NICE National Institute for Health and Care Excellence

Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis

Issued: March 2002

NICE technology appraisal guidance 35

guidance.nice.org.uk/ta35

Contents

1 Guidance

1.1 Etanercept is recommended for children aged 4 to 17 years with active polyarticular-course juvenile idiopathic arthritis whose condition has not responded adequately to, or who have proved intolerant of, methotrexate.

1.2 Etanercept should be prescribed in accordance with relevant sections of the British Paediatric Rheumatology Group (BPRG) protocol (see Appendix D), which sets out criteria for eligibility, definitions of failure of standard therapy, exclusion criteria and criteria for withdrawal of therapy. In particular, treatment should be withdrawn in the event of severe drug-related toxicity or because of lack of response at 6 months.

1.3 Initiation of etanercept therapy should only be undertaken by a consultant who regularly sees children and young people with juvenile idiopathic arthritis and who runs specialised paediatric rheumatology clinics. In addition, the prescribing centre should have a nurse specialist or an appropriately trained nurse who is able to teach children and parents injection techniques and who does this regularly. Follow up of treatment response and adverse events may be on a shared-care basis depending on local circumstances.

1.4 It is strongly recommended that all clinicians prescribing etanercept should (with the permission of the child and/or parent) register the child with the Biologics Registry established by the BPRG and forward information on dosage, outcome and toxicity on a quarterly basis.

1.5 There is currently no evidence to support treatment beyond 2 years and continuation of therapy is therefore contingent upon ongoing monitoring of disease activity and clinical effectiveness in individual cases.

2 Clinical need and practice

2.1 Juvenile idiopathic arthritis (JIA) is a term that covers a heterogeneous group of diseases characterised by persistent joint swelling, pain and limitation of movement. At its worst, JIA causes growth retardation, joint contractures, ocular problems and permanent disability. A high proportion of affected children develop destructive joint disease, often requiring early joint replacement.

2.2 JIA impairs children's personal and social functioning and development. Children often miss out on schooling and normal childhood activities, and as adults they may have poor earning capability or be unable to work. The impact on the family can also be considerable, not only emotionally but also financially because parents may restrict or give up their work so that they can care for their child.

2.3 JIA is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1000 children, equivalent to 1000 new cases per year. The prevalence is in the order of 1 per 1000 children, so about 10,000 children in the UK are affected.

2.4 Management of JIA is holistic and multidisciplinary, with physical therapy and surgical intervention running in parallel with drug treatment. Key aims of treatment include controlling joint pain and inflammation, reducing joint damage, disability and loss of function, and maintaining or improving quality of life.

2.5 Drug treatment for JIA involves, sequentially, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular, intravenous or oral corticosteroids for the management of systemic complications, and disease-modifying anti-rheumatic drugs (DMARDs). The DMARD of choice is generally methotrexate, given orally or parenterally, although no DMARDs are currently licensed for use in children in the UK. The overall response rate to oral methotrexate in polyarticular-course JIA (characterised by arthritis in at least five joints) is estimated to be 85% in the short term. The evidence base for the effectiveness of alternative drug therapies is weak and no one therapy stands out as the first

choice once methotrexate has failed. Children for whom methotrexate treatment has failed may benefit from treatment with etanercept.

3 The technology

3.1 Tumour necrosis factor alpha (TNFα) is a pro-inflammatory mediator that has been identified as a key molecule in the pathogenesis of JIA. Its over-expression is responsible for the damaging inflammatory processes that occur in articular cartilage and bone. Agents that inhibit the action of TNFα might therefore be expected to have the potential to modify the inflammatory processes of rheumatic disease.

3.2 **Etanercept** is a recombinant human TNF receptor fusion protein that acts competitively to inhibit the binding of TNF to its cell-surface receptor. Etanercept is licensed for the treatment of active polyarticular-course JIA in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Etanercept is administered as a twice-weekly subcutaneous injection.

3.3 Etanercept may be given for an indefinite period. However, once a child with JIA has had 2 disease-free years, it is common clinical practice for drug treatment to be stopped, although 30% of children would be expected to relapse.

4 Evidence

4.1 Clinical effectiveness

4.1.1 Only one randomised controlled trial of etanercept in children with JIA was identified and this was of high quality. The trial had a unique design to satisfy ethical considerations. There was an initial open-label phase in which all 69 patients, who had not responded to NSAIDs and methotrexate, received etanercept for 3 months. This was followed by randomisation of responders to a double-blind phase, in which they received either etanercept or placebo for a further 4 months.

4.1.2 In the initial phase, 74% of children achieved a JRA30 response (see Appendix E). In the second phase, 28% of children receiving etanercept experienced a flare up of symptoms compared with 81% receiving placebo ($p = 0.003$). At the end of the study, the proportion of children who still met the JRA30 definition of improvement was significantly higher in the group receiving etanercept than in the placebo group (80% vs 35%, $p < 0.01$). At the end of the double-blind phase, the JRA50 definition of improvement was met by 72% of children who had received etanercept compared with 23% who had received placebo; the JRA70 definition of improvement was met by 44% who had received etanercept compared with 19% who had received placebo.

4.1.3 In the ongoing open-label extension study, after 2 years (median duration of treatment of 26 months), 83% of children had achieved a JRA30 response, 78% a JRA50 response, and 63% a JRA70 response. Children whose disease had flared while receiving placebo regained their initial response.

4.1.4 There were no statistically significant differences in adverse events per patient month between the etanercept and placebo groups. The most common adverse events seen with etanercept were mild to moderate injection site reactions (39%), which were self-limiting and caused no withdrawals, upper respiratory tract infections (35%), headache (20%), rhinitis (16%), abdominal pain (16%), vomiting (14%), pharyngitis (14%), nausea (12%) and rash (10%).

4.1.5 In the etanercept group, functional ability measured by Child Health Assessment Questionnaire (CHAQ) score (see Appendix E) improved from 1.6 at baseline to 0.8 at month 7, whereas there was little change in the placebo group (from 1.3 at baseline to 1.2 at month 7).

4.2 Cost-effectiveness

4.2.1 No published economic evaluations were identified. A cost–utility analysis was undertaken as part of the manufacturer's submission, based upon an economic model developed for adult rheumatoid arthritis. The model is based on a number of uncertainties but was included as a starting point for future research.

4.2.2 The main assumptions are that the measures of clinical response used in children and adults are comparable, that the CHAQ is equivalent to the adult version, the Health Assessment Questionnaire (HAQ), and that the HAQ relationship to utility and mortality also applies in children.

4.2.3 The model gives a base-case incremental cost-effectiveness ratio (ICER) of £16,082 per quality adjusted life year (QALY) for etanercept versus placebo (range £3900 to £34,000).

4.2.4 The Assessment Group did not develop an economic model because the lack of empirical information precluded the construction of a model with greater validity.

4.3 Considerations

4.3.1 The Committee reviewed the available evidence on the clinical and cost effectiveness of etanercept, and considered evidence from user representatives and clinical experts on the nature of the condition and the benefits of drug therapy. They took into account that:

- no DMARDs are licensed currently for use in children
- at present, best practice is limited to methotrexate prescribed off licence

- there was convincing evidence of the clinical effectiveness of etanercept in the short to medium term
- the disease is arrested by drug therapy in a small proportion of children.

4.3.2 The Committee accepted that given the relative robustness of the manufacturer's estimate of cost-effectiveness to changes in key parameters, the ICER for etanercept is likely to be in the region of £15–30,000 per QALY.

5 Implications for the NHS

5.1 There are approximately 10,000 children with JIA in England and Wales. Assuming that 40% of these children have polyarticular-course disease, of whom 15% do not respond adequately to methotrexate, approximately 600 children would be eligible for treatment with etanercept. Assuming contraindication rates of 15%, success rates of 75% and dropout rates of 10%, over 300 children might be satisfactorily maintained on etanercept in the long term. With annual costs of £10,000 per child, the total budget impact would be £3 million per year.

5.2 The Enbrel Home Care service has been set up by Wyeth Laboratories as a home dispensing service, enabling children to administer their own etanercept. The manufacturer's submission suggests that if children received etanercept through the home delivery service, potentially there would be savings of up to 10% because the service is VAT exempt.

5.3 It is unlikely that the use of etanercept in children would have a significant impact on health services in terms of drug administration and monitoring. However, there may be an increased need for specialist nurses in rheumatology, and multidisciplinary rehabilitation and physical therapy resources. The long-term impact of etanercept treatment on joint damage is unclear at present, but the reduced risk of joint damage and destruction has the potential for delaying or even reducing the need for expensive joint replacement surgery.

6 Further research

6.1 Studies are required to determine long-term clinical outcomes, in particular joint damage, unexpected adverse events, and whether or when the drug can be withdrawn if remission is achieved.

6.2 The problems encountered in constructing an economic model indicate that further research is required to determine health-related quality of life in children, and that economic analyses of etanercept should be included in randomised controlled trials.

6.3 The use of the Biologics Registry data will be essential to establish the longer-term clinical effectiveness of etanercept as well as the potential for adverse effects. It is particularly important that the optimal duration of therapy is defined in order to target treatment to those most likely to benefit.

7 Implementation

7.1 Clinicians treating children with JIA should review their current practice in line with the guidance set out in Section 1.

7.2 To enable clinicians to audit their own compliance with this guidance, it is recommended that a system for identifying children with JIA and those who have been prescribed etanercept is in place at a local level and that a treatment plan is recorded for each child.

7.3 The following criteria, based on the BPRG protocol, can be used to measure the appropriateness and effectiveness of the prescription of etanercept for children with JIA. Further details of suggestions for audit are presented in Appendix F.

- Etanercept is initially prescribed for a child or young person aged 4 to 17 years who has polyarticular-course JIA only in the following circumstances:
  - in the last 6 months, the child has five or more swollen joints and three or more joints with limitation of motion and pain, tenderness or both, and
  - the child has not responded following adequate treatment with methotrexate for at least 3 months, and
  - the child does not have a clinical condition that would constitute a contraindication to prescription of etanercept.
- Treatment with etanercept is withdrawn if the child experiences an unacceptable adverse event or if the child does not respond during the 6 months following the initiation of treatment or does not continue to respond after the initial 6-month trial.
- Etanercept therapy is initiated only by a consultant who regularly sees children with JIA and who assumes responsibility for follow up of treatment response and adverse events.
- The consultant prescribing etanercept assumes responsibility for registering a child receiving etanercept with the Biologics Registry of the BPRG and forwarding

information on dosage, outcome and toxicity on a quarterly basis, subject to the child's and/or parent's consent.

- In units in which etanercept is prescribed, a suitably qualified and trained nurse is regularly available to teach children and parents injection techniques.
- A child or young person who is initiated on etanercept therapy is followed up for treatment response and adverse events.

7.4 Local clinical audits on the care of children who are on etanercept also could include criteria on the local monitoring protocol and on the management of the transition of older children with JIA to adult care.

8 Review guidance

8.1 Information on the review of the guidance on this technology is available on the NICE website.

Andrew Dillon
Chief Executive
March 2002

Appendix A. Appraisal Committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in Appendix B.

Dr Jane Adam
Radiologist, St George's Hospital, London

Dr Sunil Angris
General Practitioner,Waterhouses Medical Practice

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Carol Black
Consultant Physician, Royal Free Hospital & UCL, London

Professor John Brazier
Health Economist, University of Sheffield

Professor Bruce Campbell
Consultant Surgeon, Royal Devon & Exeter Hospital

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Karl Claxton
Health Economist, University of York

Professor Jack Dowie
Health Economist, London School of Hygiene & Tropical Medicine, London

Professor Trisha Greenhalgh
Professor of Primary Care Health, University College London

Sally Gooch
Director of Nursing, Mid-Essex Hospital Services Trust

Liz Heyer
Chief Executive, Barnet & Chase Farm Hospitals NHS Trust

Dr Diane Ketley
Research into Practice Programme Leader, NHS Modernisation Agency

Ruth Lesirge
Patient Representative; Director, Mental Health Foundation

Dr George Levvy
Patient Representative; Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
CEO, North & East Devon Health Authority

Professor Miranda Mugford
Health Economist, University of East Anglia

Siân Richards
General Manager, Cardiff Local Health Group

Professor Philip Routledge
Professor of Clinical Pharmacology, University of Wales

Dr Rhiannon Rowsell
Pharmaceutical Physician, AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Professor Andrew Stevens
Professor of Public Health, University of Birmingham

Professor Ray Tallis
Consultant Physician, Hope Hospital, Salford

Professor Mary Watkins
Head of Institute of Health Studies, University of Plymouth

Dr Norman Waugh
Public Health Consultant, University of Southampton

Appendix B. Sources of evidence

The following documentation and opinion was made available to the Appraisals Committee:

a. Assessment Report:

- Prepared by West Midlands Development and Evaluation Service, The University of Birmingham *(A Rapid Review of New Drug Treatments for Juvenile Idiopathic Arthritis: Etanercept)*, June 2001

b. Manufacturer/sponsor submissions:

- Wyeth Laboratories

c. Professional/specialist group and patient group submissions from:

- Royal College of General Practitioners
- Chartered Society of Physiotherapy
- British League Against Rheumatism (on behalf of Arthritis Care, British Paediatric Rheumatology Group, Children's Chronic Arthritis Association, Lady Hoare Trust for Physically Disabled Children, and Primary Care Rheumatology Society)
- Royal College of Nursing
- Department of Health

d. External expert and patient advocate submissions from:

- Dr Helen Venning, Consultant Paediatric Rheumatologist, University Hospital, Nottingham
- Neil Betteridge, Head of Public Policy & Campaigning, Arthritis Care

Appendix C. Patient information. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis

'Understanding NICE Guidance', a summary of this guidance for patients and carers can be found on our website.

Appendix D. British Paediatric Rheumatology Group guidelines

The following guidelines have been recommended by the BPRG to ensure that new anti-TNFα treatments are introduced in as systematic and planned a way as possible to ensure the greatest possible benefit to children with arthritis.

Eligibility for treatment with biologic therapies

1. Inclusion criteria

Juvenile idiopathic arthritis of the following types:

- systemic
- polyarticular (sero-negative or positive for rheumatoid factor)
- extended oligo-articular
- psoriatic
- enthesitis-related

and the following features:

- five or more swollen joints and
- three or more joints with limitation of motion and pain, tenderness or both.

2. Failure of standard therapy

Patients must have had adequate therapeutic trials of methotrexate. An adequate therapeutic trial would be defined as:

- treatment for at least 3 months at a dosage of parenteral methotrexate of 20 mg/m2 weekly (unless significant toxicity limited the dose tolerated)
- ≥5 active joints and ≥3 joints with loss of motion plus pain/tenderness

- the disease is only controlled by unacceptable side effects of high doses of corticosteroids (> 0.25 mg/kg daily) and have had active disease as defined above in the last 6 months.

3. Exclusion criteria

Reference should be made to the drug data sheet but important exclusions include:

- young women who are pregnant or breastfeeding or who are sexually active but with inadequate contraception
- active infection
- current or previous tuberculosis
- previous or present sepsis of a prosthetic joint still in situ
- malignancy or pre-malignancy states
- immunodeficiency.

4. Criteria for withdrawal of therapy

Treatment will be withdrawn in the event of:

- adverse events including:
  - malignancy
  - severe drug related toxicity
  - pregnancy (temporary withdrawal)
  - severe intercurrent infection (temporary withdrawal)
- inefficacy:
  - lack of response, but not within the first three months of treatment. At 6 months there should be a 30% improvement of 3/6 of the core set data.

Core set data include:

- number of active joints
- number of joints with loss of range of movement
- physician's global assessment
- patient or parent's global assessment
- CHAQ
- erythrocyte sedimentation rate (ESR).

Appendix E. Juvenile rheumatoid arthritis (JRA) response criteria

Response is defined using the American College of Rheumatology juvenile rheumatoid arthritis (JRA) core set criteria which include:

- global assessment of the severity of the disease by the physician
- global assessment of overall well-being by the patient or parent
- number of active joints (joints with swelling not due to deformity or joints with limitation of motion with pain, tenderness or both)
- number of joints with limitation of motion
- functional ability based on CHAQ scores (see below)
- ESR.

To meet the criteria of response, JRA30, patients had to have a 30% improvement from baseline in at least three of the six response variables, with worsening of 30% or more in no more than one of the six variables.

Child Health Assessment Questionnaire

CHAQ is a measure of functional ability and is measured on a scale of 0 (best) to 3 (worst). It is a self-administered measure which evaluates four dimensions: disability, discomfort, drug side effects and costs. In addition to assessing activities of daily living, the CHAQ quantifies the degree of assistance required by patients.

Appendix F. Technical detail on criteria for auditing the use of etanercept in the treatment of juvenile idiopathic arthritis (JIA)

Objectives for the audit

An audit on the appropriateness and safety of the use of etanercept for the treatment of children or young people with JIA can be carried out to ensure that:

- etanercept is prescribed in accordance with criteria for eligibility for treatment with biological therapies recommended by the British Paediatric Rheumatology Group (BPRG) guidelines
- etanercept is initiated only by an appropriate specialist with appropriate nursing support available
- children on etanercept are registered with the Biologics Registry of the BPRG.

Patients to be included in the audit

All children or young people with JIA who are under the care of a consultant at the time the audit is being undertaken.

Measures to be used as a basis for the audit

The measures to be used in an audit of children or young people with JIA are as follows:

Criterion	Standard	Exception	Definition of terms

1. A child is initially prescribed etanercept if the child is between 4 and 17 years old and has all of the following: a. active polyarticular-course JIA and b. 5 or more swollen joints and c. 3 or more joints with limitation of motion and pain, tenderness or both and d. no response following adequate treatment with methotrexate for at least 3 months and has experienced unacceptable side effects at high doses of corticosteroids	100% of children with JIA	A. Patient or parent choice not to try etanercept B. Young women who are pregnant or breastfeeding or who are sexually active with inadequate contraception C. Active infection D. Current or previous tuberculosis E. Previous or present sepsis of a prosthetic joint still in situ F. Malignancy or pre-malignancy states G. Immunodeficiency	For 1d, adequate treatment = treatment for at least 3 months at a dosage of parenteral methotrexate of 20 mg/m^2 weekly (unless significant toxicity limited the dose tolerated). Consultants should agree locally on what constitutes drug toxicity for audit purposes High dose of corticosteroid => 0.25 mg/kg daily No response =< 30% improvement from baseline at 6 months in at least 3/6 of the following: I. number of active (with swelling not due to deformity or joints with limitation of motion with pain, tenderness of both) joints II. number of joints with limitation or loss of range of movement III. physicians' global assessment of severity of disease IV. child's, young person's or parent's global assessment of overall well-being V. functional ability based on the Child Health Assessment Questionnaire (CHAQ) VI. erythrocyte sedimentation rate (ESR) See the patient record for reference to 1a–d

2 Treatment is withdrawn if a child experiences an adverse event or does not respond during the 6 months following the initiation of treatment or after the initial 6-month trial	100% of children prescribed etanercept	Drug is withdrawn temporarily in case of the following: A. pregnancy B. severe intercurrent infection	Adverse event = malignancy or severe drug-related toxicity. severe drug-related toxicity. malignancy or severe drug-related toxicity for audit data retrieval purposes See 1d for definition of no response following the initiation of treatment Does not respond after the initial 6-month trial = does not maintain at least 30% improvement from baseline for items listed under 1d See patient record for notation of any adverse events
3 An appropriate consultant initiates etanercept therapy for eligible children	100% of children prescribed etanercept	None	Appropriate consultant = one who regularly sees children and young people with JIA or a competent member of the medical team under the supervision of the consultant
4 A child prescribed etanercept is registered with the Biologics Registry of BPRG	100% of children prescribed etanercept	Child and/or parent does not consent to registry	Registered = information on dosage, outcome and toxicity forwarded to Registry on a quarterly basis
5 A child (or parent) has access to training in injection techniques	100% of children prescribed etanercept	None	Training is provided by a suitably qualified and trained nurse; see patient record for notation that training is provided
6 Treatment is followed up for response and adverse events	100% of children prescribed etanercept	None	Consultants should agree locally on what constitutes follow up, particularly if follow up is provided on a shared care basis. See patient record for evidence of follow up as defined

Calculation of compliance with measures

Compliance with each measure described in the table is calculated as follows.

Number of children or young people whose care is consistent with the **criterion *plus*** number of children or young people who meet any of the exceptions listed

/

Number of children or young people to whom the **measure** applies

X100

Cases that are not consistent with the audit measures in the table should be subject to individual case review by the consultant(s) involved, and any areas in which practice can be improved should be identified and acted upon.

Changes after publication

March 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Copyright