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Mycophenolate mofetil versus cyclophosphamide for remission induction in childhood polyarteritis nodosa: An open label, randomised, Bayesian, non-inferiority trial.

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Abstract

Objective

Cyclophosphamide (CYC) is used in clinical practice off-label for induction of remission of childhood polyarteritis nodosa (cPAN). Mycophenolate mofetil (MMF) might offer a less toxic alternative: we explored their relative effectiveness in a randomised controlled trial (RCT).

Methods

International, open-label, Bayesian, RCT investigating the relative effectiveness of MMF and CYC for remission induction in cPAN. Eleven newly-diagnosed patients were randomised (1:1) to MMF or intravenous-CYC; all received the same glucocorticoid regimen. The primary endpoint was remission within 6-months whilst compliant with glucocorticoid taper. Bayesian distributions for remission rates were established *a priori* for MMF and CYC by experienced clinicians, and updated to posterior distributions on trial completion.

Results

Baseline disease activity/features were similar between groups. The primary remission endpoint occurred in 4/6 patients (67%) in the MMF group and 4/5 patients (80%) in the CYC group. Time to remission was shorter in the MMF group (median 7.4 weeks versus 17.5 weeks for CYC). No relapses occurred in either group within 18-months. Two serious infections were probably related to MMF. Physical and psychosocial quality-of-life scores were superior in the MMF group compared to CYC at 6-and 18-months. Combining the prior expert opinion with results from MYPAN provided posterior estimates of remission of 71% (90% CrI 51-83%) for MMF; and 75% (90% CrI 57-86%) for CYC.

Conclusion

Taking the prior opinion and the study results together, rates of remission induction in cPAN on MMF and CYC are similar, and MMF might be associated with better health-related quality of life than CYC.

Keywords: Polyarteritis nodosa; Child; Randomised controlled trial; Bayesian; Mycophenolate mofetil; Cyclophosphamide.

Background

Polyarteritis nodosa (PAN) is a necrotising vasculitis causing aneurysmal nodules of medium-sized arteries. [1 2] Childhood PAN (cPAN) is exceptionally rare with prevalence around 1/million children.[1 3] Peak onset of cPAN is 7–11 years, with no sex bias.[4 5] Features include constitutional upset, vasculitic rash, myalgia, abdominal pain and arthropathy; but any organ system can be affected.[2 4 5] The aetiology of cPAN remains unknown. [6 7] In 2014, a monogenetic form was described, caused by deficiency of adenosine deaminase 2 (DADA2). [8 9 10 11]

Untreated, mortality was historically close to 100% within months of disease-onset;[12 13] with aggressive immunosuppression mortality is as low as 4%.[4] Cyclophosphamide (CYC) has been used off-label for over 40-years for treating PAN,[14-17] and is still recommended for induction of remission of cPAN, although never studied in a paediatric randomised controlled trial (RCT).[12] Avoidance of CYC in children is desirable if alternatives exist since adverse reactions associated with CYC include infertility and malignancy.[18]

Mycophenolate mofetil (MMF) is an alternative immunosuppressant with lymphocyte selective suppressive effects which is associated with similar remission rates to CYC in lupus nephritis,[19] and ANCA associated vasculitis (AAV).[20] MMF is not associated with urothelial malignancy or infertility and is used off-label in paediatrics.

We hypothesised that MMF may be non-inferior to CYC for induction of remission of cPAN and may be a less toxic alternative. The aim of MYPAN was therefore to investigate the relative effectiveness of MMF and CYC for remission induction in cPAN. It is infeasible to conduct a conventional, definitive phase III study in cPAN due to its rarity. We therefore opted for a Bayesian approach to assessment of the relative efficacy of MMF and CYC. This was a two-stage process. Firstly, a robust 2-day elicitation process was conducted to quantify clinical opinion in the light of results of a trial in adults (MYCYC).[20] Results of this are published elsewhere.[21] Stage 2 was to conduct a RCT (the MYPAN trial: MYcophenolate for cPAN), and use these data to further quantify the relative effectiveness of each treatment for remission induction in newly-diagnosed cPAN.

Methods

Study design and patients

MYPAN was an international multi-centre, randomised, controlled prospective open label trial comparing MMF with IV CYC for remission of cPAN **(Figure 1)**. The trial adopted a Bayesian non-inferiority design (non-inferiority margin 10%). Children were randomised 1:1 to receive either MMF (1200 mg/m^2/day, max 1g bd)[12 22], or a standard IV CYC regimen[12] via a secure web-based tool generated centrally by the Liverpool Clinical Trials Centre (LCTC), University of Liverpool, UK. Minimisation variables for randomisation were planned additional therapy at entry with methylprednisolone > 15mg/kg (Yes/No); and plasma exchange at trial entry (Yes/No). Treatment allocation prior to randomisation was concealed from recruiting clinicians. Both arms of the trial received the same protocoled glucocorticoids. The full protocol is available as a supplement **(MYPAN protocol V4.0).**

Inclusion criteria were: age at screening ≥ 4 and ≤ 18 years; new-onset (within 3-months of screening) cPAN classified according to the EULAR/PRINTO/PRES criteria;[2 23] active vasculitis of any major organ; or three or more minor Paediatric Vasculitis Activity Score (PVAS) items (**Table S1**);[24] and written informed consent and assent for study participation.

Exclusions were children who did not fulfil classification for cPAN; alternative diagnoses; chronic infection; previous reactions to one of the study medications; immunodeficiency; or malignancy. Genetic screening of *ADA2* was offered as routine workup (i.e. outside the protocol).

The trial was sponsored by University College London and coordinated by the LCTC. The protocol gained favourable opinion from the Multicentre Research Ethics Committee in the UK, and from relevant ethics committees for each participating centre internationally. The study abided by the principles of the World Medical Association Declaration of Helsinki (2013). Patient and public involvement informed the design of the protocol and patient facing trial documents. Data was stored by the LCTC. Centres were identified among members of the Paediatric Rheumatology International Trials Organisation (PRINTO, www.printo.it).[25]

Treatments

Participants received 18-months (72 weeks) treatment comprising 3-6 months induction therapy (oral MMF or IV CYC, 1: 1 randomisation); followed by 12-15 months oral azathioprine (AZA) maintenance-therapy **(Figure 1)**. Both arms of the trial received tapering glucocorticoids (see later). Prophylaxis with sulfamethoxazole/trimethoprim was mandated until week-24, unless allergic. Trial treatment ended after 18-months (72 weeks).

MMF (CellCept) was given until disease remission was achieved at 3-6 months. The starting dose was 600 mg/m²/day (maximum 1g/day) for the first week, thereafter 1200 mg/m²/day, maximum 2g/day, in two divided doses.[12 22 26]

CYC was given at weeks 0, 2, 4 and then every 3 weeks until remission was achieved (maximum 10 IV-doses, minimum 6 doses; **Table S2**). The first dose was 500 mg/m^2, thereafter 750mg/m^2, with maximum dose of 1.2g.[12] MESNA and IV-fluids were administered as per local practice. CYC could be stopped after a minimum of 6 doses provided the patient was in remission.

Oral AZA (2 mg/kg/day, maximum 200 mg/day)[12 26] was commenced the day after stopping MMF; or 10-14 days after the last IV-CYC dose.

All patients received prednisolone starting at 1 mg/kg/day (maximum 80 mg), weaning to 0.1 mg/kg/day by 6-months (24 weeks), and to 0.05-0.075 mg/kg by 9-months (36 weeks; **Table S3**). Intravenous methylprednisolone could also be given at entry (maximum 30 mg/kg for 3-doses, or 3g total) at the investigator's discretion.

Principal investigators recorded medications taken by the patient on a medication clinical research form at face to face follow up protocoled trial visits as specified below. In addition, patients completed a diary of medication taken as an outpatient which allowed careful cross-checking of the accuracy of medications taken on a daily basis.

Assessments

Assessments were performed at weeks 0, 4, 10, 16, and 24 when the primary endpoint of remission was evaluated. Thereafter, assessments occurred at weeks 36, 48, 60, and 72. A final

follow-up visit also occurred at the date of the last patient last visit, which varied considerably for each patient. Therefore, only results up to and including week 72 are reported herein.

PVAS was used to score disease activity.[24] In brief, the PVAS ranges from 0-63, with higher scores denoting active clinical disease activity across 9 organ systems, and a score of 0 indicating absent disease activity.

Safety events were MedDRA coded (v19).

Outcomes

The primary outcome was remission within six months (24 weeks), defined as the absence of disease activity (PVAS of 0/63) on two consecutive occasions at least 1-month apart, with adherence to glucocorticoid taper.[20 21 24] The primary endpoint was assessed at 6 months because this reflects the typical time point in routine clinical practice to assess the effectiveness of remission induction[12] and therefore is used in most vasculitis trials.[20] Secondary endpoints assessed over the full 18 months of the trial were: remission within six months irrespective of glucocorticoid taper; time to remission; paediatric vasculitis damage index (PVDI) score;[27 28] mycophenolic-acid 12-hour trough-levels; the cross-culturally adapted and validated version of the Childhood Health Assessment Questionnaire for disability (CHAQ) and for quality of life the Child Health Questionnaire (CHQ);[29] cost-effectiveness using National Health Service (NHS) costs and quality-adjusted life years (QALYs) based on the Child Health Utility-9D (CHU-9D) and EuroQol-5D-3L (EQ-5D-3L) questionnaires; cumulative glucocorticoid dose; growth; disease relapse within 18 months; adverse events; withdrawal from trial due to drug intolerance; and mortality.

Statistical Analysis

Sample size

A maximum target sample size of 40 was chosen pragmatically, as the largest number feasible to recruit amongst PRINTO sites. A Bayesian approach is not restricted by small sample sizes, and allows data to be combined with existing evidence. The larger the recruitment, the greater the contribution of trial results to the totality of evidence, post-MYPAN. Bayesian sample-size calculations suggested that this would give a power of 62% to ascertain non-inferiority of the

primary endpoint.[30] MYPAN sought a Bayesian design due to the challenge of low numbers, given that cPAN is extremely rare. Bayesian power was therefore also calculated for smaller samples sizes: 8 patients (41% power); 10 patients (52%); and 12 patients (53%).

Data analyses

The trial followed the recommendation of the CONSORT statement, with results reported on the intent-to-treat population (ITT).[31] Missing data were not imputed. The date at which the primary outcome was achieved was the first of the two consecutive visits where PVAS=0. The primary outcome was analysed using a Bayesian analysis: Bayes Theorem was used to combine expert prior opinion with the MYPAN data to obtain posterior distributions for remission rates on CYC (pC), remission rates on MMF (pM) and the log-odds ratio of remission on MMF vs. CYC (θ). Full details of the primary outcome analysis methods are published previously. [21 30] In brief, non-inferiority of MMF was defined as a Bayesian posterior probability of obtaining remission within 6-months, within 10% (absolute difference) of CYC. Quantities of interest were pC, pM and θ. Bayesian prior distributions for pC and pM were established during a prior elicitation workshop convened in September 2013, before recruitment to MYPAN began, using expert opinion and evidence presented from the MYCYC trial.[20 21 30] The posterior distributions for pC, pM and θ were calculated and summarised by their modes, reflecting the most likely values for these quantities, and 90% credibility intervals (CrI), quantifying our certainty. We also calculated two posterior probabilities: that the 6-month remission rate of patients on MMF is non-inferior to that on CYC ($pM \geq pC - 0.10$); and that patients on MMF are more likely to achieve remission within 6-months than those on CYC ($pM > pC$). All secondary outcomes were analysed descriptively using frequentist statistics: number, median and Inter Quartile Range (IQR) unless otherwise stated. Kaplan-Meier curves, patient profile plots, and radar plots summarised results graphically.

Total National Health Service (NHS) costs associated with primary, secondary and community care services, and medication use for each participant were measured over 18-months. This was based on resource use questionnaires completed by trial participants, their parents or guardians during clinic appointments, and via entries in case report forms. Unit costs were taken from standard NHS sources (available at: https://improvement.nhs.uk/resources/national-tariff/). Health utilities were estimated by applying preference weights for each health state generated from

responses to CHU-9D questionnaires [32]. QALYs were then computed by applying the trapezium rule for estimating the area under the curve. Second year costs and QALYs were discounted at 3.5%. Differences between treatment groups in costs and QALYs were estimated by linear regression, with per-patient cost (or QALY) as the dependent variable, and treatment group as the only independent predictor. A non-parametric bootstrap analysis using 10,000 replicates was performed to assess the joint uncertainty in mean costs and QALYs. The probability of each treatment being cost-effective was determined at the threshold of £20,000 per QALY which operates in the NHS; [33] and as per National Institute for Health and Care Excellence (NICE) guidance (https://www.nice.org.uk/process/pmg9/).

Analyses were performed using R version 3.6.1, or SAS version 9.4.

Results

Patients

Eleven cPAN patients were enrolled from January 2014 to June 2018 from 5/13 international centres: Great Ormond St Hospital, London (N=3); Alder Hey Children's NHS Foundation Trust, Liverpool (N=3); Hacettepe University Children's Hospital, Ankara (N=3); and 1 patient each from Royal Manchester Children's Hospital, UK, and Hospital Sant Joan de Déu, Barcelona. A full list of participating centres is provided in acknowledgements. **Figure 2** summarises the randomised treatment allocation. Six were randomised to MMF; 5 to CYC. All 11 patients received their allocated treatment and were retained for the primary analysis; one patient withdrew from follow-up at 26 weeks. Baseline characteristics of the patients are provided in **Table 1.**

Primary outcome

Remission within 6-months of randomisation occurred in 4/6 (67%) for the MMF group; and 4/5 (80%) for the CYC group. The Bayesian posterior distributions (mode and 90% CrI) for remission rates were 71% (57-86%) for MMF, and 75% (57-86%) for CYC; and the odds of the primary outcome for MMF compared with CYC was 0.81 (0.40 - 1.65) (**Table 2, Figure 3**). The posterior probability that MMF is non-inferior to CYC was 0.76, indicating that non-inferiority is likely; and that the 6-month remission rate is higher on MMF than CYC was 0.31, indicating that MMF superiority is unlikely (**Table 2**).

Secondary efficacy outcomes

Remission and relapses

All patients adhered to the protocol for glucocorticoids; hence remission within 6-months irrespective of glucocorticoid taper was the same as for the primary endpoint. Five patients in the MMF group achieved remission within 18-months, at a median time of 7.1 weeks (IQR 4.0-10.3; range 4-25.6 weeks). All of the CYC group achieved remission within 18-months, at median of 17.6 weeks (IQR 6.0,18.9; range 4.4-35.3 weeks) for CYC (**Figure S1**). No relapses occurred in either group.

Vasculitis Damage, glucocorticoid exposure and mortality

PVDI scores were 0/72 for both groups at trial entry. Median PVDI score at trial end (18 months) was 0/72 (IQR 0-1/72) for the MMF group; and 2/72 (0-3/72) for the CYC group (**Table S5)**.

There was no major growth disturbance in either group: at 18-months, median (IQR) height z-score was -1.0 (-1.1,1.0) for MMF; and 0.0 (-0.2,0.1) for CYC, which were similar to baseline. Cumulative oral prednisolone doses at 6 and 18-months were similar between the 2 groups (**Table S6**). Three patients received IV methylprednisolone after randomisation: 1 patient in the CYC group; and 2 in the MMF treatment group. No patient in either group died.

Disability

Both groups suffered moderate disability at baseline and the MMF group improved over time (**Table S7**). Disability at 18 months was 0/3 (IQR 0,0) for MMF and 1.0/3 (0.2,1.8) for CYC. CHAQ pain scores decreased more rapidly in the MMF group than the CYC group (**Table S8**); similarly, CHAQ general assessment score also improved more rapidly in the MMF group (**Table S9**).

Quality of life

Quality of life (CHQ) was overall better in response to MMF than CYC (**Table S10**, **Figures S2-S4).** At baseline, CHQ Physical Summary Score (PhS) was severely impaired in both groups, 5 SD below the normal for a healthy control: PhS MMF 8.3 (IQR -0.4,18); PhS CYC 9.0 (1.8,14.0). Similarly, Psychosocial Summary Score (PsS) was impaired in both groups (albeit to a lesser degree than PhS): PsS MMF 34.9 (32.5, 48.1); PsS CYC 28.9 (25.0, 32.7). PhS and PsS improved more rapidly and to an overall greater level in the MMF group than the CYC group (**Table S10, Figures S2-S4**).

Health economics

The mean total, discounted costs were £4,725 (95% CI 1480, 7157) in the CYC group and £6,071 (95% CI 640, 15555) in the MMF group. Participants in the CYC group experienced 1.18 (95% CI 1.07, 1.48) discounted QALYs, compared with 1.13 (95% CI 0.58, 1.44) in the MMF group. Therefore, compared with CYC, MMF was £1,346 (95% CI -4709, 11175) more costly and associated with 0.047 (-0.5749, 0.4798) fewer QALYs, meaning MMF was dominated. The probability of MMF being cost-effective at a threshold of £20,000 per QALY was 0.32, which was evaluated in the six UK patients only.

Safety outcomes

Total adverse events were similar between the two groups: 38 events (63% mild severity; 37% moderate severity) occurred in 5/6 MMF patients; and 31 events (97% mild; 3% moderate) in all 5 CYC patients (**Table 3, Table S11**). A total of 4 serious adverse events (SAEs; including 2 infections in the MMF group) occurred in 3/6 MMF patients: abdominal pain (deemed not related to MMF), and lower respiratory tract infection (possibly related to MMF) in one patient, which fully resolved with treatment; colitis in one patient (deemed not related to MMF), ongoing at trial end; and herpes zoster (possibly related to MMF) in one patient, fully resolved with treatment. No SAEs were observed in the CYC group (**Table S12**). There were no withdrawals from trial drug due to intolerance.

Discussion

A major challenge in rare diseases is conducting clinical trials with sufficient power to inform best clinical practice when anticipated sample sizes are small. Historically, this has been an insurmountable barrier in rare paediatric autoimmune diseases, and explains why a clinical trial for cPAN had never been undertaken until now.[21] We adopted a Bayesian clinical trial design with the objective of quantifying disease remission rates on CYC and MMF, combining a robust elicitation of prior opinion and evidence with our trial data. Six-month remission rates observed in MYPAN were consistent with prior beliefs, and as we could only recruit 11 patients, the totality of evidence is heavily influenced by those prior distributions. We calculated a Bayesian posterior probability of 76% for non-inferiority of MMF to CYC for remission within 6 months. This observation, whilst not definitive, is still clinically useful, particularly since conducting a confirmatory frequentist trial is impossible.[21] Further clinical face validity for the non-inferiority of MMF to CYC is suggested by the fact that all patients were able to successfully wean glucocorticoids and had near-identical cumulative glucocorticoid exposure. Therefore, our results suggest that MMF might represent a viable alternative to CYC for remission induction in cPAN; moreover, these results will inform prior opinions for any future trials in cPAN planned in the future (e.g. the Biologics in Refractory Vasculitis Study: https://www.isrctn.com/ISRCTN16502655).

MYPAN data are consistent with studies in AAV, most notably the MYCYC study[20] (albeit not completely independently, as the MYCYC data helped inform the prior opinion used in MYPAN) which included adults and children and found that MMF was non-inferior to CYC for inducing remission. Following remission, all patients in our trial received azathioprine and glucocorticoid

maintenance, with no relapses. This observation contrasts with the MYCYC trial that found relapses occurred earlier and more frequently in the MMF group (33%) compared to the CYC group (19%).[20] Thus, the historical suggestion that relapses of cPAN are less common than observed in AAV in children is supported by our results.[1]

Other secondary endpoints are also potentially clinically relevant, albeit purely descriptive. MMF patients achieved remission at a median of 7.1 weeks, compared to 17.6 weeks for CYC. Vasculitis damage scores (PVDI) were numerically lower in the MMF group, implying less damage, although our trial was not powered to demonstrate statistical significance of this observation. The PVDI (and the adult tool, the VDI) are not weighted scores, hence overall low numeric scores can still indicate severe (for the patient) damage. Therefore, future studies will further examine the potential clinical importance of this preliminary observation.

CHAQ scores of disability and pain at trial end were comparable for MMF and CYC, although numerically lower for MMF. Whilst we must be careful not to overinterpret this purely descriptive observation, a possible obvious explanation is that the CHAQ score mirrored a more rapid resolution of disease activity in the MMF group, resulting in faster resolution of disability and pain. Similarly, and in keeping with this suggestion, QoL improved more rapidly and to a greater extent in the MMF group compared to CYC, particularly in the physical summary score. The health economic analysis in the UK, suggested that MMF may generate fewer QALYs and be more expensive than CYC in a UK health setting, however, albeit with a significant element of uncertainty. No patient died in either arm of the trial. Lastly, all the MMF patients followed-up achieved remission.

There were no new safety signals for MMF or CYC. Of note, two infections were considered possibly linked to MMF. Improved short-term safety with MMF was thus not demonstrated. However, the longer-term safety issues are probably of more importance, and are not captured in our trial. The use of MMF alongside standard dose glucocorticoids offers clear advantages over CYC in terms of fertility preservation for younger patients, and potentially also lower malignancy rates later in life, of particular concern to paediatric patients.[18 20]

Our trial has several notable strengths. It is the first randomised trial in cPAN ever. Patients were recruited from regional tertiary centres, thus the trial cohort was fully representative of the disease spectrum of cPAN as indicated by the extent of organ involvement we observed. Our trial also utilised standardised tools developed specifically for children with vasculitis to allow accurate classification of cPAN;[34] disease activity and remission using PVAS;[24] and the first to capture vasculitis damage prospectively using PVDI, thus far only preliminarily used in retrospective studies.[27 28]

The strengths of our trial should be viewed against its limitations, notably that our clinical trial evidence is based on a small sample, augmented by a distillation of clinical experience in the form of prior distributions. However, the fact that the posterior distributions we observed largely agree with prior expert belief adds important clinical face validity to the conclusions, which must be based on the final posterior distributions in Bayesian trials, and may provide the priors for future, cumulative research of cPAN. In addition, MYPAN was not blinded, for purely practical reasons. Although glucocorticoid exposure was documented, glucocorticoid toxicity was not captured systematically using the glucocorticoid toxicity index.[35] Only 7/11 patients were screened for DADA2 as part of their routine work-up, which might have important implications for efficacy of both CYC and MMF in cPAN.[10 11] Health economic analyses were based on UK costs, and therefore may not apply uniformly in other countries (for example Turkey, where MMF is more expensive than CYC). Our trial also did not address the possibility that higher doses of MMF (e.g. up to 3 g daily) might be even more efficacious: regulatory approval for dose escalation was initially sought in MYPAN, but not granted by competent authority since it was suggested that adverse effects might also increase with higher doses. Lastly, generalizability to other ethnic groups limited as 10/11 patients in our trial were Caucasian.

In summary, MMF is probably non-inferior to CYC for induction of remission of cPAN when combined with glucocorticoids and might be associated with better quality of life than treatment with CYC.

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Tables

Baseline Characteristic	**MMF (N=6)**	**CYC (N=5)**	**All (N=11)**
Age at randomisation (years)			
Median (IQR)	10.8 (7.0,12.1)	7.9 (6.7,9.4)	12.1 (4.6,15.5)
Males	3	2	5
Females	3	3	6
Ethnicity			
White	6	4	10
Mixed	0	1	1
Height z-score			
Median (IQR)	-0.7 (-1.2,1.0)	0.2 (-0.1,0.2)	-0.1 (-0.7,1.0)
Weight z-score			
Median (IQR)	-1.3 (-2.7,-0.3)	1.3 (0.7,2.3)	-0.2 (-1.5,1.3)
eGFR (ml/min/1.73m^2)			
Median (IQR)	128.4 (125.8,152.0)	101.3 (99.6,101.9)	113.0 (101.3,129.0)
PVAS (/63)			
Median (IQR)	8.5 (7.0,12.0)	7.0 (6.0,9.0)	7.0 (6.0,12.0)
*Organ system affected			
General/constitutional	6	4	10
Cutaneous	3	3	6
Eyes	1	0	1
Abdominal	5	4	9
Renal	0	1	1
Nervous system	2	2	4
CRP (mg/L; RR <5mg/L)			
Median (IQR)	14.7 (4.0,47.4)	4.0 (4.0,38.0)	8.0 (4.0,47.4)
ESR (mm/hr; RR 0-10 mm/h)			

Median (IQR)	28.5 (7.0,63.0)	16.0 (14.0,28.0)	16.0 (7.0,63.0)
CHAQ disability index Median (IQR)	1.5 (0.6, 1.8)	1.5 (0.3, 1.5)	1.5 (0.6, 1.8)
Total dose of IV methylprednisolone pre-randomisation (mg/kg)	n=4	n=3	n=7
Median (IQR)	59.7 (45.6,291.6)	87.2 (17.3,222.2)	73.2 (45.0,222.2)
Plasma exchange pre-randomisation	0	0	0
ADA2 genetic screening and result	5 Wild type in all	2 Wild type in all	7 **DADA2 excluded in 7/7 tested

Table 1. **Baseline characteristics of the patients at trial entry.** MMF, mycophenolate mofetil; CYC cyclophosphamide; IQR, interquartile range; eGFR, estimated glomerular filtration rate (Schwartz formula); PVAS, paediatric vasculitis activity score; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; CHAQ, child health assessment questionnaire; IV, intravenous. *ADA2,* adenosine deaminase 2 gene; DADA2, deficiency of adenosine deaminase 2. *A full breakdown of all PVAS items is provided in **Table S4**. **4 patients declined genetic testing for DADA2: 1 in the MMF group, 3 in the CYC group.

Prior and Posterior Beliefs			
Parameter		**Mode**	**90% Credibility Interval**
pM	*Probability of remission within 6-months of randomisation, given that the treatment was MMF*		
	Prior	71%	(45%, 85%)
	Posterior	71%	(51%, 83%)
pC	*Probability of remission within 6-months of randomisation, given that the treatment was CYC*		
	Prior	74%	(51%, 86%)
	Posterior	75%	(57%, 86%)
θ	*Log-odds ratio of being in remission within 6 months if given MMF compared with CYC*		
	Prior	-0.17	(-0.91, 0.58)
	Posterior	-0.21	(-0.91, 0.50)
Exp (θ)	*Odds ratio of being in remission within 6 months if given MMF compared with CYC*		
	Prior	0.84	(0.40, 1.79)
	Posterior	0.81	(0.40, 1.65)
Hypotheses		**Probability**	
Non-inferiority	*Probability MMF is non-inferior to CYC within a margin of 10%*		
	Prior	0.766	
	Posterior	0.755	

Superiority	*Probability of superiority of MMF over CYC*	
	Prior	0.356
	Posterior	0.313

Table 2: Bayesian primary outcome analysis results

	MMF (N=6)		CYC (N=5)		Total (N=11)	
	Events	**Patients**	**Events**	**Patients**	**Events**	**Patients**
	n	n (%)	n	n (%)	n	n (%)
Adverse Events:						
All	38	5 (83.3%)	31	5 (100%)	69	10 (90.9%)
Mild	24	2 (33.3%)	30	4 (80%)	54	6 (54.5%)
Moderate	14	3 (50%)	1	1 (20%)	15	4 (36.4%)
Serious Adverse Events:						
All	4	3 (50%)	0	0	4	3 (27%)

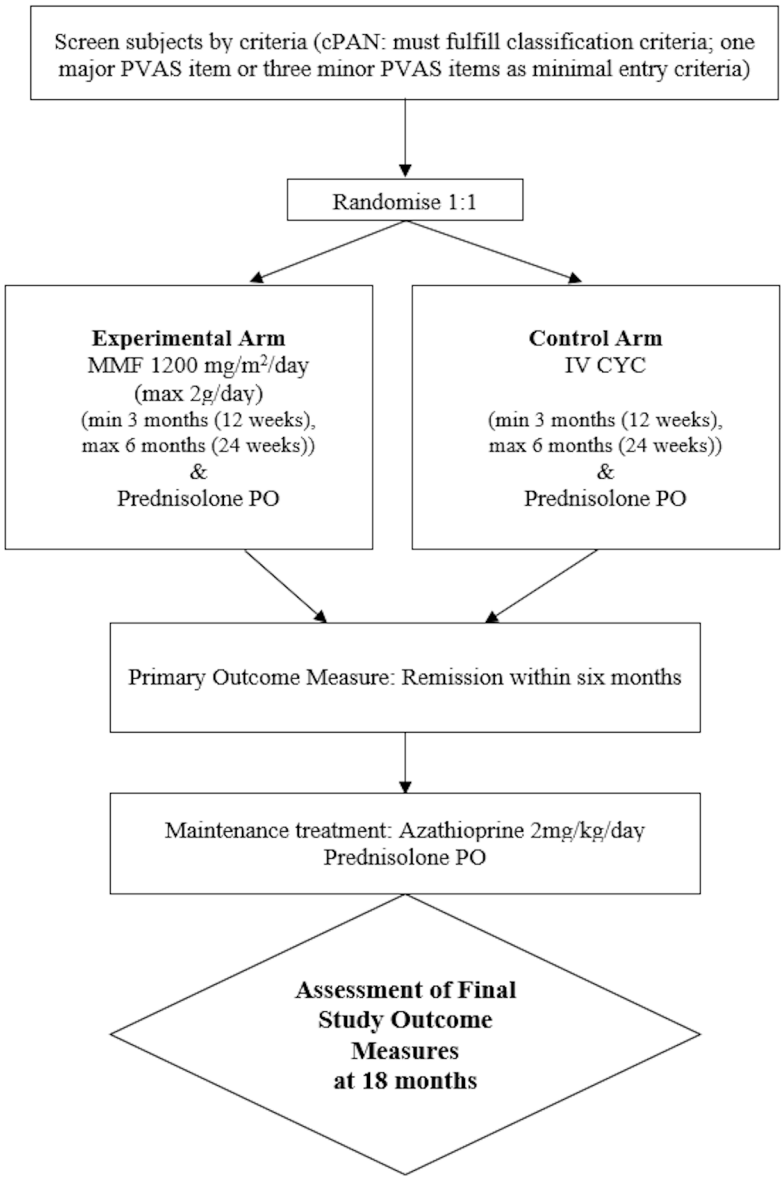
Table 3: Summary of adverse events

Figure legends

Figure 1: MYPAN trial study overview: cPAN, childhood polyarteritis nodosa; PVAS, Paediatric vasculitis activity score; mycophenolate mofetil; CYC, cyclophosphamide; min, minimum; PO, per oral.

Figure 2: MYPAN CONSORT flow-chart of recruitment, treatment allocation and follow up

Figure 3: Graphs showing prior and posterior distributions: (A) MMF 6-month remission rate; (B) CYC 6-month remission rate; (C) log-odds of 6-month remission if given MMF compared with CYC; and (D) posterior distributions for MMF and CYC 6-month remission rates.



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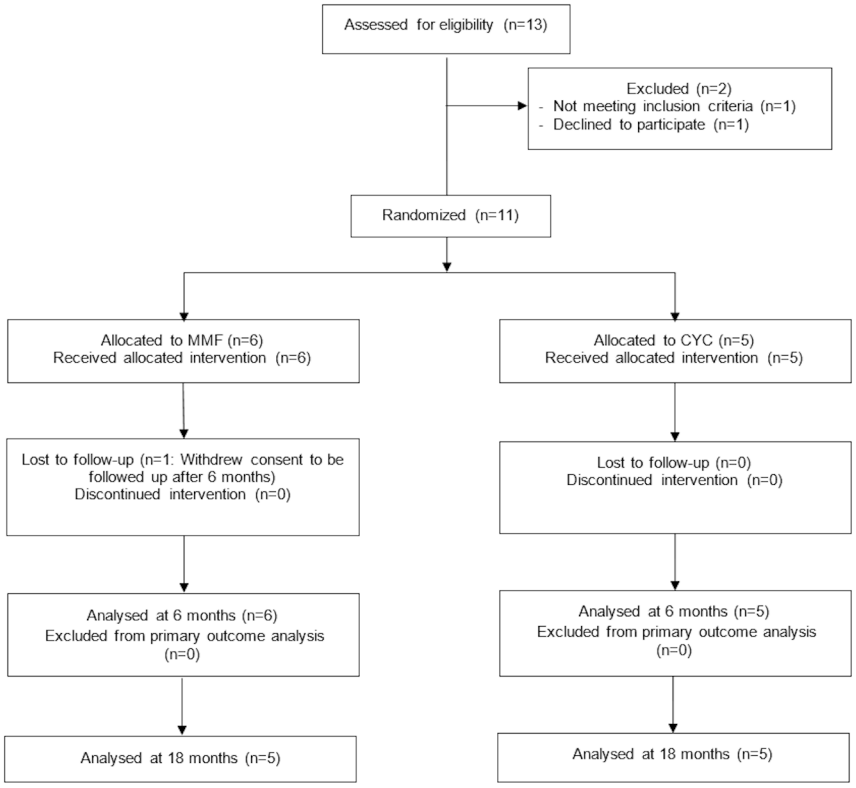

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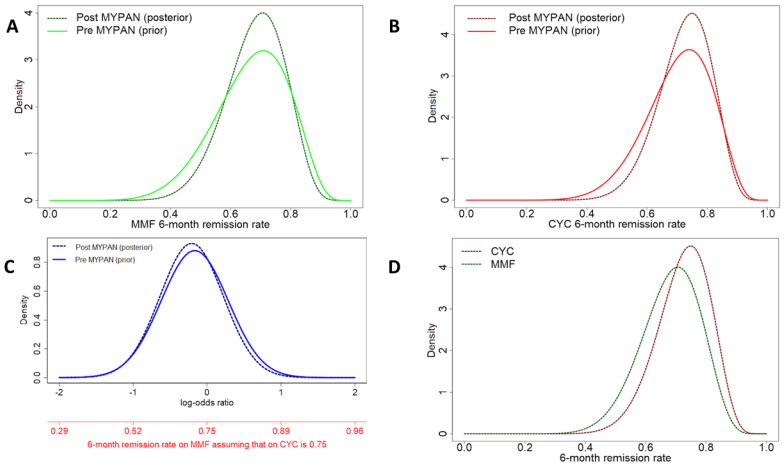

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