]	**June 2023** AZA, MMF, and Tac are among the immunosuppressant drugs investigated for treating refractory IIMs. For ILD in IIMs, there's a recommendation to consider using Tac or CsA in combination with steroids as an early part of the induction therapy, although this recommendation is based on low-quality evidence.
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

Table 8. Cyclosporine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Cyclosporine	NICE	N/A
	CADTH[24]	**June 2023** It is recommended using Tac (or csA) along with steroids, as part of induction (conditional recommendation based on low-quality evidence) for ILD.
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Tacrolimus

Tacrolimus is recommended as a monotherapy or in combination with GC in patients with GC-resistant disease. It is also recommended for ILD, in combination with steroids as an early part of the induction therapy. Tacrolimus can cross the placenta and accumulate in the placenta itself, making it detectable in the newborn. Limited data suggest that it may be considered in pregnant patients with rheumatic and musculoskeletal diseases when alternatives are not feasible, but blood pressure should be closely monitored. Tacrolimus is also found in breast milk, and the decision to breastfeed should weigh the risks to the infant.

CONCLUSION STATEMENT- Cyclosporine

Cyclosporine is recommended in combination with GC in patients with GC-resistant disease. It is also recommended for ILD, in combination with steroids as an early part of the induction therapy. Cyclosporine crosses the placenta and may be considered during pregnancy when no alternative therapies are viable, with blood pressure monitoring advised. It's found in breast milk, and the manufacturer advises weighing the importance of treatment for the mother against the potential risks to breastfeeding infant, recommending a decision to either discontinue cyclosporine or breastfeeding.

2.2.3 Mycophenolate Mofetil

Information on Mycophenolate Mofetil is detailed in the table below[28].

Table 9. Mycophenolate Mofetil Drug Information

SCIENTIFIC NAME MYCOPHENOLATE MOFETIL	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	M33
Drug Class	IMMUNOSUPPRESSANTS
Drug Sub-class	SELECTIVE IMMUNOSUPPRESSANTS
ATC Code	L04AA06
Pharmacological Class (ASHP)	Immunosuppressant agent
DRUG INFORMATION	

Dosage Form	Film-coated tablet, capsule, gastro-resistant tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	500 mg twice daily for 2 weeks then 1 g twice daily.
Maximum Daily Dose Adults*	1.5 g twice daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Neutropenia (ANC <1.3 x 103/mcL): Dosing should be interrupted, or the dose reduced. No hepatic dose adjustment. Consider therapeutic drug monitoring for eGFR<60 mL/ min/ 1.73 m2 when available. Use with caution for eGFR <25 mL/ min/ 1.73 m2 consider limiting dose to 1 g twice daily or delayed release 720 mg twice daily. Not dialyzable in intermittent hemodialysis or peritoneal dialysis. Removal by CRRT or PIRRT is expected to be insignificant for eGFR<25 <25 mL/ min/ 1.73 m2.[29] No hepatic or renal adjustment for pediatric doses. Not removed by dialysis.
Prescribing edits*	CU, MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit):	Some experts recommend overlapping Mycophenolate mofetil with preceding therapy to minimize risk for disease flares.
G (Gender Edit)	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy should prescribe Mycophenolate Mofetil.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	When myositis relapses occur following corticosteroid treatment, it is advisable to consider using Mycophenolate

	mofetil as a recommended treatment option.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** edema, hypertension, hypotension, hypercholesterolemia, hyperglycemia, hypokalemia and hypomagnesemia, abdominal pain, nausea, vomiting, anemia, leukopenia **Most serious**: Acute inflammatory syndrome, Bone marrow suppression, GI effects, Infection, Lymphoproliferative disorders, Pure red cell aplasia
Drug Interactions*	**Category X**: • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine [INT] • Cholera vaccine • Cholestyramine Resin • Cladribine • Colesevelam • Colestipol • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec

	• Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine Zoster Vaccine (Live/Attenuated)
Special Population	**Older Adult** Dosage is the same as for younger patients; however, dosing should be cautious due to possibility of increased hepatic, renal, or cardiac dysfunction. Patients ≥65 years of age may be at an increased risk of certain infections, GI hemorrhage, and pulmonary edema, as compared to patients <65 years of age.
Pregnancy	[US Boxed Warning]: Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available.
Lactation	It is not known if mycophenolate is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risks and benefits.
Contraindications	Hypersensitivity to any component of the formulation. IV formulation is also contraindicated in patients who are allergic to polysorbate 80 (Tween). Additional contraindications (not in the US labeling): Pregnancy; women of

	childbearing potential and not using highly effective contraceptive methods; or not providing a pregnancy test result; breastfeeding.
Monitoring Requirements	Obtain CBC, renal function tests, and liver function tests. Assess other medications the patient is taking. Patients with diabetes should monitor glucose levels closely. Assess for signs and symptoms of infection, neurological symptoms, skin lesions suspicious of skin cancer, lymphoma, pure red cell aplasia, and autoimmune hemolytic anemia. Monitor neurological symptoms, and signs of pure red cell aplasia or autoimmune hemolytic anemia.
Precautions	May cause CNS depression. Use caution in patients with serious digestive system disease. Avoid in patients with hypoxanthine-guanine phosphoribosyl transferase deficiency. Not interchangeable with mycophenolate sodium without healthcare supervision: different rates of absorption. Some dosage forms may contain phenylalanine. Some dosage forms may contain polysorbate 80 also known as Tweens. Patients should not donate blood or blood products during treatment and for at least 6 weeks after the last dose. Abrupt cessation in patients with myasthenia gravis may result in deterioration of symptoms and possible myasthenic crisis. Avoid live attenuated vaccines. Never administer IV solution by rapid or bolus injection.
Black Box Warning	• Should only be prescribed by an experienced physician in immunosuppressive therapy. • Serious Infections

	• Malignancies: lymphoma and other malignancies, particularly of the skin • Embryo-fetal toxicity. Avoid if safer options available
REMS	REMS Drugs COVID-19 Safety Alert: to assure safe use: consider whether there are compelling reasons or not to complete these requirements during this public health emergency and weigh with the patient the benefits and risks of continuing treatment in the absence of the laboratory testing and imaging studies.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIMs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for Mycophenolate Mofetil.

Table 10. Mycophenolate Mofetil HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Mycophenolate Mofetil	CADTH[30]	**June 2023** Steroid sparing therapy using mycophenolate mofetil may be considered in mild or moderate IIMs after initial treatment and in juvenile IIMs. No summary regarding the comparative clinical effectiveness or safety of alternatives to IVig in severe or refractory IIMs are provided.
	NICE	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Mycophenolate Mofetil

Mycophenolate Mofetil/Mycophenolate Acid is an immunosuppressive agent employed in the treatment of IIMs. Some experts recommend initiating Mycophenolate mofetil concurrently with prior therapy to reduce the risk of disease flares, or as a standalone treatment if myositis relapses occur after corticosteroid treatment. The typical dosage starts at 500mg twice daily for 2 weeks, then escalates to 1g twice daily, with a maximum dose of 1.5g twice daily. Possible gastrointestinal side effects like nausea and diarrhea may manifest. Regular blood tests are imperative to monitor for potential bone marrow suppression, which can lead to anemia and heightened susceptibility to infections. CADTH approved the use of mycophenolate mofetil in mild or moderate IIMs after initial treatment and in juvenile IIMs but no summary regarding the comparative clinical effectiveness or safety of alternatives to IVIG in severe or refractory IIMs are provided.

2.2.4 Cyclophosphamide

Information on Cyclophosphamide is detailed in the table below[31].

Table 11. Cyclophosphamide Drug Information

SCIENTIFIC NAME CYCLOPHOSPHAMIDE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Off-label
Indication (ICD-10)	M33
Drug Class	Antineoplastic, Alkylating Agent, Antirheumatic, Immunosuppressant
Drug Sub-class	Nitrogen Mustard
ATC Code	L01AA01
Pharmacological Class (ASHP)	Antineoplastic Agent
DRUG INFORMATION	
Dosage Form	Film-coated tablet, Powder for solution for injection
Route of Administration	IV use, Oral use

Dose (Adult) [DDD]*	IV: 500 to 750 mg/m2 every 4 weeks; maximum dose has not been established. Oral: 1.5 to 2 mg/kg/day: maximum dose has not been established. Duration of therapy: Continue therapy for up to 6 months, then transition to an alternative immunosuppressive agent to maintain remission.
Maximum Daily Dose Adults*	The maximum dose has not been established; some experts do not exceed 1,200 mg/dose IV. Do not exceed 200 mg/day oral.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	CrCl 10 to 29 mL/minute: Administer 75% or 100% of PO normal dose. CrCl <10 mL/minute: Administer 50%, 75%, or 100% of PO normal dose. IV: Shorter, low-dose regimen (500 mg IV once every 2 weeks for 6 doses): No dosage adjustment necessary. IV: Longer, high-dose regimen (500 to 1,000 mg/m2 IV pulses): CrCl <30 mL/minute: Reduce initial dose to 500 mg/m2 Hemodialysis, intermittent (thrice weekly): Moderately dialyzable (20% to 50% removal based on limited data with low-flux dialyzers): Administer 50% or 75% of the normal dose. On dialysis days, administer after hemodialysis, allowing at least 12 hours before the next hemodialysis session. Peritoneal dialysis: Administer 75% of the normal dose. If possible, allow at least 12 hours before next peritoneal dialysis exchange. CRRT: Administer 100% of the normal dose

	Hepatic adjustment: no dosage adjustments provided in the manufacturer's labeling. Floyd 2006 has recommended: Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose. Serum bilirubin >5 mg/dL: Avoid use.
Prescribing edits*	CU, MD, QL
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	For use as an adjunct to glucocorticoids and other immunosuppressive agents in patients with severe disease that is refractory to other preferred therapies, or as part of initial combination therapy in patients with impending respiratory failure.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy should prescribe Cyclophosphamide.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	IV: some experts do not exceed 1,200 mg/dose. PO: some experts do not exceed 200 mg/day.
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** leukopenia, neutropenia, anemia, arrythmias and pericarditis. **Most serious:** Bone marrow suppression and infection, Cardiotoxicity, Hemorrhagic cystitis, Hepatotoxicity, Pulmonary toxicity, Second primary malignancy
Drug Interactions*	**Category X:**

	• Abrocitinib • Adenovirus (Types 4, 7) Vaccine Depends on International labeling. • Baricitinib • BCG (Intravesical) (Immunization) • Brivudine [INT] • Cholera Vaccine Depends on International labeling • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) Depends on International labeling • Etanercept • Fexinidazole • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) Depends on International labeling • Japanese Encephalitis Virus Vaccine (Live/Attenuated) Depends on International labeling • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine Depends on International labeling • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) Depends on International labeling • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine Depends on International labeling • Ruxolitinib (Topical)

	• Smallpox Vaccine Live Depends on International labeling • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Voclosporin • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated) Depends on International labeling.
Special Population	Dosing adjustment for toxicity: Infants, Children, and Adolescents: Hematologic toxicity: May require dose reduction or treatment interruption. Hemorrhagic cystitis, severe: Discontinue treatment. Older Adult Considerations Toxicity to immunosuppressives is increased in the elderly. Start with the lowest recommended adult doses. Signs of infection, such as fever and elevated WBC, may not occur. Lethargy and confusion may be more prominent signs of infection; adjust dose for renal function.
Pregnancy	Cyclophosphamide crosses the placenta and can be detected in amniotic fluid. In patients with life- or organ-threatening maternal disease, cyclophosphamide may be used in the second or third trimesters only when an alternative therapy is not available
Lactation	Cyclophosphamide and its metabolites are present in breast milk. Cyclophosphamide is not recommended for use in breastfeeding mothers with autoimmune and systemic inflammatory diseases.

	breastfeeding is not recommended by the manufacturer during therapy and for 1 week after the last cyclophosphamide dose. Others recommend breastfeeding be avoided for at least 6 weeks after the last dose of cyclophosphamide
Contraindications	History of severe hypersensitivity to cyclophosphamide, its metabolites, or any component of the formulation; urinary outflow obstruction. Canadian labeling: Additional contraindications (not in the US labeling): Severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression.
Monitoring Requirements	Obtain CBC with differential and platelets, serum electrolytes, BUN, serum creatinine, and urinalysis. Dosage in the obese should be weight based. Premedicate with an antiemetic and MESNA. Assess for signs and symptoms of hemorrhagic cystitis, renal toxicity, pulmonary toxicity, cardiac toxicity, and liver toxicity.
Precautions	Use with caution in patients with hepatic or renal impairment. Hypersensitivity: Possible cross-sensitivity with other alkylating agents may occur. Some cyclophosphamide injection dosage forms may contain alcohol. The alcohol content (in some dosage forms) may affect the CNS and impair the ability to drive or operate machinery.
Black Box Warning	**N/A**
REMS*	**N/A**

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Cyclophosphamide.**

Table 12. Cyclophosphamide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Cyclophosphamide	NICE	N/A
	HAS	N/A
	CADTH[30]	**June 2023** It is recommended to use cyclophosphamide in patients with rapidly progressive ILD or in juvenile IIM who are refractory to treatment with glucocorticoids or methotrexate. It's important to note that the comparative effectiveness of IVIG and cyclophosphamide is uncertain, as most recommendations rely on case series, reports, and expert opinions. Therefore, considering it as an IVIG alternative in refractory IIM should be approached with caution.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Cyclophosphamide

Cyclophosphamide, an immunosuppressive medication, exerts its effects by interfering with the DNA synthesis and cell division process in rapidly dividing cells, including immune cells. In IIMs, it is used in cases of severe or refractory disease where other treatments have not provided sufficient relief. The dosage of cyclophosphamide for IIMs can vary, but a common starting dose is 500 mg to 1 gram orally or intravenously, with adjustments based on individual patient response. However, it is crucial to follow the specific dosing instructions provided by the treating healthcare provider. Main side effects may include gastrointestinal discomfort, increased susceptibility to infections, and potential bone marrow suppression leading to anemia or low blood cell counts. Close monitoring and regular follow-ups are essential to manage any potential side effects and ensure the

medication's effectiveness. CADTH has approved its use in patients with rapidly progressive ILD or in juvenile IIMs who are refractory to treatment with GC or methotrexate but considering it as an IVig alternative in refractory IIMs should be approached with caution.

2.2.5 Methotrexate

Information on Methotrexate is detailed in the table below[32].

Table 13. Methotrexate Drug Information

SCIENTIFIC NAME METHOTREXATE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMEA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	M33
Drug Class	Immunosuppressant Agent
Drug Sub-class	Antimetabolite (Antifolate)
ATC Code	L01BA01
Pharmacological Class (ASHP)	Immunosuppressant Agent
DRUG INFORMATION	
Dosage Form	Solution for injection, Solution for injection in pre-filled syringe, oral solution, tablet
Route of Administration	IV Injection, IM Injection, Oral use
Dose (Adult) [DDD]	**DM/PM (alternative agent) (adjunctive agent) (off-label use):** For use as an adjunct to GC, **or** as an alternative initial therapy in patients who cannot receive GC. **Oral, SUBQ, IM:** Initial: 7.5 to 15 mg once **weekly** (in combination with folic acid); adjust dose by 2.5 mg/**week** every 2 to 4 weeks if needed based on response (usual dose: 15 to 25 mg once **weekly**).

Maximum Daily Dose Adults	N/A
Dose (pediatrics)	**SubQ**, unless oral administration is possible: 15 mg/m^2 or 1 mg/kg (maximum 40 mg) once/week.
Maximum Daily Dose Pediatrics	N/A
Adjustment	The following adjustments have been recommended: Bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose. Bilirubin >5 mg/dL: Avoid use. Hepatotoxicity during treatment: Withhold, consider a reduced dose, or discontinue methotrexate as appropriate. Altered Kidney Function: • CrCl >60 mL/minute: No dose adjustment necessary. • CrCl 46 to 60 mL/minute: Administer 65% of normal dose. • CrCl 31 to 45 mL/minute: Administer 50% of normal dose. • CrCl <30 mL/minute: Avoid use.
Prescribing edits*	CU, MD, QL, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Methotrexate is to be given in combination with folic acid.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Should be prescribed by a specialist.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	Maximum: 20 to 25 mg/week
ST (Step Therapy):	MTX is an alternative initial treatment for IIMs patients who cannot receive GC.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Most common**: Diarrhea, nausea, hepatotoxicity, fatigue, headache, cough **Most serious**: Dermatologic toxicity, GI toxicity, Hematologic toxicity, Hepatotoxicity, Infection, Nephrotoxicity, Neurotoxicity, Pulmonary toxicity
Drug Interactions	**Category X:** • Abrocitinib • Acitretin • Aminolevulinic Acid (Systemic) • BCG (Intravesical) Depends on Dose • BCG (Intravesical) • BCG Vaccine (Immunization) Depends on Dose • Brivudine [INT] • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dichlorphenamide • Dipyrone • Fexinidazole • Filgotinib Depends on Dose • Foscarnet • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Nitrous Oxide • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec

	• Taurursodiol • Tertomotide • Typhoid Vaccine • Varicella Virus Vaccine Yellow Fever Vaccine
Special Population	Toxicity to MTX or any immunosuppressive is increased in the elderly. Must monitor carefully. For rheumatoid arthritis and psoriasis, immunosuppressive therapy should only be used when disease is active and less toxic, traditional therapy is ineffective. Recommended doses should be reduced when initiating therapy in the elderly due to possible decreased metabolism, reduced renal function, and presence of interacting diseases and drugs. Adjust dose as needed for renal function (CrCl).
Pregnancy	MTX crosses the placenta. Following exposure during the first trimester, methotrexate may increase the risk of spontaneous abortion, skull anomalies, facial dysmorphism, CNS, limb, and cardiac abnormalities; intellectual impairment may also occur. Intrauterine growth restriction and functional abnormalities may occur following second or third trimester exposure. Consider the benefits and risks of methotrexate and risks to the fetus when prescribing methotrexate to a pregnant patient with a neoplastic disease. The use of methotrexate for the treatment of non-neoplastic indications is contraindicated in pregnancy.
Lactation	Methotrexate and 7-hydroxymethotrexate are present in breast milk. According to the manufacturer, breastfeeding should be discontinued during treatment and for 1

	week after the final methotrexate dose. If an infant is exposed to lower doses of methotrexate (maternal doses <0.4 mg/kg/week) via breast milk, consider monitoring the infant CBC at 1 and 3 months of age.
Contraindications	History of severe hypersensitivity (including anaphylaxis) to methotrexate or any component of the formulation; breastfeeding. Additional contraindications for patients with psoriasis, rheumatoid arthritis, or polyarticular-course juvenile idiopathic arthritis: Pregnancy, alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes (overt or laboratory evidence); preexisting blood dyscrasias (e.g., bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia). Canadian labeling: Additional contraindications (not in the US labeling): Severe renal impairment (including end-stage renal disease with or without dialysis); females of childbearing potential (until pregnancy is excluded); concomitant use with nitrous oxide anesthesia
Monitoring Requirements	Obtain CBC with differential and platelets, serum creatinine, BUN, liver function tests (bilirubin, alkaline phosphatase, and transaminase), pulmonary function tests (if drug-induced lung disease suspected), and chest x-ray. Obtain methotrexate levels and urine pH with high doses. Dosage in the obese should be based on the actual body weight. Assess other medicines patient is taking; alternate therapy or dosage adjustment may be

	needed. Assess closely for toxicity in patients with ascites, pleural effusion, decreased folate stores, liver impairment, or renal impairment.
Precautions	• Do not administer nonsteroidal anti-inflammatory drugs (NSAIDs) prior to or during high dose methotrexate therapy; may increase and prolong serum methotrexate levels. • Concomitant use of proton pump inhibitors with methotrexate (primarily high-dose methotrexate) may elevate and prolong serum methotrexate levels and metabolite (hydroxymethotrexate) levels. May lead to toxicities; use with caution. • Immunization with live vaccines is not recommended; cases of disseminated vaccinia infections due to live vaccines have been reported. • Vitamins containing folate may decrease response to systemic methotrexate (in patients with neoplastic diseases); folate deficiency may increase methotrexate toxicity. Folic acid supplementation may be indicated in patients receiving methotrexate for non-neoplastic conditions. • Fatal errors have occurred when methotrexate was administered as a daily dose instead of a weekly dose. Verify the indication before administration. • Intrathecal safety: When used for intrathecal administration, intrathecal medications should not be prepared during the preparation of any other agents. • Methotrexate overexposure: Glucarpidase may be used for

	methotrexate overexposure; it is approved for the treatment of toxic plasma methotrexate concentrations (>1 micromole/L) in patients with delayed clearance due to renal impairment. • Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity.
Black Box Warning	Oral: • Serious adverse reactions of the bone marrow, GI tract, liver, lungs, skin, and kidneys. Withhold or discontinue methotrexate tablets as appropriate. • Hypersensitivity: contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis. • Embryo-fetal toxicity: contraindicated in pregnancy. Methotrexate Injection: • Intrathecal and high-dose therapy: use preservative-free formulation. Formulations with benzyl alcohol can cause severe central nervous toxicity or metabolic acidosis. Use only preservative-free methotrexate injection for treatment of neonates or low-birth-weight infants and for intrathecal use. Do not use benzyl alcohol–containing formulations for high-dose regimens unless immediate treatment is required, and preservative-free formulations are not available. • Hypersensitivity: contraindicated in patients with a history of severe

	hypersensitivity reactions to methotrexate, including anaphylaxis • Appropriate use: adverse reactions of the bone marrow, GI tract, liver, lungs, skin, and kidneys. • Pregnancy: embryo-fetal toxicity. Not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females and males of reproductive potential to use effective contraception during and after treatment with methotrexate. • Bone marrow suppression: and aplastic anemia with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). • Renal impairment: Require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration. • Hepatotoxicity: Generally, only after prolonged use • Pneumonitis: may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible. may require interruption of treatment and careful investigation. • GI toxicity: reported with concomitant administration of methotrexate (usually in high dosage) along with some NSAIDs. Diarrhea and ulcerative stomatitis require interruption of

	therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur. • Secondary malignancy: may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted. • Dermatologic toxicity: Recovery has been reported with discontinuation of therapy. • Opportunistic infections: especially Pneumocystis jirovecii pneumonia • Other serious reactions: Closely monitor for infections and adverse reactions of the bone marrow, kidneys, liver, nervous system, GI tract, lungs, and skin. Withhold or discontinue methotrexate injection as appropriate. • Radiotherapy: Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis. Experienced physician (injection): Methotrexate should be used only by health care providers whose knowledge and experience include the use of antimetabolite therapy.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIMs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methotrexate.**

Table 14. Methotrexate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methotrexate	NICE	N/A
	CADTH[24]	**June 2023** GC, such as prednisolone, often combined with DMARDs like MTX, are typically the initial treatment for IIMs. For mild or moderate cases of IIMs, steroid-sparing therapies like AZA, MMF or MTX may be considered as a subsequent treatment. In the case of juvenile IIMs, corticosteroids and MTX as the preferred first-line treatment options are recommended.
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Methotrexate

Methotrexate is recommended as an adjunct to GC, or as an alternative initial therapy in patients with IIMs who cannot receive GC. In the case of juvenile IIMs, corticosteroids and MTX as the preferred first-line treatment options. MTX crosses the placenta and poses significant risks to the fetus, particularly during the first trimester, with potential adverse effects on development. Its use during pregnancy should be carefully considered for neoplastic diseases, and it is contraindicated for non-neoplastic indications. MTX and its metabolite are found in breast milk, and breastfeeding should be discontinued during treatment and for a week after the final methotrexate dose.

2.2.6 Rituximab

Information on Rituximab is detailed in the table below[33].

Table 15. Rituximab Drug Information

SCIENTIFIC NAME RITUXIMAB	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A

EMEA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	M33
Drug Class	Immunosuppressant
Drug Sub-class	Anti-CD20 Monoclonal Antibody
ATC Code	L01FA01
Pharmacological Class (ASHP)	Monoclonal Antibody
DRUG INFORMATION	
Dosage Form	Concentrate and diluent for solution for IV infusion
Route of Administration	IV Use
Dose (Adult) [DDD]	**DM and PM, refractory disease (alternative agent) (off-label use):** For use in patients who do not respond sufficiently to conventional induction regimens (e.g., systemic GC plus AZA or MTX). Optimal dose, frequency, and duration of therapy have not been established and vary based on institutional protocols. **IV:** 1 g once every 2 weeks for 2 doses
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	**Juvenile IIMs: IV:** 375 mg/m^2
Maximum Daily Dose Pediatrics	N/A
Adjustment	No dosage adjustments in hepatic impairment. Kidney impairment prior to treatment initiation; no adjustment necessary.
Prescribing edits	AGE, CU, MD, ST
AGE (Age Edit):	Not given to children less than 6 years of age.
CU (Concurrent Use Edit):	In patients with rapidly progressive ILD and anti-MDA-5 antibodies who do not respond to GC and immunosuppressants, it is recommended to add rituximab to the treatment (combination therapy).

	Should be preceded by the appropriate premedication (acetaminophen, antihistamine, with/without corticosteroid).
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Rituximab must be prescribed by a Specialist.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Rituximab is suggested as an option for managing IIMs-related skin disease that does not respond to GC or DMARD. Rituximab is an alternative to IVig for treating skeletal muscle inflammation or skin manifestations in IIMs when they do not respond to steroid treatment.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: cardiac disorders, hypophosphatemia, nausea, anemia, hepatobiliary disease, antibody development, chills, fatigue, pulmonary toxicity, fever, infusion related reactions **Most serious**: • Hepatitis B virus reactivation • Hypogammaglobulinemia and Infection • Infusion-related reactions • Progressive Multifocal Leukoencephalopathy
Drug Interactions	**Category X:** • Abatacept • Abrocitinib • Adalimumab • Adenovirus (Types 4, 7) Vaccine • Anakinra • Anifrolumab • Baricitinib

	• BCG (Intravesical) • BCG Vaccine (Immunization) • Belimumab • Brivudine [INT] • Certolizumab Pegol • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Etanercept • Fexinidazole • Filgotinib • Golimumab • InFLIXimab • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Sarilumab • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide

	• Tocilizumab • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)
Special Population	**Pediatric:** Prior to rituximab therapy, patients should be brought up to date with all non-live vaccination if possible; any non-live vaccines should be administered ≥4 weeks prior to first rituximab dose. Pretreatment with acetaminophen and an antihistamine (diphenhydramine typically used in pediatric trials) is recommended for all indications. **Older adult:** There is a higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis), and the incidence of grade 3 or 4 adverse reactions are higher in patients ≥65 years of age.
Pregnancy	Rituximab crosses the placenta and can be detected in the newborn. Rituximab should be discontinued once pregnancy is detected in patients treated for musculoskeletal diseases; treatment during pregnancy should only be considered for pregnant patients with life- or organ-threatening disease.
Lactation	Rituximab is present in breast milk. According to the manufacturer, breastfeeding is not recommended during treatment and for 6 months after the last dose of rituximab. However, based on available data, rituximab is considered compatible with breastfeeding in patients treated for

	musculoskeletal diseases. In addition, rituximab is unlikely to be absorbed by the infant gastrointestinal tract following exposure via breast milk.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy; patients with severe, active infections
Monitoring Requirements	Obtain CBC with differential (weekly to monthly intervals), peripheral CD20 cells, and renal function tests. Screen for HBV infection prior to initiation. Monitor vital signs, fluid balance and for infusion reaction. Obtain cardiac monitoring during and after infusion in rheumatoid arthritis patients and in patients with pre-existing cardiac disease. Assess for signs of progressive multifocal leukoencephalopathy and mucocutaneous reactions.
Precautions	• Bowel obstruction/perforation: Abdominal pain, bowel obstruction, and perforation have been reported. • Cytopenias: Rituximab is associated with lymphopenia, leukopenia, neutropenia, thrombocytopenia, and anemia; the duration of cytopenias may be prolonged and may extend months beyond treatment. • Renal toxicity: May cause fatal renal toxicity in patients with non-Hodgkin lymphomas (NHL). • Tumor lysis syndrome leading to acute renal failure requiring dialysis (sometimes fatal) may occur within 12

	to 24 hours following the first dose when used as a single agent in the treatment of NHL. • Granulomatosis with polyangiitis/microscopic polyangiitis: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with granulomatosis with polyangiitis or microscopic polyangiitis after rituximab-induced B-cell depletion. • Pemphigus vulgaris: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with pemphigus vulgaris after rituximab-induced B-cell depletion. • Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported. • Immunizations: In the oncology setting, live vaccines should not be given before or during rituximab treatment.
Black Box Warning	• Infusion-related reactions • Mucocutaneous reactions • Hepatitis B virus reactivation: some cases resulting in fulminant hepatitis, hepatic failure, and death. • Progressive multifocal leukoencephalopathy
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIMs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health

Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Rituximab.**

Table 16. Rituximab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Rituximab	NICE	N/A
	CADTH[24]	**June 2023** Rituximab is recommended for the treatment of refractory myositis, particularly in patients with juvenile-onset disease, positive myositis autoantibodies, or lower disease severity. Rituximab is suggested as an option for managing IIMs-related skin disease that does not respond to GC or DMARDs. Rituximab is an alternative to IVig for treating skeletal muscle inflammation or skin manifestations in IIMs when they do not respond to steroid treatment. In patients with rapidly progressive ILD and anti-MDA-5 antibodies who do not respond to GC and immunosuppressants, it is recommended to add cyclophosphamide, MMF, rituximab to the treatment (combination therapy).
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Rituximab

Rituximab is recommended for the treatment of PM and DM refractory to GC/DMARDs, and in patients with rapidly progressive ILD who do not respond to GC/ immunosuppressants (combination therapy). Rituximab can pass through the placenta to the newborn, so it's generally advised to discontinue the treatment once pregnancy is confirmed, except for cases of severe or life-threatening disease. While the manufacturer recommends against breastfeeding during and after rituximab treatment, it is generally considered safe for breastfeeding in patients with musculoskeletal diseases, as the drug is unlikely to be absorbed by the infant's gastrointestinal tract through breast milk. Limitations for the use of rituximab include infusion related reactions and Progressive Multifocal Leukoencephalopathy.

2.3 Intravenous Immunoglobulin (IVig)

Information on IVig is detailed in the table below[34].

Table 17. Immune Globulin Drug Information

SCIENTIFIC NAME Intravenous Immunoglobulin (IVig)	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	M33
Drug Class	IMMUNOGLOBULINS
Drug Sub-class	IMMUNOGLOBULINS, NORMAL HUMAN
ATC Code	J06BA01
Pharmacological Class (ASHP)	Human immunoglobulin
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	IV use
Dose (Adult) [DDD]*	1 g/kg per day on 2 consecutive days every 4 weeks or 2 g/kg as a single dose every 4 weeks (total monthly dose: 2 g/kg). For patients who develop intolerable adverse effects, some experts give 1 g/kg per day once every 2 weeks. Dosing interval may be lengthened once complete clinical response is achieved
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Limited data available: Children: IV: 1,000 mg/kg/dose once daily for 2 days; Note: If maintenance therapy is required, the dose and frequency should be based on clinical response and doses should not exceed 2,000 mg/kg per treatment course.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	N/A
Prescribing edits*	CU, MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	In severe, life-threatening, or refractory to glucocorticoids or DMARDs treatments IIM, it is advisable to consider using IVIG in combination with other agents.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only rheumatologists and immunologists are the specialists who typically prescribe Intravenous Immunoglobulin (IVIG) for patients with IIM.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	In severe, life-threatening, or refractory to glucocorticoids or DMARDs treatments IIM, it is advisable to consider using IVIG in combination with other agents.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** mild and include headache, fever, chills, and muscle pain. **Most serious:** allergic reactions, kidney dysfunction, and blood clotting problems, aseptic meningitis, or anaphylaxis.
Drug Interactions*	**Category D:** • Pozelimab • Ravulizumab • Live vaccines
Special Population	Use with caution in older patients.
Pregnancy	**Category C:** Human IgG crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum

	concentrations, placental integrity, newborn birth weight, and GA, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester.
Lactation	Breast milk naturally contains immune globulin. The concentration of human immune globulin depends on factors like IgG subclass and the time after giving birth. A study found that a mother with IgA deficiency still provided similar IgA protection in her colostrum compared to mothers without the deficiency. If considering breastfeeding while undergoing immune globulin therapy, it's important to weigh the potential infant exposure risk, the benefits of breastfeeding for the baby, and the advantages of treatment for the mother. Immune globulin is considered safe for breastfeeding according to the manufacturer.
Contraindications	Hypersensitivity to immune globulin or any component of the formulation; IgA deficiency (with anti-IgA antibodies and history of hypersensitivity [excluding Gammagard S/D]); hyperprolinemia (Hizentra, Privigen); hypersensitivity to corn (Octagam 5%); hereditary intolerance to fructose (Gammaplex 5%); infants/neonates for whom sucrose or fructose tolerance has not been established (Gammaplex 5%); hypersensitivity to hyaluronidase, human albumin, or any component of the hyaluronidase formulation.
Monitoring Requirements	Renal function (prior to initial infusion and at appropriate intervals), urine

	output, IgG concentrations, hemoglobin and hematocrit, platelets (in patients with ITP); infusion- or injection-related adverse reactions, anaphylaxis, signs and symptoms of thrombosis, signs and symptoms of hemolysis; blood viscosity (in patients at risk for hyperviscosity); presence of antineutrophil antibodies (if TRALI is suspected); volume status; neurologic symptoms (if AMS suspected); pulmonary adverse reactions; blood pressure (prior to, during, and following infusion); clinical response.
Precautions	Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur (some severe), Aseptic meningitis, hematoma, hypertension, hemolysis, hyperproteinemia. Infusion reactions: Patients should be monitored for adverse events during and after the infusion. Stop administration with signs of infusion reaction (fever, chills, nausea, vomiting, and rarely shock). Risk may be increased with initial treatment, when switching brands of immune globulin, and with treatment interruptions of >8 weeks.
Black Box Warning	Thrombosis may occur with immune globulin products. For patients at risk of thrombosis, administer at the minimum dose and infusion rate practicable and monitor for any signs or symptoms of thrombosis.
REMS	**N/A**

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IIM treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health

(CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for IVig.**

Table 18. Intravenous Immunoglobulin (IVig) HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
IVIG	NICE	N/A
	CADTH[24]	In refractory IIMs, IVig is recommended along with options like rituximab, cyclophosphamide, and abatacept for treating muscle inflammation. For IIM-related skin issues, rituximab in addition to IVig is advised. These recommendations are based on moderate to high-quality evidence from observational studies. In treatment-resistant juvenile IIMs, IVig or rituximab are recommended as additional therapeutic options. In rapidly progressing ILD associated with IIMs, IVig is suggested if there's no response to immunosuppressant treatment.
	HAS[35]	**July 2022** IVig therapies may be proposed as a first-line approach in cases of severe DM with a risk of life-threatening complications, in association with immunosuppressants. If no treatment effect is observed after 6 months, the treatment must be discontinued. If the treatment is effective, it will be continued long-term at the doctor's discretion, based on patient response, and response to the maintenance treatment. Approval of reimbursement for the treatment of active DM treated with immunosuppressants, including corticosteroids, or in cases of intolerance to these medicinal products or contraindications to these medicinal products.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- IVig

IVig, a concentrated form of antibodies derived from pooled human plasma, is utilized for its immunomodulatory properties to alleviate muscle inflammation, particularly in IIMs cases that have proven refractory to conventional treatments. The recommended dosage typically ranges from 1g/kg per day on 2 consecutive days every 4weeks or 2g/kg of body weight over a course of several days, with the specific regimen tailored to individual patient needs. While IVig is generally well-tolerated, potential side effects may include headache, fever, chills, and, in rare cases, more serious reactions such as allergic responses or kidney dysfunction. It is crucial for healthcare providers to monitor patients closely during IVig administration to promptly address any adverse reactions. CADTH and HAS have a positive recommendation about its use in refractory severe dermatomyositis with a risk of life-threatening complications, in association with immunosuppressants.

2.4 Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

2.4.1 Hydroxychloroquine

Information on Hydroxychloroquine is detailed in the table below[36].

Table 19. Hydroxychloroquine Drug Information

SCIENTIFIC NAME HYDROXYCHLOROQUINE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMEA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	M33
Drug Class	DMARDs
Drug Sub-class	Aminoquinoline
ATC Code	P01BA02
Pharmacological Class (ASHP)	Aminoquinoline (Antimalarial)
Dose (Adults)	**Dermatomyositis, cutaneous (off-label use):** Used in combination with antipruritic medications, topical therapy, and

	nonpharmacologic measures (e.g., photoprotection). **Oral:** 300 to 400 mg daily as a single daily dose or in 2 divided doses. Assess response after 3 months.
Maximum Daily Dose Adults	Not > 5 mg/kg/day using actual body weight or 400 mg, whichever is lower.
Dose (pediatrics)	**Juvenile dermatomyositis, skin predominant: Limited data available: Children and Adolescents: Oral:** 5 mg/kg/day in 1 to 2 divided doses. Dosage range reported: 2 to 6 mg/kg/day. Use in combination with nonpharmacologic measures (eg, photoprotection), topical therapies, and/or other systemic therapies.
Maximum Daily Dose Pediatrics	400 mg/day
Adjustment	No renal or hepatic dose adjustments.
Prescribing edits	Age, CU
AGE (Age Edit):	Contraindicated use in children < 6 years
CU (Concurrent Use):	Combination with topical therapies, and/or other systemic therapies (MTX, GC)
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
Main Adverse Drug Reactions (Most common and most serious)	**Most common**: Retinopathy, reversible early changes **Most serious**: Cardiomyopathy, G6PD deficiency, delayed hypersensitivity reactions, Hypoglycemia, Neuromuscular effects, Neuropsychiatric effects, QT prolongation, Retinal toxicity

Drug Interactions	**Category X**: Cimetidine, Mefloquine, Remdesivir
Special Population	No specific recommendations for dosing in older adults. Pediatric patients may have increased sensitivity.
Pregnancy	Hydroxychloroquine can be detected in the cord blood at delivery in concentrations like those in the maternal serum. If pregnancy is detected during therapy, hydroxychloroquine should not be stopped; cessation of hydroxychloroquine could precipitate a flare in maternal disease.
Lactation	Hydroxychloroquine and the Desethylchloroquine metabolite are present in breast milk. In general, breastfeeding is considered acceptable when the relative infant dose is <10%.
Contraindications	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivatives, or any component of the formulation. Additional contraindications (not in the US labeling): Preexisting retinopathy; use in children <6 years or weighing <35 kg.
Monitoring Requirements	CBC (baseline and periodically), renal function tests, and liver function tests. Obtain ophthalmologic exam at baseline and annually after 5 years of use. Assess muscle strength during prolonged therapy. Assess for signs of cardiomyopathy, bone marrow suppression, neuromuscular effects, and retinal toxicity.
Precautions	Use with caution in patients with myasthenia gravis, avoid use in patients with porphyria and/or psoriasis unless

	benefits outweigh risks. Use with caution in renal or hepatic impairment. Use with caution in patients with G6PD deficiency due to a potential for hemolytic anemia.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for hydroxychloroquine in IIMs.

CONCLUSION STATEMENT- Hydroxychloroquine

Hydroxychloroquine is indicated for DM (off-label use) in combination with antipruritic medications, topical therapy, and nonpharmacologic measures such as photoprotection. It is also indicated for juvenile DM, particularly with skin involvement, in children and adolescents. The recommended administration is oral, either alone or in combination with nonpharmacologic measures such as photoprotection, topical therapies, and/or other systemic therapies. Hydroxychloroquine concentrations in cord blood during delivery are comparable to maternal serum levels, and if pregnancy is identified during treatment, discontinuing hydroxychloroquine is not recommended to avoid potential exacerbation of maternal disease. The presence of hydroxychloroquine and its metabolite, Desethylchloroquine, in breast milk is observed, but breastfeeding is generally deemed acceptable as long as the relative infant dose remains below 10%. Hydroxychloroquine is recommended at a dose not exceeding 5mg/kg/real body weight. Limitations for its use include the risk of retinopathy as well as the risk for cardiomyopathy.

Section 3.0 Key Recommendations Synthesis

The key recommendations are listed below along with their respective levels of evidence:

Glucocorticosteroids

1. **Prednisolone**

Prednisolone is the primary choice for treating IIMs, particularly in instances of severe or rapidly progressing symptoms. Typically, it is prescribed at a dosage of 1mg/kg as a once-daily dose until improvement (usually for 4 to 6 weeks), followed by a gradual tapering process (total duration usually 9 to 12 months). In cases where prednisolone alone proves insufficient or concerns arise about potential long-term side effects, additional treatments may be considered. There are currently no recommendations from HTA bodies regarding prednisolone. **Level 1, B, 100%.**

2. **Methylprednisolone**

In cases of severe and profound weakness or when there are worries about the gastrointestinal absorption of methylprednisolone, the administration of intravenous methylprednisolone should be considered. Intravenous administration may result in an enhanced therapeutic effect with a lower risk of toxicity compared to oral GC. The usual prescription involves a daily dosage of 1g for a duration of 5 days, followed by a transition to oral prednisone or prednisolone. Currently, there are no recommendations from HTA bodies for the use of methylprednisolone. **Level 1, B, 100%.**

Immunosuppressant Agents

1. **Azathioprine**

Azathioprine is used for its potential role in managing refractory IIMs and for cases of mild to moderate IIMs, after the initial treatment with GC, as a steroid-sparing therapy. The usual dose is 50mg once daily. Do not exceed 250 mg/day. CADTH HAS: positive recommendations. **Level 1, B, 100%.**

2. **Tacrolimus**

Tacrolimus is recommended as a monotherapy or in combination with GC in patients with GC-resistant disease. It is also recommended for ILD, in combination with steroids as an early part of the induction therapy. The recommended dose is 3 to 5mg/day or 0.1mg/kg/day in 1 or 2 divided doses. CADTH: positive recommendation. **Evidence level V, Grade B.**

3. **Cyclosporine**

Cyclosporine is recommended in combination with GC in patients with GC-resistant disease. It is also recommended for ILD, in combination with steroids as an early part of the induction therapy. The usual dose is 2.5 mg/kg/day in 2 divided doses given every 12 hours (maximum of 5 mg/kg/day). CADTH: positive recommendations. **Level 1, B, 100%.**

4. **Mycophenolate Mofetil**

MMF is indicated in the treatment of mild or moderate IIMs after initial treatment and in juvenile IIMs. Typical dosage starts at 500mg twice daily for 2 weeks, then escalates to 1g twice daily, with a maximum dose of 1.5g twice daily. CADTH: positive recommendation. **Level 2, C, 100%.**

5. **Cyclophosphamide**

In IIMs, cyclophosphamide is used in cases of severe or refractory disease where other treatments have not provided sufficient relief and in patients with rapidly progressive ILD or in juvenile IIMs who are refractory to treatment with GC or methotrexate. The dosage of cyclophosphamide for IIMs can vary, but a common starting dose is 500 mg to 1 gram orally or intravenously, with adjustments based on individual patient response. CADTH and HAS: positive recommendations. **Level 1, B, 100%.**

6. **Methotrexate**

Methotrexate is recommended as an adjunct to GC, or as an alternative initial therapy in patients with IIMs who cannot receive GC. In the case of juvenile IIMs, corticosteroids and MTX as the preferred first-line treatment options. The recommended dose is 7.5 to 15mg once weekly. CADTH: positive recommendation. **Evidence level V, Grade B.**

7. **Rituximab**

Rituximab is recommended for the treatment of PM and DM refractory to GC/DMARDs, and in patients with rapidly progressive ILD who do not respond to GC/ immunosuppressants (combination therapy). Limitations for the use of rituximab include infusion related reactions and Progressive Multifocal Leukoencephalopathy. The usual dose is 1g every 2 weeks for 2 doses. CADTH: positive recommendation.

Immune Globulin

IVig is utilized in IIMs cases that have proven refractory to conventional treatments. The recommended dosage typically ranges from 1g/kg per day on 2 consecutive days every 4weeks or 2g/kg of body weight over a course of several days, with the specific regimen tailored to individual patient needs. CADTH and HAS have a positive recommendation about its use in refractory severe dermatomyositis with a risk of

life-threatening complications, in association with immunosuppressants. **Level 1, B, 100%.**

DMARDs

Hydroxychloroquine

Hydroxychloroquine is indicated for DM (off-label use) in combination with antipruritic medications, topical therapy, and nonpharmacologic measures such as photoprotection. It is also indicated for juvenile DM, particularly with skin involvement, in children and adolescents. The recommended dose is 5mg/kg/day (maximum 400 mg/day). Limitations for its use include the risk of retinopathy as well as the risk for cardiomyopathy.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of IIMs.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
((((((((((Myositis[MeSH Terms]) OR (Myositides[Title/Abstract])) OR (Myopathy, Inflammatory[Title/Abstract])) OR (Muscle Diseases, Inflammatory[Title/Abstract])) OR (Inflammatory Muscle Diseases[Title/Abstract])) OR (Inflammatory Muscle Disease[Title/Abstract])) OR (Muscle Disease, Inflammatory[Title/Abstract])) OR (Inflammatory Myopathy[Title/Abstract])) OR (Inflammatory Myopathies[Title/Abstract])) OR (Myopathies, Inflammatory[Title/Abstract])) OR (Myositis, Proliferative[Title/Abstract])) OR (Idiopathic Inflammatory Myositis[Title/Abstract])) OR (Myopathies, Idiopathic Inflammatory[Title/Abstract])	In the last 5 years	("Myositis"[MeSH Terms] OR "Myositides"[Title/Abstract] OR "myopathy inflammatory"[Title/Abstract] OR "muscle diseases inflammatory"[Title/Abstract] OR "inflammatory muscle diseases"[Title/Abstract] OR "inflammatory muscle disease"[Title/Abstract] OR (("muscle s"[All Fields] OR "muscles"[MeSH Terms] OR "muscles"[All Fields] OR "Muscle"[All Fields]) AND "disease inflammatory"[Title/Abstract]) OR "inflammatory myopathy"[Title/Abstract] OR "inflammatory myopathies"[Title/Abstract] OR "myopathies inflammatory"[Title/Abstract] OR "myositis proliferative"[Title/Abstract] OR "idiopathic inflammatory myositis"[Title/Abstract] OR "myopathies idiopathic inflammatory"[Title/Abstract]) AND (y_5[Filter])	4,461

Appendix C. Levels of Evidence

The eligible papers were evaluated by two assessors using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. Each reference was classified as high (A), moderate (B), or low/very low (C) quality.
Scottish Intercollegiate Guidelines Network (SIGN) process was employed to assess the quality of evidence for each recommendation (graded as A, B, C, or D according to GRADE methodology). The wording, content, strength (strong=1, conditional=2), and supporting evidence quality for each recommendation were subjected to a consensus-building process through face-to-face meetings and online surveys.
The level of agreement for finalized recommendations was determined using a binary voting system, presented as a percentage. Authors were allowed to abstain from voting on areas where they did not feel clinically competent. Only recommendations with an agreement level above 80% were included in the guideline.

Levels of Evidence: Levels of evidence were categorized from (I) systematic review or randomized controlled trial (RCT) meta-analysis to (VI) expert opinion.
Recommendation Grades: Recommendation grades were classified from (A) strongly recommended to (D) recommend against use in clinical practice.

Appendix D. Treatment Algorithms

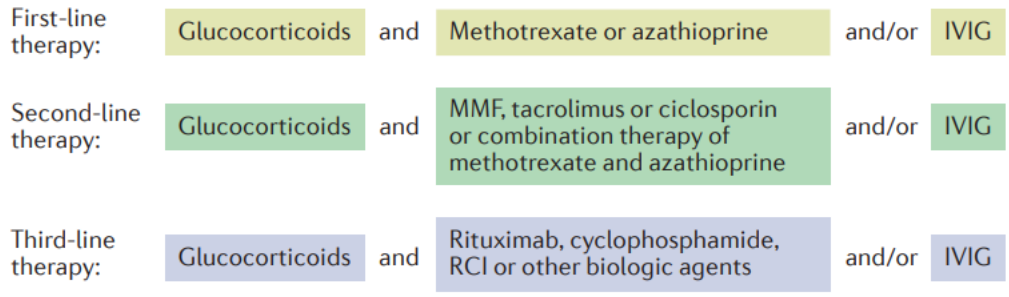

Figure 4. *Overview of pharmacological therapy in idiopathic inflammatory myopathies.*

Retrieved from Oddis C V., Aggarwal R. Treatment in myositis. *Nat Rev Rheumatol*. 2018;14(5):279-289. doi:10.1038/nrrheum.2018.42[37].

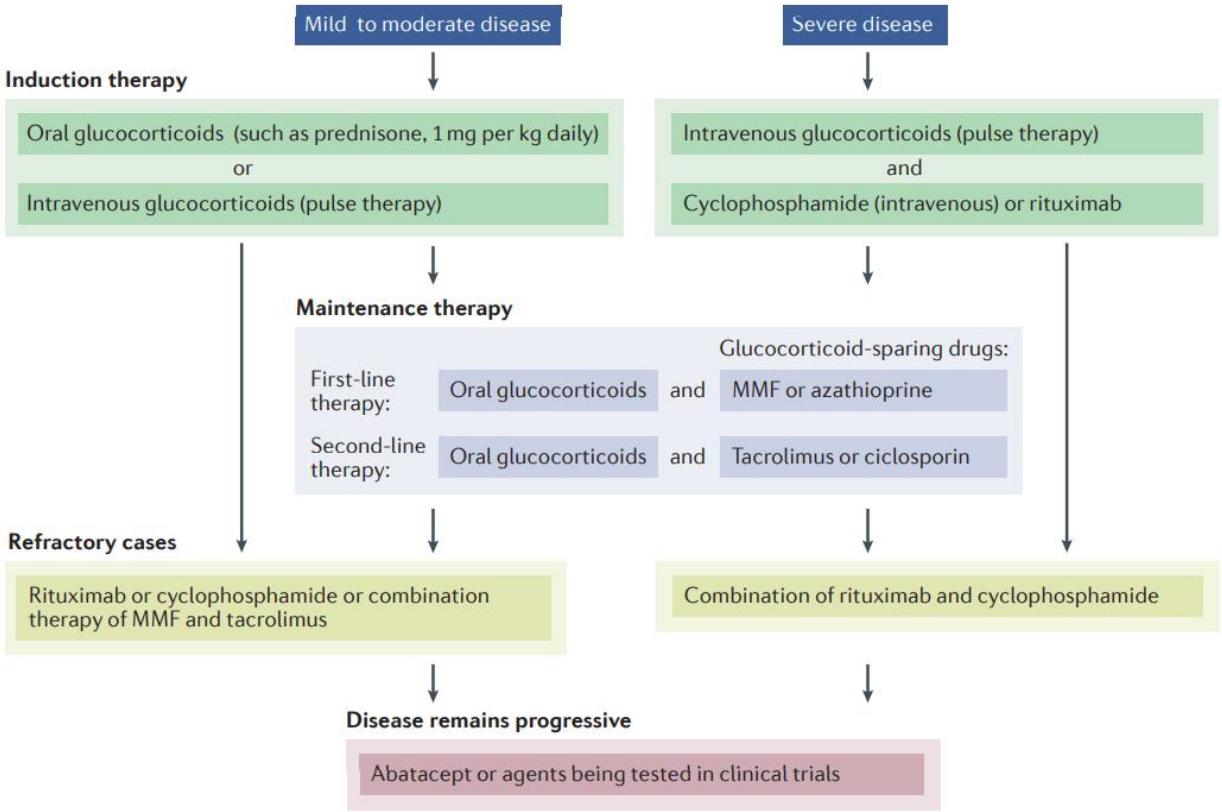

Figure 5. *Proposed approach to treating myositis-associated interstitial lung disease.*

Retrieved from Oddis C V., Aggarwal R. Treatment in myositis. *Nat Rev Rheumatol*. 2018;14(5):279-289. doi:10.1038/nrrheum.2018.42[37].