Respiratory Medicine (2013) 107, 890–896

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A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis

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Received 14 August 2012; accepted 18 February 2013
Available online 19 March 2013

KEYWORDS
Interstitial lung disease;
Polymyositis;
Dermatomyositis;
Immunosupressive agents

Summary
Introduction: We reviewed our experience with immunosuppressive agents in patients with steroid-resistant Interstitial Lung Disease in the setting of Polymyositis/Dermatomyositis (PM/DM-ILD) to determine whether there were major differences in outcomes.
Methods: We identified all patients treated for PM/DM-ILD and assessed cyclophosphamide (CYC), azathioprine (AZA) and mycophenolate (MMF) when used as first-line steroid sparing therapy for effects on pulmonary function variables, dyspnea and tolerance at six and twelve months.
Results: Among 46 patients meeting the inclusion criteria, 24 were treated with CYC, 13 with AZA and 9 with MMF. There were no baseline differences between the three treatment groups for any of the demographic or physiologic variables, dyspnea score, the presence of >30% fibrosis on CT, or the baseline steroid dose. At the six months assessment, the overall median change in FVC was 5.0% (25th, 75th percentile −3, 11.5%), corresponding to +.20 L (.09, 0.42 L) and the DLCO increased by 2.93% (−4, 9%), corresponding to 1 mm/ml/Hg (−.58, 2.3). The severity of dyspnea decreased substantially, prednisone dose could be reduced and no important difference in side effects was found in the whole group of patients. This effect was sustained after twelve months of therapy.

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0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2013.02.015

Conclusions: In patients with PM/DM-ILD related, treatment with CYC, AZA or MMF was associated with stabilization of pulmonary physiology, improved dyspnea, and a reduction of steroid dose.

Introduction

Interstitial lung disease (ILD) occurs in nearly 40% of individuals with polymyositis-dermatomyositis (PM-MD), though prevalence reported in individual series has varied widely.[2,10–14] The presence of ILD confers a high risk of death, with estimated mortality around 30%.[2,13,14] Prognostic factors that have been associated with poor outcomes include acute onset, steroid-refractoriness and more severe impairment of pulmonary physiology.[2,11–14]

The treatment for patients with PM/DM ILD is largely based on case reports and smallcase series that describe benefits from a wide range of immunosuppressants. Intravenous cyclophosphamide (CYC) has been advocated as the appropriate initial approach for patients with steroid-refractory severe ILD,[3] where it is used in combination with high doses of corticosteroids. Oral CYC is commonly believed to be effective based on extrapolation from the experience with intravenous CYC and analogy with other rheumatologic conditions, but there are no published data supporting its utility. Methotrexate has been used as well, but concerns about distinguishing toxicity from disease progression limit enthusiasm for it.

Azathioprine has historically been the most widely used steroid-sparing medication, for patients with more moderate disease or for maintenance therapy after induction with CYC.[4,5] However, there are no controlled data about outcomes compared with other agents. More recently, mycophenolate (MMF) was proposed as a viable alternative therapy.[5,6,30]

It is clear that larger experiences are necessary to delineate the expected response to commonly used therapies in PM/DM ILD. To that end, we retrospectively analyzed our patients with PM/DM ILD who were treated with steroid-sparing agents in our clinic.

Materials and methods

We identified all outpatients treated for PM/DM ILD who had adequate longitudinal follow-up and for whom we were the first physicians to start cyclophosphamide (CYC), azathioprine (AZA) or mycophenolate mofetil (MMF). PM/DM as a cause of the ILD was considered to be present in patients fulfilling the definite or probable diagnostic criteria defined by Bohan and Peter,[1,7] and who had no other ascertainable cause for their ILD. We also included patients with features of the antisynthetase syndrome and no other identifiable cause for the lung disease (antimyositis antibodies other than Anti-Jo were available in only 8 of our patients, with a positive anti-PL12 in one). We excluded patients with predominant scleroderma features, since therapy for those individuals was based on the findings from the Scleroderma Lung Study.[3] Patients with other connective tissue diseases and overlap syndromes were also excluded.

All the patients were selected to receive immunosuppressive agents due to persistently bothersome pulmonary disease despite treatment with steroids, or marked symptoms in the context of abnormal pulmonary function testing. Only patients who had been treated with steroid-sparing medications, and who had longitudinal follow-up for at least six months in our clinic were included. The study period spanned the years 2003–2010. This protocol was approved by the Cleveland Clinic Institutional Review Board (IRB# 11–499).

We routinely obtained demographic and disease-related features at the time of the initial visit, or when the diagnosis of PM/DM ILD was first made in the pulmonary clinic. All patients had chest CT performed at our institution at the time of the initial evaluation, using a standard protocol. Specifically, all CTs were obtained with no contrast and 1 mm collimation during an inspiratory breath hold with a 64-head scanner. A chest radiologist (RY) graded the proportion of subjects with fibrosis encompassing more than 30% of the lung parenchyma according to the method proposed by Goh.[8]

Pulmonary function testing was reported using reference equations derived from Hankinson.[9] We routinely assessed dyspnea at each visit in our clinic using the Modified Medical Research Council (MMRC) Dyspnea Scale. Toxicity determinations were graded according to the revised Common Terminology Criteria for Adverse Events v3.0 (CTCAE) schema. The data were analyzed by Wilcoxon Rank Sum Test or Chi–Square Test, as appropriate.

The choice of medication was made by the treating physician. We assessed the effect of the medications at 6 and 12 months on forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO), dyspnea, prednisone dose and tolerance. Two patients were intolerant of azathioprine within two months of starting it, and were switched to MMF. These two patients were analyzed after six months of the new medication, using the time of starting the new medication as a baseline value. One other patient stopped medication prior to six months due to pneumonia (MMF) and was lost to follow-up. This patient was not included in the outcomes.

Results

Clinical features

One hundred fifty-three patients were diagnosed with PM/DM but only forty-six patients met the inclusion criteria. The reasons for exclusion included insufficient evidence of ILD (42 patients), lack of adequate follow-up,[22] predominant scleroderma features,[21] use of other

immunosuppressive medications[14] and no new immunosuppressive treatment rendered.[8]

The duration of PM/DM symptoms before the diagnosis of ILD was less than six months in 15 (33%) patients, seven to twelve months in 12 (27%), thirteen to twenty-four months in six (11%), twenty-five to thirty-six months in nine (20%) and more than thirty-six months in three (7%). In only one case, ILD was diagnosed one year before the evidence of PM/DM symptoms. The duration of PM/DM symptoms did not impact grade of dyspnea, FVC or DLCO in our group of patients.

The baseline characteristics are listed in Table 1. Most of the patients (74%) had polymyositis; the remaining 26% had dermatomyositis. The median age was 53 years; 26 (57%) were females, and 37 (81%) were Caucasian. There was a trend ($p = 0.06$) for females to be treated with agents other than AZA, and former smokers were more likely to be treated with CYC ($p = 0.03$). Fibrosis encompassing more than 30% of the lung parenchyma on HRCT was present in 24 (52%) of the subjects. Specific radiologic patterns suggested by the HRCT included predominant organizing pneumonia in 17 patients (37%), NSIP in 16 (35%), UIP in 9 (19%) and a mixed pattern in 4 (9%) of the patients.

The median baseline prednisone dose for the entire population was 40 mg/d (25th, 75th percentile 28, 53 mg/d). At the time of our first evaluation, 39 (85%) of the patients were considered steroid-resistant (taking $\geq$20 mg/d of prednisone for at least three months), 10 of whom were taking methotrexate plus prednisone. These patients had generally been treated with starting prednisone doses ranging from 40 to 80 mg daily, without adequate control of their ILD. In the remaining seven patients, we started prednisone and the steroid-sparing agent contemporaneously.

Notable clinical features at the time we evaluated the patients included cough in 45 (98%) of the patients and symptomatic muscle weakness in 12 (26%). When muscle enzyme levels were determined, 21/40 (53%) had elevated creatinine kinase levels, with 11 (28%) more than 5-fold the upper limit of normal. Aldolase, was elevated in 14 of 32 cases (43%). Anti-Jo1 antibody was positive in 50% of the patients, and mechanic's hands were present in 46%, including 16 patients with both, who were thereby diagnosed with suspected antisynthetase syndrome (34% of the whole case series). Thus, the presence of mechanics hands conferred a high likelihood of anti-Jo 1 seropostivity.

Bronchoscopy with bronchoalveolar lavage was performed in 24 patients, usually to exclude infection. Elevated neutrophils (>3%) were present in 16 subjects (67%), elevated lymphocytes (>15%) in 11 (45%) and eosinophils (>1%) in 5 (21%). None of the 24 subjects were found to have infections. Among 16 patients with surgical lung biopsies, ten cases were available for review by a pulmonary pathologist (VA). These included nonspecific interstitial pneumonia (NSIP, 5 cases) and one case each of organizing pneumonia, diffuse alveolar damage, and nondiagnostic biopsy. Two patients had substantial features of both NSIP and OP. The other six cases were reported as a NSIP (five) or OP.[1] No foamy macrophages on BAL or suggestion of aspiration pneumonia on lung biopsy (bronchiolitis, giant cells) were seen. The outcomes among these 16 patients were not significantly different, but the numbers are too small to be conclusive.

Effect of treatment

The initial steroid-sparing regimen was selected at the discretion of the primary pulmonologist. There were no significant differences in prescribing pattern according to treating physician, either in terms of frequency of medication use or severity of the lung disease as measured by FVC. We do not typically use methotrexate in this setting, although it has been reported to be effective,[14] due to concern about potential toxicity masquerading as ILD progression. There were no differences between the three treatment groups for any of the demographic or physiologic variables, the presence of >30% fibrosis on CT, or the baseline steroid dose.

For the first six months, 24 patients received CYC, 13 received AZA and 9 received MMF. The average dose was

Table 1 Baseline features.

Variable	Cyclophosphamide ($n = 24$)	Azathioprine ($n = 13$)	Mycophenolate ($n = 9$)	*P* value
Age	56 (52.65)	50 (46.64)	56 (47.64)	.36
Female gender	15 (63%)	4 (31%)	7 (78%)	.06
White race[a]	18 (78%)	9 (75%	9 (100%)	.30
Former smoker[b]	17 (71%)	7 (78%)	2 (22%)	.04
Anti-Jo1	11 (46%)	7 (54%)	5 (56%)	.91
HRCT: $\geq$30% Fibrosis	12 (50%)	9 (69%)	3 (33%)	.26
Dyspnea				.32
Grade 2	2 (8%)	2 (15%)	0 (0)	
Grade 3	11 (46%)	3 (23%)	7 (78%)	
Grade 4	11 (46%)	8 (61%)	2 (22%)	
FVC (%)	58 (48.78)	63 (47.78)	64 (55.78)	.76
DLCO (%)	45 (34.58)	53 (43.61)	58 (47.64)	.17
Baseline steroid dose	40 (22.40)	40 (28.60)	40 (35.60)	.44

All values are median (25th, 75th percentile) except where specified.
[a] Fewer than 46 patients included due to missing data.
[b] No patient was a current smoker.

129 mg daily of CYC, 130 mg daily of AZA and 2.2 g/day of MMF. At the six months assessment, the overall median change in FVC was 5.0% (25th, 75th percentile −3, 11.5%), corresponding to +.20 L (.09, 0.42 L) and the DLCO increased by 2.93% (−4, 9%), corresponding to 1 mm/ml/Hg (−.58, 2.3). For the 33 patients who remained on consistent therapy for 12 months, the median change in FVC was 4.7% (−.5, 9.5%), or +.2 L (.04, 0.38 L). The DLCO had increased from baseline by 2.3% (−5, 7%), or .61 (−1.19, 2.1) mm/ml/Hg (Figs. 1 and 2).

In the whole case series, MMRC dyspnea grade >2 was present in 92% of patients at the beginning of treatment, but in only 26% at 6 months and 40% at 12 months (Table 2). The prednisone dose was reduced from 40 mg/d to a median dose of 10 mg/d (7.5, 20), 16.3 mg/d (1.25, 20) and 15 mg/d[10,20] at six months and 7.5 mg/d (0, 12.5), 7.5 mg/d (0, 20) and 10 (0, 17.5) at 12 months, in the CYC, AZA and MMF group, respectively.

None of these outcomes were statistically associated with the choice of therapy.

In 13 patients, a second agent was substituted at 6 months after the first one. The reasons for switching medications included toxicity (two patients), concern about potential CYC toxicity (6 patients) and inadequate response (5 patients). This group comprised 10 patients treated initially with CYC; four were switched to AZA and 6 to MMF. AZA was the first drug in two cases, followed by CYC in both, and MMF was the first medication used in one patient, followed by AZA. Analysis of the effect of the second medication on FVC and DLCO 6 months after starting it, demonstrated that the detected values after the first drug were maintained without any significant change, remaining improved in the eight patients in whom toxicity developed. In the five patients who did not have an adequate response to a first agent, the second agent likewise did not improve the physiologic variables after six months.

Grade 3 medication toxicity, requiring interruption of the immunosuppressive agent occurred in one patient in the CYC group (invasive pulmonary aspergillosis). Other toxic effects, classified as Grade 1 and 2, occurred in 11 (48%), 3 (23%) and 4 (44%) of the CYC, AZA and MMF groups, respectively, without need for drug discontinuation.

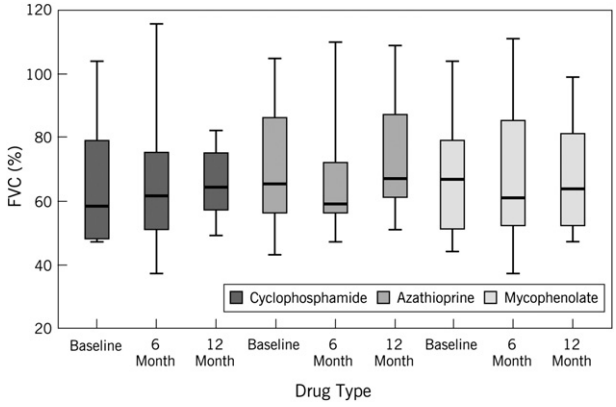

Figure 1 FVC percentage after 6 and 12 months of treatment with the three different medications.

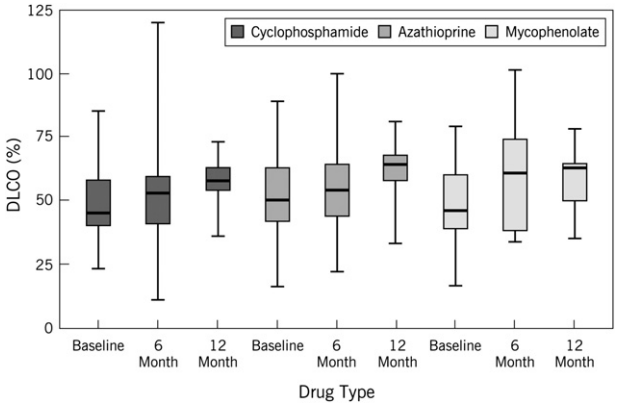

Figure 2 Percentage DLCO after 6 and 12 months of treatment.

After a median follow-up of 5.1 years since our initial evaluation, 39 patients (85%) are still living. Three required lung transplantation: two are alive at two years and at two months post-transplantation, respectively; one died three weeks after transplantation from post-operative complications. The other deaths were due to advanced primary lung disease in two cases, for unknown reasons in three cases and from septic shock in a patient no longer on immunosuppressive medication.

Discussion

Our experience suggests that cyclophosphamide, azathioprine, and mycophenolate mofetil are similarly viable alternatives for initial steroid-sparing therapy of PM/DM ILD. In our population, use of any of the three agents was associated with a stabilization of pulmonary function tests, less dyspnea, and a substantial reduction of the steroid dose. The benefits of treatment persisted over at least 12 months. In addition, the effects of treatment did not appear to be influenced by the extent of parenchymal fibrosis as assessed by the baseline chest CT study.

In eight patients who were changed to a second agent due to toxicity or side effects, the response to the second agent was similar. For five patients who were thought to have an inadequate response to the initial steroid-sparing therapy, switching to a second agent was not noticeably helpful. This could indicate that the benefits of substitute agents do not go beyond avoiding toxicity, but our numbers are too small to derive conclusions.

The usefulness of CYC and CYC-containing regimens was first described more than two decades ago in patients with acute presentations of PM/DM ILD associated with respiratory failure.[24,25,27] In a small prospective cohort study, ten patients with acute interstitial pneumonia in the setting of DM were treated with combined intravenous CYC, cyclosporine A (CSA) and intravenous corticosteroids. Compared with historical controls treated with CSA alone, the combination regimen reduced mortality from 90 to 50%.[26] In 2007, Yamasaki et al. reported that intravenous CYC reduced dyspnea and/or improved pulmonary function in 12 of 17 patients.[28] In general, CYC has been reserved for patients with severe disease and acute or subacute onset of

Table 2 Effect of treatment.

Variable	Cyclophosphamide ($n = 24$)	Azathioprine ($n = 13$)	Mycophenolate ($n = 9$)	*P* value
FVC 6 months %	66 (55.87)	59 (53.80)	67 (57.90)	.61
FVC 12 months %	67 (51.79)	61 (52.85)	64 (52.81)	.92
DLCO 6 months %	50 (40.64)	54 (44.65)	64 (58.69)	.20
DLCO 12 months %	46 (39.61)	61 (38.74)	63 (50.64)	.17
Dyspnea 6 months[a]				.49
Grade 2	13 (59%)	8 (72%)	8 (88%)	
Grade 3	8 (36%)	3 (27%)	1 (11%)	
Grade 4	1 (5%)	0	0	
Dyspnea 12 months[a]				.62
Grade 2	11 (57%)	5 (40%)	4 (80%)	
Grade 3	6 (31%)	6 (60%)	1 (20%)	
Grade 4	2 (11%)	0	0	
Prednisone dose at 6 months	10 (8.20)	16 (1.20)	15 (10.20)	.44
Prednisone at 12 months.	8 (0.13)	8 (0.20)	10 (0.18)	.86
Toxicity	12 (50%)	3 (23%)	4 (44%)	.52

All values are median (25th, 75th percentile) except where specified.
[a] Fewer than 46 patients included due to missing data.

ILD. Our experience is the first report that oral CYC is useful for PM/DM ILD, but does not support the hypothesis that oral CYC in this setting is more effective than less toxic medications.

The current data supporting the benefits of azathioprine are limited to small case series and case reports[16,23,29] where it was used for maintenance therapy after induction or for patients with milder ILD. There are no large series documenting the expected response to azathioprine. In a review of 160 patients with DM/PM, including 23% with ILD, AZA and methotrexate appeared to exhibit generally similar effectiveness, though the authors did not specifically analyze the effects on lung disease. Recently, mycophenolate was shown to be effective in general for CTD-associated ILD, in a study that included five patients with PM/DM.[30] A subsequent study reported that MMF improved pulmonary physiology, dyspnea and steroid requirements in three of four patients.[31]

Benefits from other agents have also been described in small case series, including cyclosporine for steroid-resistant pneumonitis,[20–22] tacrolimus,[32–34] leflunomide,[35] intravenous immunoglobulin[36] and rituximab.[37] We excluded analysis of those agents, since they were generally used in small number of patients, or for 3rd or 4th line therapy.

The clinical characteristics of our population resemble those described by prior authors. In those reports, cough and dyspnea were also the most common presenting symptoms.[12,14,16] The 50% prevalence of anti-Jo1 antibody in our series is similar to results in previous series, where it ranged from 31 to 75%.[13–16] We also noted that anti-Jo1 antibody seropositivity correlated strongly with the presence of mechanic's hands.

The spectrum of HRCT findings in our patients corresponded with those described in the current literature,[17,18] including patterns suggesting primarily NSIP, OP and UIP. Most patients exhibited imaging features consistent with more than one pathologic pattern. Although the presence of an OP pattern has been correlated with better response to steroids,[18,23] it is unknown whether it is also predictive of response to other therapies. Neither the imaging pattern nor the extent of fibrosis had not evident correlation with any of the outcomes, suggesting that therapeutic trials may be beneficial regardless of the HRCT findings.

Our patients had a range of pathologic patterns, predominantly NSIP and OP, similar to prior reports.[17–19] The specific pathologic pattern did not appear to correlate with the treatment response we observed, although the numbers are too small to provide reliable information. There was little evident role for bronchoscopy in our population.

The major weakness of this study is that the choice of immunosuppressive agent was uncontrolled. For example, it is possible that patients with more severe disease were treated preferentially with CYC. However, both the radiologic and physiologic severity were similar in all three treatment groups. Another weakness is that the steroid dose was not reduced in a systemic manner. Our practice is to routinely attempt to taper prednisone beginning two to three months after initiating steroid-sparing medications. Also, this experience does not inform the question of whether any of these agents should be used as a first line medication in place of corticosteroids. Finally, the reduction in dyspnea may relate more to ongoing improvement of myositis, rather than effects on the ILD. Given the discordance between the relatively unchanged PFTs and the substantially reduced MMRC Grade, effects on muscle strength are likely to underlie at least part of this symptomatic benefit.

Conclusion

We describe herein the treatment of PM/DM ILD in 46 patients. To our knowledge, this is the largest case series to date analyzing the effectiveness of steroid-sparing medications for PM/DM ILD. We did not find significant outcome differences between CYC, AZA and MMF, perhaps due to the small sample size and retrospective nature of this study. In

general, treatment with any of these agents was associated with stabilization of pulmonary physiology, improved dyspnea, and a reduction of steroid dose. Given the rarity of PM/DM ILD, it is unlikely that a randomized trial comparing these agents will occur soon.

Conflict of interest

I do not have any conflict of interest, related with the manuscript.

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