Treatment of Interstitial Lung Disease Associated with Polymyositis-Dermatomyositis

Toshinori Takada[*,1], Ichiei Narita[1] and Eiichi Suzuki[2]

[1]*Division of Respiratory Medicine, Graduate School of Medical and Dental Sciences, Niigata University, Japan*

[2]*Department of General Medicine, Niigata University Medical and Dental Hospital, Japan*

Abstract: Polymyositis and dermatomyositis (PM-DM) are forms of idiopathic inflammatory myositis. Interstitial lung disease (ILD) in PM-DM is recognized as a serious complication and a major cause of death in this disease. In particular, patients with clinically amyopathic dermatomyositis (ADM) sometimes develop rapidly progressive ILD that remains unresponsive to intensive immunosuppresive therapy. A novel autoantibody associated with PM-DM was identified and termed anti-CADM-140/MDA5 antibody. Anti-CADM-140/MDA5 antibody titer correlates with disease activity and predicts the course of ILD associated with ADM. Glucocorticoids are considered the first-line drug treatment for PM-DM patients with ILD, however they are often not sufficient to obtain improvement of ILD as a single agent. Furthermore, the addition of immunosuppressive drugs becomes necessary as steroid sparing agents to avoid the severe side-effects often seen with high-dose steroid treatment. Cyclophosphamide, cyclosporin, and tacrolimus were reported to be effective in treatment of refractory ILD in PM-DM. Although other immunosuppressive agents; mycophenolate mofetil, intravenous immunoglobulin, and anti-TNF agents have appeared as promising agents for refractory PM-DM, the efficacy on ILD in PM-DM is still unknown. Even if treatment is initiated early in the course of the disease, some patients still develop irreversible fatal lung fibrosis under aggressive immunosuppressive therapy. Recently, cases with rapidly progressive ILD associated with clinically ADM were successfully treated with direct hemoperfusion with polymyxin B-immobilized fiber column.

Keywords: Amyopathic dermatomyositis, anti-CADM-140/MDA5 autoantibody, dermatomyositis, lnterstitial lung disease, polymyxin B-immobilized fiber column, polymyositis.

INTRODUCTION

Polymyositis and dermatomyositis (PM-DM) are a family of acquired, systemic, connective tissue diseases of unknown cause whose principal manifestation is muscle weakness. DM is identified by a characteristic rash accompanying muscle weakness, whereas, PM is defined as a subacute myopathy without the skin rash seen in DM. Five diagnostic criteria have been used to distinguish PM and DM from other muscular diseases [1]. Immunohistological studies suggest different pathogeneses in these forms of myositis. In PM, clonally expanded $CD8^+$ cytotoxic T lymphocytes invade muscle fibers, which leads to fiber necrosis *via* the perforin pathway. In DM, however, the infiltrate is predominantly composed of B-lymphocytes and $CD4^+$ helper T cells in perimysial areas around the fascicles and small blood vessels. Dalakas *et al.* proposed new diagnostic criteria for inflammatory myopathies based on histopathology and immunopathology [2].

In addition, if a patient has the typical DM rash but no or little muscle weakness, the clinical diagnosis is amyopathic DM (ADM), which was not included in the original five diagnostic criteria [2]. Patients with ADM have hallmark inflammatory skin changes of DM but no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities. Even if more extensive muscle testing is carried out, the results should be within normal limits. A condition of DM with little myositis is sometimes termed as hypomyopathic DM. Although muscle strength is apparently normal, patients with hypomyopathic DM have some evidence of muscle inflammation shown as muscle enzyme elevations, electrophysiologic, and/or radiologic evaluation [3].

Interstitial lung disease (ILD) in PM-DM is increasingly recognized as a serious complication and a major cause of death in this disease [4]. Patients with ADM sometimes develop rapidly progressive ILD, which is often resistant to intensive therapy including high dose corticosteroids and immunosuppressive agents, resulting in fatal respiratory failure [5]. Since differences of ILD in ADM and hypomyopathic DM are not apparent, we could treat these two conditions in the same manner.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH PM-DM

The clinical presentation of ILD in PM-DM includes progressive dyspnea on exertion, nonproductive cough, and basilar rales, but an acute, rapidly progressive form of interstitial pneumonia may occur. A rapidly progressive interstitial pneumonia characterized by diffuse alveolar damage can cause respiratory failure. Various parameters related to ILD poor outcome in PM-DM were identified as

*Address correspondence to this author at the Division of Respiratory Medicine, Graduate School of Medical and Dental Sciences, Niigata University, 1-757 Asahimachi-dori, Niigata, 951-8510, Japan; Tel: +81-25-227-2200; Fax: +81-25-227-0775; E-mail: ttakada@med.niigata-u.ac.jp

1573-398X/13 $58.00+.00

follows: DM subtype, rapidly progressive form, features of ADM, initial FVC less than 60%, neutrophil alveolitis, and histologic usual interstitial pneumonia (UIP) [4, 6, 7]. Nonspecific interstitial pneumonia (NSIP) observed in PM-DM patients means the better survival compared with historical control subjects with idiopathic UIP [8] and mortality is similar to that seen in idiopathic NSIP [9]. In ILD with ADM, although the most common finding is idiopathic NSIP [10], the ILD often takes an aggressive course even when the radiological and histological features are consistent with NSIP [11]. Rapidly progressive ILD in ADM has been reported predominantly in Asia, including Japan, Hong Kong, and Taiwan [10, 12, 13]. The poor outcome of ILD in Korean ADM patients also suggests racial differences in the manifestation of ILD in ADM patients [7].

MYOSITIS-ASSOCIATED AUTOANTIBODIES

About 30 percent of patients with DM or PM have myositis-associated autoantibodies. These are classified into three major categories: anti-aminoacyl-tRNA synthetase (aaRS) antibodies, anti-signal recognition particle (SRP) antibodies, and anti-Mi-2 antibodies. The most common, anti-aaRS antibody specific for histidine (anti-Jo-1), is found in approximately 30% of patients with DM and is more frequently associated with ILD [14]. Others have been labeled anti-PL-7 (for threonine), anti-PL-12 (alanine), anti-EJ (glycine), anti-KS (asparagine), anti-OJ (isoleucine), and anti-Zo (phenylalanine) [15]. Each of these antibodies has been associated with antisynthetase syndrome marked by a high frequency of ILD compared with PM-DM without such antibodies [16]. In particular, anti-PL-12 is more strongly associated with the presence of ILD than with other features of the antisynthetase syndrome [17].

A novel autoantibody associated with PM-DM was identified and termed anti-CADM-140 antibody, because the patients with the antibody had clinically ADM and rapidly progressive interstitial lung disease with significantly higher frequency [18]. Furthermore, the antibody recognizes an antigen of an RNA helicase encoded by melanoma differentiation-associated gene 5 (MDA-5) [19]. That is why the antibody is also called anti-MDA5 antibody. Anti-CADM-140/MDA5 antibody titer could correlate with disease activity and predict the course of ILD associated with DM [20-25]. The antibody may be also a diagnostic and predictive marker for rapidly progressive ILD associated with juvenile DM [26, 27].

TREATMENT OF INTERSTITIAL LUNG DISEASE ASSOCIATED WITH PM-DM

Controlled trials on the effect of different treatments for ILD in PM-DM have not been published. Thus, the optimal treatment program for the disease has not been established. Available information on the efficacy of treatment is based on retrospective case collections or open trials. Drugs reported to be beneficial to the treatment of ILD associated with PM-DM are summarized in Table **1**.

INITIATING TREATMENT

Glucocorticoids

Prednisolone is considered the first-line drug for PM-DM patients with ILD [8, 28-32]. It usually is started with 1 mg/kg/day or more for 4-6 weeks. Another option is to start treatment with intravenous methylprednisolone (1 g/day for 3 days, pulse therapy, if necessary repeated after 1-2 weeks) and to be followed by oral prednisolone. Prednisolone in the 1 mg/kg/day range seems effective in suppressing the PM-DM within a few weeks in most patients, but ILD are usually slower to respond to therapy than the myositis and may require treatment over several months. High doses of prednisolone may lead to serious steroid side-effects, therefore, prednisolone is gradually tapered with careful monitoring of creatin kinase, chest radiographs, and pulmonary function.

ADDING A SECOND AGENT

Although most patients respond to some degree, corticosteroid treatment as a single agent is often not

Table 1. Drugs Beneficial to the Treatment of Interstitial Lung Disease Associated with Polymyositis and Dermatomyositis

Drug	Dose	Comments	References
Prednisone	1 mg/kg/day, 4-6 weeks	the first-line drug	[6, 13, 25-28]
Methylprednisolone	1 g/day, 3 days	followed by prednisone	[31, 35, 36]
Azathioprine	2 mg/kg/day	blood-count monitoring required	[34]
IVCY	300~800 mg/m2 every 4 weeks, 6 times	evidence remains circumstantial	[31, 35, 36-39]
Cyclosporin	150 mg/day	trough monitoring or checking levels two hours after administration required	[27, 41-45]
Tacrolimus	initially 1~3 mg/day	trough monitoring required	[46, 47]
Mycophenolate mofetil	30 mg/kg/day	blood-level monitoring not required but may improve efficacy	[51, 52]
IVIG	2 g/kg, monthly for 3 months	not studied as a first-line agent for rheumatologic diseases	[56, 57]
Adalimumab	40 mg every 2 weeks	SC every 2 weeks necessary	[60]

Abbreviations; IVCY, intravenous cyclophosphamide, IVIG, intravenous immunoglobulin, SC, subcutaneous injection.

sufficient to obtain improvement of ILD. Furthermore, the high doses required over a long period are often associated with severe side-effects and the addition of an immunosuppressive drugs becomes necessary as steroid sparing agents. Selection of immunosuppressive drugs remains empirical and depends on personal experience and the relative efficacy/safety ratio [33, 34]. Favorable outcome with immunosuppressive therapy in patients who failed to respond to steroids alone has been reported previously [31, 35]. Mira-Avendano *et al*. recently reported that no important difference was found in stabilization of pulmonary physiology, improved dyspnea, and a reduction of steroid dose among cyclophosphamide, mycophenolate mofetil (MMF) and azathioprine [36].

Azathioprine

Although controlled trials for patients with PM showed benefit of azathioprine [37, 38], ILD associated with PM was not mentioned in the reports. A DM case with lung involvement, successfully treated with azathioprine is also reported [39]. Azathioprine is often added as a steroid sparing agent [8], but it may not be effective for rapidly progressive ILD since it takes 4-6 months to work.

Cyclophosphamide

Intravenous cyclophosphamide (300-800 mg/m^2) in combination with pulse therapy has been reported to induce an initial remission of rapidly progressive ILD [35, 40, 41], but the evidence remains circumstantial. Cyclophosphamide may also improve the 5-year survival rate in patients who failed to respond to steroids alone [42]. Although it appears to be of benefit in patients with ILD in PM-DM [43, 44], controlled trials are needed.

Calcineurin Inhibitors

Cyclosporin binds to cyclophilin, then the complex inhibits calcineurin phosphatase and T-cell activation [45]. Cyclosporine was reported to be effective against both myositis and ILD, even steroid-resistant ILD, when used early in the course of the disease [31, 46-48]. In addition, retrospective studies have suggested that the initial use of the combination of cyclosporin and corticosteroids may improve the survival rate in DM patients with acute ILD [49, 50].

Tacrolimus, which is a macrolide antibiotic, engages another immunophili, FK506 binding protein 12, to create a complex that inhibits calcineurin phosphatase and T-cell activation with greater molar potency than does cyclosporine. It was first studied in the treatment of 5 patients with anti-Jo1 antibody-positive PM and led to stabilization or improvement of ILD in 4 of 5 cases [51]. Subsequently, it was adapted to anti-aaRS-positive patients with refractory ILD and myositis [52]. The retrospective study suggested that tacrolimus was a well-tolerated and effective therapy for managing refractory ILD and myositis in those patients. Since tacrolimus has superior potency over cyclosporin, it may be advantageous even in cases that are refractory to cyclosporin [50, 53].

Mycophenolate Mofetil

MMF (~30 mg/kg/day orally) has been reported to be effective in some resistant cases of PM-DM. MMF may be a suitable alternative to the conventional immunosuppressive agents because it appears to have a more favorable side-effect profile than either cyclophosphamide or cyclosporin [54, 55]. Retrospective studies of patients with ILD in PM-DM suggested that MMF was safe and well tolerated in those patients [56, 57]. In a large diverse cohort of connective tissue disease-associated-ILD including 32 patients with PM-DM, treatment with MMF was associated with either stable or improved pulmonary physiology over a median 2.5 years of follow-up [58]. Controlled trials to investigate the efficacy of MMF on ILD in PM-DM are necessary.

Intravenous Immunoglobulin

A double-blind placebo-controlled study demonstrated that intravenous immunoglobulin (IVIG) is very effective in improving both the muscle strength and the skin rash of PM-DM [59, 60]. In the murine bleomycin-induced pulmonary fibrosis model, IVIG may have a beneficial effect in the down regulation of collagen-I levels in the lungs [61]. However, the efficacy on ILD in patients with PM-DM is unknown. A few studies suggested that IVIG was effective for refractory ILD associated with DM or PM [62, 63].

Anti-TNF Agents

A retrospective study of eight patients with PM-DM refractory to corticosteroids and immunosuppressives suggested that anti-TNF agents might be useful in some patients with refractory PM-DM [64]. However, the efficacy of TNF-α inhibition on DM is still controversial [65]. Park *et al*. recently reported a case of DM-associated ILD resistant to high-dose steroid and immunosuppressants but improved with adalimumab [66].

COMBINATION THERAPY

Combination therapy with high-dose steroids and immunosuppressive agents including cyclosporin and intravenous cyclophosphamide are effective in some patients with rapidly progressive ILD in DM, in particular ADM (Fig. **1**) [11, 67]. High dose glucocorticoids, monthly intravenous cyclophosphamide, and cyclosporine may be used in combination for patients with ILD in clinically ADM, even when the ILD is still mild. Primary intensive approach by starting immunosuppressive agents simultaneously with corticosteroids might result in better survival than step-up approach by adding them sequentially for active ILD in PM-DM [68].

SALVAGE THERAPY

In spite of the combination therapies with glucocorticoids and immunosuppressive agents, respiratory dysfunction of ILD in PM-DM patients sometimes progresses (Fig. **2**). Although options for salvage therapy including rituximab and IVIG are reported [62, 69], the effects of these therapies

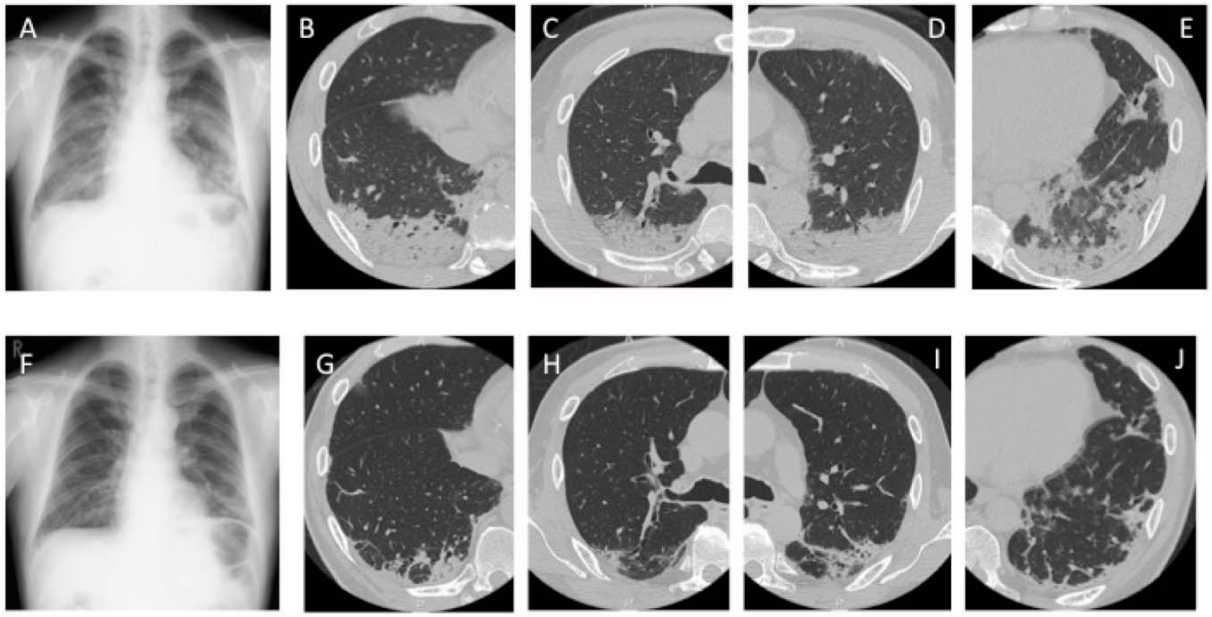

Fig. (1). Chest radiographs and computed tomography of a case with interstitial lung disease associated with amyopathic dermatomyositis successfully treated by corticosteroid, cyclosporine, and intravenous cyclophosphamide. Direct hemoperfusion with polymyxin B-immobilized fiber column was also performed on the first day of intravenous methylprednisolone pulse therapy. Subpleural consolidation in upper and lower lobes (**B**, **C**, **D**) with ground-glass opacity (**E**) was improved one month later (**G**, **H**, **I**, **J**). Anti-CADM-140/MDA5 titer before treatment was 149.9 unit.

are still unknown or limited. Recently, cases with rapidly progressive ILD associated with clinically ADM were successfully treated with direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP) [70, 71]. PMX-DHP might improve oxygenation in patients with acute lung injury/ acute respiratory distress syndrome or with acute exacerbation of IPF [72]. This could be another option for ILD in clinically ADM resistant to immunosuppressive treatment. Shoji *et al*. reported two cases rescued by living-donor lobar lung transplantation for rapidly progressive ILD associated with clinically ADM [73, 74].

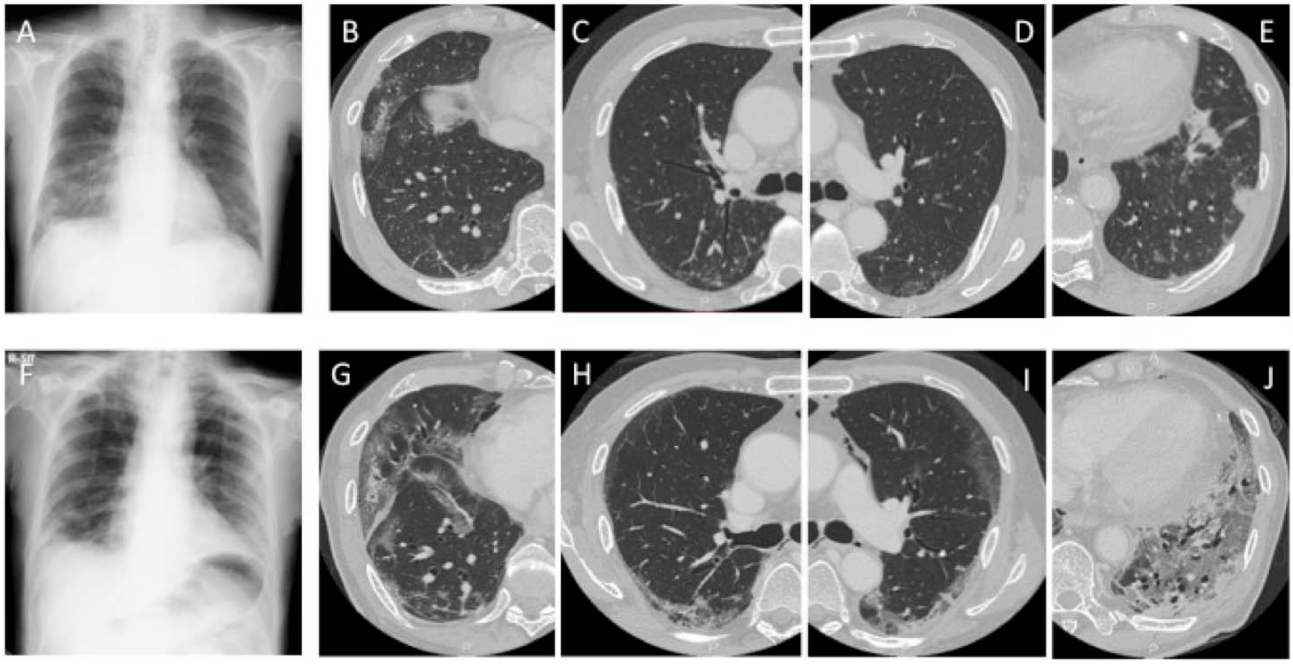

Fig. (2). Chest radiographs and computed tomography of a case with interstitial lung disease associated with amyopathic dermatomyositis resistant to treatment of corticosteroid, cyclosporine, and mycophenolate mofetil. Consolidation and linear opacities in lower lobes were almost stationary (**B**, **E**, **G**, **J**), but ground-glass opacity appeared and progressed from lower to upper lobes (**C**, **D**, **H**, **I**) resulting in fatal respiratory failure. Anti-CADM-140/MDA5 titer before treatment was 182.4 unit. Note that radiographic findings were less severe than those in the case of Fig. (**1**).

SUMMARY AND RECOMMENDATIONS

Starting from glucocorticoids, various immunosuppressive agents have been introduced to treat fatal ILD in PM-DM. However, even if treatment is initiated early in the course of the disease, some patients still develop irreversible fatal lung fibrosis. Because of the relatively small number of patients and rapid development of respiratory failure, controlled trials on the effect of different treatments may hardly be performed. For the present, respiratory physicians have to chose immunosuppressive agents for the patients with ILD in PM-DM that they face on a case by case basis. A possible sequence of management options for treatment of the disease is indicated in Fig. (**3**).

For patients with DM or PM with radiographic ILD, we recommend consulting dermatologist whether the patient has characteristic rashes of DM or not. Without rashes, the patient should be diagnosed as PM.

For patients with PM who develop chronic ILD, we recommend only initiating systemic glucocorticoids because PM subtype is associated with better outcome of ILD in PM-DM [6]. The usual starting dose is oral prednisolone at a dose of 1 mg/kg ideal body weight per day. For PM patients with development of acute ILD, we recommend initiating intravenous methylprednisolone pulse therapy followed by oral prednisolone and adding a second immunosuppressive agent such as cyclosporin or intravenous cyclophosphamide. We generally choose cyclosporin in this setting.

Patients with ILD and DM, we recommend consulting neurologist whether the patient has clinical evidence of symmetric proximal muscle weakness. If muscle weakness or serum muscle enzyme abnormalities are unremarkable**,** more extensive muscle testing such as electromyography and/or muscle biopsy should be considered.

For patients with ILD and DM not ADM, we recommend initiating systemic glucocorticoids and adding a second immunosuppressive agent such as cyclosporin or intravenous cyclophosphamide regardless of whether ILD development is acute or chronic. Since features of ADM is associated with poor outcome of ILD, we recommend intensive immunosuppressive treatment as follows.

For patients with ILD and ADM, you might measure anti-CADM-140/MDA5 antibody titer. However, measurement of anti-CADM-140/MDA5 antibody titer is commercially unavailable yet. If the titer is low, we recommend initiating systemic glucocorticoids and adding a second immunosuppressive agent such as cyclosporin or intravenous cyclophosphamide.

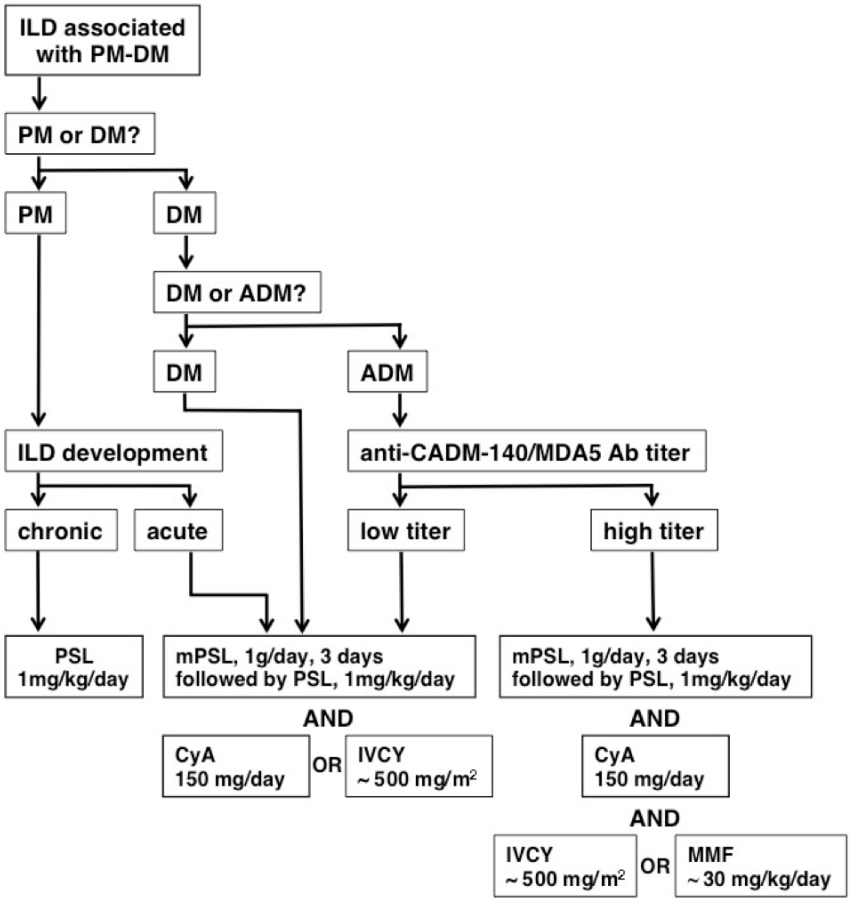

Fig. (3). A possible sequence of management options for the treatment of interstitial lung diseases (ILD) associated with polymyositis and dermatomyositis (PM-DM). When ILD is detected in PM-DM, treatment for the disease should be determined by the following factors; subtypes of PM or DM, subtypes of DM or amyopathic dermatomyositis (ADM), chronic or acute development of ILD in PM, and anti-CADM-140/MDA5 titer in ADM. Note that measurement of anti-CADM-140/MDA5 titer is commercially unavailable yet. Abbreviation, PSL, prednisolone: mPSL, methylprednisolone: CyA, cyclosporine: IVCY, intravenous cyclophosphamide: MMF, mycophenolate mofetil.

If the titer is high or you cannot measure it, we suggest initiating triple agent therapy including systemic glucocorticoids, cyclosporin, and intravenous cyclophosphamide or mycophenolate mofetil because anti-CADM-140/MDA5 antibody titer could predict disease outcome in patients with ILD associated with DM. Mycophenolate mofetil is our usual choice in this setting; intravenous cyclophosphamide is an alternative.

When the ILD is refractory to triple agent therapy, PMX-DHP may be additionally performed. Although data in support of the choice are limited, simultaneous administration of PMX-DHP with steroid pulse therapy may improve the prognosis of ILD in PM-DM/ADM (Fig. **1**).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors also offer special thanks to Dr. Katsuaki Asakawa, Dr. Takuro Sakagami, and Dr. Hiroshi Moriyama for useful discussion.

REFERENCES

[1] Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975; 292: 344-7.

[2] Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003; 362: 971-82.

[3] el-Azhary RA, Pakzad SY. Amyopathic dermatomyositis: Retrospective review of 37 cases. J Am Acad Dermatol 2002; 46: 560-5.

[4] Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: A series of 107 patients. Arthritis Rheum 2011; 63: 3439-47.

[5] Sontheimer RD, Miyagawa S. Potentially fatal interstitial lung disease can occur in clinically amyopathic dermatomyositis. J Am Acad Dermatol 2003; 48: 797-8.

[6] Fujisawa T, Suda T, Nakamura Y *et al.* Differences in clinical features and prognosis of interstitial lung diseases between polymyositis and dermatomyositis. J Rheumatol 2005; 32: 58-64.

[7] Kang EH, Lee EB, Shin KC *et al.* Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. Rheumatology (Oxford) 2005; 44: 1282-6.

[8] Douglas WW, Tazelaar HD, Hartman TE *et al.* Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001; 164: 1182-5.

[9] Tansey D, Wells AU, Colby TV *et al.* Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004; 44: 585-96.

[10] Suda T, Fujisawa T, Enomoto N *et al.* Interstitial lung diseases associated with amyopathic dermatomyositis. Eur Respir J 2006; 28: 1005-12.

[11] Miyazaki E, Ando M, Muramatsu T *et al.* Early assessment of rapidly progressive interstitial pneumonia associated with amyopathic dermatomyositis. Clin Rheumatol 2005: 1-4.

[12] Sakamoto N, Mukae H, Fujii T *et al.* Nonspecific interstitial pneumonia with poor prognosis associated with amyopathic dermatomyositis. Intern Med 2004; 43: 838-42.

[13] High WA, Cohen JB, Murphy BA *et al.* Fatal interstitial pulmonary fibrosis in anti-jo-1-negative amyopathic dermatomyositis. J Am Acad Dermatol 2003; 49: 295-8.

[14] Climent-Albaladejo A, Saiz-Cuenca E, Rosique-Roman J *et al.* Dermatomyositis sine myositis and antisynthetase syndrome. Joint Bone Spine 2002; 69: 72-5.

[15] Betteridge Z, Gunawardena H, North J, Slinn J, McHugh N. Anti-synthetase syndrome: A new autoantibody to phenylalanyl transfer rna synthetase (anti-zo) associated with polymyositis and interstitial pneumonia. Rheumatology (Oxford) 2007; 46: 1005-8.

[16] Targoff IN. Autoantibodies and their significance in myositis. Curr Rheumatol Rep 2008; 10: 333-40.

[17] Kalluri M, Sahn SA, Oddis CV *et al.* Clinical profile of anti-pl-12 autoantibody. Cohort study and review of the literature. Chest 2009; 135: 1550-6.

[18] 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: 1571-6.

[19] 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: 2193-200.

[20] Sato S, Kuwana M, Fujita T *et al.* Amyopathic dermatomyositis developing rapidly progressive interstitial lung disease with elevation of anti-cadm-140/mda5 autoantibodies. Mod Rheumatol 2012; 22: 625-9.

[21] Sato S, Kuwana M, Fujita T, Suzuki Y. Anti-cadm-140/mda5 autoantibody titer correlates with disease activity and predicts disease outcome in patients with dermatomyositis and rapidly progressive interstitial lung disease. Mod Rheumatol 2013; 23(3): 496-502.

[22] Muro Y, Sugiura K, Hoshino K, Akiyama M. Disappearance of anti-mda-5 autoantibodies in clinically amyopathic dm/interstitial lung disease during disease remission. Rheumatology (Oxford) 2012; 51: 800-4.

[23] 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: 1278-84.

[24] Gono T, Sato S, Kawaguchi Y *et al.* Anti-mda5 antibody, ferritin and il-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-mda5 antibody-positive dermatomyositis. Rheumatology (Oxford) 2012; 51: 1563-70.

[25] Cao H, Pan M, Kang Y *et al.* Clinical manifestations of dermatomyositis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene 5 antibody. Arthritis Care Res (Hoboken) 2012; 64: 1602-10.

[26] Sakurai N, Nagai K, Tsutsumi H *et al.* Anti-cadm-140 antibody-positive juvenile dermatomyositis with rapidly progressive interstitial lung disease and cardiac involvement. J Rheumatol 2011; 38: 963-4.

[27] Kobayashi I, Okura Y, Yamada M *et al.* Anti-melanoma differentiation-associated gene 5 antibody is a diagnostic and predictive marker for interstitial lung diseases associated with juvenile dermatomyositis. J Pediatr 2011; 158: 675-7.

[28] Marie I, Hatron PY, Hachulla E *et al.* Pulmonary involvement in polymyositis and in dermatomyositis. J Rheumatol 1998; 25: 1336-43.

[29] Grau JM, Miro O, Pedrol E *et al.* Interstitial lung disease related to dermatomyositis. Comparative study with patients without lung involvement. J Rheumatol 1996; 23: 1921-6.

[30] Hirakata M, Nagai S. Interstitial lung disease in polymyositis and dermatomyositis. Curr Opin Rheumatol 2000; 12: 501-8.

[31] Nawata Y, Kurasawa K, Takabayashi K *et al.* Corticosteroid resistant interstitial pneumonitis in dermatomyositis/polymyositis: Prediction and treatment with cyclosporine. J Rheumatol 1999; 26: 1527-33.

[32] Oddis CV. Current approach to the treatment of polymyositis and dermatomyositis. Curr Opin Rheumatol 2000; 12: 492-7.

[33] Dalakas MC. How to diagnose and treat the inflammatory myopathies. Semin Neurol 1994; 14: 137-45.

[34] Oddis CV. Idiopathic inflammatory myopathy: Management and prognosis. Rheum Dis Clin North Am 2002; 28: 979-1001.

[35] Shinohara T, Hidaka T, Matsuki Y *et al.* Rapidly progressive interstitial lung disease associated with dermatomyositis responding to intravenous cyclophosphamide pulse therapy. Intern Med 1997; 36: 519-23.

[36] Mira-Avendano IC, Parambil JG, Yadav R *et al.* A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respiratory medicine 2013; 107: 890-6.

[37] Bunch TW, Worthington JW, Combs JJ *et al.* Azathioprine with prednisone for polymyositis. A controlled, clinical trial. Ann Intern Med 1980; 92: 365-9.

[38] Bunch TW. Prednisone and azathioprine for polymyositis: Long-term followup. Arthritis Rheum 1981; 24: 45-8.

[39] Rowen AJ, Reichel J. Dermatomyositis with lung involvement, successfully treated with azathioprine. Respiration 1983; 44: 143-6.

[40] Schnabel A, Reuter M, Gross WL. Intravenous pulse cyclophosphamide in the treatment of interstitial lung disease due to collagen vascular diseases. Arthritis Rheum 1998; 41: 1215-20.

[41] Schnabel A, Reuter M, Biederer J *et al.* Interstitial lung disease in polymyositis and dermatomyositis: Clinical course and response to treatment. Semin Arthritis Rheum 2003; 32: 273-84.

[42] Maccioni FJ, Colebatch HJ. Management of fibrosing alveolitis with polymyositis dermatomyositis. Aust N Z J Med 1990; 20: 806-10.

[43] Schnabel A, Hellmich B, Gross WL. Interstitial lung disease in polymyositis and dermatomyositis. Curr Rheumatol Rep 2005; 7: 99-105.

[44] Yamasaki Y, Yamada H, Yamasaki M *et al.* Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford) 2007; 46: 124-30.

[45] Clipstone NA, Crabtree GR. Identification of calcineurin as a key signalling enzyme in t-lymphocyte activation. Nature 1992; 357: 695-7.

[46] Maeda K, Kimura R, Komuta K *et al.* Cyclosporine treatment for polymyositis/dermatomyositis: Is it possible to rescue the deteriorating cases with interstitial pneumonitis? Scand J Rheumatol 1997; 26: 24-9.

[47] Qushmaq KA, Chalmers A, Esdaile JM. Cyclosporin a in the treatment of refractory adult polymyositis/dermatomyositis: Population based experience in 6 patients and literature review. J Rheumatol 2000; 27: 2855-9.

[48] Miyake S, Ohtani Y, Sawada M *et al.* Usefulness of cyclosporine a on rapidly progressive interstitial pneumonia in dermatomyositis. Sarcoidosis Vasc Diffuse Lung Dis 2002; 19: 128-33.

[49] Harigai M, Hara M, Kamatani N *et al.* [nation-wide survey for the treatment with cyclosporin a of interstitial pneumonia associated with collagen diseases]. Ryumachi 1999; 39: 819-28.

[50] Takada K, Nagasaka K, Miyasaka N. Polymyositis/dermatomyositis and interstitial lung disease: A new therapeutic approach with t-cell-specific immunosuppressants. Autoimmunity 2005; 38: 383-92.

[51] Oddis CV, Sciurba FC, Elmagd KA *et al.* Tacrolimus in refractory polymyositis with interstitial lung disease. Lancet 1999; 353: 1762-3.

[52] Wilkes MR, Sereika SM, Fertig N *et al.* Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. Arthritis Rheum 2005; 52: 2439-46.

[53] Dumont FJ. Fk506, an immunosuppressant targeting calcineurin function. Curr Med Chem 2000; 7: 731-48.

[54] Ytterberg SR. Treatment of refractory polymyositis and dermatomyositis. Curr Rheumatol Rep 2006; 8: 167-73.

[55] Majithia V, Harisdangkul V. Mycophenolate mofetil (cellcept): An alternative therapy for autoimmune inflammatory myopathy. Rheumatology (Oxford) 2005; 44: 386-9.

[56] Swigris JJ, Olson AL, Fischer A *et al.* Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest 2006; 130: 30-6.

[57] Morganroth PA, Kreider ME, Werth VP. Mycophenolate mofetil for interstitial lung disease in dermatomyositis. Arthritis care & research 2010; 62: 1496-501.

[58] Fischer A, Brown KK, Du Bois RM *et al*. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol 2013; 40: 640-6.

[59] Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. Jama 2004; 291: 2367-75.

[60] Dalakas MC. The role of high-dose immune globulin intravenous in the treatment of dermatomyositis. Int Immunopharmacol 2006; 6: 550-6.

[61] Molina V, Haj-Yahia S, Solodeev I *et al.* Immunomodulation of experimental pulmonary fibrosis by intravenous immunoglobulin (ivig)dagger. Autoimmunity 2006; 39: 711-7.

[62] Suzuki Y, Hayakawa H, Miwa S *et al.* Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis. Lung 2009; 187: 201-6.

[63] Bakewell CJ, Raghu G. Polymyositis associated with severe interstitial lung disease: Remission after three doses of iv immunoglobulin. Chest 2011; 139: 441-3.

[64] Efthimiou P, Schwartzman S, Kagen LJ. Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: A retrospective study of eight patients. Ann Rheum Dis 2006; 65: 1233-6.

[65] Iannone F, Scioscia C, Falappone PC *et al.* Use of etanercept in the treatment of dermatomyositis: A case series. J Rheumatol 2006; 33: 1802-4.

[66] Park JK, Yoo HG, Ahn DS *et al.* Successful treatment for conventional treatment-resistant dermatomyositis-associated interstitial lung disease with adalimumab. Rheumatol Int 2012; 32: 3587-90.

[67] Kameda H, Nagasawa H, Ogawa H *et al.* Combination therapy with corticosteroids, cyclosporin a, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol 2005; 32: 1719-26.

[68] Takada K, Kishi J, Miyasaka N. Step-up versus primary intensive approach to the treatment of interstitial pneumonia associated with dermatomyositis/polymyositis: A retrospective study. Mod Rheumatol 2007; 17: 123-30.

[69] Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: Progress and pitfalls. Curr Opin Rheumatol 2010; 22: 633-8.

[70] Kakugawa T, Mukae H, Saito M *et al.* Rapidly progressive interstitial pneumonia associated with clinically amyopathic dermatomyositis successfully treated with polymyxin b-immobilized fiber column hemoperfusion. Intern Med 2008; 47: 785-90.

[71] Ichiyasu H, Horio Y, Tsumura S *et al.* Favorable outcome with hemoperfusion of polymyxin b-immobilized fiber column for rapidly progressive interstitial pneumonia associated with clinically amyopathic dermatomyositis: Report of three cases. Mod Rheumatol 2012.

[72] Abe S, Azuma A, Mukae H *et al.* Polymyxin b-immobilized fiber column (pmx) treatment for idiopathic pulmonary fibrosis with acute exacerbation: A multicenter retrospective analysis. Intern Med 2012; 51: 1487-91.

[73] Shoji T, Bando T, Fujinaga T *et al.* Living-donor lobar lung transplantation for interstitial pneumonia associated with dermatomyositis. Transpl Int 2010; 23: e10-1.

[74] Shoji T, Bando T, Fujinaga T *et al.* Living-donor lobar lung transplantation for rapidly progressive interstitial pneumonia associated with clinically amyopathic dermatomyositis: Report of a case. General thoracic and cardiovascular surgery 2013; 61: 32-4.

Received: March 21, 2013 Revised: June 7, 2013 Accepted: June 9, 2013