Arthritis & Rheumatology
Vol. 73, No. 9, September 2021, pp 1673–1682
DOI 10.1002/art.41730

American College of Rheumatology
Empowering Rheumatology Professionals

Mycophenolate Mofetil Versus Cyclophosphamide for Remission Induction in Childhood Polyarteritis Nodosa: An Open-Label, Randomized, Bayesian Noninferiority Trial

Paul A. Brogan,[1] Barbara Arch,[2] Helen Hickey,[2] Jordi Anton,[3] Este Iglesias,[3] Eileen Baildam,[4] Kamran Mahmood,[4] Gavin Cleary,[4] Elena Moraitis,[5] Charalampia Papadopoulou,[5] Michael W. Beresford,[2] Phil Riley,[6] Selcan Demir,[7] Seza Ozen,[7] Giovanna Culeddu,[8] Dyfrig A. Hughes,[8] Pavla Dolezalova,[9] Lisa V. Hampson,[10] John Whitehead,[10] David Jayne,[11] Nicola Ruperto,[12] Catrin Tudur-Smith,[2] and Despina Eleftheriou[1]

Objective. Cyclophosphamide (CYC) is used in clinical practice off-label for the induction of remission in childhood polyarteritis nodosa (PAN). Mycophenolate mofetil (MMF) might offer a less toxic alternative. This study was undertaken to explore the relative effectiveness of CYC and MMF treatment in a randomized controlled trial (RCT).

Methods. This was an international, open-label, Bayesian RCT to investigate the relative effectiveness of CYC and MMF for remission induction in childhood PAN. Eleven patients with newly diagnosed childhood PAN were randomized (1:1) to receive MMF or intravenous CYC; all patients received the same glucocorticoid regimen. The primary end point was remission within 6 months while 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 and features were similar between the 2 treatment groups. The primary end point was met in 4 of 6 patients (67%) in the MMF group and 4 of 5 patients (80%) in the CYC group. Time to remission was shorter in the MMF group compared to the CYC group (median 7.1 weeks versus 17.6 weeks). No relapses occurred in either group within 18 months. Two serious infections were found to be likely linked to MMF treatment. Physical and psychosocial quality-of-life scores were superior in the MMF group compared to the CYC group at 6 months and 18 months. Combining the prior expert opinion with results from the present study provided posterior estimates of remission of 71% for MMF (90% credibility interval [90% CrI] 51, 83) and 75% for CYC (90% CrI 57, 86).

Conclusion. The present results, taken together with prior opinion, indicate that rates of remission induction in childhood PAN are similar with MMF treatment and CYC treatment, and MMF treatment might be associated with better health-related quality of life than CYC treatment.

INTRODUCTION

Polyarteritis nodosa (PAN) is a necrotizing vasculitis that causes aneurysmal nodules of medium-sized arteries (1,2). Childhood PAN is exceptionally rare, with a prevalence of ~1 per 1 million children (1,3). Peak onset of childhood PAN is at age 7–11 years, with no sex bias (4,5). Features of childhood PAN include constitutional symptoms, vasculitis rash, myalgia, abdominal pain,

EudraCT database no. 2013-004668-71 and ISRCTN: 75434563.

Supported by Versus Arthritis (grant 20094), Vasculitis UK, the Lauren Currie Twilight Foundation, the Paediatric Rheumatology International Trial Organisation (PRINTO), the Great Ormond St Hospital Charity, and the Hacettepe University Research Fund (grant TK-2017-15782).

[1]Paul A. Brogan, MBChB, PhD, Despina Eleftheriou, MD, PhD: University College London Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [2]Barbara Arch, MSc, Helen Hickey, BSc, Michael W. Beresford, MBChB, PhD, Catrin Tudur-Smith, PhD: University of Liverpool, Liverpool, UK; [3]Jordi Anton, MD, PhD, Este Iglesias, MD: St. Joan de Déu Hospital, Barcelona, Spain; [4]Eileen Baildam, MD, Kamran Mahmood, FRCPCH, Gavin Cleary, MBChB: Alder Hey Children's NHS Foundation Trust, Liverpool, UK; [5]Elena Moraitis, MD, PhD, Charalampia Papadopoulou, MD, PhD: Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [6]Phil Riley, MBChB: Royal Manchester Children's Hospital, Manchester, UK; [7]Selcan Demir, MD, Seza Ozen, MD: Hacettepe University, Ankara, Turkey; [8]Giovanna Culeddu, MSc, Dyfrig A. Hughes, PhD: Bangor University, Bangor, UK; [9]Pavla Dolezalova, PhD: General University Hospital in Prague and Charles University, Prague, Czech Republic; [10]Lisa V. Hampson, PhD, John Whitehead, PhD: Lancaster University, Lancaster, UK; [11]David Jayne, MD, FMedSci: University of Cambridge, Cambridge, UK; [12]Nicola Ruperto, MD, MPH: Instituto Giannina Gaslini, IRCCS, UOSID Centro Trial, Genoa, Italy.

Dr. Brogan has received consulting fees from Sobi, Novartis, UCB, and Roche (less than $10,000 each). Dr. Cleary has received speaking fees

and arthropathy; however, any organ system can be affected (2,4,5). The etiology of childhood PAN remains unknown (6,7). In 2014, a monogenetic form of childhood PAN caused by deficiency of adenosine deaminase 2 (DADA2) was described (8–11).

If left untreated, the mortality rate of childhood PAN was historically close to 100% within months of disease onset (12,13); with aggressive immunosuppression, the mortality rate is as low as 4% (4). Cyclophosphamide (CYC) has been used off-label for over 40 years in the treatment of PAN (14–17) and is still recommended for induction of remission in childhood PAN, though this has never been studied in a pediatric randomized controlled trial (RCT) (12). If alternative treatment exists, it is desirable that CYC treatment in children be avoided, 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 remission rates similar to those observed with CYC in the treatment of lupus nephritis (19) and antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) (20). MMF is not associated with urothelial malignancy or infertility and is used off-label in pediatric patients.

We hypothesized that MMF may be noninferior to CYC for induction of remission in childhood PAN and may be a less toxic alternative. Therefore, the purpose of the present study was to investigate the relative effectiveness of MMF and CYC for remission induction in childhood PAN. It is infeasible to conduct a conventional, definitive phase III study of childhood PAN due to its rarity. We therefore opted for a Bayesian approach to assess the relative efficacy of MMF and CYC. This was a 2-stage process. Stage 1 consisted of a robust 2-day elicitation process conducted to quantify clinical opinion in light of results from a trial in adults (mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis [MYCYC]) (20). The results from this trial were previously published (21). Stage 2 was a multicenter, open-label RCT of mycophenolate mofetil versus cyclophosphamide for the induction of remission of childhood PAN (the MYPAN trial; http://www.mypan.org.uk), and these data were used to further quantify the relative effectiveness of each treatment for remission induction in patients with newly diagnosed childhood PAN.

PATIENTS AND METHODS

Study design and patients. MYPAN was an international multicenter, open-label, randomized controlled prospective trial comparing MMF treatment with intravenous (IV) CYC treatment for the remission of childhood PAN (Figure 1). The trial was sponsored by University College London, and the trial was coordinated and data were stored by the Liverpool Clinical Trials Centre (LCTC) at the University of Liverpool. Centers were identified among members of the Paediatric Rheumatology International Trials Organisation (PRINTO) (www.printo.it) (22).The trial was conducted using a Bayesian noninferiority design (noninferiority margin 10%). Children were randomized 1:1 to receive either MMF (1,200 mg/m^2/day, maximum 1 gm twice daily) (12,23) or a standard IV CYC regimen (12). Randomization was achieved using a secure web-based tool generated centrally by the LCTC. Minimization variables for randomization were planned additional therapy with methylprednisolone >15 mg/kg at trial entry (yes/no) and plasma exchange at trial entry (yes/no). Treatment allocation prior to randomization was concealed from recruiting clinicians. Both trial groups received the same glucocorticoid treatment regimen per study protocol. The full protocol is available in Supplementary MYPAN protocol V4.0 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract).

Inclusion criteria were age at screening ≥4 years and ≤18 years, new-onset childhood PAN (within 3 months of screening) classified in accordance with the European Alliance of Associations for Rheumatology/PRINTO/Paediatric Rheumatology European Society criteria (2,24), active vasculitis of any major organ, or meeting ≥3 minor components of the Pediatric Vasculitis Activity Score (PVAS) criteria (25) (see Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract).

Children were excluded if they did not meet the classification criteria for childhood PAN, if they received alternative diagnoses, if they had chronic infection, if they experienced previous reactions to one of the study medications, or if they had immunodeficiency or malignancy. Genetic screening for ADA-2 was administered as part of the routine evaluation of the patients (i.e., outside the protocol).

Ethics approval. The protocol was approved by the Multicentre Research Ethics Committee in the UK and from relevant ethics committees for each participating center internationally. The study was conducted in accordance with the ethics principles of the Declaration of Helsinki. Patient and public involvement informed the design of the protocol and patient-facing trial documents. All participants provided written informed consent.

from AbbVie (less than $10,000). Dr. Ozen has received consulting fees from Novartis and Sobi (less than $10,000). Dr. Hampson owns stock or stock options in Novartis. Dr. Jayne has received consulting fees from AstraZeneca, Chemocentryx, GlaxoSmithKline, Genentech, InflaRx, Takeda, and Vifor (less than $10,000 each). Dr. Ruperto has received consulting fees, speaking fees, and/or honoraria from Ablynx, AstraZeneca, MedImmune, Bayer, Biogen, Boehringer, Bristol Myers Squibb, Celgene, Eli Lilly, EMD Serono, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Merck, Novartis, Pfizer, R-Pharm, Synergie, Sobi, and UCB (less than $10,000 each). No other disclosures relevant to this article were reported.

Address correspondence to Paul A. Brogan, MBChB, PhD, 30 Guilfor Street, London, UK. Email: p.brogan@ucl.ac.uk.

Submitted for publication July 9, 2020; accepted in revised form March 11, 2021.

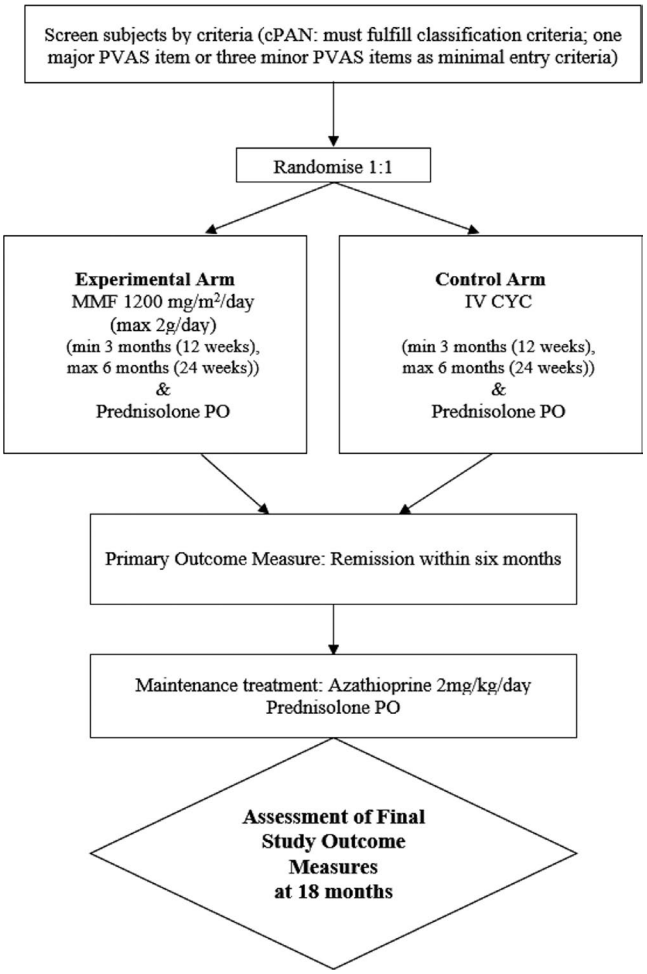

Figure 1. Overview of mycophenolate mofetil (MMF) versus cyclophosphamide (CYC) for the induction of remission of childhood polyarteritis nodosa (cPAN) (the MYPAN trial). PVAS = Pediatric Vasculitis Activity Score; PO = by mouth; IV = intravenous.

Treatments. Participants received oral MMF or IV CYC treatment for 18 months, which comprised 3–6 months of induction therapy (1:1 randomization); followed by 12–15 months of oral azathioprine (AZA) maintenance therapy (Figure 1). Both groups in the trial received tapering glucocorticoids (see below). Unless participants had an allergy, prophylaxis with trimethoprim/sulfamethoxazole was required until week 24. Trial treatment ended after 18 months.

MMF was administered to patients until disease remission was achieved at 3–6 months. The starting dose was 600 mg/m²/day (maximum 1 gm/day) for the first week, followed by 1,200 mg/m²/day (maximum 2 gm/day) in 2 divided doses (12,23,26).

CYC was administered at weeks 0, 2, and 4 and then every 3 weeks until remission was achieved (maximum 10 IV doses and minimum 6 doses) (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). The first dose was 500 mg/m^2/day, followed by 750 mg/m^2/day (maximum dose 1.2 gm) (12). Mesna and IV fluids were administered, as per local practice. CYC could be discontinued after a minimum of 6 doses if disease was in remission. Patients were administered oral AZA (2 mg/kg/day, maximum 200 mg/day) (12,26) the day following discontinuation of MMF treatment or 10–14 days after the last dose of IV CYC.

All patients received prednisolone starting at 1 mg/kg/day (maximum 80 mg dose), which was decreased to 0.1 mg/kg/day by 6 months and to 0.05–0.075 mg/kg by 9 months (Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). Intravenous methylprednisolone could also be administered at trial entry (maximum 30 mg/kg for 3 doses or 3 gm total) at the investigator's discretion.

Principal investigators recorded medications received by the patient on a medication clinical research form during protocol face-to-face follow-up trial visits as specified below. In addition, patients completed a diary listing the medications 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 end point of remission was evaluated. Thereafter, assessments occurred at weeks 36, 48, 60, and 72. A final follow-up visit also took place on the date of the last patient's last visit, which varied considerably among the patients. Therefore, only results up to and including week 72 are reported here.

Disease activity was determined using the PVAS (25). Briefly, the PVAS ranges from 0 to 63, with higher scores denoting active clinical disease activity within 9 organ systems and a score of 0 indicating the absence of disease activity. Safety events were coded using The Medical Dictionary for Regulatory Activities version 19.

Primary outcome measure. The primary outcome measure was remission within 6 months, which was defined as the absence of disease activity (PVAS 0 [of a maximum 63]) on 2 consecutive visits at least 1 month apart, with adherence to glucocorticoid taper protocol (20,21,25). The primary end point was assessed at 6 months because this reflects the typical time point to assess the effectiveness of remission induction in routine clinical practice (12) and is therefore used in most vasculitis trials (20). Secondary end points assessed over the full 18-month trial were as follows: remission within 6 months regardless of glucocorticoid taper; time to remission; pediatric 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 (C-HAQ) for disability and the Child Health Questionnaire (CHQ) for quality of life (29); cost-effectiveness using the UK NHS costs and quality-adjusted life-years (QALYs) measurement based on the Child Health Utility-9D (CHU-9D) (30) and EuroQol-5D-3L (EQ-5D-3L) questionnaires

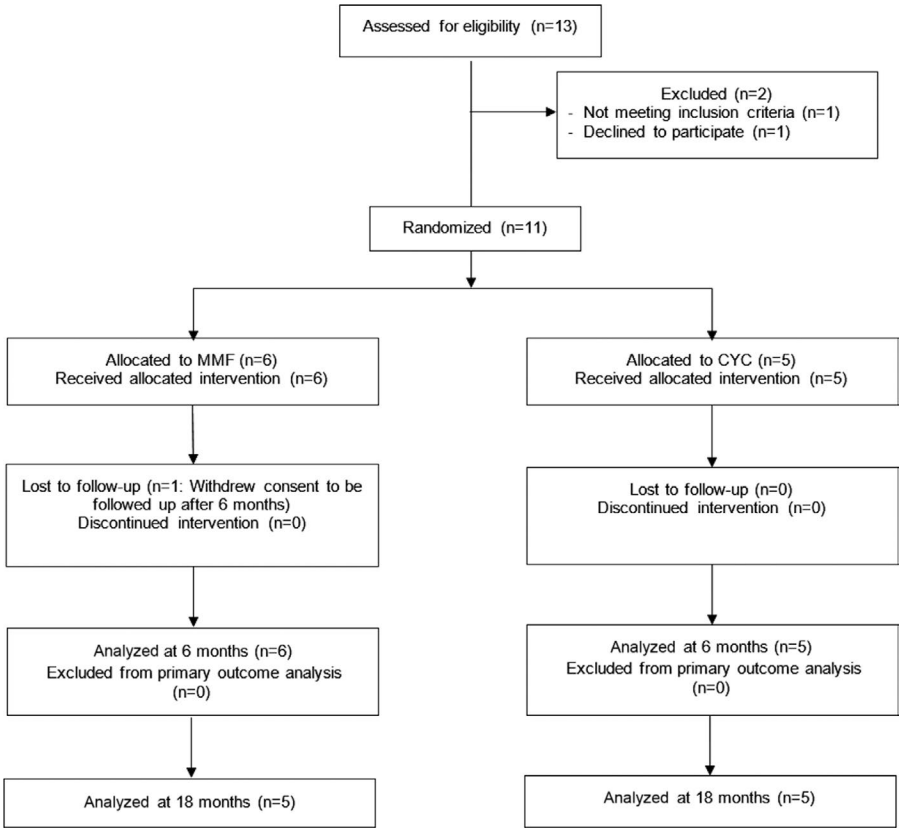

Figure 2. Flow chart of patient recruitment, treatment allocation, and patient follow-up in patients receiving mycophenolate mofetil (MMF) versus cyclophosphamide (CYC) for the induction of remission of childhood polyarteritis nodosa (MYPAN trial).

(31); 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 this was the largest number feasible to recruit among 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 trial. Bayesian sample-size calculations suggested that this would yield a power of 62% to ascertain noninferiority of the primary end point (32). The MYPAN trial was conducted using a Bayesian design due to the challenge of low participant numbers, given that childhood PAN is extremely rare. Bayesian power was therefore also calculated for smaller sample sizes (8 patients [41% power], 10 patients [52% power], and 12 patients [53% power]).

Data analyses. Per the recommendation in the Consolidated Standards of Reporting Trials statement (33), reported results are from the intent-to-treat (ITT) population. Missing data were not imputed. The date at which the primary outcome was achieved was the first of the 2 consecutive visits in which the PVAS was 0. The primary outcome was examined using a Bayesian analysis. Bayes theorem was used to combine expert prior opinion with the MYPAN data to obtain posterior distributions for remission rates with CYC treatment (pC), remission rates with MMF treatment (pM), and the log odds ratio of remission with MMF compared to CYC (θ).

Full details of the primary outcome measure analysis methods were previously published (21,32). Briefly, noninferiority 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 in September 2013 (before recruitment for the MYPAN trial began), using expert opinion and evidence presented from the MYCYC trial (20,21,32). The posterior distributions for pC, pM, and θ were calculated and summarized by their modes, which reflected the most likely values for these quantities, and by 90% credibility intervals (90% CrIs), which quantified our certainty. We also calculated 2 posterior probabilities, i.e., that the 6-month remission rate among patients taking MMF is noninferior to the 6-month remission rate among patients taking CYC ($pM \geq pC - 0.10$) and that achievement of remission within 6 months is more likely to occur among patients taking MMF than among those taking CYC ($pM > pC$). All secondary outcome measures were analyzed descriptively

Table 1. Characteristics of the patients in the MMF group and the CYC group at trial entry*

Characteristic	MMF group (n = 6)	CYC group (n = 5)	All patients (n = 11)
Age at randomization, median (IQR) years	10.8 (7.0, 12.1)	7.9 (6.7, 9.4)	12.1 (4.6, 15.5)
Male	3	2	5
Female	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/1.73 m^2), median (IQR)	128.4 (125.8, 152.0)	101.3 (99.6, 101.9)	113.0 (101.3, 129.0)
PVAS (maximum 63), median (IQR)	8.5 (7.0, 12.0)	7.0 (6.0, 9.0)	7.0 (6.0, 12.0)
Affected organ system†			
General/constitutional	6	4	10
Cutaneous	3	3	6
Eyes	1	0	1
Abdominal	5	4	9
Renal	0	1	1
Nervous	2	2	4
CRP (mg/liter; RR <5 mg/liter), median (IQR)	14.7 (4.0, 47.4)	4.0 (4.0, 38.0)	8.0 (4.0, 47.4)
ESR (mm/hour; 0–10 mm/hour), median (IQR)	28.5 (7.0, 63.0)	16.0 (14.0, 28.0)	16.0 (7.0, 63.0)
C-HAQ 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-randomization, mg/kg	4	3	7
Median (IQR)	59.7 (45.6, 291.6)	87.2 (17.3, 222.2)	73.2 (45.0, 222.2)
Plasma exchange pre-randomization	0	0	0
ADA-2 genetic screening‡	5	2	7

* Except where indicated otherwise, values are the number of patients. MMF = mycophenolate mofetil; CYC = cyclophosphamide; IQR = interquartile range; eGFR = estimated glomerular filtration rate; PVAS = Pediatric Vasculitis Activity Score; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; C-HAQ = Childhood Health Assessment Questionnaire; IV = intravenous; ADA-2 = adenosine deaminase 2.
† A full breakdown list of all PVAS items is provided in Supplementary Table 4 (http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract).
‡ Four patients declined genetic testing for deficiency of adenosine deaminase 2 (DADA2) (1 in the MMF group and 3 in the CYC group). DADA2 was excluded in all 7 patients in the MMF and CYC groups.

using frequentist statistics (i.e., number, median, and interquartile range [IQR]), unless otherwise stated. Results were summarized graphically using Kaplan-Meier curves, patient profile plots, and radar plots.

For each participant, total NHS costs associated with primary care, secondary care, and community care services, and medication use were measured over 18 months. This was based on resource use questionnaires completed by trial participants or their parents or guardians during clinic appointments, and via information from case report forms. Unit costs were obtained from standard NHS sources (https://improvement.nhs.uk/resources/national-tariff/). The estimation of preference weights for each health state was generated from patient responses to CHU-9D questionnaires (30). QALYs were then computed by applying the trapezium rule to estimate the area under the curve. Second-year costs and QALYs were discounted at 3.5%. Differences between the MMF and CYC treatment groups in costs and QALYs were estimated by linear regression, with the per-patient cost (or per QALY) as the dependent variable and the treatment group as the only independent predictor. A nonparametric 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 within the NHS (34) and in accordance with the National Institute for Health and Care Excellence 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 patients with childhood PAN were enrolled from January 2014 to June 2018 from 5 of 13 international centers (Great Ormond Street Hospital [n = 3], Alder Hey Children's NHS Foundation Trust [n = 3], Hacettepe University Children's Hospital [n = 3], Royal Manchester Children's Hospital [n = 1], and Hospital Sant Joan de Déu [n = 1]). The randomized treatment allocation is summarized in Figure 2. Six patients were randomized to receive MMF, and 5 patients were randomized to receive CYC. All 11 patients received their allocated treatment and were retained for the primary analysis; 1 patient withdrew from follow-up at 26 weeks. Baseline characteristics of the patients are provided in Table 1 and Supplementary Table 4 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract).

Prior and Posterior Beliefs			
Parameter		**Mode**	**90% Credibility Interval**
pM	*Probability of remission within 6 months of randomization, given that the treatment was MMF*		
	Prior	71%	(45%, 85%)
	Posterior	71%	(51%, 83%)
pC	*Probability of remission within 6 months of randomization, 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**	
Noninferiority	*Probability MMF is noninferior 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	

Figure 3. Bayesian primary outcome analysis results. MMF = mycophenolate mofetil; CYC = cyclophosphamide.

Findings for the primary outcome measure. Remission within 6 months of randomization occurred in 4 of 6 patients (67%) in the MMF group and 4 of 5 patients (80%) in the CYC group. The Bayesian posterior distributions for remission rates (modes) were 71% (90% CrI 51, 83) for MMF and 75% (90% CrI 57, 86) for CYC, and the odds ratio of remission within 6 months with MMF compared to CYC was 0.81 (90% CrI 0.40, 1.65) (Figures 3 and 4). The posterior probability that MMF is noninferior to CYC was 0.76, indicating that noninferiority is likely. Also, the posterior probability that the 6-month remission rate is higher in MMF than in CYC was 0.31, indicating that MMF superiority is unlikely (Figure 3).

Findings for the secondary efficacy outcome measures. *Remission and relapses.* All patients adhered to the protocol for glucocorticoids; hence, remission within 6 months regardless of glucocorticoid taper was the same as that for the primary end point. Five patients in the MMF group exhibited remission within 18 months, at a median of 7.1 weeks (IQR 4.0, 10.3; full range 4–25.6). Remission was achieved in all patients in the CYC group within 18 months, at median of 17.6 weeks (IQR 6.0, 18.9; full range 4.4–35.3) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). No relapses occurred in either group.

Vasculitis damage, glucocorticoid exposure, and mortality. The median PVDI score was 0 (of a maximum 72) for both groups at trial entry. The median PVDI score at trial end (18 months) was 0 (IQR 0, 1) in the MMF group and 2 (IQR 0, 3) in the CYC group (Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). There was no major growth disturbance in either group. At 18 months, the median height Z score was –1.0

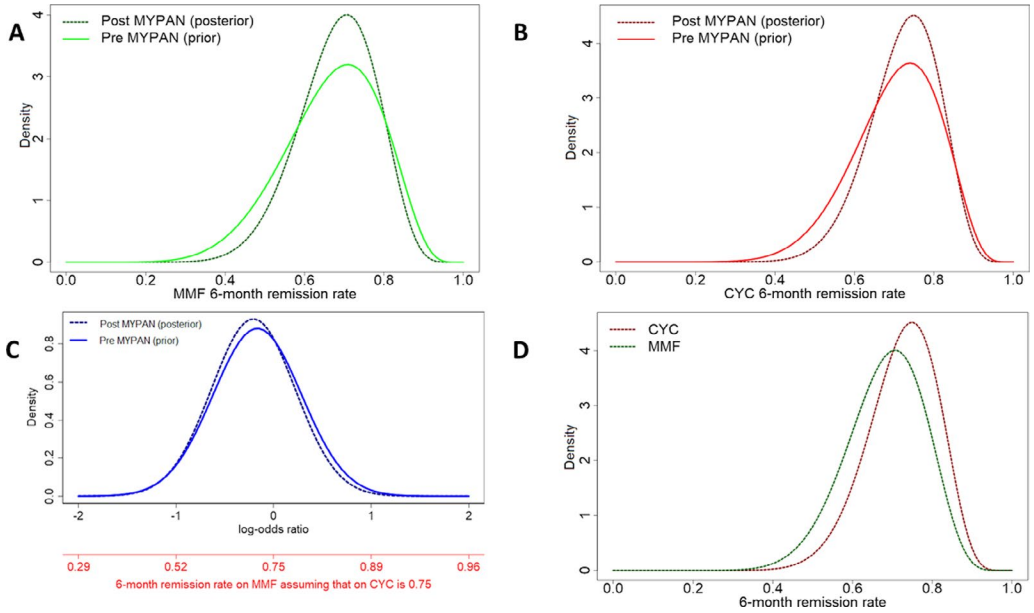

Figure 4. Graphs showing prior and posterior distributions for mycophenolate mofetil (MMF) 6-month remission rate (**A**), cyclophosphamide (CYC) 6-month remission rate (**B**), and log odds ratio of 6-month remission if given MMF compared to CYC (**C**), and posterior distributions for MMF and CYC 6-month remission rates (**D**). MYPAN = mycophenolate mofetil versus cyclophosphamide for the induction of remission of childhood polyarteritis nodosa (trial).

(IQR –1.1, 1.0) in the MMF group and 0.0 (IQR –0.2, 0.1) in the CYC group, which were similar to heights at baseline. Cumulative oral prednisolone doses at 6 and 18 months were similar between the 2 groups (Supplementary Table 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). Three patients received IV methylprednisolone after randomization (1 patient in the CYC group and 2 in the MMF group). No patients died in either group.

Disability. Patients in both groups had moderate disability at baseline, but patients with moderate disability in the MMF group improved over time (Supplementary Table 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). The median disability score (C-HAQ) at 18 months among patients with childhood PAN was 0 (of a maximum 3) (IQR 0, 0) in the MMF group and 1.0 (IQR 0.2,1.8) in the CYC group. C-HAQ pain scores decreased more rapidly in the MMF group compared to the CYC group (Supplementary Table 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). Similarly, C-HAQ general assessment scores also improved more rapidly in the MMF group compared to the CYC group (Supplementary Table 9, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract).

Quality of life. Results from the CHQ showed that quality of life was overall better in patients treated with MMF compared to those treated with CYC (Supplementary Table 10 and Supplementary Figures 2–4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). At baseline, median CHQ physical summary scores reflected severe impairment in both groups, ~5 SD below the normal for a healthy control (8.3 [IQR –0.4, 18] in the MMF group and 9.0 [IQR 1.8, 14.0] in the CYC group). Similarly, median psychosocial summary scores reflected impairment in both groups, though to a lesser degree than the physical summary scores (34.9 [IQR 32.5, 48.1] in the MMF group and 28.9 [IQR 25.0, 32.7] in the CYC group). Physical summary scores and psychosocial summary scores improved more rapidly and to an overall greater level in the MMF group compared to the CYC group (Supplementary Table 10 and Supplementary Figures 2–4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract).

Health economics. The mean total discounted costs were £4,725 (95% confidence interval [95% CI] 1,480, 7,157) in the CYC group and £6,071 (95% CI 640, 15,555) in the MMF group. Participants in the CYC group experienced discounted QALYs of 1.18 (95% CI 1.07, 1.48), compared to 1.13 (95% CI 0.58, 1.44) in the MMF group. Therefore, MMF was more costly (£1,346 [95% CI –4709, 11,175]) and was associated with fewer QALYs (0.047 [–0.5749, 0.4798]) compared to CYC. The probability of MMF being cost-effective at a threshold of £20,000 per QALY was 0.32, which was evaluated in the 7 patients from the UK only.

Safety outcome measures. Total adverse events were similar between the 2 groups. Thirty-eight events (63% mild severity and 37% moderate severity) occurred in 5 of 6 patients treated with MMF, and 31 events (97% mild and 3% moderate) occurred

Table 2. Summary of adverse events in the MMF group compared to the CYC group*

	MMF group (n = 6)		CYC group (n = 5)		All patients (n = 11)	
	Events, no.	Patients, no. (%)	Events, no.	Patients, no. (%)	Events, no.	Patients, no. (%)
Adverse events, no.						
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)
All SAEs, no.	4	3 (50)	0	0 (0)	4	3 (27)

* MMF = mycophenolate mofetil; CYC = cyclophosphamide; SAEs = serious adverse events.

in all 5 patients treated with CYC (Table 2 and Supplementary Table 11, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). A total of 4 serious adverse events, including 2 infections, occurred in 3 of 6 patients in the MMF group. One patient had abdominal pain (deemed not related to MMF) and a lower respiratory tract infection (possibly related to MMF), which fully resolved with treatment. One patient had colitis (deemed not related to MMF) ongoing at trial end, and 1 patient had herpes zoster (possibly related to MMF), which fully resolved with treatment. No serious adverse events were observed in the CYC group (Supplementary Table 12, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41730/abstract). No patients withdrew from the trial due to drug intolerance.

DISCUSSION

A major challenge in the study of rare diseases is conducting a clinical trial with sufficient power to inform best clinical practice when the anticipated sample size is small. Historically, this has been an insurmountable barrier in the study of rare pediatric autoimmune diseases, and explains why a clinical trial of childhood PAN had never been undertaken until now (21). We adopted a Bayesian clinical trial design with the objective of quantifying disease remission rates with CYC and MMF treatment, combining a robust elicitation of prior opinion and evidence with our trial data. Six-month remission rates observed in the MYPAN trial were consistent with prior opinions, and since 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 noninferiority of MMF compared to CYC for remission within 6 months. This observation, while not definitive, is still clinically useful, particularly since conducting a confirmatory frequentist trial is impossible (21). Further clinical face validity for the noninferiority of MMF compared to CYC is suggested by the fact that glucocorticoid use could be successfully tapered in all patients and all patients had nearly identical cumulative glucocorticoid exposure. Therefore, our results suggest that MMF might represent a viable alternative to CYC for remission induction in childhood PAN. Moreover, these results will inform prior opinions for any future trials in childhood PAN (e.g., the Biologics in Refractory Vasculitis Study [https://www.isrctn.com/ISRCTN16502655]).

The MYPAN data are consistent with data from studies in AAV, most notably the MYCYC study (20) (though not completely independently, as the MYCYC data helped inform the prior opinion used in MYPAN), which included adults and children and showed that MMF was noninferior to CYC for inducing remission. Following remission, all patients in our trial received AZA and glucocorticoid maintenance therapy, with no relapses. This observation contrasts with findings in the MYCYC trial which showed that relapses occurred earlier and more frequently among patients in the MMF group (33%) compared to among those in the CYC group (19%) (20). Thus, the previous suggestion that relapses in childhood PAN are less common than in childhood AAV is supported by our results (1).

Other secondary end points are also potentially clinically relevant, though the results are purely descriptive. Remission was exhibited at a median of 7.1 weeks among patients in the MMF group, compared to a median of 17.6 weeks in the CYC group. PVDI scores were lower in the MMF group, implying less damage, although our trial was not powered to demonstrate statistical significance of this observation. PVDI scores (and in adults, VDI scores) are not weighted; hence, overall low numerical scores can still indicate severe damage in patients. Therefore, future studies are needed to further examine the potential clinical importance of this preliminary observation.

C-HAQ disability scores and pain scores at trial end were comparable among patients in both groups, though scores were numerically lower among patients in the MMF group. While we must be careful not to overinterpret this purely descriptive observation, a possible obvious explanation is that the C-HAQ score reflected a more rapid resolution of disease activity among patients in the MMF group, resulting in faster resolution of disability and pain. Similarly, and in accordance with this suggestion, quality of life improved more rapidly and to a greater extent among patients in the MMF group compared to the CYC group, particularly in regard to the physical summary score. The health economic analysis in the UK suggested that MMF may generate fewer QALYs and may be more expensive than CYC, though

with a significant element of uncertainty. No patients died in either trial group. Lastly, remission was achieved in all the patients in the MMF group who completed follow-up.

There were no new safety signals for MMF or CYC. Notably, 2 infections were considered to be possibly linked to MMF. Improved short-term safety with MMF was thus not demonstrated. However, long-term safety issues are probably of more importance and are not captured in our trial. The use of MMF along with a standard dose of glucocorticoids offers clear advantages over CYC in terms of fertility preservation in younger patients, and potentially lower malignancy rates later in life, which is of particular concern among pediatric patients (18,20).

Our trial has several notable strengths. To our knowledge, it is the first randomized trial in childhood PAN. Patients were recruited from regional tertiary centers; thus, the trial cohort was fully representative of the spectrum of disease in childhood PAN, as indicated by the extent of organ involvement observed. The study also included the use of standardized tools developed specifically for children with vasculitis to allow accurate classification of childhood PAN (35), and of disease activity and remission (using the PVAS) (24). Our study was also the first to record vasculitis damage prospectively using the PVDI, which to date has been only preliminarily used in retrospective studies (27,28).

The strengths of this trial should be viewed against its limitations, notably, that the clinical trial evidence is based on a small sample size, augmented by a distillation of clinical experience in the form of prior distributions. However, the fact that the posterior distributions we observed are largely consistent with prior expert opinions adds important clinical face validity to the conclusion, which must be based on the final Bayesian posterior distributions and may provide the prior distributions for future cumulative research of childhood PAN. In addition, MYPAN was not blinded, for purely practical reasons. Although glucocorticoid exposure was documented, glucocorticoid toxicity was not systematically captured using the glucocorticoid toxicity index (36). Only 7 of 11 patients were screened for DADA2 as part of their routine evaluation, which might have important implications for determining the efficacy of both MMF and CYC in childhood PAN (10,11). Health economic analyses were based on UK costs, and therefore may not apply uniformly in other countries (e.g., in Turkey, where MMF is more expensive than CYC). Our trial also did not address the possibility that higher doses of MMF might be even more efficacious. Regulatory approval for dose escalation was initially requested in the MYPAN trial, but not granted by competent authority since it was suggested that adverse effects might also increase with higher doses. Finally, generalizability to other ethnic groups was limited as 10 of 11 patients in our trial were White.

In summary, MMF is probably noninferior to CYC for induction of remission in childhood PAN when combined with glucocorticoids. MMF may also be associated with better quality of life compared to CYC.

ACKNOWLEDGMENTS

This was a fully investigator-led trial. Sponsorship was provided by University College London. Funding was provided by Versus Arthritis (grant 20094), Vasculitis UK, and the Lauren Currie Twilight Foundation. The lead clinical trial unit was the Liverpool Clinical Trials Centre (LCTC). We also acknowledge support from the Pediatric Rheumatology International Trial Organisation (PRINTO), particularly Elisa Patrone and Marco Garrone; and Hacettepe University Research Fund (TK-2017-15782). We are grateful to all the trial investigators, subinvestigators, research nurses, and all of the patients who participated in this study. Centers that opened for recruitment in the MYPAN trial were as follows: Hospital Sant Joan de Déu (Barcelona); University Hospital Centre Zagreb, University School of Medicine; Azienda Ospedalario Meyer (Florence); IRCCS Gaslini (Genoa); Hacettepe University Children's Hospital, Ankara; Alder Hey Children's NHS Foundation Trust, Liverpool; Great Ormond Street Hospital NHS Foundation Trust, London; Royal Victoria Hospital, Newcastle Hospitals NHS Foundation Trust; Royal Hospital for Sick Children, Glasgow; Royal Manchester Children's Hospital; Sheffield Children's Hospital; Addenbrookes Hospital, Cambridge; and University College London Hospital. Authors Brogan and Elitheriou acknowledge support from the Great Ormond St Hospital Clinical Research Facility and Great Ormond St Hospital Children's Charity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Brogan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brogan, Hickey, Beresford, Ozen, Hughes, Dolezalova, Hampson, Whitehead, Jayne, Tudur-Smith, Eleftheriou.

Acquisition of data. Brogan, Arch, Hickey, Anton, Iglesias, Baildam, Mahmood, Cleary, Moraitis, Papadopoulou, Riley, Demir, Ozen, Ruperto, Tudur-Smith, Eleftheriou.

Analysis and interpretation of data. Brogan, Arch, Hickey, Ozen, Culeddu, Hughes, Hampson, Tudur-Smith, Eleftheriou.

REFERENCES

1. Dillon MJ, Eleftheriou D, Brogan PA. Medium-size-vessel vasculitis. Pediatr Nephrol 2010;25:1641–52.
2. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch–Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria. Ann Rheum Dis 2010;69:798–806.
3. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002;360:1197–202.
4. Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ, et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. Arthritis Rheum 2013;65:2476–85.
5. Ozen S, Anton J, Arisoy N, Bakkalogly A, Besbas N, Brogan P, et al. Juvenile polyarteritis: results of a multicenter survey of 110 children. J Pediatr 2004;145:517–22.
6. Brogan PA, Shah V, Bagga A, Klein N, Dillon MJ. T cell Vβ repertoires in childhood vasculitides. Clin Exp Immunol 2003;131:517–27.
7. Brogan PA, Shah V, Dillon MJ. Polyarteritis nodosa in children. Clev Clin J Med 2002;69 Suppl 2:Sii168–9.
8. Elkan PN, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med 2014;370:921–31.

9. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med 2014;370:911–20.
10. Ombrello AK, Qin J, Hoffmann PM, Kumar P, Stone D, Jones A, et al. Treatment strategies for deficiency of adenosine deaminase 2 [letter]. N Engl J Med 2019;380:1582–4.
11. Nanthapisal S, Murphy C, Omoyinmi E, Hong Y, Standing A, Berg S, et al. Deficiency of adenosine deaminase type 2: a description of phenotype and genotype in 15 cases. Arthritis Rheumatol 2016;68:2314–22.
12. De Graeff N, Groot N, Brogan P, Ozen S, Avcin T, Bader-Meunier B, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides: the SHARE initiative. Rheumatology (Oxford) 2019;58:656–71.
13. Baggenstoss AH, Shick RM, Polley HF. The effect of cortisone on the lesions of periarteritis nodosa. Am J Pathol 1951;27:537–59.
14. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, et al, on behalf of the French Cooperative Study Group for Vasculitides. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. Br J Rheumatol 1997;36:1290–7.
15. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Généreau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis: a prospective, randomized trial in sixty-two patients. Arthritis Rheum 1995;38:1638–45.
16. Guillevin L, Cohen P, Mahr A, Arène JP, Mouthon L, Puéchal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. Arthritis Rheum 2003;49:93–100.
17. Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Puéchal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010;62:1186–97.
18. Langford CA. Cyclophosphamide as induction therapy for Wegener's granulomatosis and microscopic polyangiitis. Clin Exp Immunol 2011;164 Suppl 1:31–4.
19. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.
20. Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis 2019;78:399–405.
21. Hampson LV, Whitehead J, Eleftheriou D, Tudur-Smith C, Jones R, Jayne D, et al. Elicitation of expert prior opinion: application to the MYPAN trial in childhood polyarteritis nodosa. PLoS One 2015;10:e0120981.
22. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Arch Dis Child 2011;96:596–601.
23. Downing HJ, Pirmohamed M, Beresford MW, Smyth RL. Paediatric use of mycophenolate mofetil [review]. Br J Clin Pharmacol 2013;75:45–59.
24. Ruperto N, Ozen S, Pistorio A, Dolezalova P, Brigan P, Cabral DA, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I. Overall methodology and clinical characterisation. Ann Rheum Dis 2010;69:790–7.
25. Dolezalova P, Price-Kuehne FE, Özen S, Benseler SM, Cabral DA, Anton J, et al. Disease activity assessment in childhood vasculitis: development and preliminary validation of the Paediatric Vasculitis Activity Score (PVAS). Ann Rheum Dis 2013;72:1628–33.
26. Jones R, Harper L, Ballarin J, Blockmans D, Brogan P, Bruchfeld A, et al, on behalf of the European Vasculitis Study Group. A randomized trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associated vasculitis:"MYCYC" [abstract]. Presse Med 2013;42:678–9.
27. Eleftheriou D, Varnier G, Dolezalova P, McMahon AM, Al-Obaidi M, Brogan PA. Takayasu arteritis in childhood: retrospective experience from a tertiary referral centre in the UK. Arthritis Res Ther 2015;17:545.
28. Eleftheriou D, Gale H, Pilkington C, Fenton M, Sebire NJ, Brogan PA. Eosinophilic granulomatosis with polyangiitis in childhood: retrospective experience from a tertiary referral centre in the UK. Rheumatology (Oxford) 2016;55:1263–72.
29. Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, et al. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries: review of the general methodology. Clin Exp Rheumatol 2001;19 Suppl 23:S1–9.
30. Stevens K. Valuation of the Child Health Utility 9D index. Pharmacoeconomics 2012;30:729–47.
31. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.
32. Hampson LV, Whitehead J, Eleftheriou D, Brogan P. Bayesian methods for the design and interpretation of clinical trials in very rare diseases. Stat Med 2014;33:4186–201.
33. Schulz KF, Altman DG, Moher D, Fergusson D. CONSORT 2010 changes and testing blindness in RCTs. Lancet 2010;37:1144–6.
34. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779–87.
35. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010;69:798-806.
36. Miloslavsky EM, Naden RP, Bijlsma JW, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76:543–6.