Treatment of Primary Systemic Vasculitis with the Inosine Monophosphate Dehydrogenase Inhibitor Mycophenolic Acid

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Key Words

Antineutrophil cytoplasmic antibody · Mycophenolate mofetil · Mycophenolic acid · Toxicity · Vasculitis

Abstract

Despite advances in the treatment of vasculitis, modern therapies fail to induce or maintain remission in a significant proportion of patients. Mycophenolic acid is increasingly used to treat vasculitis syndromes. Here, we consider relevant pharmacokinetic and pharmacodynamic properties of mycophenolate, with emphasis on the impact of renal impairment, and we review the existing evidence for and current trials of mycophenolate in the treatment of primary systemic vasculitides.

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Background

The introduction of cyclophosphamide and glucocorticoids dramatically changed the prognosis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides from an almost invariably fatal disease to a controllable illness. Despite this, the toxicity and partial efficacy of modern treatments represent an unmet need for better therapies [1, 2].

With standard therapy, up to 30% of patients fail to achieve complete remission. Of those who achieve complete remission, 50% experience a relapse within 5 years [3, 4]. Relapse is associated with increased exposure to toxic immunosuppressant therapies and glucocorticoids which carry a high side effect burden and predispose to infection [5]. Of particular concern is the contribution of cyclophosphamide to the increased risk of malignancy seen in vasculitis and to infertility. Alternative therapies are clearly needed.

The past decade has seen the successful introduction of mycophenolate mofetil (MMF) as rejection prophylaxis in solid organ transplantation [6, 7], and its increasing use as therapy for autoimmune diseases [8, 9]. In solid organ transplantation, MMF may be more effective than azathioprine in preventing acute rejection episodes [6, 10–13] or at least equally efficacious [14, 15], and prolongs graft survival when compared to azathioprine [16]. As azathioprine is the standard remission-maintaining drug in renal vasculitis, comparison to azathioprine in other scenarios are valid. In lupus nephritis, the MAINTAIN trial compared MMF to azathioprine after remission induction with cyclophosphamide, and found no difference in rates of relapse between groups [17]. Randomized trial evidence in lupus suggests that MMF is equivalent to cyclophosphamide for remission induction [18–22] and has been successful where other therapies

Fig. 1. In activated lymphocytes, the activity of IMPDH increases by tenfold. Lymphocytes are uniquely dependent on this pathway for DNA synthesis, whereas guanine monophosphate may be synthesized by a salvage pathway in other cells. For this reason, MMF specifically inhibits proliferation of B and T lymphocytes. Adapted from Stepkowski [79].

have failed [23, 24]. Walsh et al. [25] reported a lower rate of remission failures with MMF compared to cyclophosphamide in a meta-analysis of 4 randomized trials comprising 268 patients, and a recent large randomized trial of 370 patients reported similar response rates when MMF was compared with cyclophosphamide as induction therapy [26]. A clear rationale therefore exists for the evaluation of MMF in the treatment of vasculitis syndromes, focusing largely on the ANCA-associated vasculitides.

Mycophenolic Acid

Mycophenolic acid (MPA) was first isolated from *Penicillium brevicompactum* by Gozio [27] in 1896, and subsequently given its name in 1913 by Alsberg and Black [28]. As MPA causes severe gastrointestinal side effects when administered by mouth, it is most commonly administered as a prodrug, MMF (Cellcept®), or as enteric coated mycophenolate sodium (Myfortic®).

MMF is a morpholinoethyl ester of MPA, to which it is converted in the liver. MPA in turn noncompetitively and reversibly inhibits types I and II inosine monophos-

phate dehydrogenase (IMPDH) activity during DNA synthesis in the S phase of the cell cycle [29], preventing guanine monophosphate synthesis (fig. 1). T and B lymphocytes are uniquely dependent on the de novo synthesis of guanosine nucleotides, unlike other cell types, which are able to utilize a salvage synthesis pathway. MMF is therefore considered relatively lymphocyte selective compared to other purine antagonists such as azathioprine. In addition to this 'conventional' mechanism of action, MMF may also inhibit the migration of monocytes to and adhesion of activated lymphocytes at the site of inflammation [30, 31].

Pharmacokinetics and the Effects of Renal Impairment

After oral administration, MMF is almost completely absorbed and rapidly converted to MPA by hepatic ester hydrolysis. Accordingly, MMF levels fall below detectable blood limits within 10 min of oral administration [32, 33], and the plasma concentration of MPA peaks after 1 h. After mycophenolate sodium administration, plasma MPA peaks later, after 2 h, though pharmacokinetic properties are otherwise similar to MMF.

MPA is more than 97% protein bound [33], and undergoes phase II metabolism by hepatic and, to a lesser extent, intestinal and renal glucuronidation by several uridine- γ -transferase (UGT) enzyme isoforms. The predominant glucuronidation product is MPA 7-O-glucuronide (MPAG). MPAG is not pharmacologically active [32], is filtered by the glomerulus and actively secreted by renal tubular cells, and thus largely excreted by the kidney [33]. However, MPAG undergoes enterohepatic recirculation and is deglucuronidated to MPA in the intestine and reabsorbed, accounting for a second MPA peak in plasma 8–12 h after MMF administration. Importantly, MPAG is also highly protein bound and displaces MPA from albumin (fig. 2).

Trough Level Monitoring

Fig. 2. MMF is rapidly hydrolyzed to MPA, which peaks in plasma 1 h after administration and is 80% albumin-bound. MPA undergoes enterohepatic recirculation. It is glucuronidated by the liver, and to a lesser extent, intestine and kidneys, to MPAG and AcMPAG. MPAG is resecreted into the intestine where it is de-glucuronidated to MPA and reabsorbed, accounting for a second plasma MPA peak after 8–12 h. Both MPAG and AcMPAG are renally excreted and, in renal impairment, can reach sufficient concentrations in plasma to displace MPA from albumin.

Table 1. Published studies on the use of MMF for the treatment of ANCA-associated vasculitis

Reference	Publication type	Disease	Mean MMF dose mg/day	Mean MMF starting dose mg/day	Randomization
Kazderova [57]	Original article, uncontrolled, retrospective	AASV	1,190	1,260	No
Langford [59]	Original article, uncontrolled, retrospective	AASV	NR	2,000	No
Stassen [54]	Original article, uncontrolled, retrospective	AASV	NR	2,000	No
Koukoulaki [58]	Original article, uncontrolled, retrospective	AASV	1,600	NR	No
Hu [51]	Original article, randomized, prospective	AASV	NR	2,000	Yes
Joy [55]	Original article, uncontrolled, retrospective	AASV	NR (target 2,000)	1,000	No
Nowack [56]	Original article, uncontrolled, retrospective	AASV	NR	2,000	No
Yalcindag [80]	Original article, uncontrolled, retrospective	Ocular AASV		2,000	No
Iatrou [81]	Original article, uncontrolled, retrospective	AASV	NR		No

MMF = Mycophenolate mofetil; TTR = time to remission; CR = complete remission; PR = partial remission; NR = not reported; NA = not available.

Current evidence suggests important pharmacokinetic differences in autoimmune diseases such as ANCA-associated systemic vasculitis (AASV) and systemic lupus erythematosus (SLE) compared with solid organ transplantation. In autoimmune disease, both 12- and 24-hour MPA trough levels correlate with AUC [48] after the administration of MMF, making TLM clinically feasible. A recent small study including 10 patients with AASV and 6 patients with SLE suggested maintaining MPA 12-hour trough levels between 3.5 and 4.5 may be associated with better disease control and fewer adverse events [49]. Schaier et al. [50] reported a correlation of disease activity with low MPA trough levels in patients with AASV. However, both these studies were small, uncontrolled and recorded an insufficient number of events to draw firm conclusions. Prospective data to support the routine use of MPA TLM in autoimmune disease are lacking.

Mycophenolate in AASV

AASV remains the best studied of the primary systemic vasculitides. A number of groups have reported the use of MMF as induction and maintenance therapy for AASV. When interpreting the existing literature, the reader should consider that as with most new therapies, mycophenolate was initially used almost exclusively as salvage therapy for refractory disease or where other therapies had failed to maintain remission.

Remission Induction

Only one prospective randomized study evaluating the efficacy of mycophenolate in the treatment of AASV has been published to date [51]. In this study, 35 Chinese patients carrying a new diagnosis of AASV with renal involvement were assigned to receive MMF or cyclophosphamide, along with glucocorticoids, for remission induction. Eighteen patients were treated with MMF, all but one of whom had microscopic polyangiitis. Fourteen of 18 patients achieved remission after 6 months, compared to 8 of 13 patients in the cyclophosphamide group. Adverse event rates were similar between groups, and renal function at 6 months was not significantly different. Although this small study suggested the equivalence of mycophenolate to cyclophosphamide for remission induction, it has several important limitations: (1) the dose of cyclophosphamide used was low compared with other studies [52, 53]; (2) only 1 patient in the MMF group carried a diagnosis of Wegener's granulomatosis; (3) there was a high dropout rate in the cyclophosphamide arm; (4) the study population was exclusively Chinese, and (5) the study was not adequately powered to address the endpoint of induction failure. These results should therefore be interpreted with caution.

A number of uncontrolled series have reported mixed results after induction with MMF. Stassen et al. [54] reported complete remission in 25 of 32 patients with AASV, and partial remission in 6 patients. Only 1 patient failed to achieve remission [54], however an earlier series by Joy et al. [55] reported remission in only 7 of 12 pa-

Blind- ing	Follow-up mean months	n	Induction or maintenance	Remission achieved		Relapse on MMF, %	TTR months	Comments
				CR, %	PR, %			
No	12	34	Induction, maintenance	NR	NR	15	–	Mean time to steroid withdrawal = 8 months
No		14	Maintenance	NA	NA	43	10	
No	19	32	Induction	78	19	37 (1 year)	16	Limited to ocular involvement
No	24	51	Induction, maintenance			48	14.1	
No	6	18	Induction	77.8				
No	12	12	Induction	50	25	44	–	
No	15	11	Maintenance	NA	NA	9	14	
No	36	5	Induction	100	–	–	–	
No	42	22	Maintenance	NA	NA	31.6	21.5	

tients with AASV after 6 months. Current evidence is insufficient to support the routine use of mycophenolate for remission induction. A prospective randomized trial comparing MMF to cyclophosphamide (MYCYC) is currently recruiting (ISRCTN83027184; www.vasculitis.org), and will further assess the efficacy and safety of MMF as induction therapy.

Remission Maintenance

Mycophenolate has also been used as remission maintenance therapy in AASV. An initial uncontrolled pilot study in 11 patients with AASV evaluated MMF as maintenance therapy after conventional induction therapy with cyclophosphamide and glucocorticoids [56]. One patient experienced a relapse during 14 months of follow-up. As others have reported a mean time to relapse in AASV of 15 months [53], the duration of this study was short when considering relapse as the primary outcome.

More recently Kazderova et al. [57] reported the use of MMF in a cohort of 34 patients with glomerulonephritis due to AASV in a retrospective analysis. MMF was used either as induction therapy or as remission maintenance therapy, and proteinuria and serum creatinine were used as surrogates for disease activity. Although MMF was effective in preventing relapse in most patients, there was a high number of treatment withdrawals due to adverse events, the majority due to gastrointestinal side effects. By 6 months, 11 patients (32%) had already withdrawn from treatment with MMF, 6

due to relapse. Nevertheless, in those patients where MMF was tolerated, creatinine stabilized and proteinuria reduced in the majority of patients. This study is weakened by its retrospective nature, the heterogeneity of the study population, and the lack of data to assess conventional measures of diseases activity. In another retrospective series of 51 patients with AASV, 29/51 patients received MMF as remission maintenance [58]. Fourteen of 29 patients (48%) experienced relapse with a mean follow-up of 20 months. The remainder received MMF for induction for relapsing disease and were subsequently maintained on MMF. Of these, 19 of 22 achieved remission although 9 subsequently relapsed during follow-up. Taken together, this represents an almost 50% relapse rate with a mean time to relapse of 14 months. Although this was relatively high, the mean dose of MMF in this cohort was 1.6 g/day, and this series included patients who had previously failed on other therapies. Langford et al. [59] studied 14 patients with Wegener's granulomatosis in whom MMF was used for maintenance after conventional induction therapy with cyclophosphamide and glucocorticoids, and also reported a high relapse rate (43.8% with a mean time to relapse of 10 months). However in this series the mean time to steroid withdrawal was only 8 months. Similar to the report by Koukoulaki and Jayne [58], the relapse rate did not remain constant but increased with time as steroid therapy was withdrawn.

The International Mycophenolate Protocol to Reduce Outbreaks of Vasculitides randomized trial (IMPROVE,

ISRCTN83027184; www.vasculitis.org) compared MMF to azathioprine after conventional induction therapy with cyclophosphamide and steroids. IMPROVE aimed to evaluate the efficacy and safety of MMF for remission maintenance in a large cohort (n = 175) of patients with AASV, and publication is anticipated during 2010.

Although the Churg-Strauss syndrome is also classed as an AASV, all randomized trials of AASV to date have excluded Churg-Strauss syndrome. Anecdotal reports indicate that mycophenolate has been used successfully in its treatment [60].

Large Vessel Vasculitis

The large vessel vasculitides include Takayasu's arteritis (TA) and giant cell arteritis. As with AASV, glucocorticoids are a mainstay therapy. Although glucocorticoids are efficacious, many patients require high doses to control disease, predisposing to glucocorticoid side effects [61]. More than half of patients with TA require the addition of an immunosuppressive agent to control disease and of these, only one third demonstrate a response to therapy [62].

There are only a small number of reports on the use of MMF in TA. Daina et al. [63] reported success with MMF in 3 TA patients with steroid-dependent disease. Two patients had previously received treatment with cytotoxic agents. MMF successfully reduced disease activity and steroid dependence in all 3 patients. Conversely, in a series of 15 patients with TA treated with anti-TNF α therapy, Hoffman and Ahmed [61] reported that MMF had previously failed to control disease in 3 patients. In an open label prospective study, Shinjo et al. [64] treated 13 patients with TA with MMF for a mean duration of 23.3 months. The addition of MMF to glucocorticoid therapy was successful in inducing remission in 12/13 patients, and the remaining patient discontinued therapy due to drug intolerance.

Other Vasculitis Syndromes

Anecdotal evidence supports the use of MMF in a variety of vasculitic syndromes, including hypocomplementemic urticarial vasculitis [65], nodular vasculitis [66] and essential mixed cryoglobulinemia [67]. However, a study of the use of MMF as therapy for Behçet's disease was terminated prematurely due to lack of efficacy in the first 6 patients [68].

Pregnancy and Lactation

A review by the manufacturer of MMF identified 119 pregnancies with maternal fetal MMF exposure [69]. In this analysis only 34% of the 65 pregnancies for which the outcome was known resulted in healthy live births. Of the remainder, there were 20% elective terminations, 31% miscarriages, and 15% fetal abnormalities. These findings are congruent with a report by Sifontis et al. [70] on MMF exposure in 18 renal transplant recipients who had 26 pregnancies resulting in 11 spontaneous abortions and 15 live births. Four of the live births manifested structural malformations including microtia, cleft lip and palate, short fingers and nail hypoplasia, and 1 neonatal death with multiple abnormalities. Similar abnormalities have also been described by other authors [71, 72], leading to the recent proposal of a characteristic phenotype of mycophenolate embryopathy comprising cleft lip and palate and microtia [73].

MMF should therefore be avoided in patients actively attempting to conceive, and should not be administered during pregnancy. Women of childbearing age should have a negative pregnancy test prior to commencing treatment with MMF, and should receive contraceptive counseling. Mycophenolate is excreted in breast milk, and its use should be avoided in lactating women.

Pediatric Practice

There are few available data on the use of MMF in children with autoimmune diseases. In solid organ transplantation, MMF does appear to be safe in pediatric use. Jung-raithmayr et al. [74] studied 83 pediatric and adolescent renal transplant recipients followed for 3 years, and reported infection rates similar to those in adults, with no other adverse effects to those documented in adult patients.

Mycophenolate and Renal Fibrosis

A large body of experimental evidence suggests an inhibitory effect of MMF on renal fibrosis. As reviewed by Morath et al. [75], MMF abrogates progression of renal disease in the 5/6th nephrectomy model of chronic renal impairment, reduces glomerulosclerosis, improves renal function, prevents the onset of proteinuria, and ameliorates cyclosporine-induced arteriolopathy, and at the molecular level reduces the expression of adhesion molecules CD18 and CD11b and other pro-fibrotic molecules.

In man, MMF reduces circulating TGF- β 1 and tubular TGF- β 1, and IL-6 expression in renal transplant recipients [75]. Furthermore, MMF reduces epithelial to mesenchymal transformation to an extent rivaled only by sirolimus but not by azathioprine, calcineurin inhibitors or glucocorticoids [76]. Transferring these data to the clinical arena, Nankivell et al. [77] recently reported a protective effect of MMF against renal fibrosis compared to azathioprine in renal transplant recipients treated with calcineurin inhibitors. In AASV with renal involvement, Hu et al. [51] suggested that MMF may be superior to intravenous cyclophosphamide in reducing proteinuria and improving renal function. The results of the MYCYC and IMPROVE trials should elucidate whether treatment with mycophenolate will lead to superior long-term renal outcomes compared to conventional therapy.

Conclusion

Mycophenolate is an attractive alternative to conventional induction therapy with cyclophosphamide for vasculitis as it is not associated with infertility or bladder carcinoma, and does not require intravenous administration. The hope exists that mycophenolate will provide su-

perior efficacy with comparable or reduced toxicity compared to existing remission maintenance therapies. MMF will be off patent in 2011 but currently remains expensive, costing around ten times more than azathioprine in the United Kingdom.

MPA is now an established immunosuppressant in solid organ transplantation. Despite promising early pilot data in AASV, results from uncontrolled studies have been conflicting, and randomized trial data in vasculitis are still lacking. Furthermore, no adequately powered prospective studies of MMF in vasculitis have considered MPA level monitoring, and it is unknown whether level monitoring will improve efficacy and limit toxicity in autoimmune diseases including vasculitis. Level monitoring may be particularly important in patients with renal impairment. The ALMS study used MMF dosed at 3 g/day for lupus nephritis, and it is notable that there was no safety benefit of MMF over cyclophosphamide after 6 months [26]. ALMS did not employ level monitoring.

Based on current evidence and pending results from randomized studies, standard treatment guidelines for remission induction and maintenance therapy should apply [78]. Treatment with mycophenolate should be reserved for patients with refractory disease, or where conventional therapies are contraindicated.

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Editorial Comment

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The salts of mycophenolic acid (mycophenolate mofetil, MMF, and mycophenolate sodium) could justifiably be called the signature immunosuppressive drugs of the first decade of the 21st century. In a scholarly minireview, Hiemstra, Jones and Jayne of the renowned Lupus and Vasculitis Unit of Addenbrookes Hospital and Cambridge University focus on recent developments in the utilization of these drugs (predominantly MMF) in systemic vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA+ vasculitis). While the toxicity profile of MMF favors its use over cyclophosphamide for induction of remissions in ANCA+ small vessel vas-

culitis, we still remain uncertain over comparative efficacy – a situation that will hopefully be remedied by the MYCYC trial in progress. Maintenance of remission in ANCA+ vasculitis by MMF is encouraging, but side effects and a high relapse rate may limit its utility. The IMPROVE trial should settle the remaining issues in 2010. The role of monitoring blood levels of mycophenolic acid continues to be very uncertain. Hiemstra et al. have been properly cautious in their conclusions that mycophenolates (primarily MMF) have not yet achieved the status as a first-line treatment regimen for ANCA+ vasculitis.