Review

Classification, Diagnosis, and Management of Idiopathic Inflammatory Myopathies

Ilias N. Lazarou and Pierre-André Guerne

ABSTRACT. The detection and characterization of a large array of autoantibodies, including at least 8 different antisynthetase, anti-SRP, -200/100 (HMGCR), -Mi-2, -CADM-140 (MDA5), -SAE, -p155, -MJ (NXP-2), and -PMS1, frequently associated with distinct and well-defined clinicopathological features, allowed for significant improvement in the definition and diagnosis of idiopathic inflammatory myopathies (IIM). Classification remains difficult, with lingering divergence between the different specialties involved in IIM care, but several categories clearly stand out, including dermatomyositis (DM), overlap myositis (OM), polymyositis, necrotizing myositis, and sporadic inclusion body myositis (s-IBM). Biopsy and histological analysis remain crucial, particularly in the absence of autoantibodies, to accurately specify the diagnosis and rule out mimics such as muscular dystrophies and metabolic myopathies. Numerous infectious agents (in particular human immunodeficiency virus and human T cell lymphotrophic virus-1) and drugs (statins, tumor necrosis factor inhibitors, and proton pump inhibitors) can cause mimic IIM that must also be excluded. Pharmacological treatment, in addition to glucocorticoids and immunoglobulins, now includes mycophenolate mofetil and rituximab, which proved helpful in resistant cases, particularly rituximab in DM and OM. Exercise, initially seen as potentially deleterious, recently was shown to be efficacious and safe. IIM can thus be reasonably well controlled in most cases, although aggressive disease remains refractory to treatment, including some cases of necrotizing myopathy. Sporadic IBM still seems resistant to all medications tested to date. (J Rheumatol First Release March 15 2013; doi:10.3899/jrheum.120682)

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Idiopathic inflammatory myopathies (IIM) are characterized by inflammatory infiltration of the skeletal and sometimes cardiac muscle, muscle weakness, and occasionally pain, and can be associated with a series of extramuscular manifestations. The discovery of numerous new antibodies and refinement of efficient imaging techniques significantly improved diagnosis and comprehension of IIM, although classification and diagnostic criteria remain difficult and debatable. These classification difficulties certainly impaired treatment and management, which nevertheless improved considerably (particularly for difficult cases) with the development and better use of several drugs, including mycophenolate mofetil and rituximab. These advances, together with a better understanding of the various conditions that can mimic IIM, now allow for satisfactory care of most patients.

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Diagnostic and classification criteria. The classification and diagnosis of this heterogeneous group of diseases has long been based essentially on the Bohan and Peter diagnosis and classification criteria[1], a specific combination of signs, symptoms, and test results designed to help the clinician determine the correct diagnosis. Although still widely used, these criteria have many limitations. They recognize primary idiopathic polymyositis (PM), primary idiopathic dermatomyositis (DM), DM (or PM) associated with neoplasia, childhood DM (or PM), and PM or DM associated with collagen-vascular disease (overlap group). They were developed from 1 single institution; contained no clear instructions to rule out all other forms of myopathy; sporadic inclusion body myositis (s-IBM) had not yet been identified; and most criteria are nonspecific and the degree or number of abnormalities of each criterion are observer-dependent and were not specified. In addition, the characteristic rashes of DM were not described in detail. Finally, the sensitivity and specificity of these criteria were not studied for many confounding dermatologic or neuromuscular conditions. However, in a group of combined controls and in patients with systemic sclerosis (SSc), systemic lupus erythematosus (SLE), non-myositis overlap

syndromes, and inflammatory myopathy, sensitivity and specificity proved acceptable (83% and 93%, respectively)[2].

Two more recent classifications are those of Troyanov, *et al*[3], based on data from 100 French-Canadian patients, and the consensus-driven classification of the 119th European NeuroMuscular Centre (ENMC) workshop originally proposed by Anthony A. Amato on behalf of the Muscle Study Group[4].

The Troyanov classification includes pure PM, pure DM, overlap myositis (OM), and cancer-associated myositis (CAM). Importantly, s-IBM and rare forms of IIM were part of the exclusion criteria, as were noninflammatory myopathies[3].

The more complex and ambitious classification of the ENMC workshop recognizes s-IBM, definite PM, probable PM, definite DM, probable DM, amyopathic DM (also called DM sine myositis), possible DM sine dermatitis, nonspecific myositis, and immune-mediated necrotizing myopathy or necrotizing autoimmune myopathy (NAM). These criteria focus on muscle biopsy for classifying patients and were intended for clinical trials rather than for clinical care[4].

Classification criteria are primarily designed to generate homogeneous sets of patients for research, whereas the primary purpose of diagnostic criteria is to diagnose the conditions of individual patients, thus allowing distinction from the general population and similar conditions. However, these terms are frequently and incorrectly used interchangeably. With regard to IIM, these classifications have some advantages but also definite limits, in particular for clinical care: the misuse of the largely biopsy-based classification criteria could lead to routine and unjustified use of biopsy to diagnose otherwise clear cases of IIM such as DM or other antibody-associated IIM. The Troyanov classification was based on a single relatively homogeneous population, with the high proportion of OM being possibly the result of referral bias and a questionable definition; undetected autoantibodies, serum sampling after treatment, and non-uniform muscle biopsy may also have influenced results[3].

The International Myositis and Clinical Studies Group (IMACS) has developed new classification criteria [International Myositis Classification Criteria Project (IMCCP)] with the support of the American College of Rheumatology (ACR), the European League Against Rheumatism, and The Myositis Association. Two different models were proposed and seem to have superior performance compared to existing criteria in internal validation; external validation is in progress. In the meantime, it is probably more useful for clinicians to recognize the entities that appeared to stand out, and importantly, to identify the full extent and activity of disease so that it can be treated adequately.

DM. DM is certainly the most uniformly recognized and best-defined entity, although it is somewhat heterogeneous, notably with regard to associated autoantibodies (Table 1). It can affect both children and adults and has a marked female predominance, particularly after age 45 years. Disease is usually slowly progressive (weeks to months) and manifests essentially with symmetric proximal muscle weakness; frequency of muscle pain and tenderness (generally mild) varies (25%–50% of patients). Data suggest that fasciitis is a common lesion in DM early after disease onset[5]. It is readily detectable with magnetic resonance imaging (MRI). The skin modifications seen in DM are numerous and variable; some are rather specific, such as heliotrope rash, shawl rash, and Gottron sign, whereas others are less so, for example mechanic's hands, which is also seen in antisynthetase syndrome, livedo, erythroderma, and periungual abnormalities (Figure 1).

Numerous other organs can be involved in DM, including the lungs, heart, and gastrointestinal tract. Interstitial lung disease (ILD) is reported in up to 75% of patients with DM (depending on the methods used for diagnosis) and is one of the major causes of morbidity and mortality.

Muscle enzymes in DM are variably elevated, globally as in other myopathies, although isolated elevation of aldolase may be more frequent than in other forms of IIM. Many antibodies have now been recognized to be associated with DM: anti-Mi-2 antibodies, although rarer in white populations, are considered highly specific for DM (Table 1)[6]. Their presence appeared to markedly decrease the risk of associated malignancy, although cases of anti-Mi-2 and cancer are described in the literature[7,8]. The detection of an autoantibody (other than the anti-Mi-2) was initially thought to be related to a worse outcome, but this observation is now debatable with the discovery of new autoantibodies that are not associated with a bad prognosis. Adult DM is frequently associated with cancer. Childhood DM, considered separately in Bohan and Peter criteria, differs notably from the adult form, in particular because of more frequent muscle calcifications and virtually no association with cancer.

Clinically amyopathic DM (CADM or DM sine myositis) consists of the typical rash and skin histopathology without clinical myopathy. Many patients with CADM test positive for the anti-CADM-140 antibody. Some of these patients subsequently develop myositis and/or ILD. Further, patients with CADM share the same malignancy association with patients with classical DM[9].

OM. OM was defined in the Bohan and Peter criteria as a myositis associated with another defined collagen vascular disease (overlap group). According to the Troyanov classification, OM is defined by the existence of any clinical overlap feature other than rash and/or by the presence of "overlap autoantibodies," including most known myositis-specific autoantibodies (MSA) or myositis-associated autoantibodies (MAA; Table 1)[3], and therefore accounts for more than half of all IIM. Thus, according to this questionable classification, OM regroups myositides overlapping with connective tissue disorders that can also be seen without myopathy (such as SSc, SLE, Sjögren syndrome,

Table 1. Autoantibodies in idiopathic inflammatory myopathies (IIM)[22,102,103,104,105,106].

Antibody	Frequency in IIM, %	Clinical Significance and Associations
Myositis-specific autoantibodies		
Anti-Jo-1 (histidyl-tRNA synthetase)	15–20	Antisynthetase syndrome, including juvenile antisynthetase syndrome; sometimes clinically amyopathic
Anti-PL-7 (threonyl-)	5–10	
Anti-PL-12 (alanyl-)	< 5	
Anti-EJ (glycyl-)	5–10	
Anti-OJ (isoleucyl-)	< 5	
Anti-KS (asparaginyl-)	< 5	
Anti-Zo (phenylalanyl-)	< 1	
Anti-Ha-YRS (tyrosyl-)	< 1	
Anti-SRP	5–10	Immune-mediated necrotizing myopathy (generally severe and rapidly evolving with frequent myocardial involvement); rarely in children
Anti-200/100 (HMGCR)	40% of necrotizing myopathy[107]	Immune-mediated necrotizing myopathy, frequently associated with prior statin use
Anti-Mi-2	5–30	Classical DM, often of sudden onset with erythroderma and shawl sign, generally without ILD or malignancy and good prognosis; occasional juvenile DM
Anti-CADM-140 (MDA5)	50% of CADM	DM, sometimes juvenile, with mild or absent muscle inflammation (CADM) and increased risk of ILD that can be rapidly progressive
Anti-SAE	5%	Adult DM
Anti-p155(/p140) (TIF1-α/β/γ)	15–25% of adult DM, 40–75% of cancer-associated DM, 30% of juvenile DM	DM, especially cancer-associated (Ca in 45–75% of positive anti-TIF1-α/β/γ patients). Common in juvenile DM (without malignancy); rare in PM
Anti-MJ (NXP-2)	< 5; 25% of juvenile DM	Juvenile DM exclusively; frequently severe cases with calcinosis
Anti-PMS1	7.5	Rare DM and PM
Myositis-associated autoantibodies		
Anti-U1RNP	10	OM, MCTD
Anti-Ku	20–30	PM-SSc overlap (Japanese)
Anti-PM-Scl	8–10	PM-SSc overlap (whites)
Sporadic inclusion body myositis (s-IBM)-associated autoantibodies		
Anti-43-kDa muscle autoantigen	50% of s-IBM[22] (needs further confirmation)	s-IBM

CADM: clinically amyopathic dermatomyositis; MCTD: mixed connective tissue disease; HMGCR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; ILD: interstitial lung disease; MDA5: melanoma-differentiation-associated gene 5; OM: overlap myositis; NXP-2: nuclear matrix protein 2; SAE: small ubiquitin-like modifier activating enzyme; SRP: signal recognition particle; SSc: systemic sclerosis; TIF1-α/β/γ: transcriptional intermediary factors 1-α, β, and/or γ.

and antiphospholipid antibody syndrome), and some disorders that are usually associated with, or characterized by, myositis [such as the antisynthetase or the anti-signal recognition particle (SRP) syndromes]. Whatever its definition, this group is extremely heterogeneous and its treatment and prognosis highly variable.

Antisynthetase syndrome. The antisynthetase syndrome, which belongs to the OM in the Troyanov classification, is frequently defined as a constellation of a usually acute disease with antisynthetase antibodies (Table 1), fever, ILD (~80%), mechanic's hands (~70%; Figure 1D), Raynaud phenomenon (~60%), and polyarthritis (~60%), sometimes with erosions. Clinically evident myositis can be missing, particularly early in the disease, especially in the presence of some of the antisynthetase antibodies (anti-PL7 and PL12)[10].

Anti-SRP syndrome. The anti-SRP syndrome, which also belongs to OM in the Troyanov classification, has been sensibly defined as a distinct entity (immune-mediated necrotizing myopathy) in the ENMC workshop classification because of specific clinical and histological features. It is indeed considered to combine a severe and rapidly evolving necrotizing myositis with frequent myocardial involvement, although this later feature has been questioned[11]. It is a chronic and corticosteroid-dependent

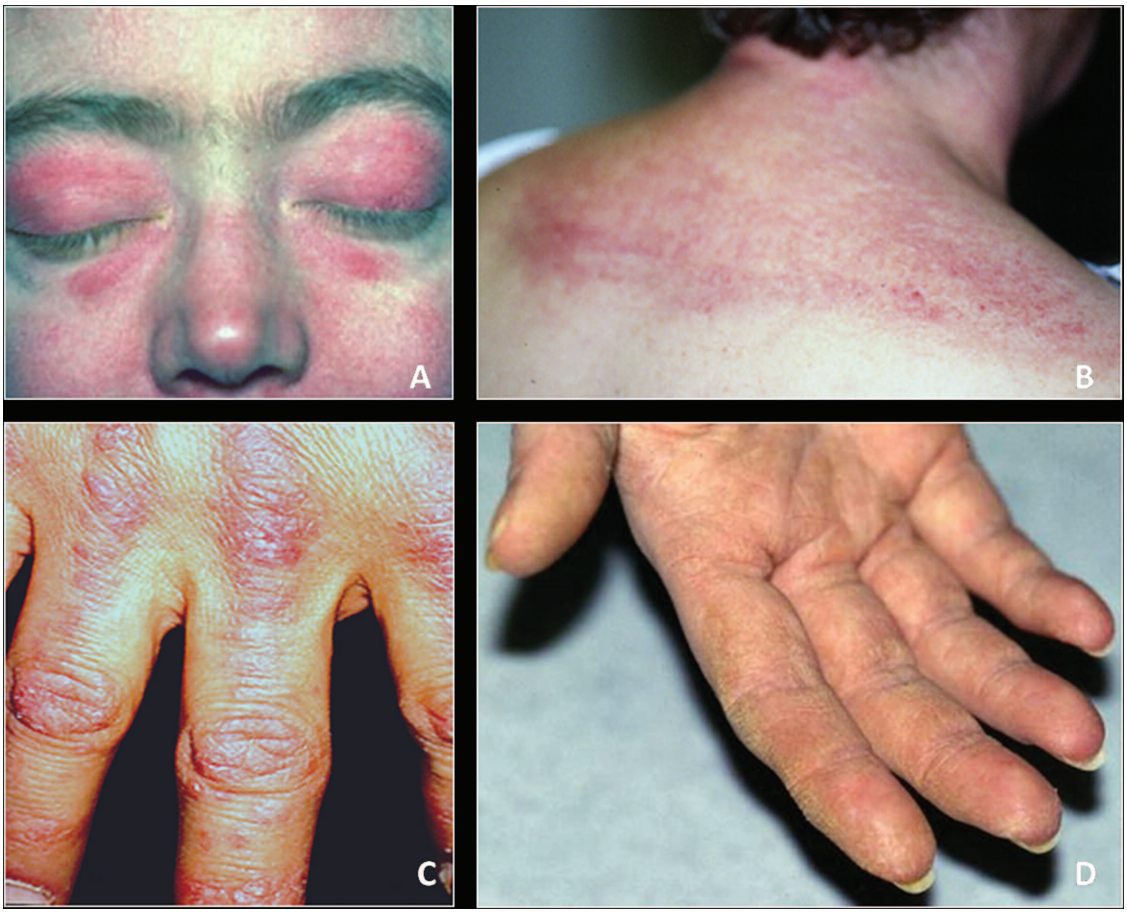

Figure 1. Specific skin manifestations in dermatomyositis. A. Heliotrope rash. B. Shawl rash. C. Gottron sign. D. Mechanic's hands.

disease with particular histological findings. With the now-broadened concept of NAM, it is probably adequate to include the anti-SRP syndrome in it. To date, however, there is no established consensus about this issue[11].

PM. PM, initially defined by Bohan and Peter by evidence of symmetric proximal myositis and the absence of histopathological signs of other myopathies or typical rash of DM, was considered relatively prevalent. According to the Troyanov classification, PM is rare, particularly "pure PM," and may include mimics of IIM. In this classification, most PM cases are in fact considered OM[3]. Indeed, with the constant discovery of new autoantibodies and depending on how aggressively they are sought and how liberally they are counted positive, pure PM might disappear. In addition, if pure PM is viewed as a PM with the total absence of any other feature (including obviously skin and lung, but also joint, vascular, and general manifestations), depending on the efforts used to rule out such manifestations, it may become even rarer. A recent study on the correlation of clinicoserologic and pathologic classifications of IIM showed that pure PM probably remains a distinct entity but is indeed very rare, and that mimics must be carefully tracked[12]. The term PM is still widely used in the broad sense to define cases positive for MSA in the absence of a specific DM rash or another defined collagen vascular disease, but diagnosis should be supported by a careful histopathological analysis, particularly in the absence of autoantibodies and rash. Whatever its definition, PM (in contrast to DM) very rarely occurs in childhood and most cases are diagnosed after the second decade of life. The muscle involvement of PM is clinically indistinguishable from that of DM, but PM and DM differ histologically.

CAM. CAM has been classified by Troyanov as a distinct entity. This separation is debatable because it may influence screening strategies and duration of followup. The significance of individualizing CAM, however, is that response to treatment and prognosis may differ considerably, which can be particularly important for clinical research. In this group, DM is more frequently represented than PM[13,14,15]. CAM appears to be particularly associated with the anti-p155 (/p140) antibody (most commonly present in DM and rarely in PM) and may account for almost half of all IIM after age 65 years, but < 10% in younger populations[16]. Types of malignancies vary depending on the study populations:

mainly breast, lung, pancreas, and colon in a northern New England (USA) population with DM[14] and nasopharyngeal, lung, breast, and cervical tumors in Taiwanese patients with DM or PM[13].

Risk factors for cancer include older age, male sex, dysphagia, and skin manifestations (such as skin necrosis, periungual erythema, and the shawl sign), refractory disease, low C4 levels, presence of the anti-p155 (/p140) antibody and absence of other autoantibodies. Protective factors appear to include concomitant ILD, antisynthetase antibodies, and low lymphocyte counts[17], although a few cases of malignancy in patients with ILD and anti-Jo-1 antibodies have been reported (Tables 1 and 2).

NAM. As classified by the ENMC workshop, NAM is clinically similar to PM, but differs histologically by the presence of marked muscle necrosis with regeneration, in the absence of an inflammatory infiltrate. It is generally classified as OM in the Troyanov classification because it is frequently associated with the anti-SRP antibody. However, in some cases, it is associated with statin treatment (and potentially related to the anti-HMGCR antibodies), malignancy, and viral infections, particularly human immunodeficiency virus (HIV)[18].

Sporadic-IBM. S-IBM was excluded from IIM in the Troyanov classification but forms a separate category in that of the ENMC workshop. Overlap manifestations are characteristically rare in s-IBM[3], although a notable association with Sjögren syndrome has been described[19,20,21]. The risk of associated cancer is very low[17].

S-IBM differs from IIM primarily in older age at diagnosis (always after 30 years and mostly 50 years old), male predominance, insidious onset with slowly progressive weakness of proximal as well as distal muscles (in particular the forearm), and more common myalgias. Muscle involvement can be asymmetric and lead to profound atrophy; dysphagia is common. Creatine kinase (CK) levels are only mildly elevated and can be normal, as can the markers of systemic inflammation. Electroneuromyography (ENMG) shows a myopathic or mixed myopathic and neuropathic pattern. Less inflammation is present in biopsies, but more fatty degeneration. A distinct autoantibody has been recognized in some patients[22] (Table 1).

Griggs, *et al* defined the diagnostic criteria[23]. S-IBM most probably has an immune-inflammatory component, but one that is definitely less obvious than in the other IIM[24], and it is not certain whether immune-inflammatory events occur before or after degenerative processes. Degenerative processes probably explain the worse response of s-IBM to immunosuppressive therapy. A recent longterm cohort study of 136 patients confirmed previous findings from smaller studies: s-IBM is slowly progressive but not lethal and its natural course does not improve with immunosuppression[25].

Subclassifying a patient into a precise category is frequently impossible but it is generally not crucial; the most important points are certainly to define the type of muscle involvement (distinguishing in particular necrotizing forms and s-IBM) and its severity, and to recognize possible extramuscular involvement.

Diagnosis. The diagnosis of IIM is typically established or confirmed by elevated serum muscle enzyme levels, electromyography, and muscle pathology. Proper muscle choice for biopsy can be guided by MRI. In the appropriate clinical setting, detection of autoantibodies can be helpful. The role of other imaging studies and biochemical assays is not yet validated, and thus their use is considered more experimental.

Laboratory tests. Serum muscle enzyme levels [CK, aldolase, lactate dehydrogenase (LDH), aspartate, and alanine aminotransferases] are generally elevated in active IIM. CK, aldolase, and LDH play important roles in diagnosis and followup of the patients. However, they are not specific and may be elevated in noninflammatory myopathies and (mildly) in denervating conditions. In addition, enzyme levels may be normal in rare cases of early, mild, or focal myositis as well as in late disease, when extensive fatty degeneration of muscle has occurred. Any of these enzymes may be elevated independently of the others. It is therefore recommended that all enzymes be tested during evaluation of suspected myositis. Importantly, pronounced muscle dysfunction can be seen with little enzyme elevation, particularly in DM, and the treatment of IIM should be guided primarily by patient strength and not enzyme concentrations.

Interleukin 1RA (IL-1RA) was found elevated in most cases of PM and DM, even in the absence of CK elevation[26]; although neither specific nor validated, IL-1RA elevation can be a diagnostic clue and can facilitate the followup and evaluation of response to therapy, in our experience. Increased expression of a variety of other cytokines (in both blood and tissue) and chemokines in affected muscles have been described in IIM[27]. None of these measurements, however, has been validated to date for diagnosis or followup.

Autoantibodies are increasingly useful, whether specific to IIM (with MSA) or not (with MAA; Table 1). Some of the

Table 2. Cancer and myositis[17].

Factors associated with occult malignancy in patients with idiopathic inflammatory myopathies (IIM).
Older age
Male sex
Dysphagia
Skin manifestations: necrosis, periungual erythema, "V" ("shawl") sign
Low C4 levels
Anti-p155 (/p140) antibody and absence of other autoantibodies
Factors protective for the development of cancer in patients with IIM
Interstitial lung disease
Antisynthetase and anti-Mi-2 antibodies
Low baseline lymphocyte count

new tests have many false positives, and more specific testing (immunoprecipitation) is not widely available. Nevertheless, the number and characterization of MSA and MAA is constantly expanding and improving, and their role in diagnosis and determination of prognosis is becoming more valuable, especially when consistent with clinical findings. In such cases biopsy may not be obligatory. In addition, most MSA are very specific not only of the IIM, but also of distinguishing phenotypes and features (Table 1); they are generally mutually exclusive.

Besides the laboratory assays, other techniques to diagnose IIM are ENMG, muscle imaging techniques, and tissue biopsies.

Electroneuromyography. ENMG in IIM shows a typical although not specific myopathic pattern consisting of the classic triad of increased insertion activity with spontaneous fibrillations, abnormal myopathic low amplitude and short duration polyphasic motor potentials, and complex repetitive discharges. In contrast to most other IIM, ENMG in s-IBM can show a mixed myopathic and neurogenic pattern in some patients. The sensitivity for IIM is good (up to 85% in some series) but the specificity is poor (33%)[28]. Changes similar to those of myositis can indeed be seen in numerous other myopathies, including metabolic; however, ENMG suitably distinguishes neurogenic diseases.

Imaging in IIM. MRI is the imaging tool of choice for both assessment of disease activity and selection of the biopsy site[29]. Generally, affected muscles are readily differentiated from normal ones by the presence of inflammatory edema. Because fat can interfere with the interpretation of the signal, T2-weighted images with fat suppression or short-tau inversion recovery (STIR) sequence with longer time to echo should be used[30]. T1-weighted images are helpful to detect fatty degeneration of affected muscles in more advanced or chronic cases. Although its sensitivity is good, very rare false-negative results represent a potential drawback of MRI, according to at least 1 study (sensitivity 96.6%–100%)[31,32]. Despite the detection of more inflammation in biopsies of sites selected by MRI, inflammatory changes, although less intense, are also found in biopsy sites that were negative for inflammation by MRI[29]. Specificity is unfortunately lower: MRI may in fact show an increased hydric signal in denervation, metabolic myopathies, traumatic neuropathy, muscular and myotonic dystrophies, rhabdomyolysis, muscle infarction, diabetes, and even after intense physical exercise, which can seriously decrease its value. Whole-body MRI (STIR) may increase sensitivity in some cases but is not universally thought to be convenient for routine care. Figure 2 illustrates MRI findings in the setting of IIM with proximal myositis and associated synovitis.

Ultrasound (US) in acute disease reveals normal or increased size, decreased echogenicity, and elevated perfusion of affected muscles, whereas size is reduced, echogenicity increased, and perfusion reduced in chronic myositis[33]. Contrast-enhanced intermittent-power Doppler US has improved specificity compared to B-mode US, but its sensitivity and negative predictive value for diagnosis remain low compared to MRI[34]. Training and experience of the operators is certainly the major limitation. These factors, combined with a lack of data in larger populations, limit the usefulness of this technique.

To assess response to therapy, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has been advocated[35]. However, its main use is for detection of associated malignancy in high-risk cases.

Histology. Biopsy with histopathological analysis remains important for IIM diagnosis in many cases; it is highly sensitive if located in an inflammatory site, but inflammatory lesions may be patchy, which clearly decreases sensitivity. On the other hand, biopsy is very specific. However, it is not regarded by many authors as obligatory for diagnosis when typical features such as skin changes and/or specific autoantibodies are present and consistent with clinical manifestations. Numerous pathologists still consider that muscle biopsy is the most sensitive tool to diagnose IIM. Immunopathologic features are complementary to clinicoserologic findings and can help to predict outcome[12,36]. Although some authors recognize a more complex classification (that includes immune myopathies with perimysial pathology, myovasculopathies, immune polymyopathies with little inflammation, immune myopathies with endomysial pathology, histiocytic inflammatory myopathies, and inflammatory myopathies with vacuoles, aggregates and mitochondrial pathology[36]), it is generally considered that muscle histology allows distinguishing 4 main subtypes of IIM on the basis of distinct immunopathologic features: DM, PM, s-IBM, and NAM[12,37,38].

Because histopathological features may be scarce, unspecific, and overlapping, to establish the proper diagnosis of IIM and exclude other entities requires proper muscle choice, proper specimen processing, and careful interpretation. In particular, correctly determining the nature of cell infiltrates is important to avoid misinterpretation of muscle biopsies[37]. For instance, multinucleated giant cells among elongated epithelioid cells, macrophages, or lymphocytes indicate granulomatous myopathy, while eosinophilic infiltrates are observed in hypereosinophilic syndromes, parasitosis, vasculitis, or eosinophilic myositis, as well as calpain gene mutations.

DM is regarded as a complement-mediated microangiopathy that combines inflammatory and microvascular alterations. Histopathology typically shows perivascular inflammatory infiltrates that predominate in the perimysium and the perifascicular endomysium, and consist of a mixture of T lymphocytes, with more CD4+ than CD8+ cells, macrophages, plasmacytoid dendritic cells, and occasional B cells. B cells are described more frequently in a distinct DM

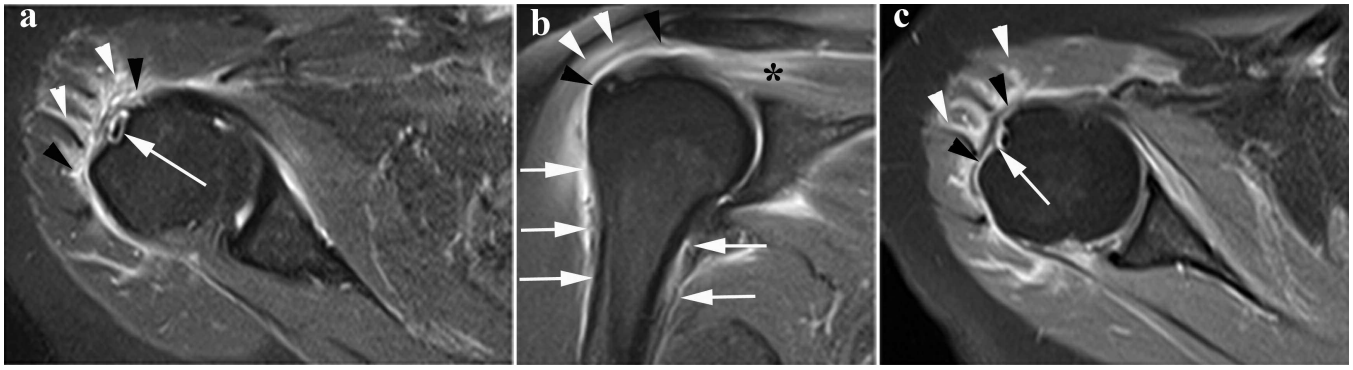

Figure 2. MRI in idiopathic inflammatory myopathies. A. Axial short-tau inversion recovery (STIR) sequence. High signal in the deep lateral part of the deltoid muscle (white arrowheads), subdeltoid bursa (black arrowheads), and synovium (white arrow), showing edema and inflammatory changes. B. Coronal STIR sequence. High signal in the deltoid muscle (white arrowheads), supraspinatus muscle and tendon (*), and subdeltoid-subacromial bursa (black arrowheads), extending around the proximal humeral shaft (white arrows), showing edema and inflammatory changes. C. Axial T1 fat saturation after intravenous gadolinium injection. Enhancement of the deep lateral part of the deltoid muscle (white arrowheads), subdeltoid bursa (black arrowheads), and synovium (white arrow), evidence of lesions of myositis, bursitis, and synovitis.

category in the pathologic classification of IIM (DM-vascular pathology) that encompasses a subset of clinical DM, possibly the subtype associated with calcinosis in children and in some adults[36]. Myofiber alterations include perifascicular atrophy, microinfarcts, and upregulation of major histocompatibility complex (MHC) class I antigens, with a distinctly predominant perifascicular enhancement. Perifascicular atrophy, although generally associated with inflammation, can be seen in isolation[39] and when typical, even in the absence of inflammatory infiltrate, is strongly suggestive of DM[37]. Microvascular changes mainly include early capillary deposition of the complement C5b9 membranolytic attack complex (MAC) and focal capillary loss predominating in perifascicular areas. That endomysial capillary loss occurs most commonly in regions of perifascicular atrophy and deposition of MAC on the remaining endomysial capillaries further supports the hypothesis of primary microvascularopathy. A recent study confirmed that the histologic pattern of DM appears to be one of, if not the most frequent; it is seen in various conditions including pure DM, OM, CAM, and also polymyositis without rash[12]. In that study, muscle biopsy by itself was not able to distinguish the different serologic subgroups reliably, even if typical immunopathologic DM was predictive of anti-Mi-2, antisynthetase, or CAM antibodies. These results further support the complementarity of the clinicoserologic classification of Troyanov, *et al*[3] and histopathological analysis.

PM is characterized by focal endomysial infiltrates, predominantly consisting of CD8+ cytotoxic T lymphocytes that surround and invade non-necrotic muscle fibers, with relative sparing of the vasculature. The MHC-1 antigen, in contrast to DM, is ubiquitously upregulated on the surface of most fibers[37,39,40]. The fundamental difference between PM and DM appears to be the targeted tissue components, which are the muscle fiber in PM and the vessel in DM[37]. MHC/CD8-positive lesions (MHC/CD8 complex seen in dual-stained sections) are regarded as an important feature of PM and s-IBM, allowing them to be distinguished from other entities. In some dystrophies, for instance, including Duchene muscular dystrophy, endomysial infiltration by lymphocytes may also occur, but these cells lack the MHC/CD8 complex[37]. Several studies showed that the histopathological pattern of PM is rare (as is clinicoserologic pure PM) and frequently correlates with myositis mimics, sometimes diagnosed during followup[12,41]. Most of the cases of IIM misdiagnosed as PM are inflammatory dystrophies, necrotizing myopathies, or s-IBM. Necrotizing myopathy is characterized on biopsies by abundant necrotic and regenerative fibers that contrast with modest inflammation. Inflammation consists essentially of macrophage invasion, with lack of T lymphocyte infiltration[37]. In contrast to PM and DM (and s-IBM), MHC-1 is generally not overexpressed except focally in necrotic fibers and reportedly in statin-induced myopathy. In some cases, there may be complement deposits on thickened vessels.

S-IBM is characterized by rather modest inflammation within the endomysium, consisting mainly of CD8+ T lymphocytes as in PM. However, an array of other modifications that can be well visualized with several different stainings can help distinguish it from PM and other IIM. These include vacuolated muscle fibers, degeneration/regeneration areas, necrotized/phagocytized fibers, β-pleated-sheet amyloid inclusions, and phoshorylated tau[42]. Further, in s-IBM, vacuoles are lined by blue granules corresponding to whorls of cytomembranes or myelin figures, detectable by electron microscopy[37]. MHC/CD8-positive lesions are also regarded as an important feature of s-IBM, distinguishing it from other entities including sporadic forms of myofibrillar myopathy and hereditary IBM due to mutations of gene UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase[37].

In the recent study, analyzing the correlation between

clinicoserologic features and histology, a significant number of histopathological samples did not meet the criteria for 1 of the 4 specific immunopathologic patterns mentioned. These cases were characterized by inflammatory changes with nonspecific localization without additional features allowing a diagnosis of pure DM or PM and by absent or only focal MHC-1 expression, and were classified as unspecified myositis. Of note, they represented the second most-frequent histologic pattern, and frequently correlated with overlap myositis, especially with anti-Ku or anti-PM-Scl autoantibodies[12].

Another study showed that in patients with anti-Jo-1 or other antisynthetase antibodies, histopathology is characterized by a high frequency of macrophage-predominant inflammation in, and fragmentation of, perimysial connective tissue, together with a paucity of vascular pathology[39].

Differential diagnosis. The differential diagnosis of the IIM is broad and includes hypothyroid myopathy (subacute proximal muscle weakness often with elevated muscle enzymes), motor neuron diseases, myasthenia gravis, muscular dystrophies, inherited metabolic myopathies, and drug-induced and infectious myopathies. Myopathies with pronounced muscle pain and weakness, associated with CK elevation, are most often the result of infectious processes[43] and drug reactions[44,45] (Tables 3 and 4). Thus, before considering specific IIM treatment such as glucocorticoids or immunosuppression, careful exclusion of such causes is mandatory. This can be challenging and should be performed by experienced clinicians, preferably in a multidisciplinary setting.

Except primarily for HIV and HTLV, most viruses cause self-limiting myopathies. Bacterial infections, except for Lyme disease and syphilis, generally cause focal myositis.

Lipid-lowering therapies, and particularly statins, warrant particular attention, because the myopathy they induce can persist after the drug is withdrawn. A retrospective study indeed showed that, after the fifth decade of life, IIM occur more frequently in patients treated with these agents than in patients who were never exposed to such medications[46]. Little consensus exists on how to define statin-induced myopathy. The adverse muscle effects of statins can in fact encompass numerous different presentations, including mere myalgia, myositis with or without autoantibodies, and/or rhabdomyolysis. Statin-induced myopathy is dose-dependent; although still debated, it might also be molecule-dependent, occurring more easily with lipophilic statins (e.g., atorvastatin, lovastatin, simvastatin) than with hydrophilic statins (pravastatin or rosuvastatin). One metaanalysis found that the highest rate of severe myotoxicity was associated with atorvastatin and the lowest risk with fluvastatin[47]. Interestingly, statin-induced myopathy can be associated with specific autoantibodies (200–100 kDa proteins; Table 1).

Management. After exclusion of mimics, management of IIM includes staging (activity measurement, research of extramuscular involvement, and cancer screening), nonpharmacological therapy, and pharmacological therapy. Treatment depends on the extent and severity of the disease. The presence of anti-SRP or other poor prognostic factors (Table 5) should be considered[48]. Specialist referral should be sought, given the possibility of severe and resistant muscle and/or systemic involvement in addition to difficulties in followup. Importantly, outcome measures as objective and reliable as possible should be used to adjust therapy.

Assessment of disease activity — outcome measures. According to the IMACS, the ideal assessment of patients with IIM should comprise disease activity and disease damage indices, as well as patient-perception measures[49]. The IMACS combined and modified the different tools that measure disease activity or disease extent and damage and created the Myositis Disease Activity Assessment Tool[50]. This instrument showed good reliability and validity, but is essentially for research purposes. However, in clinical practice, several of its components can be useful, as can MRI, which also has limitations but definitely has an interesting role. The advantages and disadvantages of the most useful indices are outlined in Table 6.

The recently published sporadic inclusion body myositis weakness composite index includes force and function measures to assess s-IBM[25].

Cancer screening. Despite the recent advances in immunology [anti-p155 (/p140) antibody] and the availability of imaging techniques such as FDG-PET/CT, the best diagnostic approach for detecting malignancy remains in dispute. One algorithm, not yet validated, has been proposed by Selva-O'Callaghan, *et al*[17]: authors advocated FDG-PET/CT use yearly for 3–5 years, depending on the patient's risk. According to a prospective study from the same group, the overall predictive value of FDG-PET/CT was the same as that of broad conventional screening, including thoraco-abdominal CT, mammography, gynecologic examination, ultrasonography, and tumor marker analysis. The main advantage of FDG-PET/CT might be that it is more convenient for both the physician and the patient, and possibly less distressing for the latter. The cost of FDG-PET/CT and the availability of both FDG-PET/CT and anti-p155 assay could limit their value.

Therapy. The optimal therapeutic regimen for IIM is not codified and remains unclear for numerous aspects, largely owing to a lack of adequate studies[51]. In addition, despite large similarities between therapies of most entities, treatment of some of the IIM clearly differs, particularly with respect to s-IBM.

DM, OM, and PM. Treatment of DM, OM (including antisynthetase syndrome), and PM is similar and depends on the severity of the myositis and on the eventual presence of extramuscular manifestations.

Table 3. Differential diagnosis of acquired myopathy — infections

	Specific Features
Virus	Diffuse myalgias
Adenovirus	
Coxsackie viruses, especially B	Pleural pain (chest muscle myalgias = Bornholm syndrome)
ECHO viruses	
Dengue virus	
Herpes group (cytomegalovirus, Epstein-Barr, herpes simplex, varicella-zoster)	
Hepatitis B, A, and C	
HIV	PM-like disease can occur at any time during infection. Could be related to antiretroviral therapy
HTLV-1	PM and/or arthritis in Japan, Caribbean, and Africa
Influenza A and B	Particularly lower calf involvement
Mumps	
Parvovirus B19	
Rubella	
SARS-coronavirus	
West Nile virus	
Bacteria	Mainly focal disease
Staphylococcus	Pyomyositis; psoas abscesses common
Streptococcus	Necrotizing myositis, pyomyositis
Gram-negative: enterobacteria	Pyomyositis, psoas abscesses are common
including *Yersinia, Pseudomonas, Aeromonas,* other; anaerobic: *Clostridium, Bacteroides, Fusobacterium, Peptostreptococcus,* other	Usually pyomyositis; psoas abscesses are common; gas gangrene (Clostridial myonecrosis)
Atypical bacteria	Mainly focal disease
Bartonella	
Borrelia burgdorferi (Lyme disease)	Focal > diffuse myalgias ± myositis; proximal predominance; rarely orbital involvement
Francisella tularensis	
Leptospira	
Mycobacteria, tuberculosis and others	Psoas abscesses are common
Mycoplasma pneumoniae	
Rickettsia (including Rocky Mountain spotted fever)	
Fungi	Mainly pyomyositis
Aspergillus	
Candida	
Cryptococcus	
Fusarium	
Pneumocystis carinii (jiroveci)	
Parasites	Mainly myalgias with eosinophilia; sometimes pyomyositis
Cysticercosis	Myalgias, fever, and eosinophilia with calcified cysts; seizures, headache, psychiatric disorders
Echinococcus	
Microsporidiae, trachipleistophora, pleistophora	
Schistosoma	Fever, abdominal pain, headache, diarrhea
Spirometra mansonoides (sparganosis)	
Toxocara	
Toxoplasma	Immunocompromised host (low CD4 count); resembles polymyositis. Lymphadenopathy common
Trichinella	Myalgias and eosinophilia (China, Thailand, Mexico, Bolivia, Argentina, ex-USSR, central Europe)
Trypanosoma cruzi	Fever, headache, lymphadenopathy, and periorbital swelling (Romana sign)

HIV: human immunodeficiency virus; PM: polymyositis; HTLV: human T cell lymphotrophic virus; SARS: severe acute respiratory syndrome.

Table 4. Differential diagnosis of acquired myopathy; drug- and toxin-induced myositis and myopathy.

Drug	Characteristics
Anti-TNF	Myositides in the context of drug-induced lupus; demyelinating syndromes
Amiodarone	Myalgias ± weakness ± neuropathy
Beta-blockers	Painless myopathies; myasthenic syndromes
Chloroquine and hydroxychloroquine	Lysosomal myopathy (painless, progressive weakness) ± neuropathy (rare); myasthenic syndrome (rare)
Cimetidine	Polymyositis-like disease (rare)
Cocaine	Polymyositis-like disease
Colchicine	Myalgias, proximal weakness (antimicrotubular myopathy); rarely rhabdomyolysis; neuromyopathies, enhanced by cyclosporine association
Corticosteroids	In general, painless weakness; CK normal
Cyclophosphamide	Acute rhabdomyolysis (high doses)
Cyclosporine A, tacrolimus	Painful myopathies ± fever (rare); mitochondrial myopathies
Dasatinib, nilotinib	Myalgia and muscle cramps, cardiotoxicity, increased CPK; rare muscle weakness
Enalapril	Painful myopathies (generally with normal CK)
Etretinate	Painful myopathies (generally with normal CK)
Fibrates	Painful myopathies (generally with normal CK)
Hydroxyurea	Dermatomyositis-like lesions; muscle weakness uncommon
Proton pump inhibitors	Polymyositis-like disease, rhabdomyolysis
Leflunomide	Severe myalgias
Methotrexate	Myalgias, in general associated with ingestion
Metoprolol	Painful myopathies (generally with normal CK)
Minoxidil	Painful myopathies (generally with normal CK)
Mycophenolate	Painful myopathy ± fever (rare)
NSAID (niflunimic acid, phenylbutazone)	Polymyositis-like disease (rare), rhabdomyolysis (rare)
Olanzapine	Myopathy with CK elevation in case of intoxication; rarely rhabdomyolysis
Penicillamine	Polymyositis-like disease, myasthenic syndrome, lupus-like disease
Penicillin	Polymyositis-like disease (rare)
Propylthiouracil	Polymyositis-like disease (rare)
Quinolones	Painful myopathy
Sulfasalazine	Polymyositis-like disease in the context of drug-induced lupus; rarely rhabdomyolysis
Statins	Myalgias; rarely myopathy or rhabdomyolysis. Risk is higher with PPI, cyclosporine, erythromycin and possibly fibrates such as gemfibrozil. Myopathy can be very slowly or only partially resolved with drug withdrawal
Sulfonamides	Polymyositis-like disease
Zidovudine	Mitochondrial myopathy, polymyositis-like disease ± neuropathy

TNF: tumor necrosis factor; CK: creatine kinase; CPK: creatine phosphokinase; NSAID: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitors.

Table 5. Poor prognostic factors.

Associated malignancy[108,109]
Anti-SRP antibodies[110]
Pulmonary involvement (respiratory muscles and/or ILD)[48,109,111]
Cardiac involvement[48,111]
Bulbar involvement — dysphagia[54]
Older age[48]
Nonwhite race[48]
Delayed treatment[48]

SRP: signal recognition particle; ILD: interstitial lung disease.

Glucocorticoids (GC). Most patients are started on a GC with or without a corticosteroid-sparing agent, to achieve remission. Corticosteroid-resistant disease, difficulties in tapering the GC, and flares of disease after induction of remission (recurrences) are generally treated with immunosuppressants, usually methotrexate (MTX) or azathioprine (AZA), plus GC.

GC is thus widely considered the cornerstone of the initial treatment[52,53] despite the lack of placebo-controlled trials proving its efficacy or any survival benefit[54,55]. In fact, prednisone is considered the first-line drug for the treatment of PM and DM[56], traditionally at a starting dose of 1 mg/kg per day, to a maximum daily dose of 80 mg[52,53]. Nevertheless, a lower dose of 0.5–0.75 mg/kg per day (depending on severity) seems to have fewer adverse effects[48]. In severe cases, intravenous bolus administration of methylprednisolone (usually 250–1000 mg for 3 days) can be helpful.

Studies (non-placebo-controlled) have demonstrated the effectiveness of GC in improving muscle strength[53,57] and achieving prolonged treatment-free remissions[58]. However,

Table 6. Advantages and disadvantages of the principal outcome assessment indices.

Index	Advantages	Limitations
Manual muscle strength testing	Strength normalization represents one major goal of treatment	Unreliable in differentiating disease activity from sequelae; delay between inflammatory response and recovery; poor quantification of response
Serum CK levels	Correlates with inflammation in some cases; easy to obtain	Unreliable in differentiating disease activity from sequelae; can be normal even in active disease
Serum LDH levels	Could be better correlated with disease activity in juvenile DM[48]	Probably comparable to CK in adult IIM. Same limitations
Global disease activity on VAS	Global assessment	Rarely objective; unreliable in differentiating disease activity from sequelae
MRI	Sensitive; reliable in differentiating disease activity from sequelae	Cost; difficult to target

CK: creatine kinase; LDH: lactate dehydrogenase; DM: dermatomyositis; IIM: idiopathic inflammatory myopathies; MRI: magnetic resonance imaging; VAS: visual analog scale.

up to 50% of patients fail to respond to GC alone, and GC discontinuation in the absence of non-GC immunosuppressants is associated with disease recurrences, mostly within 1 year[3]. In recent studies (manuscript in preparation) we and others have observed that remission can be induced with no or only minimal GC use when adequate immunosuppressants are introduced without delay[58,59], a procedure that can be very useful when GC are contraindicated, refused by the patient, or not tolerated. In addition, the potential inhibitory effects of GC on skeletal muscle mass, myogenesis, and immune responses that promote skeletal muscle regeneration after muscle injury further support minimal use of these agents when practical[60].

Non-GC immunosuppressants. Non-GC immunosuppressants used as GC-sparing agents (most commonly MTX and AZA) can be added to or initiated with this treatment to reduce GC-associated morbidity and achieve remission. Further, they are sometimes initiated simultaneously with GC in severe disease, particularly with lung involvement (Table 5). Many different non-GC immunosuppressants are used (Table 7) without, however, any firm evidence for the superiority of any one or for the best combination[48].

MTX. No randomized placebo-controlled prospective study has assessed the effectiveness of MTX. It is also uncertain whether first-line MTX therapy improves outcomes such as total GC dose, GC-related side effects, and disease activity in adults[59]. Its potential pulmonary toxicity limits MTX use in cases of ILD, but does not constitute an absolute contraindication. Dosing is usually started at 15 mg per week but can be cautiously increased to 50 mg per week, at least temporarily. Hepatic toxicity is the major limitation to longterm use.

AZA. With doses up to 3 mg/kg, AZA has been demonstrated by 1 group to improve functional ability and diminish GC requirements[52,61]; effects, however, are usually seen only after several months[56]. Hepatic toxicity is the major limitation to use[62]. In many centers, thiopurine methyltransferase (TPMT) activity is assessed before starting therapy. A recent systematic review[63] found sufficient evidence to confirm the association of reduced TPMT activity (or variant genotype) with bone marrow toxicity or leukopenia, but insufficient evidence for the effectiveness of pretesting. However, available evidence was underpowered to detect a difference in outcomes.

Combined therapy (MTX with AZA) seemed to be superior to MTX treatment alone in a study of refractory myositis[64], but the results were limited by the small number of patients and the numerous dropouts.

Other common immunosuppressants are reserved for resistant disease by most specialists. Retrospective case series indicate that mycophenolate mofetil allows improvement of muscle strength, reduction of CK levels, and tapering of GC in resistant cases of both DM and PM[65,66,67,68]. The calcineurin inhibitors cyclosporine and tacrolimus have been used successfully in cases of IIM, especially in those with pulmonary involvement[69,70,71,72,73,74,75,76]. The role of cyclophosphamide in the therapy of the IIM remains debatable because of its toxicity[77,78], but it is certainly a good alternative in very difficult cases.

Intravenous immunoglobulin (IVIG). IVIG therapy added to GC appears to be effective, as demonstrated in a double-blind, placebo-controlled trial of patients with refractory DM (2 g/kg in divided doses over 3 days)[79] and an open study of patients with PM[80]. The longterm efficacy of IVIG with or without GC use has been suggested in 3 case reports of patients with PM[81,82,83].

Table 7. Major immunosuppressants and immunomodulators used in idiopathic inflammatory myopathies.

AZA 1.5 to 3 mg/kg/day	Good efficacy-tolerance profile. Can be associated to other immunosuppressants such as MTX. Delayed onset of action (4–6 mo)
Cyclophosphamide	Particularly useful in ILD. Reserved for severe disease because of toxicity
Cyclosporine-tacrolimus	Good efficacy-tolerance profile. Can be associated to other immunosuppressants (proven superiority of cyclosporine + MTX or + IVIG). Onset of action shorter than AZA
IVIG	Efficacy demonstrated in DM, though in general insufficient in severe disease with lung involvement. Helpful in cases of concomitant chronic infections, especially viral
MTX 15–50 mg/week	Excellent efficacy-tolerance profile. Can be used in association with other immunosuppressants such as AZA. Rapid onset of action. Better to avoid in presence of lung disease
MMF ~2 g/day	Excellent efficacy-tolerance profile. Increasingly used in all autoantibody-mediated diseases
Rituximab	Excellent efficacy-tolerance profile. Increasingly used in all autoantibody-mediated diseases. Lack of controlled published data (only small case series and case reports)

AZA: azathioprine; IVIG: intravenous immunoglobulins; ILD: interstitial lung disease; MTX: methotrexate; MMF: mycophenolate mofetil.

Biological immunotherapy. The anti-tumor necrosis factor inhibitors (anti-TNF) etanercept and infliximab have shown no evident role in current treatment options of IIM[84,85,86,87,88]. Further, high incidence of disease flares has been reported with these agents[89,90], together with numerous case reports of inflammatory myopathies apparently induced by anti-TNF agents.

Rituximab, in contrast, seems a reasonable and less expensive alternative (compared to IVIG), as shown in small case series in DM and PM[91,92] and more recently in a national French registry[93]. It appears to be especially efficient in DM and when autoantibodies are present[93,94,95]. Potentially severe although relatively rare adverse effects, especially opportunistic infections including rare cases of multifocal progressive leukoencephalopathy, should be taken into consideration[96].

Nonpharmacological treatment. All subsets of IIM can benefit from nonpharmacological treatment. General measures include interventions to reduce aspiration risk in patients with dysphagia and avoidance of sunlight, use of sunscreens, and protective clothing for patients with DM rash. The role of exercise in IIM was initially seen as potentially deleterious, especially in juvenile DM, but was subsequently shown to be efficacious and safe[97]. A recent systematic review of the studies assessing exercise training programs in adult patients with IIM concluded that exercise training appears safe and effective in adult patients with active as well as inactive stable IIM[98].

NAM. NAM, including the anti-SRP syndrome, usually responds well to immunosuppressive therapies, and a rather aggressive approach is generally to be adopted. In addition, an underlying cause must be sought with particular attention, especially when anti-SRP antibodies are not present. Whenever identified, the cause must be addressed (malignancy treatment, cessation of statin, or changing antiretroviral treatment).

S-IBM. Management of s-IBM is much more challenging. No treatment has shown convincing and reproducible results. The effects of GC and non-GC immunosuppressants (such as MTX, AZA, and cyclosporine) are at most modest, probably because of the less evident immunoinflammatory reaction and the progressive decline of muscle strength[24]. In the absence of convincing alternatives, immunosuppressants have been advocated, when possible, shortly after diagnosis, because of their presumed better efficiency early in the disease course[24]. However, the observational study of 136 patients with s-IBM in 2 European centers suggested that morbidity was higher in treated than in untreated patients with s-IBM, thus reflecting a possible deleterious effect of the immunosuppressants or that more severely affected patients were treated rather than the less disabled[25]. IVIG therapy was shown to be inefficacious in one controlled study[99], but minimally effective for dysphagia in another[100], a result that has never been replicated. The possible improvement of muscle strength with oxandrolone[101] might also be an interesting alternative, but the results of that pilot study need to be confirmed.

The discovery of numerous new antibodies and the refinement of efficient imaging techniques significantly improved diagnosis and comprehension of IIM, while treatment and management have improved, particularly for difficult cases, with the development and better understanding and use of several drugs, including mycophenolate mofetil and rituximab. However, histopathological analysis definitely remains important. The diagnosis and classification of IIM is still disputed, with some entities such as DM relatively well defined and universally recognized, and

others such as pure PM more uncertain. Research efforts are continuing and it is hoped they will soon provide reliable criteria, which should accelerate assessments of different treatment options, including newer drugs, in controlled studies. Physicians guided by treatment decisions according to the type and severity of specific manifestations can offer satisfactory care to most patients. Aggressive disease, including some cases of necrotizing myopathy, remains refractory to treatment. Sporadic inclusion body myositis remains resistant to all tested medications.

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Classification, Diagnosis, and Management of Idiopathic Inflammatory Myopathies

Lazarou IN, Guerne P-A. Classification, diagnosis, and management of idiopathic inflammatory myopathies. J Rheumatol 2013;40:550-64. A photographic credit for Figure 1 should be given as follows. We regret the error.

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