NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol and golimumab for the treatment of rheumatoid arthritis not previously treated with conventional disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only (review of technology appraisal guidance 130, 186 and a part review of technology appraisal guidance 225)

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol and golimumab within their licensed indications for the treatment of rheumatoid arthritis[1].

Background

Rheumatoid arthritis is an inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. It is a systemic disease and can affect the whole body, including the lungs, heart and eyes. Rheumatoid arthritis is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive. Rheumatoid arthritis has a severe impact on quality of life and it is estimated that approximately one-third of people stop work within 2 years because of the disease, and this prevalence increases thereafter.

Rheumatoid arthritis affects approximately 0.8% of the population, or approximately 580,000 people in the UK. Of these, approximately 15% have severe disease. It is about two- to four-times more prevalent in women than in men. It can develop at any age, but the peak age of onset in the UK is about 40–70 years.

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[1] [1] This appraisal includes a review of: Technology Appraisal No. 130, October 2007, Guidance on the use of infliximab, etanercept and adalimumab for the treatment of rheumatoid arthritis; Technology Appraisal No. 186, February 2010, certolizumab pegol for the treatment of rheumatoid arthritis; and a partial review of Technology Appraisal No. 225, June 2011, golimumab for the treatment of rheumatoid arthritis after the failure of a conventional DMARD.

There is no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. Treatment for rheumatoid arthritis usually includes: non-steroidal anti-inflammatory drugs which reduce pain, fever and joint swelling/inflammation, and disease modifying anti-rheumatic drugs (DMARDs), which slow the disease process and reduce joint damage. Corticosteroids may also be used to control inflammation. The main aim of management in early disease is to suppress disease activity, prevent loss of function, control joint damage, maintain pain control and enhance self-management. In established disease, management should address complications and associated comorbidity; and the impact of the condition on the patient's quality of life.

For people with newly diagnosed rheumatoid arthritis, 'Rheumatoid arthritis: the management of rheumatoid arthritis in adults' (NICE clinical guideline 79) recommends a combination of DMARDs (including methotrexate and at least one other DMARD plus short term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate (for example where there are comorbidities or pregnancy) DMARD monotherapy is recommended. Where DMARD monotherapy is used emphasis should be on increasing the dose quickly to obtain best disease control. NICE guidance (TA130, TA186 and TA225) recommends the use of the TNF inhibitors etanercept, infliximab, adalimumab, certolizumab pegol and golimumab in people with rheumatoid arthritis after the failure of two conventional DMARDs, including methotrexate, and who have a disease activity (DAS28) severity score greater than 5.1. NICE has also issued guidance (TA195, TA225 and TA 247) on the treatment of rheumatoid arthritis after the failure of a TNF inhibitor but this will not be addressed in this appraisal.

The technologies

Adalimumab, etanercept, infliximab, certolizumab pegol and golimumab all inhibit the activity of TNF-α, a pro-inflammatory mediator that is partly responsible for damage to the joints in rheumatoid arthritis.

Adalimumab (Humira, Abbott Laboratories), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate, has been inadequate and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. It is administered subcutaneously.

Etanercept (Enbrel, Pfizer), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate (unless contraindicated), has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. It is administered subcutaneously.

Infliximab (Remicade, Merck Sharp & Dohme), in combination with methotrexate, has a UK marketing authorisation for the reduction of signs and symptoms as well as the improvement in physical function in adults with active disease when the response to DMARDs, including methotrexate, has been inadequate. It is also licensed for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs. It is administered by intravenous infusion.

Certolizumab pegol (Cimzia, UCB Pharma), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to DMARDs, including methotrexate, has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. It is administered subcutaneously.

Golimumab (Simponi, Merck Sharp & Dohme), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to DMARD therapy including methotrexate has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. It is administered subcutaneously.

Interventions	For rheumatoid arthritis not previously treated with DMARDs: • Adalimumab • Etanercept • Infliximab For rheumatoid arthritis that has not responded adequately to conventional DMARDs only:

	• Adalimumab • Etanercept • Infliximab • Certolizumab pegol • Golimumab
Populations	Adults with rheumatoid arthritis not previously treated with DMARDs. Adults with rheumatoid arthritis that has not responded adequately to conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate)
Comparators	For rheumatoid arthritis not previously treated with DMARDs: • Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide), or DMARD monotherapy with dose escalation • The interventions will be compared to each other For rheumatoid arthritis that has not responded adequately to conventional DMARDs only: • Management strategies involving conventional DMARDs (for example sulfasalazine, leflunomide) • Management strategies involving biological agents (including tocilizumab and the other technologies being appraised).
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage • pain • mortality • fatigue • radiological progression

	• extra-articular manifestations of disease • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, the appraisal will consider the costs of joint replacement therapy and hospital admissions. If the evidence allows, the appraisal will consider subgroups based on: • Severity of disease activity: moderate to severe disease and severe disease Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.130, October 2007, Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Superseded technology appraisal No. 36. Expected review date TBC Technology Appraisal No.186, February 2010, Certolizumab pegol for the treatment of rheumatoid arthritis. Expected review date TBC Technology Appraisal No 195, Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of the first TNF inhibitor. Superseded technology appraisal Nos. 126, 141 Expected review date June 2013. Technology Appraisal 224 (Terminated June 2011), Golimumab for the treatment of methotrexate-naïve

	rheumatoid arthritis. Technology Appraisal No 225, Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying anti-rheumatic drugs. Expected review date June 2014. Technology Appraisal No 234, Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs. Expected review date July 2014. Technology Appraisal in 247 (rapid review of TA 198), February 2012, Tocilizumab for the treatment of rheumatoid arthritis. Expected review date TBC Ongoing Technology Appraisals: Technology Appraisal in Preparation (Suspended September 2010), Rituximab for the treatment of rheumatoid arthritis after failure of disease-modifying anti-rheumatic drugs. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, Tofacitinib for the treatment of rheumatoid arthritis after the failure of disease modifying anti-rheumatic drugs. Earliest anticipated date of publication TBC. Related Guidelines: Clinical Guideline No. 79, February 2009, Rheumatoid arthritis: the management of rheumatoid arthritis in adults. Expected review date June 2014.

Questions for consultation

Are the interventions in the appraisal appropriately defined? Should the review include any other technologies?

- Is it appropriate to include a review of the guidance in TA247, 'tocilizumab for the treatment of rheumatoid arthritis' that considers the use of tocilizumab only after the failure of conventional DMARDs?

- Is it appropriate to include an appraisal of the terminated guidance TA225 ‘golimumab for the treatment of methotrexate naive rheumatoid arthritis’?

- Is it appropriate to include a review of the guidance for abatacept in TA234, ‘abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs’?

Is the place in the treatment pathway appropriately defined? Should the review include additional places in the treatment pathway?

Have the most appropriate comparators for adalimumab, etanercept, infliximab, certolizumab pegol and golimumab for the treatment of rheumatoid arthritis been included in the scope? Are the comparators listed routinely used in clinical practice?

Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits