NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of TA36, review of TA126 and of 141)

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, rituximab and abatacept, within their respective licensed indications, for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor[1].

Background

Rheumatoid arthritis is a chronic, disabling autoimmune disease characterised by inflammation of the synovial tissue of the peripheral joints, which causes swelling, stiffness, pain and progressive joint destruction. For a small proportion of people, inflammatory disease outside the joints (for example, eye and lung disease, vasculitis) can also pose a significant problem. Rheumatoid arthritis is usually a chronic relapsing condition, which has a pattern of flare-ups followed by periods of lower disease activity; however, in a minority of cases, the disease is constantly progressive. Most people develop damage to affected joints due to inflammation, with the amount of damage ranging from mild to severe. Rheumatoid arthritis has a severe impact on quality of life and it is estimated that 40% of people with rheumatoid arthritis will stop working within 5 years of diagnosis.

Rheumatoid factor is an autoantibody that, if present, contributes to the disease process. The presence of rheumatoid factor is not necessary for the development and progression of rheumatoid arthritis. Individuals with rheumatoid factor are said to be sero-positive, and those without, sero-negative.

Rheumatoid arthritis is three times more prevalent in women than in men. It can develop at any age, but usually starts between 40 and 60 years of age. Rheumatoid arthritis affects 1% of the population, or approximately 400,000 people in England and Wales. Of these, approximately 15% have severe disease.

[1] This appraisal includes a partial review of: Technology Appraisal No. 36, March 2002, Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis' (part of this appraisal has already been reviewed in Technology Appraisal No. 130, October 2007; Technology Appraisal No. 126, August 2007, Rituximab for the treatment of rheumatoid arthritis; and Technology Appraisal No. 141, April 2008, Abatacept for the treatment of rheumatoid arthritis.

People with rheumatoid arthritis are usually treated in an out-patient setting and then in primary care. 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 agents (NSAIDs), which reduce pain, fever and joint swelling / inflammation; disease modifying anti-rheumatic drugs (DMARDs), which slow the disease process and reduce joint damage; and corticosteroids, which also control inflammation. DMARDs may be broadly classed as either conventional or biologic, the latter group including, but not limited to, tumour necrosis factor (TNF) inhibitors. Treatment with DMARDs is typically started soon after diagnosis.

In 2002, NICE guidance (TA36) recommended the first-use of TNF inhibitors etanercept and infliximab after the failure of two conventional DMARDs, including methotrexate. Neither etanercept nor infliximab are recommended for use after the failure of a TNF inhibitor, that is to say, in sequential use. Subsequent NICE guidance (TA130) replaces the first-use component of TA36, additionally recommending the TNF inhibitor adalimumab for first-use after the failure of two conventional DMARDs, including methotrexate, and taking into account changes in the marketing authorisations for etanercept and infliximab. This guidance (TA130) does not address the use of these agents in sequential use, except where a TNF inhibitor is discontinued owing to an adverse event. NICE guidance (TA 126) recommends the use of rituximab (a biologic DMARD) after the failure of a TNF inhibitor. NICE guidance (TA 141) does not recommend the use of abatacept (a further biologic DMARD) after the failure of a TNF inhibitor.

The technologies

Adalimumab (Humira, Abbott Laboratories) is a human-sequence antibody that binds specifically to TNF and neutralises its biological function by blocking its interaction with cell-surface TNF receptors. Adalimumab is licensed for the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate, has been inadequate. It is licensed to be used in combination with methotrexate, except in cases where methotrexate is not tolerated or is considered inappropriate.

Etanercept (Enbrel, Wyeth Pharmaceuticals) is a recombinant human TNF-receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF , thereby blocking its interaction with cell-surface TNF receptors. Etanercept is licensed for use in adults with active rheumatoid arthritis whose response to DMARDs, including methotrexate, has been inadequate. Etanercept is licensed to be used in combination with methotrexate, except in cases where methotrexate is not tolerated or is considered inappropriate.

Infliximab (Remicade, Schering-Plough) is a chimeric monoclonal antibody that binds with high affinity to TNF, thereby neutralising its activity. Infliximab in combination with methotrexate is licensed for the treatment of active

rheumatoid arthritis where the response to DMARDs, including methotrexate, has been inadequate.

Rituximab (MabThera, Roche Products) is a genetically engineered chimeric monoclonal antibody that depletes the B-cell population by targeting cells bearing the CD20 surface marker. Rituximab in combination with methotrexate is licensed for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other DMARDs, including one or more TNF inhibitor therapies.

Abatacept (Orencia, Bristol-Myers Squibb) is a selective T-cell co-stimulation modulator that blocks a key co-stimulatory signal required for T-cell activation. Abatacept is licensed for use in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other DMARD, including at least one TNF inhibitor.

Intervention(s)	Adalimumab, etanercept, infliximab, rituximab and abatacept
Population(s)	Adults with active rheumatoid arthritis who have had an inadequate response to a TNF inhibitor.
Comparators	Where appropriate, management strategies involving the interventions listed above will be compared to one another. Additionally, management strategies including treatment with: • conventional DMARDs (such as methotrexate, sulfasalazine, leflunomide) • biologic agents (including tocilizumab, golimumab, and certolizumab pegol)

Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage • pain • mortality • fatigue • radiological progression • extra-articular manifestations of the 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 evidence allows, the appraisal will consider subgroups of people identified as having had primary or secondary failure of response to the first TNF inhibitor. If evidence allows, the appraisal will consider subgroups of people identified as sero-negative or sero-positive. If the evidence allows, the appraisal will include the costs of joint replacement therapy and hospital admissions. Guidance will only be issued in accordance with the marketing authorisations.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 36, March 2002, Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. Technology Appraisal No. 126, August 2007, Rituximab for the treatment of rheumatoid arthritis. Technology Appraisal No.130, October 2007, Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Technology Appraisal No. 141, April 2008, Abatacept for the treatment of rheumatoid arthritis. Ongoing Technology Appraisals: Technology Appraisal in Preparation, Tocilizumab for the treatment of rheumatoid arthritis (Earliest anticipated date of publication October 2009). Technology Appraisal in Preparation, Golimumab for the treatment of people with rheumatoid arthritis who are methotrexate naïve (Earliest anticipated date of publication January 2010). Technology Appraisal in Preparation, Golimumab for the treatment of people with rheumatoid arthritis that has failed to respond to previous anti rheumatic drugs (Earliest anticipated date of publication tbc). Technology Appraisal in Preparation, Certolizumab pegol for the treatment of rheumatoid arthritis (Earliest anticipated date of publication February 2010). Related Guidelines: Clinical Guideline No. 79, February 2009, Rheumatoid arthritis in adults. (Earliest anticipated date of publication February 2009).

Questions for consultation

NICE intends to include reviews of the current guidance for rituximab and abatacept (TA 126 and TA 141) in this appraisal. We welcome comments on the appropriateness of reviewing these technologies in this appraisal.

Have the most appropriate comparators for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor been included in the scope? Are the comparators listed routinely used in clinical practice?

Are the subgroups included in the ‘Other Considerations’ section appropriate?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?