

NICE TA implementation guidance – Biologics for ankylosing spondylitis and non-radiographic axial spondyloarthritis

Purpose

Detail local guidance supporting the implementation of NICE technology appraisal* (TA) 383 and TA 407 on biologics for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis (Appendix 1). This guidance has been developed to ensure consistency in provision of treatment across Kent and Medway, using the drug with lowest acquisition cost, taking into account extra-articular manifestations.

This guidance does not specifically address the care of patients with ankylosing spondylitis who do not respond to two TNF-alpha inhibitors and secukinumab, or patients with non-radiographic axial spondyloarthritis who do not respond to two TNF-alpha inhibitors.

What are ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nrAxSpA)?

AS and nrAxSpA are part of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis. Spondyloarthritis can be categorised as having either predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial spondyloarthritis, the predominant symptom is back pain with inflammation of the sacroiliac joints (sacroiliitis) or the spine, or both. Damage is progressive and irreversible and there is increased risk of spinal fracture later in life. Disease is classified as AS if changes to the sacroiliac joints or the spine, or both, can be seen on X-ray. Not everyone with symptoms of axial spondyloarthritis will have changes that can be seen on X-ray. Disease is then classified as nrAxSpA.

Conventional therapy for AS and nrAxSpA includes non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Biologics are typically used when the disease has not responded adequately to conventional therapy. Adalimumab, certolizumab, etanercept, golimumab and infliximab are biologics that inhibit the pro-inflammatory cytokine, tumour necrosis factor (TNF)-alpha. Secukinumab is the first IL-17A inhibitor for the treatment of ankylosing spondylitis, but it is the sixth biologic to be licensed for this indication.

* Regulations require clinical commissioning groups (CCGs), NHS England and local authorities to comply with recommendations in a technology appraisal within 3 months of its date of publication.

What does NICE say?

- NICE TA [383](#) (2016) for the treatment of AS and nrAxSpA recommends the use of adalimumab, certolizumab, etanercept, golimumab and infliximab as treatment options for severe active AS in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Adalimumab, certolizumab and etanercept are recommended as options for treating severe nrAxSpA in adults whose disease has responded inadequately to, or who cannot tolerate NSAIDs.
 - According to TA383, treatment with another 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.
- NICE [TA 407](#) (2016) recommends the use of secukinumab as an option for treating active AS in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF-alpha inhibitors)
 - TA407 does not make recommendations on downstream treatment options in people who cannot tolerate, or whose disease has not responded to, treatment with secukinumab, or whose disease has stopped responding after an initial response
- Treatment with the above biologics 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 2cm or more.

What does professional society guidance say?

According to the British Society of Rheumatology (BSR) guideline on the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics: *in the event of anti-TNF failure due to inefficacy or adverse events, an alternative anti-TNF agent should be offered if clinically appropriate*¹.

What do other CCGs say?

An internet search (undertaken April 2017) identified 11 policies on this topic, covering 51 CCGs (Appendix 2):

[†] BASDAI is a validated, composite index that records patients' responses to 6 questions relating to 5 major symptoms: fatigue, axial pain, peripheral pain, stiffness and enthesitis.

- Four policies (covering 21 CCGs) recommend three lines of treatment with biologics for AS (i.e. two TNF inhibitors and secukinumab) and two lines of treatment with TNF inhibitors for nrAxSpA
- Three policies (covering 17 CCGs) recommend two lines of treatment with biologics for AS or nrAxSpA
- Two policies were developed before TA407 on secukinumab for AS was issued
 - One (covering 6 CCGs) recommended two lines of treatment with TNF inhibitors
 - The other (covering 2 CCGs) recommends second and third line TNF inhibitors for patients with intolerance to, disease non-response to or loss of disease response to previous lines of treatment
- Two policies (covering 5 CCGs) did not explicitly specify the number of lines of treatment commissioned

What do local clinicians think?

Stakeholder engagement has been from the Kent & Medway Rheumatology network.

The consensus from the network is that they support this guidance; however the number of anti-TNF's recommended should be increased to allow up to 4 for some patients. These patients were deemed to be beyond the scope of this guidance given that NICE do not recommend third-line TNF inhibitors; according to the [equality impact assessment](#) undertaken for TA383, the committee concluded that it had insufficient cost effectiveness evidence to allow it to recommend sequential use of TNF-alpha inhibitors as a cost-effective use of NHS resources.

What does the evidence say?

A literature search identified a high-quality systematic review² and a retrospective survey³; results from both are summarised below.

According to a high-quality systematic review (2016) on the clinical effectiveness, safety and cost-effectiveness of anti-TNF agents for the treatment of AS and nrAxSpA, sequential treatment with anti-TNFs can be worthwhile but the drug survival response rates and benefits are reduced with second- and third-line anti-TNFs². However, evidence on the efficacy of second- or third-line anti-TNFs after switching was reported in only a small number of studies. Most of the studies included experience with adalimumab, infliximab and etanercept; small numbers of patients provided data on golimumab and certolizumab.

The review concluded that sequential treatment with anti-TNFs can be worthwhile in patients with AS but the response rates and benefits are reduced with second and third anti-TNFs,

with the proportion of BASDAI 50[‡] responders falling by approximately 10% with each subsequent anti-TNF and the median BASDAI and BASFIs[§] achieved increasing (worsening). The lower efficacy of a second anti-TNF relative to a first is reflected in lower median drug survival and proportion of patients remaining on therapy at 2 years. Despite a further reduction in response and efficacy with a third anti-TNF, drug survival does not fall, suggesting that at this stage in their treatment history, patients may continue with a less than optimally effective anti-TNF given the lack of any better alternative.

A retrospective survey looking at the effectiveness of sequential biologics used in AS revealed that from a cohort of 492 recruited patients treated with anti-TNFs for AS, 18% (n=88) went on to second biologics.³ A further 4 went on to receive a third biologic. Of the patients who switched treatment, 58% responded to second biologics, 3% responded to the third agent (equates to 75% of all patients who went on to receive a third agent), 8% were awaiting assessment, 15% did not achieve adequate response, 16% no documented response.

In conclusion, the currently available evidence does not appear compelling enough to suggest the commissioning of more than two anti-TNF agents per patient. As secukinumab is not an anti-TNF agent, its place in the pathway has been considered separately.

Were any equality issues identified?

See Appendix 3 for more information.

Were any issues of equity identified?

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) noted that consistent with recommendations commonly included in NICE guidance (where appropriate), patients who have already started treatment with a third or subsequent-line anti-TNF agent in the NHS should be able to continue treatment until they and their NHS clinician think it appropriate to stop.

References

1. Hamilton L, Barkham N, Bhalla A et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. *Rheumatology*. 2017;56(2):313-6. Online: <http://rheumatology.oxfordjournals.org/content/early/2016/08/01/rheumatology.kew223.1ong>
2. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor- α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systemic review and

[‡] A BASDAI 50 response equates to a $\geq 50\%$ improvement in BASDAI score.

[§] BASFI = The Bath Ankylosing Spondylitis Functional Index (BASFI) is a patient-assessed, validated, composite index made up of 10 questions that address function and the patient's ability to manage their disease.

economic evaluation. *Health Technol Assess.* 2016;20(9):1-334. Online: <http://www.journalslibrary.nihr.ac.uk/hta/volume-20/issue-9#>

3. Tang EY, Shah P. Effectiveness of Sequential Biologics use in Ankylosing Spondylitis: Result of a Large Retrospective Survey. *Rheumatology* 2015;54 (suppl 1): i138-i139. Online: http://rheumatology.oxfordjournals.org/content/54/suppl_1/i138.2.full

This briefing note was completed by the NEL CSU, Medicines Management team in May 2017.

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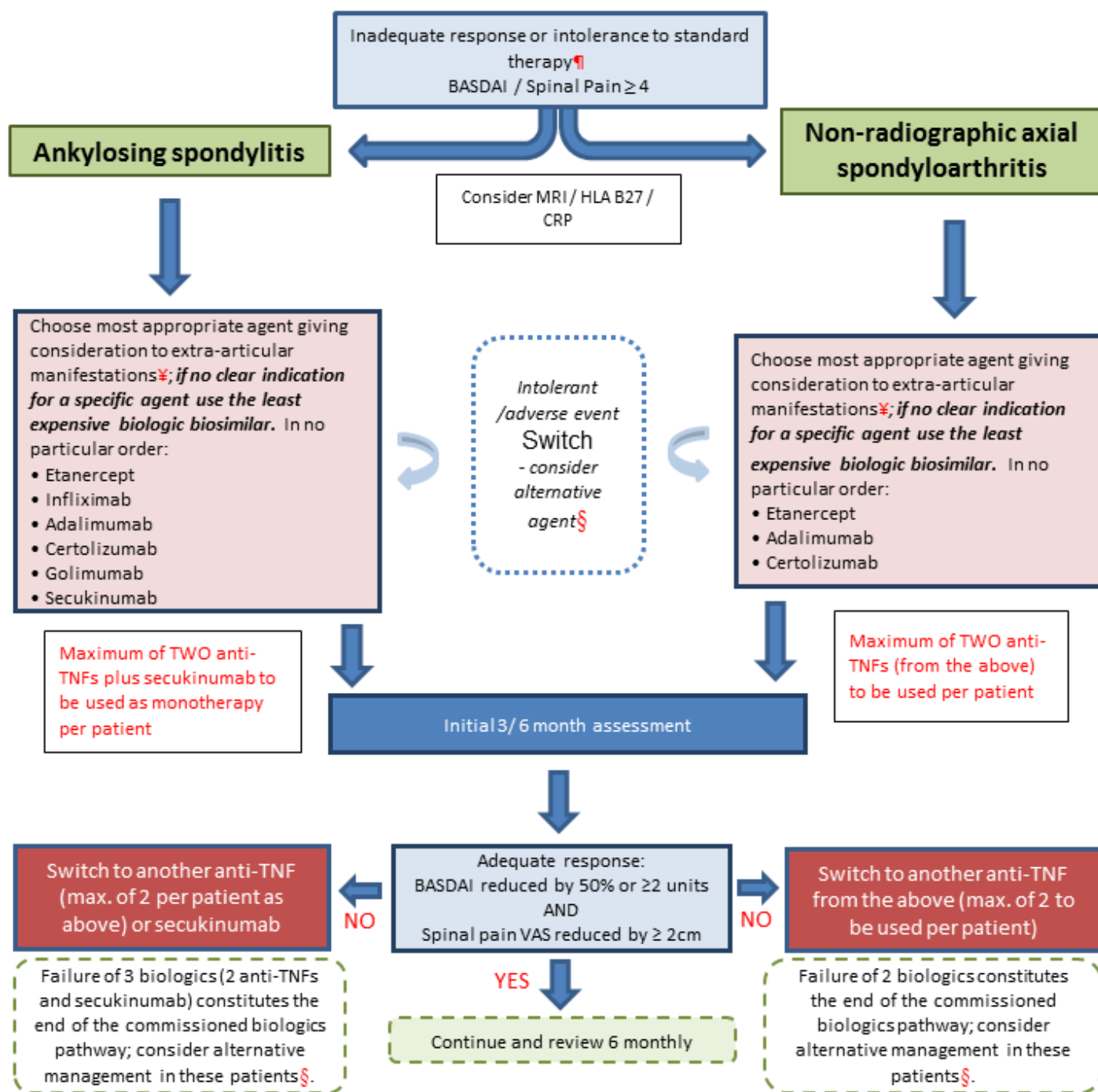
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Appendix 1 – TA implementation guidance: Biologics for ankylosing spondylitis and non-radiographic axial spondyloarthritis*



* This guidance does not specifically address the care of patients with AS who do not respond to two TNF-alpha inhibitors and secukinumab, or patients with nrAxSpA who do not respond to two TNF-alpha inhibitors.

† Standard therapy defined as two NSAIDs for at least two weeks each unless contraindicated. In the event that a patient is unable to complete a BASDAI, the decision to initiate and continue treatment should be based on the treating physician's assessment.

‡ Specific circumstances that may suggest the use of a specific agent:

Etanercept: Potential risk of TB or serious infection

Adalimumab: Uveitis (TA 383), psoriasis (TA 146), IBD (TA 187/329)

Infliximab: IBD (TA 187/329), psoriasis (TA 134), uveitis (TA 383), compliance issues/needle phobia/severely impaired manual dexterity

Golimumab: Consider if patient >100 kg (patient access to double dose), needle phobia/compliance issues/patient convenience (monthly dosing), UC (TA 329)

Certolizumab: Consider for women of child-bearing age contemplating pregnancy (BSR guidelines, 2016)

§ Consider reviewing initial diagnosis in event of poor response.

References: [NICE TA383](#) TNF-alpha inhibitors for AS and nrAxSpA (2016); [NICE TA407](#) Secukinumab for active AS after treatment with NSAIDs or TNF-alpha inhibitors (2016); BSR and BHR [guideline](#) for the treatment of axial spondyloarthritis (including AS) with biologics (2016).

Approved by PRGC May 2017; review date May 2018 or earlier if new information or NICE guidance

Appendix 2 – Other CCG policies

CCG/ organisation	Issue date	Review date	Details
Neighbouring CCGs			
East Sussex Health Economy Formulary (2 CCGs) ¹	Not specified	Not specified	AS or nrAxSpA: Number of lines of treatment with biologics not explicitly specified.
Prescribing Clinical Network (5 Surrey CCGs ² ; Crawley CCG; Horsham and Mid-Sussex CCG)	Dec. 2016	Sept. 2018	AS or nrAxSpA: Two biologics routinely funded; if response criteria are not met following trial of second biologic consider IFR if considered clinically exceptional.
South East London Area Prescribing Committee (6 CCGs) ³	March 2017	March 2018	Seronegative spondyloarthritis: A maximum trial of 2 TNF inhibitors and secukinumab (AS only) is allowed
Other CCGs			
Aylesbury Vale CCG; Chiltern CCG; Buckinghamshire Healthcare NHS Trust.	Jan. 2017	Jan. 2020	AS: A maximum trial of 2 TNF inhibitors and secukinumab is allowed, after which the patient no longer fulfils NICE criteria and will need to discontinue treatment. nrAxSpA: A maximum trial of 2 TNF inhibitors is allowed, after which the patient no longer fulfils NICE criteria and will need to discontinue treatment.
Central and Eastern Cheshire Area Prescribing Committee (3 CCGs) ⁴	Nov. 2016	Nov. 2018	AS or nrAxSpA: Number of lines of treatment with biologics not explicitly specified.
Dorset CCG	2016	Not specified	Spondyloarthritis including AS: Three biologics (secukinumab plus 2 TNF inhibitors) routinely funded.
Greater Manchester Medicines Management Group (12 CCGs) ⁵	Oct. 2016	Not specified	Ankylosing spondylitis (radiographic and non-radiographic): Maximum of three biologics (two TNF inhibitors plus secukinumab if radiographic AS) routinely funded; all other treatment options will require an IFR to be approved prior to treatment being started.
Herts Valleys CCG; East and North Hertfordshire CCG.	June 2016	Static	AS and nrAxSpA: Second and third line TNF inhibitors are commissioned for patients with intolerance to, disease non-response to or loss of disease response to previous lines of treatment. Note that this guidance was developed before TA407 on secukinumab for AS was issued.
Pan Mersey Area Prescribing Committee (7 CCGs) ⁶	Nov. 2016	Nov. 2018	AS or nrAxSpA: Two biologics routinely funded; if response criteria not met following trial of second biologic consider IFR for third TNF inhibitor if considered clinically exceptional circumstances.
South West London Medicines Optimisation Group (6 CCGs) ⁷	July 2016	Not specified	AS or nrAxSpA: Two TNF inhibitors routinely funded (if patient assessed to be intolerant to the TNF inhibitor within the first 12 weeks, an alternative may be considered). If inadequate response at 12 weeks following second TNF inhibitor, treatment should be discontinued. Note that this guidance was developed before TA407 on secukinumab for AS was issued.
Worcestershire Area Prescribing Committee (3 CCGs) ⁸	Oct. 2016	Not specified	AS or nrAxSpA: Failure of 2 biological treatments constitutes the end of the commissioned biologics pathway.

Websites included in this Table were last checked 9 May 2017.¹Members include Hastings and Rother CCG; Eastbourne, Hailsham and Seaford CCG and East Sussex Healthcare NHS Trust. ²East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG. ³Members include Bexley CCG, Bromley CCG, Greenwich CCG, Lambeth CCG, Lewisham CCG, Southwark CCG, Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, South London and Maudsley NHS Foundation Trust, Oxleas NHS Foundation Trust and Lewisham and Greenwich NHS Trust. ⁴Members include Eastern Cheshire CCG, South Cheshire CCG, Vale Royal CCG, Mid Cheshire NHS Foundation Trust and East Cheshire NHS Trust. ⁵Members include North Manchester CCG, Central Manchester CCG, South Manchester CCG, Stockport CCG, Tameside and Glossop CCG, Bolton CCG, Bury CCG, Salford CCG, Wigan CCG, Heywood, Middleton and Rochdale CCG, Trafford CCG, Oldham CCG. ⁶Members include St Helens CCG, Halton CCG, Warrington CCG, Knowsley CCG, Liverpool CCG, South Sefton CCG and Southport and Formby CCG. It is unclear whether West Lancashire CCG is also a member of the Pan Mersey Area Prescribing Committee. ⁷Members include Croydon CCG, Kingston CCG, Wandsworth CCG, Richmond CCG, Sutton CCG, Merton CCG, Croydon Health Services NHS Trust, Epsom and St Helier University Hospitals NHS Trust, Kingston Hospital NHS Foundation Trust, St George's University Hospitals NHS Foundation Trust and the Royal Marsden NHS Foundation Trust. ⁸Members include Redditch and Bromsgrove CCG, South Worcestershire CCG and Wyre Forest CCG.

Appendix 3 – Equality analysis screening tool

Date of assessment	3 May 2017
Assessor name	Kent and Medway Policy Recommendation and Guidance Committee (PRGC)
Name of the guidance	NICE TA implementation guidance – Biologics for ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nrAxSpA)
Aim/Purpose of the guidance	Support implementation of NICE TA383 and TA407 across Kent and Medway

1. Do you consider the policy/function/service development to have an adverse equality impact / health inequality impact on any of the protected groups as defined by the Equality Act 2010? Write either 'yes' or 'no' next to the appropriate group(s)

Protected Group	Yes or No	Protected Group	Yes or No	Protected Group	Yes or No
Age	No	Gender reassignment	No	Marriage/ Civil Partnership (employment matters)	No
Disability	No	Pregnancy/maternity	No	Religion/belief	No
Gender	No	Race	No	Sexual orientation	No


2. If you answered 'yes' to any of the above, give your reasons why

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3. If you answered 'no' to any of the above, give your reasons why

Disability: NICE TA383 on TNF-alpha inhibitors for AS and nrAxSpA, and NICE TA407 on secukinumab for AS both recommend that when using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and spinal pain visual analogue scale (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. This is addressed in the guidance by inclusion of the following comment: *'In the event that a patient is unable to complete a BASDAI, the decision to initiate and continue treatment should be based on the treating physician's assessment.'* No other equality considerations were identified in NICE TA383 or NICE TA407. This local guidance is consistent with recommendations in TA383 and TA407. Regulations require CCGs, NHS England and local authorities to comply with recommendations in a TA within 3 months of its date of publication.

There was no indication during development of this guidance that there is likely to be an adverse equality impact/ health inequality impact on any of the protected groups as defined by the Equality Act 2010.

4. Please indicate if a Full Equality Analysis is recommended		NO ✓	YES
Signature of Project Lead 	Date completed 04/05/2017	IF YES, BEGIN TO GATHER DATA FOR COMPLETION OF A FULL EQUALITY ANALYSIS	
Signature of reviewing CCG Equality and Diversity Lead	Date reviewed		