



Idiopathic inflammatory myopathies

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Abstract | Idiopathic inflammatory myopathies (IIM), also known as myositis, are a heterogeneous group of autoimmune disorders with varying clinical manifestations, treatment responses and prognoses. Muscle weakness is usually the classical clinical manifestation but other organs can be affected, including the skin, joints, lungs, heart and gastrointestinal tract, and they can even result in the predominant manifestations, supporting that IIM are systemic inflammatory disorders. Different myositis-specific auto-antibodies have been identified and, on the basis of clinical, histopathological and serological features, IIM can be classified into several subgroups — dermatomyositis (including amyopathic dermatomyositis), antisynthetase syndrome, immune-mediated necrotizing myopathy, inclusion body myositis, polymyositis and overlap myositis. The prognoses, treatment responses and organ manifestations vary among these groups, implicating different pathophysiological mechanisms in each subtype. A deeper understanding of the molecular pathways underlying the pathogenesis and identifying the auto-antigens of the immune reactions in these subgroups is crucial to improving outcomes. New, more homogeneous subgroups defined by auto-antibodies may help define disease mechanisms and will also be important in future clinical trials for the development of targeted therapies and in identifying biomarkers to guide treatment decisions for the individual patient.

Idiopathic inflammatory myopathies (IIM), also known as myositis, are a heterogeneous group of autoimmune disorders usually characterized by chronic inflammation of the muscle with varying clinical manifestations, treatment responses and prognoses. Muscle weakness, low muscle endurance and myalgia are frequent and shared symptoms but extramuscular manifestations, such as skin rash, arthritis, interstitial lung disease (ILD) and heart involvement, are common, emphasizing the systemic inflammatory nature of these disorders (FIG. 1). In some patients, extramuscular manifestations dominate the clinical picture and muscle weakness may be absent; diagnosing the disease in these patients can be particularly challenging. A major advancement in the field of myositis was the discovery of auto-antibodies that are specific for myositis, called myositis-specific auto-antibodies (MSAs; present in up to 60% of patients with IIM), which are helpful in establishing a diagnosis of IIM¹ (TABLE 1). Furthermore, MSAs are strongly associated with distinct clinical phenotypes and are therefore important to predict organ manifestations and may predict prognosis. In addition, patients with IIM may also have auto-antibodies that are present in other autoimmune disorders such as systemic lupus erythematosus (SLE), systemic sclerosis or Sjögren syndrome. These auto-antibodies are often named

myositis-associated auto-antibodies (MAAs) and the most frequent are anti-Ro52, anti-PM-Scl, anti-Ku and anti-U1RNP. Around 20–30% of patients with IIM have no known auto-antibodies, which can be classified as seronegative IIM².

Historically, polymyositis (PM) was the overarching name for these disorders. In 1863, a disease subgroup with skin rash was identified and named dermatomyositis (DM). A clinical definition of PM and DM was not proposed until the 1950s³. Later, based on clinical and histopathological manifestations of muscle tissue, IIM were categorized into the subgroups DM (juvenile and adult onset), PM, inclusion body myositis (IBM) and amyopathic DM (ADM). The definition of PM has become controversial and varied from the initially clinically defined to one based on specific histopathological features, including the presence of T lymphocytes in the infiltrates, requiring staining of muscle tissue sections by immunohistochemistry⁴. On the basis of MSAs, new subgroups of IIM with distinct clinical manifestations and muscle histopathological features have been identified, which include antisynthetase syndrome (ASyS) in the 1990s and immune-mediated necrotizing myopathy (IMNM) in 2006. Many patients previously classified as having PM fall into these new subgroups, resulting in a decreasing number of patients included in the PM

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subgroup⁵. Additionally suggested subgroups of IIM include cancer-associated myositis and overlap myositis (myositis that coexists with another autoimmune disorder).

Owing to the new observations that auto-antibodies are frequently present in patients with IIM and that some patients may not have lymphocytic infiltrates in muscle biopsy samples, a change of the nomenclature from IIM to systemic autoimmune myopathies has been proposed to better reflect the pathogenesis⁶. However, as this name

change has not yet been widely recognized in the myositis community, we have retained the IIM nomenclature in this Primer.

The diagnosis of IIM and its subgroups is based on a combination of clinical symptoms and signs, including muscle biopsy features, MRI pattern, serological assessment and serum levels of muscle enzymes. Treatment is largely based on high doses of glucocorticoids in combination with other immunosuppressive drugs but treatment responses vary and there is a high unmet need for new therapeutic approaches. Research to date has mainly focused on patients categorized as having DM, PM and IBM. A refined subgrouping of myositis that enables a more homogeneous classification defined by clinical, histopathological and serological data is important to improve understanding of the disease mechanisms that lead to myositis and the extramuscular manifestations to improve treatment and patient prognosis. Furthermore, data from clinical trials are mainly based on the traditional subgroups PM, DM and IBM, emphasizing the need for more clinical trials that include MSA-defined subgroups^{1,7–10}.

In this Primer, we discuss the traditional myositis subgroups recognized in adults, namely DM, ADM, IBM and PM, as well as the newly classified subgroups ASyS and IMNM, focusing on their epidemiology, pathophysiology and diagnosis if data are available. Additionally, we outline the clinical management of IIM and highlight emerging therapeutic options. Finally, we review the pressing questions in the field, suggesting directions for future research.

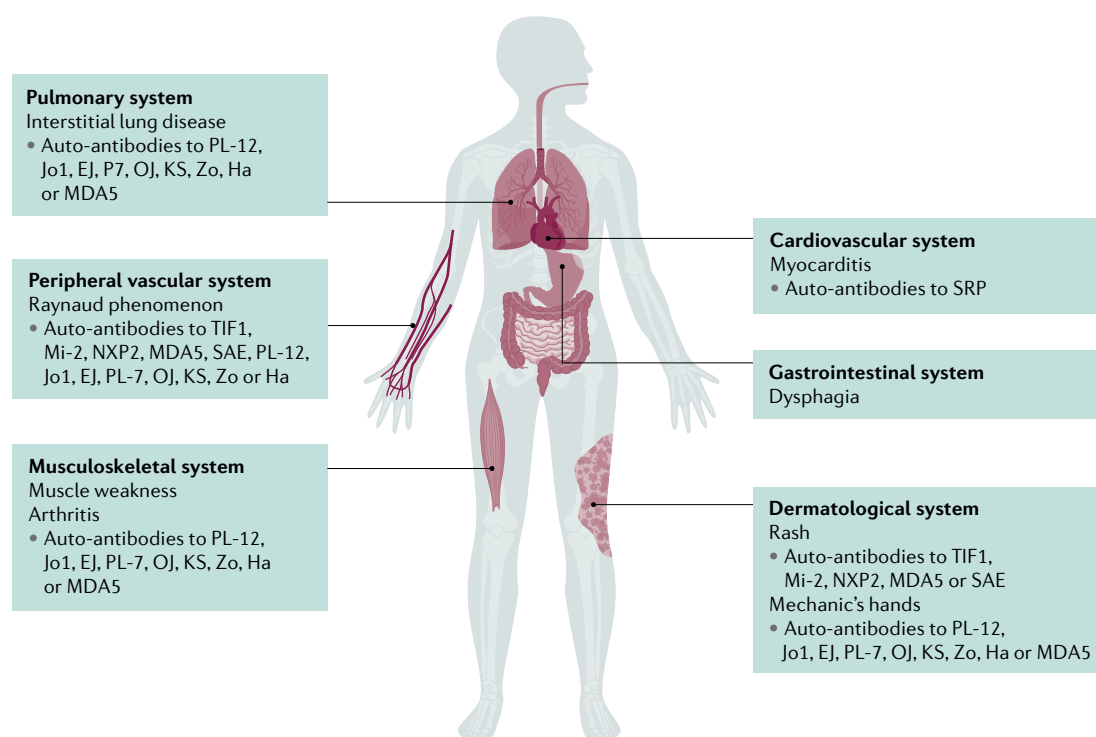


Fig. 1 | Manifestations of IIM. Idiopathic inflammatory myopathies (IIM) exhibit not only myositis but also various extramuscular complications. Some manifestations are strongly associated with the presence of specific circulating auto-antibodies. MDA5, melanoma differentiation-associated gene 5; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1, transcriptional intermediary factor 1.

Table 1 | Main clinical associations of auto-antibodies in adult IIM²⁵⁵

Auto-antibody	Target antigen	Frequency in myositis	Main clinical associations	Indirect immuno-fluorescence pattern on HEp2 cells
Myositis-specific auto-antibodies				
Anti-Jo1	Histidyl-tRNA synthetase	15–30%	ASyS	Cytoplasmic fine speckled
Anti-Ha/YRS	Tyrosyl-tRNA synthetase	<1%	ASyS	Cytoplasmic fine speckled
Anti-Zo	Phenylalanyl-tRNA synthetase	<1%	ASyS	Cytoplasmic fine speckled
Anti-EJ	Glycyl-tRNA synthetase	<2%	ASyS	Cytoplasmic fine speckled
Anti-PL-7	Threonyl-tRNA synthetase	5–10%	ASyS	Inconsistent cytoplasmic dense fine speckled
Anti-OJ	Isoleucyl-tRNA synthetase	<2%	ASyS	Cytoplasmic fine speckled
Anti-KS	Asparaginyl-tRNA synthetase	<2%	ASyS, often only ILD, arthritis	Cytoplasmic fine speckled
Anti-PL-12	Alanyl-tRNA synthetase	<5%	ASyS, often only ILD	Cytoplasmic dense fine speckled
Anti-Mi-2	Nucleosome remodelling deacetylase complex	4–20%	Classical DM	Nuclear fine speckled
Anti-TIF1	Transcriptional intermediary factor 1	10–20%	Only DM, often CDM in adults (40–75%), more severe disease	Nuclear fine speckled
Anti-MDA5	Melanoma differentiation-associated protein 5	13–30%	CADM (ILD), severe skin manifestation	Negative or cytoplasmic
Anti-SAE	Small ubiquitin-like modifier activating enzyme	<10%	Initially classic skin disease, myositis often develops later	Nuclear fine speckled
Anti-NXP2	Nuclear matrix protein 2	3–24%	DM, calcinosis, increased risk of CDM in adults	Nuclear fine speckled, nuclear multiple dots
Anti-SRP	Signal recognition particle	5–15%	IMNM	Cytoplasmic fine speckled
Anti-HMGCR	3-hydroxy-3-methylglutaryl CoA reductase	6–10%	IMNM, often statin associated	Negative
Anti-FHL1 ^a	Four and a half LIM domains 1	5–10%	IIM often with severe muscle involvement	Not known
Myositis-associated auto-antibodies				
Anti-PM-Scl	Human exosome protein complex	8–10%	PM, DM, overlap with scleroderma	Nucleolar homogeneous
Anti-U1RNP	U1 small nuclear RNP	10%	MCTD	Nuclear coarse speckled
Anti-Ku	Regulatory subunit of DNA-dependent protein kinase	<2%	Overlap with scleroderma, ILD	Nuclear fine speckled
Anti-RuvBL1 and anti-RuvBL2 ^a	Nuclear proteins RuvBL1/2	3%	Overlap with scleroderma	Nuclear speckled
Anti-Ro (52, 60)	TRIM21, ring-shaped protein binding Y RNAs	10–40%	Often second auto-antibody present, more severe disease including ILD	Negative or cytoplasmic
Anti-cN-1A	Cytosolic 5'-nucleotidase 1A	4–21%	IBM, pSS, SLE	Negative

Myositis-specific auto-antibodies are found only in patients with IIM and not in other diseases. Myositis-associated auto-antibodies are not specific for IIM and can be detected in other connective tissue diseases such as systemic lupus erythematosus (SLE), primary Sjögren syndrome (pSS) or scleroderma. ASyS, antisynthetase syndrome; CADM, clinically amyopathic dermatomyositis; CDM, cancer-associated dermatomyositis; DM, dermatomyositis; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; MCTD, mixed connective tissue disease; MDA5, melanoma differentiation-associated gene 5; NXP2, nuclear matrix protein 2; PM, polymyositis; RNP, ribonucleoprotein; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1, transcriptional intermediary factor 1; tRNA, transfer RNA. ^aDetection not routinely available.

Epidemiology

Studying the distribution and determinants of inflammatory myopathies is challenging, partly owing to the difficulty in identifying relevant disease entities representative of inflammatory myopathies in population-based data. Studies based on clinical cohorts from university hospitals, where severe cases of IIM are usually monitored, or studies based on biopsy-verified IIM could be underestimating the true incidence and prevalence. By contrast, register-based studies including all types of health care could be overestimating the true incidence and prevalence as the potential for misclassification is increased among physicians who are not specialized in IIM. A limitation of register-based epidemiological studies to date is the lack of specific International Classification of Diseases (ICD) codes and changing classification systems for the new subgroups of IIM. For example, patients with ASyS and IMNM are often coded with ICD codes for PM.

Incidence and prevalence

A wide range of estimates of incidence and prevalence as well as of risk factors for disease have been published. Globally, albeit with a majority of studies from Asia, Europe and North America, the incidence estimates range from 11 to 660 patients with newly diagnosed IIM per 1,000,000 person-years^{11–14} and between 2.9 and 34 individuals per 100,000 population are suggested to have the disease^{15–17}. There are no clear signals suggesting differences in incidence and prevalence across different regions or ethnicities but a north-to-south gradient has been suggested in both Europe and North America, with a higher prevalence of the subtype DM closer to the equator^{18,19}. All available data suggest that PM, DM and IMNM are more common in women than in men^{16,17,20,21} and that IBM is more common in men^{22–24}. The incidence increases with age and the peak age of incidence is ~50 years of age in both Europe²⁰ and North America^{11,20}.

Environmental risk factors

A few environmental factors have been associated with IIM, of which several are infectious agents, suggested on the basis of data from animal models and clinical observations. These observations include the co-occurrence of hepatitis B virus infection in PM²⁵ as well as infection with HIV or human T cell leukaemia virus type 1 (HTLV1) as triggers for PM²⁶, DM and IBM^{27,28}. In small observational studies that have not been reproduced, hepatitis C virus infection has been associated with IBM²⁹ and gastrointestinal and lower respiratory infections have been suggested as risk factors for IIM (primarily PM or DM), whereas upper respiratory tract infections have been suggested to lower the risk of disease^{30,31}. Of note, seasonality has been observed in the birthdates³² and onset^{33,34} of some clinical and auto-antibody groups. Additionally, an increase was observed in autoimmune diseases, including myositis, in World Trade Center prolonged rescue and recovery workers³⁵. Extensive physical exertion has been suggested as a risk factor for PM and DM in a small case-control study³⁰. Other important findings include

no association with vaccines and PM and DM³⁰, an association of exposure to UV radiation with the development of DM³⁶ and an association of smoking with anti-Jo1 auto-antibody-positive ASyS³⁷.

Genetic risk factors

The major genetic risk factors are involved in immune regulation and the strongest associations have been identified in the HLA region. In a study by the Myositis Genetics Consortium, in which >2,500 patients mainly of European ancestry with inflammatory myopathies were included, a strong association was noted among the alleles of the 8.1 ancestral haplotype and PM and DM³⁸. In addition, a few non-HLA loci have been associated with inflammatory myopathy in European populations: *STAT4*, *TRAF6* and *UBE2L3* with IIM overall³⁹, *PTPN22* with PM⁴⁰, *PLCL1* and *BLK* with DM⁴¹, and *CCR5* with IBM⁴².

Mortality

The mortality estimates also show large variations; 10-year survival rates vary between 20% and 90%^{43–51} in studies from Europe, North America and Japan, depending on study design and patient selection. In a large population-based cohort study in southern parts of Norway that compared death rates in 326 patients with IIM diagnosed between 2003 and 2012 with death rates in the general population⁴⁸, the mortality ratio was 2.4, 2.6 and 1.7 for PM, DM and IBM, respectively, compared with the general population. A subsequent study suggested that the overall mortality in IIM is highest during the first year after diagnosis and then decreases, whereas mortality in the general population was increasing during the >10-year follow-up period⁵². The reason for this development is yet unknown. The main causes of death in patients with IIM were malignancies, cardiovascular diseases and lung diseases⁵², although it could be speculated that deaths occurring shortly after diagnosis are due to factors related to IIM, for example, rapidly progressive ILD, and that later deaths are due to factors such as malignancy.

Mechanisms/pathophysiology

As with other types of autoimmunity, IIM phenotypes are thought to develop as a result of interactions between genetic and environmental risk factors in the relative absence of protective factors⁵³. Although our understanding of these processes is limited, it seems that both adaptive and innate immune mechanisms and non-immune mechanisms are involved, to a varying extent, in the different types of IIM. Of note, early pathological observations were made in patients diagnosed as having PM; however, many of these patients would now be classified as having IMNM or ASyS instead. Emerging data now suggest that various risk factors result in each of the major clinical and myositis auto-antibody-defined phenotypes, which also differ in many clinical features, responses to therapy and outcomes; hence, it seems that the pathogenic pathways differ between the various phenotypes. Thus, it is appropriate to focus the discussion of pathogenesis on the major IIM phenotypes DM, ASyS, IMNM, IBM and PM, for which most information is

currently available. Owing to the heterogeneity of overlap myositis, the pathogenesis of this subgroup is not discussed in this Primer. Importantly, each of the subtypes has a different spectrum of target tissues: IMNM and IBM predominantly affect skeletal muscle, whereas DM and ASyS are multiorgan diseases, which also often affect the skin, lungs and/or joints. In addition, IMNM and IBM muscle biopsy samples have characteristic histopathological features that enable distinction from DM or ASyS samples. Furthermore, although DM and ASyS muscle samples share histological similarities, such as prominent perifascicular involvement, transcriptomic analyses have revealed that each has a unique gene expression profile. For example, the expression of type 1 interferon-inducible genes is markedly higher in DM than in ASyS^{54,55}. Indeed, transcriptomic data alone can be used to identify a muscle biopsy sample from a patient with DM, ASyS, IMNM or IBM with >90% accuracy⁵⁶.

Dermatomyositis

Although certain genetic and environmental factors have been associated with adult-onset DM, the trigger of autoimmunity in patients with DM remains unclear. Similarly, the mechanisms of underlying autoimmunity remain obscure. Indeed, within muscle tissue, whether muscle cells, blood vessels and/or connective tissue are directly targeted by the immune system remains to be shown. Nevertheless, perifascicular myofibre abnormalities, including atrophy and necrosis, are typical histological features of muscle specimens from patients with DM (and may also be seen in some patients with ASyS). By contrast, myofibre necrosis and inflammation are distributed evenly throughout muscle fascicles in IMNM and IBM, respectively. One detailed histological study of DM muscle specimens revealed that endomysial capillaries in regions of perifascicular atrophy are reduced in number and size and that the remaining endothelial cells stain positive for components of the activated membrane attack complex⁵⁷. However, whether membrane attack complex deposition is a cause or effect of endothelial cell damage in DM is not clear. Of note, the abnormal perifascicular regions are preferentially located near areas of perimysium with infiltrating inflammatory cells and remnants of blood vessels but no intact intermediate-size vessels. Taken together, these observations raise the possibility that immune-mediated vascular damage may cause myofibre and capillary damage in regions of the endomysium that are most distant from an intact vascular supply.

It remains unclear how intermediate-size blood vessels in the perimysium are damaged and destroyed in patients with DM. Nevertheless, plasmacytoid dendritic cells, which are potent sources of interferon, may be found surrounding these vascular structures⁵⁸. Furthermore, type 1 interferon-inducible genes are among the most upregulated in the muscle⁵⁸, skin⁵⁹ and peripheral blood^{60,61} of patients with DM, further supporting a role for type 1 interferon in DM pathophysiology. This finding may help explain why JAK–STAT inhibitors, which target this pathway, are effective in treating DM-related damage in skin⁶², muscles⁶² and lungs⁶³.

Of note, most of the DM studies referenced above did not perform sub-analyses controlling for DM-specific auto-antibody status. As it is now appreciated that each DM-specific auto-antibody is associated with unique clinical manifestations, histological features⁶⁴ and transcriptomic profiles⁵⁶, grouping these entities together may be a limitation of these studies.

Antisynthetase syndrome

ASyS is characterized by auto-antibodies against one of many aminoacyl transfer RNA (tRNA) synthetases. As with most other forms of myositis, some genetic and environmental associations have been made with ASyS but what specifically triggers this immune response remains unclear. One of the first examples of adaptive immune mechanisms involving antigen-driven B cell responses in myositis was the finding that anti-Jo1 auto-antibodies directed against histidyl-tRNA synthetase arose months before clinical disease and, in addition to spectrophototype broadening and class switching, underwent affinity maturation to that antigen⁶⁵. Subsequent findings suggested that anti-Jo1 auto-antibodies bound common autoepitopes, changed in titre with disease activity and were therefore modulated by an immune response closely linked to that responsible for myositis⁶⁶.

Muscle biopsy samples from patients with ASyS more often include areas of perifascicular necrosis than those from patients with DM (79% versus 35%)⁶⁷. In addition, ASyS samples include endomysial infiltration by clonally expanded T cells⁶⁸, as observed in IBM. Interestingly, CD4⁺ T cells with reactivity against histidyl-tRNA synthetase are present in both blood and lungs of patients with ASyS⁶⁹. Taken together, these observations suggest that the immune response in ASyS may be directed against endothelial cells, muscle cells and lung tissue. Of note, the finding that mice immunized with histidyl-tRNA synthetase develop antisynthetase auto-antibodies along with muscle and lung infiltration⁷⁰ corroborates the possibility that an immune response against aminoacyl-tRNA synthetase proteins is associated with muscle and lung damage in patients with ASyS.

Most studies referenced above did not perform sub-analyses controlling for DM-specific rashes and therefore included patients traditionally defined as having PM or DM, who seem to have different risk factors and outcomes; hence, grouping these entities together may be a limitation of these studies.

Immune-mediated necrotizing myopathy

Patients with IMNM most often have auto-antibodies recognizing either 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) or the signal recognition particle (SRP). The HLA class II DRB1*11:01 allele is present in >70% of patients with IMNM and anti-HMGCR auto-antibodies but only in <20% of the general population⁷¹. Thus, DRB1*11:01 is one of the stronger known immunogenetic risk factors for developing an autoimmune disease. In addition, the use of statin medications is known to predispose individuals to developing anti-HMGCR-positive myositis⁷². As HMGCR

is upregulated in muscle and other tissues in response to statin exposure, it has been hypothesized that the increased expression and/or conformational changes of this protein caused by statins may contribute to breaking tolerance in genetically susceptible individuals, who then develop a necrotizing myopathy.

Muscle specimens from patients positive for auto-antibodies against HMGR and SRP are histologically indistinguishable. Furthermore, gene expression profiles from these two types of IMNM show only minor differences⁵⁶. Thus, the mechanisms underlying muscle damage in each of these IMNM subtypes may be similar, if not identical.

The observation that both anti-SRP and anti-HMGR auto-antibody titres are highly correlated with muscle weakness and elevated levels of creatine kinase, which is released into the bloodstream from damaged muscle fibres, is consistent with their pathological role in the disease process^{73,74}. Additional evidence has been provided by studies showing that SRP and HMGR proteins are localized to the muscle cell membrane surface⁷⁵, that anti-SRP and anti-HMGR auto-antibodies bind to the surface of cultured muscle cells⁷⁵, and that membrane attack complex (which can be activated by antibodies) is observed on the surface of non-necrotic muscle fibres in IMNM muscle specimens⁷⁶. Most importantly, one study showed that the passive transfer of anti-SRP or anti-HMGR auto-antibodies into immunodeficient mice caused myofibre necrosis and weakness that are dependent on an intact complement system⁷⁷. Given the strength of evidence that auto-antibody-mediated complement activation may cause muscle damage in IMNM, a phase II multicentre placebo-controlled trial of a C5 complement inhibitor was conducted in patients who were positive for anti-SRP and anti-HMGR⁷⁸. Surprisingly, the complement inhibitor did not improve creatine kinase levels, muscle strength or other relevant outcome measures in patients with IMNM⁷⁹. Consequently, the pathophysiological mechanisms underlying muscle damage in IMNM remain to be elucidated.

Inclusion body myositis

Evidence that IBM is an autoimmune disease includes the presence of predisposing immunogenetic risk factors⁸⁰, a large number of antibody-secreting plasma cells within IBM muscle tissue⁸¹, and the frequent occurrence of auto-antibodies recognizing the NT5C1A protein in the blood of patients with IBM^{82,83}. Furthermore, the observation that cytotoxic CD8⁺ T cells surround and invade muscle fibres in IBM muscle specimens provided early evidence that muscle damage could be mediated by T cells^{84–86}. Indeed, subsequent studies revealed that CD8⁺ T cells are clonally expanded in muscle tissue^{87,88} and that the same clones are found in both blood and multiple muscles from the same patient, where they persist^{89–91}. Although the T cell targets remain unknown, these findings suggest that T cell stimulation by the relevant auto-antigen persists for years in these patients. Interestingly, some of the T cell clone identities are shared between different patients with IBM, suggesting a common as yet undefined target auto-antigen among those with IBM⁶⁸. Importantly, studies showed that both CD4⁺

and CD8⁺ T cells in patients with IBM have unusual properties, including aberrant loss of CD28 or CD5 expression with the gain of CD16, CD94 and CD57 expression that is associated with terminally differentiated T cells^{92,93}. Phenotypically similar to the abnormal lymphocytes seen in patients with T cell large granulocytic leukaemia, the infiltrating T cells in IBM would also be expected to have increased cytotoxic potential and resistance to apoptosis. These features may help explain why IBM is refractory to glucocorticoids and other immunomodulatory therapies but this population of T cells could also be a promising target for therapeutic intervention.

In addition to the invasion of myofibres by CD8⁺CD57⁺ T cells, IBM muscle specimens are notable for the presence of rimmed vacuoles and protein inclusions within muscle fibres. For example, in one study, aggregates of p62 and TDP43 proteins were found in 12% of IBM myofibres but only rarely in those of other IIM subtypes⁹⁴. Although other reports suggest that p62 accumulation may be a non-specific feature of IIM^{95–97}, TDP43 positivity is recognized as highly specific for IBM⁹⁸. Hence, IBM might have a considerable degenerative component but it has not been shown whether the accumulation of these proteins would lead to muscle cell degeneration. Furthermore, it remains unclear whether these changes occur in response to intensive immune-mediated damage or reflect some other underlying non-immune pathological process.

Polymyositis

PM could be defined as a myositis phenotype with chronic muscle weakness without skin involvement and involving predominant cytotoxic T cell mechanisms. During the past two decades, it has become clear that PM has been over-diagnosed⁹⁹ and that most patients previously diagnosed with PM can now be classified as having IBM, IMNM, ASyS or genetic muscle disease; however, some patients with IIM do not have DM, ASyS, IBM, IMNM or myositis auto-antibodies and have the classic clinical and pathological findings of PM⁵. These patients, although now a small subgroup of those with IIM, are therefore appropriately classified as PM by currently accepted criteria^{8,100}. However, most historical studies of PM included samples from patients now classified as IMNM and ASyS without a rash, diseases now recognized to be pathologically distinct from each other. Thus, future studies will be required to define the risk factors and mechanisms underlying muscle inflammation and damage more completely in PM.

Diagnosis, screening and prevention

Clinical subgroups

Dermatomyositis. DM is defined by the presence of characteristic cutaneous manifestations and myositis. While muscle and skin involvement coexist in the prototype of DM (classic DM), DM can exist without muscle disease (ADM) or overt muscle symptoms despite evidence of myositis on laboratory testing (hypomyopathic DM)¹⁰¹. ADM and hypomyopathic DM are defined when the conditions last for ≥ 6 months and are collectively termed as clinically ADM (CADM)¹⁰¹. Skin manifestations in CADM are identical to those in classic DM.

Patients with CADM can still have systemic involvement such as ILD and dysphagia. Conversely, patients who have no rash but have muscle disease with classic histopathological features of DM on muscle biopsy have been described as having DM sine dermatitis¹⁰². Malignancy is occasionally associated with DM (cancer-associated DM) but can also occur in other forms of IIM^{103–105}.

Most patients with DM have one of the MSAs, anti-Mi-2 (REF¹⁰⁶), anti-melanoma differentiation-associated gene 5 (MDA5)^{107,108}, anti-transcriptional intermediary factor 1 (TIF1)^{109,110}, anti-nuclear matrix protein 2 (NXP2)¹¹¹ or anti-small ubiquitin-like modifier activating enzyme (SAE)¹¹² antibodies (TABLE 1). These auto-antibodies are closely associated with distinct clinical phenotypes, leading to the proposal to subclassify DM into six different subtypes — anti-Mi-2 DM, anti-MDA5 DM, anti-TIF1 DM, anti-NXP2 DM, anti-SAE DM and auto-antibody-negative DM^{7,8,113,114} (FIGS 2,3). Patients with anti-Mi-2 or anti-NXP2 DM tend to have prominent myositis, whereas it is milder, often asymptomatic, in those with anti-MDA5, anti-TIF1 or anti-SAE DM. These different subtypes of DM also have associations with characteristic rashes in addition to the severity^{115,116}.

Anti-Mi-2 is associated with the classic DM phenotype with high creatine kinase levels, good response to treatment and good prognosis, although relapses often occur. ILD is rare in anti-Mi-2 DM.

Patients with anti-MDA5 DM typically have mild muscle disease or no muscle disease (ADM). Anti-MDA5 DM is strongly associated with ILD in most regions and ethnicities^{108,117}. Rapidly progressive types of ILD with poor prognosis tend to occur especially in Asia. Patients often have characteristic cutaneous manifestations, including palmar papules and deep ulcerations over joints. Arthritis is also common.

Anti-TIF1 DM is characterized by extensive rash and relatively mild myositis, whereas dysphagia is frequent and sometimes severe. Anti-TIF1 DM is associated with a high risk of malignancy^{109,118,119}. Patients with anti-NXP2 DM tend to have prominent muscle disease. By contrast, cutaneous manifestations are relatively modest and pathognomonic rash may be absent in some patients (DM sine dermatitis). Patients with anti-NXP2 DM have an increased risk of calcinosis. Subcutaneous oedema is also characteristic. Anti-NXP2 DM has also been reported to have a high risk of malignancy^{109,118,119}, although this remains controversial.

In patients with anti-SAE DM, skin manifestations usually precede muscle manifestations¹²⁰. Rash may become extensive and dysphagia is common¹²⁰. Patients may have mild ILD^{121,122}. An association with malignancies has also been reported¹²².

Antisynthetase syndrome. Antisynthetase auto-antibodies bind to and inhibit the function of aminoacyl-tRNA synthetases¹. To date, eight auto-antibodies have been identified in patients with ASyS (TABLE 1). ASyS is a relatively homogeneous but multisystem disease⁶⁶ (FIG. 4) and is usually classified as IIM, although myositis is not always present¹²³. Instead, ILD, usually chronic but often progressive, is the most frequent manifestation. Patients with ASyS and anti-PL-7 or anti-PL-12 auto-antibodies

have a higher rate of ILD and higher mortality than those with anti-Jo1 auto-antibodies^{124,125}.

Immune-mediated necrotizing myopathy. IMNM is characterized by proximal muscle weakness, with symmetrical distribution, extremely high muscle enzyme serum levels, a myopathic electromyography pattern, and muscle specimens showing necrosis or regeneration with minimal lymphocytic infiltrates⁹ (FIG. 5). Patients only rarely have prominent systemic manifestations such as rash, arthritis or ILD. IMNM is not a homogeneous entity and three subgroups are recognized: anti-HMGCR⁵¹, anti-SRP¹²⁶ and auto-antibody-negative IMNM, in which myopathy associated with malignancy or induced by drugs or toxins needs to be excluded¹²⁷.

Patients with anti-SRP myopathy tend to have more severe muscle disease and extramuscular manifestations, including cardiac involvement and dysphagia, than those with anti-HMGCR myopathy¹²⁸.

Patients with anti-HMGCR myopathy have predominantly skeletal muscle disease with variable but mostly severe muscle weakness, without other organ manifestations. HMGCR is the pharmacological target of statin medications and anti-HMGCR myopathy is associated with statin use but can also be found in individuals without previous statin use¹²⁸.

Auto-antibody-negative IMNM remains poorly described but has been reported to be characterized by frequent occurrences of associated connective tissue disorders, especially systemic sclerosis, and substantially higher rates of extramuscular manifestations than seen in patients with seropositive IMNM¹²⁹.

Inclusion body myositis. IBM is clinically characterized by asymmetrical weakness of both proximal and distal muscles that often includes the quadriceps and long finger flexors¹³⁰ (FIG. 6). IBM occurs mainly in individuals >50 years of age. Dysphagia occurs in >50% of patients, whereas other extramuscular manifestations are rare. Hallmarks of muscle histopathological findings include endomysial T cell infiltrates and vacuoles rimmed by membranous cytoplasmic material¹³¹. IBM can be associated with Sjögren syndrome and other connective tissue diseases²⁴. The co-occurrence of IBM with sarcoid myopathy has also been reported¹³². IBM progresses slowly over decades and does not usually respond to immunosuppressive therapy.

Polymyositis. PM is defined by inflammatory disease in the proximal muscles, endomysial infiltrates of CD4⁺ and CD8⁺ T cells on muscle specimens, and absence of skin involvement. However, PM is now considered a rare form of IIM^{8,10,133}. Most patients previously diagnosed with PM are currently classified as having ASyS, IMNM, IBM or overlap myositis and, on the basis of this reclassification, no specific auto-antibody is associated with PM.

Overlap myositis. Myositis can occur together with other connective tissue diseases, such as SLE, systemic sclerosis, Sjögren syndrome or rheumatoid arthritis^{8,134,135}. Overlap myositis is a heterogeneous subgroup, as clinical

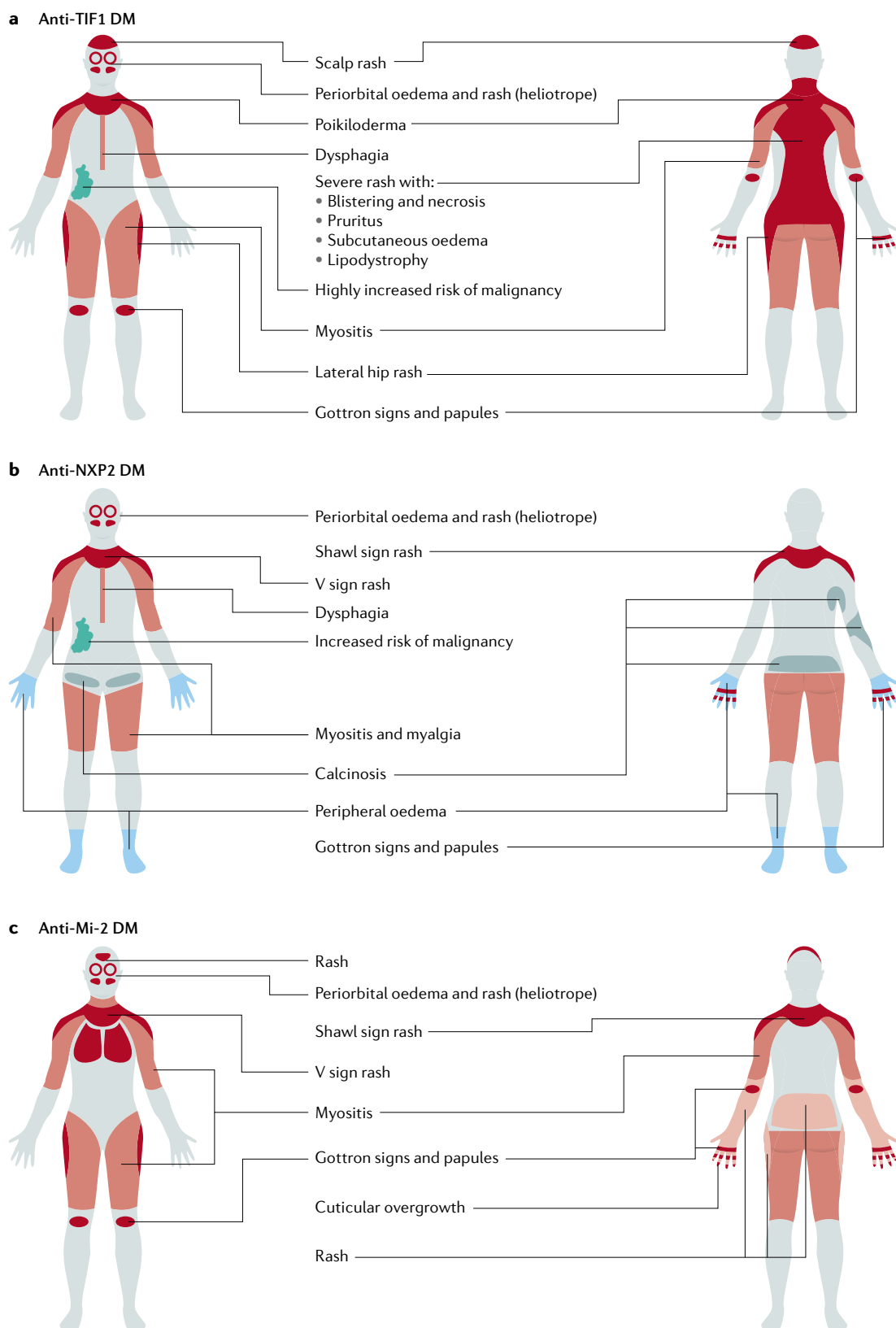


Fig. 2 | Clinical manifestations in patients with DM and anti-TIF1, anti-NXP2 and anti-Mi-2 auto-antibodies. Dermatomyositis (DM), including amyopathic DM, is one of the classical subgroups of idiopathic inflammatory myopathies. DM can be further subclassified based on specific auto-antibodies, which demonstrate various characteristic manifestations such as the distribution of muscle weakness and extramuscular manifestations. **a** | Anti-transcriptional intermediary factor 1 (TIF1) DM. **b** | Anti-nuclear matrix protein 2 (NXP2) DM. **c** | Anti-Mi-2 DM.

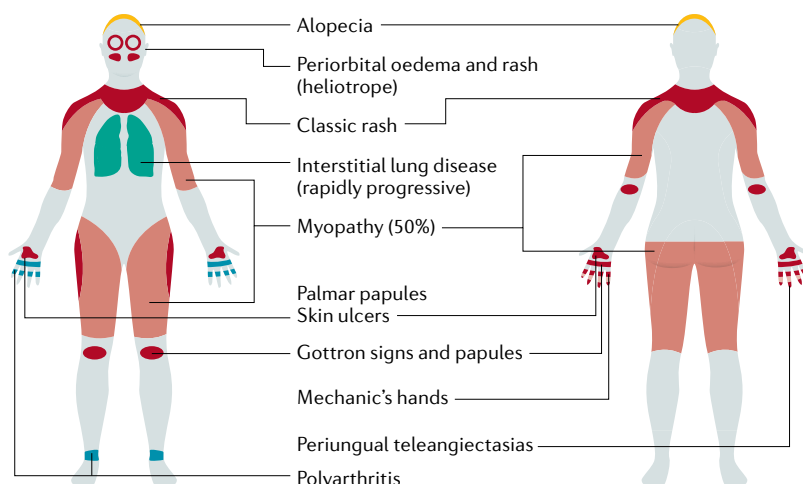
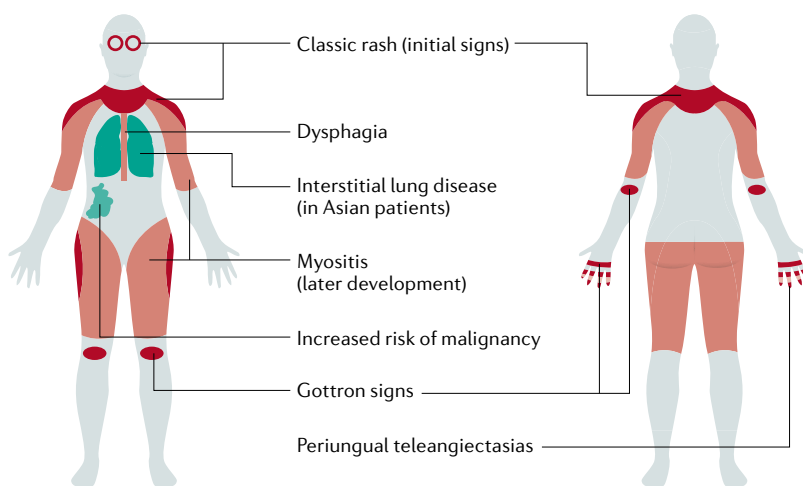
a Anti-MDA5 DM**b Anti-SAE DM**

Fig. 3 | Clinical manifestations in patients with DM with anti-MDA5 and anti-SAE auto-antibodies. Dermatomyositis (DM), including amyopathic DM, is one of the classical subgroups of idiopathic inflammatory myopathies. DM can be further subclassified based on specific auto-antibodies, which demonstrate various characteristic manifestations such as distribution of muscle weakness and extramuscular manifestations. **a** | Anti-melanoma differentiation-associated gene 5 (MDA5) DM. **b** | Anti-small ubiquitin-like modifier activating enzyme (SAE) DM.

and histological findings vary. Auto-antibodies detected in overlap myositis include anti-U1RNP, anti-Ku, anti-PM-Scl, anti-RuvBL1 and anti-RuvBL2 (REF.¹³⁶), anti-Ro/SS-A and anti-La/SS-B auto-antibodies. Patients who have features of scleroderma and myositis are referred to as having scleromyositis. Head drop and distal weakness are common and an increased rate of extramuscular manifestations are found in those without scleroderma-associated auto-antibodies. These patients have variable histopathological findings, including necrotizing myopathy¹³⁷.

Clinical presentation

The most typical symptom to suspect IIM is proximal muscle weakness with a symmetrical distribution, sometimes accompanied by pain. Muscles in the upper and

lower extremities can be involved with hip and thigh muscles being affected most often. Neck muscles, most typically flexors but sometimes also extensors, can be involved. The onset can be acute, subacute or chronic. Patients complain of difficulty getting up from a seated position, climbing steps, or raising their arms or head. Serum levels of creatine kinase and aldolase as well as of lactate dehydrogenase and aspartate transaminase are often elevated. Abnormal electrical activities of muscle fibres, signs of muscle oedema or immune-mediated changes in histopathological specimens can be detected by electromyography, imaging and muscle biopsy. In DM and ASyS, muscle involvement can be lacking. Many patients can have extramuscular symptoms as part of the presenting symptoms, particularly skin rash, (poly)arthritides and ILD.

Extramuscular manifestations

Skin manifestations. In DM, pathognomonic or highly characteristic skin lesions include periorbital violaceous erythema often associated with oedema (heliotrope rash), erythematous to violaceous papules (Gottron papules) and macules (Gottron sign) overlying the extensor surfaces of joints¹¹⁶. Moreover, periungual nailfold erythema with cuticular punctate haemorrhage is frequently observed. Erythema over lower anterior neck and upper chest (V sign) and over posterior shoulders, neck and upper back (shawl sign) are also characteristic. These skin changes can result in poikiloderma, which involves a concurrence of hyperpigmentation, hypopigmentation, telangiectasia and superficial atrophy. Pruritus is also an important symptom. Patients with anti-MDA5 DM frequently develop ulcerations over the joints and palmar papules^{138,139}. Anti-TIF1 DM and anti-SAE DM are associated with extensive skin involvement^{122,140}. Non-pruritic, hyperkeratotic eruptions on the lateral surfaces of the digits, called mechanic's hands, are the hallmark skin feature in patients with ASyS but are also seen in those with DM and in patients with anti-PM-Scl auto-antibodies. In patients with DM and more frequently in juvenile DM, abnormal depositions of insoluble calcium salts can be found in skin and subcutaneous tissue¹⁴¹. Calcinosis occurs more frequently in sites subjected to microtrauma and is most frequently present in anti-NXP2 DM.

Histological findings in DM skin specimens include interface dermatitis with dyskeratosis, dermal mucin deposition, perivascular inflammatory infiltrates, and vascular dilatation and/or damage¹¹⁶, although these findings are indistinguishable from those in SLE. A skin biopsy is recommended in patients without muscle involvement (CADM)^{100,116}.

Pulmonary involvement. ILD is found in up to 78% of patients with IIM, typically in patients with ASyS and anti-MDA5 DM^{142,143}. The most clinically alarming form is acute rapidly progressive ILD (RP-ILD) associated with anti-MDA5 auto-antibodies, which can develop into adult respiratory distress syndrome and respiratory failure and has a poor prognosis. High-resolution CT shows peribular opacities that progress rapidly to ground glass consolidations and, in later stages, traction

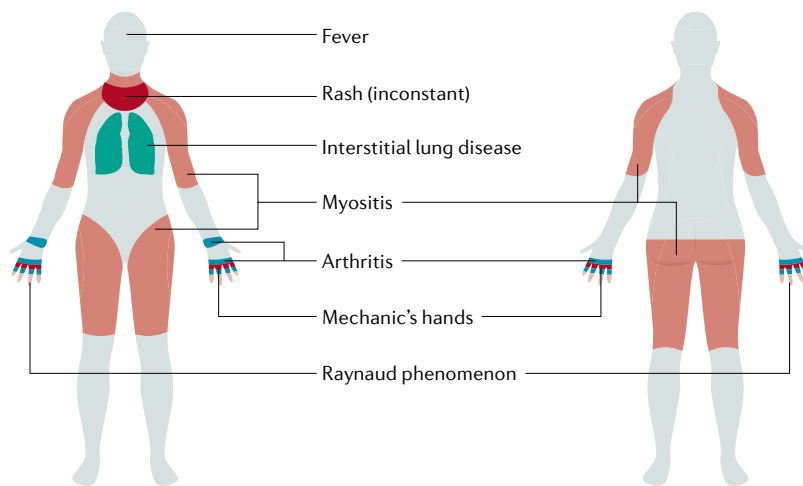


Fig. 4 | Clinical manifestations of antisynthetase syndrome. Antisynthetase syndrome is characterized by the presence of one of the eight known auto-antibodies against aminoacyl transfer RNA (tRNA) synthetases. The frequency and combination of symptoms vary according to the type of aminoacyl-tRNA synthetase auto-antibody. Some patients can have only lung disease with no muscle involvement.

bronchiectasis. Consolidation in the lower lung zones of high-resolution CT findings is particularly related to RP-ILD¹⁴⁴. Some patients with ASyS who have the high-resolution CT pattern combining organizing pneumonia plus non-specific interstitial pneumonia can develop RP-ILD but, usually, ILD is less severe and RP-ILD considerably less frequent in patients with ASyS than in those positive for anti-MDA5 (DM). In general, a non-specific interstitial pneumonia pattern on CT is a favourable prognostic factor for patients with IIM. Most patients with ILD in IIM have subacute or chronic courses. ILD may even be asymptomatic or occult and can have a reasonable response to treatment, which also includes ILD in patients with anti-PM-Scl or anti-SAE auto-antibodies.

Cardiac involvement. Heart involvement comprises myocarditis, inflammatory infiltration in the cardiac conduction system and replacement fibrosis¹⁴⁵. Only ~10% of patients with IIM have clinically overt cardiac disease; subclinical involvement is more frequent (up to 75% of patients). The initial description that cardiac involvement was more common in patients positive for anti-SRP auto-antibodies is now controversial but those with overlap myositis and systemic sclerosis are more likely to be affected²¹. Cardiac MRI is a sensitive technique that can detect inflammation in the myocardium or irreparable changes very early, even when no symptoms are present¹⁴⁶. Serum cardiac troponin I is a sensitive and specific measure of cardiac involvement, whereas troponin T levels may be elevated also owing to inflammation in non-cardiac striated muscles¹⁴⁷.

Oesophageal involvement. It can be argued whether dysphagia should be regarded as a muscle manifestation or an extramuscular manifestation. Dysphagia occurs in up to 60% of patients with myositis and is especially prevalent in IBM^{21,148}. It may be caused by muscle weakness in the pharyngeal muscles or in the upper portion of the oesophagus and may occasionally be very severe,

preventing the ability to swallow liquids. Dry mouth as in patients with secondary Sjögren syndrome may also contribute to dysphagia. Dysphagia is a risk factor for aspiration pneumonia.

Joint involvement. Arthritis is commonly found in patients with IIM, particularly in those with ASyS^{21,149}. In some patients, it may be a presenting symptom and, because it is usually symmetrical and affects small joints of the hands, it can initially be misdiagnosed as rheumatoid arthritis. In some cases, arthritis may be a dominant symptom in ASyS.

Diagnosis

Diagnosis of myositis is made when typical clinical and laboratory parameters are present and other possible causes are excluded. However, formal diagnostic criteria do not exist and classification criteria are used for guidance instead. The most recent classification criteria developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR)¹⁰⁰ published in 2017 can aid in identifying the major myositis subgroups: DM, PM, ADM, juvenile myositis and IBM. The probability of the disease can be evaluated using an [internet-based calculator](#). Muscle performance is usually assessed via muscle weakness using manual muscle testing or via muscle endurance using a functional index¹⁵⁰.

As IIM are heterogeneous conditions, they are diagnosed into subgroups on the combined basis of clinical phenotypes, auto-antibody profile and histopathological findings^{1,7,8} (TABLE 2; FIG. 7). For the new subgroup IMNM, classification criteria have been proposed¹²⁷. ASyS is usually diagnosed when one of the eight antisynthetase auto-antibodies is detected together with a single or a combination of the following clinical features: myositis, arthritis, ILD, mechanic's hands or Raynaud phenomenon¹⁵¹. No established diagnostic or classification criteria for ASyS are available yet. The European Neuromuscular Centre (ENMC) IBM research diagnostic criteria were proposed in 2011 and recognize clinicopathologically defined IBM as well as clinically defined IBM and probable IBM¹⁵². Diagnosis is based on the variable presence of combined or separate knee extension weakness equal to or greater than hip flexion weakness and finger flexion weakness greater than shoulder abduction weakness, together with age and duration limits and histopathological features in muscle tissue. The newest IBM diagnostic criteria use evaluation of finger flexor or quadriceps weakness, endomysial inflammation, and either invasion of non-necrotic muscle fibres or presence of rimmed vacuoles¹⁵³.

Laboratory testing. Muscle-derived enzymes in serum are elevated in most patients with active muscle disease. Creatine kinase is the most sensitive marker and has diagnostic and monitoring utility, although its levels can be normal in some patients with active DM, ASyS or IBM. Rarely, serum aldolase levels are selectively increased without creatine kinase level elevation¹⁵⁴. Indirect immunofluorescence using HEp2 cells as the substrate, the standard screening method for antinuclear

antibodies, has limited value in the screening of MSAs and MAAs, as many MSAs and MAAs target cytoplasmic antigens yield weak or negative nuclear staining with an indistinct pattern^{1,155}. Immunoprecipitation is the gold-standard technique to identify most MSAs and MAAs but is time-consuming and unsuitable for routine testing. Enzyme-linked immunosorbent assays and line blot assays for several MSAs and MAAs are becoming available, although their reliability needs further validation (except for anti-Jo1 antibody).

Histology. Muscle biopsy is an important tool to diagnose IIM, confirm signs of inflammation, identify signs of the different subtypes of IIM and, importantly, exclude other myopathies. The main elements in the histopathological investigations of major subtypes are summarized in TABLE 2 and FIG. 7 (REFS^{156–159}). Some findings are more common for each subtype and may enable diagnosis even in patients with uncharacteristic clinical manifestations. Some features may be non-specific and found in various frequencies in different myositis subtypes as well as in other myopathies, for example, necrotic or regenerating muscle fibres. The interpretation of pathological findings is sometimes difficult and there is interrater variability in diagnosing individual muscle specimen abnormalities¹⁶⁰.

Differential diagnosis

Several different conditions may mimic myositis. Muscle weakness, the main clinical presentation of myositis, is a non-specific symptom and misdiagnosis is possible especially when typical skin manifestations and/or MSAs are absent. Most commonly, the difficulties are encountered in patients with muscular dystrophies, metabolic myopathies, mitochondrial myopathies, endocrine myopathies or toxic myopathies^{161,162}. In particular, differentiating the slowly progressive onset of myositis from muscle dystrophies is important. Careful medical history, physical examination, electromyography,

laboratory and muscle biopsy analyses, and genetic testing are necessary to avoid incorrect diagnosis. Several warning signs exist that point to other conditions and their presence should increase the attention and prompt diagnosis verification, such as a family history of muscle weakness, slowly progressive evolution of weakness over years, and asymmetrical and considerable distal weakness^{161–164}.

Cancer association and screening

All subgroups of adult-onset myositis except ASyS and IBM have a twofold to sevenfold increased risk of malignancy compared with the general population^{103–105}. The risk of malignancy is particularly high in patients with DM, especially in those with anti-TIF1 (REFS^{118,165}) or anti-NXP2 (REFS^{119,166}) auto-antibodies, as well as in those with auto-antibody-negative IMNM¹⁶⁷. The risk is highest within 1 year before and after myositis diagnosis but remains elevated for an extended time period, up until 10 years in some subgroups.

Various types of malignancy can occur in patients with IIM. The most common are the same as seen in the general population: cancer of the lung, breast and ovary as well as lymphoma¹⁶⁸. Cancer screening includes a physical examination, investigation of the breast, pelvis, testes and prostate, CT of the chest, abdomen and pelvis, ultrasonography of the abdomen, gastroscopy and colonoscopy, and, in women, pelvic ultrasonography and mammography. In some patients, PET imaging is useful as it shows comparable performance to broad conventional screening, which requires multiple tests¹⁶⁹.

Prevention

There are no scientific studies that define a clear approach to prevent the development of IIM. Some data suggest that smoking is associated with IIM in patients who are either anti-Jo1 antibody and/or HLA-DRB1*03 positive³⁷. However, when disease is present, some steps can be taken to prevent flares of disease manifestations. In patients with anti-HMGCR IMNM, statin medications and statin-containing foods, such as oyster mushrooms, red yeast rice or Pu-Erh tea, should be avoided¹⁷⁰. Few data are available to guide treatment with statins and other lipid-lowering agents in other myositis subtypes; however, most experts favour their use¹⁷¹. Additionally, immuno-modulating drugs, such as immune-checkpoint inhibitors, TNF antagonists and type I interferons, can cause myositis but there is no recommendation not to use them when indicated, for example, owing to a malignancy¹⁷². Patients with rashes need to protect themselves from ultraviolet radiation¹⁷³.

Management

Management of myositis is challenging owing to the rarity and heterogeneous nature of this disease. Complexity also arises from variable presentation and disease courses as well as its multiorgan and systemic characteristics. No comprehensive consensus-driven guidelines or FDA-approved proven therapies exist, mostly owing to a lack of robust clinical evidence in the form of clinical trials in myositis. Fortunately, an increasing number of novel therapeutics are currently undergoing phase II

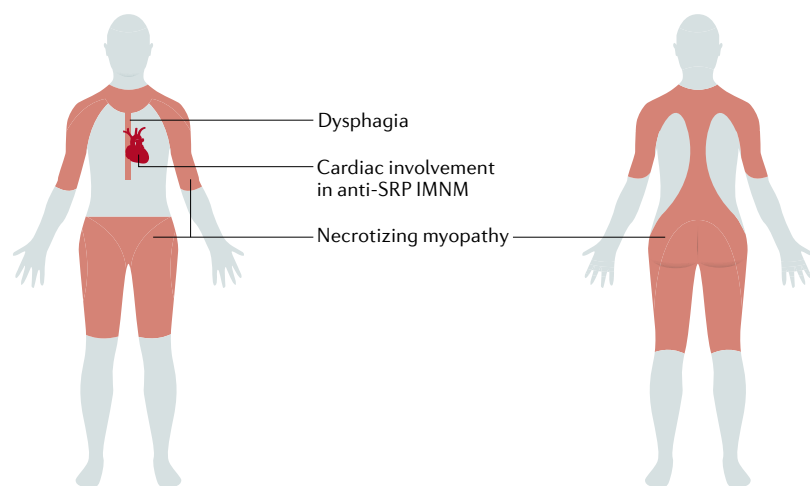


Fig. 5 | Clinical manifestations in IMNM. Most patients with immune-mediated necrotizing myopathy (IMNM) have auto-antibodies recognizing either 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) or the signal recognition particle (SRP). Severe muscle disease is the predominant manifestation of IMNM. Patients with anti-SRP auto-antibodies usually have more serious disease often accompanied with dysphagia and sometimes with cardiac involvement. In patients positive for anti-HMGCR, necrotizing myopathy prevails.

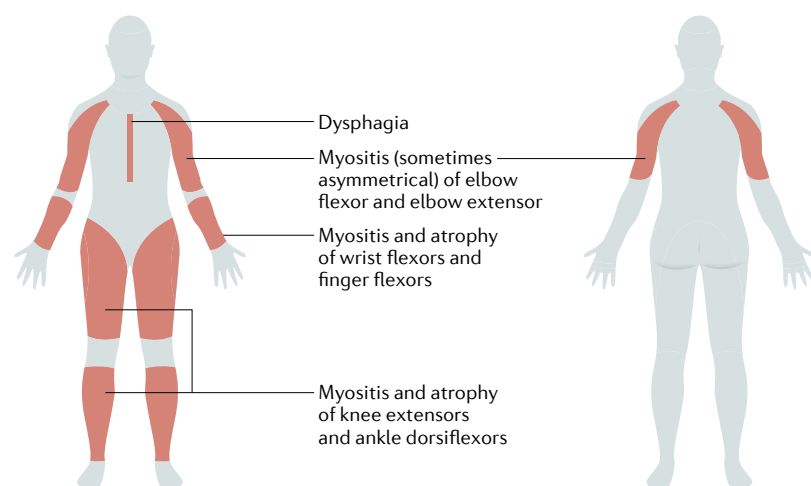


Fig. 6 | Clinical manifestations of IBM. Inclusion body myositis (IBM) is characterized by slowly progressive muscle weakness affecting mainly quadriceps and forearm muscles. Muscle involvement can be asymmetrical. The disease leads to substantial muscle atrophy and severe disability. Dysphagia is present in >50% of patients.

or III clinical trials, using validated disease classification and outcome measures. The goal of the therapy is to improve patient symptoms so that functional levels return to near baseline and for non-muscular symptoms to be manageable and not interfere with activities of daily living. Evidence is from retrospective cohort studies for all the treatments except for intravenous immunoglobulin (IVIg), rituximab and exercise, for which randomized controlled studies exist.

Glucocorticoids

Despite the lack of controlled clinical trials with proven efficacy, oral glucocorticoids are the first-line or initial treatment in most patients with PM, DM, ASyS or IMNM, especially for those with substantial muscle weakness and ILD¹⁷⁴ (FIG. 8). In patients with severe forms of myositis or extramuscular manifestation, such as ILD, pulse glucocorticoid therapy with intravenous methylprednisone is given. The chronic use of glucocorticoids should be limited, primarily because of the high rate of adverse effects and long-term complications. Clinical studies have shown normalization of muscle enzyme levels and improvement in muscle strength but glucocorticoids alone are associated with high flare rates, low remission rates and a lack of full recovery of muscle strength or function¹⁷⁵.

Adrenocorticotrophic hormone

Repository corticotropin injection (RCI) is a formulation containing adrenocorticotrophic hormone and other pro-opiomelanocortin peptides that stimulate melanocortin receptors, leading to both glucocorticoid-dependent as well as glucocorticoid-independent mechanisms of anti-inflammatory action^{176–178}. In an open-label trial of RCI biweekly for 24 weeks in 10 patients with refractory PM or DM, 70% of patients met the primary efficacy endpoint definition of improvement proposed by the International Myositis Assessment and Clinical Studies Group (IMACS)^{179,180}. RCI is an FDA-approved therapy for PM and DM; however, it is

only used as a third-line or later therapy owing to the lack of data from randomized controlled trials and high cost in the USA. Furthermore, the medication is not currently approved or available outside of the USA.

Traditional immunosuppressants

Traditional immunosuppressive drugs are commonly used together with glucocorticoids; however, the evidence for their efficacy in IIM is weak¹⁸¹. Most clinicians would start methotrexate or azathioprine in combination with glucocorticoids as initial therapy in myositis unless contraindications exist (FIG. 8). Several retrospective studies and one prospective open-label controlled study support their use in PM, DM and juvenile DM for muscle and skin disease^{175,182–186}. Azathioprine is preferred in patients with alcohol use, liver disease or concomitant ILD and is relatively safe in pregnancy. The use of mycophenolate in myositis has been increasing over the years with more retrospective and prospective studies supporting its efficacy in this disease as well as in associated conditions such as ILD and refractory DM rashes^{187–191}. It is typically used as a second-line agent except in patients with moderate to severe myositis associated with ILD, in whom it can be the first-line agent^{192–195}. Cyclosporine and tacrolimus are both calcineurin inhibitors that ultimately lead to inhibition of T cell activation. Both are used as second-line agents in patients with refractory myositis with either muscle weakness or associated ILD^{196–200} (FIG. 9). The toxic effects of calcineurin inhibitors require an aggressive monitoring plan, including checking trough blood levels periodically. The use of cyclophosphamide is limited to severe refractory muscle weakness, rapidly progressive ILD or systemic vasculitis associated with PM or DM²⁰¹. Cyclophosphamide is sometimes used in combination with rituximab as reported in a cohort of patients with antisynthetase auto-antibody positivity and severe ILD such as in patients positive for anti-MDA5 auto-antibodies; however, it may be associated with a high risk of infections²⁰².

Immunoglobulins

IVIg is a medication with anti-inflammatory and immuno-modulating mechanisms without direct immunosuppressive actions. Currently, IVIg is used in IIM as a second-line or third-line treatment either in combination with or following failure of glucocorticoids and/or other immunosuppressive drugs. It is also increasingly used as first-line treatment in myositis, especially in IMNM²⁰³. The efficacy and safety of IVIg was first reported in a double-blind, crossover, controlled trial in 15 patients with refractory DM²⁰⁴. An important large, randomized, placebo-controlled phase III study, recently published in abstract form²⁰⁵, confirmed the efficacy and safety of IVIg in refractory DM with muscle weakness and rash²⁰⁶. The trial has led to FDA and EMA approval for use of IVIg in adult DM. A subcutaneous form of IgG administered through a pump is increasingly being used in myositis²⁰⁷. IVIg has various advantages as it can be given concomitantly with other immunosuppressive drugs or in the settings of pregnancy, infection or malignancy. However, the treatment is expensive, can

be logistically challenging to administer and has limited availability in some countries.

Biologics and emerging drugs

Rituximab. Rituximab depletes CD20⁺ B cells that are likely to be involved in the pathogenesis of some myositis subgroups. Several open-label studies have reported safety and efficacy in patients with severe and refractory myositis, including the subset of patients with IMNM with anti-SRP auto-antibodies — a poor prognostic marker^{208–210}. A large, randomized, double-blind, placebo-controlled clinical trial (Rituximab in Myositis (RIM) Trial) in DM, PM and juvenile DM failed to meet its primary or secondary endpoints²¹¹. However, 83% of patients who were refractory to multiple immunosuppressive agents showed clinical improvement in muscle and skin disease as well as glucocorticoid reduction within 1 year. Furthermore, rituximab was considered relatively safe and well tolerated in this patient population. The presence of antisynthetase auto-antibodies, anti-Mi2 auto-antibodies, having juvenile DM and low disease damage at trial entry were strong predictors of a beneficial response to rituximab²¹². Rituximab is increasingly being used in myositis-associated ILD, especially ASyS, with positive outcomes in retrospective and prospective studies; however, no randomized controlled trials have been performed to date.

Anti-TNF agents

Although TNF has been implicated in the pathogenesis of myositis, the efficacy of anti-TNF agents (such as etanercept and infliximab) is somewhat disappointing^{213–217}. A case series of five patients with DM using etanercept, an open-label clinical trial of 13 patients with

refractory myositis using infliximab, and a randomized, double-blind, placebo-controlled trial in 12 patients with PM or DM using infliximab showed discouraging results^{215–217}. However, a randomized, double-blind, placebo-controlled trial in patients with DM showed positive results with etanercept²¹⁴. Currently, anti-TNF treatment is not typically recommended or considered in patients with adult myositis, although it may have a role in the treatment of calcinosis in juvenile DM²¹⁸.

Special therapeutic considerations

Most studies on myositis were performed in PM or DM; therefore, most data relate to these two clinical subsets in which muscle and/or skin is often the primary organ involved. However, slightly different treatment approaches may be beneficial in the new clinical and serological subtypes that have been identified in the past two decades. Furthermore, given the heterogeneous presentation of the disease, treatment often has to be specific to organ manifestations or associated conditions such as ILD or dysphagia. Other treatments are being explored that may eventually be helpful. Three major randomized clinical trials have been completed with only top line or abstract results currently available. The trial of IVIg in adult DM has a positive result leading to FDA and EMA approval^{205,206}. Unfortunately, two other trials, abatacept in adult IIM, which included patients with DM, PM or IMNM²¹⁹, as well as lenabasum in adult DM^{220,221}, failed to reach their primary endpoint or key secondary endpoints.

Immune-mediated necrotizing myopathy. In patients with IMNM, high doses of glucocorticoids have traditionally been used as induction therapy together with methotrexate or azathioprine. However, several case

Table 2 | Histopathological findings in different IIM subtypes

Myositis subtype	Muscle fibres and tissue	Inflammatory cell infiltrates	MHC I expression	MAC depositions	Other specific findings
Dermatomyositis	Perifascicular atrophy, reduced number of capillaries	Perivascular, perimysial, T cells, B cells, macrophages, plasmacytoid dendritic cells	Perifascicular fibres	Small blood vessels	Sarcoplasmic MxA expression
Polymyositis	Degeneration, necrosis, regeneration	Endomysial inflammatory infiltrate with T cells often surrounding and/or invading non-necrotic muscle fibres	Diffuse distribution	No specific findings	Absence of rimmed vacuoles
Immune-mediated necrotizing myopathy	Necrotic fibres with scattered distribution, different stages of necrosis and myophagocytosis and regeneration, endomysial fibrosis and proliferation	Macrophage predominant, paucilymphocytic infiltrates	Diffuse distribution, sometimes only faint	Sarcolemmal and/or on small blood vessels	No specific findings
Antisynthetase syndrome	Oedematous and/or fragmented perimysium that stains with alkaline phosphatase, sometimes perifascicular myofibre necrosis	Scattered perimysial CD68 ⁺ , CD4 ⁺ , CD8 ⁺ cells	Perifascicular predominance	Fibres adjacent to the perimysium, sarcolemmal on non-necrotic fibres	Myonuclear actin filament inclusions in electron microscopy, absence of MxA expression
Inclusion body myositis	Rimmed vacuoles, ragged red fibres, cytochrome oxidase-negative fibres, groups of atrophic fibres	Endomysial inflammatory infiltrate with mainly CD8 ⁺ cells surrounding and/or invading non-necrotic muscle fibres	Diffuse distribution	No specific findings	TDP43, p62 aggregates, 15–18 nm filaments in electron microscopy

IIM, idiopathic inflammatory myopathy; MAC, membrane attack complex.

series have suggested a more aggressive approach with the use of rituximab and/or IVIg in these patients, especially owing to the often refractory nature of disease as well as the risk of early muscle atrophy in patients who are anti-SRP positive (FIG. 9). In addition, the risk of high doses of prolonged glucocorticoid treatment in elderly patients with anti-HMGCR auto-antibodies needs to be considered^{127,208,222,223}. Some reports suggest that the use of high doses of IVIg as monotherapy without glucocorticoids may be efficacious in patients with anti-HMGCR auto-antibodies²²⁴.

ASyS-associated ILD. Often, the predominant and refractory condition in ASyS is ILD (FIG. 9). Moreover, ILD is the major cause of mortality and morbidity in myositis in general and in ASyS specifically. Mycophenolate is preferentially used in patients with moderate to severe ILD as first-line therapy, including in patients with ASyS¹⁹². Anti-T cell therapies, such as tacrolimus or cyclosporine, have been used with good success in patients with ASyS and, specifically, with ILD. In a small study including 13 patients with ILD who were positive for antisynthetase auto-antibodies, tacrolimus resulted in improvements in all pulmonary function testing parameters²⁰⁰. Furthermore, several studies in Asia have suggested survival benefits with the use of a combination of glucocorticoids with either tacrolimus or cyclosporine^{198,225}. Rituximab has increasingly been used for myositis-associated ILD, especially in patients with ASyS^{226–228}. A retrospective study of 24 patients with ASyS and severe ILD showed

clinically significant improvement in pulmonary function after rituximab²⁰². Similarly, 16 of 17 patients with anti-Jo1 auto-antibodies treated with rituximab showed more rapid and marked responses compared with conventional immunosuppressive agents²²⁸.

CADM. CADM is a unique clinical phenotype highly associated with the presence of anti-MDA5 auto-antibodies and characterized by severe cutaneous rashes and frequently with RP-ILD but without objective muscle weakness. These patients often have high mortality and need aggressive combination immunosuppression as first-line therapy, which includes glucocorticoids in combination with calcineurin inhibitors as well as cyclophosphamide²²⁹ (FIG. 9). Rituximab with or without cyclophosphamide is often used early in patients with a worsening respiratory status²³⁰. A prospective, open-label study from China demonstrated efficacy and a survival benefit of glucocorticoids with tofacitinib compared with historical controls⁶³.

Inclusion body myositis. Unlike DM and PM, IBM is typically refractory to immunotherapy. Although glucocorticoids and other immunosuppressive therapies have not been tested in randomized controlled trials, the general consensus is that they are not efficacious, even though glucocorticoids may improve muscle enzyme levels in the short term and dysphagia in some patients. IVIg might slow disease progression but its long-term effectiveness remains unclear. Methotrexate, which is commonly used in other forms of myositis, failed to

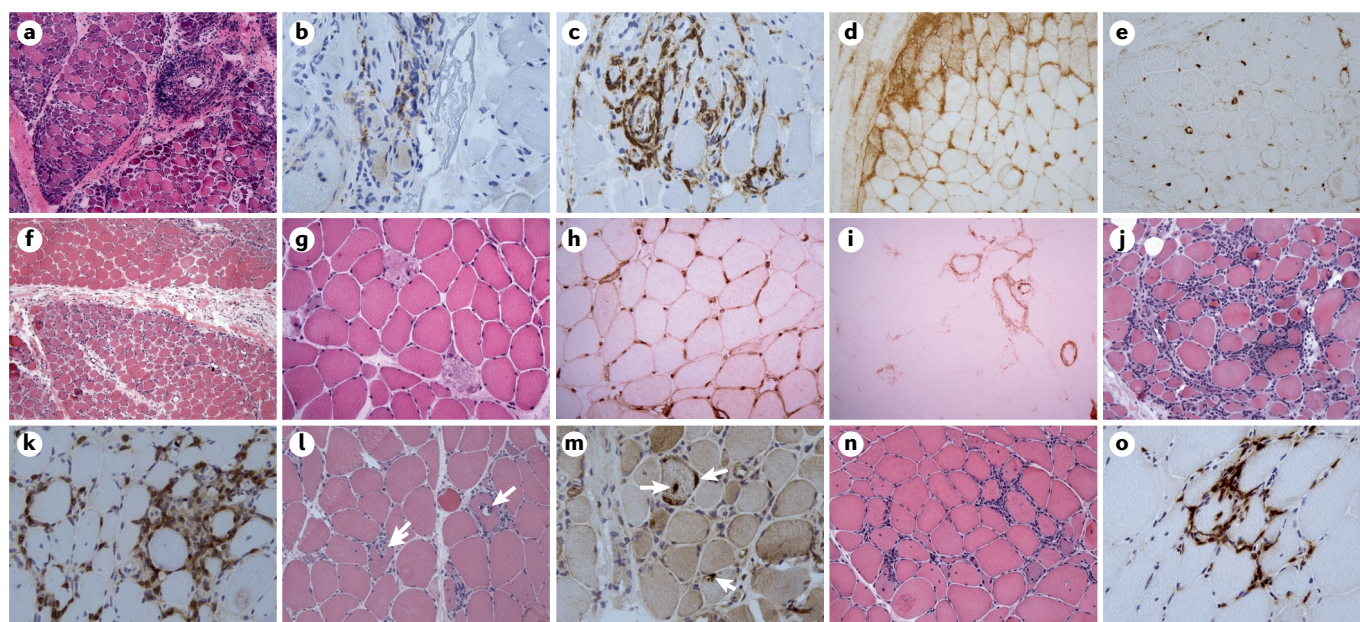


Fig. 7 | Typical histopathological changes in IIM subgroups. Dermatomyositis: perifascicular atrophy and perivascular inflammatory infiltrate (part **a**), inflammatory infiltrate with CD4⁺ cells (part **b**), inflammatory infiltrate with B cells (part **c**), MHC I expression on muscle fibres, particularly in perifascicular distribution (part **d**) and membrane attack complex depositions in capillaries (part **e**). Antisynthetase syndrome: perifascicular myofibre necrosis, perifascicular atrophy and perimysial fragmentation (part **f**). Immune-mediated necrotizing myopathy: necrotic muscle fibres (part **g**), MHC I hyperexpression on sarcolemma of muscle fibres

(part **h**), membrane attack complex deposition on capillaries and sarcolemma of muscle fibres (part **i**). Inclusion body myositis: lymphocytic and macrophage aggregates in endomysium and invasion into muscle fibres (part **j**), CD8⁺ inflammatory infiltrate (part **k**), rimmed vacuoles (part **l**, arrows) and p62 staining (part **m**, arrows). Polymyositis: endomysial infiltrate surrounding and invading non-necrotic muscle fibres (part **n**) and CD8⁺ cells surrounding and invading non-necrotic muscle fibres (part **o**). Original magnification $\times 40$ (parts **a** and **f**) and $\times 200$ (parts **b–e** and **g–o**). IIM, idiopathic inflammatory myopathies. Images courtesy of Prof. Josef Zámečník.

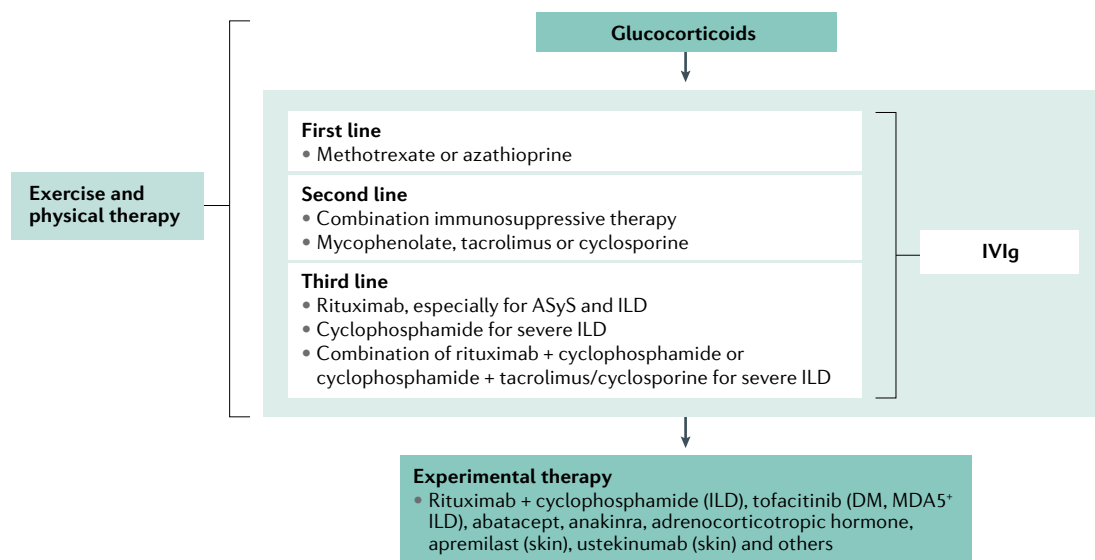


Fig. 8 | **Common pharmacological and other therapies for IIM except for IBM.** ASyS, antisynthetase syndrome; DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; IVIg, intravenous immunoglobulin; MDA5, melanoma differentiation-associated gene 5.

slow the progression of muscle weakness in a small, randomized, double-blind, placebo-controlled study in patients with IBM²³¹. Intravenous bimagrumab, an anti-activin type II receptor antibody, was evaluated in the largest phase III clinical trial in IBM to date and failed to meet its primary endpoint of 6-minute walk distance at 52 weeks²³². Pilot studies of arimoclomol, which co-induces the heat shock response by prolonging the activation of heat shock factor 1 and may promote normalization of protein handling within muscle, and rapamycin (sirolimus), which inhibits protein kinase that regulates several intracellular processes, including survival, protein synthesis and autophagy, have shown encouraging results but these have not been confirmed. Unfortunately, a phase II/III clinical trial of arimoclomol in IBM failed to meet its primary endpoint; however, a phase III clinical trial of rapamycin is ongoing^{233,234}. Exercise is currently the only treatment, which has consistently shown a varied degree of benefit in IBM, although the optimal type of exercise programme is yet to be determined.

Dysphagia. Proximal dysphagia can be a severe and life-threatening manifestation of myositis and patients with refractory dysphagia should undergo a full investigation to determine the cause of dysphagia and appropriate management. Although most patients would respond to conventional doses of glucocorticoids and immunosuppressive agents, some studies have suggested the use of IVIg for refractory dysphagia²³⁵.

Calcinosis. Calcinosis is the most severe and challenging presentation of DM. Control of active disease with traditional immunosuppressive agents is necessary but is often not sufficient for the treatment of calcinosis. Bisphosphonates, diltiazem, rituximab, IVIg and sodium thiosulfate have been tried with some success in patients with calcinosis^{236,237}.

Exercise and physical therapy

Emerging data support the safety and effectiveness of exercise in adults with IIM. Muscle function and quality of life (QoL) improve after exercise regimens²³⁸. Exercise programmes to improve strength and function have been shown to activate molecular pathways regulating aerobic capacity, capillary growth and muscle remodelling while concomitantly mitigating the inflammatory response in muscles^{239,240}. Thus, exercise, especially directed by physical therapists, should be recommended early with gradual progression based on the individual response. Most patients tolerate exercise without adverse effects. Physical exercise should be considered as standard treatment for adult and juvenile myositis.

Outcome measures

International networks of myositis researchers (IMACS) developed and validated standardized measures to assess disease activity, known as core set measures, for use in clinical trials. These are also useful tools in clinical practice. The core set includes physician and patient global disease activity as well as extramuscular disease activity on a 10-cm visual analogue scale as well as muscle enzyme analyses, manual muscle testing and patient-reported health assessment questionnaires²⁴¹. Composite response criteria using weighted changes in these core set measures have been developed and validated for patients with adult and juvenile myositis²⁴². There are several additional measures of muscle strength (such as hand-held dynamometry) and function (functional index, timed up-and-go or sit-to-stand) as well as assessment of other organ manifestations, such as ILD (lung function study) or DM rash (Cutaneous Disease Area and Severity Index (CDASI)), that are increasingly being used as secondary outcome measures. Furthermore, various patient-reported outcome measures (PROMs), especially well-validated Patient-Reported Outcomes Measurement Information

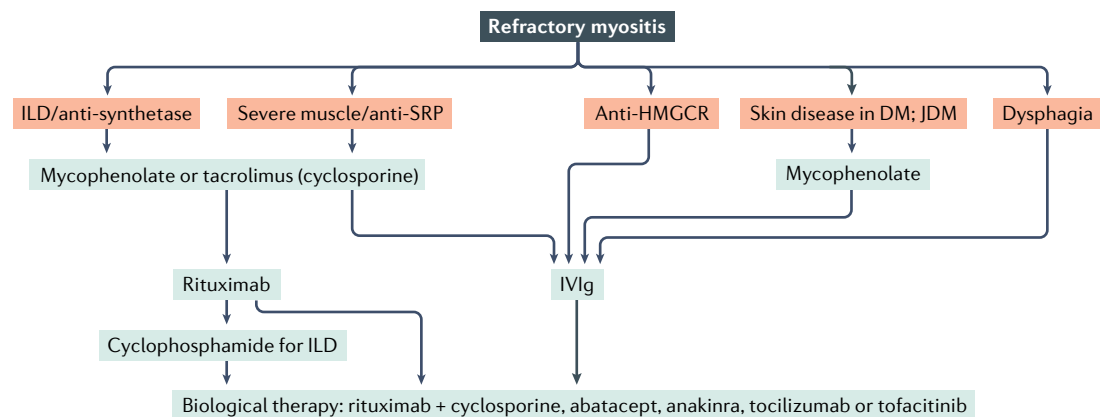


Fig. 9 | **Treatment considerations in patients with refractory myositis based on clinico-serological presentation.**

DM, dermatomyositis; HMGCR, 3-hydroxy-3-methylglutaryl CoA reductase; ILD, interstitial lung disease; IVIg, intravenous immunoglobulin; JDM, juvenile dermatomyositis; SRP, signal recognition particle.

System (PROMIS) instruments, are being evaluated for use in patients with myositis. MRI and ultrasonography of muscle as well as physical activity monitors are promising tools that can provide much needed objective outcome measures in myositis.

Quality of life

It has been increasingly highlighted that clinical trials and observational studies should include an assessment of the outcomes that matter most to patients²⁴³. Myositis unquestionably affects patients' QoL and may lead to long-term disability for some^{244,245}; however, assessing life quality in a systematic, validated and quantifiable fashion in IIM is challenging. As the disease may affect organs beyond the muscle, health-related QoL (HRQoL) indices that encompass the systemic nature of the disease are desirable but remain largely unexplored and are not validated.

Most instruments evaluated in IIM have been either generic or adopted from use in other rheumatic or neuromuscular diseases. Only the Myositis Activities Profile (MAP) was created specifically for adult PM and DM and the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR) was adapted for these two diagnoses^{132,246}. In addition, the IBM Functional Rating Scale (IBMFRS) was created and validated for patients with IBM²⁴⁷. However, the indices were assembled from the provider viewpoint with little patient involvement in their construction or improvement and review of the survey instrument by myositis patients revealed that they deemed some questions vague or irrelevant²⁴⁸. Patient engagement via focus groups and subsequent Delphi processes has now demonstrated the need to include pain and fatigue in addition to physical function²⁴⁹.

In addition to physical examination and laboratory measures, the IMACS core set of measures includes PROMs such as the patient/parent report of disease activity. IMACS also recommends including a measure of HRQoL, such as the Short Form-36 (SF-36) survey in clinical studies²⁵⁰. Disease activity and damage core set measures have been validated but no specific PROM has been developed under IMACS auspices. Similarly, the

ACR-EULAR criteria for clinical response in DM and PM were formulated using data-driven methods in the absence of patient input and include only a generic patient visual analogue scale²⁵¹. The Outcome Measures in Rheumatology (OMERACT) framework provides a complementary, non-overlapping approach to bringing the major stakeholders together within a 'patient research partner' framework to derive PROMs²⁵².

Until myositis-specific instruments are developed, generic instruments to evaluate HRQoL may be used; however, ongoing future efforts must focus on standardizing the use of PROMs for research and clinical practice to avoid ambiguity when interpreting data between different cohorts and across trials. International organizations will need to take a central role in the promotion and use of high-quality, validated PROMs in IIM research. This approach is imperative for the aggregation of collected data, for example, for meta-analysis, which is necessary when studying a collection of rare diseases²⁵³.

PROMs, when used in conjunction with clinical measures, add an important and too often dismissed patient perspective of the disease. PROM implementation can improve the patient-physician relationship, increasing physician satisfaction and improving patient care by furthering shared decision-making²⁵⁴. Given that the beliefs and perspectives of the patient and physician may not be comparable, validation and adoption of myositis-specific HRQoL instruments derived through the patient-provider partnership are fundamental for both high-quality care and research.

Outlook

Since the early 2000s, major advances have been made in understanding the pathophysiology of IIM and its subgroups. This has been possible by the identification of MSAs and owing to advances in molecular biology. The common occurrence of auto-antibodies in IIM emphasizes the influence of the immune system in the pathophysiology of these diseases. The phenotypes of inflammatory cells and their products in the most often affected organs, namely muscle and skin but also the lungs, in the newly identified subsets of IIM defined by

MSAs have been reported. However, several important gaps remain in our understanding of IIM that need to be addressed in future research to improve treatment and outcomes. One important point for future research and clinical management is a nomenclature of IIM and its subgroups that is widely accepted. This could be a task for the international networks on myositis such as the IMACS network.

A major challenge in the clinical management of myositis is that we do not know which patient will respond to which treatment. Currently used immunosuppressive treatment has broad effects on the immune system and adverse effects are common. Furthermore, in one cohort of patients with PM or DM, only 20% obtained drug-free remission⁴⁵. The chronic inflammatory process often leads to irreversible tissue damage. Thus, the need for new therapies is high. For more specific targeted therapies, more detailed information on molecular pathways, including the specificities of the targets of the immune reaction, is required. Furthermore, biomarkers for treatment response and prognosis are lacking. The availability of data to predict treatment response, prognosis and outcome to customize treatment for personalized medicine approaches would be a major advancement. To avoid chronicity and tissue damage, patients probably need to be identified earlier and treated more aggressively. An earlier diagnosis may be accomplished through increased physician awareness of IIM and its clinical phenotypes and through referral to specialist clinics for diagnostic evaluation when IIM is suspected. When the diagnosis is confirmed, intense and specific treatment should be initiated early.

Treatment can be improved through several approaches. A better understanding of the pathophysiology of IIM is an essential aspect. Elucidating the immune specificities of the IIM subtypes is critical as the target of the immune system is likely to vary between the subtypes with different clinical features and different MSAs associated with different HLA-DRB1 alleles. Knowing the site where the immune reaction leading to the autoimmune disease takes place is also important to understand the molecular pathways leading to chronic disease and to stop the disease process early. Here, both the skin and mucosal sites in the airways or gut are of interest as niches for possible initiating immune reactions. An interesting IIM subgroup in this context is that of patients with antisynthetase auto-antibodies with a high frequency of ILD and myositis, in particular patients with anti-Jo1 auto-antibodies that have a strong association with the HLA 8.1 ancestral haplotype, where smoking is a risk factor for disease and lung disease is often an early manifestation³⁷. In this subgroup, antigen-reactive, pro-inflammatory CD4⁺ T cells targeting fragments and peptides of histidyl-tRNA synthetase, the target of anti-Jo1 auto-antibodies, have been identified in peripheral blood and with highly reactive CD4⁺ T cells in the bronchoalveolar lavage⁶⁹. Identification of antigen-specific peptides that activate T cells is an important step to developing immune tolerance therapy, which could possibly 're-educate' the immune system to achieve a cure. In patients with IIM, several specific

auto-antigens targeted by auto-antibodies and associated with distinct clinical phenotypes and genotypes are now known. These auto-antigens are potential candidates to identify peptides that induce T cell reactivity. The identification of auto-antigen-specific T cells will be an important step to developing immune tolerance therapy and should have high priority in research in the coming 5–10 years. The identification of auto-antigen-specific T cells by T cell tetramers would be an excellent tool to monitor future specific immune therapies.

The identification of biomarkers for treatment response and prognosis is another important approach to improving treatment. This could be achieved through observational studies using large, well-characterized cohorts of patients with longitudinal data. As IIM are rare disorders with several clinical and serological subgroups, international multicentre collaborations are needed, which could be facilitated via international web-based registries using validated classification criteria and outcome measures. Some major steps have been taken via the IMACS network through which tools to score disease activity and damage as well as response criteria have been developed^{2,42}. The EULAR-ACR classification criteria for IIM¹⁰⁰ are also an important step towards the harmonization of patient cohorts for multicentre studies.

Muscle biopsies are still important for the diagnosis of IIM and its subgroups and to exclude mimicking conditions. Muscle biopsies, including biopsies from longitudinal studies, are also important to achieve an improved understanding of IIM pathophysiology by careful investigations of molecular expression in clinically well-defined patients. Whether muscle specimen features will have a role as biomarkers in adults with IIM is yet to be understood. However, both in the clinical and the research setting, it is essential to standardize muscle biopsy assessments as reflected by considerable variations in the evaluation of biopsy samples among experienced muscle pathologists¹⁶⁰. An important future project would be to advance the area of standardization of muscle biopsy assessment, including an international panel of muscle pathologists to review muscle biopsy samples together as is now often routine in cancer diagnosis.

The performance of commercially available auto-antibody tests is another area in need of evaluation and standardization. The discovery of new MSAs has enabled the identification of new IIM subgroups, such as IMNM associated with anti-HMGCR or anti-SRP auto-antibodies, and the elucidation that anti-TIF1 auto-antibodies are strongly associated with a risk of cancer in adult patients with DM. These MSAs are examples of biomarkers that could predict prognosis. However, the sensitivity and specificity of the different auto-antibody assays vary for anti-TIF1 auto-antibodies and several other MSAs. Thus, the validation of commercially available auto-antibody assays in large cohorts with longitudinal data is required, which should have a high priority for the international myositis community in the coming years.

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Competing interests

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