ISRCTN65360827 https://doi.org/10.1186/ISRCTN65360827

Rituximab in patients with primary Sjögren's syndrome

Submission date	Recruitment status	[X] Prospectively registered
17/06/2010	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
09/07/2010	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
16/03/2017	Musculoskeletal Diseases	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Mrs Sharon Ruddock

Contact details
Clinical Trials Research Unit
University of Leeds
Leeds
United Kingdom
LS2 9JT
+44 (0)113 343 7588
s.p.ruddock@leeds.ac.uk

Additional identifiers

Protocol serial number
RR10/9389

Study information

Scientific Title
A randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patients with primary Sjögren's syndrome

Acronym
TRACTISS

Study objectives
To assess the extent to which rituximab improves symptoms of fatigue and oral dryness in patients with primary Sjögrens syndrome.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leeds West Ethics Committee on 25/10/2010; Protocol version 3.0 approved on 12/04/2011

Study design
Multicentre randomised double-blind placebo controlled phase III trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Primary Sjögren's syndrome (PSS)

Interventions
Patients will receive two doses of rituximab (1000 mg) or placebo by intravenous (IV) infusion given with IV methylprednisolone (100 mg) at 2 week intervals at T = 0 and T = 2 weeks. This will be repeated at T = 24 weeks and T = 26 weeks.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Rituximab, methylprednisolone

Primary outcome(s)
A 30% reduction at 48 weeks from baseline in either oral dryness or fatigue measured using visual analogue scales (VAS; range 0 - 100 mm)

Key secondary outcome(s))
1. Fatigue (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
2. Oral dryness (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
3. Ocular dryness (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
4. Patient global assessments (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48

5. Physician global assessments (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
6. Salivary flow (stimulated and unstimulated salivary flow), performed at baseline, 16, 24, 36 and 48 weeks
7. Lachrymal flow (Schirmers I test of ocular function), performed at baseline, 16, 24, 36 and 48 weeks
8. Quality of life, evaluated at baseline and 16, 24, 36 and 48 weeks using the EULAR Sjögrens Syndrome Patient Reported Index (ESSPRI)
9. Quality of life, disease damage and disease activity indices, evaluated at baseline, 24 and 48 weeks using the following:
9.1. Sjögrens Syndrome Disease Damage Index (SSDDI)
9.2. Social Security Disability Insurance (SSDI)
9.3. EULAR Sjögrens Syndrome Disease Activity Index (ESSDAI)
9.4. Sjögrens Syndrome Disease Activity Index (SSDAI)
9.5. Sjögrens Systemic Clinical Activity Index (SCAI)
9.6. 36-item Short Form Health Survey (SF-36)
9.7. Profile of Fatigue and DiscomfortSicca Symptoms Inventory (PROFAD-SSI)
10. Serological and peripheral blood inflammatory features (haematology biochemistry, serology and immunology assays), taken at baseline, weeks 16, 24, 26, 36 and 48
11. Incremental cost-effectiveness ratio (EQ-5D, health economics) evaluated at baseline, weeks 24 and 48

Completion date
01/07/2013

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/09/2011:

1. Aged between 18 and 80 years of age.
2. A confirmed diagnosis of primary Sjögrens syndrome by AECG criteria (see Appendix B).
3. Positive for anti-Ro auto-antibodies.
4. Patients with a diagnosis of primary Sjögrens syndrome (by AECG criteria) with more than 10 years disease duration must have at least one systemic feature of:
4.1 Hypergammaglobulinaemia (IgG over 16)*, or
4.2 Low complement C4*, or
4.3 Cryoglobulinaemia
OR
4.4 Active/past history since diagnosis of the following (ascribed to Sjögrens Syndrome):
4.5 purpura/cutaneous vasculitis,
4.6 lymphadenopathy,
4.7 persistent parotid salivary gland swelling not due to infection,
4.8 peripheral neuropathy (previously documented by nerve conduction tests),
4.9 interstitial lung disease confirmed by HRCT,
4.10 renal tubular acidosis requiring treatment,
4.11 CNS disease ascribed to Sjögrens syndrome (confirmed by MRI),
4.12 myositis (CPK>2N and EMG or biopsy evidence of myositis),
4.13 inflammatory arthritis
5. An unstimulated salivary flow rate greater than 0ml in 15 minutes.
6. Symptomatic oral dryness (≥ 5/10 on patient-completed Likert**).

7. Symptomatic fatigue (≥ 5/10 on patient-completed Likert**).
8. Patients on corticosteroids, NSAIDS, antidepressants, methotrexate, or pilocarpine*** must have been on a stable dose for 4 weeks prior to receiving the first infusion of study medication and expected to remain on this dose throughout the study.
9. Patients who are on hydroxychloroquine at screening must have been on a stable dose throughout the preceding six-month period. If they have stopped hydroxychloroquine they should have been off it for at least 3 months prior to receiving study medication.
10. Given their written informed consent to participate in the trial and expected to be able to adhere to the study visit schedule and other protocol requirements.

*Anti-Ro antibody test, IgG, RF and C4 assays performed within 6 months of screening may be used to confirm eligibility. If greater than 6 months repeats should be performed locally at screening to confirm eligibility.

** LIKERT range 0-10 with 10 corresponding to worst severity.

*** Pilocarpine or drugs with similar pharmacological action should not be used within 12 hours of the assessment visits at screening, baseline, week 16, week 24, week 36 and week 48 (end of study).

Previous inclusion criteria:

1. Aged between 18 and 80 years of age, either sex
2. A confirmed diagnosis of of primary Sjögrens syndrome by AmericanEuropean Consensus Group (AECG) criteria with:
2.1. Positive labial gland biopsy** and/or
2.2. Positive for anti-Ro auto-antibodies greater than 1.5 upper limit of normal*
3. A stimulated salivary flow rate of greater than or equal to 0.5 ml in 5 minutes
4. An unstimulated salivary flow rate greater than 0 in 15 minutes
5. Be positive for anti-Ro auto-antibodies greater than 1.5 upper limit of normal
6. Symptomatic oral dryness (greater than or equal to 5/10 on patient-completed Likert***)
7. Symptomatic fatigue (greater than or equal to 5/10 on patient-completed Likert***)
8.1. At least one systemic feature of:
8.1.1. Hypergammaglobulinaemia (IgG over 16)*, or
8.1.2. Low complement C4*, or
8.1.3. Cryoglobulinaemia
8.2. Active/past history since diagnosis of the following (ascribed to Sjögrens syndrome):
8.2.1. Inflammatory polyarthritis
8.2.2. Purpura/cutaneous vasculitis
8.2.3. Lymphadenopathy
8.2.4. Persistent parotid salivary gland swelling not due to infection
8.2.5. Peripheral neuropathy (previously documented by nerve conduction tests)
8.2.6. Interstitial lung disease confirmed by high-resolution computed tomography (HRCT)
8.2.7. Renal tubular acidosis requiring treatment
8.2.8. Central nervous system (CNS) disease ascribed to Sjögrens syndrome (confirmed by magnetic resonance imaging [MRI])
8.2.9. Myositis (creatine phosphokinase [CPK] greater than 2N and electromyogram [EMG] or biopsy evidence of myositis)
8.2.10. Patients with inflammatory arthritis
8.2.11. If greater than 10 years since diagnosis of primary Sjögrens syndrome, must have established systemic involvement
9. If on corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDS), hydroxychloroquine,

methotrexate, or pilocarpine; have been on a stable dose for 4 weeks prior inclusion and expected to remain on this dose throughout the study
10. Given their written informed consent to participate in the trial and expected to be able to adhere to the study visit schedule and other protocol requirements

* Anti-Ro/La antibody test, IgG, RF and C4 assays performed within 6 months of screening may be used to confirm eligibility. If greater than 6 months repeats should be performed locally at screening to confirm eligibility.
** A labial gland biopsy performed within 6 months of screening may be used to confirm eligibility. The labial gland biopsy SHOULD NOT be performed as part of the screening process.
*** LIKERT range 0 - 10 with 10 corresponding to worst severity

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 20/09/2011:
1. Diagnosis of secondary Sjögrens syndrome.
2. Use of DMARDs, immunosuppressant therapies or antidepressants within 4 weeks prior to the first dose administration (except for glucocorticoids, salicylates, non-steroidal anti inflammatory drugs (NSAIDs), methotrexate and analgesics which are acceptable).
3. Pregnancy, lactation or women of child-bearing potential (WCBP) unwilling to use medically approved contraception whilst receiving treatment and for 12 months after treatment has finished.
4. Men whose partners are of child-bearing potential but who are unwilling to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment has finished.
5. Patient has active or prior hepatitis B or C, known HIV positivity or known history of tuberculosis.
6. Any history of other autoimmune diseases or other form of immunodeficiency or neutropaenia <1.5 109/l.
7. Any AECG exclusion criteria not covered elsewhere (graft versus host disease, primary lymphoma excluding PSS, sarcoidosis).
8. Any malignancies that would normally preclude the use of rituximab within the past 5 years, including solid tumours, haematological malignancies and carcinoma in situ (except basal cell or squamous cell carcinoma of the skin that has been excised and cured)
9. Participation in a clinical study involving administration of an investigational drug within the past 4 weeks prior to the first infusion.
10. A history of major surgery within 3 months prior to first infusion or planned surgery during

the study.
11. Receipt of live/attenuated vaccine within 4 weeks prior to the first infusion.
12. Previous exposure to rituximab or any other monoclonal antibody within the past 5 years.
13. History of recurring or chronic infections or underlying conditions which may further predispose patients to serious infection.
14. History of moderate to severe congestive heart failure according to the New York Heart Association (NYHA) functional classification system (see Appendix C) or other uncontrolled heart disease, or who have a clinically significant abnormal ECG at the time of screening.
15. History of receiving human/murine recombinant products or known allergy or anaphylactic reaction to a biologic agent or any component of the active substance or any of its excipients or murine components.
16. Patients with fibromyalgia or a diagnosis of significant depression or anxiety that in the opinion of the clinician would confound the interpretation of the study results.
17. Current or a history of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis).
18. Any history of organ transplant (with the exception of a corneal transplant >3 months prior to study entry).
19. Presence of a clinically significant illness or mental disorder within 4 weeks of the start of the trial where the safety of the individual might be at risk by entry into the trial, or where the individual does not have the capacity to consent or where the outcome of the therapy cannot be assessed by virtue of the illness or disorder. Each patient will be assessed individually and no person who wishes to participate will be unreasonably excluded by virtue of the illness or disorder.

Previous exclusion criteria:
1. Diagnosis of secondary Sjögrens syndrome
2. Use of disease modifying anti-rheumatic drugs (DMARDs) or immunosuppressant therapies within 4 weeks prior to the first dose administration (glucocorticoids, salicylates, NSAIDs, analgesics are acceptable)
3. Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception whilst receiving treatment and for 12 months after treatment has finished
4. Men whose partners are of child-bearing potential but who are not willing to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment has finished, unless they are surgically sterile
5. Use of other DMARDs or immunosuppressant therapies within 4 weeks prior to the first dose administration
6. Patients who are known to have serum hepatitis or are known carriers of the hepatitis B surface antigen (HBsAg), hepatitis C antibody, or have a known human immunodeficiency virus (HIV) positivity or a known history of tuberculosis
7. Any history of other autoimmune diseases or other form of immunodeficiency or neutropaenia less than 1.5 x 10^9/L
8. Any AECG exclusion criteria not covered elsewhere (graft versus host disease, primary lymphoma excluding PSS, sarcoidosis)
9. Any cancer that would normally preclude the use of rituximab within the past 5 years
10. Participation in a clinical study involving administration of an investigational drug within the past 4 weeks prior to the first infusion
11. A history of major surgery within 3 months prior to first infusion or have planned surgery during the study
12. Receipt of live/attenuated vaccine within 4 weeks prior to the first infusion
13. Previous exposure to rituximab or any other monoclonal antibody within the past 5 years
14. History of recurring or chronic infections or with underlying conditions which may further

predispose patients to serious infection
15. History of moderate to severe congestive heart failure or other uncontrolled heart disease, or who have a clinically significant abnormal electrocardiogram (ECG) at the time of screening
16. History of receiving human/murine recombinant products or known allergy to murine products or any component of the active substance or any of its excipients or murine components
17. Presence of fibromyalgia, or diagnosed significant depression or anxiety
18. Current or a history of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis)
19. Any history of organ transplant (with the exception of a corneal transplant greater than 3 months prior to screening)
20. Presence of a clinically significant illness within 4 weeks of the start of the trial

Date of first enrolment
01/01/2011

Date of final enrolment
01/07/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Leeds
Leeds
United Kingdom
LS2 9JT

Sponsor information

Organisation
University of Leeds (UK)

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type

Charity

Funder Name
Arthritis Research UK (ref: 18810)

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	results	01/07/2017		Yes	No
Protocol article	protocol	17/01/2014		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes