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Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA associated vasculitis: A randomised, non-inferiority trial.

Authors

Rachel B Jones MD[1], Thomas F Hiemstra PhD[2,3], Jose Ballarin MD [4], Daniel Blockmans PhD [5], Paul Brogan[6], Annette Bruchfeld PhD[7], Maria C Cid PhD[8], Karen Dahlsveen[1], Janak de Zoysa MD[9], Georgina Espígol-Frigolé MD[8], Peter Lanyon MD[10], Chen Au Peh PhD[11], Vladimir Tesar MD[12], Augusto Vaglio MD[13], Michael Walsh MD[14], Dorothy Walsh BSCN[1], Giles Walters MD[15], Lorraine Harper PhD[16]*, David Jayne MD [2, 1] for the European Vasculitis Study Group (EUVAS)

*Drs Harper and Jayne are joint senior authors.

Affiliations

[1]Department of Renal Medicine, Addenbrooke's Hospital, Cambridge, UK

[2]School of Clinical Medicine, University of Cambridge, Cambridge, UK

[3]Cambridge Clinical Trials Unit, Addenbrooke's Hospital, Cambridge, UK

[4] Department of Nephrology, Fundación Puigvert, Barcelona, Spain

[5] Department of General Internal Medicine, University Hospitals Leuven, and Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium'

[6] University College London Great Ormond Street Institute of Child Health, and Great Ormond St Hospital NHS Foundation Trust, London, UK

[7.] Department of Renal Medicine, Karolinska University Hospital, Stockholm, Sweden

[8.] Department of Autoimmune Diseases. Hospital Clinic. University of Barcelona. Institut d'Investigacions Biomediques august Pi I Sunyer (IDIBAPS). Barcelona Spain.

[9] Renal Service, Waitemata District Health Board, Auckland, and Department of Medicine, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand.

[10.] Department of Rheumatology, Nottingham University Hospitals NHS Trust, Nottingham, UK

[11.] Department of Renal Medicine, Royal Adelaide Hospital, Adelaide, Australia.

[12.] Department of Nephrology, 1st Faculty of Medicine , Charles University and General University Hospital , Prague , Czech Republic

[13.] Department of Biomedical Experimental and Clinical Sciences "Mario Serio", University of Firenze, Firenze, Italy; Nephrology and Dialysis Unit, Meyer Children's University Hospital, Firenze, Italy

[14] Departments of Medicine and Health Research Methods, Evaluation & Impact, McMaster University, Hamilton, Canada

[15] Department of Renal Medicine, Canberra Hospital, Yamba Drive, Garran, ACT, Australia

[16] Institute of Clinical Sciences, University of Birmingham, Birmingham, UK

Address for correspondence

Prof Lorraine Harper

Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK

Email L.harper@bham.ac.uk

Tel (+44) 0121 371 3238

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Abstract

Objectives

Cyclophosphamide induction regimens are effective for ANCA-associated vasculitis (AAV), but are associated with infections, malignancies and infertility. Mycophenolate mofetil (MMF) has shown high remission rates in small studies of AAV..

Methods

We conducted a randomised controlled trial to investigate whether MMF was non-inferior to cyclophosphamide for remission-induction in AAV. 140 newly diagnosed patients were randomly assigned to MMF or pulsed cyclophosphamide. All patients received the same oral glucocorticoid regimen and were switched to azathioprine following remission. The primary endpoint was remission by 6 months requiring compliance with the tapering glucocorticoid regimen. Patients with an eGFR<15mls/min were excluded from the study.

Results

At baseline, ANCA subtype, disease activity and organ involvement were similar between groups. Non-inferiority was demonstrated for the primary remission endpoint, which occurred in 47 patients (67%) in the MMF group and 43 patients (61%) in the cyclophosphamide group (Risk Difference (RD) 5.7%, 90%CI -7.5% to19%). Following remission, more relapses occurred in the MMF group (23 patients, 33%) compared to the cyclophosphamide group (13 patients, 19%) (IRR 1.97, 95%CI 0.96 to4.23, p=0.049). In MPO-ANCA patients, relapses occurred in 12% of the cyclophosphamide group and 15% of the MMF group. In PR3-ANCA patients, relapses occurred in 24% of the cyclophosphamide group and 48% of the MMF group. Serious infections were similar between groups (26% MMF group, 17% cyclophosphamide group) (OR1.67 (95%CI 0.68 to 4.19, p=0.3).

Conclusion

MMF was non-inferior to cyclophosphamide for remission-induction in AAV, but resulted in higher relapse rate.

(Clinical trials.gov number NCT00414128)

Key words – ANCA-associated vasculitis, induction therapy, cyclophosphamide, mycophenolate, randomised trial

Key messages

What is already known

- Cyclophosphamide remains the first line induction remission treatment for AAV for many patients but is linked with infertility, infection and malignancy.
- Mycophenolate mofetil (MMF) has been shown in small studies to have high remission rates.

What does this study add

- This study is the largest to show with sufficient power that remission rates with MMF are non-inferior to pulsed cyclophosphamide but this maybe associated with a higher rate of relapse.

How might this impact on future clinical practice

- MMF induction therapy in patients at low risk of relapse, such as those with MPO-ANCA, may be a suitable alternative to cyclophosphamide.

BACKGROUND

ANCA-associated vasculitis (AAV) [1], which includes Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), are rare potentially life-threatening multisystem autoimmune diseases. They are frequently grouped together for the purpose of treatment trials given their similar initial responses to standard therapy [2, 3]. Treatment for ANCA-associated vasculitis comprises remission induction and maintenance regimens [2]. The European League Against Rheumatism (EULAR) guidelines for the treatment of AAV suggest the use of cyclophosphamide or rituximab for remission induction therapy in new-onset organ-threatening or life-threatening AAV in combination with glucocorticoids[4]. Cyclophosphamide with high dose glucocorticoids has been standard remission induction therapy for severe ANCA-associated vasculitis for over 30 years with remission rates of 80-90% [5, 6] and a current one year mortality of 10-25% [7]. However; cyclophosphamide is toxic causing infertility and malignancy. Rituximab is associated with similar remission induction rates to those achieved with cyclophosphamide and similar relapse rates over 18-24 months follow-up [8-11]. However, the biological effect of rituximab is long and variable, and rituximab has been associated with hypogammaglobulinaemia in ANCA-associated vasculitis [12]. Due to its high cost the use of rituximab is restricted in some countries[13, 14]. For non-organ threatening AAV EULAR recommends methotrexate or Mycophenolate mofetil (MMF) in combination with glucocorticoids, although the level of evidence is rated as 1B, requiring further studies[4]. Methotrexate has similar efficacy to cyclophosphamide for remission induction in non-severe ANCA-associated vasculitis, but its toxicity precludes use in renal impairment [15, 16]. Mycophenolate mofetil is an alternative oral immunosuppressant with lymphocyte selective suppressive effects with a short duration of action, can be used in renal disease and unlike cyclophosphamide is not associated with urothelial malignancy or infertility. Small studies have suggested that MMF has efficacy for remission induction in ANCA-associated vasculitis, particularly in MPO-ANCA disease [17,

18]. Understanding the role of MMF as a remission induction agent in ANCA-associated vasculitis remains important. We conducted a randomised trial of adult and paediatric patients to investigate whether MMF was non-inferior to cyclophosphamide for remission induction in new patients with ANCA-associated vasculitis.

METHODS

Study design and patients

This trial was an open-label, two group, parallel design, randomised, non-inferiority trial involving 132 adult patients from 21 sites in six countries in Europe, Australia and New Zealand, and eight paediatric patients from four sites in the UK. All patients/parents provided written informed consent; and written assent where appropriate. Inclusion in this study required a new diagnosis of active ANCA-associated vasculitis (GPA or MPA)[1] with either a positive ANCA or histologically proven disease (see protocol for full inclusion details). Patients were excluded if they were aged < 6 years, had imminently life threatening vasculitis, rapidly declining renal function or an eGFR less than 15mls/min/m^2 or had received >2 weeks of oral cyclophosphamide or MMF or more than 1 pulse of IV CYC (15mg/kg). The trial protocol is available at http://vasculitis.org/images/documents/mycyc.pdf.

Patients were allocated in a 1:1 ratio to MMF or cyclophosphamide using a concealed system of minimization by: age greater than 60 years, the planned use of additional therapy with plasma exchange or solumedrol>0.5g at randomisation, estimated glomerular filtration rate (eGFR) less than 30mls/min/m^2 or greater than or equal to 30ml/min/m^2 with an allocation probability of 0.8. Although the minimization procedure did not include site as a stratification factor, the degree of balance of treatments within the sites was reasonable (Supplementary table 1)

The trial was sponsored by Cambridge University Hospitals NHS Foundation Trust. Vifor Pharma (previously Aspreva Pharmaceuticals) provided a research grant to cover the trial and MMF costs. The trial protocol was designed by the 'MYCYC' trial steering committee, and received ethical and regulatory approval in each participating country. The trial was conducted according to the EU clinical trials directive (Directive 2001 EU/20/EC) (EUDRACT 2006-001663-33). The trial was approved by Oxfordshire Research Ethics Committee B (ref number 06/Q1605/120). Trial data is stored by the trial management committee at Addenbrooke's Hospital, UK.

Supplementary table 1

Centre	MMF N=	Cyc N=
Adelaide	1	5
Birmingham	4	6
Birmingham paediatrics		1
Cambridge	19	14
Aberdeen	1	
Alder Hey paediatrics	1	
Oxford	1	2
Auckland		2
Coventry	1	1
Barcelona	6	4
Fundacion	4	1
Germain Del Rey	1	1
Girona	1	

Belgium	7	7
Bradford	1	3
Canberra	3	4
Edinburgh	2	2
Great Ormond Street paediatrics	2	3
Hammersmith	1	
Nottingham	2	3
Nottingham paediatrics	1	
Parma	2	6
Prague	2	2
Sweden	6	2
Reading	1	1
Total	70	70

Abbreviations: MMF, mycophenolate mofetil limb; CYC, cyclophosphamide limb; N, number of participants

Treatments

After randomisation, both groups received the same oral tapering glucocorticoid regimen (prednisolone 1mg/kg/day initially, reducing to 5mg/day at the end of 6 months supplementary figure 1D). Adult patients in the MMF group received MMF 2g/day, with dose increases to 3g/day permitted for uncontrolled disease at four weeks. Patients aged less than 17 years received a body surface area based MMF dosing regimen. Patients in the cyclophosphamide group received intravenous pulsed cyclophosphamide as given in the CYCLOPS trial (15mg/kg 2-3 weekly with reductions for age and renal function) [6, 9] . All

patients were switched from their assigned study treatment to oral azathioprine 2mg/kg/day after remission had been achieved, between 3-6 months. Azathioprine with prednisolone 5mg/day was continued until study end at 18 months.

Outcomes

The primary outcome was remission by six months. Remission was defined as the absence of disease activity with a BVAS 2003 of zero on two consecutive occasions at least one month apart and adherence to the prednisolone taper. Secondary efficacy endpoints were time to remission, remission by six months irrespective of glucocorticoid adherence, progressive disease, relapse, cumulative glucocorticoid dosing, change in eGFR, Vasculitis Damage Index (VDI)[19], and ANCA positivity at six months. Planned subgroup analyses were the effect of eGFR, age and additional intravenous methylprednisolone and/or plasma exchange pre-randomisation on remission, and ANCA subtypes, on remission and relapse. Safety outcomes were serious adverse events, serious infections, ESRD, death, malignancy, cardiovascular, thromboembolic and serious disease related events. Outcomes were adjudicated by a committee blinded to study group assignment.

Assessments

Assessments were performed at 0, 1, 1.5, 3, 4.5, 6, 9, 12, and 18 months and at the time of a relapse. Relapses could only occur after an initial remission (absence of disease activity, irrespective of glucocorticoid compliance, at any time during trial follow-up). Patients who did not achieve an initial remission were excluded from relapse analyses. Relapses were defined as the recurrence or new appearance of any disease activity, as reflected by a BVAS 2003 > 0. Major relapse required the presence of one or more major BVAS items. Renal function was assessed using eGFR, calculated using the 4 variable Modified Diet in Renal Disease (MDRD) equation in adults[20] or Haycock-Schwartz formula in patients aged less

than 16 years[21]. End Stage Renal Disease (ESRD) was defined as dialysis dependence for six weeks or more without subsequent recovery of renal function. Progressive disease was defined as on-going disease activity of sufficient severity to necessitate therapy escalation with a change in immunosuppression or intravenous methylprednisolone before remission. Serious adverse events were collected as defined by the European Medicines Agency and Food and Drug Administration. ANCA negativity was determined by the reference range of the local laboratory for both indirect immunofluorescence and enzyme linked immunosorbant assays.

Statistical Analysis

The sample size estimate was based on a non-inferiority design. We assumed a remission rate of 85% with cyclophosphamide and specified a 12% absolute risk difference as the non-inferiority margin (i.e. remission rate <73%) for MMF. Using these assumptions, we calculated that 124 patients were required to meet non-inferiority for the primary remission endpoint with a power of 80%, and a significance level of 5% in a non-inferiority test[22]. Allowing for a 10% drop out rate we recruited 140 patients.

All endpoint analyses were by intention to treat with an additional pre-specified per protocol analysis of the primary endpoint. The primary and secondary remission endpoints (non-inferiority) were assessed by calculating the risk difference (RD) of remission with corresponding two-sided 90% confidence intervals, consistent with the CONSORT extension for reporting of non-inferiority trials[23]. For the primary analyses, no attempts were made to impute missing data. Data were censored at withdrawal, loss to follow-up or death. Time to event analyses of remission (non-inferiority) were performed using a Cox proportional hazards model with a hazard ratio (HR) of 0.85 as the non-inferiority margin. Relapse rates

(superiority) were compared by calculating the incidence rate ratio (relapses per patient per year) and corresponding 95% confidence interval with significance estimates derived from the binomial distribution test. For safety and other efficacy endpoints comparison of proportions was performed using the Fisher mid-p test, as recommended[24] . All continuous variables are presented as mean ± SD or median (IQR) as appropriate to their distribution, and categorical variables are presented as count (%). All analyses were conducted using Stata SE version 15 (College Station TX).

RESULTS

Patients

Between March 2007 and July 2011, 140 patients were enrolled in the study (66 adults and four children in each treatment group). The 4 children recruited to the CYC group were ages 14, 16, 14, and 15 years old and the 4 recruited to the MMF group were 10,16, 12 and 13 years old. All patients received their allocated treatment and were retained for the primary analysis. By the end of the 6 month treatment period, four in each group had died, and three in the MMF group and two in the cyclophosphamide group had been lost to follow-up or had withdrawn consent (Figure 1, Table 1). Fifty eight patients received at least 6 pulses of cyclophosphamide, of whom 23 had 7-10 pulses. Cyclophosphamide was terminated early in six (2 infection, 2 intolerance 1 ESRD, 1 no reason) and six died or withdrew from the trial prior to 3 months. The maximum dose of MMF received by patients was 2g in 76%, 6% received >2g and 18% received <2g. MMF was withdrawn due to intolerance in 4 patients due to incontinence, rash, diarrhoea, reason not specified. At 18 months 52 patients, 26 from each study group, were not receiving azathioprine. This was due to drug intolerance in 11 patients in the CYC group and 15 patients in the MMF group.

Table 1. Baseline characteristics of the patients at trial entry.

Variable	Mycophenolate mofetil group (N=70)	Cyclophosphamide group (N=70)
Age (yrs) – median (IQR)	60 (48-70)	61 (53-68)
Paediatric <18 years (%)	4 (6)	4 (6)
Male sex – no. (%)	41 (59)	33 (47)
Diagnosis – no. (%)		

GPA	47 (67)	44 (63)
MPA	23 (33)	26 (37)
ANCA – no. (%)		
PR3 or cANCA	41 (59)	42 (60)
MPO or pANCA	28 (40)	26 (37)
Negative	1 (1)	2 (3)
ANCA ELISA – no. (%)		
PR3-ANCA	40 (57)	42 (60)
MPO-ANCA	27 (39)	26 (37)
Negative	3 (4)	2 (3)
eGFR at entry, ml/min/m^2 - median (IQR)		
All patients	51 (29-92)	51 (31-79)
Patients with renal disease	47 (27-70)	46 (29-74)
Organs involvement* – no. (%)		
Renal	57 (81)	57 (81)
Lung	30 (43)	35 (50)
ENT	41 (59)	38 (54)
BVAS# – median (IQR)	19 (13-25)	18 (14-23)
CRP (mg/L) - median (IQR)	22 (7.5-52)	19 (5-83)
ESR (mm/hr) – median (IQR)	54 (31-98)	59 (33-90)
Cyclophosphamide pre-randomisation		
Patients - no. (%)	17 (24)	22 (31)
Total dose (grams) – median (IQR)	1 (0.55-1.1)	1 (0.6-1.07)
IV methylprednisolone pre-randomisation		
Patients - no. (%)	41 (59)	35 (50)

Total dose (grams) – median (IQR)	1.5 (1.5-3)	1.5 (1.5-2)
Plasma exchange pre-randomisation		
Patients - no. (%)	8 (11)	4 (6)
Total exchanges – median (IQR)	5 (5-7)	7 (6-7)

* Renal involvement is defined as one or more renal BVAS items present at entry excluding hypertension alone. Lung and ENT require one or more lung or ENT BVAS items present at entry respectively. [#]Baseline BVAS data was missing in 1 subject in the MMF group.

Primary outcome

The primary endpoint of remission with glucocorticoid compliance within 6 months occurred in 47 patients, including 1 child, (67%) in the MMF and 43 (61%), including 1 child, in the cyclophosphamide groups (Risk Difference (RD) 5.7%, 90%CI -7.5% to19%). Given the specified non-inferiority margin of -12%, the lower bound of the 90% CI of -7.5% established non-inferiority (Figure 2).

In a pre-specified analysis restricted to per-protocol treated patients, 43 remissions (74%) occurred in 58 mycophenolate patients, compared to 33 remissions (62%) in 53 cyclophosphamide patients (RD 11.9%, 90% CI -2.6% to 26.3%, non inferior) (Figure 2). There was no evidence of interaction by PR3 ANCA positivity, age, renal function and the use of additional induction therapies with the primary endpoint (Figure 2).

Secondary efficacy outcomes

Secondary efficacy outcomes are summarised in Figure 3, supplementary Table 2 and supplementary Figure 1. The time to primary remission in the MMF group (median 91 days,

IQR 44-95) was non-inferior to the cyclophosphamide group (median 87 days, IQR 42-91), since the lower bound of the 90%CI did not cross 0.85 (HR 1.27 [90%CI 0.89 to 1.79]). Remission irrespective of steroid compliance within 6 months occurred in 61 patients (87%) in the MMF and 55 (79%) in the cyclophosphamide groups (RD 8.6%, 90%CI -1.8% to 19%). Remission at any time during trial follow up irrespective of steroid compliance occurred in 63 patients (90%), including 2 children, in the MMF and 64 (92%), including 2 children, of the cyclophosphamide groups (RD -1.4%, 90%CI -9.5% to 6.6%).

Table S2. Efficacy Outcomes

	MMF group (n=70)	**CYC group (n=70)**	**Point estimates**	**Non-inferiority margin**	**Significance**
Primary endpoint					
Primary remission – no. (%)	47 (67)	43 (61)	RD 5.7%, 90%CI -7.5% to 19%	-12%	Non-inferior
Per protocol* analysis – no (%)	43/58 ()	33 (53)	RD 11.9%, 90%CI -2.6% to 26.3%	-12%	Non-inferior
Secondary endpoints					
Remission					
§Time to primary remission by (6 months)			HR 1.27, 90%CI 0.89 – 1.79, p = 0.27	0.85	Non-inferior
Remission by 6 months irrespective of steroid compliance – no. (%)	61 (87)	55 (79)	RD 8.6%, 90%CI -1.8% to19%	-12%	Non-inferior

Remission at any time irrespective of steroid compliance – no. (%)	63 (90)	64 (91)	RD -1.4%, 90%CI -9.5% to 6.6%	-12%	Non-inferior
Progressive disease – no. (%)	5 (7)	8 (11)	–	Superiority	0.56
Relapse – no. (%)	23 (33)	13 (19)	IRR 1.97, 95%CI 0.96 to 4.23	Superiority	0.049
All patients Time to first relapse			HR 2.14, 95%CI 1.07 – 4.31	Superiority	0.03 0.03
Major relapses	4 (6)	3 (4)	IRR 1.48, 95%CI 0.25–10.13	Superiority	0.63
Time to major relapse			HR 2.4, 95%CI 0.44 to 13.13	Superiority	0.31
Minor relapses	19(27)	10(14)	IRR 2.11, 95%CI 0.93–5.09	Superiority	0.053
Time to minor relapse			HR 2.09, 95%CI 0.97 to 4.5	Superiority	0.059

RD – Risk Difference; HR – Hazard Ratio; IRR – Incidence Risk Ratio.

*The per protocol analysis was performed as an additional analysis for the primary endpoint and included patients who adhered to their assigned study treatment regimen (see appendix) for the first 6 weeks of the trial and did not receive additional intravenous steroids or immunomodulatory treatments. 29 patients were excluded from the per protocol analysis (MMF 12, CYC 17). § For the time to remission analysis, remissions were defined as for the primary endpoint.

There were more relapses after remission in the mycophenolate group (23/63 patients; 4 major and 19 minor relapses) compared with the cyclophosphamide group (13/64 patients;

3 major and 10 minor relapses, IRR 1.97, 95% CI 0.96 to 4.23, p=0.049). Relapse free survival was shorter in the mycophenolate group (HR 2.14, 95% CI 1.07 to 4.31, p=0.03). A post-hoc subgroup analysis found the higher relapse rate in MMF patients was accounted for by more relapses in PR3 ANCA patients, but not MPO ANCA patients. (Supplementary Figure 2). There was no evidence that the effect of MMF on relapse differed by ANCA subtype (p=0.52 for interaction).

Remission irrespective of steroid compliance within 6 months occurred in 61 patients (87%) in the MMF and 55 (79%) in the cyclophosphamide groups (RD 8.6%, 90%CI -1.8% to 19%). Remission at any time during trial follow up irrespective of steroid compliance occurred in 63 patients (90%) in the MMF and 64 (92%) of the cyclophosphamide groups (RD -1.4%, 90%CI -9.5% to 6.6%).

Progressive disease necessitating rescue therapy before remission occurred in five patients (7%) in the MMF and eight (11%) in the cyclophosphamide groups (p=0.56). At 6 months, 26 of 65 (40%) patients in the MMF group were ANCA negative, and 21 of 65 (32%) patients in the cyclophosphamide group were ANCA negative (RR 1.23, 95%CI 0.78 to 1.96, p=0.36).

There was no statistically significant difference in cumulative glucocorticoid exposure during the trial (MMF 6194 ± 317 mg, CYC 5800 ± 234 mg, p=0.32) (Supplementary Figure 1a). Two patients in both groups progressed to ESRD and eGFR at 18 months did not differ between groups (MMF group 68±4 ml/min, cyclophosphamide group 64±4 ml/min, p=0.46) (Supplementary Figure 1b). There was no difference in disease and treatment related damage assessed by the vasculitis damage index at study end between the two groups (MMF=1, IQR 1 to 3; CYC=2, IQR 1 to 3; p=0.80).

Safety outcomes

Serious adverse events occurred in 35 in the MMF (50% patients, 73 events) and 28 in the cyclophosphamide groups (40% patients, 64 events) and are summarised in Table 2. There were no significant differences in serious infections, death, thromboembolism, malignancy or serious disease related events between the two groups.

Table 2. Serious Adverse Events

	Mycophenolate mofetil group (n=70)		Cyclophosphamide group (n=70)		Significance
	All events	Patients with ≥1 event	All events	Patients with ≥1 event	
	No.	No. (%)	No.	No. (%)	
All serious adverse events	73	35 (50)	64	28 (40)	P=0.30
Serious events by category					
Infections	29	18 (26)	16	12 (17)	P=0.30
End stage renal disease	2	2 (3)	2	2 (3)	P=1.0
Death	5	5 (7)	4	4 (6)	P=1.0

Malignancy	1	1 (1)	1	1 (1)	P=1.0
Cardiovascular	6	3 (4)	6	5 (7)	P=0.72
Disease related events	16	10 (14)	9	7 (10)	P=0.61
Thromboembolism	2	2 (3)	2	2 (3)	P=1.0

Five mycophenolate patients died (7%) (causes of death were cardiac n=1, infections n=2 and other n=2) and four cyclophosphamide patients died (6%) (causes of death were cardiac n=1, infections n=2 and other n=1) (OR 1.27 (95% CI 0.26 to 6.68, p=1.0). Median age at death was 75 years (range 73 to 82 years) in the MMF group and 83 years (range 63 to 85 years) in the cyclophosphamide group. Malignancies were liver metastases of unknown primary in a 74 year old in the mycophenolate group and a malignant melanoma in a 63 year old in the cyclophosphamide group.

Discussion

In this randomised trial of remission induction in ANCA-associated vasculitis, excluding patients on dialysis or with life-threatening disease, MMF was non-inferior to pulsed cyclophosphamide. The relatively low remission rate for the primary outcome can be attributed to the stringent requirement for adherence to glucocorticoid taper as shown by others,[8] and the higher rate of the secondary endpoint of remission irrespective of glucocorticoid adherence is consistent with previous reports where the glucocorticoid taper was not a component of the remission definition. [6, 25] Our results demonstrate that MMF represents an alternative to cyclophosphamide for remission induction in AAV. This study provides further evidence to support the EULAR guidelines on management of AAV.

Our findings of the efficacy of MMF for remission induction are consistent with previous MMF induction studies in AAV[18, 26, 27]. After remission, relapses occurred earlier and more frequently in the MMF group (33%) compared to the cyclophosphamide group (19%). Although this was a secondary outcome and the trial was not designed or powered to detect differences in relapse rate, this observation is consistent with the increase in early relapses observed with methotrexate compared to cyclophosphamide[15], higher relapse risk with lower cumulative cyclophosphamide exposure[28], and the higher rate of relapse with MMF compared to AZA when used for maintenance therapy[29]. While treatment with MMF may be associated with a higher risk of relapse compared to pulsed cyclophosphamide, this increased risk may be acceptable to avoid the potential adverse effects of cyclophosphamide particularly when the baseline risk of relapse is low (e.g. in patients that are MPO-ANCA positive) or if rituximab is unavailable.

The use of MMF alongside standard dose glucocorticoids offers advantages over cyclophosphamide in terms of fertility preservation for younger patients and potentially

lower malignancy rates in elderly populations at greatest risk[30]. Unlike rituximab (an approved alternative to cyclophosphamide for severe ANCA-associated vasculitis), MMF is an oral drug, has a short duration of action, and unlike methotrexate, can be used in moderate or severe renal disease and was not associated with slower time to remission compared to cyclophosphamide [15]. However, there were no differences in this study in the number of adverse events between the two groups.

Our trial has several notable strengths. It is the largest randomised trial in AAV to assess the use of MMF for remission induction. Patients were recruited from 21 countries, and the trial cohort was representative of other trial populations in AAV. This is the first randomised trial in AAV to include children, although the small number of paediatric participants (n=8) limits the inferences we might draw concerning relative efficacy of MMF in this population. The primary endpoint was achieved in 1 of 4 paediatric patients in both CYC and MMF groups and response rates were similar in the MMF and CYC groups in children. Compliance was a contributory factor to the lower remission rate in children, and because of the small sample size we have not drawn conclusions of efficacy in this subpopulation.

The strengths of our trial should be viewed against its limitations. The trial was not blinded, although the similar rates of glucocorticoid adherence and exposure, progressive disease, rescue therapy requirement, ANCA negativity and the rates of ESRD is reassuring. Treating clinicians were allowed to include plasma exchange or additional solumedrol at entry; however there were no differences in additional treatments used between the two groups. The short follow up of 18 months in this study may have reduced the ability to detect the true effect on relapse and malignancy rates in the longer term. It should be noted in another study MMF was inferior to azathioprine for remission maintenance after cyclophosphamide induction, with more relapses in the MMF group, [29]. Following remission induction all

patients in our trial received azathioprine and glucocorticoid maintenance therapy. There is limited evidence for using azathioprine as induction therapy in AAV. It has been used in addition to corticosteroids for newly diagnosed non-severe eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis , or polyarteritis nodosa, however the addition of azathioprine in these patients did not improve remission rates or reduce relapse [31].

Since initiation of the trial, it has become common to use rituximab as an alternative to cyclophosphamide induction therapy, which may question the use of MMF as an alternative induction therapy. However, rituximab is expensive and its use is restricted in many countries, for example in New Zealand treatment of patients with MPO-ANCA vasculitis must first have failed with cyclophosphamide or MMF[14] prior to rituximab use. Alternative effective low cost induction therapies maybe required in some cases.

This study provides evidence that MMF is a potential alternative to cyclophosphamide for remission induction in non-life threatening, AAV, particularly in patients with low predicted relapse risk, such as the elderly that are MPO positive. With increasing remission induction treatment options for AAV, stratified treatment approaches are indicated in order to optimise long term outcomes.

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Competing Interests

RJ: consulting for ChemoCentryx. Academic secondment with GlaxoSmithKline 2011–2013.

US: consulting for Genentech/Roche. PAM: Consulting for Actelion, Alexion, Bristol Myers Squibb, ChemoCentryx, Genzyme/Sanofi, GlaxoSmithKline, Genentech/Roche, PrincipioBio. Research support from Actelion, Bristol Myers Squibb, Celgene, ChemoCentryx, Genentech/Roche, GlaxoSmithKline. DJ: consulting for Alexion, ChemoCentryx, Genzyme/Sanofi, GlaxoSmithKline, Genentech/Roche, and Takeda. Research support from ChemoCentryx, Genentech/Roche, Genzyme/Sanofi, Medimmune, and GlaxoSmithKline.

LH: consulting for ChemoCentryx, honorarium Roche.

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Figure legends

Figure 1. Randomization and inclusion in the analysis at 18 months

Figure 2. Absolute risk ratio for the primary remission endpoint, per-protocol and sub-group analyses.

The lower bound 90% CI did not cross the non-inferiority margin of 12% for the primary end-point and per protocol analyses demonstrating non-inferiority. The lower bound 90% CI only crossed the non-inferiority margin for patients with GFR<30ml/min but the upper-bound 90%CI exceeded 0. This would be described as 'inconclusive' and given this is a secondary analysis of a sub-group we are unable to draw any inference from this other than the p value for interaction being non-significant. The diamonds represent the absolute risk ratio, horizontal black lines represent 90% confidence intervals. The left side of blue shaded area represents the lower limit of non-inferiority margin (-12%).

Figure 3. Remission and relapse

a. Time to primary remission

Primary remission was remission with no disease activity and glucocorticoid protocol compliance. Analysis was censored at the first of the following events; remission (first BVAS of zero), six month study visit, withdrawal or death.

b. Time to first relapse

Relapse could only occur after an initial remission. Remissions for this analysis are not restricted to the first 6 months of follow-up, but represent remissions occurring at any time point after randomisation irrespective of glucocorticoid compliance. Time to first relapse was significantly shorter in the mycophenolate mofetil group.

Figure S1.

A. Cumulative steroid exposure

Boxes represent median (IQR), whiskers represent the nearest adjacents (nearest value to 1.5 times the IQR from the median). Dots represent outliers.

B. Change in glomerular filtration rate

Data points represent individual values for change from baseline eGFR (ml/min/m^2) over actual time. Lines represent the fitted linear regression values of change in eGFR over time.

C. Vasculitis damage index

The figure shows individual VDI values over time for the two groups. Scatter plots show individual values with jitter in both axes for clarity. Lines represent the fitted quadratic regression lines for VDI over time.

D. Steroid Taper

The figure shows the protocolised and actual steroid tapers within each study group. The black line represents the protocolised dose by weight (calculated as mean weight of the entire trial population x 1 mg/kg) and the stratified lines represent per treatment group equivalents (mean doses). This has been restricted to the first 6 months consistent with the primary outcome.

Figure S2

c. Time to relapse stratified by ANCA-PR3 and ANCA-MPO subtypes

More relapses occurred in the MMF group than the cyclophosphamide group. A post-hoc subgroup analysis found the higher relapse rate in MMF patients was accounted for by more relapses in PR3 ANCA patients, but not MPO ANCA patients. However, the study was not designed or powered to detect differences in relapses rates. There was no evidence that the effect of MMF on relapse differed by ANCA subtype (p=0.52 for interaction)