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ORIGINAL ARTICLE

Mycophenolate Mofetil: A Possible Therapeutic Agent for Children With Juvenile Dermatomyositis

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Objective. **To determine if mycophenolate mofetil (MMF) diminishes skin and muscle disease activity in children with juvenile dermatomyositis (DM), thereby permitting a decrease in corticosteroid dose.**

Methods. **A retrospective data review for 50 children with juvenile DM (mean ± SD age 12.2 ± 5.0 years) who had received MMF for 12 months identified the following characteristics: 38 (76%) were girls, 39 (78%) were white, 10 (20%) were Hispanic, and 1 (2%) was African American. The MMF dose and frequency, type of infection, white blood cell (WBC) count, corticosteroid dose, and the validated disease activity score (DAS) subscores for skin (DAS-S) and muscle (DAS-M) were obtained.**

Results. **Twelve months after the start of MMF, the mean ± SD DAS-S decreased from 5.24 ± 0.29 to 3.72 ± 0.29 ($P = 0.001$), and the mean ± SD DAS-M decreased from 2.44 ± 0.39 to 1.17 ± 0.28 ($P = 0.002$). The mean ± SD prednisone dosage decreased from 0.39 ± 0.06 to 0.23 ± 0.02 mg/kg/day ($P = 0.0001$), with resumption of linear growth ($P = 0.008$). The WBC/lymphocyte count was unchanged over the 12 months on MMF. The infection rate was assessed in a subset of 26 children with juvenile DM who were observed for 12 months before the start of MMF and then compared with the ensuing 12 months of MMF therapy. There was no significant difference between the pretreatment period and the first 6 months of MMF therapy ($P = 0.44$), but the infection rate decreased in months 7–12 ($P = 0.001$).**

Conclusion. **MMF appears to be worthy of consideration as an additional therapeutic modality for treatment of children with juvenile DM. These data suggest that the use of MMF decreases skin and muscle disease activity and is steroid sparing. MMF appears to be well tolerated, but patients should be monitored for infection.**

INTRODUCTION

Juvenile dermatomyositis (DM) is the most common pediatric inflammatory myopathy, with an incidence of 3.2 cases/million children/year in the US (1). Children present with a characteristic rash, which includes heliotrope discoloration of the eyelids, Gottron's papules on extensor surfaces, and symmetric proximal muscle weakness. The primary lesion in juvenile DM is a systemic small-vessel vasculopathy (2), which visibly progresses with delay in the institution of effective immunosuppressive therapy (3) and is reflected in the gene expression profiles of muscle from untreated children with a definite/probable diagnosis of juvenile DM (4). Gene expression profiles of muscle (5–7), as well as peripheral blood from adults (8,9) and children (10) with DM, have also demonstrated up-regulation of type I interferon (IFN)–inducible genes, as well as increased IFNα activity in the sera of untreated children with juvenile DM (11). The gene expression profiles from children with juvenile DM share features with the gene expression profiles obtained from the examination of blood from patients with lupus (12). Although distinct clinical entities, some of the commonality of gene expression suggests there may be similarities in the pathophysiology between these diseases and that treatment modalities may overlap as well.

The specific approach to therapy for juvenile DM is controversial, but corticosteroids are the cornerstone of treatment (13). The numerous side effects of corticosteroids, particularly the negative impact on growth in children, as well as the lack of adequate clinical response to this regimen in some patients, has prompted a search for alternative immunosuppressant therapy for children with

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Table 1. Demographics and clinical characteristics*

	No. (%)	Age at MMF start, years	Duration of untreated disease, months	Onset to MMF start, years	Diagnosis to MMF start, years
Female	38 (76)	12.3 (4.6–23.2)	4.5 (1.3–113.8)	3.4 (0.2–16.2)	2.8 (0.1–15.2)
Male	12 (24)	12.9 (4.2–17.1)	8.5 (1.1–22.3)	3.6 (1.1–10.5)	2.6 (0.2–10.3)
White	39 (78)	12.9 (4.2–23.2)	4.5 (1.3–113.9)	4.1 (0.2–16.2)	3.2 (0.1–15.2)
Hispanic	10 (20)	11.4 (4.6–16.5)	6.4 (1.1–22.3)	2.4 (1.1–10.5)	2.0 (0.2–11.3)
African American	1 (2)	7.1 (7.1–7.1)	9.4 (9.4–9.4)	1.8 (1.8–1.8)	1.0 (1.0–1.0)
Total	50 (100)	12.6 (4.2–23.2)	5.0 (1.1–113.8)	3.6 (0.2–16.2)	2.8 (0.1–15.2)

* Values are the median (range) unless otherwise indicated. MMF = mycophenolate mofetil.

active symptoms of juvenile DM. Mycophenolate mofetil (MMF) is established as an effective treatment for lupus nephritis and other systemic lupus manifestations in both adults (14) and children (15). Furthermore, adult DM patients were reported to have symptomatic improvement with MMF therapy (16,17). Initially approved for the prevention of organ transplantation rejection (18), MMF has been employed in the management of a range of other autoimmune diseases (19).

The mechanism of action of MMF has been studied and has shown that hepatic metabolism converts MMF to the active moiety, mycophenolic acid, which selectively inhibits de novo purine metabolism by reversibly binding to inosine monophosphate dehydrogenase. By depleting guanosine and deoxyguanosine nucleotides in T and B lymphocytes, it inhibits their proliferation and antibody production, and prevents leukocyte binding to endothelial cells (20). Our experience of the response of children with juvenile DM to MMF was assessed by comparing the clinical and laboratory information obtained at the start of MMF therapy with the clinical and laboratory information obtained at the 6- and 12-month followup visits.

PATIENTS AND METHODS

Patients. The medical records of all children diagnosed as having definite/probable juvenile DM at Children's Memorial Hospital Pediatric Rheumatology clinic were reviewed. Children with overlap syndrome were excluded. We included all patients in this retrospective analysis who had received MMF for a minimum of 12 months (n = 50). The study was approved by the institutional review board.

Indications for administration of MMF. The major indication for the addition of MMF to the therapeutic regimen was the lack of the patient's response to previous interventions. This is documented in Table 1 as the duration from the onset of symptoms to the start of MMF therapy (mean 3.6 years, range 0.2–16.2 years), as well as the duration of symptoms from the onset of the first symptom to initial treatment (mean 2.8 years, range 0.1–15.2 years). Children with juvenile DM who had already been treated (32 of 50) were referred from other centers, and they had a much more varied background of previous therapy. After evaluation, the initial therapy at our center was fairly standard and was used in 46 (92%) of 50 patients under the direction of a single physician (LMP). Intravenous methylprednisolone (IVMP) at 30 mg/kg was administered daily on 3 consecutive days when possible, followed by IVMP given 1–3 times a week with oral prednisone at 0.5 mg/kg on non-IVMP days, until the child's indicators of immune activation had normalized. In addition, the following was used: methotrexate (MTX) at a minimum of 15 mg/m^2, vitamin D to achieve a blood level in the therapeutic range (>35 ng/ml), 1 gm of folic acid, and a proton-pump inhibitor. Hydroxychloroquine was also administered on a less consistent basis and the usage of sunscreen with a minimum sun protection factor of 40 was encouraged. In the remaining 4 untreated patients with a severe rash at presentation, MMF was begun as part of the initial therapy.

Assessments. MMF effectiveness was assessed by comparing the clinical and laboratory information obtained at the start of MMF therapy with the information obtained at the 6- and 12-month followup visits. All eligible patients who had been observed for at least 12 months were included in the analyses. For analysis of the infection rate, the number and type of infections occurring in 26 of 50 patients observed by our clinic for the 12 months before the start of MMF therapy was compared with the number and type of infections occurring in the 12 months after MMF had been initiated.

Validated disease activity scores (DAS) (21), including skin (DAS-S) and muscle (DAS-M) involvement subscores, were calculated for patients at onset and at followup visits. All juvenile DM patients were started on an initial dosage of 20 mg/kg of MMF divided twice a day. Data on MMF dosing and adverse events attributed to MMF, including types of infection and frequency, were obtained. Additional medications prescribed for juvenile DM treatment, including corticosteroid dose and frequency, were recorded at the start of MMF therapy and at the 6- and 12-month followup visits.

Criteria for change of medical therapy. In addition to the DAS-S and DAS-M scores obtained at the initial visit and at each visit thereafter, the child with juvenile DM was also assessed at each visit using a consistent panel of physical and laboratory tests. This evaluation included the Childhood Myositis Assessment Score, performed by an experienced pediatric physical therapy team (22). Sero-

logic tests included muscle enzymes (creatine kinase [CK], lactic acid dehydrogenase, and aldolase), complete blood cell count, neopterin, von Willebrand factor antigen (compared with the normal range for the child's blood group), and flow cytometry evaluation of peripheral lymphocyte subsets. If the child's symptoms improved, and the laboratory tests were in the range of normal for age, then the IVMP (30 mg/kg with 1 gm maximum) was slowly decreased in frequency until it was discontinued, and then the prednisone was decreased by 1 mg/month if the interval testing showed no reactivation. In contrast, if the child did not respond clinically and/or the laboratory parameters showed continued activation, then other medications were added. The following immunosuppressive therapy was continued when MMF was started: intravenous pulse methylprednisolone (IV pulse MP; n = 15), MTX (n = 38), hydroxychloroquine (n = 19), and intravenous immunoglobulin (IVIG; n = 4). During the 12-month course, 5 (10%) of the 50 children were still symptomatic or had abnormal laboratory values despite MMF therapy in conjunction with the other medications, so these additional medications were started/restarted: cyclosporine (n = 1 started and 1 restarted), IVIG (n = 4 started and 1 restarted), MTX (n = 0 started and 5 restarted), hydroxychloroquine (n = 2 started and 2 restarted), and IVMP (n = 2 started and 5 restarted). At the 12-month followup visit, the following medications were continued to be used as treatments: IV pulse MP (n = 10), MTX (n = 36), and hydroxychloroquine (n = 18), while more patients were receiving IVIG (n = 8).

Statistical analysis. We used mean, median, and SD to describe continuous variables (e.g., age and duration of untreated disease), and we used proportions to summarize dichotomous variables (e.g., sex and race). Linear mixed models were applied to analyze the changes in DAS scores, prednisone dose, height, and weight over time. The Cochran-Mantel-Haenszel test and Poisson regression were applied to assess the changes of MMF infection rates over time. Wilcoxon's signed rank test was used for pairwise comparison of prednisone dose, height, and weight. Analyses were conducted using the statistical program SAS, version 9.3 (SAS Institute), and 0.05 was used as the criteria for the level of statistical significance.

RESULTS

Patient characteristics. The demographics and clinical characteristics for the 50 patients are presented in Table 1. The demographics are similar to previous reports from our center documenting a female bias (76%) with a predominately white (78%) population. At diagnosis, this group had a long duration of untreated disease (median 5 months) preceding the start of conventional therapy, which was given for a mean of 2.8 years before the start of MMF.

Disease activity. After the start of MMF, the mean ± SD DAS-S decreased from 5.24 ± 0.29 to 4.20 ± 0.28 at 6 months ($P = 0.003$) and to 3.72 ± 0.29 at 12 months after the start of MMF ($P = 0.001$). Correspondingly, the mean ± SD DAS-M dropped from 2.44 ± 0.39 to 1.17 ± 0.28 ($P = 0.002$) after 12 months of therapy, but not at 6 months (Figure 1). When the patients who received IVIG were removed from this analysis, and the data were reanalyzed, the conclusions remained essentially the same: the DAS-S significantly decreased over 12 months ($P = 0.0001$) and the DAS-M also improved ($P = 0.02$). Specifically, compared with the data at the start of MMF therapy, the DAS-S was significantly lower at 6 months ($P = 0.004$) and further improved at 12 months ($P < 0.0001$). Similarly, the DAS-M was significantly lower at 6 months ($P = 0.02$), but did not further change between 6 months and 12 months ($P = 0.96$).

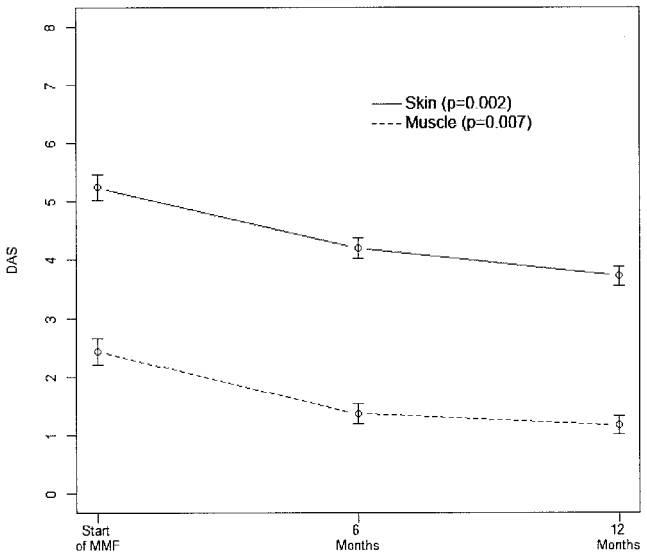

Figure 1. DAS-S and DAS-M are significantly improved over 12 months of MMF therapy ($P = 0.002$ and 0.007, respectively). The DAS-S is also significantly lower at 6 months ($P = 0.003$) compared with the values before the start of MMF. Similarly, DAS-M was significantly lower at 6 months ($P = 0.02$), but did not further change between 6 months and 12 months ($P = 0.96$). Bars show the mean and SEM. DAS-S = disease activity subscore for skin; DAS-M = disease activity subscore for muscle; MMF = mycophenolate mofetil.

Medication requirements. The prescribed dosage of prednisone (mg/kg/day) at MMF therapy followup at both 6 and 12 months was significantly lower than that at the start of MMF therapy, dropping from a mean ± SD of 0.39 ± 0.06 mg/kg to 0.34 ± 0.05 mg/kg after 6 months of MMF therapy ($P = 0.044$) then to 0.23 ± 0.02 mg/kg ($P < 0.0001$) at 12 months after the start of MMF (Figure 2). The decrease in prednisone dose, as recounted in the Methods section, was only instituted when all the laboratory data and the child's juvenile DM signs and symptoms were within normal limits.

Tolerability of MMF. Overall, the patients tolerated MMF well and there were no serious adverse events attributed to MMF between onset and the followup visit. None of our patients stopped MMF because of toxicity. We used "12 months of therapy" as an inclusion criterion for this

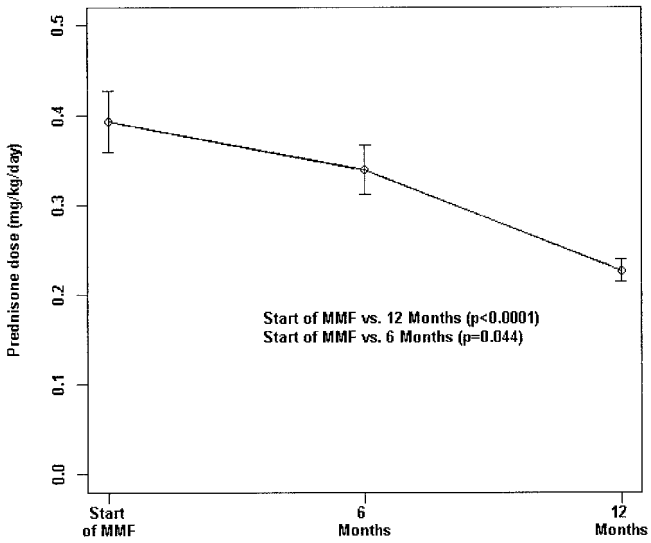

Figure 2. Daily prednisone dosage (mg/kg/day) at start of MMF was significantly higher as compared with followup visits. *P* was determined by linear mixed modeling. Bars show the mean and SEM. MMF = mycophenolate mofetil.

study in order to identify adverse reactions to MMF. Toxicity to MMF was not reported during the course of therapy at the level of 20 mg/kg taken twice a day in the setting of the other drug therapy as noted. Two children reported some abdominal discomfort, which resolved when the dose of MMF was lowered.

Infection rate. Forty-one (82%) of the 50 patients experienced 132 infections during the study period. The incidence of infections was 0.25 per month before the start of MMF, 0.21 infections per month in the first 6 months of MMF therapy, and 0.12 infections per month in the next 6 months (7–12 months). There was not a significant difference between the pretreatment period and the first 6 months after the start of MMF therapy ($P = 0.44$), but in the second 6 months (7–12 months) the infection rate was significantly lower than in the pretreatment data ($P = 0.001$). The majority of these infections were viral upper respiratory infections (53%), followed by sinusitis and otitis media occurring in 8.3% and 5.3% of the patients, respectively. Additional infections occurring in <5% of patients included herpes zoster, conjunctivitis, central line infection, thrush, dental abscess, skin abscess, infected calcification, urinary tract infection, strep throat, and mononucleosis. No serious infection related to MMF therapy requiring hospitalization occurred during the study period, and none of the children with juvenile DM developed leucopenia or B cell abnormalities as measured by flow cytometry (data not shown).

Growth parameters. Using the method of least squares means to compile the data for height and weight, the mean ± SD height of the children when MMF was started was 146.25 ± 3.69 cm, and by 12 months later their height had increased to a mean ± SD of 149.51 ± 3.69 cm ($P = 0.016$), while the mean ± SD weight increased as well, from 50.42 ± 3.31 to 53.25 ± 3.81 kg ($P = 0.005$).

DISCUSSION

To our knowledge, this is the first study that describes pediatric patients with juvenile DM treated with MMF and observed for 1 year after the start of therapy. The rationale for the use of MMF in this patient population was based on the finding that, like pediatric systemic lupus erythematosus (SLE) in which MMF has been effective (15), children with juvenile DM have a florid type I IFN-induced gene expression pattern (5,8,10). In addition, patients with SLE and juvenile DM have increased serum IFNα activity as determined by the WISH reporter cell assay (11,23). After the pharmacokinetics and safety data for MMF were obtained in children (24), MMF was reported to be an effective therapy for children with SLE (15). Some of the symptoms of juvenile DM share similarities with SLE. For example, both have a vasculitic malar rash, although the SLE band test is not present in skin from children with juvenile DM. Disease resistance to conventional therapy in juvenile DM is characterized by a persistence of skin involvement, often after the musculoskeletal symptoms normalize (13). Active skin disease at any level of severity in children with juvenile DM has been associated with calcinosis development. A goal of the therapy is to control cutaneous inflammation, which may minimize this devastating complication (25).

In 2000, Gelber et al (26) described 4 adult patients with severe cutaneous disease related to DM and improvement in skin manifestations following MMF therapy. Subsequent case reports of adults with DM, polymyositis, and myositis associated with connective tissue disease have suggested control of muscle inflammation by MMF therapy (17,26–31). It is difficult to make direct comparisons of these studies given the different outcome measures utilized in the investigations, but improvement in weakness, CK, or overall disease activity was not uncommon. Similarly, in our cohort we demonstrated a significant decrease in disease activity of both skin and muscle inflammation at followup. We did not report CK levels because children with a long disease duration of >4 months are more likely to have muscle enzymes that are in the range of normal values (32).

Recent reviews (33,34) of the treatment of DM include a discussion of MMF, and the authors report that they find MMF useful as a second-choice adjunct treatment after MTX. Given the improvement in both skin and muscle DAS in our patients, we concur that MMF may be a beneficial option in children with juvenile DM that is not responding to the traditional therapy of corticosteroids and MTX. Since IVIG had been found to potentiate the effect of MMF (31), some of the more resistant cases received this therapy as well. In addition to disease activity improvement, we found that children receiving MMF were able to decrease the dose of corticosteroids. This finding is comparable with reports in adults with idiopathic inflammatory myopathy (16,17,27–31,34). In children, there is even greater concern to minimize corticosteroid exposure given their deleterious impact on growth and bone mineral accretion. We had demonstrated that prior to corticosteroid exposure children with juvenile DM had reduced lumbar spine bone mineral density (35), which could be

intensified by the long-term administration of corticosteroids.

Increased susceptibility to infection associated with the use of MMF was highlighted in a report by Rowin et al (36) in which 3 of 10 patients with DM developed opportunistic infections with a resultant death in 1 patient. This is in contrast to our study, which did report infection as the most common side effect, but none of the patients had a serious infection requiring hospitalization. A study of patients with renal transplants receiving MMF as a maintenance immunosuppressant demonstrated no mortality from infection (18). Among adults with myositis receiving MMF, life-threatening infections were not reported (16,17,27–31,34,37,38). Gastrointestinal side effects can be associated with MMF, but in our cohort only 1 child developed vomiting while taking the liquid form of MMF; the vomiting stopped when tablets were used. Caution in female patients of childbearing potential is warranted, since MMF is contraindicated in pregnancy (39). Fortunately, none of the subjects in our cohort became pregnant (we advise practitioners to counsel female patients accordingly). A very rare but serious complication of MMF therapy, mentioned in a report of B cell lymphomas in 3 patients with SLE, was the occurrence of primary central nervous system lymphoma in a single patient with DM treated with MMF and MTX, which spontaneously resolved with discontinuation of both drugs (40). It is clear that because of the lack of controlled trials in patients with myositis, the role of MMF remains to be confirmed.

There are several limitations to this study. First is the retrospective study design and second is the lack of a concurrent control group of juvenile DM patients who were closely matched for age and disease severity and who had not been given MMF. Despite these limitations, we report the results of 50 pediatric patients treated with MMF, which is a robust sample size given that juvenile DM is a rare disease. We did not report therapeutic drug monitoring of MMF, since this remains controversial, even in the transplant literature. Further case–control pharmacokinetic studies in adult and pediatric subjects with myositis should be considered to better understand the role of therapeutic drug monitoring in this patient population.

In conclusion, MMF appears to be worthy of consideration as an additional therapeutic modality for the treatment of juvenile DM. This study suggests that both skin and muscle manifestations in children with juvenile DM respond to MMF, and that skin inflammation, which is often resistant to therapy, responds especially well. Therefore, MMF is steroid sparing and offers an alternative therapy, as well as minimizes corticosteroid exposure in children with juvenile DM. MMF appears to be well-tolerated, but clinicians should judiciously monitor patients for infectious and hematologic complications. Randomized controlled trials of MMF in patients with juvenile DM would help to establish its role in the management of this often chronic and devastating disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Pachman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rouster-Stevens, Pachman.
Acquisition of data. Rouster-Stevens, Morgan, Wang, Pachman.
Analysis and interpretation of data. Rouster-Stevens, Morgan, Wang, Pachman.

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