NHS

National Institute for Clinical Excellence

National Institute for Clinical Excellence

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Technology Appraisal Guidance – No. 36

NHS

National Institute for Clinical Excellence

Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis

March 2002

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Issue date: March 2002
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Ordering Information
Copies of this guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting ref: N0074. A patient version of this document can be obtained by quoting ref: N0076. A bi-lingual patient leaflet is also available, ref: N0077.

Distribution of Guidelines

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- Medical and Nursing Directors in England and Wales
- Consultant Rheumatologists in England and Wales
- Chief Pharmacists, Heads of Drug Purchasing, Heads of Drug Information, Pharmaceutical Advisors, GP Prescribing Advisors and Purchase Advisors in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
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- Patient advocacy groups
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Chief Medical, Nursing Officers and Pharmaceutical Officers in England and Wales
- Medical Director & Head of NHS Quality – National Assembly for Wales
- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

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This guidance is written in the following context:
This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis

1. Guidance

1.1 Etanercept and infliximab (infliximab only in combination with methotrexate) are recommended as options for the treatment of adults who have continuing clinically active rheumatoid arthritis that has not responded adequately to at least two disease-modifying anti-rheumatic drugs, including methotrexate (unless contraindicated).

1.2 Both etanercept and infliximab should be prescribed in accordance with relevant sections of the British Society for Rheumatology (BSR) guidelines, April 2001 (see Appendix D), which set 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 3 months.

1.3 Prescription of these agents and follow-up of treatment response and adverse events should be undertaken only by a consultant rheumatologist specialising in their use. The choice of which of the two agents is used should be determined by consultation between the patient and the clinician responsible, taking into account differences in treatment schedules and patient preferences.

1.4 Maintenance therapy with these agents in those who respond to treatment initially should be at the lowest licensed dose compatible with continuing clinical response.

1.5 All clinicians prescribing etanercept or infliximab should (with the patient's consent) register the patient with the Biologics Registry established by the BSR and forward information on dosage, outcome and toxicity on a 6-monthly basis.

1.6 There is currently no evidence to support treatment beyond 4 years. A decision to continue therapy should therefore be contingent on ongoing monitoring of disease activity and clinical effectiveness in individual cases. Outcomes from the BSR Biologics Registry will help inform such decisions.

1.7 There is no evidence for the consecutive use of these agents, and therefore this is not recommended.

This section (Section 1) constitutes the Institute's guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. The remainder of the document is structured in the following way:

A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0075.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0075.

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2 Clinical need and practice

2.1 Rheumatoid arthritis (RA) is a chronic, progressive, destructive and disabling condition that carries a significant morbidity and mortality rate, impacts severely on quality of life, and represents a considerable economic burden. RA affects all aspects of life from education and employment through to family and social life. It is estimated that 40% of people with RA stop working within 5 years of diagnosis.

2.2 RA is characterised by inflammation of the synovial tissue in joints, which causes pain, swelling and stiffness and can lead to joint destruction. Approximately 15% of people with RA have a particularly severe form of the disease that manifests itself as relentless pain and swelling, causing severe disability and loss of function.

2.3 RA is the most common inflammatory polyarthropathy in the UK, and affects between 0.5% and 1% of the population. Estimates in Western populations indicate an annual incidence of 0.5 per 1000 population and a prevalence of 8 per 1000 population. On the basis of these estimates, over 420,000 people in England and Wales have RA.

2.4 Management of RA 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 Conventional drug therapy for RA relies on various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). Evidence suggests that patients with RA should be treated with DMARDs soon after diagnosis, because patients in whom treatment with DMARDs is delayed have worse outcomes. DMARDs act to ameliorate symptoms and slow progression of structural damage, and are conventionally used in sequence. There are several DMARDs in use but current best practice is for initial treatment with methotrexate. Increasingly, combinations of DMARDs are used, although evidence in favour of combining DMARDs is limited.

2.6 For those people for whom treatment with DMARDs has failed, symptomatic support remains the only available option. This subgroup of the RA population has the greatest level of unmet medical need and incurs the greatest proportion of direct medical costs. It is this group that may benefit from treatment with etanercept or infliximab.

3 The technologies

3.1 Tumour necrosis factor alpha (TNFα) is a pro-inflammatory mediator that has been identified as a key molecule in the pathogenesis of RA. Its over-expression is one of the mediators responsible for the damaging inflammatory processes that occur in articular cartilage and bone.

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. It is licensed for the treatment of active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate (unless contraindicated), has been inadequate. It is administered by subcutaneous injection at a dose of 25 mg twice weekly and may be given for an indefinite period. A dose of 25 mg administered once weekly gives a slower response and may be less effective in some patients.

3.3 **Infliximab** is a chimeric monoclonal antibody that binds with high affinity to TNFα, thereby neutralising its activity. It is currently licensed for use only in combination with methotrexate:

- for the reduction of signs and symptoms of rheumatoid arthritis in patients with active disease
- to improve the physical function of patients with rheumatoid arthritis and reduce the rate of progression of joint damage

when the response to DMARDs, including methotrexate, has been inadequate. Infliximab is given by intravenous infusion at a dose of 3 mg/kg body weight at 0, 2 and 6 weeks and at 8-weekly intervals thereafter, with the co-administration of methotrexate weekly.

3.4 Etanercept costs £162.50 per week when administered at a dose of 25 mg twice weekly (*Monthly Index of Medical Specialities*, September 2001), equivalent to £8450 per annum. Infliximab costs £451.20 per vial (*Monthly Index of Medical Specialities*, September 2001), equivalent to £10,829 in the first year and an average of £8798 in subsequent years, assuming drug wastage through the use of an incomplete number of vials.

4 Evidence

4.1 Clinical effectiveness

Etanercept

4.1.1 Six randomised controlled trials (RCTs) of etanercept in patients with RA were identified, involving a total of 1710 patients (1230 of whom received etanercept). Four of these trials fell within the licensed indication for etanercept and compared etanercept with placebo, although one of these was a preliminary trial of safety and efficacy that was too small to demonstrate any statistically significant effects. Of the two remaining trials, one was a comparison between etanercept in combination with methotrexate and methotrexate alone, and the other compared etanercept alone with methotrexate alone in patients who had had RA for less than 3 years and who had not previously received methotrexate. All six trials were of high quality.

4.1.2 Results from the three Phase 3 trials that fell within the licensed indication are discussed here. Each showed a statistically significant difference in ACR20 responses (20% improvement in American College of Radiology symptom score, see Appendix E) at 3 or 6 months in favour of etanercept. ACR20 response rates ranged from 59% to 75% for etanercept at doses close to 25 mg twice weekly, compared with 11% to 14% for placebo. ACR50 response rates ranged from 34% to 57% for etanercept, compared with 5% to 7% for placebo. ACR70 response rates ranged from 13% to 15% for etanercept, compared with 1% for placebo. Open-label extension studies indicated that ACR response rates were maintained in the longer term (up to 4 years).

4.1.3 There were statistically significant differences in the rates of withdrawals from trials in favour of etanercept: withdrawal rates for etanercept ranged from 5% to 24%, compared with 19% to 67% for placebo. Lack of effectiveness was the most common reason for withdrawal in both groups.

4.1.4 The only common adverse event that was significantly ($p < 0.05$) more frequent among etanercept-treated patients was injection site reactions, which occurred in 30% to 50% of patients receiving etanercept. Infections occurred in approximately 30% of etanercept-treated patients and 16–34% of patients treated with placebo. However, postmarketing experience suggests that rates for death associated with infection are similar to the overall rate for RA patients. Postmarketing experience also suggests that small numbers of patients have developed autoimmune disorders, demyelinating diseases and serious blood disorders in association with treatment. Rates for malignancies were reported to be within the range seen in RA patients in general.

4.1.5 All three trials used Health Assessment Questionnaire (HAQ) scores to measure physical function (see Appendix E). Etanercept treatment resulted in 23% to 32% improvement in HAQ scores, compared with –6% to 6% for placebo. An open-label study demonstrated that HAQ scores were maintained in the longer term (up to 4 years).

4.1.6 The effect of etanercept on joint damage was assessed in the trial comparing etanercept with methotrexate in patients with disease duration of less than 3 years (median 7 to 8 months). Although ACR20 responses at 12 months were similar in the two treatment groups, there was a significantly smaller change from baseline in radiographically measured erosion scores in the etanercept group compared with the methotrexate group (0.47 units vs 1.03 units, $p = 0.002$).

Infliximab

4.1.7 Four RCTs of infliximab in patients with RA were identified, involving a total of 630 patients (497 of whom received infliximab). Two of these trials fell within the licensed indication for infliximab and were comparisons between infliximab in combination with methotrexate and methotrexate alone. One of these trials involved relatively small numbers of patients, but demonstrated the benefit of infliximab in terms of clinical response. The other study involved 428 patients, 340 of whom received infliximab in combination with methotrexate. The results of this key study are outlined below. The other two trials, which fell outside the licensed indication for infliximab, compared infliximab monotherapy with placebo. All four trials were of high quality.

4.1.8 The key trial showed a statistically significant difference in ACR20 responses at 30 weeks between infliximab at its licensed dose of 3 mg/kg every 8 weeks in combination with methotrexate and methotrexate alone (50% vs 20%). Response rates were maintained at 54 weeks (43% vs 17%) and at 102 weeks (42% vs 16%). ACR50 response rates at 102 weeks were 21% for infliximab in combination with methotrexate compared with 6% for methotrexate alone, and ACR70 response rates were 11% and 1% respectively. The proportion of patients who showed major progression of structural damage, measured radiographically, at 54 weeks was lower in the group treated with infliximab in combination with methotrexate than in the group treated with methotrexate alone (8% vs 31%). A greater proportion of patients in the infliximab plus methotrexate group experienced an improvement in structural damage scores (44% vs 14%). Median HAQ scores improved by 13% with infliximab and were sustained for 102 weeks, but did not change significantly with methotrexate.

4.1.9 At 54 weeks, 27% of patients had withdrawn from the infliximab regimen, compared with 50% of patients receiving methotrexate alone. The majority of withdrawals were due to lack of efficacy.

4.1.10 There were no statistically significant differences in the incidence of serious adverse events (11% vs 21%), serious infections (2% vs 8%) or infusion reactions (4% vs 2%) between infliximab and methotrexate. However, certain adverse events occurred more frequently in infliximab-treated patients including upper respiratory tract infections, sinusitis, pharyngitis, and headache. Although there have been few recorded deaths associated with the use of infliximab (46 from 206,000

patients treated), postmarketing experience suggests that infection is an important cause of mortality (58% of the deaths reported). In addition, recent reports highlight tuberculosis and congestive heart failure in association with infliximab use, and the development of anti-dsDNA antibodies which can result in clinical systemic lupus erythematosus, although this is reversible on cessation of therapy.

4.2 Cost-effectiveness

4.2.1 Three published economic evaluations of anti-TNF drugs were identified. Two of these were available only in abstract form, with insufficient detail to enable conclusions to be drawn. The third was a cost-effectiveness analysis, which did not take quality of life into account.

4.2.2 The Assessment Group developed a model to show the effect of introducing anti-TNF drugs into a treatment strategy for adults with RA. Assuming anti-TNFs are used third in the sequence of DMARDs and discounting begins at the point of divergence in the treatment arms (i.e. when anti-TNFs are introduced) rather than at the start of the programme, the incremental cost-effectiveness ratio (ICER) for etanercept is £63,974 per QALY, and for infliximab it is £99,373. A major limitation of the model is that it does not include non-drug costs or the effect of the drugs on joint replacement, hospitalisation or mortality.

4.2.3 A cost–utility analysis comparing etanercept with a sequence of other DMARDs was included in the submission from Wyeth Laboratories. The model gives a base-case ICER of £16,330 per quality-adjusted life-year (QALY) for etanercept (range £14,731 to £29,665). The model is based on a number of assumptions regarding the relationship between HAQ and utility, and HAQ and mortality, supported with evidence from the literature.

4.2.4 A cost–utility analysis comparing infliximab in combination with methotrexate with a sequence of other DMARDs was included in the submission from Schering-Plough. The model gives a base-case ICER of £23,936 per QALY for infliximab (range £17,252 to £44,894). Again, the model is based on a number of assumptions which include the relationship between responses recorded on a visual analogue scale and utility.

4.2.5 Incorporating assumptions based on more conservative estimates of clinical effectiveness, and lower estimates of disability progression for individuals who do not respond to treatment into one of the manufacturer's models, the incremental cost-effectiveness ratio of these therapies can be estimated to be in the region of £27,000 to £35,000 per QALY.

4.3 Considerations

4.3.1 The results of the available clinical trials provide strong evidence of the clinical effectiveness of etanercept and infliximab, and are supported by continuation data of up to 4 years and 2 years respectively. The results were reviewed by the Committee in the light of the evidence for the clinical effectiveness of alternative DMARD therapies.

4.3.2 The Committee was aware that other doses of these agents have been subject to randomised controlled trials. In particular, the Committee noted the results of the trial of etanercept administered at a dose of 25 mg once weekly. The results of the trial suggested that although slightly fewer people achieved an ACR20 response at 3 months, this dose provided a similar clinical response in terms of HAQ improvement. However, there are no studies on the effectiveness of this dose beyond 3 months.

4.3.3 The Assessment Group's economic model provides an upper estimate of the cost per QALY for etanercept and infliximab. However, the Committee noted the degree of uncertainty in key variables, such as whether long-term outcomes, including the likelihood of joint replacement surgery, would be affected by drug therapy. The Committee, therefore, did not accept the incremental cost-effectiveness ratios generated by this model as true estimates of cost-effectiveness.

4.3.4 The Committee noted that the models developed by the manufacturers incorporated assumptions for which there is only limited evidence. Information on the long-term effectiveness of etanercept and infliximab and their impact on disability progression was based on data of up to 4 years and 2 years respectively. The Committee questioned the assumptions which had been used for key variables and in particular: the initial HAQ improvement following initiation of treatment, the HAQ deterioration when treatment is deemed to have failed, and the rate of disability progression for individuals who do not respond to treatment.

4.3.5 In their consideration of the manufacturers' models, the Committee recognised that there were significantly different values for these variables applied in the different models, including that from the Assessment Group. The Committee considered all the assumptions that had been used for each of these variables and made a determination as to the value, in each case, which would be most likely to best predict disease progression in patients treated with these drugs. In order to do this, they took into account published evidence as well as evidence from clinical experts and patient/carer representatives. Applying these values resulted in the incremental cost-effectiveness ratio referred to in 4.2.5.

5 Implications for the NHS

5.1 Using a prevalence for RA of 8 per 1000 population, an estimated 420,000 people in England and Wales have RA. Based on estimates from the Norfolk Arthritis Register, a large database of all cases of arthritis recorded in Norfolk, approximately 15,000 of these people will be eligible for anti-TNF therapy. Using an incidence of 0.5 per 1000 population, an additional 950 people are estimated to become eligible for treatment each year. The evidence available suggests that 15% of patients will have a contraindication to treatment, 40% will not respond to treatment initially and a further 10% will withdraw from treatment each year. Assuming annual drug costs of £8500, the total budget impact of anti-TNF therapy in a steady state is estimated to be in the region of £55 million to £75 million per year. Estimates from manufacturers range from £50 million to £67 million per year. It should be noted that these figures are gross and do not take into account the costs of drugs that are currently prescribed, or that some people are already receiving treatment with etanercept or infliximab. Including these considerations would have the effect of lowering the budget impact. However, it has not been possible to calculate net figures due to the lack of reliable information in this area.

5.2 The methods of administration of etanercept and infliximab are very different (see Sections 3.2 and 3.3) and this has implications for future rheumatology service provision. For example, widespread use of infliximab and the need for hospital infusion could lead to a greater demand for day-case facilities. Widespread use of etanercept could place a greater demand on outpatient facilities. However, given the relative ease of administration and the availability of a home care dispensing service, patients are normally able to administer their own etanercept.

5.3 The long-term impact of etanercept or infliximab treatment on joint damage is unclear at present, but the reduced risk of joint damage and destruction has the potential for reducing the need for expensive joint-replacement surgery.

6 Further research

6.1 Controlled clinical studies are required to assess the long-term clinical effectiveness of anti-TNF agents and their impact on disease progression, joint replacement and mortality. In addition, studies of alternative dosage regimens are required in order to maximise the cost-effectiveness of these therapies over the longer term.

6.2 Longitudinal data on the quality of life of people with RA and the impact of anti-TNF agents and other interventions on quality of life are required to improve the reliability of economic analyses.

6.3 The use of the Biologics Registry data will be essential to establish the longer-term clinical effectiveness of these agents as well as the potential for adverse effects.

7 Implementation

7.1 Clinicians treating adults with active RA 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 adults with active RA who have been prescribed etanercept or infliximab is in place at a local level, and that a treatment plan is recorded for each individual.

7.3 The following criteria is based on the BSR guidelines. Further details of suggestions for audit are presented in Appendix F.

- Etanercept or infliximab is prescribed for an adult with continuing clinically active RA only when the person has had an adequate therapeutic trial of two standard DMARDs, of which methotrexate must have been one (unless toxicity or intolerance develops), and the person's response to the drug is inadequate.
- Treatment with etanercept or infliximab is withdrawn if the person experiences an adverse event or if the person fails to respond at 3 months following initiation of treatment.
- Etanercept or infliximab is prescribed for RA and patients are followed up only by a consultant rheumatologist specialising in their use.
- Maintenance therapy for those who respond to treatment initially is at the lowest licensed dose compatible with continuing clinical response.
- The prescribing consultant assumes responsibility for registering the person with the Biologics Registry established by the BSR and for forwarding information on dosage, outcome and toxicity on a 6-monthly basis, subject to the person's consent.

7.4 Local clinical audits on the management of adults with RA could include criteria on the local monitoring protocol and the person's knowledge of the disease, the intended effect and potential adverse effects of treatment.

8 Related guidance

8.1 The Institute has published guidance on the use of Cox II selective inhibitors for osteoarthritis and rheumatoid arthritis:

- National Institute for Clinical Excellence (2001) Guidance on the use of cyclo-oxygenase (Cox) II inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. *NICE Technology Appraisal Guidance* No. 27. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk.

9 Review of guidance

9.1 This guidance will be reviewed in March 2005.

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

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

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
School of Hygiene & Tropical Medicine

Dr Paul Ewings
Statistician
Taunton & Somerset NHS Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care
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 Committee:

a. **Assessment Report:**
   - Prepared by West Midlands Development and Evaluation Service, The University of Birmingham *(The clinical effectiveness and cost-effectiveness of new drug treatments for rheumatoid arthritis: etanercept and infliximab),* September 2001

b. **Manufacturer/sponsor submissions:**
   - Schering-Plough
   - Wyeth Laboratories

c. **Professional/specialist group and patient group submissions from:**
   - Royal College of General Practitioners
   - Chartered Society of Physiotherapy
   - Institute for the Health of the Elderly
   - British League Against Rheumatism (on behalf of Arthritis Care, Arthritis Research Campaign, British Health Professionals in Rheumatology, British Society for Rheumatology, Primary Care Rheumatology Society and the Royal College of Nursing Rheumatology Policy & Practice Group)
   - Department of Health

d. **External expert and patient advocate submissions from:**
   - Dr Ernest Choy, Department of Rheumatology, King's College Hospital, London
   - Dr Ian Griffiths, Consultant Rheumatologist, Freeman Hospital, Newcastle upon Tyne
   - Neil Betteridge, Head of Public Policy & Campaigning, Arthritis Care

APPENDIX C

Patient information

Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference no N0076 for the English patient leaflet and N0077 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment, diagnostic tests and clinical and surgical procedures and where they should be used.

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations and the groups who represent patients.

NICE was asked to look at the available evidence on etanercept and infliximab and provide guidance that would help the NHS in England and Wales decide where it should be used in the treatment of rheumatoid arthritis.

What is rheumatoid arthritis?

Rheumatoid arthritis (RA) is a chronic (long-term), progressive, destructive and disabling condition that impacts severely on a person's quality of life. RA affects all aspects of life from education and employment through to family and social life. It is estimated that 40 out of 100 people with RA stop working within 5 years of being diagnosed with the condition. RA affects up to 1 in 100 people, and it is estimated that over 420,000 people in England and Wales have RA.

RA is caused by the inflammation of tissue in the joints, which causes pain, swelling and stiffness and can destroy the joint. Approximately 15 out of 100 people with RA have a particularly severe form of the disease that causes constant pain and swelling, which results in severe disability and loss of the use of the joints.

A multidisciplinary approach is taken to the care and treatment of people with RA. This includes physical therapy (for example exercises to help keep the joints working), surgery and treatment with drugs. The main aims of treatment include controlling joint pain and inflammation, reducing joint damage and disability and preventing loss of the use of the joint, and maintaining or improving quality of life.

Traditional drug therapy for RA relies on various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics (pain-relieving drugs), corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). Evidence suggests that patients with RA should be treated with DMARDs soon after diagnosis. If treatment with DMARDs is delayed then it is likely that the patient's condition will get worse more quickly.

DMARDs act to improve symptoms and slow down damage to the joints. These drugs are usually used in sequence, starting with methotrexate.

If treatment with DMARDs does not work, the only option available to doctors and patients is to try to relieve the symptoms of RA rather than delay the course of the disease. This means that people with RA who do not respond to DMARDS are not having their medical needs met, and it is this group that may benefit from treatment with etanercept or infliximab.

What are etanercept and infliximab?

Tumour necrosis factor alpha (TNFα) is a substance produced by the body. It is involved in the process of inflammation. In people who have RA, too much TNFα is produced by the body and causes inflammation that damages the cartilage and bone.

Etanercept works by preventing TNFα attaching itself to the tissue in the joint. It is licensed for the treatment of active RA in adults when treatment with DMARDs, including methotrexate, has not worked. It is given by injection at a dose of 25 mg twice a week and may be given for an indefinite period. A dose of 25 mg given once a week gives a slower response and may be less effective in some patients.

Infliximab works by attaching itself to TNFα and making it inactive. It is currently licensed for use only in combination with methotrexate:

- for the reduction of the signs and symptoms of RA in patients with active disease
- to improve the physical ability of patients with RA and reduce the rate of progression of joint damage

when treatment with DMARDs, including methotrexate, has not worked.

Infliximab is given through a drip at 0, 2 and 6 weeks and then at 8-weekly intervals. Methotrexate is given once a week during this treatment.

What has NICE recommended about the use of etanercept and infliximab?

NICE has made the following recommendations.

Etanercept or infliximab (infliximab only in combination with methotrexate) are recommended as treatment options for adults with active RA who have not responded well to treatment with at least two DMARDs, including methotrexate.

Both etanercept and infliximab should be prescribed in accordance with the relevant sections of the guidelines that have been produced by the British Society for Rheumatology.

Only a consultant rheumatologist should prescibe etanercept or infliximab and provide follow-up treatment and monitoring. Your consultant rheumatologist should discuss with you which drug to prescibe and take into account your preferences.

The doctor who prescribes etanercept or infliximab for you should, with your consent, register you with the Biologics Registry, which has been set up by the British Society for Rheumatology. Every 6 months, the doctor will send information to the Registry on the drug you are receiving, the effects of the treatment and any side effects you have experienced. This information will help researchers to find out about the long-term effectiveness and side effects of treatment with etanercept and infliximab.

There is currently no evidence to support treatment with etanercept or infliximab for more than 4 years. A decision to continue therapy should therefore be based on how your condition is progressing and how well the drugs are working for you.

There is no evidence to suggest that these drugs should be used one after the other, and so this is not recommended.

What should I do?

If you, or someone you care for, have RA then you can discuss this advice with the doctor at your next appointment.

Will NICE review its guidance?

Yes. The guidance will be reviewed in March 2005.

Further information

Further information on NICE, and the full guidance issued to the NHS is available on the NICE website (www.nice.org.uk).

The guidance can also be requested from 0870 555 455, quoting reference N0074.

If you have access to the Internet and would like to find out more about RA visit the NHS Direct website: www.nhsdirect.nhs.uk. If you would like to speak to NHS Direct, please phone 0845 46 47.

APPENDIX D

British Society for Rheumatology guidelines

The following guidelines have been recommended by the BSR 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 people with arthritis.

Eligibility for treatment with biologic therapies

All patients must satisfy the 1987 criteria of the American College of Rheumatology Classification criteria for a diagnosis of rheumatoid arthritis.

1. Active RA

Use of the 28 joint disease activity score (see below) is favoured. A DAS28 score of > 5.1 indicates a highly active disease eligible for treatment. Measurements of disease activity should be made at two points, 1 month apart.

2. Failure of standard therapy

Patients must have had adequate therapeutic trials of at least two standard DMARDs (IM gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine, methotrexate or leflunomide, of which methotrexate must have been one). An adequate therapeutic trial would be defined as:

- treatment for at least 6 months, with at least 2 months at standard target dose (unless significant toxicity limited the dose tolerated)
- treatment for < 6 months, where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses.

3. Exclusion criteria

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

- women who are pregnant or breastfeeding; effective contraception must be practised
- active infection

- patients at high risk of infection including:
  - chronic leg ulcers
  - previous tuberculosis (Note: patients with previous TB may be eligible if they have completed a full course of anti-tuberculous therapy within the modern antibiotic era, but measures should be taken to prevent the reactivation of tuberculosis and the risk/benefit for the patient should be considered before starting treatment)
  - septic arthritis of a native joint within the last 12 months
  - sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ
  - persistent or recurrent chest infections
  - indwelling urinary catheter
  - multiple sclerosis

- malignancy or pre-malignancy states excluding:
  - basal cell carcinoma
  - malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high).

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 3 months of treatment. A response is defined as improvement in the DAS28 score by > 1.2, or the achievement of a DAS28 score of < 3.2.

APPENDIX E

American College of Rheumatology response criteria

The American College of Rheumatology (ACR) definition of response requires an improvement in both the tender joint count and swollen joint count, and an improvement in at least three of:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score e.g. Health Assessment Questionnaire (see below)
- acute phase response e.g. ESR (erythrocyte sedimentation rate) or CRP (C-reactive protein).

Response is defined as ACR20/50/70 where the figures refer to the percentage improvement required in clinical measures.

Disease activity score

The disease activity score (DAS) is an alternative scoring system that has been developed in Europe. It uses the following formula, based on a total of 28 joints, to calculate a numerical value for disease severity:

$$DAS28 = 0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.7 \times \ln ESR + 0.014 \times GH$$

where TJC is tender joint count, SJC is swollen joint count, ESR is the erythrocyte sedimentation rate in mm/h, and GH is the general health status 100 mm visual analogue scale.

Health assessment questionnaire

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

APPENDIX F

Technical detail on criteria for auditing the use of etanercept and infliximab in the treatment of rheumatoid arthritis (RA)

Objectives for the audit

An audit on the appropriateness and effectiveness of the use of etanercept and infliximab for the treatment of adults with RA could be carried out to ensure that:

- etanercept or infliximab is prescribed in accordance with criteria for eligibility for treatment with biological therapies described in the British Society for Rheumatology (BSR) guidelines
- etanercept or infliximab is prescribed only by a consultant rheumatologist specialising in the use of these agents
- adults with RA who are prescribed etanercept or infliximab are registered with the Biologics Registry of the BSR.

Patients to be included in the audit

All adults who are under the care of a consultant at the time the audit is being undertaken and who are or have been prescribed etanercept or infliximab for RA.

Measures to be used as a basis for the audit

The measures to be used in an audit of adults with RA who have been prescribed etanercept or infliximab are as follows.

Criterion	Standard	Exception	Definition of terms
1. A patient with RA is prescribed etanercept or infliximab only if there is evidence of **all** of the following: a. the patient has continuing clinically active RA **and** b. the patient has had an adequate therapeutic trial of methotrexate and at least one other standard DMARD **and** c. the patient has failed to improve following adequate treatment with methotrexate and at least one other standard DMARD	100% of patients prescribed etanercept or infliximab	A. Woman is pregnant or breastfeeding or is sexually active with inadequate contraception B. Active infection C. High risk of infection D. Malignancy or pre-malignancy states excluding basal cell carcinoma and malignancies diagnosed and treated more than 10 years previously where the probability of total cure is very high	For 1a, continuing clinically active RA = DAS28 score of > 5.1 on two occasions, 1 month apart. For 1b, adequate therapeutic trial = treatment for at least 6 months, with at least 2 months at standard target dose (unless significant toxicity limited the dose tolerated) or treatment for < 6 months, where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses. Standard DMARDs = IM gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine, methotrexate or leflunomide. For 1b, note any patient who has developed intolerance or toxicity to methotrexate. For 1c, failure = < 1.2 improvement in the DAS28 score or DAS28 score > 3.2. For C, high risk of infection includes any of the following: chronic leg ulcers; previous tuberculosis unless the patient has completed a full course of anti-tuberculous therapy and measures are taken to prevent the reactivation of tuberculosis; septic arthritis of a native joint within the last 12 months; sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ; persistent or recurrent chest infections; indwelling urinary catheter; or multiple sclerosis.

Criterion	Standard	Exception	Definition of terms
2. Treatment is withdrawn if the patient experiences an adverse event or fails to respond during the 3 months following the initiation of treatment or after the initial 3-month trial	100% of patients prescribed etanercept or infliximab who have an adverse event or fail to respond	None	Adverse event = malignancy or severe drug-related toxicity or pregnancy (temporary withdrawal) or severe intercurrent infection (temporary withdrawal). See 1c for definition of failure to respond.
3. A consultant rheumatologist carries out all of the following: a. prescribes etanercept or infliximab for eligible patients b. follows up treatment response and adverse events	100% of patients prescribed etanercept or infliximab	None	Consultant rheumatologist = one who is experienced in the use of the agents. Consultants should agree locally on what constitutes follow-up for audit purposes; see patient record for evidence of follow-up as defined.
4. Maintenance therapy is at the lowest licensed dose compatible with continuing clinical response	100% of patients prescribed etanercept or infliximab	A. Therapy is discontinued due to failure to respond	For audit purposes, consultant should agree locally on how the lowest licensed dose compatible with continuing clinical response is determined.
5. A patient prescribed etanercept or infliximab is registered with the Biologics Registry of BSR	100% of patients prescribed etanercept or infliximab	A. Patient does not consent to registry	Registry = information on dosage, outcome and toxicity forwarded to Registry on a quarterly basis.

Calculation of compliance with measures

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

$$\frac{\text{Number of people whose care is consistent with the } \textbf{criterion } \textbf{\textit{plus}} \text{ number of people who meet any of the exceptions listed}}{\text{Number of people to whom the } \textbf{measure} \text{ applies}} \times \mathbf{100}$$

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that desired improvement is being achieved.