

The British Society for Paediatric and Adolescent Rheumatology
Etanercept Cohort Study

**Dr Kimme Hyrich
The University of Manchester**

**Professor Taunton R Southwood
University of Birmingham**

**14th July 2014
Protocol Version 8.0**

1. Study Sponsor

The study is sponsored and hosted by The University of Manchester.

2. Study summary

The British Society for Paediatric and Adolescent Rheumatology (BSPAR) Etanercept Cohort Study (ECS) will prospectively collect standardised information on:

1. Children and young people who are prescribed etanercept
2. Children and young people prescribed methotrexate (who will act as a control group).

Follow-up will be for a minimum of 5 years. When young people transfer to adult services attempts will be made to continue their participation in the study at the new hospital.

Data to be collected at base-line and follow-up (six months, twelve months and subsequently yearly):

Age, gender, presentation and duration of disease, diagnosis and prior treatments. Prior history of TB and immunisation status. The Core Outcome Variables for JIA. Full blood count, auto-antibodies, electrolyte and liver enzyme profile. Height and weight. School absence. Co-morbidity and relevant history. Current therapy and month of and reasons for any discontinuation of therapy and any recommencement of therapy. Adverse events. Hospitalisations. Ophthalmological, radiological, surgical data.

Flagging of patients with the National Health Service Central Register (NHSCR) will ensure that patients can be traced and that long-term data will be available. Consent will be sought to contact patients through their doctors about further studies.

3. Background information

Efficacy of etanercept and methotrexate

Etanercept, an anti- Tumour Necrosis Factor (TNF) and the first biologic agent licensed for the treatment of JIA, has been shown to have short term therapeutic benefit on disease activity measures in the treatment of adults with rheumatoid arthritis and children with Juvenile Idiopathic Arthritis (JIA) who were methotrexate failures or who could not tolerate the drug (evidence from one placebo controlled randomised control trial(1)). No evidence is as yet available on whether etanercept has an effect on structural joint damage.

Methotrexate is now an established treatment for relatively severe and longstanding JIA. There is limited evidence on its long-term impact.

A well designed register-based cohort study presents the best opportunity to gather evidence on long term outcomes. It is recognised that an unrandomised comparison of the outcomes of the etanercept and methotrexate groups may be biased, but there are no similar long term RCTs in progress. Advanced statistical techniques, such as propensity modelling, can also account for differences in baseline severity.

Safety of etanercept

The safety information available on etanercept, the first biologic agent licensed for use in JIA is summarised below.

1. In the JRA trial, slightly more infections were reported in the etanercept treated patients (60% of patients, 0.33 events per month) than in the placebo group (31%, 0.28 events per month)(1).
2. The most common adverse events in adults with RA were injection site reactions (42% of patients) and infections (58%). In adult studies 7 out of 531 patients developed cancer, although this was not different to that seen in the placebo group or expected in the general population(2).
3. In post marketing surveillance, 10 cases of blood dyscrasias, including five with fatal sepsis, have been reported associated with the use of etanercept, confirming the need for continuing safety monitoring(3).
4. Rare cases of central nervous system disorders including demyelinating disorders have been reported in rheumatoid arthritis patients(3).
5. Twenty-eight cases of tuberculosis have been reported in association with infliximab, a chimeric monoclonal tumour necrosis factor alpha inhibitor licensed for use in rheumatoid arthritis and Crohn's disease, raising a concern that similar problems may occur with the use of agents with similar actions(4;5).
6. Regulatory bodies remain concerned that long-term patients might "develop an as yet unidentified immune defect" putting them at increased risk of malignancy and infections.

Safety of methotrexate

There are also safety issues concerning older agents used to treat JIA.

1. Lymphomas have been reported in methotrexate treated patients including children and this may be a phenomenon related to rheumatic disease or a complication of treatment(6).
2. Liver fibrosis and cirrhosis has been reported in adults following treatment with methotrexate although clinically significant fibrosis has not been reported in children(6).

Pharmacogenetics of Biologic Response

Prescribing medications in children has historically been largely empirical but it is now essential that we move away from this era and begin to generate information that will allow paediatricians to determine early in disease which patients are best suited for a particular therapeutic agent and which patients may be at risk for serious potentially life-threatening complications from standard treatment regimens. It has been shown in adults, that response is not random but associated with specific clinical, genetic, and psychological factors and the use of pharmacogenetic tests are becoming increasingly important within the clinic. Children, as well as adults, should benefit from the discoveries of the genomic era. Given that diseases that originate during childhood, including arthritis, often persist into adulthood it is important that attempts to understand the genetic basis of age-specific disease processes also take account of the fact that the period of human development encompasses the prenatal period through adolescence, and is a rapidly changing, dynamic process. Pharmacologic modulation of developing gene networks may have unintended and unanticipated consequences that do not become apparent or relevant until later in life. With this in mind it is important that as well as describing the safety and efficacy of etanercept and methotrexate, this study aims to collect the appropriate data and material that will, in the future, allow us to begin to identify early predictors of response. Setting up a Biobank of

DNA (from either blood or saliva) alongside the clinical data collection will make this a very real possibility in the near future.

Rationale for the study

There is therefore a need for further information on both short and long-term effectiveness and safety of etanercept and methotrexate in JIA. Better quality safety information on methotrexate will allow more useful comparison of the risks and benefits attached to the use of biologic agents.

4. Objectives

Aims:

1. Safety monitoring of etanercept in compliance with drug licences and NICE guidelines, and methotrexate (current standard therapy) in juvenile idiopathic arthritis patients, including monitoring of growth and developmental milestones with adverse event monitoring.
2. Collection of information on long term course of the condition, long term outcomes and use of therapeutics in a cohort of children treated with biologic agents, methotrexate or other new drugs for rheumatic disease.

Objectives:

1. To establish a register of patients with severe juvenile idiopathic arthritis
2. To collect and record data on children and young people prescribed etanercept for JIA including demographic data, disease type and activity, outcomes and safety data
3. To collect data on appropriate methotrexate treated controls
4. To provide for the future collection of data on longer term outcomes through flagging with the NHS Central Register.

5. Research question

What are the safety and other outcomes of etanercept or methotrexate in children and young people prescribed these drugs for Juvenile Idiopathic Arthritis (JIA)?

6. Study design

In this observational study, the registry will prospectively (and retrospectively where possible) collect standardised information on:

1. Children and young people who are prescribed etanercept, and on,
2. A control group prescribed methotrexate.

The primary study endpoint is drug safety.

Secondary endpoints include length of drug use, discontinuation, core outcome variables and response measured from change in core outcome variables as described by Giannini(7).

Duration of follow-up

It is anticipated that follow-up within the paediatric register will be for the five year duration of the study in the first instance (the follow-up of some patients may be longer) or until such time as young people transfer to adult services which do not wish to participate in the register.

The project will be designed and carried out in compliance with the Department of Health Research Governance Framework, and the relevant parts of the International Conference on

Harmonisation Good Clinical Practice guideline. It will follow the guidelines for the establishment of a register suggested in the RCPCH report on case registers(8).

Ancillary sub studies

Consent will be sought to contact patients through their doctors about further studies. Preliminary advice on the suitability of the patient population for such studies should be sought from the register team (T. Southwood or K Hyrich), before submission of such studies to the Research Committee of the BSPAR and then the Management Committee for the register. Full ethical approval is required.

7. Selection of participants

Children and young people treated with biologics:

Inclusion criteria:

1. Any child or young person and treated at one of the contributing centres, prescribed a biologic for JIA according to the ILAR disease classification within the previous 6 months. It is anticipated that prescribing will be in line with the NICE guidelines and any subsequent revisions. Patterns of prescribing may well change over time.
2. Extension to other rheumatic disease in childhood where etanercept is prescribed if this is agreed with the Steering Committee.

Exclusion criteria:

1. Any child or young person who withholds consent or whose carer withholds consent (as appropriate, given young person's competence).
2. Any child or young person who withdraws for inclusion in the register.

Methotrexate controls

Inclusion criteria:

1. Any child or young person prescribed methotrexate for JIA starting methotrexate treatment within the previous 6 months.
2. Use of other non-biologic DMARDs in combination with methotrexate is allowed.

Exclusion criteria:

1. Any child or young person who withholds consent or whose carer withholds consent (as appropriate, given young person's competence).
2. Any child or young person who withdraws from the register.

Withdrawal of participants

Participants will be withdrawn from the study if:

1. Any child or young person withdraws their consent or assent or any person with parental responsibility for a child not competent to consent for themselves withdraws consent.
2. Any participant moves to another centre that is not willing to participate in the BSPAR ECS.

Participants who are no longer receiving methotrexate or etanercept will still be included for follow-up

Enrolment

Notification of cases

It will be the responsibility of the treating rheumatologist or designate to obtain

parent/patient consent prior to registration. Participant information sheets, consent forms and a copy of this protocol will be made available on The University of Manchester Arthritis Research UK Epidemiology Unit's website.

Consent

Informed consent to be included in the register will be obtained from parents or carers and consent or assent from patients as appropriate. This will need to include permission to approach patients regarding further research and permission for audit of medical records and other source documents to check the integrity of the registry data if required. Consent for flagging with the National Health Service Information Centre will be sought separately, as will consent to contact patients through their doctors about further studies. Finally, separate consent will also be obtained to collect a single blood sample for genetic analysis. Where transfer of a patient's care to another centre is planned, consent will have to be sought anew and trust R&D approval sought from that centre. Once signed consent has been obtained, a register identification number will be obtained from the register. GPs will be informed that patients are in the study.

Patients and their families need sufficient time, at least twenty-four hours, to consider whether to take part in the BSPAR ECS.

Some paediatric rheumatology centres however serve geographically dispersed populations and have shared care and satellite clinic arrangements. Although clinicians in such centres have long term responsibilities for patients, patients may attend clinics infrequently, although there may be telephone contact and support for patients between clinics. This presents problems in gaining informed consent for the study, particularly if information is given in clinic and the next scheduled visit is scheduled for some months later. In centres where these circumstances impede recruitment, information can be posted to families and informed consent later in a telephone discussion. On telephoning the patient, the delegated person seeking consent should first check whether the parent or patient wishes to discuss the study. If not, they should end the phone conversation without further discussion of the study. If the parent or patient is willing to discuss the study, the delegated person should check whether the phone call is taking place at a convenient time and if not reschedule the phone call. The delegated person should ensure that both parent and child have had a chance to discuss the study and ask questions, if necessary arranging to telephone at another time.

A record will be made in the notes of the consent and will be signed by the person who took the consent.

The clinician seeing the patient at the next clinic visit should check that the parent or patient still consents to the study.

8. Assessments and procedures (for all patients in the study)

Baseline information

1. Age, gender, presentation and duration of disease, diagnosis (ILAR) and prior treatments (including cumulative steroid dose) with dates and duration will be recorded.
2. The Core Outcome Variables will be used to assess response and will be measured at entry, based at two points one month apart, in line with the current BPRG eligibility

- criteria for etanercept treatment.
3. Height and weight will be recorded.
 4. Existing co-morbidity and relevant history, including previous tuberculosis will be recorded.
 5. Immunisation history will be ascertained.
 6. The Child Health Utility 9D (CHU9D) will be collected through the clinic team

Follow-up information

1. Follow-up information will be reported at six months and twelve months and subsequently at yearly intervals.
2. Current therapy and the dates of any discontinuation of therapy and any recommencement of therapy will be recorded. Reasons for discontinuation will be recorded.
3. The Core Outcome Variables will be used to assess response in line with the Food and Drugs Administration (FDA) guidelines.
4. Height and weight will be recorded.
5. The CHU9D will be collected through the clinic team.
6. Adverse events will be recorded using a schedule designed in collaboration with the contributing centres. Relatively common and relatively less serious events will be recorded as well as serious adverse events; as such events are important for informed patient choice of therapies and may have an important impact on health-related quality of life.
7. Hospitalizations, length of stay and reason for hospitalization will be recorded.
8. Other relevant data (ophthalmological, radiology, surgery, concomitant morbidity) will be recorded.
9. Flagging of patients with the NHS-IC will ensure that long term data on mortality and cancer and other health outcomes will be available.
10. The "Transition to Adulthood" questionnaire will be provided to patients by the nurse at the relevant time points

Biobank

In addition to the collection of core clinical data, a blood sample or saliva sample will be collected from all children for genetic analysis (with informed consent). The costs of specific gene / pharmacogenetic investigations will be carried out by separate funding.

9. Data handling and record keeping

Collection of data

All core baseline and follow-up data will be collected by a web-based system, which in most cases will be completed by a nurse affiliated with the local centre. Where access to the web system is not possible, CRFs may be posted directly to the University of Manchester for input by the study team. Strenuous attempts will be made to follow-up non-responding centres and will include an initial notification email at the time a follow-up is due, with a reminder email at 4 weeks if no response to the first email. A second postal reminder 4 weeks later will be sent if there is no response to the first 2 email contacts, which will finally be followed-up with a phone call from the study coordinator to understand the reason for lack of response. All centres will be asked to provide a phone number and postal address in case of changes to staff or email address.

The online database is protected with SSL level security and the online database is password protected. Usernames and passwords are issued to named individuals from recruiting centres who need to access the online database.

The security of the BSPAR web-collection system will be governed by the corporate security policy of The University of Manchester which can be found at (<http://www.itservices.manchester.ac.uk/medialibrary/pdf/secureguidance/A-InformationSecurityPolicy.pdf>). A risk management / security improvement plan will be established to address all unacceptable risks in terms of data security. The UoM has data protection registration to cover the purposes of data collection and analysis (<http://www.ico.gov.uk/ESDWebPages/search.asp>, Registration number Z6787610).

All BSPAR staff or others having access to BSPAR data are required to sign statements each year concerning conflicts of interest, disclosure and confidentiality undertakings.

Where patients' care is transferred to another centre, the new treatment centre will be approached about participation in the BSPAR ECS and assistance will be given with Trust R&D application if required.

10. Data access and quality assurance

Each patient will be allocated a study number by the register that will be used in all communications with the register once informed consent has been obtained in the collaborating centre. If a registered patient transfers to another centre that contributes to the register, the study number will need to be communicated to the new centre. Initial registration forms linking identifiable data and study numbers, however, will be stored securely and confidentially under the custody of Dr. Kimme Hyrich.

The Registry Office is locked when unoccupied and is an area of the building with restricted access. All personal data is stored in locked cabinets within the Registry Office.

11. Sample size and recruitment

Sample size estimates should ideally be based on estimates of the risk of the outcome of interest in an untreated population. However, there is limited information available on either how often these drugs are being prescribed in routine clinical practice or how frequently serious adverse events occur with either methotrexate or etanercept. It is expected that use of these treatments and therefore, recruitment to the study will continue to increase over time. As recruitment increases the number of risk hypotheses that can be investigated will also increase. The other issue that will influence statistical power is the duration of follow-up. Under a model that proposes that the increased risk of a long term hazard is constant over the duration of follow-up, then the number of person-years at risk increases in direct proportion to the length of follow up.

We will aim to recruit the maximum number of children starting etanercept and/or methotrexate and will aim for a minimum of 100 children/year. As recruitment increases, the number of risk hypotheses that can be investigated will increase. In addition, continued follow-up of these children will allow exploration of issues related to long-term use of these agents with respect to the developing immune system.

Comparability of exposed and non-exposed cohorts

The greatest concern with this study is the risk of confounding by indication. In general, treated and untreated subjects in an observational study will differ in a number of variables which are related to the outcome under study. This may be particularly true in observational treatment studies in JIA, where, due to the current treatment paradigm, after failure with MTX, most children will move on to etanercept rather than another traditional DMARD. Therefore, by definition, the treated cohort will have more severe disease. The recruitment process outlined above will be monitored on a 6 monthly basis and comparisons undertaken between the distributions of covariates between the cohorts recruited to both groups to take into account any substantive shift from non-exposed to exposed status. Residual differences will be adjusted for in the analysis.

12. Planned analyses

Review of target numbers of registrations and inclusion and exclusion criteria for biologic and control groups.

In view of the above uncertainties over recruitment, the Steering Committee will keep under review recruitment targets and inclusion and exclusion criteria and suggest amendments, should these prove necessary.

Analysis

A report will be prepared for the annual report to the Steering Committee, with descriptive statistics and updates of registration progress available more frequently.

In addition to summaries of adverse events, statistical analysis appropriate to the outcomes under consideration will be carried out, for example survival analysis of time to relapse, repeated measures ANOVA or summary measures as appropriate, for example, area under the curve, for core outcome variables. Confounders will as far as possible be controlled in the analyses.

Adverse events will be monitored and ad hoc reports prepared in consultation with the Steering Committee as required. It remains the responsibility of collaborating centres to report severe adverse events to the regulatory authority as well as to the register.

13. Adverse events

In order to ensure that regulatory authorities are aware of serious adverse events, the Registry will report anonymised details of serious adverse events occurring on etanercept information to Pfizer, the pharmaceutical company responsible for the manufacture and marketing of etanercept.

14. Finance

The study is funded by BSPAR and supported by Pfizer.

15. Ethics approval

Ethical approval was obtained from the West Midlands Multi-centre Research Ethics Committee.

References

(1) Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *Pediatric*

Rheumatology Collaborative Study Group [see comments]. New England Journal of Medicine 2000; 342(11):763-769.

(2) Committee for Proprietary Medicinal Products: European Public Assessment Report (EPAR): Enbrel. Scientific Discussion. CPMP/146/00. 13-1-2001.

(3) Committee for Proprietary Medicinal Products. EMEA Revised public statement on etanercept (Enbrel) - reports of serious hematological reactions and demyelination disorders. EMEA/H/30871. 3-10-2000.

(4) Committee for Proprietary Medicinal Products: European Public Assessment Report (EPAR): Remicade. Scientific Discussion. CMCP/1901/99. 13-12-2000.

(5) Committee for Proprietary Medicinal Products. EMEA Public state on infliximab (Remicade) - reports of tuberculosis infections. EMEA/CMCP/4445/00. 20-12-2000.

(6) Ravelli A, Martini A. Methotrexate in juvenile idiopathic arthritis: answers and questions [editorial] [In Process Citation]. J Rheumatol 2000; 27(8):1830-1833.

(7) Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997; 40(7):1202-1209.

(8) Thornes R. Case registers in 1999: ethical and legal issues, ownership and accountability. 2000. London, Royal College of Paediatrics and Child Health.

(9) Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley and Sons, 1981.

(10) Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. Health Technol Assess 2002; 6(17):1-43.

(11) National Institute for Clinical Excellence. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. Technology appraisal 35. 2002.

(12) PSI Statisticians in the Pharmaceutical Industry. GUIDELINES FOR STANDARD OPERATING PROCEDURES for Good Statistical Practice in Clinical Research. PSI Professional Standards Working Party. 12-1-2001.