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# Switching to alternative tumour-necrosis factor (TNF)-blocking drugs or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-blocking drug

**Submission date**
22/11/2010

**Registration date**
24/11/2010

**Last Edited**
04/08/2022

**Recruitment status**
No longer recruiting

**Overall study status**
Completed

**Condition category**
Musculoskeletal Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

## Plain English summary of protocol

Background and study aims
Rheumatoid arthritis (RA) is the most common treatable cause of disability in the Western world. RA affects over 600,000 people in the UK: symptoms impact heavily on patients' ability to perform daily activities at home and ability to undertake work commitments. It is therefore vital to treat this condition effectively and with the minimum of time delay. There have been dramatic advances recently in the development of effective drugs to treat RA with the use of Tumour Necrosis Factor (TNF)-blocking drugs which have transformed the lives of people suffering from RA. While these drugs are highly effective overall, some patients do not respond well for reasons we do not fully understand yet. Initial studies have shown that when a TNF-blocking drug does not work, switching to one of the other TNF-blocking drugs can be effective. In addition to these drugs, two new drugs, rituximab and abatacept, have also been licensed for patients who do not respond to a TNF-blocking drug. However, the National Institute of Clinical Excellence (NICE) have only approved the use of rituximab, which means that patients have only one option (rituximab); this option is unsuccessful in reducing disease symptoms in a third of patients. This study aims to provide those RA patients who have failed to respond with an initial TNF-blocker with more treatment choices based on a thorough evaluation of the currently licensed drugs available.

Who can participate?
Patients aged 18 or over with rheumatoid arthritis who have not responded to treatment with a TNF-blocking drug

What does the study involve?
In order to make a fair assessment to whether the alternative treatments we propose are as good as rituximab, patients will be randomly allocated into three groups: one group will receive rituximab, another group will receive abatacept, and the third group will receive an alternative TNF-blocking drug. Patients will receive their allocated treatment for 48 weeks, after which they will be followed-up for up to 96 weeks and treated as per the local clinician's discretion.

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

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
The study started in October 2011 and will run until December 2015. Each patient's participation in the study will last up to 96 weeks.

Who is funding the study?
NIHR Health Technology Assessment Programme - HTA (UK)

Who is the main contact?
Ms Claire Davies

### Study website
http://ctru.leeds.ac.uk/switch

# Contact information

### Type(s)
Scientific

### Contact name
Ms Claire Davies

### Contact details
Clinical Trials Research Unit (CTRU)
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# Additional identifiers

### EudraCT/CTIS number
2010-023880-17

### IRAS number

### ClinicalTrials.gov number
NCT01295151

### Secondary identifying numbers
RR10/9589

# Study information

## Scientific Title
Randomised-controlled trial of switching to alternative tumour-necrosis factor (TNF)-blocking drugs or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-blocking drug

## Acronym
SWITCH

## Study objectives
The principal aim of this study is to fill a clear knowledge gap and provide guidance for rheumatologists and reassurance to the patient group on a management challenge faced daily in rheumatology practice. Specifically, it aims to provide robust evidence on the optimal management of patients with established rheumatoid arthritis (RA) who have failed an anti-tumour-necrosis factor (anti-TNF) therapy (the first of the biological therapies to be introduced); in particular, we wish to address whether the currently licensed but non NICE-approved treatment options, TNF-blocking drug or abatacept, are equivalent to the NICE-approved treatment, rituximab. If so, the intention is to broaden treatment options and target these specific therapies to disease subgroups.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Yorkshire and the Humber - Leeds West, 21/02/2011, ref: 11/H1307/6

## Study design
Multicentre open-label parallel-group randomised controlled trial

## Primary study design
Interventional

## Secondary study design
Randomised parallel trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

## Health condition(s) or problem(s) studied
Rheumatoid arthritis

## Interventions
Current interventions as of 03/04/2014:
Following confirmation of written informed consent, potential patients will be registered into

the study in order to perform an eligibility screening. Patients with refractory RA who have failed an initial TNF-antagonist drug and meet the eligibility criteria will then be randomised. Patients will be allocated into three equal groups:
1. Alternative mechanism TNF-antagonist drug
2. Abatacept
3. Rituximab

Allocation will be by minimisation, stratified by centre, disease duration, primary versus secondary non-response to initial TNFi agent, rheumatoid factor status (RF seropositive or RF seronegative) +/- Anti-Citrullinated Peptide Antibody (ACPA) status and type of initial TNFi agent. All trial patients will have been maintained on a stable dose of MTX to ensure all can be potentially randomised to drugs requiring MTX co-prescription (infliximab), to optimise response to TNF-antagonist drug (synergy demonstrated) and maintain consistency in concomitant medication in the randomised arms. The treatment arms do not include randomisation to conventional DMARDs as patients would have already exhausted/failed DMARDs.

Patients will receive their randomised treatment for 48 weeks as part of the interventional phase. Following this, patients will enter the observational phase and be followed-up for up to 96 weeks. During the observational phase, patients will be treated as per the local clinicians discretion.

Following randomisation, patients will receive treatments as per standard regimen. For patients randomised to the subcutaneous treatments a week 4 safety visit may also be scheduled. Information on adverse events will be recorded at each visit. Formal clinical assessment (including DAS28 assessment, quality of life and health economic assessment as outlined in the secondary outcomes) will be undertaken at 3 monthly intervals. Data at 6 months will form the basis for evaluation of the primary outcome. All patients will be followed up until completion of the study; the period following the first 12 months will constitute an observational, clinical follow-up period. The clinical follow-up period will capture any such cessation of randomised drug. Screening prior to drug commencement will be in line with standard BSR guidelines. Baseline and 1-year plain x-ray of hands and feet and bone densitometry scan will also be undertaken to look for structural changes (retardation) and bone density change with the three therapies.

Previous interventions:
Following confirmation of written informed consent, potential patients will be registered into the study in order to perform an eligibility screening. Patients with refractory RA who have failed an initial TNF-antagonist drug and meet the eligibility criteria will then be randomised. Patients will be allocated into three equal groups:
1. Alternative mechanism TNF-antagonist drug
2. Abatacept
3. Rituximab

Allocation will be by minimisation, stratified by disease duration, primary versus secondary non-response to initial TNF-antagonist, seropositive versus seronegative type and centre. All trial patients will be maintained on a stable dose of MTX to ensure all can be potentially randomised to drugs requiring MTX co-prescription (infliximab), to optimise response to TNF-antagonist drug (synergy demonstrated) and maintain consistency in concomitant medication in the randomised arms. The treatment arms do not include randomisation to conventional DMARDs as patients would have already exhausted/failed DMARDs.

The duration of this study will be 60 months: 12 months for clinical trial set-up; the recruitment period will last 29 months; the screening period is a maximum of four weeks. Patients will be followed-up for 12 months.

Following randomisation, patients will receive treatments as per standard regimen. For patients randomised to the subcutaneous treatments a week 4 safety visit will also be scheduled. Information on adverse events will be recorded at each visit. Formal clinical assessment (including DAS28 assessment, quality of life and health economic assessment as outlined in the secondary outcomes) will be undertaken at 3 monthly intervals. Data at 6 months will form the basis for evaluation of the primary outcome. All patients will be followed up until completion of the study; the period following the first 12 months will constitute an observational, clinical follow-up period. Patients that flare (defined an increase in DAS28 of = 1.2) will discontinue study treatment and further treatment will be at the discretion of the treating clinician. The clinical follow-up period will capture any such cessation of randomised drug. Screening prior to drug commencement will be in line with standard BSR guidelines. Baseline and 1 year plain x-ray of hands and feet and bone densitometry scan will also be undertaken to look for structural changes (retardation) and bone density change with the three therapies.

## Intervention Type
Drug

## Phase
Not Applicable

## Drug/device/biological/vaccine name(s)
Abatacept, rituximab

## Primary outcome measure
Current primary outcome measures as of 03/04/2014:
Change in Disease Activity Score 28 (DAS28) at 6 months (24 weeks)

Previous primary outcome measures:
Proportion of patients who achieve a reduction in DAS28 of at least 1.2 at 6 months with no toxicity

## Secondary outcome measures
Current secondary outcome measures as of 03/04/2014:
The following outcomes will be measured at baseline and at weeks 12, 24, 36 and 48 unless otherwise stated:
1. DAS28
1.1. Proportion of participants who achieve a reduction in DAS28 score of greater than 1.2 from baseline at weeks 12, 24, 36 and 48 with no toxicity.
1.2. DAS28 Score
1.3. Low Disease Activity (LDA) Rate and Remission Rate
2. EULAR Response Scores and American College of Rheumatology (ACR) Response Scores (evaluated at weeks 12, 24, 36, 48)
3. CDAI (Clinical Disease Activity Index)
3.1. Change in CDAI score from baseline at weeks 12, 24, 36 and 48
3.2. Proportion of participants in each CDAI category at weeks 12, 24, 36 and 48
4. SDAI (Simplified Disease Activity Index)
4.1. Change in SDAI score from baseline at weeks 12, 24, 36 and 48

4.2. Proportion of participants in each SDAI category at weeks 12, 24, 36 and 48
5. ACR/EULAR Boolean remission rates
5.1. Proportion of participants that achieve Boolean remission rate at weeks 12, 24, 36 and 48
6. Quality of Life Assessments
6.1. RA Quality of Life (RAQoL) score
6.2. Health Assessment Questionnaire Disability Index (HAQ-DI©) (also evaluated at weeks 60, 72, 84 and 96)
6.3. Hospital Anxiety and Depression Scale (HADS)
7. Safety and Toxicity
7.1. Toxicity
7.2. Adverse Events and Reactions
8. Economic Evaluation
8.1. EuroQol 5-dimensions (EQ-5DTM) (also evaluated at weeks 60, 72, 84 and 96)
8.2. Health Utilities Index (also evaluated at weeks 60, 72, 84 and 96)
8.3. Health and Social Care Use & Expenditure due to Rheumatoid Arthritis (evaluated at weeks 12, 24, 36 and 48)
8.4. Incremental Cost Effectiveness
9. Imaging (at the discretion of individual sites)
9.1. Change in plain x-ray score of hands and feet (Modified Genant score - evaluated at baseline and week 48)
9.2. Bone densitometry scan scores (T-scores unilateral neck of femur and lumbar spine - evaluated at baseline and week 48)

Previous secondary outcome measures:
DAS28 score: reduction of greater than or equal to 1.2 from baseline with no toxicity at baseline and months 3, 9, and 12

The following outcomes will be measured at months 3, 6, 9 and 12:
2. Low Disease Activity (LDA) and Remission rates (DAS28 - baseline and evaluated at months 3, 6, 9 and 12)
3. Response Scores (EULAR and American College of Rheumatology (ACR) response scores)
4. Quality of Life Assessments (Evaluated at baseline and months 3, 6, 9, 12):
4.1. RA Quality of Life (RAQol) score
4.2. Health Assessment Questionnaire Disability Index (HAQ-DI)
4.3. EuroQol 5-dimensions (EQ-5D)
4.4. SF-6 with health economic analysis
4.5. Hospital Anxiety and Depression Scale (HADS)
5. Change in plain x-ray score (Modified Genant score - evaluated at baseline and 12 months)
6. Patient acceptability of treatment questionnaire

### Overall study start date
01/10/2011

### Completion date
31/12/2015

## Eligibility

### Key inclusion criteria
Current inclusion criteria as of 03/04/2014:
Patients meeting all of the following criteria will be considered for enrolment into the study:

1. Male and female subjects aged ≥18 years at the time of signing the Informed Consent Form.
2. Patients with a diagnosis of rheumatoid arthritis as per the ACR/EULAR 2010 classification criteria confirmed at least 24 weeks prior to the screening visit.
3. Patients who have failed conventional DMARD therapy as per NICE/BSR Guidelines i.e. failure of at least two DMARDS including MTX.
4. Patients with persistent RA disease activity despite having been treated with a current initial TNFi agent for at least 12 weeks. Active RA defined as (these criteria are consistent with BSR guidelines):
4.1. Primary non-response: failing to improve DAS28 by > 1.2 or failing to achieve DAS28 ≤ 3.2 within the first 12 to 24 weeks of starting the initial TNFi. This may include patients that have shown a reduction in DAS28 of > 1.2 but still demonstrate unacceptably high disease activity in the physicians judgement with evidence of an overall DAS28 of ≥ 3.2
OR
4.2. Secondary non-response: defined as inefficacy to first TNFi (having demonstrated prior satisfactory response) as per clinician judgement; with intolerance not the reason for cessation of first TNFi.
5. MTX dose stable for 4 weeks prior to the screening visit and to be continued for the duration of the study.
6. Patients on NSAIDs and/or corticosteroids (oral prednisolone not exceeding 10 mg daily) who have been on an unchanged regimen for at least 4 weeks prior to the screening visit and are expected to remain on a stable dose until the baseline assessments have been completed.
7. Provided written informed consent prior to any trial-specific procedures.

Previous inclusion criteria:
Subjects meeting all of the following criteria will be considered for enrolment into the study:
1. Male and female patients aged over 18 years
2. Diagnosis of rheumatoid arthritis (1987 revised American College of Rheumatology [ACR] criteria) confirmed at least 6 months prior to screening
3. Patients that have exhausted conventional disease modifying anti-rheumatic drugs (DMARD) options (including methotrexate [MTX])
4. Patients with persistent RA disease activity whilst being treated with a TNFi agent for at least 12 weeks defined as:
4.1. Primary non-response: failing to improve 28-item Disease Activity Score (DAS-28) by greater than or equal to 1.2 within the first three months
4.2. Secondary non-response: determined by physician decision with evidence of flare and deterioration in DAS28 of greater than or equal to 1.2 (having previously demonstrated a response to the TNFi)
5. MTX dose stable for 12 weeks prior to screening and to be continued for the duration of the study
6. Patients on non-steriodal anti-inflammatory drugs (NSAIDs) and/or corticosteroids must have remained on an unchanged regimen for at least 28 days prior to study drug administration
7. Patients must be able and willing to comply with the terms of this protocol

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
477

## Total final enrolment
122

## Key exclusion criteria
Current exclusion criteria as of 03/04/2014:
Patients will be excluded from this study for any of the following reasons:
General
1. Major surgery (including joint surgery) within 8 weeks prior to the screening visit or planned major surgery within 52 weeks following randomization.
Study Specific
2. Patients with inflammatory joint disease of different origin, mixed connective tissue disease, Reiters syndrome, psoriatic arthritis, systemic lupus erythematosus, or any arthritis with onset prior to 16 years of age.
3. Patients receiving doses of prednisolone > 10 mg/day within the 4 weeks prior to the screening visit.
4. Patients receiving intra-articular or intra-muscular steroid injections within 4 weeks prior to the screening visit.
Excluded Previous or Concomitant Therapy:
5. Patients who have previously received more than one TNFi drug OR any other biological therapy for the treatment of RA.
6. Patients unable or unwilling to stop treatment with a prohibited DMARD (i.e synthetic DMARD aside from MTX e.g. oral or injectable gold, chloroquine, hydroxychloroquine, cyclosporine, azathioprine, leflunomide, sulphasalazine) prior to the start of protocol treatment.
7. Treatment with any investigational drug in the last 12 weeks prior to the start of protocol treatment.
Exclusions for general safety
These criteria should be considered in the context of BSR guidance.
8. Patients with other co-morbidity including acute, severe infections, uncontrolled diabetes, uncontrolled hypertension, unstable ischaemic heart disease, moderate/severe heart failure (Class III/IV of the New York Heart Association [NYHA] functional classification system), active bowel disease, active peptic ulcer disease, recent stroke (within 12 weeks before the screening visit), or any other condition which, in the opinion of the investigator, would put the patient at risk to participate in the study or would make implementation of the protocol difficult.
9. Patients with any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 12 weeks of start of treatment protocol or oral antibiotics within 4 weeks of start of protocol treatment.
10. Patients at significant risk of infection, which in the opinion of the investigator would put the patient at risk to participate in the study (e.g. leg ulceration, indwelling urinary catheter, septic joint within 52 weeks [or ever if prosthetic joint still in situ]).
11. Patients with known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections including herpes zoster (for tuberculosis and hepatitis B and C see below), but excluding fungal infections of nail beds as per clinical judgment.
12. Patients with untreated active current or latent tuberculosis (TB). Patients should have been screened for latent TB (as per BSR guidelines) within 24 weeks prior to the screening visit and, if positive, treated following local practice guidelines prior to the start of protocol treatment.

13. Patients with active current hepatitis B and/or C infection. Patients should have been screened for hepatitis B and C within 24 weeks prior to the screening visit and if positive, excluded from the study.
14. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.
15. Pregnancy, lactation or women of child-bearing potential (WCBP) unwilling to use an effective birth control measure whilst receiving treatment and after the last dose of protocol treatment as indicated in the relevant SmPC/IB.
16. Men whose partners are of child-bearing potential but who are unwilling to use an effective birth control measure whilst receiving treatment and after the last dose of protocol treatment as indicated in the relevant SmPC/IB.
Laboratory value exclusions
17. Patients with known significantly impaired bone marrow function as for example significant anaemia, leukopaenia, neutropaenia or thrombocytopaenia as shown by the following laboratory values at the time of the screening visit:
17.1. Haemoglobin < 8.5 g/dl
17.2. Platelet count < 100 x 109/L
17.3. White blood cell count < 2.0 x 109/L
17.4. Neutrophil count < 1 x 109/L
18. Patients with known severe hypoproteinaemia at the time of the screening visit, e.g. in nephrotic syndrome or impaired renal function, as shown by serum creatinine > 150 umol/L

Previous exclusion criteria:
Additional exclusion criteria tailored to this study (including factors that may influence accurate assessment of response/investigation) include:
1. Patients who have previously received more than 1 TNFi drug or any other biological therapy
2. Patients unwilling or unable to receive MTX for the duration of the study
3. Patients with inflammatory joint disease of different origin, mixed connective tissue disease, Reiter's syndrome, psoriatic arthritis, systemic lupus erythematosus, or any arthritis with onset prior to 16 years of age
4. Patients with other co-morbidity: examples include uncontrolled diabetes, uncontrolled hypertension, unstable ischaemic heart disease, active bowel disease, active peptic ulcer disease, recent stroke (within three month before study entry [screening]), or other condition which, in the opinion of the investigator, would put the patient at risk to participate in the study or would make implementation of the protocol or interpretation of the study results difficult. Patients with significantly impaired bone marrow function as for example significant anaemia, leukopaenia, neutropaenia or thrombocytopaenia as shown by the following laboratory values:
4.1. Haemoglobin less than 8.5 g/dl
4.2. Haematocrit less than 30%
4.3. Platelet count less than 100 x 10^9/L
4.4. White blood cell count less than 3.5 x 10^9/L
4.5. Neutrophils count less than 1 x 10^9/L
5. Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome or impaired renal function, as shown by:
5.1. Serum Creatinine greater than 150 umol/L
5.2. Creatinine Clearance greater than or equal to 50 ml/min
6. Discontinuation of a prohibited DMARD (e.g. oral or injectable gold, chloroquine, hydroxychloroquine, cyclosporine, azathioprine, leflunomide, sulphasalazine) must occur at least 28 days prior to study drug administration (week 0). Of the TNFi, infliximab should be discontinued at least 8 weeks prior and etanercept, adalimumab and certolizumab 2 weeks prior to study drug administration.
7. Doses of prednisolone greater than 10 mg/day within the previous 28 days before study drug

administration (week 0)
8. Intra-articular or intra-muscular steroid administration within 28 days before screening
9. Any known condition or circumstance which would prevent compliance or completion of the study
10. Scheduled or anticipated surgery (particularly surgery to the involved knee joint within the study period)
11. Treatment with any investigational drug in the last 90 days before study entry
12. Female patients will only be enrolled into the study if they are of non child bearing potential (surgically sterile or at least 2 years postmenopausal) or have satisfied the investigator as having an adequate form of contraception
13. Male patients must consent to practice contraception during the study

### Date of first enrolment
01/10/2011

### Date of final enrolment
18/12/2014

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre
### Clinical Trials Research Unit (CTRU)
Leeds
United Kingdom
LS2 9JT

## Sponsor information

### Organisation
University of Leeds (UK)

### Sponsor details
Faculty of Medicine and Health
Room 110, Level 10, Worsley Building
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**Sponsor type**
University/education

**ROR**
https://ror.org/024mrxd33

# Funder(s)

**Funder type**
Government

**Funder Name**
Health Technology Assessment Programme

**Alternative Name(s)**
NIHR Health Technology Assessment Programme, HTA

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Publication and dissemination plan**
Not provided at time of registration

**Intention to publish date**

**Individual participant data (IPD) sharing plan**
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources

available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

## IPD sharing plan summary

Other

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | protocol | 23/12/2014 | | Yes | No |
| Results article | results | 01/06/2018 | | Yes | No |
| Results article | results | 01/11/2020 | 02/09/2020 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |