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Concise Report

Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy

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Objectives. **Mycophenolate mofetil (MMF) is a new immunosuppressive agent currently being used for the prevention of renal allograft rejection. MMF is a specific inhibitor of lymphocytes and is well tolerated leading to its use in other autoimmune diseases. We have used MMF for the treatment of seven patients with inflammatory myopathy and are hereby reporting our results.**

Case series. **All of our patients were females (age 17–65 yr). They were symptomatic upon presentation and met classification criteria for idiopathic inflammatory myopathy. Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein as well as creatine kinase were significantly elevated in all the patients, indicating active disease. Corticosteroids were concomitantly being administered (20–60 mg/day of prednisone). Initial therapy with conventional immunosuppressives was either ineffective or had significant adverse effects leading to their discontinuation. MMF was started in doses of 500 mg twice a day and titrated up to 1 g twice a day.**

Results. **Our patients have exhibited an impressive serological response to therapy with MMF and six patients had a marked improvement in their weakness. One patient had incomplete improvement in her weakness and has required additional therapies. MMF has been well tolerated during the treatment period (12–36 months).**

Conclusion. **A striking clinical and laboratory response of active myositis in six out of seven patients in this series illustrates that MMF can be effectively used in management of autoimmune inflammatory myopathy and may be a suitable alternative to the conventional immunosuppressive agents.**

KEY WORDS: Mycophenolate mofetil, autoimmune inflammatory myopathy, immunosuppressives.

Inflammatory myopathies are a diverse group of disorders and may occur in an isolated form or in association with a systemic autoimmune disorder, infections, malignancy and rarely drugs. The isolated form is also called idiopathic inflammatory myopathy and common clinical varieties are dermatomyositis (DM), polymyositis (PM) and inclusion-body myositis (IBM). These disorders share a number of clinical features, although they are entirely different diseases in pathogenesis, epidemiology, clinical presentation and prognosis. The initial classification criteria were proposed in 1975 by Peter and Bohan [1] (Table 1) and are still commonly used, although their utility continues to be debated.

The treatment of idiopathic inflammatory myopathy is largely empirical as there are only limited data from controlled trials to allow an evidence-based approach [2]. The treatment usually consists of the use of corticosteroids and immunosuppressive agents [2]. The currently available immunosuppressive agents are not effective in all patients and can have side-effects limiting their use in a number of patients [2]. Hence there is always an impetus to try alternative therapies in management of these diseases.

Mycophenolate mofetil (MMF) is a novel immunosuppressive agent currently being used for the prevention of renal allograft rejection in combination therapy. It has been used successfully in the treatment of a variety of autoimmune inflammatory diseases such as myasthenia gravis [3, 4], chronic idiopathic polyneuropathy [3] and inclusion body myositis [3]. There have been case reports of its use in treatment of refractory disease in dermatomyositis [5, 6] and polymyositis [7]. MMF is metabolized in the liver and gastrointestinal tract to its active metabolite mycophenolic acid (MPA). MPA selectively and non-competitively inhibits the type 2 isoform of inosine monophosphate dehydrogenase in activated lymphocytes impairing lymphocyte mitosis and proliferation of B and T lymphocytes [8]. A number of adverse events have been associated with mycophenolate, the most prominent being cytopenia and infections. Overall it is felt to be safe and well tolerated.

We have used mycophenolate mofetil for the treatment of inflammatory myopathy (polymyositis/dermatomyositis) in seven patients and hereby describe our initial experience.

Case series

All seven of our patients met classification criteria for idiopathic inflammatory myopathy. Muscle biopsy was performed in all of our patients showing inflammatory myopathy. Four out of seven patients had characteristic skin manifestations diagnostic for dermatomyositis. Conventional immunosuppressive drugs either had an insignificant response or major adverse effects leading to their discontinuation. MMF was started in doses of 500 mg twice a day and titrated up to 1 g twice a day. The patients were followed for 12–36 months following the initiation of MMF. Prednisone was continued concomitantly at the previous dose at the start and

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Table 1. Classification criteria for inflammatory myopathy (definite PM requires four criteria without the rash and definite DM requires three criteria with the rash)

Symmetric proximal muscle weakness
Elevated plasma muscle enzymes
Myopathic changes on electromyography
Characteristic muscle biopsy abnormalities and the absence of histopathological signs of other causes of myopathy
Typical rash of dermatomyositis

Table 2. Demographics: F = female, W = white, AA = African-American

	Patient number						
	1	2	3	4	5	6	7
Age (yr)	44	53	48	65	28	20	17
Sex	F	F	F	F	F	F	F
Race	AA	W	AA	AA	AA	AA	W

tapered to lowest effective dose in most patients. A five-point scale was used to measure and document the muscle strength. Anti Jo-1 antibodies were positive in two out of seven patients and are noted below, but other myositis specific antibodies were negative.

This case series meets and is in compliance with ethical standards in medicine and informed consent was obtained in all patients included in this series.

Demographics

Patient 1

A 44-yr-old African-American female was diagnosed with dermatomyositis 15 yr ago. She was initially treated with 2 mg/kg/day of azathioprine for 1 yr which was ineffective. She also developed a major idiosyncratic reaction to methotrexate and cyclophosphamide, which had to be discontinued. She was requiring more than 20 mg of prednisone for maintenance and had repeated flare-ups requiring i.v. immunoglobulin (IVIG) infusions monthly at doses of 0.4 g/kg/day for 3–5 days. She had improvement with the infusions but had persistent weakness, skin rash and elevated muscle enzymes. MMF was initiated 6 yr ago with resultant improvement of weakness, skin rash and decline of creatine kinase (CPK) from 2874 to 934 and 527 U/l at 6 and 12 months, respectively. Prednisone dose was decreased successfully to 5 mg/day at 12 months from 20 mg/day initially and she did not have another episode of disease worsening requiring hospitalization or IVIG infusion while taking MMF. She had no adverse events during 2½ yr of follow-up. No further data are available since she moved out of state 3 yr ago.

Patient 2

A 53-yr-old White female was diagnosed with dermatomyositis 6 yr ago. She had persistent disease activity despite treatment with methotrexate (15–20 mg/week). MMF was started 2 yr ago with an improvement of weakness and adequate control of disease. Her CPK decreased from 568 to 354 and 249 U/l at 6 months and 1 yr, respectively. She has had no worsening of her disease and no adverse events during 2 yr of follow-up. She has not required any prednisone during this time.

Patient 3

A 28-yr-old African-American female with polymyositis diagnosed 4 yr ago by another physician. She initially presented to us 1 yr after the initial diagnosis. At that time she was confined to bed and had a CPK of 10 000 U/l. She was on 37.5 mg/week of methotrexate and 80 mg/day of prednisone. Addition of azathioprine 2 mg/kg/day resulted in only minimal improvement. Methotrexate was discontinued and MMF was started 2 yr ago and resulted in a significant, but incomplete, response. Her CPK decreased from 7546 to 3249 U/l at 6 months and her strength improved but she was still confined to a wheelchair. She finally responded to monthly IVIG infusions 0.4 mg/kg/day–1 g/kg/day for 3–5 days with decrease in CPK to 458 U/l, and was able to walk and live independently. Her disease worsened again 9 months ago, MMF was discontinued and she was treated with monthly i.v. cyclophosphamide 500–750 mg/m^2 and IVIG 0.4 g/kg/day infusions. Her course was complicated by sepsis and respiratory failure and she died 3 months ago.

Patient 4

A 48-yr-old African-American female with polymyositis for 4 yr. Initial treatment with methotrexate (25 mg/week) was ineffective and she did not tolerate azathioprine and cyclophosphamide. Treatment with MMF for the last 1 yr has resulted in improvement of strength and a decrease of CPK from 987 U/l to 342 U/l. Prednisone dose has been decreased from 10 mg/day to 5 mg/day and she has had no adverse events.

Patient 5

A 65-yr-old African-American female with dermatomyositis had incomplete response to methotrexate (25 mg/week) and azathioprine (150 mg/day). She has positive anti Jo-1 antibodies but no significant lung disease. MMF was started 3 yr ago with an excellent improvement of weakness and skin rash. She was confined to a wheelchair prior to starting MMF and is now walking with a stick. CPK decreased from 323 to 76 and 131 U/l at 6 and 12 months, respectively. Her current daily dose of prednisone is 15 mg/day compared with 60 mg/day initially. The patient has had no medication-related adverse events during the follow-up.

Patient 6

A 20-yr-old African-American female with polymyositis diagnosed 2 yr ago. She had elevated liver enzymes on initial presentation and hence MMF was chosen as the initial immunosuppressive agent with significant improvement of weakness and decline of CPK from 5546 to 1054 and 458 U/l at 6 and 12 months, respectively. Prednisone was decreased to 15 mg/day at 1 yr from initial dose of 60 mg/day. She had no adverse events during 1 yr of therapy but has been lost to follow-up.

Patient 7

A 17-yr-old White female with dermatomyositis and pulmonary infiltrates diagnosed 4 yr ago. She had positive anti Jo-1 antibodies. She responded well to i.v. cyclophosphamide but it had to be discontinued due to neutropenia. She could not tolerate methotrexate (20 mg/week) either, hence MMF was initiated. Her disease has remained stable with no worsening of her weakness and pulmonary disease. CPK has been stable in normal range at 6, 12 and 24 months and prednisone has been decreased to 12.5 mg/day at 24 months from 20 mg/day initially. She has had no adverse events during 2 yr of follow-up.

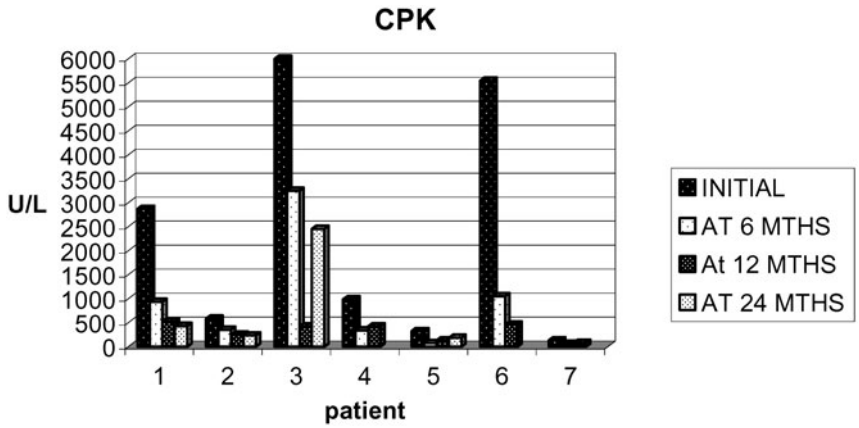

FIG. 1. Change in serum muscle enzyme during therapy with mycophenolate mofetil. Patient 3 was treated with concomitant monthly IVIG infusions.

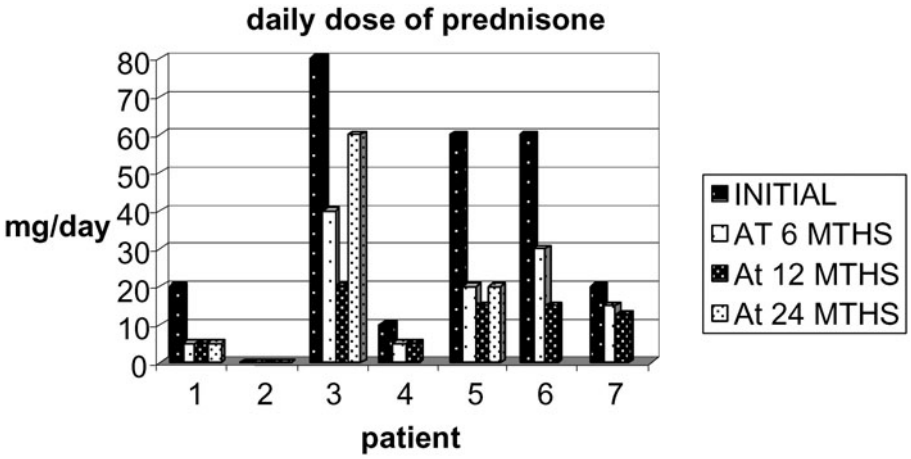

FIG. 2. Change in average daily dose of prednisone during therapy with mycophenolate mofetil.

TABLE 3. Summary of results

	Patient number						
	1	2	3	4	5	6	7
Proximal muscle strength	↑	↑	↑	↑	↑	↑	↑
Muscle enzymes	↓	↓	↓	↓	↓	↓	↓
Skin rash	↓	↓	—	—	↓	—	↓
ESR/CRP	↓	↓	↓	↓	↓	↓	↓
Prednisone dose	↓	—	↓	↓	↓	↓	↓
Adverse events	None	None	Cytopenia	None	None	None	None
Additional immunosuppressive	None	None	IVIG, Cyc, Aza	None	None	None	None
Duration of follow-up after MMF	2½ yr	2 yr	2 yr	1 yr	2½ yr	1 yr	1 yr
Outcome	Lost to follow-up	Stable	Death	Stable	Stable	Lost to follow-up	Stable

Abbreviations: Cyc, cyclophosphamide; Aza, azathioprine.

Results

In this case series most of the patients did well after initiation of treatment with MMF. There was improvement in muscle strength, a decline in serum muscle enzymes, reduction of inflammatory markers and decrease in the requirement of maintenance dose of prednisone in all of the patients. These results are well illustrated in the Figs 1 and 2 and Table 3. MMF was also well tolerated by these patients, although one patient developed cytopenia while on a combination of azathioprine and MMF leading to their discontinuation for 3 months. The same patient remained refractory to the therapy and required monthly IVIG infusions and cyclophosphamide after MMF was permanently stopped. She ultimately died secondary to sepsis 3 months ago. In addition, in this case series, one patient moved out of state after 2½ yr of follow-up and another was lost to follow-up after 1 yr, although MMF was effective and well tolerated in these two patients. In summary, MMF was felt to be a safe and effective therapy.

Conclusion

A striking clinical and laboratory response of active myositis in six out of seven patients in this series illustrates that MMF can

be effectively used in management of autoimmune inflammatory myopathy. It can be effective not only in controlling the active disease and potentially induce remission in some patients with active myositis but can also avoid high doses and prolonged therapy with corticosteroids, thereby decreasing significant long-term toxicity. We suggest that it may be a suitable alternative to the conventional immunosuppressive agents in patients who fail or are intolerant to the usual therapy or can be considered initial therapy in some patients. It is probably safer and better tolerated than a number of conventional immunosuppressive agents.

Despite encouraging results in this case series with MMF, it should be noted that not all the patients had a complete response to MMF and also some were refractory to a number of therapies prior to MMF initiation. The death of one patient was related to both the underlying disease and its therapy. These findings highlight that these aggressive diseases are associated with significant morbidity and mortality and can be very refractory. The use of activity and damage indices (MITAX, MYOACT and MDI) is currently undergoing validity testing and can help in an objective assessment of the disease upon initial presentation and the response to therapy [9]. Prospective, controlled trials of MMF either as an initial treatment, an alternative agent or in combination therapy for patients with adult inflammatory myopathy, preferably utilizing these objective indices, are indicated to further elucidate the use of this agent in these disorders.

The authors have declared no conflicts of interest.

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