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# Clinical Guideline

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## Seronegative Spondyloarthropathy Drug Treatment Pathway

### Guideline Summary

This clinical guideline outlines the drug treatment pathway for adult patients with Seronegative Spondyloarthropathy.

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Change History		
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10.10.16	Secukinumab added to pathway as per NICE TA 407	
10.10.16	Added: free of charges schemes, extended interval dosing and biological withdrawal in remission, biologic choice in women planning pregnancy.	
10.10.16	References updated	
1.11.16	Updated as per NICE TA 383 (removed two BASDAI measurements 12 weeks apart pre-biologic therapy)	
09.12.16	Golimumab 50mg twice monthly dosing statement added to notes box	
27.01.17	7 – added information on administration of vaccinations by early outpatient biologic initiation service	
27.01.17	11 – added information on administration of first dose biologic via outpatient clinic and VAT charge to commissioners	
14.3.17	5.3 – Updated as per NICE TA 433 added apremilast as option pre-biologic therapy	
29.6.17	13.1 – Updated as per NICE TA 445 Added secukinumab as option in Psoriatic Arthritis	
8.10.17	Corrected: Assess response at 24 weeks for ustekinumab	
17.10.17	Added updates to choice of biologic 13.1	

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17.10.17	Clarified secukinumab dosing for PsA patients who are inadequate responders to anti-TNF therapy	
22.2.18	5.2 Clarified NSAID treatment prior to biologic initiation (as per NICE)	
22.2.18	5 Updated wording relating to subcutaneous methotrexate use	
22.2.18	13.1 Notes section – updated to include infliximab not commissioned for non-radiographic axial spondyloarthritis	
13.3.18	13.1 Certolizumab added as a second line option for patients with Inflammatory Arthritis with inflammatory bowel disease	
21.12.18	13.1 Tofacitinib added as option for patients with PsA	
Jan-July 2019	Added section 15 - information around treatment options following multiple biologic failures in patients with PsA Amendments made as per discussions at January 2019 and May 2019 pathway group meetings. Added Appendix 1 Best Value Biologic	MPRG, Aug 19
30.11.20	Tofacitinib monotherapy added for PSA (off –label)	
30.11.20	Secukinumab dose escalation added for AS	
July 2021	Covid-19 vaccination information added Ixekizumab added as treatment option for NRAS/AS (NICE TA published) Secukinumab added as treatment option for NRAS (NICE TA published) Guselkumab added as treatment option for PSA (NICE TA published)	
18.2.22	Upadacitinib added as a treatment option for PSA (NICE TA published)	
25.10.22	Risankizumab – added to the pathway as treatment option for PSA (NICE TA published) Guselkumab – updated pathway to remove need for PASI ≥ 10 as NICE TA 711 replaced by TA815 Upadacitinib – added to the pathway as treatment option for AS (NICE TA published) References to “CCG” updated to “ICB” (Integrated Care Board In section 16, reference to B* forms removed and amended to the outcomes monitoring framework	
18.7.23		
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June 2016	Use of sub-cutaneous methotrexate added as an option	SEL
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Aug 2021	Updated in line with latest NICE TAGs – see change history	SEL
Oct 2022	Updated in line with latest NICE TAGs and formation of the ICB – see change history	SEL
Jul 2023	Updated in line with latest NICE TAGs – see change history	SEL

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## 1. Scope

This treatment pathway applies to adult patients with a diagnosis of seronegative spondyloarthropathy who are approaching treatment with biologic therapy.

## 2. Rationale

This treatment pathway provides an evidence based approach for the treatment of seronegative spondyloarthritis whilst maximising cost effectiveness and clinical outcome.

## 3. Principles

This treatment guideline is based on current available national guidance (National Institute for Health and Care Excellence, NICE, and British Society for Rheumatology, BSR), locally approved guidance and is subject to frequent change as guidance is updated and costs change.

**This pathway is correct at the time of publication. NICE Technology Appraisals (TAs) relating to seronegative spondyloarthropathies in adults which are published after the approval date of this guideline will be commissioned no later than 90 days (30 days for fast track TAs) from publication in line with the TA recommendations.**

## 4. Definitions

### 4.1 Adequate response

- Psoriatic Arthritis
  - An improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks\*, one of which has to be *tender or swollen joint count* with no worsening in any of the 4 criteria.
  - A Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks\*, but a PsARC which does not justify continuation of treatment; with review by a dermatologist where skin improvement justifies continuation of treatment.
- Ankylosing Spondylitis
  - Reduction of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units AND reduction of the spinal visual analogue scale (VAS) by 2cm or more.

### 4.2 Inadequate response

- Psoriatic Arthritis
  - Improvement in less than 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks\* or worsening in any of the 4 criteria
  - Not achieving a PASI 75 response at 12 weeks\*
- Ankylosing Spondylitis
  - Less than 50% reduction in the BASDAI score of the pre-treatment value or by less than 2 units OR a less than 2cm reduction in the spinal VAS at 12 weeks\*.

### 4.3 Primary failure – patient does not achieve an adequate response after 12 weeks treatment\*

### 4.4 Secondary failure – patient initially achieves an adequate response after 12 weeks\* but this is not sustained, resulting in an inadequate response.

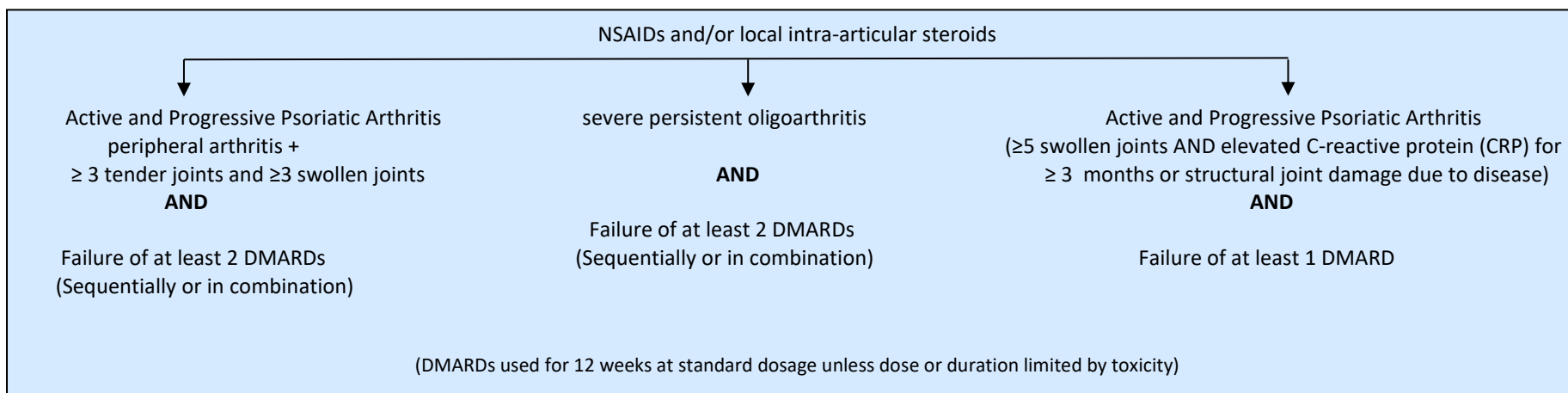
### 4.5 Oligoarthritis

- Persistent pain and swelling of less than 3 joints with failure of 2 Disease Modifying Anti-Rheumatic Drugs (DMARDs), and short-lived or no response to intra-articular corticosteroid.

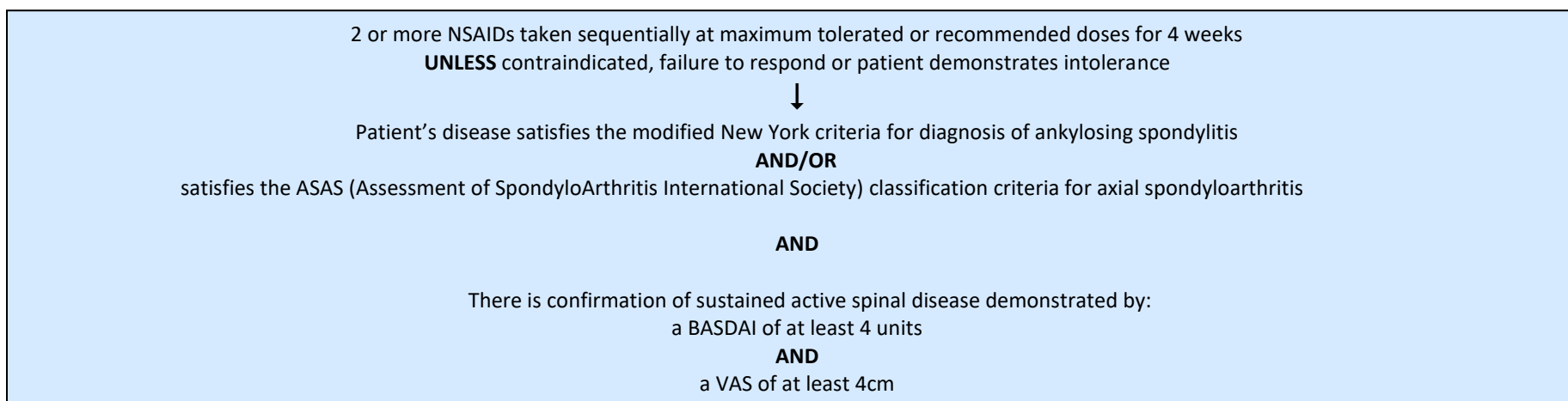
\*Apremilast, secukinumab, ixekizumab, risankizumab – 16 weeks \* Ustekinumab and Guselkumab – 24 weeks

## 5. Pre-biologic therapy [Non-steroidal anti-inflammatory drugs (NSAIDs), steroids, DMARDs or Apremilast]

### 5.1. Psoriatic Arthritis (PsA)



### 5.2. Axial Spondyloarthritis (including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis)



## Strategies for maximising the use of DMARDs prior to apremilast and biologic therapy:

- Adjusting folic acid dose/frequency/formulation to improve tolerance to oral methotrexate (e.g. folic acid liquid 1mg daily except day methotrexate is taken)
- Subcutaneous methotrexate where clinically appropriate (e.g. gastrointestinal adverse effects with oral methotrexate or poor compliance). When used in this situation, subcutaneous methotrexate is billable to ICBs for approved indications.
- Where appropriate, maximum intensification of combination therapy using maximum tolerated doses.

### 5.3 Apremilast in Psoriatic Arthritis

Apremilast, alone or in combination with DMARDs, is recommended as an option for treating active psoriatic arthritis if:

- Peripheral arthritis with  $\geq 3$  tender joints and  $\geq 3$  swollen joints  
AND
- Their disease has not responded to adequate trials of at least 2 DMARDs given either alone or in combination

Assess response at 16 weeks (see section 15).

If minor adverse effects develop at any time or initial response is not sustained (secondary failure) go to section 14.2.

## 6. Pre-biologic Infection screen

- Tuberculosis (T spot or quantiferon and chest x-ray)
- Viral serology: hepatitis B, C and Human Immunodeficiency Virus (HIV)

## 7. [Vaccinations](#) (click for Department of Health and Social Care Green Book)

- Patients should be counselled on the need to **avoid live vaccines** and the implication that may have for travelling. **To avoid inadvertent administration of live vaccines, on receipt of clinic letters GPs should update practice records to indicate the patient is currently receiving biologic treatment.**
- Patients should receive annual influenza vaccine and pandemic influenza vaccine when recommended, and pneumococcal vaccination prior to biologic therapy. This can be prescribed and administered in the community or by the hospital as part of an outpatient biologic initiation service. **GPs must be informed if the hospital administers to outpatients.**
- Patients should be offered the COVID-19 vaccine in line with the Department of Health and Social Care green book guidance [available by clicking here](#).
- Eligible patients may be offered vaccination against shingles (herpes zoster vaccine) in line with Department of Health and Social Care guidelines. Two preparations are available: Shingrex (non-live vaccine) and Zostavax (live vaccine). The live vaccination (Zostavax) **must not be administered** to patients who are prescribed/ have recently stopped biologics, JAK inhibitors, some of the conventional DMARDs or who are on certain doses of corticosteroid. Refer to the [Department of Health and Social Care website](#) for full information, including eligibility criteria and the confirmation as to whether the patient should receive the live or non-live vaccine preparation.

Patients initiated on Janus kinase (JAK) inhibitors should be counselled on the risk of shingles. Patients should be advised to contact their GP urgently if infection is suspected for initiation of aciclovir treatment. The Rheumatology team should inform the GP in writing of the initiation of a JAK inhibitor and advise them of the need for urgent aciclovir treatment in the event of shingles. Current management of patients due to start JAK inhibitors does not include the routine administration of the varicella zoster virus vaccination. Patients who are eligible for the vaccine should be counselled that they should have the vaccine prior to initiation of biologic therapy, if not already done so. This should be documented in communication to the GP and patient.

## 8. Recruitment into clinical trials

Where possible patients should be invited to participate in clinical trials currently recruiting within local rheumatology departments. Where a clinical trial does not meet the requirements of the pathway, approval should be obtained from commissioners prior to initiation.

## 9. Free of charge schemes

New biologics and non-biologic DMARDS are often licensed and made commercially available many months before NICE are due to issue their NICE Technology Appraisal Guidance. Where this situation exists, individual rheumatology departments may enter discussions with the pharmaceutical company to determine if a 'free of charge' (FOC) early access scheme is feasible.

When a FOC is proposed it must satisfy the following criteria:

- The scheme must not replace or override the agreed pathway and the FOC drug should only be considered if pathway options are exhausted or not clinically appropriate
- Fund the treatment at zero cost to the commissioners or negligible cost to the NHS Trust up to and for 90 days after the positive NICE Technology Appraisal Guidance is issued and formally commissioned
- Continue to fund treatment in the event of a negative NICE Technology Appraisal Guidance until
  - 90 days after a future positive NICE Technology Appraisal Guidance
  - Until the rheumatologist considers it no longer clinically appropriate to continue the drug
- All schemes require sign off in each NHS Trust and this usually requires the Chief Pharmacist, the Pharmacy Procurement Lead and Director of Finance to authorise the scheme.

## 10. Extended interval dosing ('off-label' indication) and biologic withdrawal in remission

After discussion with the patient a Consultant may decide to extend the dosage interval or withdraw biologic therapy completely as appropriate for the clinical situation. This may require the use of ultrasound to confirm if the patient is in remission. If patients flare following the extension in dose interval or withdrawal; re-initiation of the previous biologic at the same dosage regimen is acceptable but consider using an alternative agent due to immunogenicity. Whilst a patient maintains remission or low disease activity on an extended dose interval, the Trust can recover a share of the savings from the commissioner. This is subject to local discussion and contractual agreement.

## 11. Method of medication supply

Subject to local arrangements patients may be offered a choice of method of supply. This may include a traditional homecare service or enhanced outpatient pharmacy service via outsourced outpatient pharmacies on main hospital sites. Where there is agreement with pharmaceutical companies, unbundling of homecare and direct procurement via outsourced pharmacies may result in a reduction in the drug acquisition cost. This may further influence the biologic choice at local Trust level.

In order to reduce the time to biologic initiation, the first biologic doses (2 – 4 weeks supply) may be given in clinic as part of an outpatient biologic initiation service. This provides sufficient supply, improved patient training and assessment in clinic prior to initiation on homecare. As the first dose(s) are administered in the outpatient clinic, the cost will incur VAT and this will be passed onto commissioners.

## 12. Biologic choice in women planning pregnancy

Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer when compared with other tumour necrosis factor  $\alpha$  (TNF) inhibitors. For these reasons it is the biologic of choice before, during and after pregnancy (whilst breast feeding). Patients may require to be switched from their current biologic to certolizumab pegol in advance of conception. This should not count as a routine biologic switch and is subject to clinical judgment. Certolizumab should be stopped approximately 2 weeks

before the expected delivery date of the baby and restarted once fully healed from any pregnancy trauma or surgical intervention.

Adalimumab and etanercept are compatible with the first and second trimesters of pregnancy. Female patients of child-bearing potential or pregnant and stable on either of these TNF inhibitors will have their biologic therapy reviewed with their clinician regularly as it may be clinically more appropriate to remain on their current regimen rather than switch therapy. Treatment can then be stopped temporarily in the third trimester.

For further recommendations on biologic or DMARD choice in pregnancy or breast feeding, refer to the British Society for Rheumatology (BSR) / British Health Professionals in Rheumatology (BHPR) guideline.

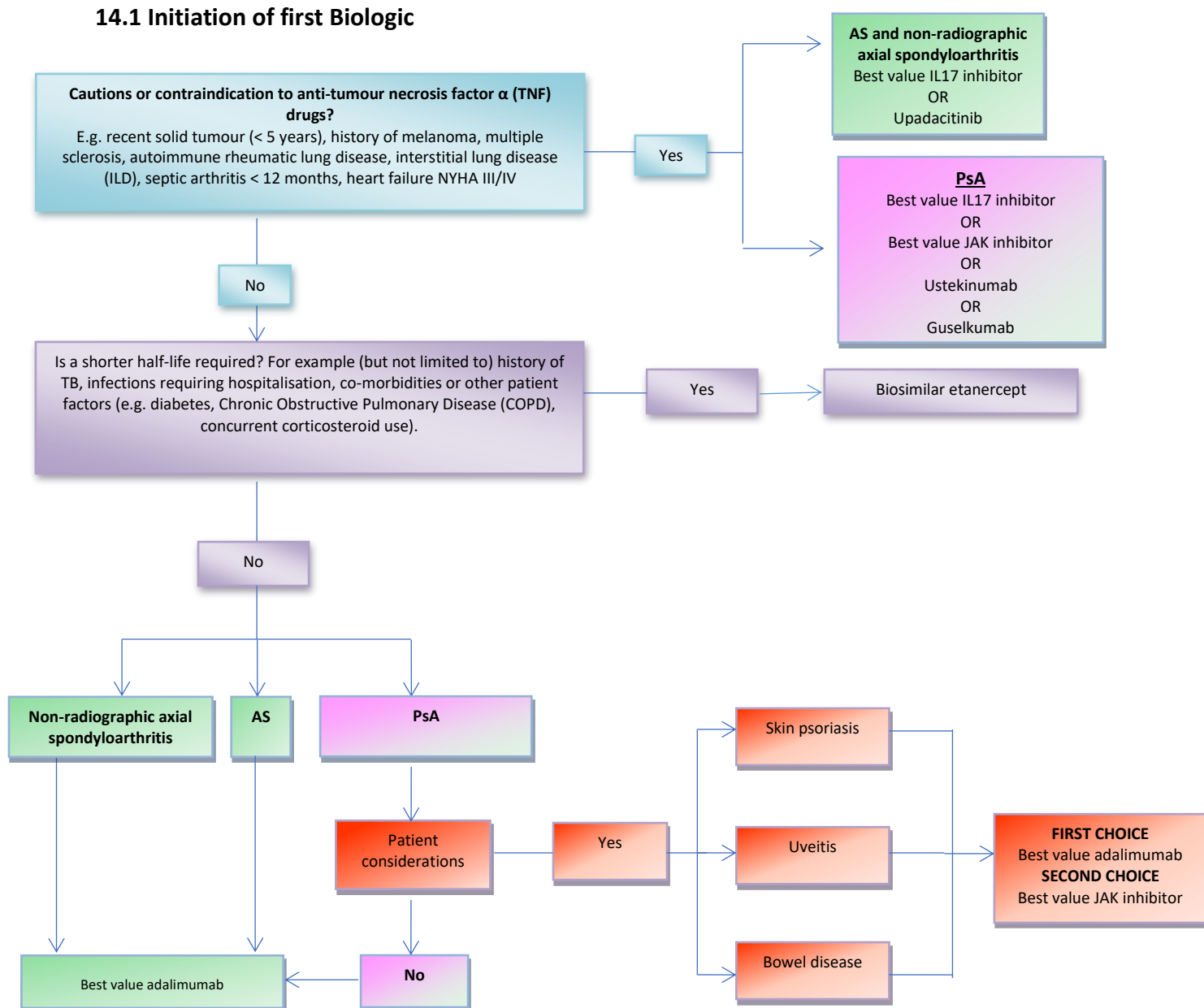
<http://www.rheumatology.org.uk/resources/guidelines/default.aspx>

### 13. **MHRA drug safety updates**

Some of the drugs included in this pathway are subject to MHRA drug safety updates which should be taken into account by the prescriber when initiating or switching therapy. Further information can be found on the MHRA website: <https://www.gov.uk/drug-safety-update>.

## Biologic Treatment Pathways

### 14.1 Initiation of first Biologic



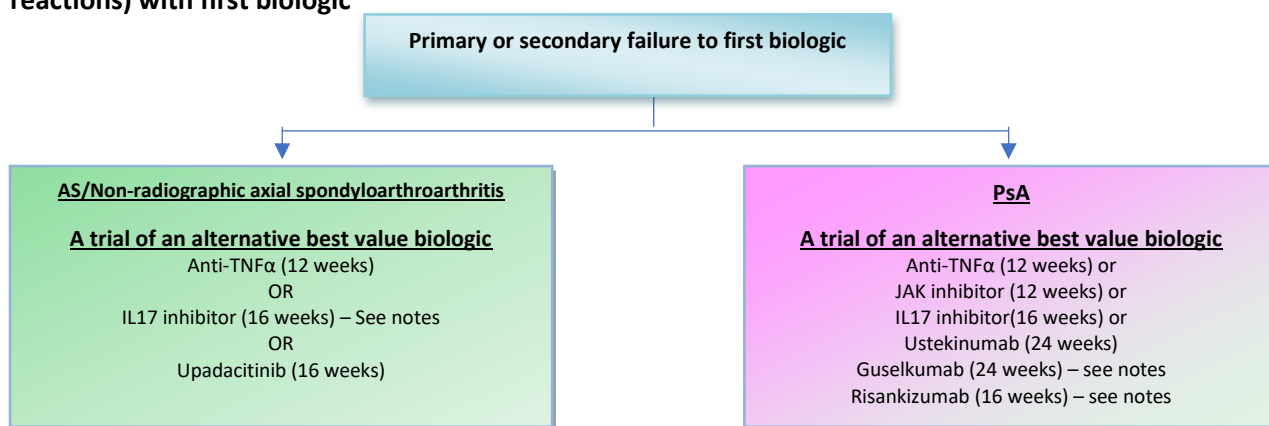
#### NOTES

1. If unable to administer subcutaneous injection or history of poor adherence consider intravenous biosimilar infliximab (AS or PsA) or tofacitinib/ upadacitinib (PsA only).
2. Infliximab is not commissioned for use in non-radiographic axial spondyloarthritis. IL-17 inhibitors (secukinumab and ixekizumab) may be used where there are objective signs of inflammation (i.e. elevated CRP or MRI).
3. Certolizumab pegol first line in pregnancy see section 12.
4. Avoid IL-17 inhibitor in inflammatory bowel disease.
5. For PSA, Upadacitinib should be used in preference to tofacitinib for patients who are not on methotrexate. Tofacitinib may be used as monotherapy where methotrexate is not tolerated or is contraindicated (off-label use) if upadacitinib is not appropriate.
6. Ixekizumab – if patient has severe psoriasis liaise with dermatology for prescribing to allow access to optimal dose.
7. The second choice agent should be used if there are patient contra-indications or specific clinical factors that make it more preferable than first choice options; tofacitinib is an option where an oral agent is preferred to improve compliance and concordance, and based on individual patient factors.
8. See Best Value Biologic table in **Appendix 1** for further information on drug selection

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## 4.2 Primary or Secondary Failure (loss of efficacy) or minor adverse effects (e.g. injection site reactions) with first biologic



### NOTES

1. For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders, the recommended dose of secukinumab is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing
2. Ixekizumab – if psoriasis main issue then liaise with Dermatologists to consider prescription of higher dose. If higher dose appropriate; prescribing should be taken over by the Dermatology team.
3. IL-17 inhibitor – Secukinumab is commissioned for AS/NRAS; Ixekizumab is commissioned for AS only
4. Risankizumab – In addition to  $\geq 3$  tender and  $\geq 3$  swollen joints the patient must have concomitant moderate to severe psoriasis defined as a BSA of  $\geq 3\%$  & PASI > 10. Patient must also have failed 2 conventional DMARDs and 1 biological DMARD. Patient's with an insufficient PASI should be referred to Dermatology in the presence of psoriasis on high impact sites as they may be able to access treatment in line with criteria in the local [psoriasis treatment pathway](#).

#### 5. Guselkumab dose escalation

The standard dose is 100mg every 8 weeks. The dose may be escalated to 100mg every 4 weeks if the following criteria are met:

- The patient has had a partial response to guselkumab 100mg 8 weekly as determined by a Rheumatology consultant after 16 weeks of therapy
- The patient has previously failed or has a contraindication to anti-TNF and IL-17 inhibition
- The patient has objective evidence of synovitis and is considered to be at high risk of joint damage as assessed by a Consultant Rheumatologist
- The decision to escalate treatment is made in conjunction with the MDT, including input from the Dermatology team
- Clinical audit or Blueteq will be used to monitor outcomes and usage
- Response to the escalated dose must be assessed between 16-24 weeks. Treatment should be stopped if there is no improvement in disease activity defined as:
  - Improvement in at least two of the four PsARC criteria (one of which must be joint tenderness or swelling) with no worsening in any of the four criteria when compared to baseline
- Ongoing treatment should be assessed at least 6 monthly, and dose de-escalation should be considered at regular intervals.

#### 6. Secukinumab dose escalation

The standard dose is 150mg monthly when treating ankylosing spondylitis and when treating anti-TNF naïve psoriatic arthritis patients.

The dose may be escalated to 300mg monthly if the following criteria are met:

- The patient has had a partial response to secukinumab 150mg as determined by a Rheumatology consultant after **at least** 16 weeks of therapy **and**
  - In the case of ankylosing spondylitis the patient has previously failed or has a contraindication to anti-TNF, **or**
  - In the case of psoriatic arthritis the patient has a contraindication to anti-TNF
- The decision to escalate treatment is made in conjunction with the MDT
- Clinical audit or Blueteq will be used to monitor outcomes and usage

Response to the escalated dose must be assessed after 16 weeks. Treatment should be stopped if there is no improvement in disease activity defined as:

- Improvement in at least two of the four PsARC criteria (one of which must be joint tenderness or swelling) with no worsening in any of the four criteria when compared to baseline for **psoriatic arthritis patients**
- A greater than 50% reduction in the BASDAI score of the baseline value, OR by 2 unit and 2cm reduction in BASDAI and spinal VAS

## 15. Assessment of Response following initiation of biologic

Psoriatic Arthritis	PsARC – response in 2 out of 4 PsARC criteria with no worsening in any of the 4 criteria OR PASI 75 response + dermatologist review of skin response				
Anti-TNF $\alpha$ inhibitor	JAK inhibitor	Apremilast	IL17 inhibitor	Guselkumab/ Risankizumab	Ustekinumab
12 weeks		16 weeks		16-24 weeks	24 weeks

Ankylosing Spondylitis	Reduction of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units AND reduction of the spinal visual analogue scale (VAS) by 2cm or more.				
Anti-TNF $\alpha$			IL17 inhibitor/ Upadacitinib		
12 weeks			16 weeks		

Continue to assess response every 6 to 12 months if adequate response achieved. Treatment should be stopped and switched to alternative biologic if adequate response not achieved.

## 16. Treatment options following multiple biologic treatment failures including where biologics are contraindicated, not tolerated or in cases of hypersensitivity in PsA and AS

For a small number of patients all pathway therapeutic options may be exhausted, the following is recommended for this patient cohort:

- Consultant rheumatologist to determine if active disease present.
- Consider novel agents if accessible via clinical trials or free of charge patient access schemes
- Revert back to biologic that delivered best clinical outcomes or use alternative biologic in same mode of action class with lowest acquisition costs.
  - Decision should be made in a multidisciplinary team (MDT) discussion in the local rheumatology department.
  - Clinical outcomes will be reported in line with the outcomes monitoring framework.
  - Include concurrent corticosteroid dose or use of methylprednisolone in previous 6-12 months.
  - Measure disease activity scores e.g. HAQ, BASDAI, tender and swollen joint counts.

## 17. Monitoring adherence with the guideline

Adherence to this pathway will be reviewed using the South East London Rheumatology Pathways, Outcomes and Monitoring Framework which includes Key Performance Indicators agreed by South East London Integrated Medicines Optimisation Committee. The Rheumatology and Pharmacy Departments may undertake separate clinical audits as part of their annual clinical audit plan.

## 18. Supporting documents

- See relevant local guidelines

## References

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## Consultation Process for the current version

South East London Rheumatology sub-Group: consultation and approval: July 2023

## Appendix 1: Best value biologics cost tool - seronegative spondyloarthropathies

Drug	Mode of action	Route of administration	NICE approval		Intravenous (requiring day case admission)	Cost tier
			AS	PsA		
Pricing tier one						
Adalimumab biosimilar	TNF inhibitor	subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	£
Pricing tier two section						
Etanercept best value product	TNF inhibitor	subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	££
Adalimumab originator	TNF inhibitor	Subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	££
Upadacitinib	Janus kinase inhibitor	oral	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	££
Secukinumab 150mg dosing	IL-17A inhibitor	subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> if anti-TNF naïve 150mg dosing (see notes)	x	££
Tofacitinib	Janus kinase inhibitor	oral	x	<input checked="" type="checkbox"/>	x	££
Pricing tier three section						
Apremilast	Phosphodiesterase 4 (PDE4) inhibitor	oral	x	<input checked="" type="checkbox"/>	x	£££
Etanercept originator	TNF inhibitor	Subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	£££
Infliximab biosimilar	TNF inhibitor	Intravenous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	£££
Secukinumab 300mg dosing	IL-17A inhibitor	subcutaneous	<input checked="" type="checkbox"/> (if failure to respond to 150mg)	<input checked="" type="checkbox"/>	x	£££
Certolizumab	TNF inhibitor	subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	£££
Ixekizumab	IL-17A inhibitor	subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	£££
Guselkumab (including escalated dose)	IL-23 inhibitor	subcutaneous	x	<input checked="" type="checkbox"/>	x	£££
Risankizumab	IL-23 inhibitor	subcutaneous	x	<input checked="" type="checkbox"/>	x	£££
Pricing tier four section						
Golimumab	TNF inhibitor	subcutaneous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	x	££££
Ustekinumab	IL-23 & IL-12 inhibitor	subcutaneous	x	<input checked="" type="checkbox"/>	x	££££
Infliximab originator	TNF inhibitor	intravenous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	££££

Diagnosis key:	
AS	Ankylosing spondylitis
PsA	Psoriatic arthritis

### Notes:

- Choice of best value biologic will be dependent upon a number of factors (for example, contraindications to therapy, co-morbidities and other patient factors). Where more than one agent is suitable for the patient, the agent with the lowest acquisition cost (taking into account method of administration) will be chosen.
- £ rating is a banded price range of £ (low) to ££££ (high)
- Price banding is based on average drug cost per patient per year (average for first 3 years on therapy)
- For anti-TNF naïve patients starting secukinumab the 150mg dose should be initiated, this may be increased to 300mg if failure to respond.