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RITUXILUP - A study to assess if the combination of Rituximab, mycophenolate mofetil (MMF) and no oral steroids is as effective as mycophenolate mofetil and oral steroids in treating lupus nephritis

Submission date
13/11/2013

Recruitment status
Stopped

Registration date
20/01/2014

Overall study status
Stopped

Last Edited
14/05/2019

Condition category
Skin and Connective Tissue Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Systemic lupus erythematosus (SLE) is a severe, long-term relapsing disease of unknown cause that predominantly affects young women. In this disease, the immune system attacks and injures various tissues in the body, including kidneys (nephritis). Lupus nephritis causes leakage of protein from the kidneys resulting in swelling of the legs and face, can cause kidney failure and can be life threatening. The use of high doses of steroids and other drugs, such as MMF, can control the disease. However, the steroids in particular are toxic with serious short- and long-term side effects that damage patients. There is a need to reduce the use of steroids in patients with lupus. Rituximab has been used in many patients already and appears to be effective and our initial studies suggest it is effective when used with MMF but without oral steroids. We aim to find out if the drug combinations are effective in treating lupus nephritis.

Who can participate?
Adult patients (aged 18-75 years old) and children aged 12-17 years old with lupus nephritis can participate in the study.

What does the study involve?
Patients will be randomly allocated to one of two groups: intervention group and control group. Interventional arm patients receive rituximab and methylprednisolone through a vein and those in the control arm gets methylprednisolone through a vein and oral prednisolone (standard of care treatment). Patients will be asked to take part in the study for a minimum of 2 years, up to 4 years. In that time patients will be followed closely to collect information about their progress. There will be a maximum of 29 research visits - the same as if the patients was not in the study.

What are the possible benefits and risks of participating?
Infusion reactions are seen with rituximab but all patients in this study will receive

methylprednisolone through a vein prior to the rituximab infusion and will additionally be given antihistamines and paracetamol. There are no severe side effects or serious infections with the rituximab group. It is important to balance the potential risks of any new therapy with the serious consequences of uncontrolled lupus nephritis and the toxicity of current treatments. Patients will be recruited and followed up in experienced centres familiar with both routine treatment and the use of rituximab. Participants in the intervention group may be at an increased risk for flare compared with patients who take MMF and oral steroids. Renal flare is a risk factor for developing end-stage renal disease. However, our initial data do not suggest a high flare rate and it is possible that exposure to rituximab early in treatment, as proposed in the current study, may reduce later risk of flare.

Where is the study run from?
The study is conducted from the following hospitals across the UK and also from centres in Europe:
Hammersmith Hospital, University of Manchester, University of Leicester, New Queen Elizabeth Hospital, Great Ormond Street Hospital, King's College London, Royal Free Hospital, Guy's Hospital, Chapel Allerton Hospital, Royal Stoke Hospital, Churchill Hospital Oxford.

When is study starting and how long is it expected to run for?
The study has been terminated early. The last participant was recruited in March 2017 planned to be 14 April 2017 and the study close out will commence in late 2017 and early 2018.

Who is funding the study?
Arthritis Research UK (UK).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2012-004893-25

ClinicalTrials.gov (NCT)
NCT01773616

Protocol serial number
CRO2035

Study information

Scientific Title
RITUXILUP - An open label randomised multicentre controlled trial of RITUXImab and mycophenolate mofetil (MMF) without oral steroids for the treatment of LUPus nephritis

Acronym
RITUXILUP

Study objectives
RITUXILUP is a proof of concept open labeled randomized controlled multicentre trial that sets out to address two key questions:
1. What is the role of Rituximab in treating lupus nephritis?
2. Does Rituximab permit removal of oral steroids and does this increase the safety of the treatment?
Based on published data, our pilot data and the huge experience of the detrimental effects of steroids, we plan to test the hypothesis that in steroid-naïve patients with a new flare of lupus nephritis, the addition of Rituximab to mycophenolate mofetil (MMF) but without oral steroids, is at least as effective at inducing a response as the standard of care therapy comprising MMF and oral steroids. By demonstrating non-inferiority of the Rituximab-based, oral steroid-free regimen, this trial would change the fundamental landscape of the treatment of lupus nephritis for the first time in 60 years. Patients who fulfil the eligibility criteria and have provided informed consent will be randomised on a 1:1 basis to either the Rituximab and no oral steroid arm or the standard of care arm.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East Midlands - Nottingham 2, 07/05/2014, ref. 14-EM-0121

Study design
Design: 1:1, international open label, phase III, multicentre, controlled randomised trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Lupus nephritis

Interventions
Participants are randomised to two groups:
1. Treatment group - You will receive the study drug Rituximab and Methylprednisolone by intravenous ('in the vein') therapy. Rituximab can sometimes make you itchy and can give you a fever. To prevent this, we will also give you an anti-allergy medicine, antihistamine, either as a tablet or intravenously and an anti-fever medicine, paracetamol.
2. Control group - You will not be given Rituximab. You will receive methylprednisolone by intravenous therapy and start oral prednisolone. The oral prednisolone is taken as tablets and the dose of oral prednisolone will go down during the trial and may even be stopped as decided by the Research Doctor or Principal Investigator.

We will be recruiting patients like you all over in the UK, Europe and United States of America. You will be asked to take part in the study for at least 2 years and possibly up to 4 years. There will be a maximum of 29 research visits during this time. There is a 2-year follow-up. The number of assessments will not be more than your routine visits.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Rituximab, mycophenolate mofetil and oral steroids

Primary outcome(s)
The primary outcome is to demonstrate non-inferiority difference in the proportion of patients achieving complete renal response (CR) at week 52 in each arm of the study without the need for steroid prescription.

Key secondary outcome(s))
1. Safety outcomes:
1.1. Serious infectious episodes
1.2. Serious adverse events
1.3. Evidence of metabolic abnormalities, particularly new onset diabetes
2. Disease control over time:
2.1. Proportion of patients achieving Partial Response (PR)
2.2. Time to stable CR
2.3. Time to PR
2.4. Proportion of patients in PR who achieve histological remission
2.5. Proportion of patients with renal or extra flare
2.6. Cumulative steroid exposure
2.7. Deviation from the steroid taper in the steroid arm and/or introduction of steroids in the steroid-free arm
2.8. Proportion of patients achieving a response as defined by the SLE Responder Index (SRI) at week 52 and annually thereafter as defined by:
2.8.1. a more than 4-point reduction in SELENA-SLEDAI score

2.8.2. no new BILAG A organ domain score
2.8.3. no more than I new BILAG B score
2.8.4. no worsening in physician's global assessment (PGA) by >10%
2.8.5. must not have received non-protocol treatment
2.9. Proportion of patients achieving a response as defined by the BILAG-based Composite Lupus Assessment (BICLA) at week 52 and annually thereafter as defined by: BILAG 2004 improvement (BILAG A to B/C/D, BILAG B to C/D and no BILAG worsening, no deterioration in SLEDAI total score, no worsening in physician's global assessment (PGA) by >10% and must not have received non-protocol treatment

Completion date
31/07/2018

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current participant inclusion criteria (as of 22/01/2018):
1. Adults aged 18-75 years old and children aged 12-17 years old.
2. Active lupus nephritis, as defined by kidney biopsy within prior 8 weeks assessed by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification:
2.1. class III (A or A/C) with active lesions in at least 20% of the viable glomeruli, or
2.2. class IV-S (A or A/C) with active lesions in at least 20% of the viable glomeruli, or
2.3. class IV-G (A or A/C) with active lesions in at least 20% of the viable glomeruli and / or
2.4. class V and
2.5. urine protein-to-creatinine ratio equal to or greater than 100mg/mmol (>1mg/mg) at randomisation or at any time within 28 days before randomisation
3. No contraindications to the use of IV methyl prednisolone, MMF, oral steroids or rituximab or any other required medications such as antipyretics, antihistamines
4. Ability to provide informed consent
5. As MMF is teratogenic and on basis of advice from NHS England (The updated recommendations (https://www.gov.uk/drug-safety-update/mycophenolate-mofetil-mycophenolic-acid-new-pregnancy-prevention-advice-for-women-and-men) for patients whilst on MMF and after stopping are:
5.1. Women who have child bearing potential should be willing to use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment
5.2. Men (including those who have had a vasectomy) should be willing to use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products
5.3. Female partners of male patients treated with mycophenolate mofetil should use highly effective contraception during treatment and for 90 days after the last dose

Previous participant inclusion criteria:
1. Adults aged 18-75 years old and children aged 12-17 years old
2. Active lupus nephritis, as defined by kidney biopsy within prior 8 weeks assessed by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification:
2.1. Class III (A or A/C) with active lesions in at least 20% of the viable glomeruli, or
2.1. Class IV-S (A or A/C) with active lesions in at least 20% of the viable glomeruli, or
2.3. Class IV-G (A or A/C) with active lesions in at least 20% of the viable glomeruli and/or

2.4. Class V
2.5. Urine protein-to-creatinine ratio >100 mg/mmol (>1 mg/mg) at visit -1 or at any time within 14 days before visit -1
3. No contraindications to the use of IV methylprednisolone, MMF, oral steroids or rituximab or any other required medications such as antipyretics or antihistamines
4. Ability to provide informed consent
5. Willing to use appropriate contraception if at risk of pregnancy (including but not limited to a diaphragm, an intrauterine device, progesterone implants or injections, oral contraceptives, the double-barrier method, or a condom)

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 years

Upper age limit
75 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria (as of 22/01/2018):
1. Obsolescence of >50% of the glomeruli or tubulointerstitial scarring of >50% or cellular crescents in >50% of the glomeruli
2. Severe “critical” SLE flare defined as:
2.1. BILAG 2004 A flare in CNS system
2.2. or any SLE manifestation requiring more immunosuppression than allowed within the protocol in the physician's opinion
3. Pregnant or lactating. Woman who have child bearing potential must have two negative pregnancy test results with a sensitivity of ≥ 25 mIU/mL: one from a serum pregnancy test at day -8 to day -10 of screening and another from a urine pregnancy test at day 1 prior to randomisation. If the timeline is shortened because of clinical urgency, then there must be a negative serum pregnancy test with a sensitivity of ≥ 25 mIU/mL within 1-2 days before study start
4. Patients not willing for their GP to be informed of their participation in this study
5. Patients should not be on or require maintenance steroids and should not have had more than 12 weeks of steroids in the period immediately preceding recruitment irrespective of dose
6. Patients that had received more than 2.0g of IV methyl prednisolone in the previous 4 weeks
7. Prior use within 12 months of screening visit of therapeutic monoclonal antibody, or B or T cell modulating ‘biologic’ use
8. Prior use within 6 months of the screening visit of Intravenous immunoglobulin / plasma exchange OR Cyclophosphamide
9. Active infections, including but not limited to the human immunodeficiency virus (HIV), and

hepatitis B (including prior infection as judged by positive Hepatitis B core antibody) or Hepatitis C or tuberculosis
10. Receipt of a live-attenuated vaccine within 3 months of study enrolment
11. In the investigator's opinion, patients that are at high risk for infection (including but not limited to indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent severe urinary tract infection)
12. Prior history of invasive fungal infections
13. History of any cancer
14. In female patients, known history of cervical dysplasia CIN Grade III cervical high risk human papillomavirus or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS) within the past 3 years. The patient will be eligible after the condition has resolved (e.g., follow-up HPV test is negative or cervical abnormality has been effectively treated >1 year ago)
15. Any concomitant medical condition or abnormal blood results that in the investigator's opinion, or after discussion with the CI, places the participant at risk by participating in this study.
16. Comorbidities requiring systemic corticosteroid therapy.
17. Current substance abuse

Previous participant exclusion criteria:
1. Aged <12 years or >75 years
2. Obsolescence of >50% of the glomeruli or tubulointerstitial scarring of >50%
3. Severe 'critical' SLE flare defined as:
3.1. BILAG 2004 A flare in CNS system
3.2. or any SLE manifestation requiring more immunosuppression than allowed within the protocol in the physician's opinion
4. Pregnancy
5. Breastfeeding
6. At risk of pregnancy and unwillingness to use a medically acceptable form of birth control
7. Patients should not be on or require maintenance steroids and should not have had more than 4 weeks of steroids in the period immediately preceding recruitment irrespective of dose
8. Patients that had more than 1.5 g of IV methylprednisolone in the previous 4 weeks
9. Prior use within 12 months of visit 1 of therapeutic monoclonal antibody, or B or T cell modulating 'biologic' use
10. Prior use within 6 months of visit 1 of intravenous immunoglobulin/plasma exchange OR cyclophosphamide
11. eGFR <30 ml/min/1.73m2
12. Serious infection with the previous 1 month requiring hospitalization or IV antibiotic therapy
13. Active infections, including but not limited to the human immunodeficiency virus (HIV), and hepatitis B (including prior infection as judged by positive Hepatitis B core antibody) or Hepatitis C or tuberculosis
14. Receipt of a live attenuated vaccine within 3 months of study enrolment
15. In the investigator's opinion, patients that are at high risk for infection (including but not limited to indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent severe urinary tract infection)
16. Prior history of invasive fungal infections
17. History of any cancer
18. In female patients, known history of cervical dysplasia CIN Grade III cervical high-risk human papillomavirus or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS) within the past 3 years. The patient will be eligible after the condition has resolved (e.g., follow-up HPV test is negative or cervical abnormality has been effectively treated >1 year ago)
19. Severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal,

pulmonary, cardiac or neurological disease (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study) with the exception of diseases or conditions related to active SLE
20. Comorbidities requiring systemic corticosteroid therapy
21. Current substance abuse
22. IgG below lower limit of local laboratory range

Date of first enrolment
14/04/2015

Date of final enrolment
27/03/2017

Locations

Countries of recruitment
United Kingdom

England

Austria

Brazil

Canada

Chile

Denmark

France

Germany

Italy

Netherlands

Poland

Portugal

Russian Federation

Spain

Sweden

United Arab Emirates

Study participating centre
Imperial College London
Imperial Clinical Trials Unit
ICCH Building
59-61 North Wharf Road
London
United Kingdom
W2 1PG

Sponsor information

Organisation
Imperial College London (UK)

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK (UK) (ref: 20108)

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