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

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Word Count

235 abstract, 2679 text

Acknowledgements

Sponsorship for this trial was provided by Cambridge University Hospitals NHS Foundation Trust. Funding for this trial and the cost of the mycophenolate mofetil was provided in the form of a research grant from Vifor Pharma (previously Aspreva Pharamaceuticals). We are very grateful to the trial writing committee for blinded data adjudication, and to Dr Pani Gopaluni and Dr Mark McClure for independent data adjudication. We are also grateful to Dr Afzal Chaudhry for the trial database design, all the trial investigators, sub-investigators, research nurses, and all the patients who participated in this study. Support was also provided by the Cambridge Biomedical Research Centre. PB acknowledges support from the Great Ormond St Hospital Clinical Research Facility and Great Ormond St Biomedical Research Centre, and Great Ormond St Hospital Children's Charity.

Abstract

Introduction

Cyclophosphamide induction regimens are effective for ANCA-associated vasculitis, with remission rates of 80-90%. However, cyclophosphamide is associated with malignancies and infertility. Mycophenolate mofetil has been associated with high remission rates in small studies of ANCA-associated vasculitis.

Methods

We conducted a randomised controlled trial to investigate whether mycophenolate mofetil was non-inferior to cyclophosphamide for remission induction in ANCA-associated vasculitis. 140 newly diagnosed patients were randomly assigned to mycophenolate mofetil or intravenous 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.

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 mycophenolate mofetil group and 43 patients (61%) in the cyclophosphamide group (RD 5.7%, 90%CI -7.5%–19%). Following remission, more relapses occurred in the mycophenolate mofetil group (23 patients, 33%) compared to the cyclophosphamide group (13 patients, 19%) (IRR 1.97, 95%CI 0.96–4.23, p=0.049). Relapses in the mycophenolate mofetil group

were more frequent in patients with PR3-ANCA (48%) than MPO-ANCA (15%). Serious infections were similar between groups (26% mycophenolate mofetil group, 17% cyclophosphamide group) (OR1.67 (95%CI 0.68 to 4.19, p=0.3).

Conclusion

Mycophenolate mofetil was non-inferior to cyclophosphamide for remission induction in ANCA-associated vasculitis, but was associated with more frequent relapse. (Clinical trials.gov number NCT00414128)

Background

ANCA-associated vasculitis{Jennette, 2013 #4232}, 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{Mukhtyar, 2009 #4233;Hellmich, 2007 #3076}. Treatment for ANCA-associated vasculitis comprises remission induction and maintenance regimens{Mukhtyar, 2009 #4233} (Mukhtyar 2009). 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%{Jayne, 2009 #3435;de Groot, 2009 #3239} and a current one year mortality of 10-25%{Flossmann, 2011 #3648}. However; cyclophosphamide is toxic causing infertility and malignancy. Methotrexate has similar efficacy to cyclophosphamide for remission induction in non-severe ANCA-associated vasculitis, but is associated with

a high relapse rate and its toxicity precludes use in renal impairment{de Groot, 2005 #2758} {Faurschou, 2012 #4234}. Rituximab, is associated with similar remission induction rates to those achieved with cyclophosphamide; and similar relapse rates over 18-24 months follow-up{Stone, 2010 #3538;Jones, 2010 #3549;Specks, 2013 #4235;Jones, 2015 #4240}. However, the biological effect of rituximab is long and variable, and rituximab has been associated with hypogammaglobulinaemia in ANCA-associated vasculitis{Roberts, 2015 #4236}. Mycophenolate mofetil (MMF) is an alternative oral immunosuppressant with lymphocyte selective suppressive effects which is associated with similar remission rates to cyclophosphamide in lupus nephritis {Appel, 2009 #4237}. Mycophenolate has 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{Han, 2011 #4239;Hu, 2008 #3011} Understanding the role of MMF as a remission induction agent in ANCA-associated vasculitis is therefore 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){Jennette, 2013 #4232} 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. The trial protocol is available at http://www.vasculitis.org.

Patients were randomised in a 1:1 ratio to MMF or cyclophosphamide. Randomisation was stratified according to: age, the planned use of additional therapy at randomisation, estimated glomerular filtration rate (eGFR) less than 30mls/min/m^2 or greater than or equal to 30ml/min/$m^{2.}$

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). Trial data is stored by the trial management committee at Addenbrooke's Hospital, UK.

Treatments

Before enrolment patients were permitted a maximum of two weeks prior treatment with cyclophosphamide or MMF and a maximum of 3g of intravenous methylprednisolone and/or plasma exchange. 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, see appendix). 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 (see appendix). Patients in the cyclophosphamide group received a validated regimen of intravenous cyclophosphamide{de Groot, 2009 #3239}{Jones, 2010 #3549} (see appendix). 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.

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. Remission, for the primary endpoint, was defined as the absence of disease activity with a BVAS 2003 of zero on two consecutive occasions at least one month apart, and with compliance with glucocorticoid dosing according to the protocol within the same disease free period. A secondary remission endpoint was defined as remission by six months irrespective of glucocorticoid adherence. 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. 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 (see appendix). Renal function was assessed using eGFR, calculated using the 4 variable Modified Diet in Renal Disease (MDRD) equation in adults{Levey, 1999 #2899} or Haycock-Schwartz formula in patients aged less than 16 years{Haycock, 1978 #4241}. End Stage Renal Disease (ESRD) was defined as dialysis dependence for six weeks or more without subsequent recovery of renal function. 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.

Outcomes

The primary outcome was remission by six months. 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){Exley, 1997 #3837}, 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.

Statistical Analysis

The sample size estimate was based on a non-inferiority design, that assumed the remission rate with MMF would be the same or higher than that seen with cyclophosphamide (i.e. truly non-inferior to cyclophosphamide), similar to that observed in lupus nephritis{Appel, 2009 #4237}. We assumed a remission rate of 85% with cyclophosphamide and specified a 12% absolute risk difference as the non-inferiority margin, based on the assumption that lower proportions of patients in remission at six months would be associated with worse clinical outcomes. Using these assumptions we calculated that 124 patients were required to meet non-inferiority for the primary remission endpoint{Makuch, 1978 #4242} and 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. 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. For safety and other efficacy endpoints comparison of proportions was performed using Fisher's exact test. 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). 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).

Primary outcome

The primary endpoint of remission with glucocorticoid compliance within 6 months occurred in 47 patients (67%) in the MMF and 43 (61%) in the cyclophosphamide groups (Absolute Risk Reduction (ARR) 5.7%, 90%CI -7.5%–19%). Given the specified 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 (see appendix), 43 remissions (74%) occurred in 58 mycophenolate patients, compared to 33 remissions (62%) in 53 cyclophosphamide patients (ARR 11.9%, 90% CI -2.6%–26.3%, non inferior) (Figure 2). There was no evidence of interaction of 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 1 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, HR 1.27 [90%CI 0.89–1.79, p=0.27]).

Remission irrespective of steroid compliance within 6 months occurred in 61 patients (87%) in the MMF and 55 (79%) in the cyclophosphamide groups (ARR 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%–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 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 – 4.31, p=0.03).

In a subgroup analysis by ANCA subtype, 19 of 37 PR3-ANCA positive patients in the mycophenolate group relapsed, compared with 10 of 37 PR3-ANCA positive patients in the cyclophosphamide group (IRR 2.3, 95%CI 1.03 to 5.58, p=0.03). In MPO-ANCA positive patients, 4 relapses occurred in 25 patients in the mycophenolate mofetil group, and 3 relapses in 26 patients in the cyclophosphamide group (IRR 1.35, 95%CI 0.23 to 9.24, p=0.71).

There was no 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 (mycophenolate mofetil 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=0.8).

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 was no difference in serious infections, death thromboembolism, malignancy or serious disease related events between the two groups.

Discussion

In this randomised trial of MMF versus cyclophosphamide for remission induction in severe ANCA-associated vasculitis, we demonstrated non-inferiority with MMF for

the primary remission endpoint requiring both absence of disease activity and compliance with glucocorticoid taper by both intention to treat and per protocol analyses. 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,{Stone, 2010 #3538} and the higher rate of the secondary endpoint of remission irrespective of glucocorticoid adherence is equally consistent with previous reports where glucocorticoid taper was not rigorously enforced. {Jayne, 2003 #2377}{de Groot, 2009 #3239} We did not identify an interaction for the primary endpoint with age > 60 years, GFR < 30ml/min, the use of additional induction therapy or with PR3-ANCA positivity. Our results demonstrate that MMF represents a viable alternative to cyclophosphamide for remission induction in AAV.

Our findings of comparable efficacy of MMF for remission induction compared to cyclophosphamide are consistent with previous MMF induction studies in AAV. However, it is notable that MMF was not superior to azathioprine for remission maintenance after cyclophosphamide induction, with numerically more relapses in the MMF group. {Hiemstra, 2010 #3637} Following remission induction all patients in our trial received azathioprine and glucocorticoid maintenance therapy. After remission, relapses occurred earlier and more frequently in the MMF group (33%) compared to the cyclophosphamide group (19%). This observation is similar to the increases in early relapses observed with methotrexate compared to cyclophosphamide{de Groot, 2005 #2758} as well as higher relapses with lower cumulative cyclophosphamide exposure{Harper, 2012 #3979}. Subgroup analyses revealed proportionally greater relapses in MMF patients with PR3-ANCA (48%) compared to MPO-ANCA (15%). Despite the lower background relapse risk for the

MPO-ANCA subgroup, the similarity in relapse rates between the two induction agents supports the hypothesis that MMF might be a valid alternative induction agent for MPO-ANCA. This hypothesis requires further investigation.

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{Hellmich, 2006 #4243}. 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 {de Groot, 2005 #2758}.

Our trial has several notable strengths. It is the first 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, and although the small number of paediatric participants (n=8) limit the inferences we might draw concerning relative efficacy of MMF in this population, inclusion of these patients increase the generalisability of these results and provide much needed data on treatment of childhood AAV. Further, the toxicity of cyclophosphamide makes MMF particularly attractive in the paediatric population.

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. Second, although our trial was relatively large for a rare disease, the inferences drawn from all subgroup analyses for the primary endpoint, and all secondary analyses, can only be viewed as exploratory.

Death in ANCA-associated vasculitis is strongly associated with ESRD and older age. In this trial mortality was similar between groups (7% MMF, 6% cyclophosphamide groups) and similarly low compared to other trials excluding severe renal disease{Jayne, 2003 #2377}{de Groot, 2005 #2758}{de Groot, 2009 #3239}. Serious adverse event rates and serious infection rates did not differ between groups. Improved short term safety with MMF was not demonstrated {Appel, 2009 #4237}{Ginzler, 2005 #4247}.

In summary we observed non-inferiority with MMF compared to cyclophosphamide for remission induction of AAV alongside a standard high dose glucocorticoid tapering regimen. Relapses were higher in the MMF group, most notably in the PR3-ANCA patient subgroup, highlighting the importance of initial induction regimen on subsequent relapse risk.

Our results suggest that with standard high dose glucocorticoids, MMF is a potential alternative to cyclophosphamide for remission induction in non-life threatening, ANCA-associated vasculitis. With increasing remission induction treatment options for AAV, stratified treatment approaches are indicated in order to optimise long term outcomes.

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Table and 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 subgroup analyses

Figure 3. Remission and relapse

a. Time to primary remission

b. Time to first relapse

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

Table 1. Baseline characteristics of the patients at trial entry

Table 2. Serious adverse events

Supplementary Figure 1. Other secondary outcomes

a. Glucocorticoid dosing

c. Glomerular filtration rate

b. Vasculitis Damage Index

Supplementary Table 1. Summary of efficacy outcomes

Tables and Figures

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

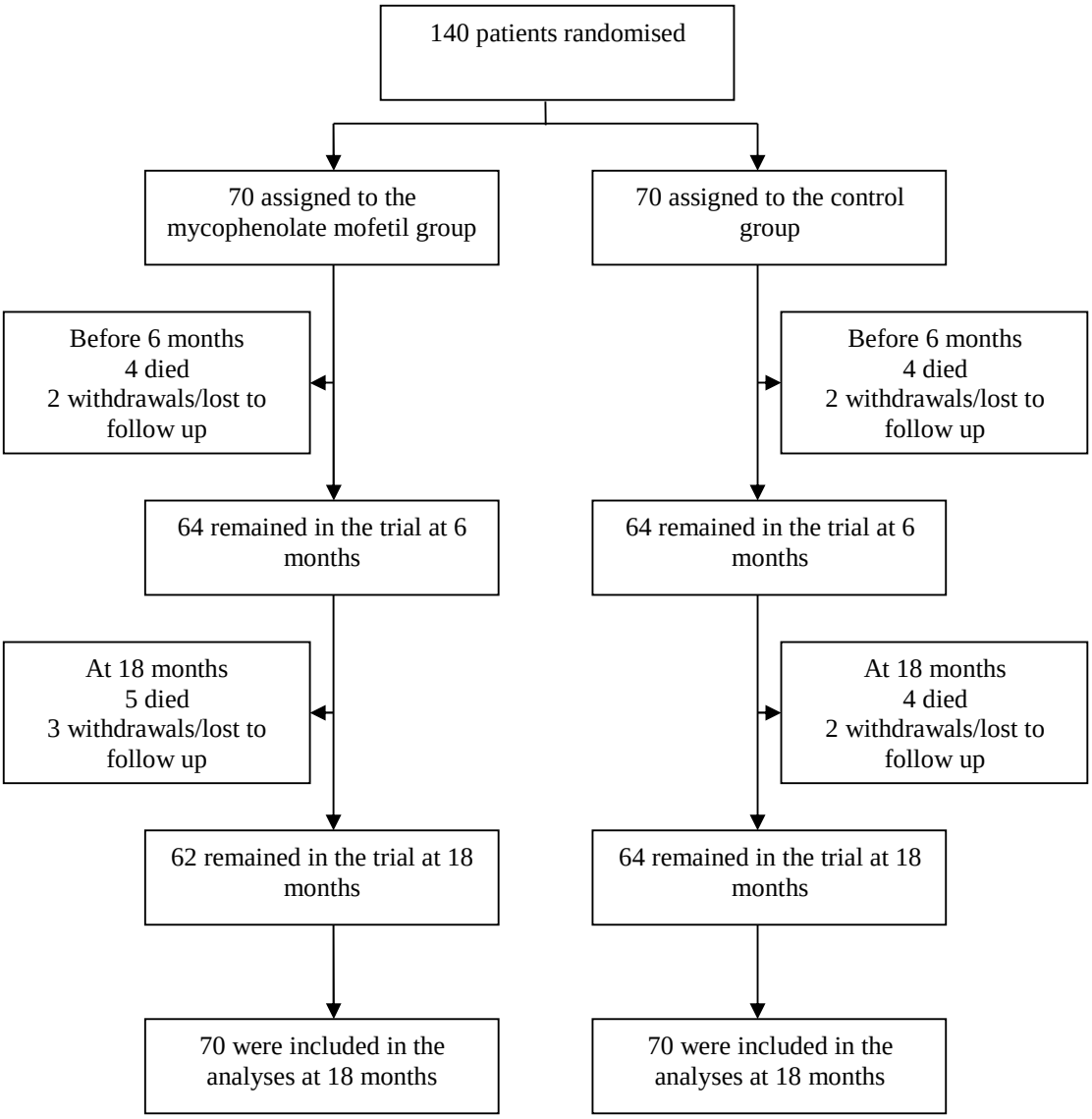
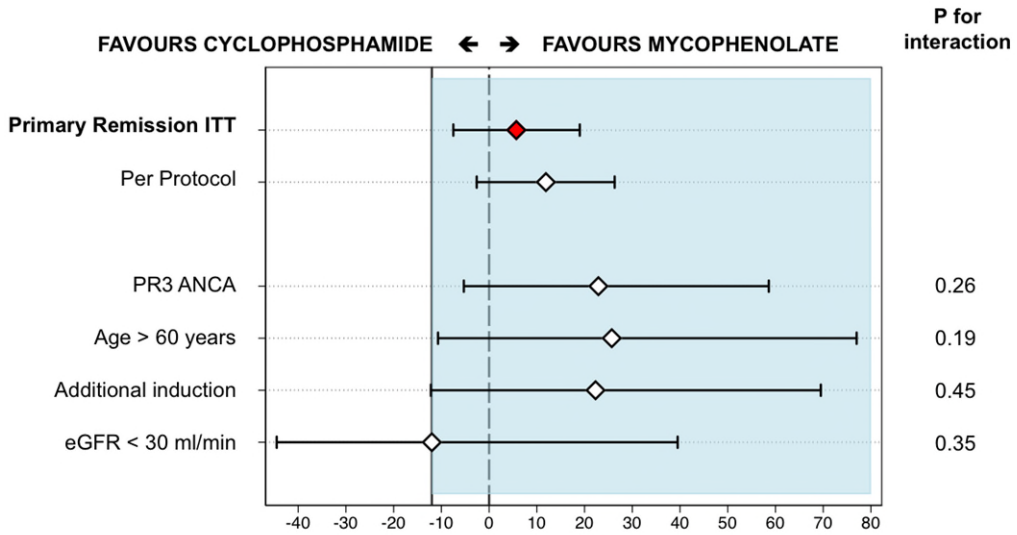


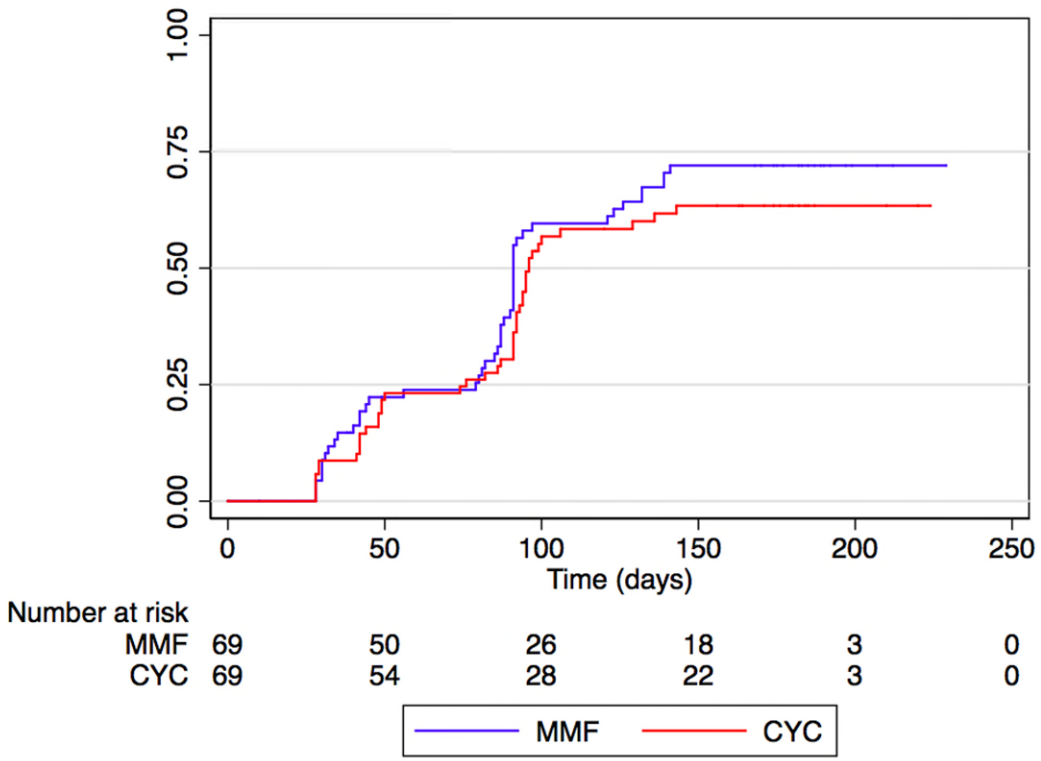
Figure 2. Absolute risk ratio for the primary remission endpoint, per-protocol and sub-group analyses



The 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%).

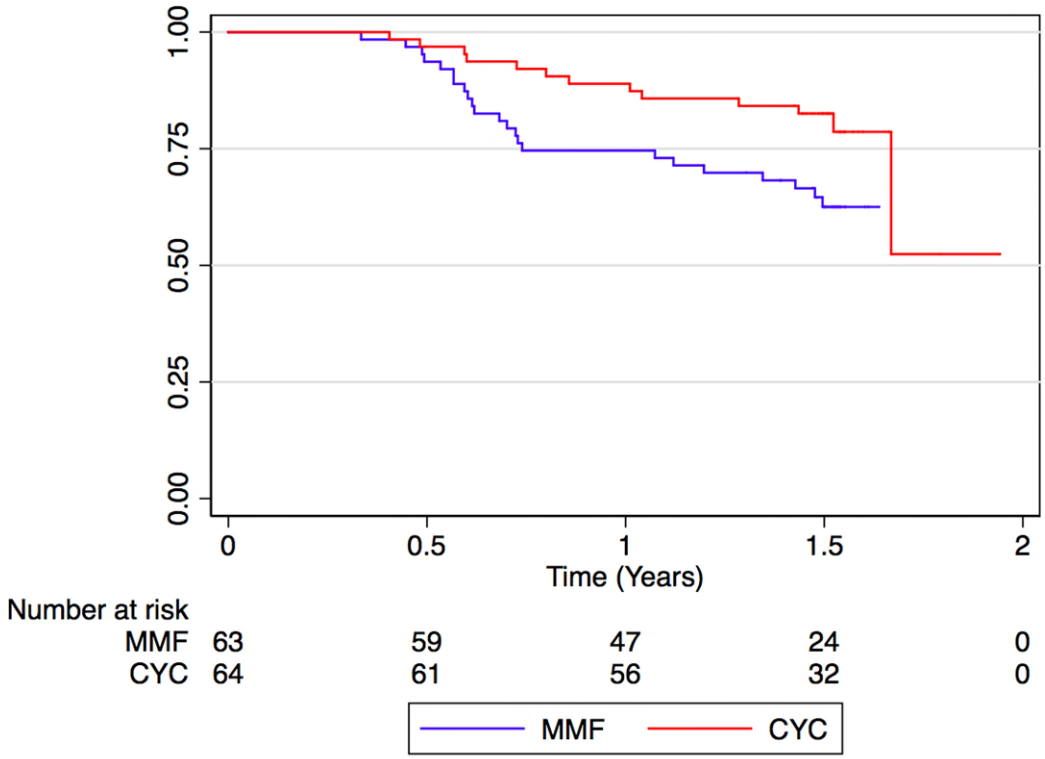
Figure 3. Remission and relapse

a. Time to primary remission



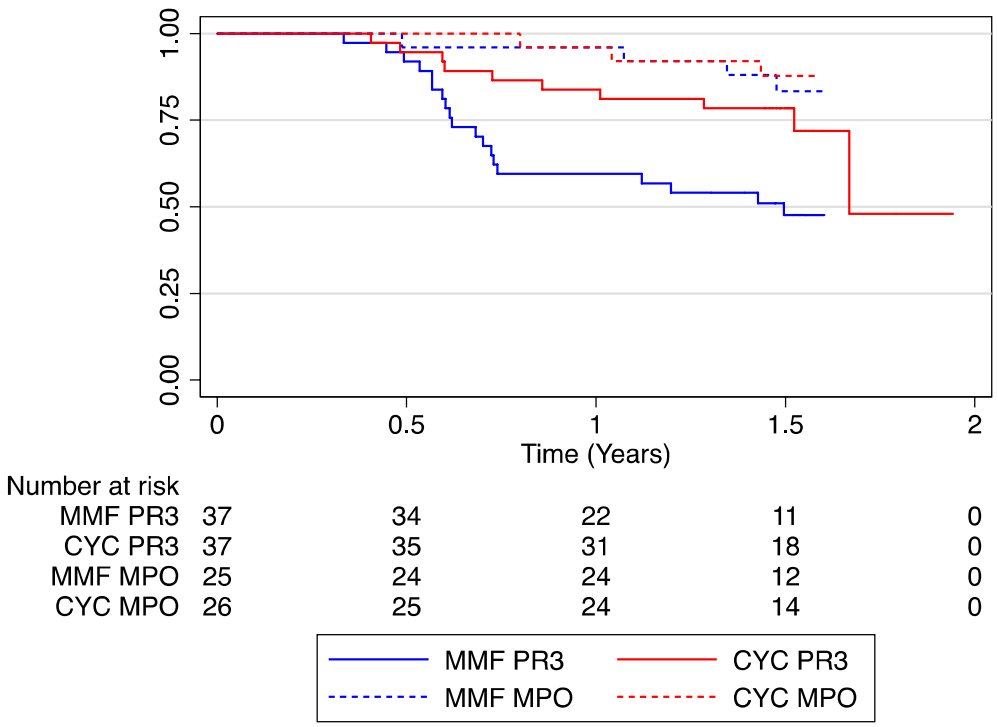
Primary remission was remission with no disease activity and glucocorticoid protocol compliance. Analysis was censored at the first of the following events; remission (first BVAS of zero), six month study visit, withdrawal or death.

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 quicker in the mycophenolate mofetil group.

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.

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 mycophenolate mofetil group.

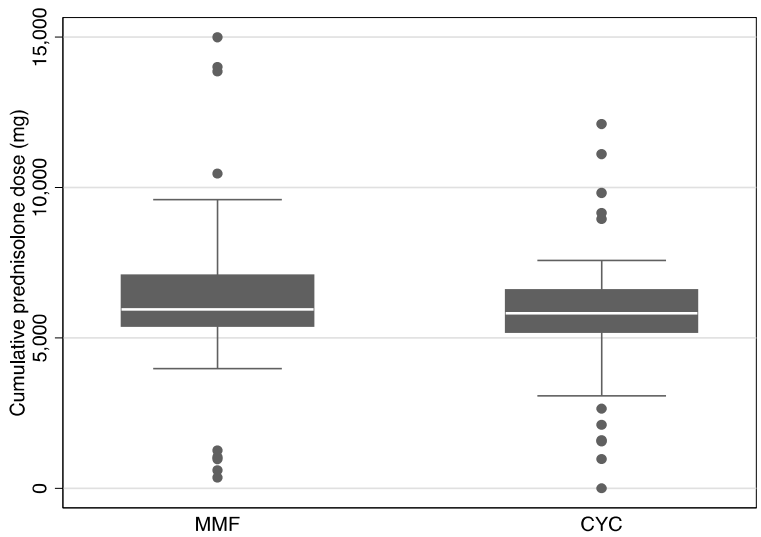
Table 2. Serious Adverse Events

	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 (0.26 to 6.68, p=1.0). Median age at death was 75 years (range 73 to 82 years) in the mycophenolate 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

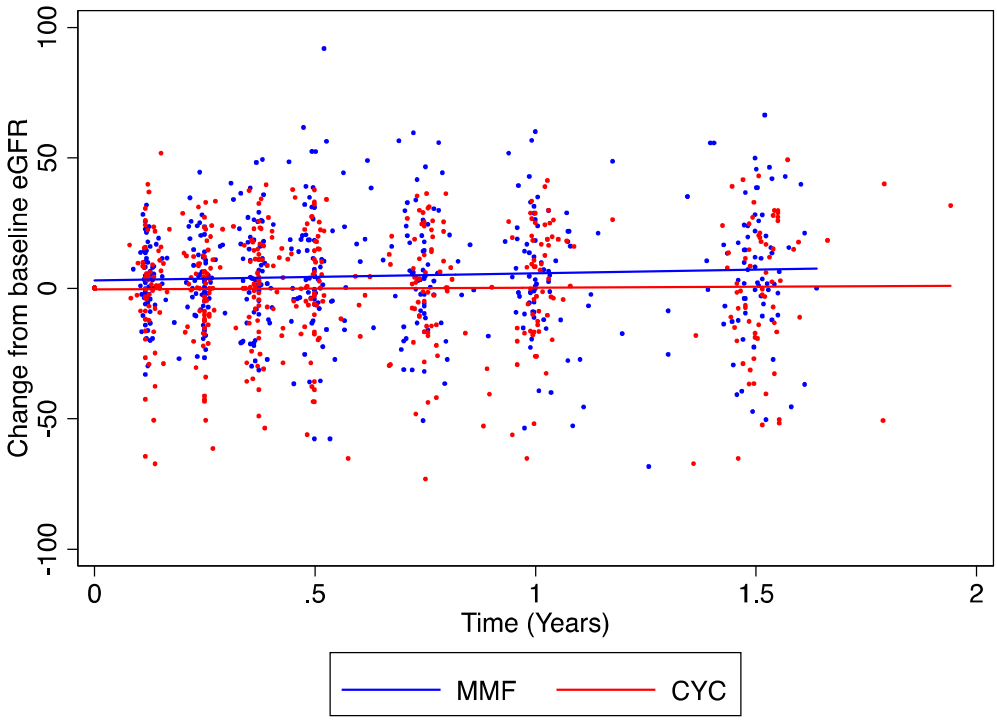
Supplementary Figure 1.

A. Cumulative steroid exposure



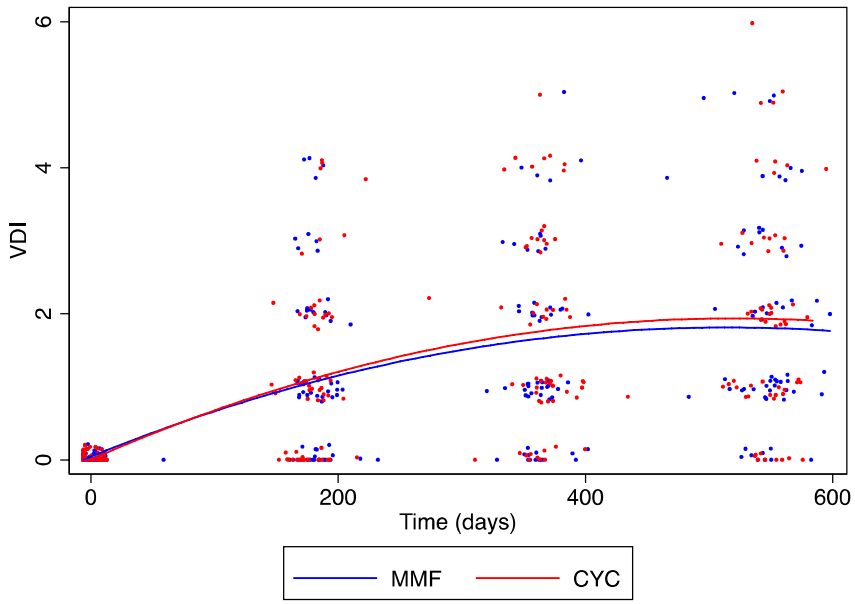
Boxes represent median (IQR), whiskers represent the nearest adjacents (nearest value to 1.5 times the IQR from the median). Dots represent outliers.

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.

Supplementary table 1. 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)	ARR 5.7%, 90%CI -7.5% to 19%	-12%	Non-inferior
Per protocol* analysis – no (%)	43/58 ()	33 (53)	ARR 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. (%)	63 (90)	56 (80)	RD 10%, 90%CI -2%–22%	-12%	Non-inferior
Remission at any time irrespective of steroid compliance – no. (%)	63 (90)	64 (91)	RD -1.4%, 90%CI -9.5%–6.6%	-12%	Non-inferior
Progressive disease – no. (%)	5 (7)	8 (11)	–	Superiority	0.56
Relapse – no. (%)				Superiority	
All patients	23 (33)	13 (19)	IRR 1.97, 95%CI 0.96–4.23		0.049
Time to first relapse			HR 2.14, 95%CI 1.07 – 4.31		0.03
PR3 positive at entry	19/40 (48)	10/42 (24)	IRR 2.31, 95%CI 1.03–5.58		0.029
MPO positive at entry	4/27 (15)	3/26 (12)	IRR 1.35, 95%CI 0.23–9.24		0.71
Major relapses	4 (6)	3 (4)	IRR 1.48, 95%CI 0.25–10.13		0.63
Time to major relapse			HR 2.4, 95%CI 0.44–13.13		0.31
Minor relapses	19(27)	10(14)	IRR 2.11, 95%CI 0.93–5.09		0.053
Time to minor relapse			HR 2.09, 95%CI 0.97–4.5		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.