A Randomised, open labelled study in anti-TNFa inadequate responders to investigate the mechanisms for Response - Resistance to Rituximab versus Tocilizumab in RA (R4-RA)

Published: 01-09-2016
Last updated: 20-04-2024

The main aim of this project is to test the hypothesis that the presence or absence of specific synovial cellular and molecular signatures (B cells and B cell-associated signatures), assessed following a synovial tissue biopsy, will enrich for...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON46338

Source
ToetsingOnline

Brief title
R4-RA

Condition

- Autoimmune disorders

Synonym
RA, Reumatoid Atrhritis

Research involving
Human

Sponsors and support

Primary sponsor: Queen Mary University of London
Source(s) of monetary or material Support: Co sponsor Queen Mary University of London

Intervention

Keyword: anti-TNFa inadequate responders, Biopsy, RA

Outcome measures

Primary outcome

Patients will be assessed for disease activity using the CDAI (Clinical disease activity index), DAS 28 (CRP/ESR), Health Assessment Questionnaire (HAQ), Short Form 36 and FACIT Fatigue questionnaire as described below.

Primary Endpoint Efficacy Analysis

Treatment response assessed using the Clinical Disease Activity Index (CDAI) at 16 weeks. Section 4.11, defines treatment response/failure criteria.

Patients deemed treatment failures at 16 weeks, will be switched to the other therapeutic option. Such patients will be considered a new patient starting at week 0 with treatment response assessed again at 16 weeks for primary response.

The primary analysis will focus on whether there is a superiority of Tocilizumab over Rituximab in histologically defined *B cell poor* patients.

Secondary outcome

Secondary Endpoint Efficacy Analysis

1. For the B-cell rich synovial pathotypes, we aim to show non-inferiority of Rituximab compared to Tocilizumab.

2. Germinal Centre pathotypes will constitute an exploratory component to the

trial as insufficient power will be generated to show a significant difference in clinical response between each treatment.

3. Area under the curve (AUC) of mean improvement in DAS28 over time between 0, 16 and 48 weeks.

4. Percentage of patients with low disease activity (DAS28 < 3.2) at 12, 24, 36, 48, 96 weeks

5. Percentage of patients in remission (DAS28 < 2.6) at 16, 48 and 96 weeks

6. Percentage of patients with ACR 20, 50 and 70 response rates at 16, 48 and 96 weeks

7. Percentage of patients with a low clinical disease activity index score (CDAI)

8. Mean % change in DAS28 between baseline and 16, 48 and 96 weeks

9. Mean % change in clinical disease activity index score (CDAI) between baseline and 16, 48 and 96 weeks

10. Mean change in HAQ score between baseline and 16, 48 and 96 weeks

11. Change in Fatigue score between baseline and 16, 48 and 96 weeks

12. Serious adverse events over 12 months; the rate of serious adverse events in the 16 week period following a switch from one technology to the other will be compared

13. Mean change in erosive score by the van der Heijde/Sharp scoring system at 24 and 48 weeks.

14. Reduction in US 2D grey scale and power Doppler signal at 16, 48 and 96 weeks.

6.3 Exploratory end point

1. The effect of synovial immuno-histology on drug response rates and disease

outcome.

Study description

Background summary

Rheumatoid arthritis (RA) is one of the most important chronic inflammatory disorders in the UK. The diagnosis of RA leads to considerable morbidity and an increased mortality1, 2. According to the National Audit Office (2009 - http://www.nao.org.uk/) there are 26,000 new cases of RA each year with 582,000 prevalent cases in England. 45% of these people are of working age and within 1 year of diagnosis 30% are unemployed. RA is characterized by a symmetrical, erosive polyarthritis, resulting from chronic synovitis, and the presence of circulating autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACPA), strongly suggesting an autoimmune pathogenesis. Although biological therapies have revolutionized the treatment of RA, a sizable group of patients (30-40%) are *resistant*3, 4.
Recently there has been a greater understanding of the importance of B cells in driving the inflammatory processes involved in RA. B cells may drive synovial inflammation by production of autoantibodies, acting as effective antigen-presenting cells and may promote synovial inflammation by producing pro-inflammatory cytokines5. Thus, depletion of B cells could interfere with important mechanisms involved in the perpetuation of the inflammatory response in RA. Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed by B cells, has been approved by the US Food and Drug Administration and by the European Medicines Agency in Europe for the treatment of patients with RA who have had an inadequate response (ir) or were intolerant to tumour necrosis factor alpha (TNF) inhibitors. Current evidence on the efficacy of Rituximab relates primarily to rheumatoid factor positive patients, although even within this population clinical responses are heterogeneous with only 60% achieving an ACR20 response at 6 months6, 7. Recent synovial-based studies suggest that the heterogeneous clinical response may in part be explained by variable B cell depletion within the synovial tissue rather than simply in the peripheral blood8-10. A growing body of evidence would suggest that a more rational approach to Rituximab therapy and a stratified approach to patients may be required11-13. Despite this, NICE guidelines have recommended that all patients with inadequate response to anti-TNF therapy should receive Rituximab (NICE, http://www.nice.org.uk/CG79). A *blind* implementation of these guidelines will result in many patients, unlikely to respond, receiving a B Cell depleting agent with the associated risks with none of the potential benefits. A tailored approach to this intervention with patient stratification is required to better identify both responders and non-responders. In this

proposed study we will test the hypothesis that the presence or absence of B cells and B cell-associated signatures within the joint will enrich for response/non-response to the B cell depleting agent Rituximab. We also hypothesize that in patients with a B-cell poor synovial biopsy, alternative biologics such as the IL-6 receptor blocker Tocilizumab will be more effective. This study is considered a type A clinical study according to MHRA risk.

Study objective

The main aim of this project is to test the hypothesis that the presence or absence of specific synovial cellular and molecular signatures (B cells and B cell-associated signatures), assessed following a synovial tissue biopsy, will enrich for response/non-response to the B cell depleting anti-CD20 monoclonal antibody (mAb) Rituximab. In addition, we will examine if clinical response is associated with inhibition of B cell-linked pathways within the synovium and dependent on local B cell lineage depletion and whether survival of auto-reactive B cells within *protected* synovial niches are responsible for B-cell joint re-population and disease resistance-relapse?

Study design

This is a multi-site, multi-country, open-label randomised controlled clinical trial. Patients recruited to this study will undergo a synovial biopsy prior to randomisation. Possible synovial biopsy sites are the knee, elbow, shoulder, wrist, ankle, MCP, PIP, and MTP joints.
Patients will subsequently be stratified in to 3 groups (B Cell Poor, B Cell Rich, Germinal Centres (GC) Rich) according to the following B-cell score prior to therapeutic intervention. All participating site staff will be blinded to the pathotype (B Cell Poor, B Cell Rich, Germinal Centre). This result will be recorded centrally prior to randomisation of the patient.

Intervention

Rituximab:
Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences.
OR Tocilizumab:
Tocilizumab humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology
Biopsy:
Patients will receive a synovial biopsy between 1 to 3 weeks prior to their baseline visit.

Study burden and risks

In this study patients will be randomised to receive either Rituximab or Tocilizumab. No placebo arm has been included, as withholding an approved potentially beneficial therapy would not be comparable with good standards of clinical practice. Tocilizumab has been approved for the use in patients with moderate to severe RA Thus, there will be no greater risk from administered pharmacotherapy during this study than would be expected in routine clinical care.
All patients will have arthroscopic synovial biopsies which would not necessarily be considered routine clinical care and thus the main risks to patients enrolled would be associated with this interventional procedure. The procedure itself has excellent safety and tolerability and can be applied to both large and small joints in most patients. Arthroscopic biopsies, whilst being technically more complicated and requiring theatre time, have been extensively validated with respect to tissue quality in therapeutic intervention studies.

Contacts

Public
Queen Mary University of London

Walden Street 5
London E1 2EF
NL
Scientific
Queen Mary University of London

Walden Street 5
London E1 2EF
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients will be recruited with active RA:
1. Patients who have failed anti-TNF therapy (inadequate responders * ir). Note: this includes patients that have failed anti-TNF therapy because of reactions.
2. Who are eligible for Rituximab/TCZ therapy according the Dutch guidelines*
3. Patients should be receiving a stable dose Methotrexate for at least 4 weeks prior to biopsy visit.
4. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of Rheumatoid Arthritis.
5. Over 18 years of age

Exclusion criteria

1. Women who are pregnant or breast-feeding
2. Women of child-bearing potential, or males whose partners are women of child-bearing potential, unwilling to use effective contraception during the study and for at least 12 months after stopping study treatment.
3. History of or current primary inflammatory joint disease or primary autoimmune disease other than RA.
4. Prior exposure to Rituximab or Tocilizumab for the treatment of RA
5. Treatment with any investigational agent * 4 weeks prior to baseline (or < 5 half lives of the investigational drug, whichever is the longer).
6. Intra articular or parenteral corticosteroids * 4 weeks prior to biopsy visit (Visit 2).
7. Oral prednisolone more than 10mg per day or equivalent * 4 weeks prior to biopsy

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rituximab
Generic name:	Mabthera
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tocilizumab
Generic name:	RoActemra
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-09-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-09-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002535-28-NL
ClinicalTrials.gov	NCT??volgt
CCMO	NL56487.058.16