NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA383; TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis

Original publication date:	1 February 2016
Review date	February 2019
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA383, see Appendix A.

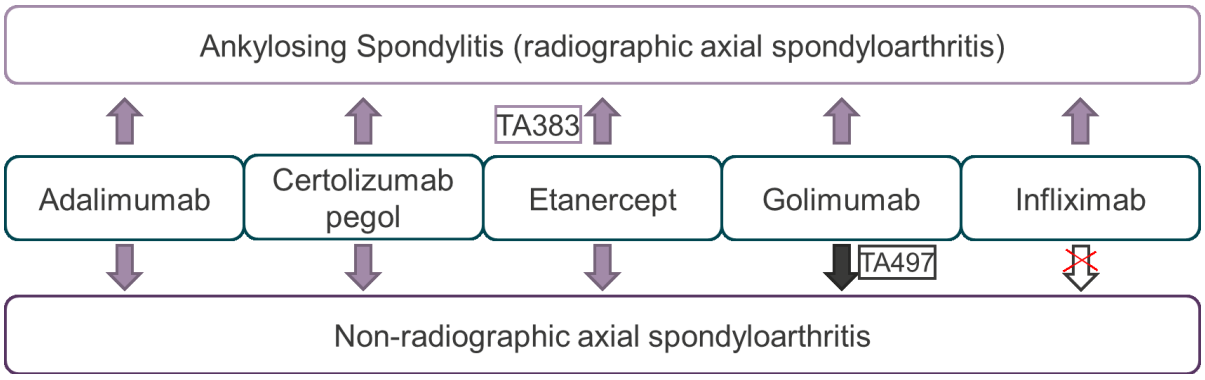
1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

There is no new evidence to suggest the recommendations should change. The guidance has already been incorporated into NG65 Spondyloarthritis in over 16s: diagnosis and management, published in February 2017.

3. Summary of new evidence and implications for review



TA383 recommends 5 TNF-alpha inhibitors for ankylosing spondylitis and 3 TNF-alpha inhibitors for non-radiographic axial spondyloarthritis. There is no new evidence to suggest these recommendations should change. There is new evidence supporting golimumab for non-radiographic axial spondyloarthritis, however this was appraised and recommended later in TA497 and does not fall into the remit of this review of TA383. Infliximab does not have a marketing authorisation for treating non-radiographic axial spondyloarthritis.

Has there been any change to the price of the technologies since the guidance was published?
Adalimumab – The list price of adalimumab has not changed, however in November 2018, biosimilar adalimumab was launched in the UK at a reduced price. The pricing is subject to a tendering process and originator adalimumab is also likely to reduce in price. This is not anticipated to decrease the likelihood of adalimumab being cost effective for the indications in TA383. Certolizumab pegol – The list price of certolizumab pegol has not changed. Certolizumab pegol has a complex patient access scheme which is 12 weeks free of charge stock. This has not changed since publication of TA383 and is unlikely to affect the likelihood of certolizumab pegol being cost effective for these indications. Etanercept – The list price of etanercept has not changed, however in January 2016, 2 biosimilar etanercept products were launched in the UK at a reduced price. This is not anticipated to decrease the likelihood of etanercept being cost effective for the indications in TA383. Golimumab – The list price of golimumab has not changed. Golimumab has a complex patient access scheme which is free stock, a larger dose is provided for patients weighing over 100kg at the same price as the standard dose. This is not anticipated to decrease the likelihood of etanercept being cost effective for the indication in TA383. Infliximab – The list prices of originator and biosimilar infliximab have not changed since the publication of TA383, however the price paid by the NHS is subject to the tendering process and is therefore lower than in TA383. This is not anticipated to decrease the likelihood of infliximab being cost effective for the indication in TA383.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
The marketing authorisation for golimumab has expanded to include an indication for adults with non-radiographic axial spondyloarthritis, however this was appraised in TA497 in January 2018. There are no other proposed changes to the marketing authorisations.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Comparative effectiveness – The committee noted that TNF-alpha inhibitors had broadly similar effectiveness as a class of treatment. Most trials included in the appraisal were compared to placebo and there were no robust head to head comparisons. The committee agreed that infliximab appeared to be more effective at 12 weeks but considered this may be due to the different route of administration. There were no new randomised controlled trials against placebo identified in the literature, there were also no new comparative trials. There are 2 more recent network meta-analyses and indirect comparisons (Ungprasert et al, 2017; Wang et al, 2018) but these were performed using the same evidence base

for the TNF-inhibitors as in TA383. Wang et al (2018) concluded that the apparent increased efficacy of infliximab at 12 weeks had diminished by 24 weeks, supporting the committee's conclusion. Sequential use of TNF-alpha inhibitors – The committee noted that sequential use of TNF-alpha inhibitors was not modelled, however the committee recommended treatment with a second TNF-alpha inhibitor for those whose disease has not responded to the first TNF-alpha inhibitor. A recent systematic review (Cantini et al, 2017) supports this statement, but it notes the paucity of controlled trials measuring outcomes of treatment with a second TNF-alpha inhibitor.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None

The search strategy from the original Assessment report (for MTAs) was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References January 2014 to December 2018. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

The recommendations in TA383 require taking a person's BASDAI and spinal pain visual analogue scale (VAS) scores. The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.

Contributors to this paper:

Information Specialist: Daniel Tuvey

Technical Analyst: Adam Brooke

Associate Director: Nicole Elliott

Project Manager: Emily Richards

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of TNF inhibitors within their licensed indications for treating ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

6. Current guidance

1.1 Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.

1.2 Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs.

1.3 The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

1.4 The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

1.5 Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response.

1.6 When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

Adalimumab
The price of adalimumab is £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8 ml vial (excluding VAT; 'British National Formulary' [BNF] edition 68). The annual cost of treatment with adalimumab is estimated at £9156, assuming the patient has 40 mg every other week.

Certolizumab pegol
The price of certolizumab pegol is £357.50 for a 200-mg pre-filled syringe (excluding VAT; BNF edition 68). UCB Pharma has agreed a patient access scheme with the Department of Health. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials. Assuming the recommended dosage is followed (see section 3.7), the annual cost for first year of treatment with certolizumab pegol is estimated at £10,368 (or with the patient access scheme, £6793).

Etanercept
The price of etanercept is £89.38 for a 25-mg pre-filled syringe or a 25-mg vial containing powder for reconstitution (with solvent), and £178.75 for a 50-mg pre-filled pen or pre-filled syringe (excluding VAT; BNF edition 68). The annual cost of treatment with etanercept, using either twice weekly or once weekly dosage frequency (see section 3.10), is estimated at £9296.

Golimumab
The price of golimumab is £762.97 for a 50-mg pre-filled pen or pre-filled syringe and £1525.94 for a 100-mg pre-filled pen (excluding VAT; BNF edition 68). Merck Sharp & Dohme has agreed a patient access scheme with the Department of Health. This will make the 100-mg dose of golimumab available to the NHS at the same cost as the 50-mg dose. Assuming the patient has 50 mg every month, the annual cost of treatment with golimumab is estimated at £9156. Because of the patient access scheme, this cost would remain the same for patients with a body weight greater than 100 kg whose disease does not respond adequately to the 50 mg per month dosage and who subsequently have monthly doses of 100 mg (see section 3.13).

Infliximab
The NHS list price of the infliximab originator (Remicade) is £419.62 for a 100-mg vial containing powder for reconstitution (excluding VAT; BNF edition 68). For a patient with a body weight of 73 kg, the annual cost for first year of treatment with infliximab therapy (including 3 induction doses) is estimated at between £16,785 and

£13,428 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks).

Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion/Napp) have a marketing authorisation in the UK for the same indications. The therapeutic indications, dosage and method of administration for Inflectra and Remsima are identical to those for Remicade. The NHS list price of Inflectra and Remsima is £377.66 for a 100 mg vial. For a patient with a body weight of 73 kg, the annual cost for first year of treatment with Inflectra or Remsima therapy is estimated at between £15,106 and £12,085 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks).

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should bNe flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	*No*

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Spondyloarthritis in over 16s: diagnosis and management (2017) NICE guideline NG65

Apremilast for treating active psoriatic arthritis (2017) NICE technology appraisal guidance 433

Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (2017) NICE technology appraisal guidance 445

Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010) NICE technology appraisal guidance 199

Golimumab for the treatment of psoriatic arthritis (2011) NICE technology appraisal guidance 220

Golimumab for treating non-radiographic axial spondyloarthritis (2018) NICE technology appraisal guidance 497

Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs (2018) NICE technology appraisal guidance 537

Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (2016) NICE technology appraisal guidance 407

Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs (2018) NICE technology appraisal guidance 543

Ustekinumab for treating active psoriatic arthritis (2015) NICE technology appraisal guidance 340

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"Golimumab has a marketing authorisation for non‑radiographic axial spondyloarthritis. However, regulatory approval was received at a late stage in the appraisal process so golimumab was not included for this indication."	Golimumab would now be included for this indication and has the following MA: "Golimumab is indicated for the treatment of adults with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP)

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
	and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs)." However, golimumab is now recommended separately in TA497 The indications and price for all drugs are unchanged.

3. Registered and unpublished trials

Trial name and registration number	Details
A Phase-IV, Multicenter, Noncomparative, Open-Label Study Evaluating the Safety and Efficacy of Golimumab (a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously) in the Treatment of Indian Patients With Active Spondyloarthropathy of Ankylosing Spondylitis or Psoriatic Arthritis (NCT03733925)	100 participants Study Completion Date: January 25, 2021 Not yet recruiting
COmparison of the Effect of Treatment With NSAIDs Added to Anti-TNF Therapy Versus Anti-TNF Therapy Alone on Progression of StrUctural Damage in the Spine Over Two Years in Patients With ankyLosing Spondylitis: a Randomized Controlled Multicentre Trial (NCT02758782)	170 participants Study Completion Date : January 2020 Recruiting
A Multicenter Open-label Study Of Etanercept Withdrawal And Retreatment In Subjects With Non-radiographic Axial Spondyloarthritis Who Achieved Adequate 24 Week Response (NCT02509026)	210 participants Study Completion Date : November 2019 Active, not recruiting

Appendix C

Trial name and registration number	Details
A Multicenter, Open-label (Part A) Followed by a Randomized, Double-blind, Parallel-group, Placebo Controlled Study (Part B) to Evaluate Maintenance of Remission in Subjects With Active Axial Spondyloarthritis (axSpA) Receiving Either Certolizumab Pegol 200 mg Q2W or 200 mg Q4W as Compared to Placebo (NCT02505542)	317 participants Study Completion Date : April 2019 Active, not recruiting
Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Efficacy and Safety of Certolizumab Pegol in Subjects With Active Axial Spondyloarthritis (axSpA) Without X-Ray Evidence of Ankylosing Spondylitis (AS) and Objective Signs of Inflammation (NCT02552212)	736 participants Study Completion Date : April 2020 Active, not recruiting
Rotation or Change of Biotherapy After TNF Blocker Treatment Failure for Axial Spondyloarthritis (NCT03445845)	300 participants Study Completion Date : June 2021 Not yet recruiting

Appendix D – References

Cantini F et al (2017) Second-line biologic therapy optimization in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *Seminars in Arthritis and Rheumatism* 47 (2): 183-192

Ungprasert P et al (2017) Indirect comparisons of the efficacy of biological agents in patients with active ankylosing spondylitis: a systematic review and meta-analysis. *Clinical rheumatology* 36 (7): 1569-1577

Wang R et al (2018) Comparative Efficacy of Tumor Necrosis Factor-alpha Inhibitors in Ankylosing Spondylitis: A Systematic Review and Bayesian Network Metaanalysis. *The Journal of rheumatology* 45 (4): 481-490