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Review Article

The Role of Autoantibodies in Idiopathic Inflammatory Myopathies

In Seol Yoo, Jinhyun Kim
Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Korea

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune muscle diseases with systemic involvement. Patients with IIM present with varying degrees of muscle disease, cutaneous manifestations, and internal organ involvement. The diagnosis and classification of IIM is based primarily on the classification system composed of clinical features, laboratory value and muscle biopsy. In addition, the identification and characterization of myositis-related autoantibodies can help diagnosis and classification. Recently, many studies have also demonstrated that the physician can define the clinical syndromes, establish treatment strategy and predict outcomes based on the patients' myositis-specific autoantibodies (MSA) and myositis-associated antibodies (MAA) profiles. MSAs are found exclusively in IIMs and facilitate the identification of subsets of patients with relatively homogeneous clinical features. MAAs are frequently found in association with other MSA; however, they may also be detected in various connective diseases. **(J Rheum Dis 2019;26:165-178)**

Key Words. Myositis, Dermatomyositis, Polymyositis, Antinuclear antibody

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are characterized by symmetric skeletal muscle weakness, neurophysiological or histological signs of muscle inflammation, elevated skeletal muscle enzymes, skin rashes and systemic organ involvement [1,2]. Based on the different clinical features and pathologic findings, they are classified into four subtypes: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myositis (IMNM), and inclusion-body myositis [3-9]. Due to this heterogeneity, patients with IIM can present with varying degrees of muscle disease, cutaneous manifestations and internal organ involvement [10-12].

The identification and characterization of autoantibodies (autoAbs) is quite helpful for the diagnosis and classification of systemic autoimmune diseases [13,14]. Recent reviews have discussed the clinical associations of myositis-related autoAbs, along with the clinical outcomes to develop appropriate management strategies [15-18]. More than 20-myositis-related autoAbs have been identified in patients with a range of clinical manifestations such as interstitial lung disease, cutaneous manifestations and cancer-associated myositis. This review highlights the current advances in autoAbs based on clinicopathological features, diagnostic utility and response to treatment.

MAIN SUBJECTS

Definition of myositis-specific antibodies and myositis-associated antibodies

Conventionally, myositis-related autoAbs have been classified into two categories: myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) [16-22]. MSAs show high specificity for IIM and are rarely found in other conditions except anti-aminoacyl transfer RNA (tRNA) synthetases (ARS). Anti-ARS

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Corresponding to : Jinhyun Kim http://orcid.org/0000-0001-5235-2612
Department of Internal Medicine, Chungnam National University College of Medicine, 266 Munhwa-ro, Jung-gu, Daejeon 35015, Korea. E-mail : jkim@cnuh.co.kr

Table 1. Target autoantigens and prevalence of myositis specific antibodies

Antibody	Antigen	Antigen function	Protein (kDa)	Prevalence in IIM (%)				
				DM	PM	OVM	CAM	JDM
Anti-ARS				20	29	13	13	1～3
Anti-Jo-1	Histidyl tRNA synthetase	Incorporate histidine into proteins	50	11	21	4	7	
Anti-PL-7	Threonyl tRNA synthetase	Incorporate threonine into proteins	80					
Anti-PL-12	Alanyl tRNA synthetase	Alanine and aspartate biosynthesis and alanine incorporation into proteins	110					
Anti-EJ	Glycyl tRNA synthetase	Glycine, serine and threonine metabolism, and aminoacyl tRNA biosynthesis	75					
Anti-OJ	Isoleucyl tRNA synthetase	Incorporate isoleucine into proteins	150+70/ 130/75					
Anti-KS	Asparaginyl tRNA synthetase	Glutamate, alanine and aspartate metabolism	65					
Anti-Zo	Phenylalanyl tRNA synthetase	Incorporate phenylalanine into proteins	60/70					
Anti-YRS/HA	Tyrosyl tRNA synthetase	Incorporate tyrosine into proteins	59					
Anti-Mi-2	Nucleosome remodelling Deacetylase (NuRD) (Mi-2 α / β)	Transcription regulation	240+200/ 150/75/65/ 63/50/34	9	1	8	9	＜10
Anti-SAE	Small ubiquitin-like modifier 1 activating enzyme (SAE1/2)	Post-translational protein modification	40/90	Adult: 3～5				1
Anti-MDA5 (anti-CADM140)	Melanoma differentiation-associated gene 5 (MDA5)	Recognizes the viral RNAs and initiate signaling events leading to type I interferon production	140	Adult: 1～30				7
Anti-TIF1 γ / α (anti-p155/p140)	Transcription intermediary factor 1 (TIF1 γ / α)	Regulation of transcription, tumor suppression, DNA damage repair and modulation of TGF-β signaling	155/140	Adult: 7				18～30
Anti-NXP-2 (anti-MJ)	Nuclear matrix protein 2	Transcription regulation and p53 activation	140	Adult: 2～17				15～20
Anti-SRP	Signal recognition particle	Regulate the recognition and translocation of proteins across the endoplasmic reticulum	72/68/54/ 19/14/9	1	5	5	11	＜1
Anti-HMGCR	HMG-CoA reductase	Rate-limiting enzyme of cholesterol synthesis	200/100	Adult: 6				1

IIM: idiopathic inflammatory myopathies, DM: dermatomyositis, PM: polymyositis, OVM: overlap myositis, CAM: cancer associated myositis, JDM: juvenile myositis, ARS: aminoacyl transfer RNA (tRNA) synthetases, Jo-1: histidyl, PL-7: threonyl, PL-12: alanyl, EJ: glycyl, OJ: isoleucyl, KS: asparaginyl, Zo: phenylalanyl, YRS/HA: tyrosyl, SAE: small ubiquitin-like modifier activating enzyme, MDA5: melanoma differentiated-associated protein 5, CADM: clinically amyopathic dermatomyositis, TIF1: transcription intermediary factor 1, NXP: nuclear matrix protein, SRP: signal recognition particle, HMGCR: 3-hydroxy-3-methylglutaryl CoA reductase, NuRD: nucleosome remodeling deacetylase, TGF: transforming growth factor.

antibodies, especially anti-PL-7, PL-12 and KS, are found in patients with idiopathic interstitial lung disease (ILD), independent of muscular involvement [23-25]. MAAs are associated with myositis; however, they are also found in other related conditions including systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). A few MAAs, such as anti-PM-Scl, U1/U2 ribonucleoprotein (RNP) and Ku are associated with overlap syndromes with muscular involvement [26]. Anti-Ro52 is usually classified as MAA. It is frequently detected in patients with MSAs such as anti-ARS, anti-melanoma differentiated-associated protein 5 (MDA5) and anti-signal recognition particle (SRP), and also frequently in patients with SLE, SSc, Sjögren syndrome, and other diseases [27].

Myositis-specific autoantibodies

MSA are found in IIMs exclusively and facilitate the identification of subsets of patients with relatively homogeneous clinical features. MSAs are summarized in Table 1.

1) Anti-ARS antibodies

Anti-ARS are a group of autoAbs directed against the aminoacyl tRNA synthetases. Currently, autoantibodies that recognize eight ARSs have been described as follows: histidyl (Jo-1), threonyl (PL-7), alanyl (PL-12), glycyl (EJ), isoleucyl (OJ), asparaginyl (KS), phenylalanyl (Zo), and tyrosyl (YRS/HA) tRNA synthetases [28,29]. They are associated with anti-synthase syndrome characterized by myositis, interstitial lung disease, non-erosive arthritis, Raynaud's phenomenon, fever, and mechanic's hands [30,31].

Anti-Jo-1 has been identified in 15%～25% of patients with PM/DM and overlap syndrome, but not in SLE, SSc, or other diseases [16,28]. Other ARS antibodies, such as anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-Ha, anti-KS and anti-Zo antibodies, are usually found only in 0.5%～6% of patients of IIM [17,22,32-34]. Regardless of race, ethnicity, or nationality, the reported frequency of various anti-ARS is very similar [17,22,32-34], except for the high frequency of anti-PL-12 antibodies detected in southern USA [35] and the high prevalence of anti-PL-7 in a Japanese cohort [36].

Several studies have reported differences in clinical manifestations depending on the types of anti-ARS. Muscle involvement and arthritis are common in patients carrying anti-Jo-1, whereas anti-PL-7 positive patients usually manifest milder muscular involvement [36]. The presence of anti-PL-7, anti-KS, anti-OJ or anti-PL-12 antibodies is associated with a higher prevalence of severe ILD [35-41]. In this group, usual interstitial pneumonia and acute interstitial pneumonia are usually detected early in disease [15,39-44]. A few studies suggested that anti-PL-12 and anti-KS are common in ILD without myositis [23,24,35]. In a recent study of 31 patients testing positive for anti-PL-12, a strong association with ILD was found but limited association with myositis and arthritis [45].

Compared with adults, juvenile dermatomyositis (JDM) is rarely associated with anti-ARS antibodies. Rider et al. [46] investigated the sera from 77 children with myositis and overlap connective tissue disease, and anti-ARS antibodies were detected in only 2.6% cases. Even in the studies reported by Feldman et al. [47] and Wedderburn et al. [48], no patient with positive anti-ARS antibodies was found [49].

2) Anti-Mi-2 antibodies

Anti-Mi-2 autoAbs were first reported as MSA in DM in 1985 [50,51]. Mi-2 antigen is a helicase belonging to the nucleosome remodeling deacetylase multi-protein complex with nucleosome remodeling and histone deacetylase/demethylase activities [16,52]. Although anti-Mi-2 immunoprecipitates this entire complex, including Mi-2 protein, histone deacetylases, histone binding proteins, and others, the 240 kDa Mi-2 protein is the major antigen composed of two proteins, Mi-2 α and Mi-2 β [53,54].

The prevalence of anti-Mi-2 ranges from 2% to 38% within adult DM populations and 4% to 10% within JDM populations [20,50,51]. These differences of prevalence are mainly attributed to differences in countries and races; however, they often differ between studies conducted in the same country [15,55]. The prevalence of anti-Mi-2 in adults varies from 5% to 27% in Italy and 2% to 19% in Japan [15]. Two studies reported very high prevalence of anti-Mi-2 in a majority of countries in Central and South America [55,56]. The prevalence was as low as 3.2% in Montreal (Canada), compared with 60% in Guatemala City (Guatemala), 36.1% in Mexico City (Mexico), and 23.1% in Santiago (Chile) [56]. These geographical variations of anti-Mi-2 positivity suggest that ultraviolet (UV) irradiation may influence the development of anti-Mi-2 and DM [56,57]. However, Petri et al. [55] showed a 59% prevalence of anti-Mi-2 among DM patients living in Mexico City, whereas it was only 12% in Guadalajara, suggesting that UV exposure was not the

only risk factor for the development of anti-Mi-2 autoAbs. A few studies reported the association between human leukocyte antigen (HLA) alleles and anti-Mi-2. HLA-DRB1*0302 was identified as the primary allelic risk factor among African Americans and HLA-DRB1*0701/DQA1*0201 as the primary allelic risk factor among European Americans [58-60].

Anti-Mi-2 is myositis-specific; it is usually associated with DM rather than PM [20]. It is associated with the classic features of DM including Gottron's papules, heliotrope rash, shawl sign, and V-sign, high creatine kinase (CK) levels, without lung involvement or cancer [15,20,50]. Anti-Mi-2-positive patients respond well to corticosteroid therapy with favorable outcomes [20,61,62]. More recently, rituximab therapy resulted in favorable treatment outcomes in anti-Mi-2 autoantibody-positive patients [63,64].

3) Anti-SAE antibodies

Anti-SAE autoAb targets the A and B subunits of small ubiquitin-like modifier 1 (SUMO-1) activating enzyme and were first identified in DM patients in 2007 [65]. SUMOs play a key role in post-transcriptional modification of specific proteins similar to ubiquitination. This process is controlled by the SUMO-Activating Enzyme (SAE), a heterodimer composed of two subunits, SAE-1 (40 kDa) and SAE-2 (90 kDa), representing the targets of anti-SAE [66]. The prevalence of anti-SAE1/2 autoAbs varies from 1% to 3% in Asian populations and 5% to 10% in European populations [66-71].

The cutaneous involvement of anti-SAE positive patients is usually severe and typically precedes muscular involvement, while another subset presented with skin and muscle disease simultaneously [66-69,71]. Dysphagia was noted in a majority of patients and was significantly more common in a Chinese study [69-71]. ILD in anti-SAE1/2-positive patients is usually mild and rare, except Japanese [69,71]. Also, patients diagnosed with pulmonary arterial hypertension were identified in Chinese and Japanese studies [69,70].

4) Anti-MDA5 antibodies

AutoAbs to MDA5 were first described by Sato et al. [72]. Anti-MDA5 autoAbs were initially designated as anti-CADM-140, because they were detected in immunoprecipitation as a 140 kDa band among patients with clinically amyopathic dermatomyositis (CADM) and rapidly progressive interstitial lung disease (RP-ILD) [72]. *MDA5* encodes a cytosolic double-stranded RNA sensor, which is a member of the family of retinoic acid-inducible gene I-like receptors, and it recognizes the viral RNAs and initiates signaling events leading to type I interferon production [73].

Anti-MDA5s are more prevalent in Asian (11%～57%) than in Caucasian populations (0%～13%) [51,61,73-77]. The HLA-DRB1*0401 and DRB1*1202 alleles in Japanese patients and the DRB1*1201 allele in Chinese patients are associated with anti-MDA5 [78,79]. Also, the DRB1*0901 is identified as a poor prognostic factor in anti-MDA5-positive patients [79].

A meta-analysis demonstrated that the anti-MDA5 autoAbs are significantly associated with DM-ILD in both Asian and Caucasian patients (odds ratio [OR], 16.47) [51,80]. The RP-ILD is associated with high mortality and poor prognosis in anti-MDA5 patients [51,81].

Numerous studies have reported the unique clinical features of anti-MDA5-positive patients. The cutaneous phenotype is often particularly severe in anti-MDA5 patients. Cutaneous manifestations include alopecia, tender papules or macules on the palmar surfaces of the metacarpophalangeal and interphalangeal joints known as 'inverse Gottron's papules', cutaneous ulcers and oral erosions [18,50,61,76,77]. Wolstencroft et al. [82] recently suggested that clinical remission of skin disease is less likely in the anti-MDA5-positive group. A high prevalence of inflammatory arthritis among anti-MDA5-positive patients has been reported in numerous studies [73,76,83]. Anti-MDA5-positive DM patients have been misdiagnosed with psoriatic or rheumatoid arthritis due to symmetric polyarthritis [76,84]. Particularly, high ferritin levels above 1,500 ng/mL are associated with poor prognosis [85,86]. A large number of anti-MDA5-positive patients (35%～74%) present fever compared with anti-MDA5-negative patients [51,87,88].

The anti-MDA5 antibody titer appears to reflect disease activity and response to therapy. Muro et al. [89] demonstrated that anti-MDA5 antibody decreased to negative levels in nine of 10 patients tested with ELISA during the remission after treatment. Among the 10 patients diagnosed with DM and RP-ILD, the mean anti-MDA5 titer before treatment was significantly lower in patients who responded to therapy and survived than in those who failed to respond, resulting in death [90].

5) Anti-TIF1 antibodies

About 20% of adults diagnosed with DM were related to

malignancies [91]. Several factors, such as male gender, old age, and severe skin lesions were positively associated with cancer [91]. Further, autoAbs to transcription intermediary factor 1 (TIF1) are associated with cancer in DM. In 2006, Targoff et al. [92] and Kaji et al. [93] independently identified two antibodies directed against 155 (TIF1 γ) and 140 (TIF1 α) kDa proteins. In addition, a third 120 kDa protein was identified as TIF1 β [94-96]. TIF1 α, TIF1 β, and TIF1 γ belong to the tripartite motif-containing protein (TRIM) superfamily (TRIM24, TRIM28, and TRIM33, respectively) involved in cell cycle regulation, mitosis and innate immunity [91]. Based on the two studies, TIF1 γ played an important role in the regulation of transcription, tumor suppression, DNA damage repair, and modulation of transforming growth factor-β signaling [96,97].

Anti-TIF1 γ autoAbs are more prevalent in Caucasian (38%～41%) than in Asian populations (7%～21%) [61,94,98-101]. The risk of malignancy was significantly higher in adult patients carrying both anti-TIF1 α and anti-TIF1 γ antibodies than in those with anti-TIF1 γ antibodies alone (73% vs. 50%; $p<0.05$) [95]. The prevalence of anti-TIF1 γ/α in cancer-associated DM varied from 22% to 100% [15]. The prevalence of malignancy in anti-TIF1 γ/α antibody-positive patients ranges from 42% to 100% [15]. A meta-analysis showed that the pooled sensitivity of anti-TIF1 γ for the diagnosis of cancer-associated DM was 78% (95% confidence interval [CI], 45%～94%), and the specificity was 89% (95% CI, 82%～93%) [102]. Solid cancers, such as those associated with ovary, lung and breast as well as hematologic malignancies are associated with anti-TIF1 γ positivity [16].

Patients with anti-TIF1 γ/α antibody manifest classic skin lesions (heliotrope rash, Gottron's papules, V-sign, and shawl sign) and rarely develop Raynaud's disease, arthralgia, or ILD [93,99].

6) Anti-NXP-2 antibodies

The autoAb to nuclear matrix protein (NXP-2 or MORC3) was found in a cohort of JDM patients, initially designated as anti-MJ [103]. NXP-2 is a 140 kDa protein, which plays an important role in epigenetic regulation, RNA metabolism, and preservation of nuclear chromatin architecture [103,104].

The prevalence of anti-NXP-2 in adult DM varies from 1.6% to 17% [105-107]. Ichimura et al. [105] reported a 1.6% (8/507) prevalence of anti-NXP-2 in a Japanese cohort, and four of eight patients were associated with malignancy. In the first study of anti-NXP-2 involving adult DM conducted in UK, the prevalence was 3% (11/393) in PM/DM, 6% in DM, and none in PM [106]. The typical signs of DM rash and ILD were more common in anti-NXP-2 positive patients. Another study involving adult patients with DM in USA reported anti-NXP-2 antibodies in 13% (16/126) of cases, associated with calcinosis (OR, 15.52) [107]. In an Italian study, the prevalence of anti-NXP-2 was 30% in DM and 17% in PM/DM [108], which was higher than in any other adult DM studies. Also, no case of malignancy was detected in the Italian cohort; however, it appeared to be related with young age compared with malignancies involving other cohorts [15,100].

A few studies of anti-NXP-2 positivity in JDM patients have been reported [109-111]. Oddis et al. [109] first described the anti-NXP-2 antibodies in 1997. The JDM patients carrying anti-NXP-2 were characterized by severe refractory DM associated with polyarthritis, joint contractures, severe calcinosis, and intestinal vasculitis [109]. In an Argentinian cohort of pediatric myositis, 16 (25%) patients had anti-NXP-2 autoAbs, which were diagnostic of a subset of patients with severe pediatric myositis characterized by muscle contractures and atrophy, and significant functional impairment [110]. In the UK/Ireland study, 37 (23%) of 162 patients with JDM tested positive for anti-NXP-2 autoAbs and were associated with a significantly higher prevalence of calcinosis (54% vs. 15% in anti-NXP-2 negative patients) [111].

Based on numerous studies, the anti-NXP-2 positive patients, especially males, carried a high risk of cancer [100,105,112,113]. Fiorentino et al. [100] reported that anti-NXP-2 was specifically associated with cancer in males (OR, 5.78; 95% CI, 1.35～24.7). In addition to cancer, the anti-NXP-2 positive patients exhibited unique clinical features, such as frequent and severe muscle weakness, myalgia, dysphagia, and peripheral edema [105,112,113]. Also, calcinosis cutis was a distinguishing feature of anti-NXP-2 in both adult DM and JDM patients [107-109,111-113].

7) Anti-SRP antibodies

The autoAbs to SRP were originally detected in a patient diagnosed with PM [114]. SRP is a complex of six proteins (9, 14, 19, 54, 68 and 72 kDa) and a 7SL RNA, which regulate protein recognition and translocation across the endoplasmic reticulum. Anti-SRPs are more frequently

bound to the 54 kDa subunit of the SRP than the others [114].

The anti-SRPs are found in 4% to 6% of patients with IIM, and a majority of them were thought to be associated with PM [115-119]. After IMNM was identified as a new subtype of IIM distinctive from PM, it was revealed that the anti-SRP antibodies was are strongly associated with IMNM, which is characterized by scarce inflammatory CD8+ endomysial mononuclear cell infiltrate, class I MHC up-regulation, necrosis and myofiber regeneration with poor response to therapy, mimicking muscular dystrophy [16,120,121]. Prevalence of IMNM in patients with anti-SRP antibodies ranges from 0% to 54% [122-125].

Anti-SRP-positive patients generally present with acute or subacute onset severe myopathy with high CK levels (often 10-fold higher than the upper limit of normal) and dysphagia caused by esophageal involvement [115-118]. A number of studies have described ILD and cardiac involvement, which has yet to be corroborated [115,117,126]. Remarkably, a striking correlation was observed between the degree of myositis based on the CK levels and the anti-SRP levels in patients receiving therapy [127].

8) Anti-HMGCR antibodies

The 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR) is the second autoantigen identified in IMNM [128,129]. HMGCR is the rate-limiting enzyme of the mevalonate pathway, which is essential for cholesterol synthesis [130]. The skeletal muscle-specific HMGCR-knockout mice exhibited postnatal myopathy with elevated serum CK levels and necrosis. Myopathy in knockout mice was completely rescued by the oral administration of mevalonate [131].

The anti-HMGCR antibodies were strongly associated with statin exposure and HLA-DRB1*11. The highest risk for the development of anti-HMGCR antibodies was observed among HLA-DR11 carriers exposed to statins [132,133]. A history of statin use is not essential to develop anti-HMGCR positive IMNM. Only 40% to 60% of patients with anti-HMGCR-positive IMNM with reported prior statin use [134-136]. Nevertheless, 76.5% to 92% of patients aged 50 and older were exposed to statins. The anti-HMGCR antibodies have been detected in 4% to 6% of patients in American and European cohorts [134,136]. Among the patients with IMNM, anti-HMGCR antibodies have been detected among nearly 62% [130].

The anti-HMGCR levels are correlated with CK levels and represent disease activity in IMNM [137,138]. Extramuscular manifestations such as skin involvement and ILD are relatively rare [137,138]. Severe limb muscle weakness, neck weakness, dysphagia, respiratory insufficiency and muscle atrophy were more frequently observed in patients carrying anti-SRP antibodies than in those with anti-HMGCR antibodies [139]. Importantly, the anti-HMGCR-positive IMNM patients carried a modestly increased risk of malignancy (standardized incidence ratio, 2.79) [140].

Anti-HMGCR-positive patients with IMNM require treatment with steroids and other immunosuppressive therapies to control the disease [135,138]. The combination of intravenous immunoglobulin (IVIG) and oral immunosuppressive agents or IVIG monotherapy may be an effective therapeutic approach to achieve remission [135,138,141]. Younger anti-HMGCR-positive patients manifest more severe disease, and may develop progressive and permanent weakness [142,143].

Myositis-associated autoantibodies

MAA are frequently found in association with other MSA (ARS, anti-MDA5 and anti-SRP, in particular); however, they also can be detected in various connective diseases. MAA are summarized in Table 2.

1) Anti-PM-Scl antibodies

The PM-Scl autoantigen was first identified in 1977 in the sera of patients diagnosed with PM [144]. In 1984, Reichlin et al. [145] and Treadwell et al. [146] reported that anti-PM-Scl were most prevalent in patients with PM-SSc overlap syndrome.

Anti-PM-Scl autoAbs are directed against a nucleolar macromolecular complex composed of 11 to 16 proteins (ranging from 20 to 110 kDa). The two key proteins of the complex are PMScl-75 (75 kDa) and PM-Scl-100 (100 kDa) with PMScl-75 considered as the main autoantigen. This macromolecular complex is the human counterpart of the yeast exosome, which is involved in RNA degradation and processing [147-149]. According to a recent meta-analysis, the anti-PM-Scl antibodies have been detected in 17% of patients diagnosed with PM/SSc overlap syndrome, compared with only 6% of patients with PM alone and 9% of patients with DM alone [150]. Also, the frequency of anti-PM/Scl antibodies appears to vary between different ethnic groups. Brouwer et al. [151] reported that anti-PM-Scl antibodies were more often de-

Table 2. Target autoantigens and prevalence of myositis associated antibodies

Antibody	Antigen	Antigen function	Prevalence in IIM (%)					Clinical association
			DM	PM	OVM	CAM	JDM	
Anti-PM-Scl	Exosome (PMScl) complex; PMScl-75 (75 kDa)/PMScl-100 (100 kDa)	RNA degradation	9	6	17	0	5	PM/SSc overlap syndrome classically SSc
Anti-U1-RNP	Small ribonucleoprotein	Splicing of mRNA	6	5	32	0	5	PM/SSc overlap syndrome MCTD
Anti-Ro52	Ro52/TRIM21	Mediates proteasome-related degradation of target proteins	13	12	19	0	6	ILD Frequently associated with MSA
Anti-Ku	DNA-binding protein consisting of 70 and 80 kDa subunits	DNA repair through the non-homologous end-joining pathway	1	2	13	0	<1	PM/SSc overlap syndrome

IIM: idiopathic inflammatory myopathies, DM: dermatomyositis, PM: polymyositis, OVM: overlap myositis, CAM: cancer associated myositis, JDM: juvenile myositis, SSc: systemic sclerosis, MCTD: mixed connective tissue disease, ILD: interstitial lung diseas, MSA: myositis-specific autoantibodies, RNP: ribonucleoprotein.

tected in European patients than in North American and Japanese groups (6% vs. 2% vs. 0%). On the other hand, they were not detected in a large series of 275 Japanese patients with SSc [152]. Patients diagnosed with anti-PM/Scl-positive PM/SSc overlap syndrome frequently presented with Raynaud's phenomenon, arthritis, mechanic's hands and ILD [150,153]. The PM/SSc overlap syndrome appeared to show a benign and chronic disease course, and the anti-PM/Scl antibodies have been shown to predict limited cutaneous involvement [154]. Also, the anti-PM/Scl-positive patients responded favorably to low-to-moderate doses of corticosteroids [154-156].

2) Anti-U1-RNP antibodies

Anti-RNP were first observed in SLE patients with speckled IIF pattern in 1971 [157]. The RNP/Sm complex consists of several proteins (70 kDa, A, A′, B, B′, B″, C, D, E, F, G) constituting the common core of U1, U2, U4 and U5 small nuclear ribonucleoprotein (snRNP) particles [158,159]. The anti-RNP antibodies react with U-rich 70 kDa (U1), 33 kDa (A) and 22 kDa (C) proteins that are associated with U1 RNA and form U1snRNP [158,159]. However, only the elevated 70 k anti-U1-RNP titers are considered specific markers of mixed connective tissue disease [158].

Anti-U1-RNP antibodies have been found in 32% of patients diagnosed with overlap myositis, compared with only 5% of patients with PM alone and 6% of patients with DM alone [150]. The patients with anti-U1-RNP positive myositis usually manifest a mild disease course and respond well to corticosteroids [160,161].

3) Anti-Ro52 antibodies

The Ro/La system is composed of three different proteins (52 kDa Ro, 60 kDa Ro, and 48 kDa La) and four small RNA particles (hY1, hY3, hY4, and hY5-RNA) [162]. The Ro/SSA autoantibody-system (Ro60 and Ro52) is the most prevalent nuclear antigen specifically identified in autoimmune diseases, such as SLE, overlap syndrome, subacute cutaneous LE, neonatal lupus and primary biliary cirrhosis with similar prevalence [162,163]. Notably, anti-Ro52 is detected more frequently in myositis (35.4% vs. 0.0%, $p<0.001$) and SSc (19.0% vs. 6.0%, $p<0.005$) than anti-Ro60 [163]. In IIM, anti-Ro52 autoAbs are frequently associated with MSAs. Yamasaki et al. [164] reported that anti-Ro52 antibodies were frequently detected with anti-ARS (59%) (57% in anti-Jo-1 and 67% in anti-PL-7) (vs. 21% in anti-ARS-negative, $p<0.0002$) in a Japanese IIM cohort. In this study, anti-Ro52 was also associated with overlap syndrome (26%) (vs. 7% in anti-Ro52-negative, $p=0.0119$). Furthermore, compared with IIM patients testing negative for anti-Jo-1-positive/anti-Ro52, the anti-Jo-1/anti-Ro52-positive IIM patients more commonly manifested severe myositis, joint involvement, ILD, and cancer with poor prognosis [165]. Also, anti-Ro52s are associated with anti-MDA5 [67] and anti-SRP [166].

4) Anti-Ku antibodies

In 1981, anti-Ku antibodies were originally linked to PM/SSc overlap syndrome by Mimori et al. [167]. Ku is a DNA-binding protein consisting of 70 and 80 kDa subunits involved in DNA repair via the non-homologous end-joining pathway [168].

According to a recent meta-analysis, the anti-Ku antibodies have been found in 13% of patients diagnosed with PM/SSc overlap syndrome, compared with only 2% of patients with PM alone and 1% of patients with DM alone [150]. Anti-Ku antibodies are not associated with specific clinical manifestations such as cancer-associated myositis. Interestingly, the anti-Ku positive patients respond well to treatment and appear to show a favorable prognosis [168].

Prevalence of MSA and MAA in Korea

There are only a few reports about the prevalence of MSA and MAA in Korean patients with IIM. Previously, Kang et al reported the test results using IP with the serum of 49 patients with IIM: 6 (12.2%) had anti-ARS, 7 (14.3%) had anti-Mi-2, 1 (2.0%) had anti-SRP, 8 (16.3%) had anti-p155/140 [anti-TIF1γ] and nine (18.4%) had anti-p140 [anti-MDA5]. Among MAA, 6 patients had anti-U1 RNP, and 4 had anti-Ro [101]. Recently, Chung et al. [169] presented the result of MSA and MAAs in 67 Korean patients with IIM using immunoblot assay which can detect 15 myositis-related autoantibodies in 2018 Korean College of Rheumatology Annual Conference: 21 (31.3%) patients had anti-ARS, 14 (20.9%) had anti-SRP, 14 (20.9%) had anti-MDA5, 8 (11.9%) had anti-Mi2, 9 (13.3%) had anti-TIF1γ, 2 (3.0%) had anti-SAE, 32 (47.8%) had anti-Ro52, and 2 had (3.0%) anti-Ku. Anti-ARS Abs specificity included anti-Jo-1 (29.2%), anti-OJ (4.6%), anti-EJ (6.2%), anti-PL-7 (3.1%), and anti-PL-12 (4.6%).

Implication for patients care

For classification of IIM, there have been several classification systems, which mainly did not include the presence of autoantibodies. However, with recent discovery of many MSA and MAA, Troyanov et al. [170] proposed the clinicoserologic definition introducing the several subgroups according to the presence of specific MSA [171]. In 2017, European League Against Rheumatism/American College of Rheumatology classification criteria also included the presence of anti-Jo-1 antibody as one of items for the classification IIM although other antibodies could not investigated for the purpose of classification because of the lack of data [172]. Recently, new classification system based on clinical manifestations and myositis-specific autoantibodies was suggested [173]. Comparing the conventional classification systems, seroclinical classification might designate the patients into the subgroup more appropriately.

As mentioned in the each MSA and MAA section, each autoAb is related to clinical features which have prognostic implication. Patients with anti-ARS and anti-MDA5 showed frequent grave pulmonary manifestation such as AIP or RP-ILD [37,44,51,81] and patients with anti-TIF1γ, anti-NXP-2 and anti-HMGCR were often accompanied with malignancy [95,100,102,105,139]. Thus, clinician should be alert to care those IIM patients. The titer of anti-MDA5, anti-SRP and anti-HMGCR can be associated with disease activity [89,90,127,138]. The patients with anti-HMGCR may show good treatment response with IVIG [138,141]. Considering these research findings, the detection and measurement of MSA and MAA is crucial in patients care.

CONCLUSION

Various MSA and MAA are found in patients diagnosed with IIM. Based on the MSA and MAA profile, patients can be categorized into specific clinical syndromes, and managed via appropriate treatment strategies for predictable outcomes. With advances in knowledge regarding these autoantibodies and their pathogenic role in IIM, new immunoassays and treatment modalities will become widely available for clinical application in the near future.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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