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Efficacy of Mycophenolate Mofetil as Single-Agent Therapy for Refractory Immune Thrombocytopenic Purpura

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Refractory disease occurs in 25% or more of adults with idiopathic (immune) thrombocytopenic purpura (ITP). Therapy to elevate the platelet count may be required in a proportion of these patients. Immunosuppressive agents such as prednisone, azathioprine, cyclophosphamide, and cyclosporin have been shown to be effective treatments in a proportion of patients with refractory ITP. A newer immunosuppressive medication, mycophenolate mofetil (MMF), has been used successfully with acceptable toxicity in solid organ transplant patients to reduce the risk of organ rejection. The goal of this study was to determine whether MMF is an effective treatment for refractory ITP. Efficacy, defined as a sustained platelet increase to a level greater than 50×10^9/L, was seen in 7 of 18 patients with refractory ITP. Three of these 7 patients have had intermittent thrombocytopenic episodes while continuing the medication. No severe toxicity was seen, although two of the 18 patients discontinued MMF within the first month of treatment because of side effects, i.e., headache. In summary, MMF may be a useful component of a combination protocol but does not appear to be highly effective as sole therapy in patients with refractory ITP. The data suggests that response rates to MMF may be higher in patients who have had a shorter duration of their ITP. Am. J. Hematol. 81:19–25, 2006. © 2005 Wiley-Liss, Inc.

Key words: mycophenolate; immune thrombocytopenia; refractory; immunosuppression

INTRODUCTION

Idiopathic (immune) thrombocytopenic purpura (ITP) is an autoimmune disorder in which platelets are opsonized with antiplatelet autoantibodies and/or immune complexes and removed prematurely by the reticuloendothelial system, resulting in a reduced peripheral-blood platelet count [1,2]. The etiology of ITP in adults is unknown, and the clinical course is variable and unpredictable. The commonest clinical consequences of thrombocytopenia are bruising and bleeding, and, while serious hemorrhage is rare, clinicians often treat severe thrombocytopenia (platelets $< 30 \times 10^9$/L) to avoid the risk of such bleeding, particularly at initial presentation.

Standard first-line treatments for ITP include prednisone [3–7], intravenous gamma globulin (IVIg) [6], and intravenous anti-D [8–13]. If ITP is persistent despite first-line therapies, then splenectomy is usually the second-line approach in adults. While the majority of adults will respond well to splenectomy, 30–40% of patients will fail splenectomy either immediately or within 5–10 years and may require additional therapy. These patients typically have severe, persistent thrombocytopenia and a substantial risk of severe hemorrhage.

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In children, ITP improves spontaneously in 80% of cases. In persistent cases, splenectomy is usually deferred for at least 1 year from onset and preferably until the patient is older than 5 years of age [14].

It is clear from recent natural history studies that treatment-related toxicity is substantial and that as many as half of all ITP patients who die, may do so because of the complications of severe immunosuppression [15]. For this reason there is a need to develop therapies that are effective even if immunosuppressive but are associated with minimal toxicity.

Currently, there is no well-defined approach to those patients refractory to splenectomy or who have chronic disease but do not, or will not, undergo splenectomy [6,16–18]. Single-agent studies have shown that immunosuppressive medications such as azathioprine, cyclophosphamide, and cyclosporin increase the platelet count in a proportion of patients with ITP, but the number of patients responding to single-agent therapy is small and toxicities may be severe and unacceptable, including severe immunosuppression and predisposition to secondary malignancies [19].

Mycophenolate mofetil (MMF) is an immunosuppressive agent that has been used to reduce the risk of solid-organ transplantation rejection. Its overall use to suppress T cells is similar to that of azathioprine and cyclosporin, although the mechanisms of effect are different (see Table I) [20–24]. MMF is a prodrug of mycophenolic acid (MFA), a non-competitive inhibitor of inosine 5′-monophosphate dehydrogenase (IMPDH), which is a key enzyme involved in the purine biosynthesis pathway [20]. Inhibition of IMPDH leads to an excess of adenine with a relative lack of guanine, which results in cell-cycle inhibition. Most body cells are protected from the effects of MFA through two mechanisms: (1) purine nucleotide recycling, which occurs in most cells but does not occur in lymphocytes, and (2) MPA, a more potent inhibitor of the type II isoform of IMPDH, which is the predominant isoform found in lymphocytes. Type I IMPDH is found in most other cells [20]. Interference with the cell cycle leads to diminution of lymphocyte proliferation. In addition, some T-cell activation steps are dependent on guanosine triphosphate (GTP), and therefore there is inhibition of activation of T cells following treatment with MMF through depletion of guanine and hence GTP. Finally, depletion of GTP also results in reduced expression of adhesion molecules on white blood cells and interferes with the recruitment of white cells to sites of inflammation and transplant rejection. MMF has an acceptable toxicity profile, suggesting that this drug may be of value for the treatment of refractory ITP patients. Two pilot studies of the use of MMF in refractory ITP suggest that MMF is efficacious in patients with ITP [25,26].

This pilot study explored the use of MMF to determine (i) its efficacy as measured by platelet count, clinical symptoms and signs, and frequency of requirement for IVIG to maintain adequate platelet count, and (ii) its toxicity in the treatment of refractory ITP.

PATIENTS AND METHODS

Patients

Eighteen patients from The Platelet Disorders Center at the New York Presbyterian Hospital, Weill Medical College of Cornell, and The Royal London Hospital, U.K., were included. Informed written consent was obtained from all patients prior to inclusion in the study. MMF was used as part of standard treatment for these refractory patients, and then the decision was made to report the results as a pilot study. Those at risk were tested for HIV and were negative. Seventeen patients were adults and all but one had undergone splenectomy. One child was included in the study; the child had not undergone splenectomy, was under 5 years of age, and had previously been treated with other therapies. All patients persistently had platelet counts less than 20×10^9/L in the absence of an effective treatment. The background demographics of the 18 patients are shown in Table II. Ten of the patients had had major bleeds: six intracranial, one of whom also had bright red blood per rectum, three heavy menses; one patient had frequent severe epistaxes; and one suffered with hematuria.

Mycophenolate Mofetil Administration

A dose of 250 mg twice daily was used initially, and increased to 500 mg twice daily after 1 week, achieving a dose of 1 g twice daily by 3 weeks. The pediatric patient's dose was started at 250 mg/day and increased to 750 mg/day. The concomitant treatments (Table II) remained unchanged throughout the study.

Weekly to biweekly platelet counts, WBC counts, and Hb levels were obtained; the higher the platelet count, the less frequent the counts. During physical exams, particular attention was focused on bleeding symptoms, bruising, petechiae, and headaches.

Response Criteria

Complete response—normalization of the platelet count; good response—stable platelet count $> 30 \times 10^9$/L without the need for other treatments; and partial response—no consistent change in the platelet count but lessening of the need for other treatment, i.e., less frequent infusion of IVIG or bolus steroids.

TABLE I. Immunosuppressive Treatments Used in ITP*

	Azathioprine	Cyclophosphamide	Cyclosporin	Mycophenolate mofetil	Rituximab
Mechanism	Inhibition of DNA and RNA synthesis T-cell > B-cell inhibition	Inhibition of DNA synthesis and cell proliferation	Inhibits IL-2 production leading to inhibition of T-cell activation	Inhibits inosine monophosphate dehydrogenase activity resulting in inhibition of T-cell and B-cell proliferation	Complement-mediated lysis of B cells; induces antibody-dependent cellular cytotoxicity; affects B-cell proliferation and differentiation
Proven efficacy	Crohn's disease, IBD Renal transplantation	SLE nephritis, chemotherapy for malignancy, Wegner granulomatosis, rheumatoid arthritis	Post-solid-organ transplant immunosuppressive	Solid-organ transplantation (renal, cardiac and hepatic)	
Toxicities	Common N/V, diarrhea	Common N/V, mucosal ulcerations, alopecia, diarrhea, dizziness	Common HTN, hirstuism, acne, neurologic	Common Headache diarrhea, HTN nausea, abdominal pain	Common Infusional reactions, nausea & vomiting, fatique, headache, pruritus, urticaria, dyspnoea or bronchospasm, rhinitis, hypotension, flushing
	Severe Leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis	Severe Hemorrhagic cystitis, leukopenia, secondary malignancies	Severe Seizures, leucopenia, thrombocytopenia, hepatotoxicity, nephrotoxicity	Severe Leukopenia, anemia, thrombocytopenia	Severe Death from cardiopulmonary reactions: 0.04–0.07%
ITP	53 patients [32] CR 45% PR 6% Minor 13% Response may take up to 6 months, and continued treatment is required	20 patients [33] CR 65% PR 20% No response 15% Effective in patients refractory to splenectomy. Significant toxicity limits its use in ITP	20 patients [28] OR 55% CR 25% PR 30%	21 patients [26] CR 24% PR 29% Minor 10%	Several small studies [34–37] largest study: 57 patients [38] CR 32% PR 23% Minor 17%

*Abbreviations: CR, complete response; HTN, hypertension; IBD, inflammatory bowel disease; IL-2, interleukin-2; Minor, minor response; N/V, nausea and vomiting; OR, overall response; PR, partial response; SLE, systemic lupus erythematosus.

TABLE II. Background Demographics and ITP History of the 18 Study Patients*

Patient	Age (years)	ITP duration (years)	Splenectomy	Prior major bleed (if any)	Previous ITP treatments	ITP treatments at entry
1	***25***	***3***	***Yes***	***Heavy menses***	***Pred, IVIG, Dan, Dap, Aza, Vinc, CSA***	—
2	4	***4***	***No***	***None***	***Pred, IVIG, Aza, Dan, MP***	***Dan***
3	***31***	***15***	***Yes; accessory Sx***	***Heavy menses***	***Pred, CSA, Vinc, CP, IL-11, Aza, BG9588***	—
4	***58***	***8***	***Yes***	***Severe epistaxes***	***Pred, Dan, Aza, Ritux***	***Pred***
5	***64***	***3***	***Yes***	***ICH 2002***	***Pred, IVIG, Aza, Dex, MP***	—
6	***65***	***2***	***Yes***	***None***	***Pred, IVIG, Aza***	***Aza***
7	***53***	***10***	***Yes***	***ICH 1998***	***Pred, IVIG, Aza, CSA, Ritux***	***Pred, Aza***
8	25	9	Yes	None	Pred, IVIG, MP, Aza, Dan, CSA, Vinc, IDEC-131	Pred, Dan, Dap, EACA
9	46	12	Yes	Heavy menses	Pred, IVIG, Dan, Vinc, Aza, BG9588, IDEC-131	—
10	51	10	Yes	ICH: 3/99	IVIG, MP, Dan, Aza, Vinc, Dex, VBL, CSA, Dap	Pred, EACA
11	17	12	Yes	None	Pred, IVIG, Vinc, IL-11, CSA, BG9588, Dan, Aza	—
12	54	20	Yes	ICH: 1996 & 1998, rectal bleeding	IVIG, MP, Aza, Dan, CP, Vinc, VBL, CSA, SPA	—
13	50	20	Yes	None	Pred, IVIG, MP, Dan, Aza	—
14	50	5	Yes	None	Pred, IVIG, MP, Dan, Dap, Aza, Vinc	EACA
15	61	5	Yes	ICH 2003	Pred, IVIG, Aza, CP, Dap, Dan, Anti-D, CP	Pred, tranexamic acid
16	43	3	No	None	Pred, IVIG, Dex, Dan	—
17	25	2	Yes	Hematuria	Pred, IVIG, Dan, Anti-D, Ritux	—
18	66	27	Yes	ICH 2003	Pred, IVIG, Aza, CSA, Dex, Dap, Anti-D	—

***Legend**: "—", no ITP medication at entry; Aza, azathioprine; BG9588, anti-CD40 ligand that targets T cells and interrupts the interaction with B cells to lower excessive antibody production, study was canceled due to thrombotic side effects; CP, cyclophosphamide; CSA, cyclosporin A; Dan, danazol; Dap, dapsone; Dex, dexamethasone; EACA, ε-aminocaproic acid; IDEC 131, anti-CD40 ligand with fewer thrombotic side effects than BG9588; IL-11, interleukin-11; IVIG, intravenous immunoglobulin; MP, methylprednisolone; Pred, prednisone; Ritux, rituximab (anti-CD20); SPA, staphylococcal Protein A column; Sx, splenectomy; VBL, vinblastine; Vinc, vincristine. Bold italic text rows represent patients who responded to MMF.

RESULTS

Toxicity

Of the 18 original patients, two discontinued MMF within 1 month, one patient because of persistent headaches (patient 9) and the other from light-headedness (patient 10). An additional patient (patient 18) could not tolerate a dose of above 1 g/day because of headache. Of the 14 adult patients that remained on MMF, doses were increased to 2 g daily without apparent side effects; the pediatric patient also reported no side effects. MMF had no adverse effects on either white blood cell count (WBC) or hemoglobin concentration (Hb). None of the patients required hospital admission during the course of use.

Efficacy

Platelet response. Seven of the 18 patients had unequivocal platelet increases in response to MMF. There were no complete responses, but 5 good responses and 2 partial responses were seen. Those in whom ICH occurred had no further serious bleeding, although they continued to receive other treatment unless their platelets achieved a good response. The patient with frequent severe epistaxes (patient 4) suffered no further bleeding. Signs such as bruising continued to occur but to a lesser extent. Demographic and clinical data for responders and nonresponders are shown in Table II, and specific counts are listed in Table III.

Good responders. Patient 3 experienced an increase in platelet count from 19×10^9/L to a range of 181×10^9/L to 650×10^9/L at a dose of 2 g of MMF/day. When this patient was recently tapered to 1.5 g/day after 1 year of normal platelet counts, the platelet count decreased to 90×10^9/L. The platelet count rose again to 200×10^9/L 3 weeks after the MMF dose was resumed at 2 g/day. Of note, this patient had had a long-lasting response to cyclosporin before losing responsiveness to it.

Patient 1, while on azathioprine for 8 months, showed a good response to azathioprine with an average platelet count in the first month of 200×10^9/L. Azathioprine had to be discontinued twice due to worsening of hepatitis during the patient's course of treatment. During the last month of azathioprine treatment, the average platelet count decreased to 51×10^9/L. MMF was started when azathioprine was discontinued. After week 4 of treatment, her platelets stabilized. At 2 g/day, however, this patient's platelet

TABLE III. Platelet Counts During MMF Treatment*

Patient no.	No. of weeks MMF Tx	No. of IVIg Tx on MMF	Max MMF dose at week *n* (*n*)	Max platelet count at week *n* (*n*)	Max platelet count ($\times 10^9$/L)	No. of consecutive weeks with plt count $>30 \times 10^9$/L
1	***28***	***3***	***8***	***1***	***127***	***4***
2	***56***	***6***	***16***	***4***	***164***	***20***
3	***28***	***0***	***8***	***12***	***311***	***24***
4	***24***	***0***	***6***	***22***	***66***	***20***
5	***34***	***28***	***33***	***25***	***55***	***3***
6	***14***	***4***	***3***	***12***	***208***	***2***
7	***32***	***6***	***6***	***15***	***69***	***13***
8	32	6	24	24	43[b]	4
9	2	0	0	NA	<10	0
10	4	1	0	NA	66[b]	3
11	28	3	16	28	<10	0
12	33	30	20	16	51[b]	0
13	28	6	12	20	76[b]	2
14	20	8	8	8	<10	0
15	12	0	4	NR	<10	0
16	11	0	6	NR	<10	0
17	12	0	3	NR	<10	0
18	31	0	4[a]	5	<10	0

*Legend: NA, not assessed; NR, no response; Tx, treatment; Bold italic text rows represent responders.
[a]Patient could not tolerate MMF >1 g/day due to headache.
[b]Platelet count elevation due to administration of IVIg.

counts would cycle and occasionally fall, and eventually she received other treatment.

Patient 4 had failed multiple therapies, including rituximab. Clinically, the predominant problem was frequent (daily) severe epistaxes. Her platelet count rose to 55×10^9/L with MMF and a small dose of prednisone; she had been taking the latter for many months before MMF was started and slowly was able to discontinue it altogether.

Patient 6 had ITP of short duration and had failed azathioprine therapy. He responded rapidly to MMF with a maximal dose achieved within 3 weeks and maximal platelet count of 208×10^9/L by week 12.

Patient 5 had severe refractory ITP with platelet counts $<10 \times 10^9$/L persistently and had failed conventional immunosuppression (cyclophosphamide and azathioprine). She had suffered an ICH in 2002. Her response to MMF was slow, with a maximal platelet count of 55×10^9/L at week 25.

Partial responders. Patient 7 had severe refractory ITP for 10 years, had failed splenectomy, and no response to multiple immunosuppressive agents. Before MMF therapy, he required IVIg once every 3 weeks to avoid serious bleeding. He achieved maximal MMF dose by week 21 and platelets $>30 \times 10^9$/L by week 3. The IVIG infusions were required less frequently at intervals of 4–6 weeks while on MMF therapy.

Patient 2 also showed a significant increase in platelet count to over 30×10^9/L on week 4 of MMF at her maximum dose of 0.75 g/day. The interval between her IVIG treatments increased from 14 days to 30 days.

Non-responders. Table III depicts the effect of MMF treatment on the platelet count. The 11 non-responding patients in this study who completed a full course of MMF have highly refractory ITP (Table II). The average number of years that these patients have had ITP is 11.4 years; all but one had undergone splenectomy, 4 have had intracranial hemorrhages, and 2 have had other substantial bleeding episodes.

IVIG requirements before and after MMF treatment. The frequency of IVIG infusions was evaluated in 5 patients whose platelet counts failed to rise with MMF treatment (patients 8, 11, 12, 13, and 14). Only one patient (patient 13) showed a statistically significant increase in the time between IVIG treatments.

Duration of ITP and platelet response to MMF. Patients who had had ITP for a shorter period of time (<8 years vs. >8 years) showed a trend to a better response rate; 55% versus 22% ($P = 0.16$).

DISCUSSION

ITP is considered to be an autoantibody-mediated disease, but it may be driven either by dysregulated T lymphocytes or antigen-presenting cells. The rationale behind the use of azathioprine and other immunosuppressives is that these drugs inhibit lymphocyte

proliferation with consequent reduction in autoantibody production. Immunosuppressive agents, such as azathioprine [3,27], cyclosporin [28], and cyclophosphamide [9], have been used to increase the platelet count in patients with ITP with variable success.

The data acquired from this study indicate that MMF has efficacy for severe patients with refractory ITP. Responses were seen in 7 patients (39%). One patient who failed to show an increase in platelets above 30×10^9/L had a reduced frequency of IVIG infusions, suggesting that clinical responses may occur in the absence of numerical increase in the platelet count by augmenting the effects of other treatments.

MMF was well tolerated by most patients in the study group (82%) with a minority unable to achieve full dose because of headache and other side effects. Overall, MMF has certain advantages as compared to other available such immunosuppressive agents as azathioprine and cyclosporine based in part on its relatively low degree of toxicity. Azathioprine is infrequently hepatotoxic and may lower the neutrophil count; it appears not to be as potent as MMF. Cyclosporin is clearly more toxic, and renal and blood monitoring of drug levels is required.

The patients in the study group reported here failed to respond to multiple therapies including splenectomy and are, by definition, highly refractory. The response rate of 39% may therefore underestimate the efficacy of MMF in less severe ITP. Table IV shows that most patients had failed to respond to other immunosuppressants. One patient (10) had an initial response to vincristine but with severe adverse side effects. This patient also responded to a combination of azathioprine with dapsone for a period but eventually became refractory to this.

TABLE IV. Patients' Responses to Other Immunosuppressants*

Patient no.	Cyclophosphamide	Cyclosporin	Azathioprine
1	No response	—	No response
10	No response	No response	No response
2	—	—	—
14	—	—	R + Dan
8	—	—	R + Dan
9	No response	No response	No response
11	—	No response	No response
13	—	—	No response + Dan
AM	—	—	R
3	No response	R	No response
4	—	—	No response
15	R	No response	No response
5	—	No response	No response
16	—	—	—
6	—	—	No response
17	—	—	—
18	—	No response	No response

*Legend: "—", not assessed (drug not used); R, response to treatment; Dan, danazol.

Hou et al. have recently conducted a small study using MMF at similar doses to our study [26]. The response rate in their study was 64% and was independent of whether or not patients had undergone splenectomy. Part of the explanation for their higher response rate, in comparison to that reported here, may be that the duration of ITP in their patient group was an average of 27.6 months, compared to 113 months in this study. MMF appears to have greater benefit in patients with ITP of shorter duration and these data support this. Howard and colleagues carried out a similar, but smaller, study; the response rate reported was 83%, and the average duration of ITP in their responding group was 59.6 months. In their study, the patient who failed to respond to MMF had ITP for 41 years [25].

CONCLUSIONS

In summary, MMF appears to be effective in a subgroup of refractory ITP patients and may be of particular value if used earlier in the disease history and, perhaps, as part of a combination regimen. Further work is required in order to determine the optimal drug combination(s) to use in difficult ITP and whether it should include MMF. Within the renal transplant arena, MMF is used in combination with tacrolimus, prednisone, cyclosporin, or azathioprine [29–31]. The additive effects of such immunosuppressants do not appear to be associated with an increased incidence of opportunistic infections, which is an important factor to consider with any immunosuppressive agent. ITP patients, because they are generally healthy, are less likely to develop infectious complications with MMF than renal patients post-transplant who also have to deal with a transplanted organ in their body.

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