Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 51, No. 2, April 15, 2004, pp 278–283
DOI 10.1002/art.20240

ORIGINAL ARTICLE

Mycophenolate Mofetil for Remission Maintenance in the Treatment of Wegener's Granulomatosis

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Objective. **To examine the safety of mycophenolate mofetil (MMF) for remission maintenance in patients with Wegener's granulomatosis (WG) who had been treated with daily cyclophosphamide (CYC) and glucocorticoids to induce remission.**
Methods. **Fourteen patients were treated for active WG using a standardized regimen of CYC and glucocorticoids for induction of remission and MMF for remission maintenance. Outcome was assessed using predetermined definitions based on clinical characteristics and pathologic, laboratory, and radiographic findings.**
Results. **Remission occurred in all 14 patients (100%) at a median time of 3 months. The median time to discontinuation of glucocorticoids was 8 months. No patients died during protocol treatment and 6 patients (43%) relapsed at a median of 10 months after achieving remission. MMF was well tolerated and no patients had to be withdrawn as a result of medication toxicity.**
Conclusion. **The use of CYC and glucocorticoids for induction of remission and MMF for remission maintenance was well tolerated, but disease relapses were observed.**

KEY WORDS. Wegener's granulomatosis; Mycophenolate mofetil; Remission maintenance.

INTRODUCTION

Daily cyclophosphamide (CYC) and glucocorticoids are a highly effective treatment for Wegener's granulomatosis (WG) (1,2). Unfortunately, long-term followup of patients treated with this regimen has shown that disease relapse is not uncommon and prolonged use of CYC can result in substantial long-term toxicity. For these reasons, we have continued to search for less toxic yet efficacious treatments that would be applicable to a wide range of patients.

Mycophenolate mofetil (MMF) is an immunosuppressive agent currently used in preventing rejection of solid organ transplants. MMF is hydrolyzed to mycophenolic acid, which is a potent and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) (3,4). Inhibition of IMPDH blocks de novo purine synthesis, a pathway critical to normal lymphocyte function. In vitro, mycophenolic acid has been shown to inhibit proliferative responses of both T and B lymphocytes, suppress antibody formation by B lymphocytes, and prevent the glycosylation of glycoproteins involved in intercellular adhesion of leukocytes to endothelial cells.

Recently, MMF has been used with some success in the treatment of several autoimmune diseases, including systemic lupus erythematosus, psoriasis, and inflammatory eye disease (5–7). Anecdotal case reports and 1 pilot study have also examined the therapeutic use of MMF in patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (8–14). This report describes our results in 14 patients with active WG who were treated with a prospective standardized regimen using daily CYC and glucocorticoids until remission, at which time MMF was substituted for CYC for remission maintenance.

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Submitted for publication December 18, 2002; accepted in revised form April 26, 2003.

PATIENTS AND METHODS

Patients. Fourteen patients with active WG were studied at the Warren Grant Magnuson Clinical Center of the National Institutes of Health (NIH). Thirteen had biopsy-proven WG with necrotizing vasculitis, granulomatous inflammation, or both in a typical organ system. The remaining patient did not undergo biopsy and was diagnosed with WG based on the presence of upper airway disease, lower airway disease where infection had been ruled out,

Table 1. Clinical characteristics of 14 patients with Wegener's granulomatosis treated with mycophenolate mofetil for remission maintenance*

Patient no.	Age, years/ sex	Sites of active disease at study entry	Major organ manifestations at study entry	Outcome
1†	61/M	E, A, S, K, PNS	Glomerulonephritis with creatinine 7.5 mg/dl Mononeuritis multiplex	Creatinine improved to 2.1 mg/dl Relapse after 1 month on MMF - A, K (peak creatinine 2.6 mg/dl)
2†	63/M	L	Multiple pulmonary nodules	Relapse after 5 months on MMF - A, F
3†	52/M	E, L	Multiple pulmonary nodules	In remission for 26 months, tapering MMF
4†	43/F	L, K	Multiple pulmonary nodules	Creatinine improved to 1.0 mg/dl
			Glomerulonephritis with creatinine 2.8 mg/dl	In remission for 6 months
5†	58/F	PNS, K	Mononeuritis multiplex Glomerulonephritis with creatinine 1.0 mg/dl	In remission for 21 months
6‡	22/F	L	Multiple pulmonary nodules and endobronchial stenosis	Relapse after 25 months on MMF - L
7‡	57/M	L	Multiple pulmonary nodules and infiltrates	Relapse after 11 months on MMF - E, L, F
8‡	28/M	E, H	Pericarditis with large pericardial effusion	In remission 42 months, now off MMF
9‡	37/M	K	Glomerulonephritis with creatinine 2.4 mg/dl	Creatinine improved to 1.5 mg/dl In remission 50 months, now off MMF
10‡	67/M	L	Multiple pulmonary nodules and infiltrates	In remission 32 months, tapering MMF
11‡	36/M	K	Glomerulonephritis with creatinine 2.6 mg/dl	Creatinine improved to 1.3 mg/dl In remission 28 months, tapering MMF
12‡	46/M	L	Multiple bilateral pulmonary nodules	Relapse after 8 months on MMF - L
13‡	67/M	L	Multiple pulmonary nodules and infiltrates	In remission for 16 months
14‡	45/M	GI, K	Necrotizing granulomatous vasculitis of gallbladder Glomerulonephritis with creatinine 1.0 mg/dl	Relapse after 13 months on MMF - L

* E = upper respiratory tract; A = arthritis; S = skin; K = kidney; PNS = peripheral nervous system; MMF = mycophenolate mofetil; L = lung; F = fever; H = cardiac disease; GI = gastrointestinal involvement.
† Patients enrolled during initial presentation of Wegener's granulomatosis.
‡ Patients enrolled during relapse of Wegener's granulomatosis.

an active urine sediment including red blood cell casts, and proteinase 3 ANCA. All patients met the American College of Rheumatology criteria for the classification of WG and had active disease requiring therapy (15). Exclusion criteria were pregnancy, evidence of infection with the human immunodeficiency virus, transitional cell carcinoma of the bladder, or hemocytopenia defined by the presence of a total leukocyte count $<3{,}000/mm^3$, platelet count $<80{,}000/mm^3$, or hematocrit $<20\%$ (in the absence of gastrointestinal bleeding or hemolytic anemia).

Demographic and clinical characteristics of these patients are summarized in Table 1. Five patients (36%) were enrolled during their initial episode of WG. The remaining patients had a history of WG and were experiencing a relapse. All patients had active disease involving 1 or more major organ systems (lung, kidney, heart, gastrointestinal tract, nervous system). In 1 patient, relapse was manifest as upper airway disease and pericarditis. His pericarditis worsened despite nonsteroidal antiinflammatory drug therapy followed by prednisone. All cultures and serologic studies were negative for evidence of infection, and he did not improve until the addition of CYC. At the time of study entry, 13 patients had cytoplasmic ANCA (cANCA) and 1 had perinuclear ANCA (pANCA) by immunofluorescence with antibodies to myeloperoxidase detected by enzyme-linked immunosorbent assay (ELISA).

Treatment protocol. All patients initially received an induction regimen consisting of daily CYC and glucocorticoids. Oral CYC was begun at a dosage of 2 mg/kg/day given as a single dose in the morning together with oral prednisone at 1 mg/kg/day, as previously described (1). During CYC therapy, a complete blood count (CBC) was obtained every 1–2 weeks with the CYC dosage being adjusted downward to maintain the total white blood count >3,000/mm^3 (or a neutrophil count >1,500/mm^3). If significant improvement had occurred after the first month of treatment, prednisone was tapered with the dosage being gradually converted to an alternate-day regimen and eventually discontinued. Significant improvement was defined as clear-cut suppression of disease activity with stabilization of renal function, partial or complete resolution of pulmonary parenchymal abnormalities, and the absence of new signs of disease in other organ systems (16). Once remission was achieved (as defined below), CYC was discontinued and MMF was started. The first dose of MMF was given within 1–2 days after the last dose of CYC in the setting of acceptable blood counts. MMF was started at a dosage of 1,000 mg twice per day by mouth. Patients were monitored with CBC and liver function tests weekly during the first month, every-other week during the second and third months, and monthly thereafter. The criteria for MMF dosage reduction included an absolute neutrophil count <1,500/mm^3, platelet count <80,000/mm^3, or hematocrit <20% (in the absence of gastrointestinal bleeding or hemolytic anemia). If remission was sustained for 2 years, the MMF was tapered by 250 mg each month until discontinuation.

In addition to immunosuppressive therapy, all non–sulfa-allergic patients received *Pneumocystis carinii* prophylaxis with trimethoprim/sulfamethoxazole (160 mg/800 mg; 1 tablet 3 times weekly) while they were receiving either CYC or MMF in combination with prednisone (16). While taking prednisone, patients were placed on an osteoporosis-prevention regimen consisting of either calcium carbonate and calcitriol (17) or calcium carbonate and etidronate (18).

The treatment protocol was approved by the National Institute of Allergy and Infectious Disease (NIAID) Institutional Review Board, the NIAID Clinical Director, and the Director of the NIH Clinical Center. All patients provided written informed consent.

Assessment of disease activity. Disease activity was assessed using the following guidelines: 1) unequivocally active disease was determined by typical histologic abnormalities seen on biopsy of a clinically involved major-organ site; 2) high probability of active disease was defined as progressive lower airway or vision-threatening ocular disease in the absence of infection or other illness, progressive renal impairment as determined by active urinary sediment including red blood cell casts, and/or progressive polyneuropathy (nonvasculitic causes having been ruled out); 3) moderate probability of active disease was defined as an elevated erythrocyte sedimentation rate >2 times the upper limit, symptoms or signs related to the upper airways, cutaneous disease, otitis media with or without sensory-neural hearing loss in the absence of infection, constitutional symptoms, fever, or arthralgias and myalgias not related to identifiable non-WG processes. If none of the abnormalities in category 1 or 2 were present, overtly active WG was considered to be absent. Abnormalities in category 3 were serially evaluated to ensure that they did not represent an impending flare of overt major-organ disease activity or a secondary process. In the event that a secondary process was not identified, it was assumed that abnormalities noted in category 3 were part of "smoldering" or low-grade active WG. In such a setting, medications would not be increased but further tapering of medication would be delayed. Remission was defined as the absence of all abnormalities in category 1 and 2. Relapse was then defined as a return of category 1 or 2 disease after remission had been achieved.

ANCA measurements. ANCA was detected by indirect immunofluorescence as has been previously described (19). Once a sample was assessed to be positive, samples were then prepared in further 2-fold dilutions to a maximum of 1:640. As the maximum interassay variability was a 1-tube dilution (2-fold), a titer change of 2-tube dilutions (a 4-fold change) was considered significant. When a pANCA was present by immunofluorescence, an ELISA was performed to confirm the presence of antibodies to myeloperoxidase.

RESULTS

Clinical response. Induction treatment with prednisone and daily CYC resulted in remission in all 14 patients (100%; Table 2). The median time to achievement of remission was 3 months (range 1–7 months). The median time to conversion from daily to alternate-day prednisone was 4 months (range 3–8 months). The median time to complete discontinuation of prednisone was 8 months (range 6–24 months).

No patients enrolled in this study died. Six (43%) of the 14 patients in whom remission was achieved relapsed during the study period. The median time from remission to relapse was 10 months (range 1–25 months). Four of these 6 patients were taking MMF alone at the time of relapse and had been off of prednisone a median of 5 months (range 1–9 months) when relapse occurred. Of the 2 remaining patients, disease relapse occurred during the course of their prednisone taper while taking dosages of 10 mg and 45 mg every-other day, respectively. Two patients relapsed after being enrolled in this study for the initial episode of their disease while the other 4 had a history of prior relapses. All 6 patients were treated at the NIH through this or other protocols and successfully had remission reinduced.

Median followup for these 14 patients was 18 months (range 1–50 months) from remission until the current time of data analysis or disease relapse. With the exception of the 2 patients discussed previously, all of the remaining patients enrolled in this study have been able to discontinue prednisone. Of the 8 patients who have not experienced a relapse, 2 have tapered off of MMF and have

Table 2. Clinical response of 14 Wegener's granulomatosis patients treated with a cyclophosphamide and glucocorticoid induction and mycophenolate mofetil remission-maintenance regimen

Response	Result
Surviving, no. (%)	14 (100)
Achieving remission, no. (%)	14 (100)
Relapse after achieving remission, no. (%)	6 (43)
Time to remission, median (range) months	3 (1–7)
Time to tapering to alternate-day prednisone, median (range) months	4 (3–8)
Time discontinuation of prednisone, median (range) months	8 (6–24)
Time from remission to relapse in 6 patients, median (range) months	10 (1–25)
Time off prednisone before relapse in 6 patients, median (range) months	5 (1–9)

remained in remission without immunosuppressive medication for 3 and 6 months, respectively. An additional 3 patients have been in remission for >2 years and are tapering their MMF. The remaining 3 patients have been in remission <2 years and continue to be in the maintenance phase of treatment receiving MMF. The median followup time since remission of these 8 individuals is 27 months (range 6–50 months).

Toxicity. The toxicities observed in the 14 patients treated with this protocol are summarized in Table 3. No patient had to come off protocol due to drug intolerance. The CYC dosage was decreased in 2 patients with anemia and thrombocytopenia, and 2 patients developed leukopenia while receiving MMF, which resolved with dosage reduction. The definition of leukopenia used in this study was designed to prevent severe neutropenia and, although these patients met the criteria for dosage reduction, they did not have an absolute neutrophil count $<1{,}500/mm^3$.

Four patients experienced a serious infection defined as that requiring hospitalization or treatment with intravenous antibiotics. None were neutropenic prior to or at the time of infection. One patient receiving daily prednisone and CYC developed a lobar pneumonia with pleural effusion of presumed bacterial origin that resolved with antibiotics. A postobstructive pneumonia due to *Streptococcus pneumoniae* occurred in 1 patient with severe endobronchial stenosis while taking MMF alone. Two patients developed *Pneumocystis carinii* pneumonia. Both patients were receiving daily prednisone and CYC and were not taking trimethoprim/sulfamethoxazole prophylaxis. One of these patients had a prior history of an anaphylactic reaction to sulfa and the other was in the process of screening for protocol eligibility and had not been prescribed trimethoprim/sulfamethoxazole by his personal physician. No other opportunistic infections occurred during this study.

Table 3. Drug toxicities in 14 Wegener's granulomatosis patients treated with a cyclophosphamide and glucocorticoid induction and mycophenolate mofetil remission-maintenance regimen

Toxicity	Number (%)
Bone marrow toxicity requiring dosage reduction	
Cyclophosphamide	2 (14)
Mycophenolate mofetil	2 (14)
Cataracts	1 (7)
Diabetes mellitus	2 (14)
Dermatomal cutaneous herpes zoster	4 (29)
Bacterial pneumonia	2 (14)
Pneumocystis carinii pneumonia	2 (14)

Three patients developed side effects attributable to prednisone, including 1 patient with cataracts and 2 who developed prednisone-induced diabetes mellitus managed with oral agents. Of note was that no patients developed CYC-induced bladder injury (20) or gastrointestinal symptoms associated with MMF.

Laboratory findings. Ten of the 13 patients who were cANCA positive at study entry have remained consistently cANCA positive despite clinical remission. Of the 3 patients whose ANCA titer became negative, 2 subsequently developed positive titers and 1 patient relapsed. During the course of this study, 9 of 13 patients experienced a 4-fold rise in cANCA titer. Four of these 9 patients have relapsed and the other 5 have remained in remission, with a median time from the rise in titer to last followup of 16 months (range 7–29 months).

Of the 4 patients who had a serum creatinine of ≥2.4 mg/dl due to active glomerulonephritis at study entry, only 1 did not have a return of renal function to previous baseline (Table 1). However, this patient did have improvement of the serum creatinine level from 7.5 mg/dl at study entry to 2.1 mg/dl. None of the patients experienced any decline in renal function during MMF treatment.

DISCUSSION

Glucocorticoids and daily CYC are highly effective for the treatment of WG with >90% of patients experiencing a complete remission or marked improvement (1,2). However, in trials in which CYC treatment was continued for at least 1 year past remission, disease relapse eventually occurred in 50% of patients (2). Subsequent treatment of disease relapses with repeated courses of CYC, while effective, was found to be associated with a high rate of serious CYC-related morbidity, including infertility, myeloproliferative disorders, and transitional cell carcinoma of the bladder (2,20). For this reason, current clinical research has focused on finding less toxic alternatives to

CYC for the treatment of WG. Several studies have demonstrated that methotrexate (MTX) can effectively induce and maintain remission in selected patients (16,21–24). The use of azathioprine (AZA) has also been examined in WG. This agent has not been found to effectively induce remission of active major organ disease (1), but results from a large randomized trial suggest that AZA can maintain remission following induction with CYC (25). Although MTX and AZA both have a favorable toxicity profile compared with CYC, the use of these agents continues to be associated with a high rate of disease relapse, prompting the need for additional treatment options.

Recently, MMF has attracted attention as a possible alternative immunosuppressive agent for the treatment of autoimmune diseases in general and WG in particular. In the setting of renal transplantation, MMF has been shown to be superior to AZA in reducing the risk of acute rejection during the first 6–12 months following transplantation (26,27). In addition, the putative mechanism of action of MMF suggests that it may be less myelosuppressive than AZA (3,4). Although MMF and AZA are both purine antimetabolites, AZA blocks multiple enzymes involved in purine synthesis through competitive inhibition thus effecting not only lymphocytes but also neutrophils and platelets. The selectivity of mycophenolic acid for IMPDH may theoretically result in an inhibition of the proliferative responses of T and B cells with less potential for inducing myelotoxicity, although this has yet to be demonstrated in comparative trials.

Several previously published case reports and small series have examined the use of MMF in patients with ANCA-associated small-vessel vasculitis (8–14). The largest of these was a prospective pilot study by Nowack and colleagues who examined the use of MMF for maintenance therapy in 9 patients with WG and 2 patients with microscopic polyangiitis (9). In this 15-month study, patients were treated with MMF and low-dose glucocorticoids for maintenance of remission following induction with CYC. Of the 11 patients, only 1 WG patient (9%) relapsed in the 14th month of maintenance therapy. MMF was generally well tolerated, with adverse effects including abdominal pain (n = 3), diarrhea (n = 2), respiratory infection (n = 2), leukopenia (n = 2), and cytomegalovirus colitis (n = 1).

Compared with previous reports, the findings of our study reflect a greater length of followup, allowing for a fuller appreciation of the long-term outcome of MMF-treated patients. An additional strength of this study was the enrollment of well-characterized patients with active WG involving a major organ system who were treated with a prospective, rigorously standardized protocol beginning from the time of induction therapy with daily CYC and prednisone. The same protocol for tapering the prednisone dosage was followed in all patients and the transition to MMF was based on predetermined definitions of remission.

In this trial, the rate of remission and time to remission were consistent with other studies that utilized daily CYC and prednisone for remission induction (2,24). The duration of prednisone treatment was also similar to that observed in previous trials utilizing MTX-containing regimens (16,24). Although MMF effectively maintained remission in 8 patients for a median time of 27 months, disease relapse occurred in 43% of enrolled participants. This relapse rate is in contrast to the series by Nowack et al in which only 9% of their cohort had experienced a relapse at the time of reporting (9). Although the cause of this difference cannot be concluded with certainly, this could possibly reflect the longer duration of our study, differences in the prednisone tapering schedule, as well as individual variations of a relapsing systemic disease, which can be encountered in small series.

MMF was well tolerated in this trial. Although gastrointestinal side effects were the most frequent toxicities seen in the renal transplant trials, these were not observed in our patients. In a previous study of 5 patients with ANCA-associated vasculitis and end-stage renal disease, gastrointestinal complaints and bone marrow toxicity led to dosage reduction or MMF cessation in all patients (14). In our study, MMF-associated leukopenia that resolved with dosage reduction was seen in 2 patients. This frequency of leukopenia was similar to that observed in our previous study using MTX for maintenance of CYC-induced remission (24) and underscores the importance of close hematologic monitoring in WG patients during treatment with MMF.

The serious infections that were observed during this study occurred almost exclusively while patients were receiving daily prednisone in combination with CYC. The only serious infection that occurred during MMF treatment was a bacterial postobstructive pneumonia in a patient with severe endobronchial stenoses.

Maes and coworkers recently reported on an acute inflammatory syndrome characterized by fever, arthralgias, and muscle pain that developed in 2 WG patients receiving MMF (28). Although the cause of such symptoms remains unclear, the authors questioned whether this reaction was specific for WG, as it had not been reported in other settings. Although the sample size of our study is small, no patients developed symptoms similar to those described by Maes et al.

In summary, the data from this study would suggest that MMF is associated with a favorable toxicity profile in patients with WG. In contrast to the study by Nowack et al, we found a high rate of disease relapse during MMF therapy. However, the interpretation of both studies is limited by the small sample sizes. Larger randomized trials are needed to better appreciate what role MMF may have in the treatment of WG.

ACKNOWLEDGMENTS

The authors wish to thank Kristen E. McCabe, RN, the clinical fellows, and Clinical Center nursing staff at the National Institute of Allergy and Infectious Diseases for the care of our patients; and Dr. Anthony S. Fauci for his work in establishing the National Institute of Allergy and Infectious Diseases Vasculitis Program.

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