NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Health Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept within their marketing authorisations for treating moderate rheumatoid arthritis.

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. Severity of disease can be classified into 4 categories, based on the disease activity score (DAS28) scoring system. A DAS28 greater than 5.1 indicates high disease activity or severe disease, between 3.2 and 5.1 indicates moderate disease activity, less than 3.2 indicates low disease activity, and less than 2.6 indicates disease remission.

The prevalence of rheumatoid arthritis in the UK is estimated to be 0.44% in males and 1.16% in females;[1] which is approximately 450,000 people in England (122,000 males and 328,000 females).[1,2] There are approximately 17,500 people diagnosed with rheumatoid arthritis every year in England.[2,3,4] It can develop at any age, but the peak age of onset in the UK is between 45 and 75 years.[4]

There is no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. 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.

- For people with newly diagnosed rheumatoid arthritis, NICE guideline 100 ('Rheumatoid arthritis in adults: management') recommends monotherapy with conventional disease modifying anti-rheumatic drugs (DMARDs; including oral methotrexate, leflunomide and sulfasalazine) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms.

- When disease remission or low disease activity has not been achieved with DMARD monotherapy it is recommended that additional conventional

DMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) are used in combination.

Biological DMARDs are recommended for people with **severe disease**:

- Where the disease has not responded to intensive combination therapy with conventional DMARDs, NICE Technology appraisal guidance 375, 466, 480 and 485 recommend biological DMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept and sarilumab) or other immunomodulatory therapies (baricitinib and tofacitinib) each in combination with methotrexate. Adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, sarilumab and tofacitinib can be used as monotherapy if methotrexate is not appropriate

- Where the disease has not responded adequately or in the case of intolerance to other DMARDs, including at least one TNF inhibitor (a therapy subset of biological DMARDs), rituximab in combination with methotrexate is recommended (NICE Technology appraisal guidance 195).

- Where rituximab is contraindicated or withdrawn because of an adverse event, biological DMARDs (adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab, certolizumab pegol and sarilumab) or other immunomodulatory therapies (tofacitinib and baricitinib) each in combination with methotrexate are recommended as options (NICE Technology appraisal guidance 195, 225, 247 ,415, 466, 480 and 485).

- Where rituximab therapy cannot be given because methotrexate is not appropriate, biological DMARDs (adalimumab, etanercept, certolizumab pegol and sarilumab) or other immunomodulatory therapies (tofacitinib and baricitinib) each as a monotherapy, can be used (NICE Technology appraisal guidance 195, 415, 466, 480 and 485).

- When the disease has not responded adequately to therapy with rituximab in combination with methotrexate, tocilizumab and sarilumab, both in combination with methotrexate are recommended (NICE Technology appraisal guidance 247 and 485)

Biological DMARDs are not currently recommended in NICE Technology appraisal guidance for people with **moderate disease**.

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, etanercept, infliximab, certolizumab pegol and golimumab all have marketing authorisations in combination with methotrexate or as monotherapy if methotrexate is not appropriate for 'the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate'.

Tocilizumab and abatacept have marketing authorisations in combination with methotrexate or as monotherapy if methotrexate is not appropriate 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 disease-modifying anti-rheumatic drugs or tumour necrosis factor antagonists'.

Intervention(s)	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept
Population(s)	Adults with moderate, active rheumatoid arthritis, whose disease has responded inadequately to, or who are intolerant of conventional DMARDs
Comparators	• The interventions will be compared to each other • Combinations of two or more conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) • Conventional DMARD monotherapy with dose escalation • Best supportive care
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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the interventions will be taken into account.
Other considerations	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals**: Sarilumab for moderate to severe rheumatoid arthritis (2017) NICE Technology Appraisal 485. Tofacitinib for moderate to severe rheumatoid arthritis (2017) NICE Technology Appraisal 480. Baricitinib for moderate to severe rheumatoid arthritis (2017) NICE Technology Appraisal 466. Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (2016) NICE Technology Appraisal 415. Review Date October 2019 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016) NICE Technology Appraisal 375 (previously TA130, TA186 and TA280). Tocilizumab for the treatment of rheumatoid arthritis (2012) NICE Technology Appraisal 247. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease modifying anti-rheumatic drugs. (2011) NICE Technology Appraisal 225. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a

	TNF inhibitor. (2010) NICE Technology Appraisal TA195. **Appraisals in development:** Filgotinib for treating moderate to severe rheumatoid arthritis. NICE technology appraisals guidance [ID1632] Expected publication date: To be confirmed Upadacitinib for treating moderate to severe rheumatoid arthritis. NICE technology appraisals guidance [ID1400] Expected publication date: To be confirmed Sirukumab for previously treated moderate to severe active rheumatoid arthritis NICE technology appraisals guidance [ID1002] (suspended appraisal) Rituximab for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs NICE technology appraisals guidance [ID333] (suspended appraisal) **Related Guidelines:** Rheumatoid arthritis in adults: management (2018) NICE guideline NG100. Review date to be confirmed. **Related Quality Standards:** Rheumatoid arthritis in over 16s (2017) NICE Quality Standard QS33. **Related NICE Pathways:** 'Rheumatoid arthritis' (2019). NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Adult highly specialist rheumatology services [section 5, page 30-32] Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1-5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 National Service Frameworks for Older People: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/198033/National_Service_Framework_for_Older_People.pdf

References

1 Symmons D et al. (2002) The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology 41 (7): 793-800.

2.Office for National Statistics (2019) 'Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2018'. Accessed July 2020.

3. Symmons D et al. (2012) The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the Rheumatic Diseases 72: 1315-1320.

4. Arthritis Research UK Musculoskeletal Calculator. Accessed July 2020.

Appendix A
How we will approach this multiple technology appraisal

Background

This multiple technology appraisal is a partial review of NICE Technology appraisal guidance 375 and includes people with moderate active disease only. A partial review has been recommended because biosimilar versions of adalimumab and etanercept are now available and there have been changes in price for some of the other technologies.

Cost-effectiveness modelling

This partial review will take a pragmatic approach and the committee will assess cost-effectiveness using the original economic model developed by the Assessment Group (School of Health and Related Research, Sheffield) with only minor updates and reflecting the price changes.

The Assessment Group will update the model to address a limitation which means that in the current model, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Targeted submission

We will invite targeted submissions from consultees. These should be limited to:

- comments on the assessment group model
- evidence identified to answer specific questions detailed in the targeted submission template
- comments on the potential for a change in the recommendations for moderate active disease
- comments on whether there any potential equality issues that should be taken into account when considering these treatments.

Except in relation to the specific questions that will be detailed in the targeted evidence submission template, no new clinical effectiveness data will be sought. The companies involved in the review will not be invited to submit cost-effectiveness models.

Engagement on the Assessment Group report

Consultees and commentators will have the opportunity to provide comments on the report produced by the Assessment Group. These comments will be considered by the appraisal committee.