Treatment of Interstitial Lung Disease Associated with Polymyositis-Dermatomyositis

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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 immunosuppressive therapy. 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, Interstitial 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 pathogenesis 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
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-aminocyl-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 is usually 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

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

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

**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. Favorable outcome in patients who failed to respond to steroids alone has been reported previously. 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.

**Azathioprine**

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

**Cyclophosphamide**

Intravenous cyclophosphamide (300-800 mg/m²) in combination with pulse therapy has been reported to induce an initial remission of rapidly progressive ILD, but the evidence remains circumstantial. Cyclophosphamide may also improve the 5-year survival rate in patients who failed to respond to steroids alone. Although it appears to be of benefit in patients with ILD in PM-DM, controlled trials are needed.

**Calcineurin Inhibitors**

Cyclosporin binds to cyclophilin, then the complex inhibits calcineurin phosphatase and T-cell activation. Cyclosporine was reported to be effective against both myositis and ILD, even steroid-resistant ILD, when used early in the course of the disease. 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.

Tacrolimus, which is a macrolide antibiotic, engages another immunophilin, 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. Subsequently, it was adapted to anti-aaRS-positive patients with refractory ILD and myositis. 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.

**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. Retrospective studies of patients with ILD in PM-DM suggested that MMF was safe and well tolerated in those patients. 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. 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. 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. 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.

**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. However, the efficacy of TNF-α inhibition on DM is still controversial. Park et al. recently reported a case of DM-associated ILD resistant to high-dose steroid and immunosuppressants but improved with adalimumab.

**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. 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.

**SALVAGE THERAPY**

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

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 choose 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.](image-url)
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.

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