Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan 26. 81 p. (Technology appraisal guidance; no. 375).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Certolizumab pegol for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Feb. 31 p. (Technology appraisal guidance; no. 186).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis (RA), only if:

- Disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
- Disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) and
- The companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes

Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in the above paragraph are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.

After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to

be varied for some people because of differences in the mode of administration and treatment schedules.

People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab or abatacept is not recommended in this National Institute of Health and Care Excellence (NICE) guidance, but was started within the National Health Service (NHS) before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Rheumatoid arthritis (RA)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, and abatacept for rheumatoid arthritis (RA) not previously treated with disease-modifying anti-rheumatic drugs (DMARDs) or after conventional DMARDs only have failed

Target Population

Adults with severe rheumatoid arthritis (RA) (i.e., a disease activity score [DAS28] greater than 5.1) whose disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs)

Interventions and Practices Considered

1. Adalimumab
2. Etanercept
3. Infliximab
4. Certolizumab pegol
5. Golimumab
6. Tocilizumab
7. Abatacept

Note: The above biologics are all considered in combination with methotrexate, unless contraindications or intolerance to methotrexate exist.

Major Outcomes Considered

- Clinical effectiveness
  - Disease activity (disease activity score [DAS28], American College of Rheumatology [ACR] and European League against Rheumatism [EULAR] responses, swollen and tender joint counts and patient and physician global assessments of disease activity)
  - Physical function (Health Assessment Questionnaire Disability Index [HAQ-DI], but not modified versions of HAQ)
  - Joint damage/radiological progression
  - Pain
  - Mortality
  - Fatigue
  - Extra-articular manifestations of disease
  - Adverse effects of treatment
  - Health related quality-of-life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the technology considered in this appraisal and prepare an assessment report. The Assessment Report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Methods for Reviewing Effectiveness

Identification of Studies

The aims of the search were to provide as comprehensive retrieval as possible of clinical effectiveness evidence relating to abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab and to identify additional relevant treatments for potential inclusion in the network meta-analysis (NMA).

Electronic Databases

Studies were identified by searching the following electronic databases and research registers:

- Medline(R) In-Process & Other Non-Indexed Citations and Medline(R) (Ovid) 1948 to July 2013
- EMBASE (Ovid) 1980 to July 2013
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996 to May 2013
- Cochrane Central Register of Controlled Trials (Wiley Interscience) 1898 to May 2013
- Health Technology Assessment Database (Wiley Interscience) 1995 to May 2013
- Database of Abstracts of Review of Effects (Wiley Interscience) 1995 to May 2013
- Cumulative Index to Nursing and Allied Health Literature (EBSCO) 1982 to April 2013
- Toxline to July 2013

Given the broad scope of interventions to be included in the review and the high volume of potentially relevant studies to be sifted, the keyword searches of electronic resources were undertaken in three stages. No language or date restrictions were applied to any database. Details of keywords strategies are reported in Appendix 2 of the Assessment Report.

Stage 1 was undertaken using keywords relating to the population only (i.e., rheumatoid arthritis [RA]) and did not include keywords relating to the interventions specified in the decision problem. The purpose was to keep the scope of the search broad in order to identify potentially relevant evidence for inclusion in the NMA, in addition to identifying randomised controlled trials (RCTs) and systematic reviews of the interventions of interest. For the searches of Medline, EMBASE, and CINAHL methodological filters were added to restrict search results to RCTs and systematic reviews. To maximise the efficiency of the search process at this stage, filters aimed at maximising the precision of search results were applied.

Stage 2 was undertaken using keywords relating to the population (RA) combined with keywords relating to the interventions of interest (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab) and any interventions identified as potentially allowing indirect comparisons to be made within the NMA. Keyword synonyms relating to the interventions included generic drug names, product names and drug registry numbers. The purpose of Stage 2 was to identify RCTs that might not have been retrieved by the 'high precision' Stage 1 searches. Therefore, RCT search filters aimed at maximising the sensitivity of search results were applied. In the first instance, Medline and EMBASE were searched. Given the high volume of references retrieved, and the low yield in terms of relevant references identified it was decided that searches would not be extended to other databases or to other treatments to be potentially included in the NMA.

Stage 3 involved the undertaking of searches for potential supplementary adverse events evidence through the combination of keywords relating to the population (RA) with keywords relating to the interventions of interest (abatacept, adalimumab, atacicept, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, tofacitinib). For the searches of Medline and EMBASE, adverse events filters were applied, whereas no filter was required for the Toxline database.

Where possible, and to minimise duplication between search results, the results retrieved by earlier search strategies were excluded from the results retrieved by later search strategies using the 'not' Boolean operator. The results retrieved by the Medline and EMBASE high precision searches (Stage 1) were excluded from Medline and EMBASE high sensitivity searches (Stage 2). The results retrieved by the Medline and EMBASE high precision and high sensitivity searches (Stage 1 and 2) were excluded from the adverse events searches (Stage 3).

Other Resources

To identify additional studies, the reference lists of relevant studies (including existing systematic reviews) were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify articles that cite the relevant articles. It was originally intended in the protocol that searches be performed to identify ongoing research and unpublished studies using the Current Controlled Trials *meta*Register of Controlled Trials (mRCT), the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP), the European Union Clinical Trials Register (EU-CTR), the Food and Drug Administration (FDA) and European Medicines Agency (EMA) Web sites and the WOS Conference Proceedings Citation Index – Science (CPCI-S). However, this was not possible within the timescales dictated by the NICE appraisal process. Hand searching of relevant documents included sponsor submissions to the NICE technology appraisal update process, recent systematic reviews, and documentation associated with previous relevant NICE technology appraisal guidance (TAs 130, 186, 224, 234, 225, 247). Grey literature was also sought using the sources listed in the international grey literature search toolkit produced by the Canadian Agency for Drugs and Technologies in Health (CADTH).

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for the selection of clinical effectiveness and safety evidence were defined according to the decision problem outlined in the NICE scope.

The inclusion of potentially relevant articles was undertaken using a two-step process. Firstly, all titles and abstracts were examined for inclusion by one reviewer. Any citations that clearly did not meet the inclusion criteria (e.g., animal studies, studies unrelated to RA) were excluded. Secondly, full text articles were initially examined by one reviewer. It was intended in the original protocol that a second reviewer would check approximately 10% of citations. However, because of the very large number of citations identified in the clinical effectiveness searches, this was not possible in the timescales available for this appraisal process. Any uncertainty in the inclusion and exclusion of potential full text articles was resolved through discussion with the review team. Where agreement could not be reached, expert clinical advice was sought for a final decision.

The relevance of each article for the systematic review was assessed according to the following criteria:

Population

The three populations under consideration in this assessment were:

- Adults with severe active RA not previously treated with methotrexate (defined by a disease activity score [DAS] of ≥5.1). In the original protocol this population was defined as "adults with severe active RA not previously treated with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs, defined by a DAS score of ≥5.1)." However, this definition was subsequently modified and broadened by the Assessment Group (in consultation with clinical experts) to include "adults with severe active RA not previously treated with methotrexate" to permit the inclusion of trial populations relevant to the decision problem which were methotrexate-naïve but may have had some prior experience of other conventional DMARDs (cDMARDs).
- Adults with severe active RA that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate) (defined by a DAS score of ≥5.1)
- Adults with moderate to severe active RA that have been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate) (defined as a DAS score between 3.2 and 5.1)

The following populations were considered outside the appraisal scope and were therefore excluded:

- Patients with a DAS score below 3.2
- Patients with a DAS score below 5.2 if they have not been previously treated with methotrexate
- Patients who have been previously treated with one or more biologic DMARDs (bDMARDs)

Interventions

The following interventions were included:

- For RA not previously treated with methotrexate:
  - Adalimumab
  - Etanercept
  - Infliximab
  - Golimumab
- For RA that has been previously treated with conventional DMARDs only:
  - Adalimumab
  - Etanercept
  - Infliximab
  - Certolizumab pegol
  - Golimumab
  - Abatacept (intravenous and subcutaneous preparations)
  - Tocilizumab

The above interventions were assessed in accordance with licensed indications and could be delivered in conjunction with cDMARDs or as monotherapy (as defined in licensed indications).

Comparators

The relevant comparators differed according to the population considered and included the following:

- For severe active RA not previously treated with methotrexate:
  - Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) or DMARD monotherapy with dose escalation
  - Biologic interventions versus (vs.) each other
- For severe active RA that has been previously treated with conventional DMARDs only:
  - Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), nonsteroidal anti-inflammatory drugs (NSAIDS) and corticosteroids
  - Biologic interventions vs. each other
- For moderate to severe active RA that has been previously treated with conventional DMARDs only:
  - Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDS and corticosteroids
  - Biologic interventions vs. each other

Outcomes

Refer to the "Major Outcomes Considered" field.

Study Design

The systematic review of clinical effectiveness was based on RCT evidence. It was stated in the protocol that, if insufficient data were available from RCTs, observational studies or non-randomised trials may be considered, for example for safety evidence. The Assessment Group supplemented the adverse events data identified in the included RCTs with safety data from long-term extension studies reporting on individual included RCTs. Studies published as abstracts or conference presentations were only included if sufficient details were presented to allow both an appraisal of the methodology and an assessment of the results to be undertaken. Systematic reviews could be used as potential sources of additional references of efficacy evidence.

The following study types were also excluded:

- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Studies presenting secondary analyses of RCT data or pooled RCT data
- Non-English language papers

Results

A total of 43,764 citations were identified for the review of clinical effectiveness and safety. This was reduced to 27,464 following deletion of duplicate citations. The study selection process is represented as a PRISMA diagram (see Figure 2 of the Assessment Report). A total of 27,334 citations were excluded at title and abstract levels (1606 being non-English language records). Of the remaining records, a total of 60 studies were included in the review. Studies excluded at full text are presented (with rationale for exclusion) in Appendix 1 of the Assessment Report.

Assessment of Cost-effectiveness

Methods for Reviewing Existing Cost-effectiveness Evidence

Systematic searches of online databases were undertaken to identify all published economic evaluations of disease modifying therapies for RA. To ensure that the systematic search had high sensitivity, the search was developed by applying economic terms to a general disease search for RA and disease modifying therapies. Database filters to identify economic evaluations were used from the InterTASC Information Specialists' Sub-Group (ISSG) Web site (www.york.ac.uk/inst/crd/intertasc/index.htm).

See Table 47 of the Assessment Report for keywords used for systematic review.

The search strategies used Medical Subject Headings (MeSH) terms, including 'rheumatoid arthritis' and 'economics' and text string terms which were combined in the search strategy using Boolean logic. The search strategies were designed to maximise sensitivity (i.e., the identification of all appropriate studies); however, this was at the cost of poor specificity (the rejection of inappropriate studies). This meant the search returned a lot of inappropriate studies and was reliant on hand sifting, including the removal of economic evaluations of treatments that are not included in this appraisal (rituximab, conventional DMARDs, anakinra etc.).

Systematic searches were conducted in ten databases (see Table 48 of the Assessment Report). Reference search was undertaken on all included

studies, including any identified reviews of published economic evaluations of disease modifying therapies for RA.

All database searches were undertaken on 1st February 2013, and no date restriction was applied. No study type or language restrictions were applied to the electronic search. The search strategies were reviewed by an information specialist.

The objective of the systematic search was to identify economic evaluations of abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab within Populations 1, 2 and 3. The search was irrespective of the decision-making context or the geographical location. The eligibility criteria are presented below.

Inclusion Criteria

- Economic evaluation including a comparison of costs and benefits based on outcomes data or undertaken using decision-analytic methods
- Economic evaluations of interventions targeting a change to the natural disease profile of people with RA (i.e., disease-modifying therapies)
- Studies reporting costs and health outcomes

Exclusion Criteria

- Evaluations of treatments not under review in the appraisal
- Evaluations in patient populations not under review in this appraisal (e.g., sequential biologics)
- Partial or non-comparative economic evaluations
- Cost analyses/cost-of-illness/burden-of-illness studies
- Methodological papers which do not report economic and health benefit outcomes
- Commentaries, letters, editorials
- Conference abstracts
- Studies which claim cost-effectiveness but with no empirical estimation of the costs and effectiveness outcomes
- Economic evaluations of therapies and treatments which do not modify the natural progression of RA
- Non-English language

The identified studies were appraised using the commonly used and validated Drummond 'Critical appraisal of a published article' checklist.

Results

From the systematic searching of electronic databases, 8,281 citations were identified (see QUOROM flow-diagram provided in Figure 28 of the Assessment Report). After excluding 3,250 duplicate citations electronically, the remaining 5,031 citations were screened by their abstract. Of these, 4,913 abstracts did not meet the inclusion criteria and 118 full papers were retrieved for a full inspection. A total of 97 papers were excluded for not meeting the inclusion criteria, and 9 other studies were identified by reference searches and searching any identified systematic reviews. Thirty studies were included in the systematic review.

No studies were identified that evaluated golimumab and certolizumab pegol, with the majority focussing on etanercept, infliximab and adalimumab.

Number of Source Documents

Clinical Effectiveness

A total of 60 studies were included in the review.

Cost-effectiveness

- Thirty studies were included in the systematic review.
- Each manufacturer submitted an economic model (a total of 7 models).
- The Assessment Group also submitted and independent economic assessment.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the technology considered in this appraisal and prepare an assessment report. The Assessment Report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Methods for Reviewing Effectiveness

Data Abstraction and Critical Appraisal Strategy

Data relevant to the decision problem were extracted by one reviewer. Data were extracted without blinding to authors or journal. Study arms where intervention treatments were administered in line with licensed indications were extracted; where there was a slight divergence between the regimen used in the randomised controlled trial (RCT) and the licensed regimen, this was explicitly highlighted. It was proposed in the original protocol that at least 10% of data extraction forms be checked by a reviewer. However, the Assessment Group ensured that all data included in the network meta-analysis (NMA) were double checked by a second reviewer. For data not contributing to the NMA, data were extracted for the following time points: primary endpoint (for selected efficacy data), latest available controlled RCT endpoint (for efficacy and safety data) and latest available long-term extension study endpoint (for safety data only). The safety data extracted were informed by the Summary of Product Characteristics (available at http://www.medicines.org.uk/emc/) and U.S. Food and Drug Administration (FDA) prescribing information for each intervention. Graphical data contributing to the NMA were estimated using Engauge software (version 4.1) and graphical data not contributing to the NMA were estimated manually by a reviewer. Where multiple publications of the same study were identified, data extraction was undertaken on all relevant associated publications, and findings were presented as a single study. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

The methodological quality of each included study was assessed by one reviewer. It was originally intended in the protocol that quality assessment would be checked by a second reviewer, but this was not feasible within the timescales available for the appraisal process. The quality assessment of included studies was informed by selected items listed in the National Health Service Centre for Reviews and Dissemination (NHS CRD) report and Cochrane Risk of Bias tool. Additional quality issues specific to the assessment of rheumatoid arthritis RCTs (as described by Karsh et al., 2011) were also considered during the evaluation of studies.

Methods of Data Synthesis

The extracted data and quality assessment variables were presented for each study, both in structured tables and as a narrative description.

As the identified evidence base permitted the undertaking of network meta-analyses for the estimation of treatment effects, supplementary meta-analyses were not undertaken. Network meta-analyses were conducted to determine efficacy using two different disease activity measures (American College of Rheumatology [ACR] and European League against Rheumatism [EULAR] responses).

Methods for the Estimation of Efficacy Using Network Meta-analysis

Selection of Evidence Contributing to the Network Meta-analysis

Evidence considered relevant to the decision problem was selected according to the additional inclusion criteria detailed in Section 5.1.5.1 of the Assessment Report.

Sensitivity analyses were also undertaken to include trials relevant to populations 2 (adults with severe active rheumatoid arthritis [RA] that have

been previously treated with conventional disease-modifying anti-rheumatic drugs [cDMARDs] but not biologic DMARDs [bDMARDs]) and 3 (adults with moderate to severe active RA that have been previously treated with cDMARDs only, including methotrexate [MTX, unless contraindicated or inappropriate]) where the population may not have adequately failed cDMARDs (either there was a sufficient response, MTX treatment duration was too short or a proportion of the population were MTX-naive).

Evidence was sought in which bDMARDs not considered as interventions or comparators within the NICE scope were evaluated in head to head trials with an included intervention in the first line treatment of RA. To establish whether any such identified data could be used to inform indirect comparisons within the NMA, a review of these interventions against cDMARDs was undertaken. If such trials were found and met the inclusion criteria for the review, then the bDMARD was considered part of the evidence base for the NMA.

Assessment of Cost-effectiveness

Critique of the Manufacturers' Submissions

The Assessment Group received submissions for seven interventions. These were from six manufacturers as golimumab and infliximab are both manufactured by the same company. Each submission contained a mathematical model.

An initial review of the submissions indicated that there were a multitude of methods employed and that attempting to summarise all seven submissions individually would likely not aid the reader. With this aim, the submissions have been summarised jointly under a number of categories to allow the reader to compare and contrast the methodologies used.

Decision Problem Addressed

Table 53 in the Assessment Report summarises the decision problems addressed within the manufacturers' submissions for those drugs that are licensed as monotherapy and for those that are not. No detailed information is given in the table which serve as reference only, with subtleties regarding each analysis provided in later sections of the Assessment Report. Four interventions (abatacept intravenous [i.v.], abatacept subcutaneous [s.c.], certolizumab, and tocilizumab) are not licenced before the use of MTX. Four interventions (abatacept i.v., abatacept s.c., golimumab and infliximab) are not licenced as monotherapy.

Strategies Modelled

The strategies modelled for each submission have been detailed individually (see Section 6 of the Assessment Report) for each manufacturer. These are:

1. Population 3 in combination with MTX
2. Population 2 in combination with MTX
3. Population 1 in combination with MTX (adults with severe active RA not previously treated with cDMARDs)
4. Population 3 monotherapy
5. Population 2 monotherapy
6. Population 1 monotherapy
7. General RA population who can receive MTX
8. MTX intolerant or contraindicated RA population

Most strategies appeared reasonable although it is noted that there were a few anomalies compared with NICE guidance or intervention licences.

Model Structure/Time Cycle

Broad Summary

Four individual patient models and two cohort models were submitted. Of the four individual patient level models three used discrete event simulation (DES) techniques, which do not need time cycles, with the remainder using a 6 month cycle. Of the two cohort models one used a 6 month time cycle, whilst the other adopted this after the initial year, with either three cycles of 6, 3 and 3 months in the first year, or 3, 4.5 and 4.5 months depending on the user input. Both cohort models used a half-cycle correction.

Four of the models were constructed in Microsoft Excel (©Microsoft Corporation); one in Arena (©Rockwell Automation); and one in Simul8 (©Simul8 Corporation).

Time Horizon

All models adopted a lifetime, or approximately lifetime time horizon.

Independent Economic Assessment

Description of the Assessment Group's Model

None of the models submitted by the manufacturers replicated the clinical reality within England and Wales to the satisfaction of the Assessment Group. Primarily this is because the majority of models assumed that the efficacy of the intervention was based on improvements in American College of Rheumatology (ACR) score, whereas NICE guidance has defined stopping rules where an intervention is stopped unless a Disease Activity Score 28 joints (DAS28) reduction of 1.2 points is achieved. The criterion of achieving a 1.2 point reduction in DAS is associated with a good or moderate EULAR response.

Furthermore clinicians in the UK predominantly measure EULAR, rather than ACR responses; the use of EULAR is recommended by the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR), who consider the EULAR response to be an evidence-based and validated measure of response to treatment.

For these reasons the Assessment Group constructed a model where the assessment of treatment response was based upon EULAR response at six months.

The Strategies Modelled

This Assessment Group model considers strategies of sequencing treatments but acknowledges that due to the scope NICE can only make recommendations on the first-line use of bDMARDs. Therefore this report will assume that NICE guidance after the first biologic treatment is routinely followed. This means that rituximab with MTX will be used after failure of the first bDMARD should a patient be able to take MTX and following this a patient receives tocilizumab and MTX if not previously received.

For simplicity, it was assumed that it would be known whether a patient required monotherapy at the time of the first bDMARD initiation based on their experience to cDMARDs and also that any patient who could tolerate MTX could also receive rituximab. This would not be correct when analysing Population 1, adults with severe active RA not previously treated with cDMARDs, but is likely to be of limited impact as: (i) it would only be apparent if bDMARDs were recommended in advance of intensive cDMARDs, and (ii) the effect would be dampened as each treatment sequence would have to replace rituximab with a bDMARD that is licenced for use in monotherapy and any impact would be relatively equal across all strategies.

Although the Assessment Group model can incorporate sequences of up to seven treatments, for simplicity it was decided that modelling large number of cDMARDs would not be overly informative. The rationale for this is that there is insufficient data on the effectiveness of cDMARDs after either bDMARDs or multiple cDMARDs. For this reason, once a patient had received intensive cDMARD therapy and/or the allotted bDMARDs within the sequence, patients were assumed to have one further cDMARD (typically MTX, but an alternative cDMARD if MTX was not suitable) before moving to 'non-biologic therapy', which was a term defined to encompass a selection of treatments that clinicians may feel was appropriate for individual patients. It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response.

For populations 2 and 3, it was assumed that all patients would have previously received intensive cDMARD therapy prior to the first bDMARD and thus this intervention was not explicitly modelled.

Table 156 of the Assessment Report provides the broad strategies that were deemed appropriate by the Assessment Group for consideration in patients who could receive MTX. Table 157 of the Assessment Report provides the broad strategies that were deemed appropriate by the Assessment Group for consideration in patients who could not receive MTX.

Model Structure/Time Cycle

A simplified schematic of the Assessment Group's model is shown in Figure 101 of the Assessment Report. The model is individual-patient based, written in Microsoft Excel and uses a discrete event simulation approach. Therefore a time cycle was not employed. The model allows only legitimate Health Assessment Questionnaire (HAQ) scores (the 25 points defined in the 0 to 3 range) with time to a change in HAQ score being a competing risk. The advantage of using discrete HAQ scores means that if some outputs (such as costs, utility or risk of mortality) are assumed related by HAQ there is no need to be continually updating the output as a HAQ score is assumed to linearly progress between legitimate HAQ points.

Time Horizon

The Assessment Group model employs a lifetime patient horizon but assumes that no patient will live beyond 101 years. This is similar to the

approaches undertaken in the manufacturers' submissions.

Refer to Section 6 of the Assessment Report for additional information on economic evaluation.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an Assessment Report. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the Appraisal Consultation Document (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the Final Appraisal Determination (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Assessment Group's model used the European League Against Rheumatism (EULAR) response measure, which was considered appropriate

by the Committee and accurately reflected rheumatoid arthritis (RA) care in the UK. Using EULAR response had meant that a smaller number of trials could be taken into account, but the effect of the full set of trials was considered, by mapping American College of Rheumatology (ACR) response data to EULAR scores when necessary.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee considered that the following factors introduce uncertainty into the evidence base for the cost effectiveness of biological disease-modifying anti-rheumatic drug (DMARD) therapies:

- The Assessment Group modelled the underlying disease progression for people on conventional DMARDs on the basis of the Early Rheumatoid Arthritis Study (ERAS) dataset, which differed from the method used in the companies' models, which assumed linear Health Assessment Questionnaire (HAQ) progression of 0.045 while on conventional DMARDs, based on the assumptions used in previous National Institute for Health and Care Excellence (NICE) technology appraisals. The Committee concluded that the Assessment Group's method more accurately represented disease progression on conventional DMARDs than the assumptions used in previous NICE technology appraisals.
- To obtain EuroQual-5D (EQ-5D) from HAQ scores the Assessment Group used a function from a mixture model developed using the US National Data Bank for Rheumatic Diseases (NDB) and ERAS datasets. This estimated EQ-5D using both HAQ score and pain score. The Committee noted that previous appraisals and some of the company models used an alternative approach and dataset, but concluded that the Assessment Group's method was more appropriate to use for decision-making.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Assessment Group included pain and HAQ in its estimation of EQ-5D values. There were some concerns about model fit to data in the Assessment Group's model, but the Committee concluded that the Assessment Group's method of estimating EQ-5D from HAQ was appropriate to use in decision-making. No other health-related benefits have been identified that have not been captured in the quality-adjusted life year (QALY) calculation.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

This technology appraisal included people who had had methotrexate and who had moderate active and severe active disease, and people who had never been treated with methotrexate and who had severe disease. The Committee concluded that biological DMARDs can only be considered a cost-effective use of National Health Service (NHS) resources for the severe active RA population who had been treated with methotrexate both as monotherapy and in combination therapy.

What Are the Key Drivers of Cost-effectiveness?

The key drivers of the cost-effectiveness for biological DMARDs were the assumption about mapping of HAQ to utility, discount rates and underlying disease progression while on treatment with conventional DMARDs.

Most Likely Cost-effectiveness Estimate (Given as an Incremental Cost-effectiveness Ratio [ICER])

For the population with severe active RA who had not had methotrexate before, the Committee noted that the most plausible ICER was £68,300 per QALY gained for the population who could have methotrexate and £77,500 per QALY gained for the population who could not have methotrexate.

The Committee considered that the most plausible ICER for biological DMARDs used in severe active RA previously treated with methotrexate was likely to lie between the Assessment Group's base-case ICER (that is, £41,600 per QALY gained) and the Assessment Group's ICER for the severe group with the fastest HAQ progression (that is, £25,300 per QALY gained).

The Assessment Group's base-case ICER for biological DMARDs was £51,100 per QALY gained for the moderate active population. This was approximately £10,000 higher than the Assessment Group's base-case ICER for severe active disease.

For biological monotherapy, the Committee concluded that the most plausible ICERs for both subgroups were higher than those for the combination therapy, but it accepted that this was mainly because of the costs of later treatments. Therefore it concluded that people with severe disease who cannot have methotrexate should not be treated differently from other people with severe disease, as far as possible.

For people with moderate active disease previously treated with methotrexate and with severe active disease not previously treated with methotrexate, it concluded that biological DMARDs were not cost effective.

Refer to Section 4 of the original guideline document for details of the economic analyses provided by the manufacturer, the Assessment Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination (FAD).

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept from a systematic review prepared by an independent Assessment Group. The main clinical effectiveness evidence came from randomised controlled trials (RCTs). For cost-effectiveness, the Appraisal Committee considered economic models prepared by both the manufacturers and the Assessment Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Rheumatoid arthritis (RA) can affect parts of the body other than the joints and it has a significant impact on social life, employment and mental health. Biological DMARDs can enable patients to continue working.
- Biological DMARDs have significantly changed the management of RA. The Committee agreed that the biological DMARDs should be considered an innovative class of drugs. Patient experts emphasised that biological DMARDs provided extensive benefits for people with RA.
- The Committee concluded that the evidence of greater clinical effectiveness for biological DMARDs compared with conventional DMARDs was more compelling in disease previously treated with methotrexate and that the evidence did not suggest differential effectiveness between the biological DMARDs.

Potential Harms

- The summary of product characteristics for adalimumab notes the following adverse reactions as very common: respiratory tract infections, leukopenia, anaemia, increased lipids, headache, abdominal pain, nausea and vomiting, elevated liver enzymes, rash, musculoskeletal pain and injection site reaction.
- The summary of product characteristics for etanercept notes the following adverse reactions as very common: infections and injection site reactions.

- The summary of product characteristics for infliximab notes the following adverse reactions as very common: viral infection, headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea, infusion-related reaction and pain.
- The summary of product characteristics for certolizumab pegol lists no adverse reactions as very common but notes that in clinical trials the most common adverse reactions were bacterial and viral infections.
- The summary of product characteristics for golimumab notes that upper respiratory tract infections are very common adverse events.
- The summary of product characteristics for abatacept notes that upper respiratory tract infections are very common adverse events.
- The summary of product characteristics for tocilizumab notes the following adverse reactions as very common: upper respiratory tract infections and hypercholesterolaemia.

For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

- Adalimumab, infliximab, certolizumab pegol, and golimumab are contraindicated in people with active tuberculosis or other severe infections, and people with moderate or severe heart failure.
- Etanercept is contraindicated in people with sepsis or who are at risk of sepsis, and people with active infections including chronic or localised infections.
- Abatacept is contraindicated in people with severe and uncontrolled infections.
- Tocilizumab is contraindicated in people with active, severe infections.

For full details of contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- The recommendations in this guidance represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the National Health Service (NHS) Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales

must usually provide funding and resources for it within 3 months of the guidance being published.

- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has rheumatoid arthritis (RA) and the doctor responsible for their care thinks that adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health, Bristol–Myers Squibb and Roche have agreed that abatacept and tocilizumab will be available to the NHS with patient access schemes which make the drugs available with a discount. The size of the discount is commercial in confidence. It is the responsibility of each company to communicate details of their drug's discount to the relevant NHS organisations. The Department of Health and Merck, Sharp & Dohme have agreed that golimumab will be available to the NHS with a patient access scheme which makes it available with a discount. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. The Department of Health and UCB Pharm have agreed that certolizumab pegol will be available to the NHS with a patient access scheme. UCB Pharma will provide the first 12 weeks of the drug free of charge, which is equivalent to 10 vials. Refer to the original guideline document for email addresses for enquiries about the patient access schemes.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan 26. 81 p. (Technology appraisal guidance; no. 375).

Adaptation

Not applicable: The guideline was not adapted from another source.

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National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

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Guideline Committee

Appraisal Committee

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Certolizumab pegol for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Feb. 31 p. (Technology appraisal guidance; no. 186).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Resource impact report. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan. 3 p. (Technology appraisal guidance; no. 375). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Stevenson MD, Archer R, Tosh J, Simpson EL, Everson-Hock E, Stevens JW, Hernandez M, Paisley S, Williams K, Scott D, Young A, Wailoo A. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only: systematic review and economic evaluation. Technology assessment report. Sheffield (UK): School of Health and Related Research (ScHARR), University of Sheffield; 2015 Mar. 826 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan. 3 p. (Technology appraisal guidance; no. 375). Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on February 21, 2011. This summary was updated by ECRI Institute on October 12, 2011 following the U.S. Food and Drug Administration (FDA) advisory on Tumor Necrosis Factor-alpha (TNFα) Blockers. This summary was updated by ECRI Institute on March 28, 2016.

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