NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247)

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept 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 England. 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.

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). DMARDs may be broadly classed as either conventional or biologic. Conventional DMARDs include methotrexate, leflunomide and sulfasalazine, while the latter group includes, but is not

[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; Technology Appraisal No. 224 (Terminated June 2011), Golimumab for the treatment of methotrexate-naïve rheumatoid arthritis; Technology Apraisal No. 234, Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs; 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; and Technology Appraisal No. 247 (rapid review of TA 198), February 2012, Tocilizumab for the treatment of rheumatoid arthritis.

limited to, tumour necrosis factor (TNF) inhibitors. DMARDs 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 and induce disease remission, 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. TA247 recommends tocilizumab as a potential alternative to TNF-inhibitors in the same circumstances as in TA130, that is in patients with a DAS28 score greater than 5.1, after a trial of two conventional DMARDs. NICE guidance TA 234 does not recommend the use of abatacept in people with rheumatoid arthritis after the failure of conventional DMARDs only. Terminated NICE guidance TA 224 was unable to issue recommendations for the use of golimumab in people with rheumatoid arthritis that has not been treated with methotrexate. 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.

Tocilizumab inhibits the activity of the cytokine interleukin-6 (IL-6), a pro-inflammatory that is also partly responsible for damage to the joints in rheumatoid arthritis.

Abatacept is a selective modulator of the T lymphocyte activation pathway. It binds to molecules on the surface of antigen presenting cells preventing full activation of the T lymphocytes and interrupting the inflammatory process.

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.

Abatacept (Orencia, Bristol-Myers Squibb) in combination with methotrexate has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more DMARDs including methotrexate or a tumour necrosis factor-alpha inhibitor. It is administered by intravenous infusion and is currently in development for subcutaneous administration.

Tocilizumab (RoActemra, Roche), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active

rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or tumour necrosis factor antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate. Tocilizumab is administered by intravenous infusion.

Interventions	For rheumatoid arthritis not previously treated with methotrexate, or other DMARDs: • Adalimumab • Etanercept • Infliximab • Golimumab For rheumatoid arthritis that has been previously treated with conventional DMARDs only: • Adalimumab • Etanercept • Infliximab • Certolizumab pegol • Golimumab • Abatacept (intravenous and subcutaneous formulations) • Tocilizumab
Populations	Adults with severe active rheumatoid arthritis not previously treated with methotrexate, or other DMARDs. Adults with severe active rheumatoid arthritis that has been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate) Adults with moderate to severe active rheumatoid arthritis that has been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate)
Comparators	For severe active rheumatoid arthritis not previously treated with methotrexate, or other 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 severe active rheumatoid arthritis that has been previously treated with conventional DMARDs only: • Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDs and corticosteroids. • The interventions will be compared to each other • Tofacitinib, subject to NICE guidance For moderate to severe active arthritis that has been previously treated with conventional DMARDs only: • Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDs and corticosteroids. • The interventions will be compared to each other • Tofacitinib, subject to NICE guidance
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. Guidance will only be issued in accordance with the marketing authorisation. The sequence of treatments used after the failure of the first biologic treatment should be included as part of the cost effectiveness modelling.
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. Subject to this appraisal review. Technology Appraisal No.186, February 2010, Certolizumab pegol for the treatment of rheumatoid arthritis. Subject to this appraisal review 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 Review proposal date June 2013. Technology Appraisal 224 (Terminated June 2011), Golimumab for the treatment of methotrexate-naïve rheumatoid arthritis. Subject to this appraisal review. Technology Appraisal No 225, Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying anti-rheumatic drugs. Subject to part review in this appraisal review. Other aspects of the guidance have a review proposal date June 2013. Technology Appraisal No 234, Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs. Subject to this appraisal review. Technology Appraisal in 247 (rapid review of TA 198), February 2012, Tocilizumab for the treatment of rheumatoid arthritis. Subject to part review in this appraisal review. Other aspects of the guidance have a review proposal date June 2013.

	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.