Clinical Evaluation of Anti-Aminoacyl tRNA Synthetase Antibodies in Japanese Patients with Dermatomyositis

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ABSTRACT. ***Objective.*** To investigate the distribution of anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies among patients with autoimmune diseases, and to analyze the clinical features of patients with dermatomyositis (DM) with anti-ARS antibodies.

Methods. Serum samples from 315 patients with autoimmune diseases or related disorders who had visited Kanazawa University Hospital or affiliated facilities were assessed for anti-ARS antibodies by immunoprecipitation. In particular, the association between anti-ARS antibodies and clinical features was investigated in detail in patients with DM.

Results. Anti-ARS antibody was positive in 16 (29%) of 55 patients with DM, 2 (22%) of 9 patients with polymyositis, and 7 (25%) of 28 patients with idiopathic pulmonary fibrosis. Although anti-ARS antibody was detected with high frequency (63%, 15/24) in DM patients with interstitital lung disease (ILD), the incidence of anti-ARS antibody was very low (3%, 1/31) in DM patients without ILD. Anti-ARS antibody-positive patients with DM had significantly higher incidences of ILD (94% vs 23%) and fever (64% vs 10%) than the antibody-negative patients. Some immunosuppressive agents, in addition to oral corticosteroids, were required more frequently in the antibody-positive patients with DM than the antibody-negative patients (88% vs 26%). Although 60% of DM patients with ILD simultaneously developed ILD and myositis, ILD preceded myositis in 33% of patients.

Conclusion. Among patients with DM, anti-ARS antibodies are found in a subset with ILD. DM patients with anti-ARS antibodies appear to have a more persistent disease course that requires additional therapy compared to those without anti-ARS antibodies. (First Release Feb 15 2007; J Rheumatol 2007;34:1012–8)

Key Indexing Terms:
ANTI-AMINOACYL tRNA SYNTHETASE ANTIBODY
ANTISYNTHETASE SYNDROME
DERMATOMYOSITIS
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Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory diseases affecting skeletal muscles. A subset of patients with PM has interstitial lung disease (ILD), and there are some subsets of patients with DM who have ILD or internal malignancy[1]. Early studies showed that anti-Jo-1 antibody is positive in 20%–30% of patients with PM and is associated with the involvement of ILD[2]. Six autoantibodies to aminoacyl-tRNAsynthetase (ARS) have been detected to date, including anti-Jo-1 antibody[3]. ARS is an enzyme catalyzing the binding of the corresponding amino acid to the 3'-terminal of transfer RNA to yield aminoacyl-tRNA. Anti-ARS antibodies include anti-Jo-1 (histidyl-tRNA synthetase),

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anti-PL-7 (threonyl-tRNA synthetase), anti-PL-12 (alanyl-tRNA synthetase), anti-OJ (isoleucyl-tRNA synthetase), anti-EJ (glycyl-tRNA synthetase), and anti-KS (asparaginyl-tRNA synthetase). Recent studies showed that anti-ARS antibodies are detected in patients with DM as well as those with PM[4,5]. Anti-ARS antibody-positive patients present common symptoms such as myositis, ILD, polyarthritis, Raynaud's phenomenon, fever, and mechanic's hand. Further, anti-ARS antibody-positive individuals showing these abnormalities are defined as having antisynthetase syndrome[6-9]. No valid method based on enzyme linked immunosorbent assay (ELISA) has been established, except anti-Jo-1 antibody, to detect anti-ARS antibody. Immunoprecipitation is therefore indispensable and an excellent method in terms of both sensitivity and specificity to detect these antibodies, although the number of facilities capable of carrying out this assay is limited.

ARS can be divided into class I and class II by its molecular structure and the aminoacylation-initiating codon. Other than isoleucyl-tRNA synthetase, all targets of anti-ARS antibodies identified to date correspond to class II. It is estimated that class II ARS is present in a free form in the cytoplasm, and that it is likely to be exposed on the surface to serve as an autoantigen[10]. It has recently been reported that histidyl-tRNA synthetase and asparaginyl-tRNA synthetase have a chemokine-like function, and may induce the migration of T lymphocytes and monocytes through their interaction with chemokine receptors (CCR3 and CCR5) expressed on dendritic cells[11]. Therefore, the presence of ARS in inflamed tissue may stimulate the uptake of ARS by the invading dendritic cells, and the resultant presentation of ARS as an autoantigen may induce the production of autoantibody against ARS[11]. Nonetheless, it remains unknown whether anti-ARS antibodies induce the development of antisynthetase syndrome.

We investigated the clinical features and the prevalence of anti-ARS antibodies in Japanese patients with DM.

MATERIALS AND METHODS

Patients. Serum samples were obtained from 315 Japanese patients with autoimmune diseases or related disorders who had visited Kanazawa University Hospital or collaborating medical centers. These included 55 patients with DM, 9 with PM, 28 with idiopathic pulmonary fibrosis (IPF), and 223 with other diseases [126 with systemic sclerosis (SSc); 27 with systemic lupus erythematosus (SLE); 10 with mixed connective tissue disease (MCTD); 10 with Sjögren's syndrome; 9 with rheumatoid arthritis (RA); 9 with localized scleroderma; 6 with overlap syndrome; 6 with adult-onset Still's disease; 6 with primary antiphospholipid syndrome; 4 with unclassified connective tissue diseases; 4 with cryoglobulinemia; 3 with Behçet's disease; and 3 with eosinophilic fasciitis]. Patients with DM visit our department (specializing in dermatology) more frequently than patients with PM. Therefore, the percentage of patients who visited the dermatology associations was 71% (39/55) in patients with DM, 22% (2/9) in patients with PM, 0% (0/28) in patients with IPF, and 77% (203/223) in patients with other diseases.

All patients with DM and PM fulfilled the Bohan and Peter criteria[12,13]. We distinguished DM from PM by the presence of heliotrope rash or Gottron's lesions (Gottron's papules and/or Gottron's sign). The diagnosis of IPF was based on the presence of unexpected dyspnea, progressive bilateral pulmonary infiltrates, and evidence of pulmonary fibrosis in histological specimens obtained by lung biopsy[14]. Patients with IPF were examined for muscle weakness using a manual muscle test and muscle enzyme levels (creatine phosphokinase and aldolase) during the followup period (44 ± 12 mo), since the onset of ILD might precede the onset of myositis. Some patients were also examined by electromyogram and muscle magnetic resonance imaging, and by pathologic analysis of the muscle.

The criteria proposed by the American College of Rheumatology[15-18] were used to diagnose patients with SSc, SLE, RA, or Sjögren's syndrome. MCTD was diagnosed according to preliminary diagnostic criteria proposed by Kasukawa and Miyawaki[19]. Localized scleroderma was diagnosed when a patient had typical symptoms characterized by fibrosis of skin and subcutaneous tissue[20]. Overlap syndrome was diagnosed by the coexistence of 2 or more connective tissue diseases, such as SLE, DM, PM, SSc. Adult-onset Still's disease was diagnosed according to the criteria proposed by Medsger and Christy[21]. Primary antiphospholipid syndrome was diagnosed according to the Sapporo criteria[22]. Unclassified connective tissue disease was diagnosed by the presence of various connective tissue disease symptoms without meeting the full criteria for any one of them[23]. Cryoglobulinemia was diagnosed by the presence of single or mixed immunoglobulins that undergo reversible precipitation at low temperatures[24]. Behçet's disease was diagnosed according to the criteria of the International Study Group for Behçet's Disease[25]. Eosinophilic fasciitis is diagnosed by symmetrical scleroderma-like induration of the skin over one or more distal extremities, accompanying thickened fascia and eosinophil infiltrations[26].

Immunoprecipitation. The presence of anti-ARS antibody, anti-Mi-2 antibody, anti-signal recognition particle antibody, anti-PM/Scl, anti-Ro, or anti-La was confirmed by the immunoprecipitation assay. The immunoprecipitation assay was performed using extracts of the leukemia cell line K562 as described[10]. A total of 10 μl of patient serum was mixed with 2 mg of protein A-sepharose beads (Amersham Biosciences, Piscataway, NJ, USA) in 500 μl of immunoprecipitation buffer (10 mM Tris HCl, pH 8.0, 500 mM NaCl, 0.1% Nonidet P40) and incubated for 2 h at 4°C, and then washed 5 times with immunoprecipitation buffer.

For polypeptide studies, antibody-coated sepharose beads were mixed with 100 μl of ^{35}S-methionine-labeled K562 cell extracts derived from 2×10^5 cells, and rotated at 4°C for 2 h. After 5 washes, the sepharose beads were resuspended in sodium dodecyl sulfate (SDS) sample buffer and the polypeptides were fractionated by 8.5% SDS-polyacrylamide gels (PAGE). Radiolabeled polypeptide components were analyzed using autoradiography.

For the analysis of RNA, the antigen-bound sepharose beads were incubated with 300 μl of K562 cell extracts (3×10^6 cell equivalents per sample) for 2 h at 4°C. The bound RNA from the sepharose beads was extracted using Isogen (Nippon Gene, Toyama, Japan) in accordance with manufacturer's protocols. After ethanol precipitation, the RNA was resolved using a 7 M urea-10% PAGE, which was subsequently silver stained (Bio-Rad, Hercules, CA, USA).

Indirect immunofluorescence. Indirect immunofluorescence was performed using HEp-2 cells and fluorescein-labeled antihuman immunoglobulin (Medical & Biological Laboratories, Nagoya, Japan) in patients with DM, as described[27].

Clinical studies. Complete medical histories, examinations, and laboratory tests could be obtained from 35 patients among 55 patients with DM analyzed for anti-ARS antibody. Therefore, the associations between anti-ARS antibody and clinical features were assessed in these 35 patients with DM. The patients were diagnosed as having ILD according to chest radiography, chest computed tomography, and pulmonary function testing, which included the percentage-predicted values for forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO). Serum KL-6 levels were determined by ELISA, as described[28]. Internal malignancy was carefully examined using chest and abdominal computed tomography, gastrointestinal fiberscope, gallium scintigraphy, and other procedures according to need. The protocol was approved by the Kanazawa University Graduate School of Medical Science

and Kanazawa University Hospital, and informed consent was obtained from all patients.

Statistical analysis. Statistical analysis was performed using the Mann-Whitney U-test for the comparison of values, and Fisher's exact probability test for the comparison of frequencies. p values less than 0.05 were considered to be statistically significant.

RESULTS

Prevalence of anti-ARS antibody in patients with autoimmune diseases. We investigated the existence of anti-ARS antibodies by immunoprecipitation. Representative immunoprecipitation for RNA or protein with anti-ARS antibody-positive sera is shown in Figure 1. Of the 315 patients with autoimmune diseases or related disorders, 25 patients (8%) were anti-ARS antibody-positive. Among these 25 patients, 18 satisfied the diagnostic criteria for PM/DM, and 7 were diagnosed with IPF without myositis. The anti-ARS antibody-positive rate was 29% (16/55) in patients with DM, 22% (2/9) in patients with PM, and 25% (7/28) in patients with IPF (Table 1). No significant association was detected between each anti-ARS antibody and the disease subset. It was striking that no patients with the other autoimmune diseases were positive for anti-ARS antibody (Table 1).

Association between ILD and anti-ARS antibody. The frequency of patients having ILD was 44% (24/55) in patients with DM, 33% (3/9) in patients with PM. ILD was detected in 54 (52 SSc and 2 MCTD) of the 223 (24%) patients with other diseases (Table 2A). Almost all DM (94%, 15/16) or PM (100%, 2/2) patients with anti-ARS antibody had ILD (Table 2A). Anti-ARS antibody was detected with high frequency in DM (63%, 15/24) or PM patients (67%, 2/3) with ILD (Table 2B). In contrast, the incidence of anti-ARS antibody was very low in DM (3%, 1/31) or PM (0%, 0/6) patients without ILD (Table 2B). These findings indicate that anti-ARS antibody is not myositis-specific, but rather an ILD-specific marker in patients with DM or PM.

Clinical correlation of anti-ARS antibodies in Japanese

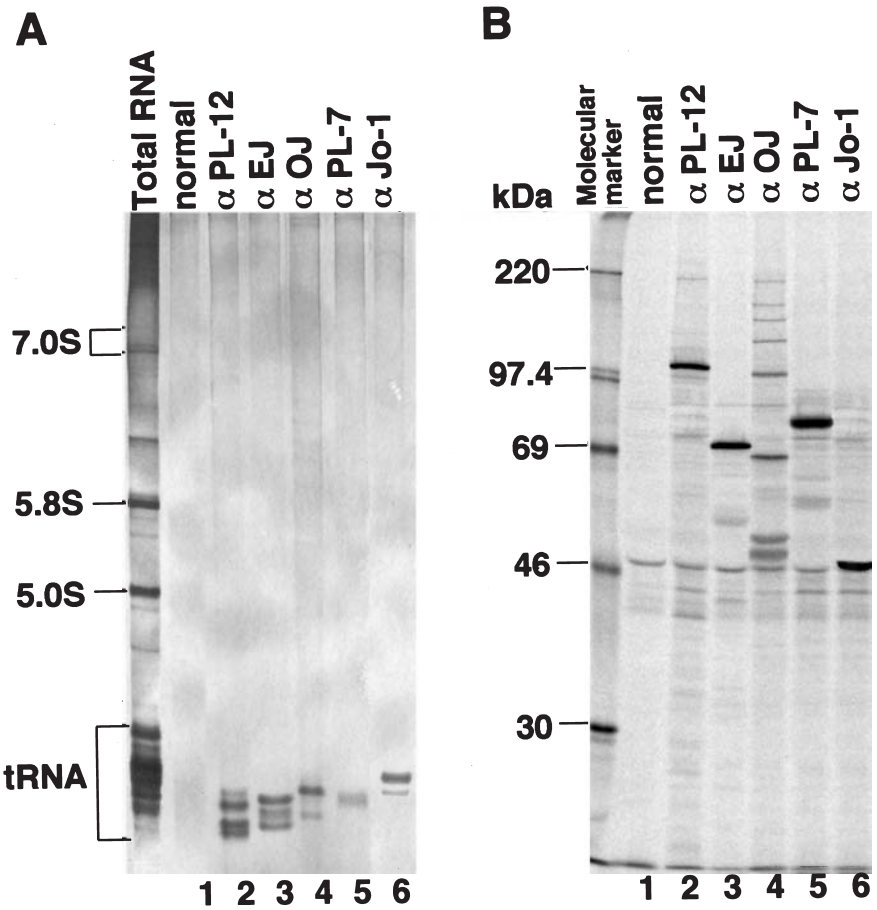

Figure 1. A. Representative immunoprecipitation for RNA with anti-aminoacyl tRNA synthetase (anti-ARS) sera and the normal control. 7 M urea-10% polyacrylamide gel (PAGE) of phenol-extracted immunoprecipitates from K562 cell extract, developed with silver stain. Total RNA lane indicates the 7.0S, 5.8S, and 5.0S small ribosomal RNA and the tRNA region. Sera used for immunoprecipitation: Lane 1: normal control serum indicated; Lanes 2–5: anti-ARS sera indicated, with antibodies to PL-12 (alanyl-tRNA synthetase), EJ (glycyl-tRNA synthetase), OJ (isoleucyl-tRNA synthetase), PL-7 (threonyl-tRNA synthetase), Jo-1 (histidyl-tRNA synthetase). B. Representative immunoprecipitation for proteins with anti-ARS sera and normal control. Autoradiogram of 8.5% SDS-PAGE of immunoprecipitates from ^{35}S-methionine-labeled K562 cell extract.

Table 1. Prevalence of anti-ARS antibodies in autoimmune diseases.

	Clinical Composition, no. (%)			
	DM, n = 55	PM, n = 9	IPF, n = 28	Others, n = 223
Anti-ARS (total)	16 (29)	2 (22)	7 (25)	0 (0)
Anti-Jo-1	3 (5)	1 (11)	1 (4)	0 (0)
Anti-EJ	6 (11)	0 (0)	2 (7)	0 (0)
Anti-PL-7	4 (7)	1 (11)	0 (0)	0 (0)
Anti-PL-12	3 (5)	0 (0)	3 (11)	0 (0)
Anti-OJ	0 (0)	0 (0)	1 (4)	0 (0)
Anti-Mi-2	3 (5)	0 (0)	0 (0)	0 (0)
Anti-SRP	1 (2)	1 (11)	0 (0)	0 (0)
Anti-PM/Scl	0 (0)	0 (0)	0 (0)	0 (0)
Anti-Ro	9 (16)	2 (22)	2 (7)	56 (26)
Anti-La	0 (0)	0 (0)	0 (0)	8 (4)

DM: dermatomyositis; PM: polymyositis; IPF: idiopathic pulmonary fibrosis; SRP: signal recognition particle.

patients with DM. Table 3 shows the association between anti-ARS antibody and clinical features in 35 patients with DM who were examined in detail. Of these 35 patients, 16 were anti-ARS antibody-positive. There was no significant difference in age or sex between the anti-ARS antibody-positive group and the antibody-negative group. However, the disease duration (interval from initial symptom to diagnosis) was significantly longer in patients in the antibody-positive group compared to the antibody-negative group [1.4 ± 1.5 vs 0.4 ± 0.4 yrs (mean ± SD); $p < 0.01$]. The patients with anti-ARS antibody frequently had fever and elevated CRP levels, indicating that the inflammation was remarkable in the antibody-positive patients. The percentage of patients with ILD was dramatically elevated in the antibody-positive group compared to the antibody-negative group (94% vs 23%; $p < 0.005$). In addition, respiratory function, such as %FVC and %DLCO, declined significantly ($p < 0.005$) and the levels of serum KL-6, a serum marker for ILD, were elevated significantly ($p < 0.05$) in the antibody-positive group compared to the antibody-negative group. The frequency of Raynaud's phenomenon and arthritis was higher in the antibody-positive group than in the antibody-negative group, although the difference was not significant. The complication of internal malignancy was not seen in any DM patient with anti-ARS antibodies, while internal malignancy was detected in 16% of DM patients without the antibody. The incidence of DM-specific eruptions, such as heliotrope rash, Gottron's lesions, and flagellate erythema, was similar between the 2 groups. While mechanic's hands were detected in 19% of patients with, but not in patients without the antibody, the difference between the 2 groups was not significant. The antinuclear antibody-positive rate was significantly lower in the anti-ARS antibody-positive group. In contrast, the frequency of anti-cytoplasmic antibody was significantly higher in the anti-ARS antibody-positive group than in the anti-ARS antibody-negative group (75% vs 5%; $p < 0.005$), since ARS is localized at cell cytoplasm. The anti-ARS antibody-positive patients with DM did not have other myositis-specific antibodies, such as anti-Mi-2 antibody and anti-signal recognition particle antibody.

Treatment with other immunosuppressive agents in addition to oral corticosteroid was significantly more frequently needed for anti-ARS antibody-positive patients with DM for the treatment of ILD or myositis compared to the anti-ARS antibody-negative patients (88% vs 26%; $p < 0.005$). Among the immunosuppressive agents, mainly cyclosporine or cyclophosphamide was used as an additional treatment (Table 4).

PM patients with anti-ARS antibody showed clinical features and received therapy similar to patients with DM, although the number of patients was too small to analyze (data not shown). The complication of internal malignancy was not found in any patient with PM, irrespective of anti-ARS antibody status (data not shown). Only one IPF patient with the antibody had developed lung cancer that preceded IPF by 2 years (data not shown).

Onset time of ILD and myositis in DM patients with anti-ARS antibodies. When the onset time of ILD or myositis was analyzed in the 15 anti-ARS antibody-positive cases of DM

Table 2A. Prevalence of ILD in patients with anti-ARS antibodies.

	Clinical Composition, no. (%)				
	DM	PM	IPF	Others	Total
Anti-ARS-positive	15/16 (94)	2/2 (100)	7/7 (100)	0/0 (0)	24/25 (96)
Anti-ARS-negative	9/39 (23)	1/7 (14)	21/21 (100)	54/223 (24)	85/290 (29)
All	24/55 (44)	3/9 (33)	28/28 (100)	54/223 (24)	109/315 (35)

Table 2B. Prevalence of anti-ARS antibodies in patients with ILD.

	Clinical Composition, no. (%)				
	DM	PM	IPF	Others	Total
ILD-positive	15/24 (63)	2/3 (67)	7/28 (25)	0/54 (0)	24/109 (22)
ILD-negative	1/31 (3)	0/6 (0)	0/0 (0)	0/169 (0)	1/206 (0.5)

ILD: interstitial lung disease; DM: dermatomyositis; PM: polymyositis; IPF: idiopathic pulmonary fibrosis.

Table 3. Clinical and laboratory data of DM patients with anti-ARS antibodies.

	Dermatomyositis	
	Anti-ARS-positive, n = 16	Anti-ARS-negative, n = 19
Age at onset, mean ± SD, yrs	57 ± 13	50 ± 20
Sex (female/male)	13/3	13/6
Disease duration, mean ± SD, yrs	1.4 ± 1.5**	0.4 ± 0.4
Clinical features		
Fever	64***	10
Raynaud's phenomenon	31	5
Arthritis	43	21
Interstitial lung disease	94***	23
Internal malignancy	0	16
Skin eruptions		
Heliotrope rash	38	47
Gottron's lesions	69	53
Flagellate erythema	19	16
Periungual erythema	38	47
Nailfold capillary changes	31	42
Mechanic's hands	19	0
Laboratory findings		
Positive antinuclear antibody	6***	58
Positive anti-cytoplasmic antibody	75***	5
Positive anti-Mi-2 antibody	0	16
Positive anti-SRP antibody	0	5
Positive anti-Ro antibody	25	16
CPK, IU/L, mean ± SD	1476 ± 2963	2801 ± 6301
CRP, mg/dl, mean ± SD	2.7 ± 2.4***	0.7 ± 1.0
IgG, mg/ml, mean ± SD	1716 ± 602	1561 ± 542
FVC, %, mean ± SD	73 ± 14***	98 ± 25
DLCO, %, mean ± SD	47 ± 13***	72 ± 23
KL-6 U/ml, mean ± SD	2088 ± 2304*	497 ± 491
Usage of other immunosuppressive agents, in addition to oral steroid	88***	26

Values are percentages unless indicated. SRP: signal recognition particle; CPK: creatine phosphokinase; CRP: C-reactive protein. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$ vs DM patients without anti-ARS antibodies.

patients with ILD (Table 5), the onset of ILD preceded the onset of myositis in 5 (33%) patients, myositis preceded ILD in one patient (7%), and myositis and ILD developed simultaneously in 9 patients (60%). These results suggest that patients diagnosed as having IPF need to be checked for anti-ARS antibody and that if antibody is positive, close attention is needed for the development of myositis.

DISCUSSION

In our study, the frequency of anti-ARS antibodies was similar (22%–29%) among patients with DM, PM, and IPF (Table 1). Anti-ARS antibody was negative in all patients with other autoimmune diseases, including SSc, SLE, and MCTD. These findings indicate that anti-ARS antibody is a highly disease-specific autoantibody for a proportion of patients with DM, PM, or IPF. In addition, virtually all DM or PM patients with anti-ARS antibody had ILD (Table 2A). Although anti-ARS antibody was detected with high frequency in DM or PM patients with ILD, the incidence of anti-ARS antibody was very low in DM or PM patients without ILD (Table 2B). Therefore, it is likely that anti-ARS antibody is a marker of ILD but not for myositis in patients with DM or PM.

In our Japanese patients with DM, symptoms of antisynthetase syndrome, such as ILD, arthritis, Raynaud's phenomenon, fever, and mechanic's hand, were frequently detected in anti-ARS antibody-positive patients (Table 3). In general, ILD with anti-ARS antibody-positive patients can be characterized by the chronic course of the disease and elevation of the diaphragm (so-called "shrinking lung")[29]. On the other hand, it has recently been shown that cases of therapy-resistant rapidly progressive ILD, often accompanied by amyopathic DM, are negative for anti-ARS antibody and positive for anti-CADM-140 antibody[30]. In our study, there was no DM patient with anti-CADM-140 antibody. While the characteristics of DM-specific eruptions, such as heliotrope coloration, Gottron's lesions, and flagellate erythema[31], were similar between DM patients with anti-ARS antibody and those without antibody, mechanic's hands were found only in the antibody-positive DM group. Therefore, mechanic's hands may be closely associated with the existence of anti-ARS antibody. Our study showed that the disease duration was significantly longer in patients with the anti-ARS antibody-positive group compared to the antibody-negative group (Table 3) and there was no significant seasonal pattern of disease onset in the anti-ARS antibody-positive group (data not shown). However, prior studies demonstrated a rather more acute onset with a seasonal pattern in DM patients with the anti-ARS antibody[32,33]. The reasons for this discrepancy may be due to the small population or ethnic difference in our study. However, ILD preceded myositis for a long period (20 ± 20 mo) in 33% of the DM patients with ILD (Table 5). By contrast, only one of 15 (7%) DM patients with ILD showed myositis 2 months earlier than ILD. Other patients (60%) simultaneously developed ILD and myositis. These findings indicate that the onset of antisynthetase syndrome is acute, but the development of myositis may lag behind the onset of ILD in patients with DM. Nonetheless, future large studies will be needed to determine this in various ethnic populations.

Although corticosteroids remain the mainstay of therapy in DM patients with anti-ARS antibodies, most patients failed to fully respond to this treatment or manifested recurrent flares when the steroid dosage was tapered (data not shown), consistent with previous reports[34,35]. Most patients with anti-ARS antibody need to be treated with the other immunosuppressive agents such as cyclosporine A and/or cyclophosphamide, in addition to corticosteroids therapy (Table 4). Oddis, *et al* showed that tacrolimus (FK-506), an immunosuppressant pharmacologically similar to cyclosporine, is effective for managing refractory ILD and myositis in patients with anti-ARS antibodies[35,36]. The therapeutic guideline of antisynthetase syndrome should be established in the near future.

Immunological specificity differs among different types of

Table 4. Treatment history in DM patients with anti-ARS antibodies.

Anti-ARS	Age, yrs	Sex	ILD	Treatment
Anti-Jo-1	58	F	+	PSL 40 mg, steroid pulse, CYC
Anti-Jo-1	66	F	+	PSL 60 mg, steroid pulse, CyA
Anti-Jo-1	64	F	+	PSL 60 mg, steroid pulse, CyA
Anti-PL-7	56	F	+	PSL 50 mg, CYC pulse, CyA
Anti-PL-7	56	M	+	PSL 60 mg, CYC pulse
Anti-PL-7	72	F	+	PSL 60 mg, steroid pulse, CYC pulse, CyA
Anti-PL-7	83	F	+	PSL 60 mg, CYC pulse
Anti-PL-12	59	F	+	mPSL 120 mg, CyA, CYC
Anti-PL-12	58	F	+	PSL 30 mg, AZP, CyA
Anti-PL-12	38	F	+	PSL 30 mg, CYC pulse
Anti-EJ	58	M	+	PSL 60 mg, steroid pulse, CyA, MTX
Anti-EJ	20	F	–	PSL 60 mg, steroid pulse, CyA
Anti-EJ	50	F	+	PSL 40 mg, steroid pulse, CyA
Anti-EJ	56	F	+	PSL 55 mg, CyA
Anti-EJ	52	M	+	PSL 55 mg
Anti-EJ	62	F	+	PSL 40 mg

Anti-ARS: anti-aminoacyl-tRNA synthetase; ILD: interstitial lung disease; PSL: prednisolone (initial dose); mPSL: methylprednisolone (initial dose); CYC: cyclophosphamide; CyA: cyclosporine A; MTX: methotrexate; AZP: azathioprine.

Table 5. The onset time of ILD and myositis in DM patients with anti-ARS antibodies.

	ILD Preceded Myositis	Myositis Preceded ILD	ILD and Myositis Developed Simultaneously†
Frequency of patients (%)	5/15 (33)	1/15 (7)	9/15 (60)
Duration, mean ± SD, mo	20 ± 20	2	

† Both ILD and myositis developed within 1 month. Anti-ARS: anti-aminoacyl-tRNA synthetase; ILD: interstitial lung disease.

ARS, and differences in clinical features have also been reported depending on the type of anti-ARS antibody. Anti-Jo-1 antibody has been reported to be specific for PM rather than DM, while anti-EJ antibody is often positive in patients with DM[37]. Anti-PL-12 and anti-KS are detected in ILD patients with myositis that is poor in symptoms[10,38], while anti-PL-7 is related to sclerodactyly[39]. Although the reason is unclear, each anti-ARS antibody is mutually exclusive[40]. In our study, no significant difference in the clinical features was found depending on the type of anti-ARS antibody (data not shown), probably due to the small population. Alternatively, this may be due to the racial difference, since our patients were restricted to those of Japanese ethnicity. Further studies will be needed to determine the association between each anti-ARS antibody and the clinical features in a large population.

Anti-ARS antibodies appear to be associated with 2 subgroups of subjects: those who develop myositis with a high prevalence of ILD, and those who develop ILD without clinical evidence of myositis. Further, DM patients with anti-ARS antibodies appear to require additional therapy compared to those without anti-ARS antibodies.

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