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Randomized trial of enteric-coated mycophenolate sodium versus mycophenolate mofetil in multi-system autoimmune disease

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Abstract

Background. The use of mycophenolate mofetil (MMF) in autoimmune disease is often limited by adverse effects. In this single-centre, open label, parallel design study, we investigated whether enteric-coated mycophenolate sodium (MS) is better tolerated and therefore more efficacious than MMF in primary systemic vasculitis (PSV) and systemic lupus erythematosus (SLE).

Methods. Forty patients with vasculitis or systemic lupus erythematosus (SLE) due to commence MMF for active disease or remission maintenance were randomized to receive either 1440 mg/day MS or 2000 mg/day MMF (18 PSV, 2 SLE per group) in addition to corticosteroids. Random allocation was performed by minimization for age, diagnosis and renal function using a computer algorithm. Twenty-five were treated for active disease (5 first-line therapy, 20 salvage therapy) and 15 for remission maintenance. The composite primary end point was treatment failure and/or drug intolerance over 12 months. Treatment failure was defined as failure to achieve remission by 6 months or disease relapse and treatment intolerance was defined as inability to tolerate and maintain the target dose of MS or MMF within 12 months.

Results. Forty patients were included in the analyses. MS was associated with a lower primary end point rate [hazard ratio (HR) 0.37; 95% CI 0.17–0.80; P = 0.012] (11/20, 55% patients) compared with MMF (17/20, 85% patients). Treatment failure alone was less common in the MS group (HR 0.28; 95% CI 0.095–0.82; P = 0.020), although drug intolerance did not differ between groups (HR 0.53; 95% CI 0.20–1.42; P = 0.21). Despite randomization, patients in the MMF group may have had a higher baseline risk for treatment failure; more MMF patients had refractory disease and granulomatosis with polyangiitis (Wegener's). A glomerular filtration rate (GFR) $\leq$40 mL/min was associated with intolerance. Serious adverse events were common (55% MMF and 45% MS patients).

Conclusions. No differences in treatment tolerance were observed between the MS and MMF groups. Despite similar treatment intolerance, MS was associated with improved efficacy in PSV and SLE compared with MMF. However, baseline group imbalances in factors potentially affecting remission and relapse may have influenced the results. Treatment intolerance was common and strongly associated with low GFR. Further treatment trials are warranted to investigate the effect of GFR on mycophenolic acid pharmacokinetics and clinical outcomes (ISRCTN83027184; EUDRACT 2005-002207-16; Funding Novartis UK).

Keywords: enteric-coated mycophenolate sodium; mycophenolate mofetil; primary systemic vasculitis; randomized trial; systemic lupus erythematosus

Background

Primary systemic vasculitis (PSV) and systemic lupus erythematosus (SLE) are the two major subgroups of multi-system autoimmune disease. Both conditions demonstrate similar treatment responses and untreated are associated with poor outcomes. The standard therapy, cyclophosphamide with high-dose corticosteroid [1–3], is associated with primary treatment failures, relapses and toxicity [4], particularly infections, malignancies and infertility [5]. Improved therapies are required.

Mycophenolic acid (MPA) is an immunosuppressant that reversibly inhibits inosine 5-monophosphate dehydrogenase (IMPDH), a critical enzyme in *de novo* guanosine nucleotide synthesis [6]. T- and B-lymphocyte proliferation is dependent on the *de novo* pathway [7], unlike other cells which utilize the salvage pathway for guanosine synthesis. MPA is associated with lower rates of amenorrhoea and malignancy compared with the alkylating agent, cyclophosphamide which inhibits cell division [8, 9].

The MPA ester, mycophenolate mofetil (MMF) is an effective component of anti-rejection therapy in solid-organ

transplantation. Treatment with MMF is complicated by dose-dependent gastrointestinal intolerance, which may result in suboptimal dosing and loss of efficacy. MMF undergoes rapid gastric absorption and systemic de-esterification to MPA, whereas another MPA preparation, enteric-coated mycophenolate sodium (MS), developed as a strategy to reduce gastrointestinal toxicity, allows delayed MPA release in the small intestine [10]. In transplantation there is no difference in efficacy between MMF and MS [11, 12]. Results of transplant cross-over studies suggest that gastrointestinal intolerance is less with MS compared with MMF [13–18]; however, no difference in tolerance has been demonstrated in blinded randomized trials [19, 20].

MMF is a promising treatment for autoimmune disease. Trials in lupus nephritis have found MMF to have similar efficacy to cyclophosphamide for remission induction [8, 21–24] and maintenance [25]. In one small ANCA-associated vasculitis (AAV) trial remission occurred in 77.8% of MMF patients compared with 47.1% of cyclophosphamide patients [26]. Uncontrolled prospective series provide further support for MMF use in PSV for both remission induction [27, 28] and maintenance [29–31]. However, a 156 patient randomized trial found MMF to be less effective than azathioprine for remission maintenance in AAV [32]. There is considerable 'off label' use of MMF as a second line therapy for these disorders. Because MS may reduce drug intolerance, it has the potential to be an effective therapy. We performed a randomized controlled trial of MMF compared with MS in patients with SLE and PSV to investigate differences in efficacy and tolerability.

Materials and methods

This is an open-label, two group, single centre randomized trial was performed. Patients were recruited from the Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge. All patients provided written informed consent. The trial was designed by the investigators, received ethical and regulatory approval and was conducted according to the European Union Clinical Trials Directive 2001, and the Declaration of Helsinki (EUDRACT 2005-002207-16, clinical trials registration: ISRCTN 83027184). The trial was sponsored by Cambridge University Hospitals NHS Foundation Trust and a research grant to fund trial conduct was provided by Novartis UK.

Patients were included if they had a diagnosis of vasculitis [33] or SLE [34] according to American College of Rheumatology criteria and were about to commence MPA as part of their routine care or had been taking MMF 2000 mg/day or less for at least 3 months with inadequate disease control. Patients with active disease or those requiring remission maintenance therapy were eligible. Patients were excluded if they had active infection, hypersensitivity to MMF, a history of cancer, elective surgery planned, had received an investigational drug within 4 weeks of recruitment, any condition that would cause the study to be detrimental to the patient, or were breastfeeding, pregnant or female with inadequate contraception, or were less than 18 years old.

Random allocation to MS or MMF was performed by minimization using a computer algorithm. Minimization strata were age ($\geq$ versus <40 years), diagnosis (SLE versus PSV) and baseline renal function (serum creatinine > versus $\leq$120 μmol/L [1.36 mg/dL]).

Patients in the MMF group were commenced on 2000 mg/day in two divided doses, and increased to 3000 mg/day if disease control was inadequate and the drug was tolerated. Patients in the MS group were commenced on 1440 mg/day in two divided doses, with increases to 2160 mg/day permitted for inadequate disease control. The MS and MMF therapeutic regimens targeted equimolar MPA doses and are considered bioequivalent in terms of MPA area under the curve (AUC) in transplant patients [35]. Other immunosuppressive drugs were discontinued at trial entry. Daily oral prednisolone was prescribed as needed and reduced according to clinical improvement.

The primary outcome was a composite of treatment failure and/or treatment intolerance by 12 months. Treatment failure was defined as failure to achieve remission by 6 months or disease relapse, in those achieving remission and remaining on therapy to 12 months. Treatment intolerance was defined as an inability to tolerate and maintain the target dose of (ECMS 1440 mg/day or MMF 2000 mg/day) within the 12 month study period. Patients who died during the trial were recorded as treatment failures and those lost to follow-up were censored. This composite end point was chosen to reflect the overall relative clinical utility of the different MPA preparations. Secondary end points were: treatment failure (failure to achieve remission or relapse), treatment intolerance, time averaged prednisolone dose, serious adverse events and serious infection rates.

Evaluations were performed at entry and then three monthly until trial completion at 12 months. At baseline, patients were classified according to reason for commencing MPA therapy; new disease, relapsing disease, refractory disease or remission maintenance either after cyclophosphamide induction therapy or after withdrawal of a poorly tolerated maintenance immunosuppressant. Refractory disease was defined as disease unresponsive to all prior immunosuppressive therapies [36]. At each assessment disease activity was scored using British Isles Lupus Activity Grade (BILAG) [37] for SLE and Birmingham Vasculitis Activity Score (BVAS) [38] for vasculitis. Glomerular filtration rates (GFR) were calculated using the four variable MDRD equation. Adverse events were classified using the EU Clinical Trials Directive (2001/20/EC), according to severity (mild, moderate, severe, life-threatening or death), seriousness (not serious, death, life-threatening, permanently disabling, requiring hospitalization, prolongation of hospitalization, cancer, or congenital anomaly) and relation to study medication (not related, unlikely, possibly, probably or definitely related). Pre-dose MPA measurements were obtained on up to three occasions per patient after a stable dose of study drug had been established. Samples were analysed for total MPA at trial end by high performance liquid chromatography (HPLC).

For SLE complete remission required the absence of BILAG grade A, B and C level disease activity and partial remission required the absence of BILAG A and B activity. For vasculitis complete remission was defined as BVAS $\leq$1 and partial remission required $\geq$50% reduction in BVAS compared with entry. Relapse was defined as the appearance of symptoms attributable to PSV or SLE necessitating a change in immunosuppressive therapy or an increase in corticosteroid dose by at least 10 mg/day [36].

Based on results of previous studies [8, 21–31] the frequency of the primary composite outcome of treatment failure or treatment intolerance was estimated at 70% in the control (MMF) group (30% intolerance, and at least 20% remission failure and 20% relapse). With 20 patients per limb this study was powered to detect an absolute risk reduction of 35% in MS patients with a power of 0.8 and a

two sided significance level of 0.05. All analyses were performed according to the intention to treat principle. The results are expressed as values and percentages for categorical variables and medians and ranges for continuous variables. The primary outcome and secondary efficacy and tolerability outcomes were assessed using unadjusted Cox proportional hazards model. Continuous variables were analysed by Wilcoxon signed rank test (paired data) or Mann–Whitney test (unpaired data). Adverse events were expressed as incidence rates. A value of $P < 0.05$ was considered significant for all statistical tests.

Table 1. Patient characteristics at entry to the trial

Demographics (median and range)		MS *N* = 20	MMF *N* = 20
Age (years)		58.5 (29–79)	57.5 (34–75)
Sex M:F		12:8	10:10
Patients previously treated with CYC		13/20	14/20
Prior cumulative CYC (grams)		9.9 g(5.67–163)	9 g(3–13.5)
Prior relapses		1 (0–3)	1 (0–3)
Disease duration (months)		22.4 (1–196)	26.5 (1–127)
MDRD GFR (mL/min)		83 (15–153)	71.5 (10–151)
ANCA positive at entry		6	6
Prior IS therapies		2 (0–6)	2 (0–5)
Dialysis at entry		0	2
Diagnoses (*patient no.*)			
SLE		2	2
Vasculitis		18	18
	AAV (GPA/MPA/CSA)	9 (5/2/2)	12 (9/2/1)
	HSP	3	2
	PAN	1	1
	Other	4	3
Treatment prior to entry (*patient no.*)			
CYC/AZA		13 (8/5)	12 (6/6)
IVIG		0	2
PEX		0	1
Dapsone		1	0
Prednisolone alone		4	2
Hydroxychloroquine		0	1
None		2	3
Disease state at entry (*patient no.*)			
Active disease	New	2	3
	Refractory	1	3
	Relapsing	9	7
	Total	12	13
Remission maintenance	Post CYC induction	4	2
	Switch from other IS	4	5
	Total	8	7

Results

Forty patients (20 MMF and 20 MS) were enrolled between November 2005 and September 2006. One MMF patient was lost to follow-up shortly after trial entry, and two in the MMF group died (Supplementary Figure S1). The baseline characteristics of the patients are shown in Table 1. At entry, active disease was present in 12/20 MS (2 new disease, 9 relapsing, 1 refractory) and 13/20 MMF (3 new disease, 7 relapsing, 3 refractory). The remainder received therapy for remission maintenance either after cyclophosphamide induction, or after withdrawal of another therapy due to intolerance (8/20 MS, 7/20 MMF). All patients were receiving immunosuppressive therapies prior to entry, except those with new disease.

The groups were broadly similar except the MMF group contained more patients with refractory disease, granulomatosis with polyangiitis (GPA, Wegener's) and had worse renal function (Table 1).

Primary outcomes

The primary outcome at 12 months, a composite end point of treatment and/or tolerability failure, occurred in 11/20 (55%) MS and 17/20 (85%) MMF patients. Analysis by Cox proportional hazard model found the primary outcome to be significantly lower in the MS group (hazard ratio 0.37; 95% CI 0.17–0.80; P = 0.012). Multivariable analysis found that the lowest tertile of GFR (≤40 mL/min/1.73 m^2) was strongly associated with the primary outcome (P = 0.003). This association decreased over time becoming neutral at 158 days. The dominant outcome during the first 158 days was treatment intolerance rather than treatment failure. Overall, treatment withdrawal due to intolerance occurred in 6/13 (46%) patients with GFR ≤40 mL/min compared with 4/27 (15%) with GFR >40 mL/min. Figure 1A and B illustrates time to primary outcome with stratification according to entry GFR and Table 2 shows a breakdown of the composite end point.

Secondary outcomes

Efficacy. Treatment failure by Month 12 occurred in 6/20 (30%) MS and 8/20 (40%) MMF patients (hazard ratio 0.28;

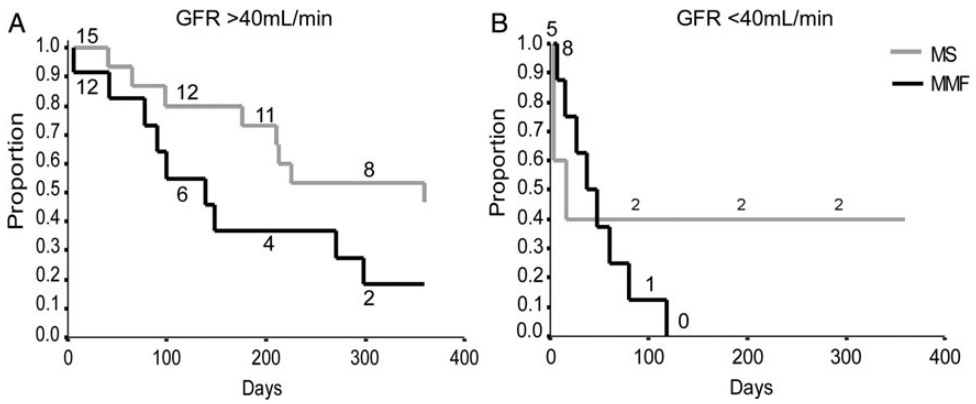

Fig. 1. (**A**) Primary composite end point; treatment and tolerability failure stratified for GFR > 40 mL/min. One MMF patient with GFR > 40 mL/min was lost to follow-up and censored at 30 days, 9/12 patients reached the primary end point during follow-up and 2/12 patients were free from the primary end point at 360 days. (**B**) Primary composite end point; treatment and tolerability failure stratified for GFR ≤40 mL/min. Treatment failure is defined as failure to achieve remission with study drug or relapse with study drug. Tolerability failure is defined as withdrawal from study drug due to intolerance or inability to maintain target dose (2000 mg/day MMF, 1440 mg/day MS). Time to failure to achieve and maintain target dose is time of dose reduction below target dose.

Table 2. Breakdown of composite primary end point

	6 months		12 months	
	MS	MMF	MS	MMF
Primary composite end point	7	15	11	17
Treatment failure	2(2)	5(6)	5(6)	7(8)
Remission failure	1(1)	1(2)	1(2)	2(3)
Relapse[a]	1(1)	4(4)	4(4)	5(5)
Treatment intolerance	5(6)	10(10)	6(7)	10(10)
Treatment withdrawal due to intolerance	5(5)	5(5)	5(5)	5(5)

[a]Relapses are reported for patients in remission at entry and for patients who achieved remission with the study drug; not for patients who failed to achieve remission with the study drug. First event for each patient is recorded for the primary composite end point. Numbers in brackets indicate total number of patients suffering each event. Follow-up was censored after the first event for composite primary end point, intention to treat analysis. Numbers in brackets indicate total number of patients suffering each event.

95% CI 0.095–0.82; P = 0.020). However, there was no significant difference between groups with respect to prednisolone use. Time averaged median prednisolone doses were 9.1 mg/day (range 0–14.1 mg/day) for MMF patients versus 7.6 mg/day (range, 0–18.6 mg/day) for MS patients (P = 0.53).

Failure to achieve remission occurred in 2/20 (10%) MS patients and 3/20 (15%) MMF patients treated for active disease. Relapses were recorded for patients who achieved remission or were in remission at trial start. Relapse by 12 months occurred in 4/18 (22%) MS patients and 5/17 (29%) MMF patients (Table 2).

Intolerance. Target dose intolerance occurred in 7/20 (35%) MS patients (treatment withdrawal *n* = 5) versus 10/20 (50%) MMF patients (treatment withdrawal *n* = 5). Analysis by Cox proportional hazard model found no significant difference between treatment groups (Hazard ratio 0.53; 95% CI 0.20–1.42; P = 0.21). Treatment withdrawal for intolerance was strongly associated with low GFR. In MMF patients median GFR was 23.5 mL/min (range 0–131 mL/min) for those intolerant of target dose and 85.5 mL/min (range 40–151 mL/min) for those tolerant of target dose (P = 0.0015) (Supplementary Figure S2). Gastrointestinal disturbance was the dominant reason for intolerance in both groups (75% MS, 65% MMF).

Pre-dose MPA samples were obtained from 16 MS patients (*n* = 34) and 13 MMF patients (*n* = 33) at a median of two occasions per patient. Samples were obtained from patients receiving stable treatment doses; therefore no samples were obtained from patients withdrawing from treatment early due to intolerance. In those patients who continued treatment long enough to achieve a stable daily dosing pattern, median MPA levels were 1.45 mg/L (range, 0.4–7.8 mg/L) MS versus 3.4 mg/L (range, 0.4–8.5 mg/L) MMF (P = 0.003). Drug-related toxicity at the time of MPA sample occurred in 2/22 with MPA levels <1.5 mg/L compared with 10/45 with levels >1.5 mg/L.

Adverse events. Severe adverse events were those that resulted in alteration, discomfort or disability that was damaging to the patient's health and prevented normal everyday activities, or those that resulted in a life-threatening situation or death. Severe events occurred in 18/20 (90%) MS (*n* = 27), and 16/20 (80%) MMF patients (*n* = 35), including two deaths in the MMF group. One 43-year-old with SLE, cardiac disease and end-stage renal failure suffered a sudden cardiac death at 8 months, having had MMF withdrawn at 5 months. One 72 year old with microscopic polyangiitis, end-stage renal failure and peripheral vascular disease died as a result of septic and cardiogenic shock following surgery for a gangrenous leg at 11 months. At the time of hospitalization this patient was still receiving MMF (Table 3).

Table 3. Adverse events

Any event Total number (%patients)	MS (*N* = 20)	MMF (*N* = 20)
Severity grade 1/2	116 (100%)	36 (80%)
Severity grade 3/4/5	27 (90%)	35 (80%)
Serious events		
Hospitalization/life-threatening	13 (55%)	23 (45%)
Cancer	0	0
Death	0	2 (10%)
Drug-related events occurring in ≥10% patients in either group		
Gastrointestinal	15(75%)	13 (65%)
Anaemia	3 (15%)	3 (15%)
Low mood	5 (25%)	4 (20%)
Rash	4 (20%)	0
Leucopenia	2 (10%)	1 (5%)
Insomnia	0	4 (20%)
Tremor	2 (10%)	2 (10%)
Infections		
All infection	38 (75%)	15 (50%)
Serious infections[a]	5 (20%)	2 (10%)
Moderate[b]/severe[c] infections ≥10% patients in either group		
Chest	3 (10%)	4 (20%)
Gastroenteritis	4 (20%)	2 (10%)
Upper respiratory tract	4 (15%)	0
Skin	4 (15%)	2 (10%)
Herpes Zoster	2 (10%)	1 (5%)

Adverse events were graded according to severity (Grades 1–5) and seriousness.
Grade 1 = Mild: The adverse event does not interfere with the subject's daily routine. It causes slight discomfort. Grade 2 = Moderate: The adverse event interferes with some aspects of the subject's daily routine, not damaging health. Grade 3 = Severe: The adverse event results in alteration, discomfort or disability that is damaging to the patient's health and prevents normal every day activities. Grade 4 = Life-threatening. Grade 5 = Death. Serious adverse events were those that resulted in hospitalization, prolongation of hospitalization, permanent disability, a life-threatening situation, cancer or death.
[a]Serious infections were those that resulted in hospitalization, prolongation of hospitalization, permanent disability, a life-threatening situation, or death.
[b]Moderate infections were those that interfered with some aspects of the patient's daily routine, not damaging health.
[c]Severe infections were those that resulted in alteration, discomfort or disability that is damaging to the patient's health and prevents normal everyday activities, or were life-threatening or caused death.

Moderate or severe infections occurred in 10/20 (50%) MS patients (*n* = 19) and 7/20 (35%) MMF patients (*n* = 11) (Table 3).

Serious adverse events occurred in 11/20 (55%) MS patients and 9/20 (45%) MMF patients. Thirteen events occurred in MS (incidence rate 1.29 per patient year), and 23 events occurred in MMF patients (incidence rate 3.03 per patient year) meaning that a difference of 1.74 events per patient year occurred between MS and MMF groups (95% CI 0.26–3.2; P = 0.015). No serious events were directly attributed to the study medications. In MS patients serious events were 5 infections (0.5 per patient year), 1 active disease whilst taking MS, 7 relating to medical comorbidities. In MMF patients serious events were 2

infections (0.29 per patient year), 13 active disease (7 whilst taking MMF, 6 after MMF withdrawal), 8 relating to medical comorbidities. The observed difference in serious infection rates of 0.21 between groups was non-significant (95% CI 0.38–0.80; P = 0.55).

Events related to the study medications were similar between groups. Most frequent were gastrointestinal side effects in 15/20 (75%) MS and 13/20 (65%) MMF patients. These were moderate or severe in 8/20 (40%) MS and 10/20 (50%) MMF patients and resulted in drug withdrawal in 5/20 (25%) of both MS and MMF groups. A further 2/20 (10%) MS and 5/20 (25%) MMF patients failed to achieve and maintain study drug target dose.

Discussion

In this randomized trial of MS versus MMF in vasculitis and SLE, MS was associated with a significantly lower rate of the composite primary end point of treatment failure and/or treatment intolerance. Intolerance rates alone did not differ between groups; however, MS was associated with a significant reduction in treatment failure alone. Differences in baseline characteristics between groups may account for some of the observed effect of MS in our trial, with more MMF patients having GPA (Wegener's) and/or refractory disease. Overall intolerance rates were higher than previous studies. However, unlike previous studies, we included patients with renal failure. Kidney disease with an estimated GFR ≤40 mL/min was common (35% patients) and was strongly associated with intolerance leading to treatment withdrawal.

Treatment intolerance rates between MS and MMF may differ. The absorption characteristics of MS and MMF influence MPA pharmacokinetic profiles. Equimolar MS and MMF are associated with equivalent total MPA area under the curve concentrations and IMPDH blockade; however, MS has been associated with a longer time to maximum plasma concentration [33]. In transplantation, cross-over studies have found a reduction in gastrointestinal intolerance after switching from MMF to MS [13–17], although blinded randomized trials have not demonstrated a difference in tolerability [19, 20]. In autoimmunity, higher doses of MMF (2000–3000 mg/day) and pre-dose target MMF MPA levels (3.5–4.5 mg/L) [39] are used compared with transplantation (1000–2000 mg/day MMF, 1.0–3.5 mg/L trough MMF MPA range with ciclosporin) [40]. Correspondingly MMF intolerance rates are higher in autoimmunity. Theoretically pharmacokinetic differences between MS and MMF may have a greater impact on intolerance and loss of efficacy in autoimmunity compared with transplantation. However, in our trial comparing MS and MMF in autoimmune disease, no significant difference in treatment intolerance was identified.

Overall, our intolerance rates were high compared with previous MMF trials in autoimmunity, with 70% of the patients suffering gastrointestinal side effects and 45% being unable to tolerate the target dose. In lupus nephritis gastrointestinal intolerance rates of 30% have been reported with similar MMF doses [41]. In this trial intolerance correlated strongly with a GFR ≤40 mL/min, which was present in 35% at baseline. The majority of previous randomized SLE and vasculitis trials have excluded patients with severe renal impairment. Our results are consistent with a previous report of MMF intolerance in five AAV patients with end-stage renal failure [42], none of whom could tolerate 2000 mg/day. In renal failure, accumulation of the MPA metabolites, inactive MPA-glucuronide (MPAG) and active toxic acyl MPA-glucuronide (AcMPAG) occurs. Increased MMF intolerance in advanced renal failure may be a direct toxic effect of AcMPAG or indirectly by an increase in free MPA, due to altered protein binding and the displacement of MPA from protein by MPAG [35, 43, 44]. Efficacy was not affected by low GFR in those patients who continued treatment albeit at sub-target dose. Our results confirm that cautious dosing of MS and MMF is required in renal failure. This study has not addressed whether lower doses are sufficient for disease control in renal failure; however, the increase in free MPA and MPA metabolites in renal failure would support this hypothesis.

Combined remission failure and relapse rates were significantly lower in MS patients compared with MMF patients. It is unclear whether this is a true effect of treatment or due to imbalances between groups. More MMF patients had GPA (Wegener's), which is associated with high relapse rates, and more MMF patients had refractory disease, which is associated with remission failure. Overall, our remission failure and relapse rates were higher compared with previous trials of MMF in AAV [26] and lupus nephritis [21–23]. Unlike previous trials, the majority of our patients had relapsing or refractory diseases and a few had non AAV diagnoses whose optimal treatment responses are less well established. Our efficacy rates are consistent with those observed in retrospective studies of MMF in PSV [31], as well as those achieved in uncontrolled refractory vasculitis trials of intravenous immunoglobulin [45], alemtuzumab [46] and gusperimus [47]. Notably the B-cell-depleting anti-CD20 therapy, rituximab licensed for remission induction in AAV, has been associated with remission rates of 80% in similar patient groups and, although relapses subsequently occur, further rituximab courses are effective in the majority [48].

During this trial, pre-dose MPA levels were obtained from patients achieving stable maintenance doses of study drug. We observed a trend towards higher treatment intolerance with MPA levels above 1.5 mg/L. Because 25% of patients from both groups withdrew from treatment early due to intolerance, samples were obtained from a subgroup of patients only. Interpretation of tolerability correlations was therefore limited. MMF and MS produce equivalent steady state MPA exposure (AUC) [35]; MS trough levels have been more variable and generally higher than MMF trough levels due to the delayed absorption characteristics of MS [35, 49, 50]. Our MPA levels in MMF patients were comparable to levels previously observed in autoimmunity [39] whereas MS levels were significantly lower than MMF levels despite adjustment for dose and GFR. We confirm the low predictability of MS trough levels in an autoimmune clinical setting.

Serious adverse event rates were higher in MMF patients compared with MS patients as a result of differences in hospitalizations due to active disease (MS 1 event, MMF 13 events in 7 patients). This high rate in MMF patients may largely be attributable to group imbalances with more MMF patients having refractory disease or GPA (Wegener's) with increased susceptibility to relapse or remission failure. Serious infection rates did not differ between groups and were comparable with other cohorts with longstanding disease treated with MMF [31] or therapies such as gusperimus [47] and rituximab [48]. Lower serious infection rates have been observed in trials of MMF in patients with new disease in whom prior disease damage and immunosuppression exposure is low.

Conclusion

In this trial of MS versus MMF in multi-system autoimmune disease, MS was associated with a significantly lower rate of the composite primary outcome: treatment failure and/or tolerability failure. No difference in treatment intolerance was detected; however, MS was associated with a lower treatment failure rate. Given the limitations of our study, small sample size and differences in baseline characteristics that potentially affect efficacy outcomes, larger studies are warranted to further investigate any efficacy differences between MS and MMF in patients with multi-system autoimmune disease. This trial identified that GFR was strongly associated with treatment intolerance. Future studies should include detailed assessment of MPA pharmacokinetics in different stages of chronic kidney disease.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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Authors' contribution

R.B.J. contributed to trial design, and led trial conduct and manuscript preparation. M.W. performed the statistical analyses and provided a significant contribution to manuscript writing. A.N.C. contributed to trial conduct and manuscript writing. K.G.C.S. contributed to trial design and manuscript writing. D.R.W.J. led the trial design, oversaw trial conduct and provided a significant contribution to manuscript writing. All authors read and approved the final manuscript.

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