High cost drugs pathway for adults with psoriasis

Based on GMMMG High cost drugs pathway for psoriasis May 2018 V2.1

Document Number and Version: Version 1.2 October 2018
Date ratified: October 2018
Ratified by: Managed Service Drug and Therapeutics Committee
Next review date: October 2020
Document authors: Ann Sergeant, Consultant Dermatologist
Reviewed by: Duncan Wilson, Senior Clinical Pharmacist
<table>
<thead>
<tr>
<th>Contents Page</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduction</td>
<td>3</td>
</tr>
<tr>
<td>2. Aims</td>
<td>3</td>
</tr>
<tr>
<td>3. NICE guidance</td>
<td>4</td>
</tr>
<tr>
<td>4. SMC advice</td>
<td>5</td>
</tr>
<tr>
<td>5. Clinical reasoning for using biologic drugs</td>
<td>6</td>
</tr>
<tr>
<td>6. Drug choice</td>
<td>6</td>
</tr>
<tr>
<td>a) 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} and 4\textsuperscript{th} choice</td>
<td></td>
</tr>
<tr>
<td>b) Apremilast</td>
<td></td>
</tr>
<tr>
<td>c) Dimethyl fumarate</td>
<td></td>
</tr>
<tr>
<td>7. Biosimilars</td>
<td>8</td>
</tr>
<tr>
<td>8. Research recruitment</td>
<td>8</td>
</tr>
<tr>
<td>9. Biologics treatment flow chart</td>
<td>9</td>
</tr>
<tr>
<td>10. Contraindications, special warnings and precautions</td>
<td>10</td>
</tr>
<tr>
<td>11. Special situations:</td>
<td>11</td>
</tr>
<tr>
<td>a) Peri-operative risk</td>
<td></td>
</tr>
<tr>
<td>b) Pregnancy and breast feeding</td>
<td></td>
</tr>
<tr>
<td>i) Pregnancy</td>
<td></td>
</tr>
<tr>
<td>ii) Breast feeding</td>
<td></td>
</tr>
<tr>
<td>c) Vaccination of infants</td>
<td></td>
</tr>
<tr>
<td>12. Vaccinations</td>
<td>12</td>
</tr>
<tr>
<td>a) Live vaccines</td>
<td></td>
</tr>
<tr>
<td>b) Non-live vaccines</td>
<td></td>
</tr>
<tr>
<td>c) Vaccination scheduling during biologic therapy</td>
<td></td>
</tr>
<tr>
<td>13. Suggested checklist for patient screening for biologic agents</td>
<td>13</td>
</tr>
<tr>
<td>14. References</td>
<td>14</td>
</tr>
</tbody>
</table>
1. Introduction

Psoriasis is a common inflammatory skin condition which is frequently (30%) associated with an inflammatory arthropathy known as psoriatic arthritis (PsA). It is often life ruining if left untreated. Compelling data demonstrate that the impact on quality of life for patients living with psoriasis is comparable or worse than diabetes, heart disease and cancer. Thus, it is imperative that, for those with the most severe disease, effective treatment strategies are utilised.

The National Institute for Health and Care Excellence (NICE) has published individual Health Technology Assessments (HTAs) for the 8 licensed systemic biological therapies for psoriasis; namely adalimumab, etanercept, infliximab (Anti-TNF’s), ustekinumab (IL12/23 inhibitor), secukinumab, ixekizumab and brodalumab (IL 17 inhibitors) and guselkumab (IL 23 inhibitor). See section 3.

Apremilast, (oral phosphodiesterase 4 inhibitor) and dimethyl fumarate have been approved by NICE for use with the same requirements as for the biologic therapies for psoriasis, (see section 5 for further details).

In line with NICE we propose that all biologics can be used 1\textsuperscript{st} line. The 6 core agents in the algorithm are adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab and guselkumab.

The following rarer scenarios are also applicable:

- Infliximab for patients who have unstable disease and rapid control is required.
- Etanercept when infection risk is a significant concern.

2. Aims

The aims of the high cost drug pathway for psoriasis are:

- To present the evidence behind the use of each biologic/high cost drug in order to enable consistent evidence based clinical practice
- To illustrate particular instances where the use of a particular biologic drug may be preferred over another, based on mode of action and current safety data.
- To promote cost containment by using the most appropriate biologic therapy, by supporting the use of biosimilar drugs and by promoting dose reduction, where appropriate.
- To alert clinicians to on-going recruitment into clinical trials/studies where appropriate.
- To improve patient care by ensuring appropriate use of biologics/high cost drugs for psoriasis and reducing the number of dermatology hospital admissions.
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.

**NICE psoriasis pathways overview**

**NICE TA146; Adalimumab for the treatment of adults with psoriasis; June 2008**

Adalimumab is recommended as a treatment option for adults with plaque psoriasis only if:

- their condition is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.

and

- their condition has not improved with other treatments such as ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments

- Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks.

An adequate response is defined as either:

- a 75% reduction in the PASI score (PASI 75) from when treatment started, or
- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment

**NICE TA180: Ustekinumab for the treatment of adults with moderate to severe psoriasis; Sep 2009**

As adalimumab.

**NICE TA103: Etanercept (and efalizumab) for the treatment of adults with psoriasis; July 2006**

As adalimumab.

**NICE TA350: Secukinumab for treating moderate to severe plaque psoriasis; July 2015**

As adalimumab plus:

- The company provides secukinumab with the discount agreed in the patient access scheme
- Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks.

**NICE TA442: Ixekizumab for treating moderate to severe plaque psoriasis; April 2017**

As secukinumab.

**NICE TA511: Brodalumab for treating moderate to severe plaque psoriasis; March 2018**

As secukinumab.

**NICE TA521: Guselkumab for treating moderate to severe plaque psoriasis; June 2018**

As adalimumab plus:

- The company provides guselkumab according to the commercial arrangement
- If patients and their clinicians consider guselkumab to be one of a range of suitable treatments including ixekizumab and secukinumab, the least costly (taking into account administration costs and commercial arrangements) should be chosen

**NICE TA134: Infliximab for the treatment of adults with psoriasis; Jan 2008**
Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met:

- The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18.
- The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments.
- Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.

NICE TA419: Apremilast for treating moderate to severe plaque psoriasis; Nov 2016
As adalimumab plus:
- The company provides apremilast with the discount agreed in the patient access scheme.

MHRA Drug Safety Update: Apremilast (Otezla▼): Risk of suicidal thoughts and behaviour; Feb 2017
- Apremilast is associated with an increased risk of psychiatric symptoms, including depression, suicidal thoughts, and suicidal behaviours.
- Suicidal thoughts and behaviour, including completed suicide, have been reported in patients with or without a history of depression.
- Carefully assess the benefits and risks of starting or continuing treatment in patients with a history of psychiatric symptoms, or in those who are taking other medicines likely to cause psychiatric symptoms.
- Stop treatment if patients experience new psychiatric symptoms or if existing symptoms get worse.
- Advise patients to inform a healthcare professional if they notice changes in their mood.

NICE TA475; Dimethyl fumarate (Skilarence®) for treating moderate to severe plaque psoriasis; September 2017
Dimethyl fumarate is recommended as an option for treating plaque psoriasis in adults, only if the disease:
- is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
- Has not responded to other systemic therapies, including, ciclosporin, methotrexate and PUVA or these options are contraindicated or not tolerated.

4. Scottish Medicines Consortium advice

Links for the most recent SMC advice (within the past 2 years)

Ixekizumab (Talz®) April 2017
Brodalumab (Kyntheum®) May 2018
Guselkumab (Tremfya®) June 2018
Dimethyl fumarate (Skilarence®) April 2018
5. Clinical reasoning for using biologic drugs

- Each of the 6 core drugs targets a different cytokine, or has varying affinity or avidity where the target is the same cytokine: adalimumab (TNF); ustekinumab (IL12/23); guselkumab (IL23); secukinumab (IL17), ixekizumab (IL17), brodalumab (IL17R). It is likely that the key driver of any individual’s disease is one of these 3 cytokines so if one agent fails, a subsequent line of therapy is likely to work. Published data supports this. 2-4
- Each of the 6 drugs has clinical trial data demonstrating a 75% reduction in PASI, (PASI 75) of at least 70%. 5-13
- Ustekinumab, secukinumab and ixekizumab have demonstrated superiority to etanercept in large well-designed clinical trials. 5, 7, 8
- Secukinumab and ixekizumab have demonstrated superiority to ustekinumab in a large well-designed clinical trial. 9, 10
- Guselkumab has demonstrated superiority to adalimumab in a large well-designed clinical trial.11
- Although all 6 drugs are highly efficacious in the short term, biologic drugs do have an attrition rate year on year of approximately 15% such that, if switches are not allowed, longer term disease control, for what is a life-long condition, will be lost. Ustekinumab has a lower attrition rate than adalimumab.11 No such data is currently available for the IL-17 inhibitors.
- Consideration can be given to escalating the dose of biologic therapy in adults when feasible when an inadequate primary response may be due to insufficient drug dosing, for example in obese patients or when psoriasis relapses during the treatment cycle. Take into account that this may be associated with an increased risk of infection. Dose escalation must be within the product license and included in the relevant NICE guidance.
- Ustekinumab and adalimumab have both been shown to be effective following failure of other biologics.2-4
- As secukinumab, ixekizumab, brodalumab and guselkumab have come to the market later, many patients in the clinical trial programmes had failed prior biologics and these biologics were shown to be efficacious in such scenarios. 7-15
- Ongoing research/audit is addressing whether sequential use of the IL-17 inhibitors is effective: a small retrospective study suggests it is16. The pathway will be adapted if it is unsuccessful.
- All 6 drugs have efficacy for psoriatic arthritis 17-23 although the anti-TNF drugs (adalimumab from core set) are the gold standard drugs in this scenario. The anti-IL-17 drugs demonstrate a TNF like response in published clinical trials and may, in time, challenge this position.17, 20,22

6. Drug choice

1st Line

- There are numerous factors which would influence the choice of which drug should be used at which point in the pathway.
- In those with psoriasis without signs of, or risks of psoriatic arthritis, ustekinumab is the 1st line treatment option, in accordance with NICE, on the basis of better drug survival and a now well-established safety record.11
- In those with both psoriasis and PsA (or signs of early PsA / risk of PsA) adalimumab is the 1st line treatment option in accordance with NICE.
- There are other clinical factors which will inform the decision around choice of drug. These include, but are not limited to:
  - Presence of inflammatory bowel disease would mean that caution would be needed when using IL-17 inhibitors
• Body weight – ustekinumab has 2 dosing regimens with those > 100kg getting access to the higher dose of drug; for heavier patients this may be of relevance
• Immunogenicity risk – emerging data show that certain biologics may be neutralised by anti-drug antibodies. It is not immediately clear which populations are at risk of this but ongoing work will help inform this
• Genetic factors - Certain HLA subtypes may make patients more or less likely to respond to biologics

• Whilst safety data is being accrued, IL-17 inhibitors would only be 1st choice options where there are concerns or possible problems with the other 2 drugs e.g. demyelination risk / tuberculosis risk OR when a patient is looking for a very high level of clinical response.
• Local and national access costs also need to be considered as some of the newer therapies are being made available to the NHS at competitive prices. Thus, agents such as secukinumab, ixekizumab, brodalumab and guselkumab may, in a short period of time (1-2 years), be considered 1st line in an increasing range of scenarios as experience is gained in the real world setting.
• Shared decision making between clinicians and patients plays an important role in the choice of treatment. Clinicians and patients should utilise suitable clinical decision aids (e.g. as suggested in the BAD guidelines for biologic therapies 201721) to tailor the most appropriate biologic therapy to the patients’ wishes and values.

2nd Line

NICE guidance recommends considering changing to an alternative biological drug in adults if:
• the psoriasis does not respond adequately to a first biological drug as defined in NICE technology appraisals (at 10 weeks after starting treatment for infliximab, 12 weeks for etanercept, ixekizumab, secukinumab and brodalumab, and 16 weeks for adalimumab, ustekinumab and guselkumab [primary failure]) or
• the first biological drug cannot be tolerated or becomes contraindicated.
• After failing either adalimumab or ustekinumab, either secukinumab, ixekizumab, brodalumab or guselkumab would be used based on the high efficacy levels in psoriasis, as the clinical trial data shows that these agents will work in patients who have failed other biologics and are efficacious for the treatment of PsA.
• If secukinumab, ixekizumab or brodalumab has been used 1st line we would recommend either ustekinumab or adalimumab depending on signs of, or risk of PsA (adalimumab) or not (ustekinumab).
• In the rare scenarios when etanercept or infliximab has been used 1st line we would recommend secukinumab, ixekizumab or brodalumab based on the same logic given above.

3rd and 4th Choice
Choice depends on previous biologics used and the comorbidities of the patient. See clinical factors above (1st choice) when deciding which would be most appropriate.

B) Apremilast
• In patients with significant comorbidities and therefore at higher risk of developing adverse effects OR when laboratory parameters may preclude other therapies, apremilast can be considered as an alternative for patients with either psoriasis alone or psoriasis in combination with PsA.

C) Dimethyl fumarate
• When compared indirectly, dimethyl fumarate is less effective than systemic biologic therapies but it is also less costly.
In patients with a significant risk of infection or significant comorbidities, such as demyelination, OR when laboratory parameters may preclude other therapies, dimethyl fumarate can be considered as an alternative for patients with moderate to severe psoriasis in the absence of psoriatic arthritis.

Fumaderm® is unlicensed for the treatment of psoriasis in the UK, and should no longer be initiated now that Skilarence® is available.

7. Biosimilars

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). You may be expected to retrospectively audit your practice, for which we recommend keeping an accurate record of the cheapest biologic for NHS Fife (and update this on a 6-12 monthly basis).
- 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.
- 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 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 the BADBIR register which gathers data on the safety and effectiveness of the medicine in clinical practice.

Changing from originator to a biosimilar

- There is 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 be done after discussion and agreement with individual patients.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing and in discussion with the hospital pharmacy department.
- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

8. Research Recruitment

British Association of Dermatologists Biologic Interventions Register (BADBIR):

- All patients starting a biologic therapy should be given the opportunity to participate in BADBIR, a national long-term safety registry within 6 months of initiation in accordance with NICE recommendations.

Clinical trials:

- Where possible consideration should be made to enter patients into observational/clinical studies.
- All free of charge schemes and clinical trials should be approved in accordance with trust guidance and in conjunction with the Research and Development Department.
- There must be clear exit criteria that do not place financial burden on the trust and do not raise patients’ expectations of continuation of treatment.
9. Biologics treatment flow chart for psoriasis

Severe PASI ≥10 and DLQI >10

1st line

1st choice if NO signs or risk of PsA
Ustekinumab Review at 16 weeks

1st choice if signs or risk of PsA
Adalimumab Review at 16 weeks

Risk of demyelination /TB or high level of clinical response required
Secukinumab, ixekizumab, brodalumab, guselkumab Review at 12 weeks

If unstable disease and rapid control required
Infliximab Review at 10 weeks

2nd line

If biologic discontinued for criteria listed below *
Adalimumab/Brodalumab/Guselkumab/Ixekizumab/Secukinumab/Ustekinumab
Please refer to section 5 of the main guidance

3rd and 4th line
Choice depends on previous biologics used and the comorbidities of the patient.
Adalimumab/Brodalumab/Guselkumab/Ixekizumab/Secukinumab/Ustekinumab
Please refer to section 5 of the main guidance

*Discontinue if the biologic is not tolerated or becomes contraindicated.
Discontinue if response is not adequate at the review date or there is loss of response.
Adequate response is defined as either:
a 75% reduction in the PASI score from when treatment started or
a 50% reduction in the PASI score and a 5 point reduction in DLQI from start of treatment.

Etanercept is 1st line treatment choice only if there are significant concerns about risk of infection. Review at 12 weeks. If discontinued, follow 2nd line as above.
10. Contraindications, special warnings and precautions

a. Contraindications to anti-TNF’s (infliximab, adalimumab)
   • Moderate to severe heart failure (NYHA class III/IV heart)
   • Active 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 adalimumab:
   Medicines.org.uk: Adalimumab special warnings and precautions

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

b. Contraindications to anti IL-23 (ustekinumab and guselkumab)

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

   Special warnings and precautions for use with guselkumab
   Medicines.org.uk: Guselkumab special warnings and precautions

c. Contraindications to anti-IL-17 (secukinumab, ixekizumab and brodalumab)
   • Hypersensitivity to the active substance or to any of the excipients
   • Active Crohn’s disease
   • Clinically important active infections (e.g. active tuberculosis)

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

   Special warnings and precautions for use with ixekizumab
   Medicines.org.uk: Ixekizumab special warnings and precautions

   Special warnings and precautions for use with brodalumab:
   Medicines.org.uk: Brodalumab special warnings and precautions

d. Contraindications to apremilast
   • Hypersensitivity to the active substance(s) or to any of the excipients
   • Pregnancy

   Special warnings and precautions for use with apremilast:
   Medicines.org.uk: Apremilast special warnings and precautions

e. Contraindications to dimethyl fumarate
   • Hypersensitivity to the active substance or to any excipients
   • Severe gastrointestinal disorders.
   • Severe hepatic or renal impairment.
   • Pregnancy and breast-feeding.

   Special warnings and precautions for use with dimethyl fumarate:
11. 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 psoriasis. Should treatment be stopped prior to surgery, consider stopping the drug 3-5 times the half-life for the relevant drug (Level IV evidence, grade of recommendation C). Treatment should be recommenced post operatively once infection is excluded and the wound is healed (Level IV evidence, grade of recommendation C).

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Half-life*</th>
<th>Time to stop treatment prior to surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>3 days (approx. 70 hours)</td>
<td>9-15 days</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12-14 days</td>
<td>6 – 10 weeks</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9 days</td>
<td>4 – 7 weeks</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Median half-life 3 weeks (15-32 days)</td>
<td>9 – 15 weeks</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Median half-life 27 days (18-46 days)</td>
<td>12 – 19 weeks</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>13 days</td>
<td>6 – 10 weeks</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>11 days</td>
<td>5 – 8 weeks</td>
</tr>
<tr>
<td>Guselkumab</td>
<td>15-18 days</td>
<td>11-13 weeks</td>
</tr>
</tbody>
</table>

*summary of product characteristics (SPC)

b) Pregnancy and breast feeding

i) Pregnancy

There is limited data for safety of biologic drugs in pregnancy and lactation. The decision to continue biologic agents 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 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. Consideration should be given to stopping biologic therapy in a woman who becomes pregnant as listed below:

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Compatible with 1st trimester</th>
<th>Compatible with 2nd/ 3rd 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>Ustekinumab</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Limited data</td>
<td>Limited data</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>Limited data</td>
<td>Limited data</td>
</tr>
<tr>
<td>Apremilast</td>
<td>Limited data</td>
<td>Limited data</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Limited data</td>
<td>Limited data</td>
</tr>
</tbody>
</table>

To ensure low/no levels of drug in cord blood at delivery, etanercept and adalimumab should be avoided in the third trimester and infliximab stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age.

Certolizumab pegol is licensed in the US for use in psoriasis and in the UK for the treatment of psoriatic arthritis. PEGylated anti-TNF has reduced placental transfer compared with other biologic drugs.

ii) Breast feeding
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 breastfeed 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 breastfeed during drug treatment or for the duration specified below after treatment has stopped.

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Time to elapse between stopping treatment and starting breast feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>5 months</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>6 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>15 weeks</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Gusekumab</td>
<td>20 weeks</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>No data</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>No data</td>
</tr>
<tr>
<td>Apremilast</td>
<td>No data</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>No data</td>
</tr>
</tbody>
</table>

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.

In the case of in utero exposure to an anti-TNF and other biological medicines, this period should be until the infant is aged 7 months, after which time vaccination should be considered.

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\textsuperscript{25}.

Current vaccination strategies with non-live vaccines for infants who have been exposed to anti-TNF in utero do not differ from those for unexposed infants\textsuperscript{25}.

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.

Refer to Immunisation Against Infectious Diseases (The Green Book – Chapter 27B).

12. Vaccinations

a) Live vaccines

Please refer to \textit{Immunisation against Infectious Diseases} (The Green Book - Chapter 7).

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.
For patients on established conventional DMARD treatment, immunosuppression treatment should be stopped for 6 months before administration of a live vaccine. Therapy may then be restarted 2 to 4 weeks after the administration of the live vaccine.

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

<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>Etanercept</td>
<td>1 month</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>6 months</td>
</tr>
<tr>
<td>Gusekumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>6 months</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>6 months</td>
</tr>
<tr>
<td>Brodalumab</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.

Please refer to the [Green Book](#) and the ADTC website for a list of non-live vaccines.

**c) Vaccination scheduling during biologic therapy**

Influenza vaccine – receive annually.

Pneumococcal vaccine – receive once.

**13. Checklist for patient screening for pre-biologic**

- [BAD UK Biologics checklist (2014)](#)
References


