Myositis-specific antibodies: Overview and clinical utilization

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Purpose of review—To review autoantibodies associated with different subtypes of idiopathic inflammatory myopathy (IIM) and their clinical applications. IIM are a heterogenous group of autoimmune disorders characterized by muscle weakness, cutaneous features, and internal organ involvement. The diagnosis and classification, which is often challenging, is made using a combination of clinical features, muscle enzyme levels, imaging, and biopsy. The landmark discoveries of novel autoantibodies specific to IIM subtypes have been one of the greatest advancements in the field of myositis. The specificity of these autoantibodies has simplified the diagnostic algorithm of IIM with their heterogenous presentation and outdated the earlier diagnostic criteria. Myositis-specific antibodies (MSAs) have improved diagnostics, clinical phenotyping, and prognostic stratification of the subtypes of IIMs. Furthermore, the levels of certain MSAs correlate with disease activity and muscle enzyme levels such that titers may be able to be used to predict disease course and treatment response.

Abstract

Progressive muscle weakness and arthritis can significantly impair the functioning of individuals, which leads to the loss of independence. IIM are also associated with interstitial lung disease and increased malignancy risk that are accompanied by significant morbidity and mortality making early diagnosis imperative. In addition, IIM have a heterogenous phenotype that can make diagnosis challenging. The initial 1975 Bohan and Peter’s diagnostic criteria of myositis is markedly outdated as it was formulated before the discovery of myositis-specific antibodies (MSAs). Targoff and Colleagues modified these criteria by proposing an addition of a sixth criterion of MSA.

Autoimmunity is well established to be at the root of the pathogenesis of IIM with unique autoantibodies targeting nuclear and cytoplasmic antigens identified. While the autoantibodies that are specific to myositis are referred to as MSAs, the antibodies that are frequently seen in connective tissue diseases (CTD) associated with myositis are termed as myositis-associated antibodies (MAA). In the era of improved autoantibody testing and availability, an estimated 60–70% of patients with juvenile and adult onset of myositis have a recognizable MSA. These MSAs are crucial in the diagnosis, clinical phenotyping, and prognostication of IIMs. They are especially useful in delineating non-classical presentation and muscle enzyme levels such that titers may be able to be used to predict disease course and treatment response.

Keywords
autoantibodies • anti-synthetase syndrome • dermatomyositis • inclusion body myositis • myositis • necrotizing myopathy

Introduction

Idiopathic inflammatory myopathy (IIM), collectively referred to as “myositis,” comprise a group of autoimmune diseases characterized by proximal muscle weakness, skin disease, and internal organ involvement. Based on their clinicopathologic features, they can be subclassified into dermatomyositis (DM), polymyositis, inclusion body myositis (IBM), immune-mediated necrotizing myopathy (IMNM), and anti-synthetase syndrome (ASS). IIM have an estimated prevalence of 2.4–33.8 per 100,000 and a projected annual incidence of 1.16–19 new cases per million from a systematic analysis.

Progressive muscle weakness and arthritis can significantly impair the functioning of individuals, which leads to the loss of independence. IIM are also associated with interstitial lung disease and increased malignancy risk that are accompanied by significant morbidity and mortality making early diagnosis imperative. In addition, IIM have a heterogenous phenotype that can make diagnosis challenging. The initial 1975 Bohan and Peter’s diagnostic criteria of myositis is markedly outdated as it was formulated before the discovery of myositis-specific antibodies (MSAs). Targoff and Colleagues modified these criteria by proposing an addition of a sixth criterion of MSA.

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This review will briefly discuss the clinical features of IIM subtypes with an emphasis on the role of their respective MSA in improving diagnostics, clinical phenotyping, and prognostic stratification. Where applicable, we will discuss the potential role of MSAs in monitoring disease activity. The delivery of personalized treatment regimens based on certain MSA, while tantalizing, is beyond the scope of this review.

How are MSAs Detected?

MSAs can be detected using a variety of methods, each of which has its own advantages and disadvantages. While immunofluorescence has the advantage of being widely available, it is frequently unable to detect MSA/MAA.[8] The counter-immune electrophoresis and immunodiffusion can be used to screen for multiple MSA/MAAs but it is limited by low sensitivity.[7] While enzyme-linked immunosorbent assay (ELISA) is a very reliable method and can screen multiple samples at once and further quantify antibody titer, not all MSAs are amenable to this testing.[7] Specialist laboratories are able to utilize immunoblotting and line-blotting, radiolabeled immunoprecipitation. Immunoprecipitation has high sensitivity and can detect both known and unknown antibodies; however, it is labor intensive and limited to specialist centers.[8] In recent years, the introduction of commercial line immunoblot assay (LIA) has helped to improve both the availability and diagnostic accuracy of myositis subtypes, given that the routine use of IP is very hard in clinical practice.[9]

Myositis-Associated Antibodies (MAAs)

The general adult population has an estimated 20% identifiable MAA.[10] These MAAs can be found in many CTD-associated with myositis. Despite limited specificity, these MAAs are useful in predicting clinical phenotype and aiding diagnosis.

The important MAAs noteworthy of mention are anti-PMScl, anti-U1-snRNP, anti-Ku, anti-SSA (Ro60, Ro52), and anti-SSB (La).

Anti-PMScl

Anti-PMScl, which is erroneously named, is not only closely associated with a scleroderma/polymyositis overlap, but a DM/scleroderma overlap as well. Lega et al.[10] detected anti-PMScl in 17% of patients with overlap syndrome of PM and systemic sclerosis compared to 6% in PM alone in their meta-analysis. It is one of the most common MAAs. When present, it increases the risk of Interstitial lung disease (ILD), arthritis, mechanics hands, and Raynaud’s phenomenon.[11] Where prognosis is concerned, only a 10% remission was found by Marie et al.[12] in their long-term study of polymyositis/DM found when anti-PMScl is present. It is the authors’ experience that the scleroderma features may be very subtle. Patients may only present with Raynaud’s or small telangiectasias on the chest or face in the absence of frank sclerodactyly or tight skin on the face or extremities. Thus, a high level of diagnostic suspicion is warranted in such overlap syndromes.

Anti-U1-snRNP

Anti-U1-snRNP is classically found in mixed connective tissue disease (MCTD) in which patients have at least two of either systemic sclerosis, myositis, or SLE. Patients with anti-U1-snRNP usually have Raynaud’s phenomenon and are at increased risk of arthritis, ILD, and pulmonary arterial hypertension.[13] It is only seen in 3–8% of adult and juvenile DM/PM compared to the 25–40% of patients with MCTD.[13] In contrast to anti-PMScl, anti-U1-snRNP positivity has been associated with a more robust steroid responsiveness.[13]

Anti-Ku

Anti-Ku antibodies are found in myositis patients that have overlap syndromes of SLE, scleroderma, and Sjogren’s syndrome. Their estimated prevalence is 9–19% of patients with overlap syndromes.[10] Anti-Ku positivity is associated with increased arthralgia, musculoskeletal manifestations, Raynaud’s phenomenon, and ILD.[14] Prognosis varies depending on clinical manifestations, with musculoskeletal features responding well to high dose steroids and ILD often being steroid resistant.[14]

Anti-SSA (Ro60, Ro52) and Anti SSB (La)

These MAAs were first described in SLE and Sjogren’s syndrome. Anti-SSA is seen in 9–19% of adult PM/DM patients and 6% of juvenile DM patients while anti-SSB is seen in 2–7% of PM/DM.[15] Sole anti-Ro52 positivity in the absence of anti-Ro52 and anti-SSB (La) is associated with CTD only.[15] In CTD, anti-Ro60 and anti-Ro52 are seen in equal frequency, whereas in myositis anti-Ro52 is more common occurring in 30% of patients.[16] Anti-Ro52 antibodies frequently co-exist with anti-Jo1 antibodies with an estimated 72% co-existence.[15] The occurrence is linked with increased mechanics hands, malignancy, and poorer outcome than if anti-Jo1 alone was present, often with an increased severity of ILD when present.[16]

Clinical Implications of Myositis-Specific Autoantibodies

IIM have a heterogenous phenotype that can make diagnostics challenging. On the other hand, MSAs are exclusive to IIM, and it is also very rare for >1 MSA to be identified in the same individual making it an ideal biomarker.[11] More than 20 MSAs have been identified, and they allow the classification of IIM into subtypes with homogenous clinical features. Here, we discuss the different MSAs according to their IIM subset. Under each MSA, we discuss discovery, prevalence,
associated clinical features, prognosis, and where relevant titer monitoring. For simplification purposes, ILD is mostly discussed under Mmelanoma differentiation-associated protein 5 (MDA5) and the ASS where it is seen with the highest frequency. Non-anti-synthetase related ILD is discussed separately. Additionally, cancer-associated myositis is discussed both within individual IIMs and separately to allow recognition of the different IIM MSAs that have been linked with malignancy.

**Anti-synthetase Syndrome (ASS)**

ASS is the most common phenotype of myositis encountered in adult IIM.\(^1\) It presents with ILD, Raynaud’s phenomenon, mechanic’s hands, nonerosive arthritis, and occasionally a cutaneous rash. The juvenile form of ASS presents very similarly to adult ASS including the rates of ILD, but anti-synthetase antibodies (ASA) occur at a much lower frequency in juvenile ASS (2–4%) and it is less fatal.\(^16,18\) Eight distinct subtypes of ASA have been described: anti-Jo-1, anti-PL7, anti-PL12, anti-Zo, anti-Ha, anti-KS, anti-OJ, and anti-EJ.\(^2\)

**Anti-synthetase Antibodies (ASA)**

ASA target the aminoacyl-tRNA synthetase which is a cytoplasmic enzyme that catalyzes the loading of specific amino acids unto their respective tRNA. ASA are the most common MSA detected in up to 35–40% of patients with IIM.\(^20\) Within the ASS subgroups, phenotypic differences exist depending on the subtype of ASA present. Outside of a few exceptions, usually only autoantibody against one synthetase is found in a given ASS. For simplification purposes, we will discuss the ASA subdividing them into anti-Jo-1 and non-anti-Jo-1.

**Anti-Jo-1**

Anti-Jo-1 or anti-histidyl-tRNA synthetase was first detected in 1980 from the serum of a patient, John P with PM and ILD where the name is derived from. ASA is the most common MSA, found in an estimated 9–24% of adult IIM patients while the other non-Jo-1 antibodies are found in 10–20% IIM.\(^16,21\) In their meta-analysis of 27 studies to delineate the clinical characteristics of ASA, Lega et al.\(^16\) found the presence of anti-Jo1 is associated with more frequent mechanic’s hands, arthritis, and myositis. Raynaud’s phenomenon is an early feature in anti-Jo-1 positive patients and may precede myositis onset.\(^23\) ILD is very closely related to ASS with an estimated 70–95% occurrence of ILD in ASS patients.\(^23\) It can be the presenting symptom in 33% patients, ILD and myositis developed simultaneously in 60%, while myositis preceded ILD in only 7%.\(^24\) The presentation of ILD can be incidental, subacute, or very acute. ASA positive ILD is more likely to respond to steroids than ASA negative ILD.\(^25\) Anti-Jo-1 positive ASA patients appear to have better 5- and 10-year survival when compared to non-Jo-1 counterparts but it is unclear if this is the result of widespread anti-Jo1 testing availability allowing for earlier diagnosis.\(^20\) Furthermore, the RIM study looking at Rituximab response in myositis, found presence of anti-Jo-1 to strongly predict clinical response.\(^25,26\) Anti-Jo-1 levels modestly correlate with Creatine kinase (CK) levels and activity in muscle and joints that titers could be useful in predicting both disease course and response to treatment.\(^27\)

**Non-Jo-1 Antibodies**

The remaining non-Jo-1 antibodies are anti-Jo-1 (anti-histidyl-tRNA synthetase), anti-PL7 (anti-threonyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-Zo (anti-phenylalanyl-tRNA synthetase), anti-Ha (anti-tyrosyl-tRNA synthetase), anti-KS (anti-asparagyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), and anti-EJ (anti-glycyl-tRNA synthetase).\(^4\) The frequency of each individual autoantibody varies from 1% to 5%.\(^26\) Given the rarity of the non-Jo-1 antibodies and the paucity of information available on them, data should be interpreted with caution.

Anti-PL12 is very rare, found in <2% of myositis patients.\(^22\) The presence of anti-PL-12 is associated with features that overlap with systemic sclerosis such as skin sclerosis, esophageal involvement, and pulmonary hypertension.\(^23\) ILD, the most common cause of death correlates with presence of anti-PL12, anti-PL 7, anti-OJ, and especially anti-KS has been linked with severe ILD.\(^26\) Cutaneous manifestations, while not always classical DM rashes, are more common in anti-EJ, anti-PL12, and anti-PL7.\(^29\) Within ASS, the identification of anti-Jo 1, anti-PL7, and anti-EJ correlates strongly with prominent myopathic features.\(^26\) Arthritis is rare in anti-OJ positive patients.\(^29\) Anti-Ha and anti-Zo are the most recently identified ASA, limited to case reports and there is a paucity of information regarding their clinical phenotype or prognosis. ASS may have a poorer prognosis owing to the irreversibility of pulmonary involvement and the potential development of secondary pulmonary hypertension, especially in longstanding disease.\(^17\)

**Dermatomyositis (DM)**

DM uniquely stands out from other IIM by the presence of characteristic cutaneous features of heliotrope rash, Gottron’s papules, V sign, and shawl sign.\(^30\) The groundbreaking discovery of anti-Mi-2 marks the identification of the first MSA, which was later proven to be specific to DM. The subsequent detections of anti-transcription intermediary factor 1γ (TIF1γ), anti-MDA5, anti-nuclear matrix protein 2 (NXP2), and anti-small ubiquitin like modifier activating enzyme (SAE) have expanded the pool of DM MSA.

A subgroup of DM patients stand out for their lack of clinical evidence of myopathy; these patients are classified as “amyopathic.” While the term denotes absence of muscle disease,
a subset of these patients actually harbor underlying subclinical muscle disease such that the term "clinically amyopathic DM" is the correct terminology. This clinical phenotype is most often associated with autoantibodies directed against MDA5 and SAE, and while the former may stay free of myopathy through the years the latter often do develop clinically detectable muscle involvement within months.

While this review focuses on adult IIM, MSAs are central in the diagnosis of juvenile DM, the most common IIM in children. MSAs are detected in 60% of juvenile DM, a number that is comparable to the adult population but the subsets of MSAs detected varies. In the juvenile population the three most commonly encountered MSAs are anti-TIF1γ, anti-NXP2, and anti-MDA5 compared to the anti-ASS, anti-Ro 52 seen in adult counterparts. Additionally, anti-TIF1γ and anti-NXP2 do not confer an increased risk of malignancy in children.

### Anti-Mi-2

Anti-Mi-2 targets a nuclear helicase protein which is a component of the nucleosome remodeling deacetylase complex that regulates gene transcription. Potentially, it may have a role in DM pathogenesis as Mi-2 is crucial in epidermal remodeling with higher levels of expression seen in DM muscle samples. The initial discovery of anti-Mi-2 was by Reichlin and Mattioli in 1976 but it was not until 1985 when Targoff et al established its specificity to DM. Anti-Mi-2 has been reported in 11–59% of adult DM patients and 4–10% of juvenile DM patient in cohort studies. Its presence is associated with classic cutaneous features such as shawl sign, increased muscle weakness, higher creatine kinase levels, and more prominent necrosis. Arthralgia, arthritis, and Raynaud's phenomenon is more prominent in the anti-Mi-2 positive DM cohorts. Conversely, anti-Mi-2 positivity has been linked with lower rates of ILD and malignancy. Patients respond well to treatment with regain of muscle strength and decline in CK levels thus boding a favorable prognosis. Significantly lower mortality rates are seen in anti-Mi-2 positive DM compared to anti-Mi-2 negative cohort. Anti-Mi-2 levels correlate well with CK levels and muscle strength, and maybe used to assess disease activity.

### Anti-SAE

Anti-SAE, which was first described by Betteridge et al in 2009, is one of the rarer MSAs seen in DM with prevalence of 2.6% in EuroMyositis registry and 0.89% in a North American Cohort. It targets the SAE that is crucial in post-translational modification of proteins through sumoylation. All the reported cases described have a cutaneous manifestation, classically the typical DM rash. Muscle weakness at presentation is often mild and can be subclinical such that patients maybe initially diagnosed with amyopathic DM which becomes more apparent as disease progresses or with more vigorous muscle screening. ILD is rare, and often mild in both European and North American cohorts with common prevalence reported in Asian cohorts. Presence of anti-SAE has been closely linked with dysphagia, with 78% compared to 43% in anti-SAE negative group. While anti-SAE antibodies were initially proposed to bear no relationship with malignancy, a 10% cancer-associated myositis was reported in North American cohort. SAE-related DM generally has a good prognosis, although skin disease can be difficult to control requiring multiple medication changes.

### Anti-TIF1γ

The TIF1 family composed of TIF1α, TIF1β, TIF1γ, and TIF1δ and these proteins are vital in many cellular pathways. Targoff et al in 2006 and Kaji et al in 2007 first identified autoantibodies targeting a 155-kDa protein and 140-kDa protein which were later identified as TIF1γ and TIF1α, respectively. Afterward, a 120-kDa protein target was identified as TIF1β. Anti-TIF1γ, which is the main target, is involved in regulation of transcription and post-translational modification. It is important in regulating cellular proliferation and tissue homeostasis through the TGF-β pathway utilizing SMAD 2/3/4. Anti-TIF1-γ have been detected in 7–31% of adult DM patients and 22–32% of juvenile DM patients with similar frequencies reported across different ethnic cohorts. Paramount to the finding of anti-TIF1-γ is its strong correlation with cancer, with an estimated 50% malignancy found in anti-TIF-γ DM patients. Trallero-Araguas et al found anti-TIF-γ to have a 78% sensitivity (95% CI 45–94%) and 89% specificity (95% CI 82–93%) for diagnosing cancer-associated myositis in their meta-analysis. This increased risk of malignancy is not seen in the under 40 age group such that Fujimoto et al have proposed classifying anti-TIF1-γ DM patients in two subgroups with a 25–39 younger group with a clinically amyopathic DM phenotype plus low malignancy risk and an older over 40 group with increased myopathy and malignancy.

Paradoxically while anti-TIF1-γ are more common in Juvenile DM than adult DM cohort, no cancer association has been reported. While the finding of anti-TIF1-γ prompted earlier screening and diagnosis of malignancy, such cancers were usually advanced at diagnosis and prognosis often hinged on feasibility of primary cancer treatment and response to immunosuppression. Malignancy aside, anti-TIF1-γ positive DM patients have a lower risk of Raynaud’s phenomenon, calcinosis, ILD with increased pruritus and lower muscle enzyme levels. Cutaneous manifestations are prominent with extensive skin involvement, and occasionally non-classic features can be seen including hyperkeratotic papules and psoriasis-like lesions.
Anti-NXP2

Anti-NXP2 targets NXP2, which functions in regulation of transcription.\(^{[59]}\) It was first identified in a US Juvenile DM cohort, initially termed anti-MJ, with subsequent characterization of its molecular role by Targoff et al.\(^{[60]}\) It has been documented in 23% of a UK Juvenile dermatomyositis (JDM) cohort and 25% of an Argentinian JDM cohort.\(^{[65,66]}\) But, while the UK cohort reported a high rate of calcinosis cutis, this was not seen in the Argentinian cohort who conversely demonstrated significant contractures of muscles. Anti-NXP2 was later identified in adults, with 1.6% prevalence in adult Japanese PM and DM cohort and 17% in both US myositis cohort and 17% of Italian myositis cohort.\(^{[62,63]}\)

Clinically, its unique feature is calcinosis cutis seen more in the JDM population than adult DM patients.\(^{[64]}\) Tansley et al. studied 285 JDM patients with a 20% anti-NXP2 prevalence in whom 33% developed calcinosis cutis, risk of which was significantly higher with younger age group.\(^{[65]}\) Anti-NXP2 presence has been robustly linked with malignancy with 31–38% cancer risk and a surprising male preponderance.\(^{[62,65]}\)

Therefore, phenotype in anti-NXP2 depends on age with increased calcinosis cutis in JDM and increased cancer risk in adult DM patients. Where myopathy is concerned, anti-NXP2 positive DM patients had severe muscle disease with greater prevalence of distal muscle weakness but no difference in proximal weakness when compared to DM without anti-NXP2.\(^{[66]}\) Furthermore, anti-NXP2 positivity was associated with increased risk of dysphagia, myalgia, and subcutaneous edema.\(^{[66]}\)

Anti-MDA5

Anti-MDA5 targets melanoma differentiation associated gene, a cytoplasmic protein involved in innate immune responses against viruses.\(^{[67]}\) It was first identified as a novel autoantibody in 2005 in a Japanese cohort.\(^{[68]}\) Anti-MDA5 positive DM patients often have mild or no obvious muscle involvement and are frequently classified under the “amyopathic dermatomyositis” category.\(^{[51]}\) Anti-MDA5 has been reported in 10–48% of an East Asian adult DM cohort with a much lower occurrence of 6.9% and 13% of US DM cohorts.\(^{[69–71]}\) The East Asian cohorts are characterized with the development of an acute and rapidly progressing ILD that is often refractory to immunosuppression with a high mortality rate.\(^{[72]}\) Death occurred from respiratory failure within 6 months of diagnosis in 45% of anti-MDA5 positive DM in a study by Nakashima et al.\(^{[72]}\) Intriguingly, when the US and European myositis cohorts were studied, anti-MDA5 positivity, while associated with ILD, did not have a rapidly progressing phenotype.\(^{[71,74]}\)

Apart from clinical amyopathy and ILD, anti-MDA5 positivity was shown to strongly correlate with cutaneous manifestations of skin ulceration, palmar papules, hand swelling, arthritis, mechanic’s hands, alopecia, and oral ulcers by Fiorentino et al.\(^{[73]}\) Phenotypically, anti-MDA5 positive DM appears like ASS but without amino-acyl-tRNA synthetases.\(^{[71]}\) Diagnosis can be delayed due to attenuated myopathy and prognosis varies from the rapidly progressing ILD that is resistant to immunosuppression to the clinically amyopathic picture with cutaneous manifestations that is steroid responsive.\(^{[71]}\)

Where JDM is concerned, anti-MDA5 was found in 7% of UK JDM patients with a 19% non-progressive ILD similar to the adult cohorts in the United Kingdom and Europe with comparable cutaneous, myopathic, and arthritic manifestations.\(^{[70]}\)

Muro et al.\(^{[70]}\) reported disappearance of anti-MDA5 titer during periods of remission highlighting a possible utility in monitoring disease activity but Hall et al. did not find connection between titers and clinical course.\(^{[71]}\)

Immune-Mediated Necrotizing Myositis (IMNM)

Aside from associations with anti-SRP, IMNM was often classified as one of the autoantibody negative IIM until 2009 when a novel antibody later defined as anti-HMGCR was discovered in necrotizing myopathy.\(^{[63,77]}\) Classically IMNM presents with prominent myopathy, significant elevations in creatine kinase level with muscle biopsy showing prominent necrosis of myocyte fibers with minimal inflammatory infiltrate.\(^{[78]}\) Statin exposure is a well-established risk factor, with persistence of myopathy post cessation of statins being the main distinction between IMNM and self-limited statin-induced myopathy.\(^{[63]}\)

Anti-HMGCR

Anti-HMGCR targets 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), an enzyme in the rate limiting step of cholesterol synthesis and is the main site of action of statins.\(^{[77]}\) The discovery of anti-HMGCR first started in 2009 with the identification of a novel antibody in necrotizing myopathy targeting anti-200/100 kDa protein.\(^{[79]}\) This autoantigen was later characterized in 2010 by the same team as HMGCR, a 100 kDa protein.\(^{[77]}\) Presence of DRB1*11:01 haplotype increases risk of being positive for anti-HMGCR.\(^{[80]}\)

Statin exposure is used extensively in cardiovascular prevention, and their main target is HMGCR. While statin use upregulates HMGCR expression, interestingly, statin exposure was only found in 40–60% of IMNM.\(^{[81]}\) Association with statins is more robust in elderly population, with 92% of patients in over age 50 anti-HMGCR cohort reporting a history of statin exposure.\(^{[77]}\) Conversely, a weaker association was seen in French and Japanese cohorts with 44% and 38% respectively endorsing past statin exposure.\(^{[82,83]}\)
Anti-HMGCR positivity was associated with more insidious onset of muscle weakness.\textsuperscript{[82]} Patients respond variably to steroids with some clinicians electing to omit using steroids, but relapse is frequent with weaning of steroids. Steroid refractoriness occurs more in statin naïve patients and younger patients.\textsuperscript{[83]} Anti-HMGCR titers are reliable markers of disease activity, levels correlate well with CK levels with decrease in titers seen with clinical response.\textsuperscript{[84]}

**Anti-SRP**

Anti-SRP targets signal recognition protein which is a cytoplasmic ribonucleolar protein which transports synthesized proteins to the endoplasmic reticulum.\textsuperscript{[85]} It was first described in 1986 by Reeves \textit{et al}\textsuperscript{[86]} as a novel autoantibody in sera of patients with polymyositis. Anti-SRP is found in 4% of Caucasian DM/PM cohorts, 13% in a Chinese IIM cohort and 10.5% in an African American IIM cohort.\textsuperscript{[87–89]} Love \textit{et al} hypothesized that variations in frequency across ethnic groups could potentially be ascribed to a DR5 HLA genotype.\textsuperscript{[90]}

Anti-SRP commonly presents with IMNM with classic features of severe necrotizing myopathy in the form of a rapidly progressive, debilitating muscle weakness.\textsuperscript{[90]} Creatinine kinase is markedly elevated, minimal or absent inflammation on muscle biopsy with partial or no response to steroids.\textsuperscript{[90]}

Patients have increased risk of esophageal dysmotility with lower rates of cutaneous involvement.\textsuperscript{[86]} Presence of anti-SRP heralds a poor prognosis with increased mortality rates by virtue of myopathy that is refractory to conventional immunosuppression.\textsuperscript{[91]} Anti-SRP titers have been shown to correlate with CK enzyme level proposing possible utility in monitoring disease activity but this yet to be established.\textsuperscript{[92]} The presence of anti-SRP in juvenile myositis patients remains limited to case reports due to its very rare occurrence with the few cases reported showing a comparable presentation to adult cohorts.\textsuperscript{[85]}

**Inclusion Body Myositis Autoantibody**

IBM is uniquely different from other IIMs with its slowly progressive course, distal or asymmetric myopathy, and steroid refractoriness.\textsuperscript{[92]} Peculiar muscle groups are affected including quadriceps, finger flexors, and pharyngeal muscle causing dysphagia.\textsuperscript{[93]} Diagnosis is established using clinical features, muscle enzyme levels and biopsy showing rimmed vacuoles and eosinophilic cytoplasmic inclusions.\textsuperscript{[86]} There is often delay in diagnosis due to insidious nature of IBM, and characteristic histology features may be absent early in disease.\textsuperscript{[94]} Anti-cN1A is the only MSA recognized in IBM.

**Anti-cN1A**

Anti-cN1A targets cytosolic 5’nucleotidase 1A, a cytoplasmic protein involved in hydrolysis of adenosine monophosphate to adenosine and dephosphorylation of nucleotides to nucleosides.\textsuperscript{[95]} IBM was long believed to be a cytotoxic T cell mediated disease devoid of a humoral response which led to its labeling as a primary neurodegenerative disease until Salajegheh \textit{et al}\textsuperscript{[96]} and Pluk \textit{et al} in 2001 identified a 43-kDa protein and 44-kDa protein, respectively. Anti-cN1A was found in 37% of a European IBM cohort in a study by Herbert \textit{et al}.\textsuperscript{[97]} Comparing anti-cN1A positive with anti-cN1A negative IBM patients in a European cohort; the only significant difference found was increased esophageal dysmotility in the anti-cN1A group.\textsuperscript{[93]} There was no difference in age or disease duration and functional score, while lower in the anti-cN1A positive group, was not statistically significant.\textsuperscript{[93]} Anti-cN1A enables early IBM diagnosis, and while, there is no effective treatment, accurate diagnosis is essential as patients misclassified with polymyositis will receive steroids which worsens IBM course.\textsuperscript{[98]} Furthermore, presence of anti-cN1A has been linked with increased mortality risk that persists when age and comorbidity are accounted for.\textsuperscript{[94]} It is important to highlight that while anti-cN1A was initially hailed for its specificity a high prevalence reported in primary Sjogren’s syndrome (36%) and SLE (20%) is now also appreciated.\textsuperscript{[97, 99]}

**Polymyositis**

Historically, polymyositis was used to describe patients with muscle weakness and elevated muscle enzymes who lacked cutaneous features. More recently, it has become recognized that true polymyositis is actually a rare entity, most of the labeled patients eventually develop connective tissue disease or are found in conjunction with the ASS in the absence of a rash.\textsuperscript{[100]} Additionally, some are now appreciated to be more correctly labeled as IMNM. Finally, IBM can be frequently misdiagnosed as PM, especially when primary inflammation is present on muscle biopsy while other classical features such as red-rimmed vacuoles are absent. Additional diagnoses to consider upon referral of a patient with “polymyositis” are metabolic myopathies and muscular dystrophies.

**Cancer-Associated Myositis**

Cancer-associated myositis refers to myositis diagnosed within 3 years of a malignancy. IIM are strongly associated with cancer, with an estimated prevalence between 6.7% and 32% in myositis patients.\textsuperscript{[101]} The strongest association is seen with DM and a weaker association with IMNM. The two antibodies worth mentioning in cancer-associated myositis are antibodies targeting TIF1γ and less commonly NXp2.\textsuperscript{[62]} Anti-NXP2 autoantibodies are associated with a non-statistically significant increase in malignancy risk.\textsuperscript{[62]} Other antibodies that have been proposed to confer an increased risk of malignancy include ant-HMGCR, anti-Mi2, and antibodies to SAE.\textsuperscript{[102,103]}
Interstitial Lung Disease

ILD can be seen in IIM, and sometimes may be the only manifestation of myositis.\(^7\) Its presence signifies an increased risk of mortality due to its irreversible nature.\(^33,104\) The autoantibodies seen frequently in IIM-related ILD include anti-Jo 1, anti-PM/Scl, and anti-MDA5.\(^30,105\) A rapidly progressing ILD with a high mortality rate is seen in anti-MDA5; these patients may lack clinical evidence of myopathy which further delays the diagnosis.\(^106\) Conversely, anti-Jo1 antibody confers a better prognosis than ILD with anti-PL7 and anti-PL 12 which are associated with more severe ILD.\(^20,105\)

While, anti-PM/Scl is considered an MAA because it is specific to systemic sclerosis, its ILD can present very similarly to anti-synthetase.\(^107\)

Conclusions

In this review, we have highlighted MSA and their autoantigen target. Over the last decade, an increasing number of MSAs/MAAs have been identified. MSAs have improved diagnostics, clinical phenotyping, and prognostication. It is conceivable that their titers can be used to predict disease course and treatment response. Utilization of these MSA has allowed an additional 20% of adult IIM cases and 55% of juvenile myositis to be diagnosed.\(^33\) As more MSAs are identified, the future focus will be on the delivery of personalized treatments defined by specific MSA. Additionally, there is need to increase both availability of assays and standardization in MSA detection to ensure uniformity.

References

[1] Meyer A, Meyer N, Schaeffer M, et al. Incidence and Prevalence of Inflammatory Myopathies: A Systematic Review. Rheumatology (Oxford), 2015;54(1):50–63.
[2] Bohan A, Peter JB. Polymyositis and Dermatomyositis (Second of Two Parts). N Engl J Med, 1975;292(8):403–407.
[3] Targoff IN, Miller FW, Medsger TA Jr, et al. Classification Criteria for the Idiopathic Inflammatory Myopathies. Curr Opin Rheumatol, 1997;9(6):527–535.
[4] Betteridge Z, McHugh N. Myositis-Specific Autoantibodies: An Important Tool to Support Diagnosis of Myositis. J Intern Med, 2016;280(1):8–23.
[5] Mahler M, Fritzler MJ. Detection of Myositis-Specific Antibodies: Additional Notes. Ann Rheum Dis, 2019;78(5):e45.
[6] Kavanaugh A, Tomar R, Reveille J, et al. Guidelines for Clinical Use of the Antinuclear Antibody Test and Tests for Specific Autoantibodies to Nuclear Antigens. American College of Pathologists. Arch Pathol Lab Med, 2000;124(1):71–81.
[7] Phan TG, Wong RCW, Adelstein S. Autoantibodies to Extractable Nuclear Antigens: Making Detection and Interpretation More Meaningful. Clin Diagn Lab Immunol, 2002;9(1):1–7.
[8] Tansley S, Gunawardena H. The Evolving Spectrum of Polymyositis and Dermatomyositis – Moving Towards Clinicoserological Syndromes: A Critical Review. Clin Rev Allergy Immunol, 2014;47(3):264–273.
[9] Ghirardello A, Rampudda M, Ekholm L, et al. Diagnostic Performance and Validation of Autoantibody Testing in Myositis by a Commercial Line Blot Assay. Rheumatology (Oxford), 2010;49(12):2370–2374.
[10] Lega JC, Fabien N, Reynaud Q, et al. The Clinical Phenotype Associated with Myositis-Specific and Associated Autoantibodies: A Meta-analysis Revisiting the So-called Antisynthetase Syndrome. Autoimmun Rev, 2014;13(9):883–891.
[11] Muro Y, Hosono Y, Sugiuira K, et al. Anti-PM/Scl Antibodies are found in Japanese Patients with Various Systemic Autoimmune Conditions Besides Myositis and Scleroderma. Arthritis Res Ther, 2015;17(1):57.
[12] Marie I, Lahaxe L, Benveniste O, et al. Long-term Outcome of Patients with Polymyositis/Dermatomyositis and Anti-PM-Scl Antibody. Br J Dermatol, 2010;162(2):337–344.
[13] Coppo P, Clauvel JP, Bengoufa D, et al. Inflammatory Myositis Associated with Anti-U1-small Nuclear Ribonucleoprotein Antibodies: A Subset of Myositis Associated with a Favourable Outcome. Rheumatology (Oxford), 2002;41(9):1040–1046.
[14] Rigolet A, Musset L, Dubourg O, et al. Inflammatory Myopathies with Anti-Ku Antibodies: A Prognosis Dependent on Associated Lung Disease. Medicine (Baltimore), 2012;91(2):95–102.
[15] Defendenti C, Atzeni F, Spina MF, et al. Clinical and Laboratory Aspects of Ro/SSA-52 Autoantibodies. Autoimmun Rev, 2011;10(3):150–154.
[16] Marie I, Hatron PY, Dominique S, et al. Short-term and Long-term Outcome of Anti-Jo1-positive Patients with Anti-Ro52 Antibody. Semin Arthritis Rheum, 2012;41(6):890–899.
[17] Witt LJ, Curran JJ, Strek ME. The Diagnosis and Treatment of Antisynthetase Syndrome. Clin Pulm Med, 2016;23(5):218–226.
[18] Rider LG, Shah M, Mamroyva G, et al. The Myositis Autoantibody Phenotypes of the Juvenile Idiopathic Inflammatory Myopathies. Medicine (Baltimore), 2013;92(4):223–243.
[19] Tansley SL, Simou S, Shaddick G, et al. Autoantibodies in Juvenile-onset Myositis: Their Diagnostic Value and Associated Clinical Phenotype in a Large UK Cohort. J Autoimmun, 2017;84:55–64. doi: 10.1016/j.jaut.2017.06.007.
[20] Aggarwal R, Cassidy E, Fertig N, et al. Patients with Non-Jo-1 Anti-rRNA-synthetase Autoantibodies have Worse Survival than Jo-1 Positive Patients. Ann Rheum Dis, 2014;73(1):227–232.

[21] Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and Distinct Clinical Features in Adult Patients with Anti-aminoacyl-tRNA Synthetase Antibodies: Heterogeneity Within the Syndrome. PLoS One, 2013;8(4):e60442.

[22] Cojocaru M, Cojocaru IM, Chicos B. New Insights into Antisynthetase Syndrome. Maedica (Bucur), 2016;11(2):130–135.

[23] Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-Associated Interstitial Lung Disease. Am J Respir Crit Care Med, 2001;164(7):1182–1185.

[24] Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase Syndrome. Curr Rheumatol Rep, 2011;13(3):175–181.

[25] Yoshifuji H, Fujii T, Kobayashi S, et al. Anti-aminoacyl-tRNA Synthetase Antibodies in Clinical Course Prediction of Interstitial Lung Disease Complicated with Idiopathic Inflammatory Myopathies. Autoimmunity, 2006;39(3):233–241.

[26] Hozumi H, Enomoto N, Kono M, et al. Prognostic Significance of Anti-aminoacyl-tRNA Synthetase Antibodies in Polymyositis/Dermatomyositis-associated Interstitial Lung Disease: A Retrospective Case Control Study. PLoS One, 2015;10(3):e0120313.

[27] Stone KB, Oddis CV, Fertig N, et al. Anti-Jo-1 Antibody Levels Correlate with Disease Activity in Idiopathic Inflammatory Myopathy. Arthritis Rheum, 2007;56(9):3125–3131.

[28] Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific Autoantibodies: Their Clinical and Pathogenic Significance in Disease Expression. Rheumatology (Oxford), 2009;48(6):607–612.

[29] Shi J, Li S, Yang H, et al. Clinical Profiles and Prognosis of Patients with Distinct Antisynthetase Autoantibodies. J Rheumatol, 2017;44(7):1051–1057.

[30] Sigurgeirsson B, Lindelöf B, Edhag O, et al. Risk of Cancer in Patients with Dermatomyositis or Polymyositis. A Population-based Study. N Engl J Med, 1992;326(10):1621–1625.

[31] Bailey EE, Fiorentino DF. Amyopathic Dermatomyositis: Definitions, Diagnosis, and Management. Curr Rheumatol Rep, 2014;16(12):465.

[32] Betteridge ZE, Gunawardena H, Chinoy H, et al. Clinical and Human Leucocyte Antigen Class II Haplotyping of Autoantibodies to Small Ubiquitin-like Modifier Enzyme, a Dermatomyositis-specific Autoantigen Target, in UK Caucasian Adult-onset Myositis. Ann Rheum Dis, 2009;68(10):1621–1625.

[33] McHugh NJ, Tansley SL. Autoantibodies in Myositis. Nat Rev Rheumatol, 2018;14(5):290–302.

[34] Wang HB, Zhang Y, Mi2, an Auto-antigen for Dermatomyositis, is an ATP-dependent Nucleosome Remodeling Factor. Nucleic Acids Res, 2001;29(12):2517–2521.

[35] Kashiwagi M, Morgan BA, Georgopoulos K. The Chromatin Remodeler Mi-2beta is Required for Establishment of the Basal Epidermis and Normal Differentiation of its Progeny, Development, 2007;134(8):1571–1582.

[36] Reichlin M, Mattioli M. Description of a Serological Reaction Characteristic of Polymyositis. Clin Immunol Immunopathol, 1976;5(1):12–20.

[37] Targoff IN, Reichlin M. The Association Between Mi-2 Antibodies and Dermatomyositis. Arthritis Rheum, 1985;28(7):796–803.

[38] Feldman BM, Reichlin M, Laxer RM, et al. Clinical Significance of Specific Autoantibodies in Juvenile Dermatomyositis. J Rheumatol, 1996;23(10):1794–1797.

[39] Petri MH, Satoh M, Martin-Marquez BT, et al. Implications in the Difference of Anti-Mi-2 and -p155/140 Autoantibody Prevalence in Two Dermatomyositis Cohorts from Mexico City and Guadalajara. Arthritis Res Ther, 2013;15(2):R48.

[40] Hengstman GJD, Egberts WTMV, Seelig HP, et al. Clinical Characteristics of Patients with Myositis and Autoantibodies to Different Fragments of the Mi-2 beta Antigen. Ann Rheum Dis, 2006;65(2):242–245.

[41] Aggarwal R, Bandos A, Reed AM, et al. Predictors of Clinical Improvement in Rituximab-treated Adult and Juvenile Dermatomyositis and Adult Polymyositis. Arthritis Rheumatol, 2014;66(3):740–749.

[42] Liang L, Zhang YM, Chen H, et al. Anti-Mi-2 Antibodies Characterize a Distinct Clinical Subset of Dermatomyositis with Favourable Prognosis. Eur J Dermatol, 2020; Publish Ahead of Print

[43] Pinal-Fernandez I, Mecoli CA, Casal-Dominguez M, et al. More Prominent Muscle Involvement in Patients with Dermatomyositis with Anti-Mi2 Autoantibodies. Neurology, 2019;93(19):e1768–e1777.

[44] Betteridge Z, Tansley S, Shaddock G, et al. Frequency, Mutual Exclusivity and Clinical Associations of Myositis Autoantibodies in a Combined European Cohort of Idiopathic Inflammatory Myopathy Patients. J Autoimmun, 2019;101:48–55.

[45] Albayda J, Mecoli C, Casciola-Rosen L, et al. A North American Cohort of Anti-SAE Dermatomyositis: Clinical Phenotype, Testing, and Review of Cases. ACR Open Rheumatol, 2021;3(5):287–294.

[46] Fujimoto M, Matsushita T, Hamaguchi Y, et al. Autoantibodies to Small Ubiquitin-like Modifier Activating Enzymes in Japanese Patients with Dermatomyositis: Comparison with a UK Caucasian Cohort. Ann Rheum Dis, 2013;72(1):151–153.

[47] Targoff IN, Mamyrova G, Trieu EP, et al. A Novel Autoantibody to a 155-kd Protein is Associated with Dermatomyositis. Arthritis Rheum, 2006;54(11):3682–3689.

[48] Kaji K, Fujimoto M, Hasegawa M, et al. Identification of a Novel Autoantibody Reactive with 155 and 140 kDa Nuclear Proteins in Patients with Dermatomyositis: An Association with Malignancy. Rheumatology (Oxford), 2007;46(1):25–28.

[49] Targoff I, Trieu E, Levy-Neto M, et al. Autoantibodies to Transcriptional Intermediary Factor 1-gamma (TIF1-γ) in Dermatomyositis. Arthritis Rheum, 2006;54:518.

[50] De Vooght J, Vulsbeck JB, De Haes P, et al. Anti-TIF1-γ Autoantibodies: Warning Lights of a Tumour Autoantigen. Rheumatology (Oxford), 2020;59(3):469–477.

[51] Fujimoto M, Watanabe R, Ishitsuka Y, et al. Recent Advances to Transcriptional Intermediary Factor 1-gamma (TIF1-γ) in Dermatomyositis. Arthritis Rheum, 2006;54:518.

[52] Hoshino K, Muro Y, Sugiu K, et al. Anti-MDA5 and Anti-TIF1-γ Autoantibodies have Clinical Significance for Patients with Dermatomyositis. Rheumatology (Oxford), 2010;49(9):1726–1733.

[53] Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O’Callaghan A, et al. Usefulness of Anti-p155 Autoantibody for Diagnosing Cancer-associated Dermatomyositis: A Systematic Review and Meta-analy-
Clinical and Serological Characterization of the Anti-MJ Antibody in Childhood Myositis. Arthritis Rheum, 1997;40:139.

Targoff I, Trieu E, Levy-Neto M, et al. Sera with Autoantibodies to the MJ Antigen React with NXP2. Arthritis Rheum, 2007;56:787.

Espada G, Cocco JAM, Fertig N, et al. Clinical and Serologic Characterization of an Argentine Pediatric Myositis Cohort: Identification of a Novel Autoantibody (anti-MJ) to a 142-kDa Protein. J Rheumatol, 2009;36(11):2547–2551.

Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most Patients with Cancer-associated Dermatomyositis have Antibodies to Nuclear Matrix Protein NXP-2 or Transcription Intermediary Factor 1y. Arthritis Rheum, 2013;65(11):2954–2962.

Ichimura Y, Matsuhashi T, Hamaguchi Y, et al. Anti-NXP2 Autoantibodies in Adult Patients with Idiopathic Inflammatory Myopathies: Possible Association with Malignancy. Ann Rheum Dis, 2012;71(5):710–713.

Tansley SL, Betteridge ZE, Shaddick G, et al. Calcinosia in Juvenile Dermatomyositis is Influenced by Both Anti-NXP2 Autoantibody Status and Age at Disease Onset. Rheumatology (Oxford), 2014;53(12):2204–2208.

Tansley S, Betteridge Z, Gunawardena H, et al. Clinical Differences Between Adult and Juvenile Dermatomyositis Associated with Anti-NXP2 Autoantibodies. Arthritis Rheum, 2012;64:S229.

Albayda J, Pinal-Fernandez I, Huang W, et al. Antinuclear Matrix Protein 2 Autoantibodies and Edema, Muscle Disease, and Malignancy Risk in Dermatomyositis Patients. Arthritis Care Res (Hoboken), 2017;69(11):1771–1776.

Sato S, Hoshino K, Satoh T, et al. RNA Helicase Encoded by Melanoma Differentiation-associated Gene 5 is a Major Autoantigen in Patients with Clinically Amyopathic Dermatomyositis: Association with Rapidly Progressive Interstitial Lung Disease. Arthritis Rheum, 2009;60(7):2193–2200.

Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd Polypeptide, CADM-140, in Japanese Patients with Clinically Amyopathic Dermatomyositis. Arthritis Rheum, 2005;52(5):1571–1576.

Chen Z, Cao M, Plana MN, et al. Utility of Anti-melanoma Differentiation-associated Gene 5 Antibody Measurement in Identifying Patients with Dermatomyositis and a High Risk for Developing Rapidly Progressive Interstitial Lung Disease: A Review of the Literature and a Meta-analysis. Arthritis Care Res (Hoboken), 2013;65(8):1316–1324.

Bodoki L, Nagy-Vincze M, Griger Z, et al. Four Dermatomyositis-specific Autoantibodies-anti-TIF1γ, Anti-NXP2, Anti-SAE and Anti-MDA5-in Adult and Juvenile Patients with Idiopathic Inflammatory Myopathies in a Hungarian Cohort. Autoimmun Rev, 2014;13(12):1211–1219.

Hall JC, Casciola-Rosen L, Samedy LA, et al. Anti-melanoma Differentiation-associated Protein 5-associated Dermatomyositis: Expanding the Clinical Spectrum. Arthritis Care Res (Hoboken), 2013;65(8):1307–1315.

Ye S, Chen XX, Lu XY, et al. Adult Clinically Amyopathic Dermatomyositis with Rapid Progressive Interstitial Lung Disease: A Retrospective Cohort Study. Clin Rheumatol, 2007;26(10):1647–1654.

Nakashima R, Imura Y, Kobayashi S, et al. The RIG-I-like Receptor IFIH1/MDA5 is a Dermatomyositis-specific Autoantigen Identified by the Anti-CADM-140 Antibody. Rheumatology (Oxford), 2010;49(3):433–440.

Betteridge Z, Tansley S, Gunawardena H, et al. Clinical Phenotypes of Caucasian Adult and Juvenile Dermatomyositis Patients with anti-MDA5 Autoantibodies. Arthritis Rheum, 2012;64:S715.

Fiorentino D, Chung L, Zwerner J, et al. The Mucocutaneous and Systemic Phenotype of Dermatomyositis Patients with Antibodies to MDA5 (CADM-140): A Retrospective Study. J Am Acad Dermatol, 2011;65(1):25–34.

Muro Y, Sugiyuki K, Hoshino K, et al. Disappearance of Anti-MDA-5 Autoantibodies in Clinically Amyopathic DM/Interstitial Lung Disease During Disease Remission. Rheumatology (Oxford), 2012;51(5):800–804.

Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies Against 3-hydroxy-3-methylglutaryl-coenzyme A Reductase in Patients with Statin-associated Autoimmune Myopathy. Arthritis Rheum, 2011;63(3):713–721.

Basharat P, Christopher-Stine L. Immune-Mediated Necrotizing Myopathy: Update on Diagnosis and Management. Curr Rheumatol Rep, 2015;17(12):72.

Christina-Stine L, Casciola-Rosen LA, Hong G, et al. A Novel Autoantibody Recognizing 200-kd and 100-kd Proteins is Associated with an Immune-Mediated Necrotizing Myopathy. Arthritis Rheum, 2010;62(9):2757–2766.

Mammen AL, Gaudet D, Brisson D, et al. Increased Frequency of DRB1*11:01 in Anti-Hydroxymethylglutaryl-Coenzyme A Reductase-Associated Autoimmune Myopathy. Arthritis Care Res (Hoboken), 2012;64(8):1233–1237.

Mammen AL. Necrotizing Myopathies: Beyond Statins. Curr Opin Rheumatol, 2014;26(6):679–683.

Allenbach Y, Drouot L, Rigolet A, et al. Anti-HMGCR Autoantibodies in European Patients with Autoimmune Necrotizing My-
ophathies: Inconstant Exposure to Statin. Medicine (Baltimore), 2014;93(3):150–157.

[83] Watanabe Y, Suzuki S, Nishimura H, et al. Statins and Myotoxic Effects Associated with Anti-3-hydroxy-3-methylglutaryl-coenzyme A Reductase Autoantibodies: An Observational Study in Japan. Medicine (Baltimore), 2015;94(4):e416.

[84] Mammen AL, Pak K, Williams EK, et al. Rarity of Anti-3-hydroxy-3-methylglutaryl-coenzyme A Reductase Antibodies in Statin Users, Including those with Self-Limited Musculoskeletal Side Effects. Arthritis Care Res (Hoboken), 2012;64(2):269–272.

[85] Rouster-Stevens KA, Pachman LM. Autoantibody to Signal Recognition Particle in African American Girls with Juvenile Polymyositis. J Rheumatol, 2008;35(5):927–929.

[86] Reeves WH, Nigam SK, Blobel G. Human Autoantibodies Reactive with the Signal-Recognition Particle. Proc Natl Acad Sci U S A, 1986;83(24):9507–9511.

[87] Targoff IN, Johnson AE, Miller FW. Antibody to Signal Recognition Particle in Polymyositis. Arthritis Rheum, 1990;33(9):1361–1370.

[88] Wang L, Liu L, Hao H, et al. Myopathy with Anti-signal Recognition Particle Antibodies: Clinical and Histopathological Features in Chinese Patients. Neuromuscul Disord, 2014;24(4):335–341.

[89] Love LA, Weinberg CR, McConnaughey DR, et al. Ultraviolet Radiation Intensity Predicts the Relative Distribution of Dermatomyositis and Anti-Mi-2 Autoantibodies in Women. Arthritis Rheum, 2009;60(8):2499–2504.

[90] Miller T, Al-Lozi MT, Lopate G, et al. Myopathy with Antibodies to the Signal Recognition Particle: Clinical and Pathological Features. J Neurol Neurosurg Psychiatry, 2002;73(4):420–428.

[91] Love LA, Leff RL, Fraser DD, et al. A New Approach to the Classification of Idiopathic Inflammatory Myopathy: Myositis-Specific Autoantibodies Define Useful Homogeneous Patient Groups. Medicine (Baltimore), 1991;70(6):360–374.

[92] Benveniste O, Drouot L, Jouen F, et al. Correlation of Anti-signal Recognition Particle Autoantibody Levels with Creatine Kinase Activity in Patients with Necrotizing Myopathy. Arthritis Rheum, 2011;63(7):1961–1971.

[93] Lucchini M, Maggi L, Pegoraro E, et al. Anti-cN1A Antibodies are Associated with More Severe Dysphagia in Sporadic Inclusion Body Myositis. Cells, 2021;10(5):1146.

[94] Lilleker JB, Rietveld A, Pye SR, et al. Cytosolic 5'-nucleotidase 1A Autoantibody Profile and Clinical Characteristics in Inclusion Body Myositis. Ann Rheum Dis, 2017;76(5):862–868.

[95] Rietveld A, van den Hoogen LL, Bizzaro N, et al. Autoantibodies to Cytosolic 5'-Nucleotidase 1A in Primary Sjögren’s Syndrome and Systemic Lupus Erythematosus. Front Immunol, 2018;9:1200.

[96] Salajegheh M, Lam T, Greenberg SA. Autoantibodies Against a 43 KDa Muscle Protein in Inclusion Body Myositis. PLoS One, 2011;6(5):e20266.

[97] Herbert MK, Stammen-Vogelzangs J, Verbeek MM, et al. Disease Specificity of Autoantibodies to Cytosolic 5'-nucleotidase 1A in Sporadic Inclusion Body Myositis Versus Known Autoimmune Diseases. Ann Rheum Dis, 2016;75(4):696–701.

[98] Benveniste O, Guiguet M, Freebody J, et al. Long-term Observational Study of Sporadic Inclusion Body Myositis. Brain, 2011;134(11):3176–3184.

[99] Aggarwal R, Dhillon N, Fertig N, et al. A Negative Antinuclear Antibody Does Not Indicate Autoantibody Negativity in Myositis: Role of Anticytoplasmic Antibody as a Screening Test for Antisynthetase Syndrome. J Rheumatol, 2017;44(2):223–229.

[100] van der Meulen MFG, Bronner IM, Hoogendijk JE, et al. Polymyositis: An Overdiagnosed Entity. Neurology, 2003;61(3):316–321.

[101] Aussie A, Boyer O, Cordel N. Dermatomyositis and Immune-Mediated Necrotizing Myopathies: A Window on Autoimmunity and Cancer. Front Immunol, 2017;8:992. doi: 10.3389/fimmu.2017.00992.

[102] Allenbach Y, Keraen J, Bouvier AM, et al. High Risk of Cancer in Autoimmune Necrotizing Myopathies: Usefulness of Myositis Specific Antibody. Brain, 2016;139(Pt 8):2131–2135.

[103] Yang H, Peng Q, Yin L, et al. Identification of Multiple Cancer-Associated Myositis-Specific Autoantibodies in Idiopathic Inflammatory Myopathies: A Large Longitudinal Cohort Study. Arthritis Res Ther, 2017;19(1):259.

[104] Johnson C, Pinal-Fernandez I, Parikh R, et al. Assessment of Mortality in Autoimmune Myositis with and without Associated Interstitial Lung Disease. Lung, 2016;194(5):733–737.

[105] Watanabe K, Handa T, Tanizawa K, et al. Detection of Antisynthetase Syndrome in Patients with Idiopathic Interstitial Pneumonias. Respir Med, 2011;105(8):1238–1247.

[106] Koga T, Fujikawa K, Horai Y, et al. The Diagnostic Utility of Anti-melanoma Differentiation-Associated Gene 5 Antibody Testing for Predicting the Prognosis of Japanese Patients with DM. Rheumatology (Oxford), 2012;51(7):1278–1284.

[107] Mahler M, Raimakers R. Novel Aspects of Autoantibodies to the PM/Scl Complex: Clinical, Genetic and Diagnostic Insights. Autoimmun Rev, 2007;6(7):432–437.