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Mycophenolate mofetil versus cyclophosphamide for the induction of remission of childhood polyarteritis nodosa

Submission date
23/10/2014

Recruitment status
No longer recruiting

Registration date
23/10/2014

Overall study status
Completed

Last Edited
21/09/2021

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Polyarteritis nodosa (PAN) is a serious inflammatory blood vessel disease (vasculitis) in children. It is the third most common vasculitis in childhood and presents with fever, arthritis, skin rash and stomach pain, amongst other symptoms. Following the introduction of steroid treatment in the 1950s, death rates fell from 100% to 50%. The introduction of cyclophosphamide (CYC) in the 1970s resulted in further significant reductions in death rate. Surprisingly there have been no further advances in treatment since then, and no clinical studies ever performed in children with PAN. Currently, the death rate is between 3 and 10%, although this comes at a cost: 25 to 50% experience a serious side effect of CYC including severe infection, nausea and hair loss, and increased risk of late infertility and malignancy. Clinical studies of alternative drugs to replace CYC are therefore important. The drug mycophenolate mofetil (MMF) is believed to be a safer treatment option than CYC. The main aim of the study is to find out how safe and effective MMF is for the treatment of PAN, compared to the standard drug CYC.

Who can participate?
Children aged 4 to 18 years diagnosed with PAN can take part.

What does the study involve?
Participants will be randomly allocated to one of two groups: 3-6 months (12-24 weeks) treatment with either MMF or CYC. This is followed by 12-15 months (48-60 weeks) azathioprine plus prednisolone for all. The study ends after 18 months (72 weeks) treatment.

What are the possible benefits and risks of participating?
Not provided at time of registration.

Where is the study run from?
The study takes place in various vasculitis centres across Europe:
1. Great Ormond Street Hospital, UK
2. Sheffield Children's Hospital, UK
3. University Hospital Bristol, UK

4. Royal Manchester Children's Hospital, UK
5. Royal Hospital for Sick Children, Glasgow, UK
6. Birmingham Children's Hospital, UK
7. Nottingham University Hospital, UK
8. Norfolk and Norwich University Hospital NHS Trust, UK
9. Royal Victoria Hospital, Newcastle, UK
10. Alder Hey Children's NHS Foundation Trust, UK
11. Universitair Ziekenhuis Gent, Belgium
12. University Hospital Centre Zagreb, University School of Medicine, Croatia
13. Charles University in Prague and General University Hospital, Czech Republic
14. Klinikum Bad Bramstedt, Germany
15. Charite University Hospital Berlin, Germany
16. Helios Kliniken Berlin, Germany
17. University Medical Center Freiburg, Germany
18. Kinderklinik Garmisch-Partenkirchen gGmbH, Germany
19. Athens Medical School, University of Athens, Greece
20. IRCCS Istituto G. Gaslini, Italy
21. Azienda Ospedaliero-Universitaria Meyer, Italy
22. Ospedale Santa Chiara, Università di Pisa, Italy
23. Ospedale Pediatrico Bambin Gesu, Italy
24. Wilhelmina Kinderziekenhuis, Netherlands
25. Medical University of Silesia, Poland
26. Wojewódzki Specjalistyczny Szpital Dziecięcy św. Ludwika w Krakowie, Poland
27. Hospital Sao Joao, Portugal
28. Hospital Santa Maria, Portugal
29. University Children's Hospital, University Medical Centre Ljubljana, Slovenia
30. Hospital Ramon y Cajal, Spain
31. Hospital Universitario La Fe, Spain
32. Hospital Sant Joan de Deu, Universitat de Barcelona, Spain
33. Kanuni Sultan Süleyman Education and Research Hospital, Turkey
34. The Queen Silvia Children's Hospital, Sweden
35. Gulhane Military Medical Academy School of Medicine, Turkey
36. Hacettepe University Children's Hospital, Turkey

When is the study starting and how long is it expected to run for?
November 2014 to June 2019.

Who is funding the study?
Arthritis Research UK.

Who is the main contact?
Mr Ben Hardwick
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2013-004668-71

Protocol serial number
17395

Study information

Scientific Title
An open-label randomised controlled trial of mycophenolate mofetil versus cyclophosphamide for the induction of remission of childhood polyarteritis nodosa

Acronym
MYPAN

Study objectives
MMF (experimental therapy) is non-inferior for induction of remission to CYC (standard therapy) but with less
or comparable short-term toxicity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London Bloomsbury; submitted on 25/09/2014; ref. 14/LO/1565 - pending approval

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Polyarteritis nodosa

Interventions
CYC: 1. CYC is given as intravenous pulses at weeks 0, 2, 4 and then every 3 weeks until remission is reached from start of therapy (max 10 doses, min 6 doses) at a dose of 500-750 mg/m2 (maximum 1.2 g).
MMF: MMF (experimental arm: 1200 mg/m2/day, max 1 g bd as standard dose; in those with suboptimal response MMF dose can be increased to 1800 mg/m2/day, max 3 g/day; Follow Up Length: 18 month(s)

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
Remission within 6 months of randomisation defined as PVAS (modified paediatric BVAS) of zero on two consecutive readings ≥ 1 month apart, with adherence to the protocolised corticosteroid taper

Key secondary outcome(s))
Not provided at time of registration

Completion date
30/04/2020

Eligibility

Key inclusion criteria
1. Age at screening = 4 and = 18 years
2. Children to be included must fulfil the new EULAR/PRINTO/PReS classification criteria for childhood systemic PAN (4) as defined by: Histopathological evidence of necrotising vasculitis in medium- or small-sized arteries or angiographic abnormality as a mandatory criterion (4); plus one of the following five:
2.1. Skin involvement
2.2. Myalgia or muscle tenderness
2.3. Hypertension
2.4. Peripheral neuropathy
2.5. Renal involvement
3. Newly diagnosed* and with active disease that would normally require treatment with CYC:
3.1. One or more of major PVAS items (see below)
3.2. and/or three or more minor PVAS items
3.3. and/or either of the two additional entry criteria:
3.3.1. Severe systemic inflammation and/or features of macrophage activation syndrome due to PAN where the
investigator would routinely use cyclophosphamide
3.3.2. Demonstration of severe angiographic changes consistent with systemic PAN with other compatible clinical features, but not necessarily including the major PVAS items listed above

4. Written informed consent for study participation obtained from the patient or parents/legal guardian, with assent as appropriate by the patient, depending on the level of understanding.
Sufficient disease activity for trial entry (see inclusion criteria 3 above) requires at least one major or three minor PVAS
items as listed below, and/or at least one of the additional criteria listed:

Major PVAS items:
Trial entry criteria or major relapse require the recurrence or new appearance of major organ involvement, if they are
attributable to active vasculitis:
1. Severe cutaneous vasculitis: significant infarct, ulcer or gangrene. Other significant cutaneous vasculitis such as widespread bullous vasculitic skin disease would also be an inclusion criterion
2. Threatened vision from any of: retinal vasculitis, retinal vessel thrombosis, scleritis, retinal exudates, or retinal haemorrhages
3. Major chest involvement: major pulmonary bleeding, with shifting pulmonary infiltrates; other causes of bleeding should be excluded if possible
4. Cardiovascular involvement: loss of pulses, bruits over accessible arteries, blood pressure discrepancy more than 10 mmHg in any limb, claudication of extremities, ischaemic cardiac pain, cardiomyopathy, congestive cardiac failure, valvular heart disease, pericarditis
5. Abdominal involvement: abdominal pain, blood in stools or bloody diarrhoea, or bowel ischaemia. Pancreatitis, whilst not specifically listed as a PVAS item, would also be an indication for inclusion
6. Renal involvement: hypertension, significant proteinuria, significant haematuria (if microscopic haematuria > 5 red
blood cells per high power field, or red cell casts), GFR < 80 ml/min/1.73m2 , rise in creatinine > 10% or creatinine
clearance (GFR) fall > 25%. Biopsy is strongly recommended for recurrent haematuria or unexplained rise in creatinine
EXCEPT where large renal arterial aneurysms have been demonstrated
7. Nervous system involvement: meningitis or encephalitis, organic confusion/cognitive dysfunction, non-hypertensive seizures, stroke, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, or motor mononeuritis multiplex.
(Imaging of brain/cord providing supportive evidence that these lesions are due to vasculitis are usually present for those items pertaining to the brain or cord)

Minor PVAS items:
Minor entry criteria or minor relapse require the recurrence of disease activity of less severity, such as the following, if they are attributable to active vasculitis:
1. Myalgia, arthralgia, arthritis
2. Less severe cutaneous vasculitis: polymorphous exanthema; livedo reticularis; panniculitis; purpura; skin nodules; other less severe cutaneous vasculitic phenomena
3. Mouth ulcers
4. Non-imminently sight threatening eye involvement: episcleritis; blepharitis; conjunctivitis; uveitis

*Newly diagnosed is defined for the purposes of the trial as a diagnosis of systemic PAN less than 3 months (12 weeks) prior to screening for MYPAN. If the PAN diagnosis was more than 3 months (12 weeks) prior to the date of initial screening, please discuss with the Chief Investigator.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
4 years

Upper age limit
18 years

Sex
All

Total final enrolment
11

Key exclusion criteria
Exclusions related to vasculitis type and/or severity
1. Diagnosis of alternative vasculitic syndrome e.g. HSP, or ANCA vasculitis
2. Patients requiring dialysis

Exclusions related to general health
3. Evidence of other significant uncontrolled concomitant disease that in the investigators view would preclude or interfere with patient participation. This will be recorded in the screening log
4. Primary or secondary immunodeficiency including known history of human immunodeficiency virus (HIV) infection
5. Known active and/or chronic infection of any kind (excluding fungal nail and/or minor fungal skin infections)
6. History of serious recurrent or chronic infection including tuberculosis (a screening chest radiograph will be performed if not performed within 12 weeks prior to randomisation)
7. History of cancer, including solid tumours, haematologic malignancies and carcinoma in situ
8. Participation in a clinical trial testing a medicinal product within 3 months (12 weeks) preceding randomisation for the MYPAN trial

Exclusions related to medication
9. History of a severe allergic or anaphylactic reaction to any of the study medications or their excipients
10. More than 3 g of IV methylprednisolone within 1 month (4 weeks) prior to randomisation
11. More than 3 weeks of oral prednisolone/prednisone at dose of 2 mg/kg once daily within 1 month (4 weeks) prior
to randomisation
12. Treatment with MMF or azathioprine for more than 2 weeks; or more than one intravenous dose of cyclophosphamide (>500 mg/m2) within 1 month (4 weeks) prior to randomisation
13. Rituximab or high dose intravenous immunoglobulin within the last 12 months (48 weeks)
14. Intolerance or contraindications to intravenous glucocorticoids
15. Participant of reproductive potential not prepared to use a reliable means of contraception (e.g. hormonal contraceptive patch, intrauterine device, physical barrier) throughout study participation

a. Sexually active female not prepared to use two reliable forms of contraception for the complete duration of the trial

Exclusions related to laboratory findings
16. Positive urine human chorionic gonadotropin (hCG) measured at screening (if appropriate) or a positive urine pregnancy test prior to study entry or breastfeeding
17. Positive tests for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C serology at randomisation
18. Absolute neutrophil count <1.5 x 10^9/l
19. Estimated GFR <15 mL/min/1.73m2 (calculated using the Schwartz GFR formula)

Date of first enrolment
10/11/2014

Date of final enrolment
30/06/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Liverpool
Liverpool
United Kingdom
L69 3GA

Sponsor information

Organisation
University College London (UK)

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK; Grant Codes: 20094

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/09/2021	21/09/2021	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes