Biologics pathway for ankylosing spondylitis (including non-radiographic axial spondyloarthritis - AS) and psoriatic arthritis PsA)

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Revision history

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Biologics pathway for ankylosing spondyloarthritis (radiographic and non-radiographic) and psoriatic arthritis

1. Introduction

This pathway is to be used as a guideline for the use of biologic agents in ankylosing spondyloarthritis (radiographic and non-radiographic) AS and psoriatic arthritis (PsA). It has been written using up to date published research and evidenced based medicine. This has been a clinical project implemented by the Manchester Academic Health Science Centre (MAHSC) and managed jointly between The University of Manchester and the rheumatology departments at Manchester University Hospital Foundation Trusts (Wythenshawe and MRI).

The flowchart below shows a summary of the pathway:

```
Spondyloarthritis

Ankylosing Spondyloarthritis
Radiographic and non-radiographic

Psoriatic Arthritis

Follow AS pathway

Follow PsA pathway
```

2. Aims

The aims of the harmonised biologics pathway for AS and PsA are:

1. To present the evidence for switching biologic in cases of loss of efficacy in PsA in order to enable consistent evidence based clinical practice and reduce the number of Individual Funding Requests (IFRs) across the region.
2. To illustrate particular instances where the use of a particular biologic drug may be preferred over another, incorporating current safety data.
3. To support use of a 3rd biologic, where one treatment line is stopped within one month of initiation due to severe adverse events (e.g. injection site reaction).
4. To present the evidence and recommendations for dose reduction in patients who have responded to biologics and whose disease is stable.
5. To support the use of biosimilars.
6. To alert clinicians about on-going recruitment into clinical trials/studies where appropriate.
7. Cost containment by using the most appropriate biologic and by supporting the use of biosimilar drugs.

3. NICE guidance

The relevant NICE guidelines links are listed below.

The NICE recommendations also apply to biosimilar products of the technologies that have a marketing authorisation, allowing the use of the biosimilar for the same indication.

When there are a range of suitable treatments that have a positive NICE recommendation, the least expensive should be chosen (taking into account biosimilar availability, administration costs and patient access schemes.)
Any new high-cost drugs or biologics that are approved between GMMMG AS & PsA pathway iterations will be considered for inclusion in this pathway. The use of any new high-cost drugs or biologics prior to inclusion in the pathway should be in accordance with the associated NICE TA.

### 3.1 Ankylosing spondylitis

**NICE (2016): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis TA383**

- Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, 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.

- GMMMG pathway utilises eligibility criteria as set by NICE of:
  - On one occasion, without any change in treatment, there is confirmation of sustained active spinal disease, demonstrated by:
    - Score of ≥ 4 units on BASDAI and
    - ≥ 4cm on 0-10cm spinal pain VAS
    - MR/X-ray evidence of spinal disease

- Adalimumab, certolizumab pegol and etanercept are recommended, 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.

- 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.

- 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.

- 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.

**NICE (2018): Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors TA407**

- Secukinumab is recommended as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

- Assess the response to secukinumab after 16 weeks of treatment and only continue 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.

- 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.

**NICE (2018): Golimumab for treating non-radiographic axial spondyloarthritis TA497**

- Golimumab is recommended, within its marketing authorisation, as an option for treating severe non-radiographic axial spondyloarthritis in adults whose disease has
responded inadequately to, or who cannot tolerate, nonsteroidal anti-inflammatory drugs.

- If patients and their clinicians consider golimumab to be one of a range of suitable treatments, including adalimumab, etanercept and certolizumab pegol, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

- Assess the response to golimumab 12 weeks after the start of treatment. Continue treatment only 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 pretreatment value or by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) score by 2 cm or more.

Infliximab and secukinumab do not have NICE approval for use in adults with severe, active non-radiographic axial spondyloarthritis. They are included in the pathway for use in radiographic axial spondyloarthritis.

### 3.2 Psoriatic arthritis

**NICE (2010): Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis TA199**

**NICE (2011): Golimumab for the treatment of psoriatic arthritis TA220**

- **Etanercept, infliximab, adalimumab and golimumab** are all recommended for the treatment of active and progressive psoriatic arthritis, when the following criteria are met:
  - the person has peripheral arthritis with three or more tender joints and three or more swollen joints. **and**
  - The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination.
  - The manufacturer must provide the 100 mg dose of golimumab at the same cost as the 50 mg dose.

- Treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.

- **Etanercept, adalimumab, golimumab or infliximab** treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with no worsening in any of the four criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response. (see ‘Etanercept and efalizumab for the treatment of adults with psoriasis’ [NICE TA 103], ‘Infliximab for the treatment of adults with psoriasis’ [NICE TA 134] and ‘Adalimumab for the treatment of adults with psoriasis’ [NICE TA 146] for guidance on the use of tumour necrosis factor [TNF] inhibitors in psoriasis).

**NICE (2015): Ustekinumab for treating active psoriatic arthritis TA340**

- Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:
  - treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered
  - the person has had treatment with 1 or more TNF-alpha inhibitors.

- Ustekinumab is recommended only if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.

- Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which
must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response, see NICE (2009): Ustekinumab for the treatment of adults with moderate to severe psoriasis TA180

NICE (2017): Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs; TA445

Certolizumab pegol alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:
   o it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
   o the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has stopped responding after the first 12 weeks

Certolizumab pegol is only recommended if the company provides it as agreed in the patient access scheme.

Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:
   o it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
   o the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or
   o TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NIC TA 199

Secukinumab is only recommended if the company provides it as agreed in the patient access scheme.

NICE (2017): Apremilast for treating active psoriatic arthritis; TA433

Apremilast, alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is recommended as an option for treating active psoriatic arthritis in adults only if:
   o they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
   o their disease has not responded to adequate trials of at least 2 standard DMARDs, given either alone or in combination and
   o the company provides apremilast with the discount agreed in the patient access scheme.

4. **Switching to a second biologic in Psoriatic Arthritis (PsA)** 21-30

   - Evidence for the sequencing of biologic treatments is limited and derived from trials for people with rheumatoid arthritis. NICE concluded that there were insufficient data to make a recommendation on the sequential use of biologics in psoriatic arthritis.
   - There are registries that collect data for the long-term outcomes of treatment with biologics for rheumatoid arthritis and psoriasis. NICE noted the importance of these in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about these treatments in psoriatic arthritis can be captured.
   - NICE TA 340 recommends ustekinumab for treating active psoriatic arthritis in adults when the person has had treatment with one or more anti-TNFs
5. **Biosimilars**


A generic biosimilars position statement has been approved by GMMMG and by the region’s rheumatology centres and is included in this pathway:

**Initiating treatment with a biologic**

- The choice of biologic used should be guided by clinical judgement, national or local guidance and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.

- If more than one treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

- When the biologic treatment has been selected, the least expensive product, either biosimilar or originator should be prescribed.

- If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if required.

- Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.

- In line with MHRA guidelines: [Gov.uk/drug-safety-update/biosimilar-products](https://www.gov.uk/drug-safety-update/biosimilar-products) biologics, including biosimilars must be prescribed by brand name to support on-going pharmacovigilance of the individual products.

- Pharmacovigilance is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the black triangle. Patients prescribed a biologic should be enrolled on to relevant registries which gather data on the safety and effectiveness of the medicine in clinical practice.

**Changing from originator to a biosimilar**

- There is accumulating evidence that patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. This should only be done after discussion and agreement with individual patients with an explanation for the reason for changing.

- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing.

- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

6. **Individual Funding Requests (IFR)***

- IFRs for AS will not be required for a first or second biologic.

- IFRs for PsA will not be required for 1st or 2nd line treatment with a biologic or for ustekinumab after 1 or 2 anti-TNFs.

- All other treatment options will need an IFR to be approved prior to starting treatment.
• Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the PbR excluded high cost drugs will be made by meeting the accepted criteria outlined on completion and submission of a Blueteq form. Any patients who do not meet these criteria will require an individual funding request.

7. Research Recruitment

Consideration should be made to enter patients into observational/clinical studies. All patients initiated on a biosimilar drug are encouraged to be recruited to a biologics register. Many sites recruit into clinical trials for AS and PsA. Below are the longer-term observational studies currently recruiting around the region.

Recruitment into OUTPASS:
(Predictors of treatment response in PsA)
Patients must have PsA according to the Classification Criteria for PsA (CASPAR).
Patients should be about to commence treatment with a biologic therapy.
Patients must be of Northern European Caucasian descent and ≥ 16 years of age.

Recruiting sites:
Wrightington, Wigan Leigh NHS Foundation Trust
Manchester University Hospital NHS Foundation Trust (MRI)
Salford Royal NHS Foundation Trust

Recruitment in BSRBR AS
(Long term safety and efficacy of biologics in AS)
Modified New York criteria for AS (5) or
An imaging-based ASAS definition of inflammatory spondyloarthropathy (6)
≥ 16 years of age
Etanercept, adalimumab and certolizumab pegol only
New starters on biosimilar etanercept are being recruited.
Pathway A: 1st choice biologic agent and primary non-responders for ankylosing spondylitis (radiographic and non-radiographic AS)

3-6 month response assessment:
- Defined as:
  - Reduction of BASDAI to 50% of the pretreatment value or by ≥ 2 units
  - And reduction of spinal pain VAS by ≥ 2cm
  - And tolerated/no adverse effects

**Golimumab:**
- Psoriasis (TA 383)
- Ulcerative colitis (TA 329)
- Enthesitis (TA 392)
- Dactylitis (level II evidence, grade of recommendation C)
- Nail psoriasis (level II evidence, grade of recommendation C)

**Infliximab:**
- Psoriasis (TA 383)
- Ulcerative colitis (TA 329, TA 392)
- Enthesitis (level II evidence, grade of recommendation C)
- Dactylitis (level II evidence, grade of recommendation C)
- Nail psoriasis (level II evidence, grade of recommendation C)

Secukinumab:
- Psoriasis (TA 350)

In alphabetical order below are specific circumstances that may suggest the use of a specific agent (please highlight where applicable):

- **Adalimumab:** Psoriasis (TA 146)
- Crohn's (TA 187)
- Ulcerative colitis (TA 329)
- Uveitis (level II evidence, grade of recommendation B)
- Women of child-bearing age (compatible with first and second trimester of pregnancy)
- Women of child-bearing age (compatible with all three trimesters of pregnancy)
- Dactylitis (level II evidence, grade of recommendation C)
- Enthesitis (level II evidence, grade of recommendation C)
- Nal psoriasis (level II evidence, grade of recommendation C)
- Enter into clinical trial or observational study, where criteria met (e.g. BSRBR AS)

- **Can repeat cycle once**

- If continued NICE response and stable, consider reducing dose of anti-TNFα. Consider drug levels and ADAb if considering reducing dose.

*Intravenous infusion; **monthly dosing; # extrapolated from RA data
Pathway B: Secondary non-responders to biologic therapy for ankylosing spondylitis (radiographic and non-radiographic AS)

Axial SpA secondary non-response: Previous response at 3 months but inadequate response thereafter with a decline in improvement in BASDAI score and increased in spinal pain VAS.

Check compliance/adherence, is the dose weight adjusted? If compliant, consider increasing dose/frequency (case by case evaluation with drug and ADAbs levels). This would require an iFR.

Patient Factors: Device, level of dexterity, frequency, route, compliance/adherence

Adalimumab (TA 383)
Certolizumab (TA 383)
Golimumab (TA 383, TA 497)
Infliximab (TA 383) (only radiographic AS)
Secukinumab (TA 407) (only radiographic AS)

YES: Continue biologic therapy NICE 6 monthly review of treatment
If continued NICE response and stable, consider reducing dose of anti-TNF. Consider drug levels and ADAbs if considering reducing dose.

NO: Switch to etanercept (less immunogenic) or secukinumab (TA 407) (only radiographic AS)

Has the patient used etanercept 1st line?

YES: Continue biologic therapy NICE 6 monthly review of treatment
If continued NICE response and stable, consider reducing dose of anti-TNF. Consider drug levels and ADAbs if considering reducing dose.

NO: Switch to etanercept (less immunogenic) or secukinumab (TA 407) (only radiographic AS)

Developed a CI to biologic or biologic withdrawn due to an adverse event or non-response to biologic?

Secukinumab (TA 407) (only radiographic AS) or anti-TNF if used secukinumab 2nd line

Enter into clinical trial or observational study, where criteria met (e.g., BSRBR AS)

Developed a CI to biologic or biologic withdrawn due to an adverse event or non-response to biologic?

Secukinumab (TA 407) (only radiographic AS) or etanercept if used secukinumab 2nd line

Enter into clinical trial or observational study, where criteria met (e.g., BSRBR AS)

Secondary Non-response: Initial response to drug followed by lack of efficacy with time and adverse reactions such as injection site reactions. Drug trough level: Blood sample collected before drug administration (lowest level). ADAbs: Antidrug antibodies
Psoriatic arthritis secondary non-response: Previous response at 3-6 months but inadequate response thereafter with a decline in improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with worsening in any of the four criteria.

Check compliance/adherence, is the dose weight adjusted? If compliant, consider increasing dose/frequency (case by case evaluation with drug and ADAbs levels). This would also require an IFR.

Patient Factors: Device, level of dexterity, frequency, route, compliance/adherence (review DMAIRD treatment, consider addition of s/c MTX for psoriatic arthritis)

Adalimumab (TA199)
Cetolizumab (TA445)
Golimumab (TA220)
Infliximab (TA199)
Secukinumab (TA445)
Ustekinumab (TA340)

YES

Has the patient used etanercept 1st line?

NO

Switch to etanercept (less immunogenic) or ustekinumab (TA340) or secukinumab (TA445)

NICE 6 monthly review of treatment
If continued NICE response and stable, consider reducing dose of anti-TNF. Consider drug levels and ADAbs if considering reducing dose.

Developed a CI to biologic or biologic withdrawn due to an adverse event or non-response to biologic?

YES

Ustekinumab (TA340) or secukinumab (TA445) or anti-TNF depending on 2nd line biologic

Enter into clinical trial or observational study, where criteria met.

NO

NICE 6 monthly review of treatment
If continued NICE response and stable, consider reducing dose of anti-TNF. Consider drug levels and ADAbs if considering reducing dose.

Developed a CI to biologic or biologic withdrawn due to an adverse event or non-response to biologic?

YES

Ustekinumab (TA340) or secukinumab (TA445) or etanercept depending on 2nd line biologic

Enter into clinical trial or observational study, where criteria met.
Pathway D: secondary non-responders to biologic therapy for psoriatic arthritis - PsA

Psoriatic arthritis secondary non-response: Previous response at 3-6 months but inadequate response thereafter with a decline in improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with worsening in any of the four criteria.

Check compliance/adherence, is the dose weight adjusted? If compliant, consider increasing dose/frequency (case by case evaluation with drug and ADAbs levels). This would also require an IFR.

Patient Factors: Device, level of dexterity, frequency, route, compliance/adherence (review DMARD treatment, consider addition of s/c MTX for psoriatic arthritis)

Adalimumab (TA199)  
Certolizumab (TA445)  
Golimumab (TA220)  
Infliximab (TA199)  
Secukinumab (TA445)  
Ustekinumab (TA340)

Has the patient used etanercept 1st line?

NO  
Switch to etanercept (less immunogenic) or ustekinumab (TA340)

YES

NICE 6 monthly review of treatment  
If continued NICE response and stable, consider reducing dose of anti-TNF. Consider drug levels and ADAbs if considering reducing dose.

Developed a CI to biologic or biologic withdrawn due to an adverse event or non-response to biologic?

YES

Ustekinumab (TA340) or anti-TNF if used ustekinumab 2nd line

Enter into clinical trial or observational study, where criteria met.

NO

Developed a CI to biologic or biologic withdrawn due to an adverse event or non-response to biologic?

YES

Ustekinumab (TA340) or etanercept if used ustekinumab 2nd line

Enter into clinical trial or observational study, where criteria met.

Secondary Non-response: Initial response to drug followed by lack of efficacy with time and adverse reactions such as injection site reactions.  
Drug trough level: Blood sample collected before drug administration (lowest level).  
ADAbs: Antidrug antibodies
8. Contraindications, special warnings and precautions

a) Contraindications to anti-TNF’s (infliximab, golimumab, adalimumab, certolizumab pegol)
   - Moderate or severe heart failure (NYHA class III/IV heart)
   - Tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections
   - History of hypersensitivity to the active substance, to other murine proteins, or to any of the excipients

Special warnings and precautions for use with infliximab
Medicines.org.uk: Infliximab special warnings and precautions

Special warnings and precautions for use with golimumab
Medicines.org.uk: Golimumab special warnings and precautions

Special warnings and precautions for use with adalimumab
Medicines.org.uk: Adalimumab special warnings and precautions

Special warnings and precautions for use with certolizumab pegol
Medicines.org.uk: Certolizumab special warnings and precautions

b) Contraindications to etanercept
   - Hypersensitivity to the active substance or to any of the excipients.
   - Sepsis or risk of sepsis.
   - Treatment with etanercept should not be initiated in patients with active infections including chronic or localised infections.

Special warnings and precautions for use with etanercept
Medicines.org.uk: Etanercept special warnings and precautions

c) Contraindications to ustekinumab
   - Hypersensitivity to the active substance or to any of the excipients.
   - Clinically important, active infection (e.g. active tuberculosis)

Special warnings and precautions for use with ustekinumab
Medicines.org.uk: Ustekinumab special warnings and precautions

d) Contraindications to secukinumab
   - Hypersensitivity to the active substance or to any of the excipients.
   - Clinically important, active infection (e.g. active tuberculosis)

Special warnings and precautions for use with secukinumab
Medicines.org.uk: Secukinumab special warnings and precautions

e) Contraindications to apremilast
   - Hypersensitivity to the active substance or to any of the excipients.
   - Pregnancy

Special warnings and precautions for use with apremilast
https://www.medicines.org.uk/emc/product/3648

Safety Data:
The information on safety data for biologic drugs in PsA and AS has been extrapolated from the published data in RA. Where available in the pathway, disease-specific data has been used to determine the evidence for safety in PsA and AS.
9. Special situations

a) Peri-operative risk

Prevention of potential post-operative infection risk by temporarily stopping a patient’s biologic treatment should be carefully balanced against the possibility of a peri-operative flare of PsA. Should treatment be stopped prior to surgery, consider stopping the drug 3-5 times the half-life for the relevant drug.14 (See table 1)

Treatment should not be restarted post operatively until infection is excluded and the wound is healed.14

Table 1

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Half-life (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>3 (approx 70 hours)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12-14</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9</td>
</tr>
<tr>
<td>Golimumab</td>
<td>12-14</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>14</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Median half-life 3 weeks (15-32 days)</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Median half-life 27 days (18-46 days)</td>
</tr>
</tbody>
</table>

*summary of product characteristics (SPC)

b) Pregnancy and Breast feeding

i) Pregnancy

BSR issued guidance on prescribing drugs in pregnancy and breastfeeding in January 2016: BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding

There is limited data for safety of biologic drugs in pregnancy and lactation.

The decision to continue biologic therapy in pregnancy needs to be individualised. This needs to take into account alternative therapies, the severity of the mother’s condition prior to therapy, the risk of a disease flare caused by cessation of therapy, and the impact of a flare on the mother and the unborn child. This should be discussed by a multi-disciplinary team.

Patients who stop therapy during pregnancy should be re-loaded with biological therapy soon after delivery.

Women of childbearing potential should use effective contraception during treatment.

For secukinumab, effective contraception should continue for at least 20 weeks after treatment. For ustekinumab, effective contraception should continue for at least 15 weeks after treatment.

Consideration should be given to stopping biologic therapy in a woman who becomes pregnant whilst taking a biologic as listed in table 2 below.

Table 2

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Compatible with First Trimester</th>
<th>Compatible with Second/Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Yes</td>
<td>Second but not third</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Yes</td>
<td>Second but not third</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Yes</td>
<td>Stop at 16 weeks</td>
</tr>
<tr>
<td>Golimumab</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Yes</td>
<td>Yes but data limited</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

*summary of product characteristics (SPC)
ii) Breast feeding

There is limited data on compatibility with breast feeding or with paternal exposure.

There is insufficient information on the excretion of biologics in breast milk. Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot be excluded.

A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy should be made taking into account the benefit of breastfeeding to the child and the benefit of therapy to the woman.

The manufacturers recommend that it is not advisable to breast feed during drug treatment or for a specified duration after treatment has stopped. Refer to SPC for individual drugs.

Low levels of infliximab and adalimumab can be detected in breast milk but the level of oral absorption by the infant is unclear. Follow-up of infants exposed in utero and breastfed during maternal infliximab therapy have found no adverse effects and normal development.

It is not known whether golimumab, ustekinumab or secukinumab are excreted in human milk or absorbed systemically after ingestion. Due to the lack of data the manufacturer does not recommend breast feeding during treatment. It is therefore not advisable to breast feed during treatment.

c) Vaccination of infants

Any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible.\(^3\)

In the case of in utero exposure to a biologic medicine, this period should be until the infant is aged 6 months, after which time vaccination should be considered.\(^1\)

MHRA has received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to an anti-TNF in utero; they were probably not known to be immunosuppressed at the time of vaccination.\(^3\)

Current vaccination strategies with non-live vaccines for infants who have been exposed to a biologic medicine in utero do not differ from those for unexposed infants.\(^1\)

The risk of a natural rotavirus infection is high. Although the vaccine is a live attenuated virus, with the exception of severe combined immune-deficiency (SCID), the benefit from vaccination may exceed any risk in other forms of immunosuppression. Therefore, there are very few infants who cannot receive rotavirus vaccine. Vaccination should be discussed on an individual basis.

10. Vaccinations

a) Live vaccines

During biologic therapy, patients should receive influenza vaccine annually and pneumococcal vaccine once. (Check titre every 5-10 years).

The administration of live vaccines is contraindicated in patients on biologic agents. It is safe to administer a live vaccine 4 weeks prior to commencing biologic therapy, when necessary.

There is no contra-indication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

Table 3 shows all live vaccines available in the UK.
Table 3

<table>
<thead>
<tr>
<th>Live Vaccine</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guerin Vaccine</td>
</tr>
<tr>
<td>Measles, Mumps and Rubella combined vaccine (MMR)</td>
<td>MMRvaxPRO®, Priorix®</td>
</tr>
<tr>
<td>Poliomyelitis (Live oral vaccine)</td>
<td>Poliomyelitis Vaccine, live (oral) GSK OPV</td>
</tr>
<tr>
<td>Rotavirus (Live oral vaccine)</td>
<td>Rotarix®</td>
</tr>
<tr>
<td>Typhoid (Live oral vaccine)</td>
<td>Vivotif®</td>
</tr>
<tr>
<td>Varicella-Zoster Vaccine</td>
<td>Varilrix®, Varivax®, Zostavax®</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Stamaril®</td>
</tr>
</tbody>
</table>

When a live vaccine is required by a patient on a biologic, the cessation of treatment may permit a necessary vaccination to be administered. Table 4 shows the time period required to elapse for each biologic therapy, prior to the administration of a live vaccination.

Table 4

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Time to elapse before giving a live vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2 months</td>
</tr>
<tr>
<td>Golimumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1 month</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>3 months</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>6 months</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>6 months</td>
</tr>
</tbody>
</table>

b) Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies.

Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor.

Table 5 below gives a list of non-live vaccines available in the UK.

Table 5

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera Vaccine (Oral preparation only)</td>
<td>Dukural®</td>
</tr>
<tr>
<td>Diptheria</td>
<td>Given as combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation.</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Avaxim®, Epaxal®, Havrix Monodose®, Vaqta Paediatric®</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Engerix®, Fendrix®, HBvaxPRO®</td>
</tr>
<tr>
<td>Hepatitis A and B Combined</td>
<td>Ambrix®, Twinrix®</td>
</tr>
<tr>
<td>Influenza</td>
<td>Agrippal®, Begrivac®, Enzira®, Fluarix®, Fluvirin®, Imuvac®, Influvac® Sub-unit, Mastaflu®, Optaflu® and Virflu®</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Pneumovax II® (Adults and Children over 5 years), Prevenar® (Primary childhood immunisation)</td>
</tr>
<tr>
<td>Poliomyelitis (Injection)</td>
<td>Inactivated Poliomyelitis Vaccine (non-proprietary) IPV</td>
</tr>
<tr>
<td>Meningococcal Group C</td>
<td>Menjugate Kit®, NeisVac-C®</td>
</tr>
<tr>
<td>Meningococcal polysaccharide A,C, W135 and Y vaccine</td>
<td>ACWY Vax®</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabipur®</td>
</tr>
<tr>
<td>Tetanus</td>
<td>*Single preparation no longer available. Combined Adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation given.</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>TicoVac®</td>
</tr>
<tr>
<td>Typhoid (Polysaccharide injection for vaccination)</td>
<td>Typherix®, Typhim Vi®</td>
</tr>
</tbody>
</table>
# 11. Checklist for Patient Screening on Pre-Admission for Biologic Agents

**Name:**………………………………………..**Number:**…………………………………..**Consultant:**………

## Screening Tests Requested in Clinic

<table>
<thead>
<tr>
<th>Test</th>
<th>Y/N</th>
<th>Initial</th>
<th>Results/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC/U&amp;E/LFT/ESR/CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA (If positive also order ENA/dsDNA/C3/C4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV, HBV (surface antigen, core antibody), HCV (antibody test)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella Zoster IgG (If negative inform GP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB screening (p-IFN testing) <strong>ONLY ONCE</strong> (If positive refer to respiratory)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-Ray (within the last 6 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR checked by date</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Screening Questions Asked in Clinic

<table>
<thead>
<tr>
<th>Question</th>
<th>Y/N</th>
<th>Initial</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of heart failure (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of recurrent infections (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of interstitial lung disease (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of multiple sclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cancer (Type/Date when occurred/Date of all clear)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of last mammogram (50yr +) (Encourage patient to visit GP if &gt;3 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of last smear (25yr +) (Encourage patient to visit GP if &gt;3 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous TB/contact (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent travel abroad (i.e. TB high risk countries) Which Country/Dates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of infusion reaction to any agent (To what/type of reaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient education pack given</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient consent to be approached for research</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Education and Funding

<table>
<thead>
<tr>
<th>Education and Funding</th>
<th>Initial</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request for funding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy/breastfeeding advice given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual influenza vaccination advice given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccination advice given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient counselled and educated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homecare system explained and leaflet given</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
12. References


Rahman P, Choquette D, Bensen WG, Kraishi MM, Fortin I, Chow A et al. Prevalence Of Peri-Articular Manifestations (Enthesitis and Dactylitis) and Disease Activity In Psoriatic Arthritis Patients: Impact Of Treatment With TNF Inhibitors In a Real-World Canadian Population. Arthritis Rheum. 65[S10], 345. 25-10-2013.

Ref Type: Abstract


NICE Technology appraisal references
1. NICE TA146- Adalimumab for the treatment of adults with psoriasis
   http://guidance.nice.org.uk/TA146
2. NICE TA199- Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis
   http://guidance.nice.org.uk/TA199
3. NICE TA103 - Etanercept and efalizumab for the treatment of adults with psoriasis
   http://guidance.nice.org.uk/TA103
4. NICE TA134 - Infliximab for the treatment of adults with psoriasis
   http://guidance.nice.org.uk/TA134
5. NICE TA220 - Golimumab for the treatment of psoriatic arthritis
   http://guidance.nice.org.uk/TA220
6. NICE TA 383 – TNF- alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.
   http://guidance.nice.org.uk/TA383
7. NICE TA 340- Ustekinumab for treating psoriatic arthritis
   http://guidance.nice.org.uk/TA340
8. NICE TA 350- Secukinumab for treating moderate to severe plaque psoriasis
   http://guidance.nice.org.uk/TA350
9. NICE TA 180- Ustekinumab for the treatment of adults with moderate to severe psoriasis
   http://guidance.nice.org.uk/TA180
11. NICE (2017): Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs; TA445
12. NICE (2017): Apremilast for treating active psoriatic arthritis; TA433