West Midlands Health Technology Assessment Collaboration

Anakinra for rheumatoid arthritis

Finalised Protocol August 2002

A  Details of review team

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B  Full title of research question

What is the clinical effectiveness and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis (RA) in adults who have not responded to conventional disease modifying anti-rheumatic drug (DMARD) treatments?

C  Clarification of the research question and scope

Anakinra (TN: Kineret®) offers a new treatment approach for the management of RA. Anakinra is a recombinant form of human interleukin-1 receptor antagonist (IL-1ra). It is the first drug in this therapeutic class to be approved for use in this patient group. It is licensed for use in combination with methotrexate in adult patients who have responded inadequately to methotrexate alone.

The aim of this review is therefore to provide a rapid systematic evaluation of both the clinical and cost-effectiveness of anakinra in adult patients (18 years and older) who have not responded to conventional DMARD treatments.

This review will address three core questions:

1. What is the clinical effectiveness of anakinra for the treatment of RA in terms of:
   1.1 Relieving symptoms?
   1.2 Delaying disease progression?
2. What are the risks (frequency and severity of adverse events) associated with anakinra treatment in these patients?
3. What is the cost-effectiveness of anakinra for the above indication compared to standard practice?

Only randomised controlled trials comparing anakinra with other drug treatments or placebo will be considered in the assessment of clinical effectiveness.

D  Report Methods

Search strategy
The following electronic bibliographic databases will be searched:

Cochrane Library, Medline, Embase, Science Citation Index (SCI), National Research Register (NRR), NHS Database of Reviews of Effectiveness (DARE), Index to Scientific and Technical Proceedings (ISTP), NHS Economic Evaluation Database (NHS EED), Health Economic Evaluation Database (HEED).

Search terms will include the text words: anakinra; kineret; interleukin-1 receptor antagonist; IL-1ra; rhu-IL-1Ra; and the index terms; arthritis, rheumatoid; receptors, interleukin-1; interleukin-1.

Studies will be limited to humans. No language, date or age restrictions will apply. A meta-search engine will be used to search the Internet, and links followed up. Proceedings from the American College of Rheumatology and European Congress of Rheumatology meetings will be searched electronically for the years 2001 and 2002.

Electronic searches will be stopped on 1st November 2002. Studies identified after this date, and which are considered appropriate, may still be included within the review.
Scrip, FDA submissions for new drug applications, EMEA reports and the pharmaceutical company submission to the National Institute for Clinical Excellence (NICE) will be hand searched. The reference lists of identified publications will be reviewed to identify any additional studies and/or citations.

Experts in the field will be contacted after the electronic searches are complete to check that all relevant studies have been identified.

**Inclusion and exclusion criteria**
Two reviewers will independently apply the following inclusion/exclusion criteria to all potential studies. Any disagreements will be resolved by discussion, referring to a third party if necessary. Reviewers will not be blinded to any features of the report including authorship however inclusion/exclusion decisions will be made prior to detailed scrutiny of the results.

**Inclusion criteria**
The criteria for inclusion related to the population, intervention and comparator considered and the publication status of the report is applicable to both the clinical effectiveness and cost-effectiveness parts of the review.

**Population**
Adults aged 18 years and above with rheumatoid arthritis

**Intervention:**
Anakinra (Kineret) alone or in combination with other drugs

**Comparator:**
Placebo, or other drug treatments for RA

**Publication**
All data to be included irrespective of publication status.

Studies will be included in the final analysis of the review if they meet the above criteria and the additional criteria for study design and outcomes as specified below for the clinical and cost-effectiveness parts of the review.

**Clinical effectiveness review**
Study design: Randomised or quasi-randomised controlled trials

Outcomes:
To include: mortality, morbidity (eg disability/mobility, disease progression, joint damage, pain, adverse events), response rates and quality of life.

**Cost-effectiveness review**
Study design: Economic evaluation studies: cost analysis, cost-effectiveness, cost-utility and cost-benefit studies. Existing health economic reviews will also be assessed.

Outcomes:
To include: quality of life, costs, incremental cost-effectiveness ratio.

**Exclusion criteria**
- Trials only recruiting children with juvenile idiopathic arthritis.
- Trials with no comparator arm.
- Trials which are not randomised. *(clinical effectiveness part of review only)*
- Articles reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms.

**Data extraction strategy**
Two reviewers will independently extract data using a pre-designed data extraction form (Appendix 1a {clinical effectiveness} 1b {cost-effectiveness}). Disagreements will be resolved by discussion, consulting with a third party if there is still disagreement.
Translations will be obtained where necessary. Where information is missing, further information will be sought from the authors or industry. Data from studies with multiple publications will be extracted and reported as a single study.

**Clinical effectiveness review**
The following data will be extracted:
- Details of the study population and baseline characteristics of the intervention and control groups, with particular reference to disease characteristics and previous treatment history.
- Details of the intervention, such as dose, mode of administration, frequency of administration and duration of treatment.
- Details of completion rates across the groups, reasons for withdrawal, loss to follow up.
- Details of individual outcomes measured such as:
  - Changes in disease activity eg ACR improvement criteria, swollen joint count, pain, joint space narrowing and erosion.
  - Changes in quality of life
  - Adverse events reported

Results will be extracted, where possible for the intention to treat population, as raw numbers, plus any summary measures with standard deviations, confidence intervals and p-values where given.

**Cost-effectiveness review**
The following data will be extracted:
- Details of the study characteristics, including type of economic analysis, intervention and comparator, perspective, time frame, modelling used.
- Details of the data used to populate the evaluation and the key assumptions made such as effectiveness data, cost data, health state valuations, discounting rate.
- Details of the results and sensitivity analysis

**Quality assessment strategy**
Two reviewers will independently, using a structured form (Appendix 2a {clinical effectiveness} 2b {cost-effectiveness}), undertake quality assessments. Disagreements will be resolved by discussion, with reference to a third party if there remains disagreement. The information on quality assessment will be presented in table form and summarised within the text of the report.

**Clinical effectiveness review**
The validity of included studies will be assessed by looking at the method of randomisation, the concealment of allocation, the comparability of baseline characteristics between the different arms, blinding, withdrawals and losses to follow-up for each patient group. A Jadad score will be calculated (Appendix 2a).

Assessment will be made of the clinical relevance of the outcomes reported. Outcomes anticipated to be of clinical relevance include: ACR 20%, ACR 50%, ACR 70%, swollen joint count, pain, radiographic changes in affected joints.

**Cost-effectiveness review**
The quality of these studies will be assessed using a checklist (Appendix 2b). The study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and presentation of results will all be evaluated as part of this process.
Methods of analysis/synthesis

**Clinical effectiveness review**

A narrative summary of the studies will be presented. Results for each of the specified outcome measures, for the intention to treat population (where available), will be abstracted from the reports.

The way in which results are reported may vary. Where possible, reported results will be tabulated in a common format to assist comparison between studies; the original data abstracted from the reports, and the methods used to obtain those in the summary will be reported.

The format in which the results are presented will depend to some extent on what is available from the trial reports. Where possible binary outcomes will be presented as Relative Risks or Odds Ratios; ‘time to event’ outcomes will be presented as hazard ratios, with some indication of location (e.g., median survival); for continuous outcomes particular attention will be paid to the use of transformations and/or the use of ANCOVA to obtain estimates adjusted for baseline.

Where available, unadjusted results analysed on an intention to treat basis will be emphasised. Exclusions and analyses adjusted for covariates (other than baseline score on the outcome) will be noted.

Where sufficient information is available and the studies are sufficiently homogenous, both clinically and statistically, a formal meta-analysis will be undertaken. Where data are pooled χ² tests of heterogeneity will be performed. Possible explanations for unanticipated heterogeneity will be explored. Sensitivity analysis will be used to explore the impact of the quality of the studies on the summary results obtained; the results of any restricted analysis (excluding one or more studies) will be interpreted with caution.

The results will be analysed overall and for the subset of the population that fulfil the licensed indications for anakinra i.e., adult patients with rheumatoid arthritis who have had an inadequate response to methotrexate and in whom anakinra is being prescribed in combination with methotrexate.

The frequency and nature of adverse effects will be collected and reported.

**Cost-effectiveness review**

Details of each of the published economic evaluations identified will be presented in structured tables. Where appropriate data are presented, indications of uncertainty underlying point estimates of cost-effectiveness will be assessed and an appropriate statistic presented.

A detailed assessment of each economic model including any model provided by the pharmaceutical industry will be carried out.

It is intended to develop a decision analytic model to assess the cost-effectiveness of anakinra to the NHS. This model will continue the work commissioned by the UK NCCHTA to revise the Birmingham Preliminary Model (BPM). The BPM was developed to evaluate the cost-effectiveness of TNF inhibitors in patients with RA. It follows patients with RA from the time at which they start using DMARDs and for the remainder of their life. The structure of this model overcomes many of the restrictive assumptions required by Markov models.
**E Handling the company submissions**

All data submitted by the pharmaceutical industry by 30th October 2002 will be examined in detail. Efficacy and safety data contained in the company submission will be extracted and incorporated into the review if appropriate. Studies not identified in our searches that meet inclusion criteria will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any confidential information will be clearly underlined in the final report.

A technical commentary on the decision analytical model used in the economic analysis reported in the manufacturers submission will also be provided.

**Project Management**

**Timetable/milestones - submission of:**

- Draft protocol     30th July 2002
- Final protocol     20th August 2002
- Progress report    13th November 2002
- Complete near final draft for peer review 20th December 2002 (provisional date)
- Draft final report  22nd January 2003

**Competing Interests**

None of the members of the review team have any conflicts of interest. Dr P Jobanputra is a member of the British Society for Rheumatology, but is not involved in formulating guidelines for the use of Anakinra (currently underway) nor involved in making the BSR submission to NICE.

**External Reviewers**

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers’ signed copies to NCCHTA. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.
Appendix 1a: Clinical effectiveness data extraction form – Anakinra for RA

Title of study:        Reviewer:       Date:
Reference:
Sponsorship:

Study Design & Methodology

Inclusion criteria
Age:
Duration of RA:
Diagnostic criteria:

Exclusion criteria

Concomitant treatment
Permitted
Not allowed

No. Patients screened

No. Randomised

Number excluded
Main reasons

METHODOLOGY

Design
Study visits:

Placebo
Anakinra
Anakinra
Anakinra
Anakinra
Anakinra

Withdrawals
lack of efficacy
adverse event
other
Withdrawals
lack of efficacy
adverse event
other
Withdrawals
lack of efficacy
adverse event
other
Withdrawals
lack of efficacy
adverse event
other
Withdrawals
lack of efficacy
adverse event
other
Withdrawals
lack of efficacy
adverse event
other

Dose mode
admin frequency

Duration of study

Number (%)
completing

Planned Endpoints:

Primary
Secondary
Clinical effectiveness data extraction form– Anakinra for RA cont.

**Study design and Methodology cont.**

*Any comments e.g. problems with design, potential biases*

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<th>Was ITT analysis used: Yes / No</th>
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**Baseline Characteristics**

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*Comments (including any statistically significant differences)*
### Outcomes:  ITT population / Efficacy population  
*(circle as appropriate)*

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<th>Intervention – C n=</th>
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<th>Intervention – E n=</th>
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Comments

Were any outcome evaluations planned but not reported?
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<th>Adverse Events</th>
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<th>B (n= )</th>
<th>C (n= )</th>
<th>D (n= )</th>
<th>E (n= )</th>
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**Others:**

**Comments:**
Appendix 1b: Cost- effectiveness data extraction form

Anakinra for RA

Title of study: Reviewer: Date:

Reference:

Sponsorship:

Methodology and study design

1. Type of economic evaluation  circle as appropriate
   Review / cost analysis / cost-effectiveness / cost utility / cost benefit

2. Currency used

3. Year to which costs apply

4. Perspective used

5. Characteristics of study population

6. Interventions evaluated

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose &amp; frequency</th>
<th>Route of administration</th>
<th>Duration of treatment</th>
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</table>
7. Source of effectiveness data

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single study</td>
<td></td>
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<tr>
<td>Review/synthesis of previous studies</td>
<td></td>
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<tr>
<td>Expert opinion</td>
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<tr>
<td>Other state</td>
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</table>

8. Source of unit cost data

9. Link between cost and effectiveness data

10. Clinical outcomes measured

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Valuation method</th>
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11. Handling of cost data *summary of methods used e.g. to discount, inflate etc*

12. Modelling – summary of key characteristics

<table>
<thead>
<tr>
<th>Type of model</th>
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<tbody>
<tr>
<td>Purpose of model</td>
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<tr>
<td>Components of model</td>
<td></td>
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<tr>
<td>Key input parameters</td>
<td></td>
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<tr>
<td>Model outputs</td>
<td></td>
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</table>
### Outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Economic outcome measure</th>
<th>Results</th>
<th>Statistical significance</th>
<th>Uncertainty e.g. CI’s</th>
<th>Sensitivity analysis</th>
</tr>
</thead>
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Comments e.g. appropriateness of statistical tests, uncertainty measures, sensitivity analysis, modelling inputs and techniques

Any implications for practice - comments
Appendix 2a: Clinical effectiveness Quality Assessment

Jadad score for the evaluation of quality of clinical trials

1. Was the study described as randomised?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring of items:

Give a score of one point for each ‘yes’ and no points for each ‘no’.

Give an additional point if:

- For question one, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated etc).

  And/or:

- If for question two the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy etc)

Deduct one point if:

- For question one, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number)

  And/or

- For question two, the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy)
### Appendix 2b: Cost-effectiveness quality assessment

**Criteria to assess quality of cost-effectiveness studies**

(Adapted from Drummond et al\(^2\))

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Adequately addressed?</th>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
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<tr>
<td><strong>Study question</strong></td>
<td></td>
</tr>
<tr>
<td>1. Costs and effects examined</td>
<td></td>
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<tr>
<td>2. Alternatives compared</td>
<td></td>
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<tr>
<td>3. Perspective clearly stated <em>e.g.</em> NHS, society</td>
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<tr>
<td><strong>Selection of alternatives</strong></td>
<td></td>
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<tr>
<td>4. All relevant alternatives compared</td>
<td></td>
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<td>5. Alternatives compared are clearly described</td>
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<td>6. Rationale for choosing alternatives stated</td>
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<tr>
<td><strong>Form of evaluation</strong></td>
<td></td>
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<tr>
<td>7. Choice of form of economic evaluation is justified in relation to the questions addressed</td>
<td></td>
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<tr>
<td>8. If cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?</td>
<td></td>
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<tr>
<td><strong>Effectiveness data</strong></td>
<td></td>
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<tr>
<td>9. Sources of effectiveness data used are stated</td>
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<tr>
<td>10. Effectiveness data from RCT or review of RCTs</td>
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<tr>
<td>11. Potential biases identified</td>
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<tr>
<td>12. Details of methods of synthesis or meta-analysis of estimates are given (if based on &gt;1 study)</td>
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<tr>
<td><strong>Costs</strong></td>
<td></td>
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<tr>
<td>13. All important and relevant resource use included</td>
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<tr>
<td>14. Key resources measured accurately (with methodology)</td>
<td></td>
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<tr>
<td>15. Appropriate unit costs estimated (with methodology)</td>
<td></td>
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<tr>
<td>16. Unit costs reported separately from resource use data</td>
<td></td>
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<tr>
<td>17. Productivity costs treated separately from other costs</td>
<td></td>
</tr>
<tr>
<td>18. The year and country to which unit costs apply is stated, with appropriate adjustments for inflation and/or currency conversion</td>
<td></td>
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<tr>
<td><strong>Benefit measurement and valuation</strong></td>
<td></td>
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<tr>
<td>19. Primary outcome measure clearly stated <em>e.g.</em> QALYs, life years <em>etc</em></td>
<td></td>
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<tr>
<td>20. Methods to value health states and other benefits are stated <em>e.g.</em> time trade off</td>
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</table>
21. Details of individuals from whom valuations were obtained are given (patients, members of the public etc)

Decision modelling

22. Details of any decision model used are given e.g. decision tree, Markov model

23. The choice of model and key input parameters on which it is based are adequately detailed and justified.

24. All model outputs described adequately

Discounting

25. Discount rate used for both costs and benefits

26. Are discount rates in line with NICE guidance? (1.5% -2% for benefits; 6% for costs)

Allowance for uncertainty

Stochastic analysis of patient level data

27. Details of statistical tests and confidence intervals are given for stochastic data

28. Uncertainty around cost-effectiveness given e.g. CIs

29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. discount rate) and analytic decisions (e.g. handling of missing data)

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?

31. Is second order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?

32. Are probability distributions adequately detailed and appropriate?

33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. discount rate) and analytic decisions (e.g. handling of missing data)

Deterministic analysis

34. The approach to sensitivity analysis is given e.g. threshold analysis

35. The choice of variables for sensitivity analysis is justified

36. The ranges over which the variables are varied are stated

Presentation of results

37. Incremental analysis is reported using the appropriate decision rules

38. Major outcomes are presented in a desegregated as well as aggregated form

39. Applicable to the NHS setting
Background

Rheumatoid arthritis (RA) is the most common inflammatory arthritis. It is a chronic disabling condition associated with a high degree of disability. The clinical hallmark of RA is persistent synovial inflammation of peripheral joints, causing pain, stiffness and in the majority of patients some degree of irreversible joint damage. In addition many other tissues may also be affected.3

RA affects around 0.5 to 1% of the population worldwide. Recent estimates in Western populations indicate an annual incidence of 0.5 per 1000 population and a point prevalence of 8 per 1000. Based on this approximately 476,000 people are likely to have RA in the UK.4

Whilst the clinical course of the disease in each individual patient is highly variable RA can be considered to follow three broad patterns: progressive disease with significant functional limitations in time; intermittent disease (where disease is punctuated by partial, or complete, remissions); disease with long clinical intervals.5

The pathogenesis of RA is unclear. It appears to be a multi-factorial disease in which there are important genetic and environmental influences.3,4,6 There is abundant evidence that RA is immune mediated.6 The activation of T lymphocytes and the consequent release of a range of cytokines plays a key role in the initiation and maintenance of the chronic systemic and synovial inflammation seen. In particular tumour necrosis factor α (TNFα) and interleukin-1 (IL-1) are considered pivotal mediators in RA. TNFα is believed to be the primary mediator of inflammation and IL-1 bone and cartilage destruction. The interplay between these two cytokines is however complex.7

Current service provision

The overall annual cost of RA in the UK is believed to lie between £0.8 and £1.3 billion. This includes costs for medical care (£240-600m), time lost from work (£650m) and nursing/residential care for severely disabled patients (£130m).8

Effective management of patients with RA, apart from those with the mildest form of the disease, requires a multidisciplinary approach usually co-ordinated by a rheumatologist.

The objectives of treatment are to control symptoms of joint pain and inflammation, to minimise loss of function and to maintain or improve quality of life, to reduce the risk of joint damage and disability, and to treat the extra-articular complications of RA.9

Conventional drug therapy for RA falls into two broad categories – symptomatic relief and disease modifying therapy. Symptomatic relief of pain in patients with mild RA may be achieved with the use of simple analgesics (eg paracetamol and/or opioid analgesics) non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids alone or in combination. NSAIDs represent the mainstay of symptomatic treatment and are taken by the majority of patients with RA. NSAIDs significantly reduce early morning stiffness but have no effect on the long-term outcome or progression of RA.10

Disease modifying anti-rheumatic drugs (DMARDs) are slow acting drugs which provide symptomatic relief. They aim to suppress the disease and prevent further disease progression. Whilst the precise mechanism of action for each DMARD is unclear they are believed to regulate cytokine and T cell activity. Long-term data support the view that DMARDs reduce long term disability in RA patients. However, while DMARDs can modify disease activity, they do not abolish it. A true remission that allows the withdrawal of treatment is rare, and eventual progression of the disease is generally the rule. A number of DMARDs (approx 10) are available in the UK for the treatment of RA.7,10 On current
evidence it is not possible to predict which patient will respond to which DMARD, or whether a combination may be helpful and which combination is best. Selection is usually made on the basis of efficacy versus toxicity.\textsuperscript{7,11}

Early treatment with a DMARD soon after diagnosis is now widely advocated. DMARD treatment can be anticipated to improve symptoms, wellbeing and physical function and to slow the radiological progression associated with RA. DMARDs are usually given with symptomatic treatment at least initially, with moderation of the symptomatic treatment as disease control is achieved with the DMARD.\textsuperscript{9}

Biological therapies for the management of RA have recently been developed. Two approaches have been targeted, inhibitors of TNF\textsubscript{α} and most recently antagonists for the IL-1 receptor. These target the cytokines believed to be of pivotal importance in the mediation of inflammation and joint destruction within the arthritic joint.\textsuperscript{8} Such treatments are currently reserved for use in patients who have responded inadequately to conventional DMARD therapy.

Whilst standard pharmaceutical preparations (as discussed above) are most widely used in the treatment of RA, there are other options for amelioration of symptoms. The value of physical measures, such as resting acutely inflamed joints; local application of heat or cold and stretching exercises are well established. Regular exercise to strengthen muscles can help to stabilise damaged joints and should be initiated as early in the disease as practical.\textsuperscript{8}

**Description of new technology**

Anakinra (TN Kineret\textsuperscript{R}) is a recombinant form of human interleukin-1 receptor antagonist (IL-1ra). It is administered as a daily subcutaneous injection. It is the first biologic agent of this type designed specifically to modify the biological immune response of IL-1.\textsuperscript{12} It was launched in the UK in April 2002 by Amgen.

Anakinra is licensed in Europe ‘for the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone’.\textsuperscript{13}

It should be used with caution in patients with: a history of recurring infections or with underlying conditions which may pre-dispose them to infections; moderate renal impairment.\textsuperscript{13}

Anakinra is not recommended for use in patients with neutropenia, those with pre-existing malignancies and those with severe renal impairment.\textsuperscript{13}

The cost of one year’s treatment with anakinra 100mg daily by subcutaneous injection is £7471. Additional costs associated with supervision and training in the use of the drug (in some cases administration of the drug) and monitoring of efficacy and safety may be incurred.

Currently usage of anakinra in the NHS is likely to be low. If uptake of anakinra post-launch is similar to TNF- inhibitors then it has been suggested that initial usage may be of the order of 8 patients per 100,000 of the population each year.\textsuperscript{14}

A key issue will be whether anakinra will be used in addition to TNF inhibitors. In the US prescribers have been warned against combined use due to the potentially higher risk of serious infections.\textsuperscript{15}
References


