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Randomised Efficacy and Discontinuation Study of Etanercept and Adalimumab (RED SEA): A pragmatic open label study in rheumatoid arthritis

Submission date
28/09/2007

Recruitment status
No longer recruiting

Registration date
28/09/2007

Overall study status
Completed

Last Edited
29/08/2012

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
N0265189640

Study information

Scientific Title

Study objectives
Please note that, as of 2nd January 2008, the public title of this trial has been changed from "A Randomised, Pragmatic, Open-label study of Adalimumab versus Etanercept for Rheumatoid Arthritis" to "Randomised Efficacy and Discontinuation Study of Etanercept and Adalimumab (RED SEA): A pragmatic open label study in rheumatoid arthritis."

Study aims:
1. To compare the proportions of people still taking adalimumab or etanercept one year after starting treatment for rheumatoid arthritis. Our objective is to determine whether adalimumab is inferior to etanercept for the treatment of rheumatoid arthritis.
2. To measure, by routine clinical procedures and by questionnaires: whether the two drugs are equally beneficial for rheumatoid arthritis; whether side effects, adverse reactions and reasons for discontinuing treatment are similar; and whether patients taking the drugs are equally satisfied with their medication.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Added as of 02/01/2008: Nottingham Research Ethics Committee 2, approved on 24th January 2007. Protocol amendment approved on 21 March 2007.

Study design
Randomised pragmatic open-label study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Musculoskeletal Diseases: Rheumatoid arthritis (RA)

Interventions
Please note that the anticipated end date of this trial has been extended from 30 November 2007 to 30 November 2009 as of 2nd January 2008.

Background
Rheumatoid arthritis (RA) affects around 1% of the UK population and is the most common form of inflammatory arthritis. RA is characterised by inflammation of the synovial lining membrane of affected joints and causes pain, swelling, and stiffness in joints that may lead to deformity and permanent joint damage. Patients also often feel generally unwell, are fatigued and may have a poor quality of life. In some there may be severe disability; though outcomes vary greatly and early use of effective treatments is important for reducing the impact of disease. Disease can be effectively suppressed, but not cured, by Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate, sulphasalazine, gold, and newer agents such as the tumour necrosis factor-alpha (TNF) inhibitors. Prolonged use of DMARDs is usually necessary in RA. Therefore drugs that are most effective are those which are more likely to be continued over

many years. Observations of groups of people with RA show that methotrexate, which is now regarded as the standard against which new drugs should be compared, is more likely to be continued after several years than other older DMARDs.

Randomised clinical trials of DMARDs rarely follow patients for more than 6 months and infrequently compare one DMARD with another. Modern management of RA has changed enormously because of TNF inhibitors but these new drugs are expensive, have potentially serious adverse effects and are subject to NICE guidance which restricts their use to patients with certain characteristics. Three drugs are available: adalimumab (Humira®), etanercept (Enbrel®) and infliximab (Remicade®). Adalimumab and etanercept are self-administered by subcutaneous injection at home and therefore offer greater convenience. Infliximab is given as an intravenous drip and administered in hospital: patients need to attend hospital as day-cases. These drugs also differ in important ways on their mechanism of action: adalimumab and infliximab are monoclonal antibodies directed against TNF and etanercept is a TNF receptor antagonist. All three TNF inhibitors have been assessed in high quality randomised controlled clinical trials and shown to be highly effective and comparable to methotrexate. However no trials have compared any one of these agents against another. Some indirect comparisons, using data from randomised trials, indicate that the drugs may be similarly efficacious; however recent data suggests that this may not be the case (see below).

A majority of patients treated in the UK have been registered with a database managed by the British Society for Rheumatology (BSRBR). We have, in unpublished data and indirect comparisons of randomised trials, found that there may be important differences in the drug continuation rates for different agents. There may be many explanations and confounding factors for this. Cost effectiveness models of TNF inhibitors show that the likelihood of prolonged use of a drug is a key factor in determining cost-effectiveness.

Hypothesis
Patients taking adalimumab are not less likely to be using treatment than those taking etanercept for rheumatoid arthritis a year after starting therapy. Our intention is to show that adalimumab is not inferior to etanercept in terms of the proportion of patients still taking the drug after 1 year. This type of trial is called a non-inferiority trial. Unpublished data and preliminary evidence from indirect comparisons of clinical trials indicates that around 15% of fewer patients take adalimumab than etanercept a year after starting therapy. We believe that this level of difference is clinically important. It is also important on health economic grounds, as shown by our health economic analyses for NICE.

Involvement of research participants
Patients have not been involved in planning this study but a copy of our protocol is being submitted to the rheumatology department patient user group at Selly Oak Hospital in Birmingham for feedback. Our project has been debated by all the consultant rheumatologists involved in the study.

Outcomes & Definitions
Primary outcome
The proportions of patients still taking adalimumab and etanercept one year after starting treatment.
Patients will be deemed to be still on treatment if an injection of adalimumab or etanercept has been used 12
months after starting therapy, with a window of 2 weeks either side of the 12 month anniversary.
Study Population
Patients with rheumatoid arthritis attending the rheumatology outpatients departments of Selly

Oak, City or
Solihull Hospitals in Birmingham and St Marys Hospital, Newport, Isle of Wight. Patients will be identified as
those likely to fulfill NICE criteria for receiving a TNF inhibitor and who are starting a TNF inhibitor for the first
time.

Inclusion Criteria
1. Men and women over the age of 18 years with rheumatoid arthritis meeting international disease
classification criteria.
2. NICE Criteria for treatment with TNF-inhibitors in regard to lack of response to at least two DMARDs (one
of which must be methotrexate at adequate doses and for an appropriate length of time).
3. Willing to enter study and able to understand the procedures and comply with the study protocol

Exclusion Criteria
4. Any condition(s) which, in the opinion of the physician caring for the patient, makes that patient unsuitable
for a TNF inhibitor for their arthritis.
5. Any individual unable to understand study procedures or unwilling to comply.
6. Previous treatment with any licensed or experimental biological TNF inhibitor.

Schedule of Procedures - Overview
Each patient will be monitored at 3 monthly intervals for one year or until they have ceased taking the drug during the study. Patients who have done well after 12 months and are still taking treatment and wish to continue may do so according to current practice. Visits will be arranged to suit patients and will be co-ordinated with routine clinical care. Suitability for TNF inhibitor therapy is usually evaluated by senior clinicians at clinic visits when a full medical evaluation is done. Once a patient meets eligibility criteria for TNF inhibitor therapy they will asked to consider being involved in the trial. Subsequent visits will take place at three, six and twelve months after starting treatment. More frequent visits may take place as determined by the judgement of the treating physician. No constraints will be placed on such visits. In addition there will be no restrictions on referrals to professionals allied to medicine, including physical therapy, additional DMARDs, corticosteroids given orally or parenterally, analgesics, non-steroidal anti-inflammatory drugs and surgical treatment, if these are judged to be necessary by the clinicians caring for that patient. Patients who cease treatment between planned study visits will be assessed as soon as possible and final study data will be collected.

Screening Visit & Baseline
1. Consent signed in presence of Investigator (or sub-investigator).*
2. Detailed medical and drug history.
3. Chest X-Ray according to NICE guidance and as judged appropriate by consultant rheumatologist in
charge of the patients care.
4. DAS (Disease activity score based on28 joint count, blood tests (ESR or CRP), and patient assessed
disease severity or general health)
5. Randomisation into treatment group*
6. Confirmation of funding for therapy from the Primary Care Trust
(*- study specific procedure)

Patient will be notified of their allocated drug and funding approval will be confirmed with the Primary Care Trust according to current procedures. Once therapy has commenced an appointment will be arranged 12 to 16 weeks after initiation to evaluate response, or before if there are difficulties. Patients may have access to a local telephone help-line (supported by clinical nurse specialists in rheumatology). All patients will have access to their hospital consultant through their secretaries for advice about any aspects of their treatment and condition. All clinicians will have access to research staff by telephone (land lines and mobiles) and for advice about any aspect of the study.

Visit at 12 to 16 weeks
1. Assess disease activity (DAS28)
2. Assess satisfaction with medication with Treatment Satisfaction Questionnaire for medication (vII)
3. Concomitant medication changes
4. Adverse events

Visit at 6 months (± 2 weeks)
1. Assess disease activity (DAS28)
2. Adverse effects

Visit at 12 months (± 2 weeks)
1. Assess disease activity (DAS28)
2. Assess satisfaction with medication with Treatment Satisfaction Questionnaire for medication (vII)
3. Concomitant medication changes
4. Adverse events

Patients ceasing treatment (within 0 to 2 weeks)
1. Assess disease activity
2. Reasons for cessation: lack of benefit, adverse effect, both or other reason.
3.Adverse events

Sample Size, statistical considerations & interim analyses
Our intention is to show that adalimumab is not inferior to etanercept in terms of the proportion of patients still taking the drug after 1 year. This type of trial is called a non-inferiority trial. Unpublished data and preliminary analyses of randomised trials suggests that around 15% of fewer patients take adalimumab than etanercept a year after starting therapy. The proportion of patients still using a TNF inhibitor (data for all TNF inhibitors combined) a year after starting treatment is around 75%. We calculate that 124 patients (62in each treatment group) would be required to have an 80% chance of showing this with 95% confidence (one-sided analysis). These data correspond to an assumed scenario where the true proportion of patients taking adalimumab at 1 year would be 75% compared with 70% for etanercept. All patients receiving at least one dose of treatment will be included in the analysis. Patients who are randomised but do not receive any drug will be excluded from the analyses and the treatment allocation will be re-assigned to the next eligible patient. The proportions of patients remaining on adalimumab and etanercept will be compared using Fischers exact test and survival analyses using the intention to treat principle. Interim analyses of the percentage of patients still taking their allocated drug 6 months after starting will be done after at least one half of the patients have been recruited. This will be done to review the sample size calculation

and ensure that there are no overwhelming differences between treatments. Review by a formal data monitoring committee is not proposed but a consensus of participating colleagues will be sought if any concerns are identified.

Randomisation
Patients will be allocated etanercept or adalimumab randomly using a random number sequence generated by StatsDirect Statistical Software. Randomisation will be done according to whether it is planned for the patient to continue taking methotrexate with their allocated TNF inhibitor. This is standard practice and there is some evidence that this may be more effective than using a TNF inhibitor alone. However some patients are not keen to do this or have experienced adverse effects with methotrexate. A random sequence of numbers will be generated both for patients on methotrexate and for patients taking adalimumab or etanercept without methotrexate. Randomisation will be done in random block sizes. Opaque sealed envelopes of the allocation sequences will be prepared and managed at the co-ordinating centre (University Hospital Birmingham, Department of Rheumatology) by a member of staff not involved in patient management. A copy of the random sequences will be lodged, at the outset, with the R&D department of University Hospital Birmingham NHS Foundation Trust NHS Foundation Trust to discourage tapering with the sequence of allocated treatments.
Implications for the NHS There are no additional cost implications for the National Health Service. Only patients being put forward for TNF-inhibitor therapy will be approached for the study. A chest X-Ray and blood tests are required as part of routine management and are stipulated within NICE guidance for the use of these agents. Similarly follow up arrangements and monitoring are as stipulated in NICE guidance. Patients who cease treatment are normally reviewed as soon as possible and alternative treatment offered.

Adverse events
Adverse events are defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All adverse events will be recorded whether or not they are considered to be related to the TNF-inhibitor therapy. Hospital records will be retrieved and reviewed for verification of adverse events, where necessary.

Serious Adverse events
Data on serious adverse events (SAE) will be collected as part of the processes of clinical care and clinicians caring for patients will be asked to report serious SAEs as soon as they have been identified. A formal assessment of all adverse events will be made at scheduled study visits. SAEs are defined as:
1. Fatal events
2. Events judged to be life-threatening
3. Events leading to hospitalisation or prolongation of existing hospitalisation
4. Events leading to persistent or significant disability/incapacity
5. Congenital anomaly/birth defect during therapy
6. Medically significant events or events that require intervention to prevent one or other of the outcomes listed above

Risks & benefits for patients
Both adalimumab and etanercept appear to have similar side effects and both are licensed for the treatment of RA. Some are described below. The researchers will make every effort to ensure that risks are minimised and patients will be provided with contact details in case of emergency. Any complaints will be handled by current NHS procedures. All research done in UK hospitals is covered by insurance schemes. As far as we can tell there are no disadvantages or additional risks associated with participation in this study. Both drugs are believed to be

amongst the most effective drugs for rheumatoid arthritis currently available. These drugs are available without taking part in this research. In any research study the researchers are obliged to take extra care often because of the need to do more measurements about a persons condition. People often do well because of this extra care but other than this there are no added benefits except for the potential benefits to future patients.

Potential adverse effects
Injection site reactions: The most common side-effect with these drugs is a reaction at the injection site. Redness, itching, bruising and discomfort at the site of injections is quite common. Most people can continue treatment despite these reactions which are usually of a minor nature.
Other common side-effects: Common colds, chest infections and flu-like symptoms are reported commonly by people, including those who have tried adalimumab and etanercept. Similarly headaches, skin rashes, sinusitis, accidental injury, nausea, abdominal pain, back pain, urinary tract infection, and raised blood
pressure are commonly reported. Infection risk. Treatment with TNF inhibitors may make people more susceptible to infections and some may be severe. Those who currently have an infection and are on antibiotics should not start a TNF inhibitor. Care is also necessary in someone who is prone to repeated infections needing antibiotic treatment. If an infection develops whilst you are taking a TNF inhibitor you should seek medical advice early as it may be necessary to stop taking the TNF inhibitor. A risk of tuberculosis has been identified with these drugs. This is very uncommon but patients who have previously had tuberculosis need special care. Cardiovascular risk. There are rare reports of people with heart trouble suffering heart failure which is related to using a TNF inhibitor. If you suffer from heart disease you must discuss this with your doctor.
Cancer risk. It is known that people with rheumatoid arthritis have a slightly increased risk of developing lymphoma, which is a type of blood and lymph gland cancer. This seems to be the case particularly in people with more joint inflammation. It is not known for certain whether TNF inhibitors increase the risk of these cancers. This is being investigated but so far there is no definite answer. It is possible that adalimumab and etanercept may slightly increase the risk of these cancers.
Neurological risk. There have been rare cases of nerve damage in people taking these drugs. Symptoms in some cases have been similar to those of multiple sclerosis. It is not known for certain whether these symptoms were caused by a TNF inhibitor but this possibility has been considered.
Other risks. Some other serious side-effects that have been seen include allergic reactions, abnormal laboratory blood tests including low levels of platelet cells which are responsible for clotting blood and of white and red blood cells.

Vaccinations. People using adalimumab or etanercept should not receive a live vaccine whilst taking these drugs. The MMR (mumps, measles and rubella) vaccine and the BCG vaccine (for tuberculosis) are examples of live vaccines. Most vaccines given to adults are not live.

Unknown risks. As with all drugs it is not possible to predict all adverse events. In the event of unexpected effects patients will be asked to communicate these to the research team. Telephone contacts will be provided.

Study Timetable
It is planned to start this study towards the end of 2006. It is believed that a pre-mixed syringe for etanercept will become available at this time. This will make the two preparations more comparable as, at present, patients (or their carers) are required to prepare a solution of etanercept before injecting. We believe that recruitment could take up to 18 months although

with 4 centres this could be much shorter. Each treated patient need to be followed for 12 months. Thus this study is likely to take up to 3 years to complete, allowing for data analysis, interpretation and publication.

Site of Interviews & Assessments
All procedures will be done at local rheumatology clinics. Key data will be forwarded to the co-ordinating centre as it is collected. Data will be stored on NHS computers and patients will be identified by code and local hospital number. Names and addresses will not be recorded.
Researcher Bias
Some clinicians may favor etanercept and others may favor adalimumab. These preferences may arise from their personal experiences or their interpretation of published results. Some centres may also prefer one drug over another. The larger participating centres have at least 3 consultant rheumatologists likely to contribute patients. Allocating treatments randomly according to each consultant is not practicable and even
allocating treatments according to each centre poses problems because of the likelihood of fewer than 40 patients at each site. We believe that the different views of individual clinicians are such that in practice individual biases will not be problem and are unlikely to influence the data.

Study Data Management & Communicating Results to Patients
Information from each patient will be collected as the study proceeds and analysed. Data will be collected centrally at University Hospital Birmingham. Each patient will be allocated a code and identified only by their local hospital number. Details of the medical history and outcomes of treatment will recorded on NHS computers and will only be available to NHS staff and treated with the strictest confidence. At the end of the study centres will be asked to send a report of the study to their participants. This report will be prepared by the co-ordinating centre in a language that is understandable by lay people.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Adalimumab, Etanercept

Primary outcome(s)
The proportions of patients still taking adalimumab and etanercept one year after starting treatment. Patients will be deemed to be still on treatment if an injection of adalimumab or etanercept has been used 12 months after starting therapy, with a window of 2 weeks either side of the 12 month anniversary.

Key secondary outcome(s))
1. Proportions of patients still taking etanercept and adalimumab 6 months after starting treatment (definition
for continued drug use as for primary outcome).
2. Disease activity score (DAS28) assessed 12 to 16 weeks after starting treatment.
3. Adverse effects defined by severity.
4. Proportions of patients discontinuing therapy for different reasons classified as lack of efficacy; toxicity;

both; other reasons. Classification to be agreed by two investigators.
5. Satisfaction with medication assessed with the Treatment Satisfaction Questionnaire for medication (vII)
assessed 12 to 16 weeks and one year after starting treatment.
6. Changes in concomitant medication at 12 months (± 2 weeks) from a review of medical records and
patient interview.

Completion date
30/11/2009

Eligibility

Key inclusion criteria
The participants will be patients with rheumatoid arthritis who attend the Rheumatology Outpatients Department at Selly Oak, City or Solihull Hospitals in Birmingham and St Mary's Hospital, Newport, Isle of Wight. They will be identified as likely to fulfill NICE criteria for receiving a TNF-inhibitor and will be provided with written information about this study and these drugs. Patients will then attend a hospital clinic where their Disease Activity Score (DAS) will be measured, to ensure they meet National criteria. Their medical history will be reviewed at that clinic visit to ensure that there are no contra-indications to them receiving a TNF inhibitor. In addition any screening procedures for tuberculosis or any other areas of clinical concern will be
completed. At this time, in cases where patients or clinicians have a strong preference for a particular TNF
inhibitor (any one of adalimumab, etanercept or infliximab), a plan of treatment will be agreed with patients.
Other patients - we believe a majority of those eligible for a TNF inhibitor - will be asked whether they are willing to be involved in this study. It will be explained to them that, in the study, they will be randomly allocated to adalimumab or etanercept. The study and drug information leaflets will be discussed in detail and any questions answered. All patients will have had the opportunity to think about their treatment options for at least 24 hours by this time. A consent form will be completed for patients willing to be involved.

Inclusion criteria:
1. Men and women over the age of 18 years with rheumatoid arthritis meeting international disease
classification criteria.
2. NICE Criteria for treatment with TNF inhibitors in regard to lack of response to at least two DMARDs (one of which must be methotrexate at adequate doses and for a defined period of time - according to NICE criteria).
3. Willing to enter study and able to understand the procedures and comply with the study protocol

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Any condition(s) which, in the opinion of the physician caring for the patient, makes that patient unsuitable for a TNF inhibitor for their arthritis
2. Any individual unable to understand study procedures or unwilling to comply
3. Previous treatment with any licensed or experimental biological TNF inhibitor

Date of first enrolment
30/11/2006

Date of final enrolment
30/11/2009

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Rheumatology
Birmingham
United Kingdom
B29 6JD

Sponsor information

Organisation
University Hospital Birmingham NHS Foundation Trust (UK)

ROR
https://ror.org/014ja3n03

Funder(s)

Funder type
Government

Funder Name
University Hospital Birmingham NHS Trust

Funder Name
NHS R&D Support Funding

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?
Poster results	results (no. 178 from poster session)	01/05/2012		No	No