Guideline for the Prescribing of Biologic Therapy in adult patients (≥ 16 years) with active and progressive Psoriatic Arthritis (PsA) within NHS Fife
1. Introduction

The management of psoriatic arthritis (PsA) is aimed at suppressing inflammation in all domains of the disease, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis and nail disease involvement. Current practice is aimed at early diagnosis and intervention with disease modifying anti-inflammatory medicines (DMARDs) then, if necessary, progression to biological therapy to suppress persistent inflammation and improve outcomes.

2. Principles

The protocol utilises current available national guidance to optimise treatment in terms of clinical outcomes and cost-effectiveness. Optimal management of all the domains of psoriatic disease is a challenge and will require collaboration between rheumatology and dermatology departments in many cases.

3. Eligibility for treatment with biologic therapy

**Peripheral arthritis (polyarticular disease)**

Patients must:

- Have active arthritis defined as at least three tender and three swollen joints.
- Have failed treatment with at least two conventional DMARDs, administered either individually or in combination. An adequate therapeutic trial is defined as either failure to tolerate a DMARD or active disease despite treatment of at least 12 weeks at the target therapeutic dose of conventional DMARDs (e.g. leflunomide, methotrexate, sulfasalazine or ciclosporin)

**Oligoarthritis**

Biologic therapy should be considered in patients with severe persistent oligoarthritis (fewer than three tender / swollen joints), which has a major demonstrable influence on well-being and who have failed treatment with at least two conventional DMARDs and appropriate intra-articular steroids.

4. Exclusion criteria

Reference should be made to the individual summary of product characteristics for each medicine but important exclusions include:

- Active serious infection
- Septic arthritis of a native joint within the last 12 months or sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ
- New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure (CCF)
- Clear history of demyelinating disease
- Malignancy
- TNF inhibitors are contraindicated in interstitial lung disease
**Extreme caution** needs to be taken in the following circumstances:

- Patients prone to infection for example:
  - Chronic leg ulcers
  - Persistent or recurrent chest infections
  - Indwelling urinary catheter
- Patients with hepatitis B infection (treat with anti-viral if indicated, monitor serum aminotransaminases and HBV DNA load during therapy)
- Patients with hepatitis C infection (monitor serum aminotransaminases and HCV RNA load during therapy)
- Patients who are HIV positive
- Previous TB (consider prophylactic anti-mycobacterial therapy in latent TB)
- Prior history of malignancy unless the malignancy was diagnosed and treated > 10 years ago
- Pre-malignant conditions such as Barrett’s oesophagus, cervical dysplasia and large bowel polyps
- New York Heart Association (NYHA) grade 1 or 2

5. Pre-biologic Screening

The following tests must be completed and reported as normal prior to treatment with biologic therapy:

Exclude TB:
- Chest x-ray (within past 6 months)
- IGRA if any of the following risk factors:
  - Personal/ family history of TB
  - No evidence of BCG
  - Asian/ Eastern European in origin
  - Recent travel to country of high incidence of TB

Hep B surface antigen
Hep B core antibody
Hep C core antigen
HIV
FBC, U&Es, LFTs

6. Blood Monitoring during biologic therapy

<table>
<thead>
<tr>
<th>Anti-TNF, Ustekinumab, Secukinumab</th>
<th>Biologic monotherapy:</th>
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<tr>
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<td>FBC/CRP, U&amp;Es and LFTs one week prior to attending outpatient rheumatology clinic appointments for disease monitoring</td>
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| Biologic plus concomitant cDMARD | FBC/CRP, LFTs and U&Es - Refer to the blood monitoring requirements in the Shared Care Agreement for the particular oral DMARD |
7. Alternative to biologic therapy in PsA

Apremilast (Otezla®) is an oral phophdiesterase-4 inhibitor accepted for restricted use within NHS Scotland either alone or in combination with disease modifying anti-rheumatic drugs (DMARDs), for the treatment of active PsA in adult patients who have had an inadequate response with at least two prior DMARD therapies or who are intolerant of such therapies.

Apremilast may be considered as a suitable treatment option prior to biologic therapy in those patients whom adherence to blood monitoring is considered to be a concern, those patients who would prefer a tablet over injection and as a treatment when other drugs are contraindicated. NB with the emergence of biosimilars, apremilast is now more expensive than some biologic therapy.
8. Biologic Treatment pathway

When a patient is eligible for biologic treatment, a “biologics referral form” is completed and the choice of biologic will be agreed at the Virtual Biologics Clinic (VBC), taking into consideration previous treatment and co-morbidities. The VBC is held on a weekly basis and consists of at least 2 consultant rheumatologists, the rheumatology pharmacist and a rheumatology nurse specialist. The time frame from the decision to start biologic treatment to administration of first injection is 6 weeks. If psoriasis is severe, treatment needs to be agreed with dermatology and share the cost of the biologic.

1<sup>st</sup> line biologic therapy:

- Secukinumab 150mg dose - not to be used in patients with inflammatory bowel disease (IBD).
  - mAB anti-TNF with lowest acquisition cost in patient with IBD – to be discussed with GI.
  - Patients with uveitis to be agreed with Ophthalmology.

2<sup>nd</sup> line biologic therapy:

- In the case of biologic failure, in patients not previously treated with Etanercept (Enbrel or Benepali), Benepali will be considered as the next treatment option unless contraindicated/ not appropriate.
  - mAB anti-TNF with lowest acquisition cost in patients already treated with Etanercept (Enbrel or Benepali)/ patients with IBD.
  - Secukinumab 300mg (if agreed to share costs with Dermatology in severe psoriasis) – not to be used in patients with IBD.

3<sup>rd</sup> line biologic therapy:

- Ustekinumab

4<sup>th</sup> line biologic therapy:

- Abatacept (off-label, blanket ULM form approved)
9. Pregnancy, breast feeding and paternal exposure

Patients who are (or planning to become) pregnant and/or breastfeeding, men planning to conceive and patients who have accidentally conceived should discuss treatment options with their rheumatologist.

- Infliximab may be continued until 16 weeks. Etanercept and adalimumab may be continued until the end of the second trimester.
- 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 compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors (TNFis).
- Golimumab is unlikely to be harmful in the first trimester
- Women should not be discouraged from breast-feeding on TNFis, but caution is recommended until further information is available.
- Based on limited evidence infliximab, etanercept and adalimumab are compatible with paternal exposure

Following 4 neonatal deaths from disseminated BCG or tuberculosis infections after exposure to a TNF-inhibitor in utero, the MHRA have produced advice stating that live attenuated vaccines are contraindicated in infancy up until 6 months following in utero exposure to TNF-inhibitors and other biologics, after which time vaccination should be considered. Any infant who has been exposed to immunosuppressive treatment from the mother 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.

At the point of writing, the only live vaccine, which forms part of immunisation programme, is the rotavirus, and selected infants may also receive the live BCG vaccine if deemed to be at risk of TB. The rheumatologist should include in their correspondence with primary care a statement of their opinion on the patient’s suitability for the vaccine.

- **Ustekinumab**
  - **Women of childbearing potential**
    Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.
  - **Pregnancy**
    There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid use in pregnancy.
  - **Breast-feeding**
    It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is
not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

- **Fertility**
  The effect of ustekinumab on human fertility has not been evaluated. In animal studies neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed.

- **Secukinumab**
  - **Women of childbearing potential**
    Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.
  
  - **Pregnancy**
    There are no adequate data from the use of secukinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Cosentyx in pregnancy.
  
  - **Breast-feeding**
    It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast-feeding to the child and the benefit of Cosentyx therapy to the woman.
  
  - **Fertility**
    The effect of secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

- **Apremilast**
  - **Women of childbearing potential**
    Pregnancy should be excluded before treatment can be initiated. Women of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment.
  
  - **Pregnancy**
    There are limited data about the use of apremilast in pregnant women. Apremilast is contraindicated during pregnancy.
  
  - **Breast-feeding**
    Apremilast was detected in milk of lactating mice. It is not known whether apremilast, or its metabolites, are excreted in human milk. A risk to the breastfed infant cannot be excluded; therefore apremilast should not be used
during breast-feeding.

- **Fertility**
  No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure.

### 10. Peri-operative infection risk

The potential benefit of preventing post-operative infections by stopping biologic treatment prior to surgery should be balanced against the risk of peri-operative flare in PsA disease activity. Should treatment be stopped prior to surgery, this should be stopped at 3 – 5 times the drugs half-life.

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Half life (days)*</th>
<th>Time (weeks)##</th>
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<tbody>
<tr>
<td>Etanercept</td>
<td>3 (approx. 70hours)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>14</td>
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<tr>
<td>Certolizumab</td>
<td>14</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Golimumab</td>
<td>12 +/- 3 days</td>
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<tr>
<td>Infliximab</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Secukinumab</td>
<td>27 (ranging 18 – 46)</td>
<td>11 weeks</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>21 (ranging 15 – 32)</td>
<td>9 weeks</td>
</tr>
</tbody>
</table>

## Time frame agreed within rheumatology department

Biologic therapy can be recommenced 2 weeks after surgery provided there is no evidence of infection and the wound is healing well.

### 11. Vaccination advice

Patients with PsA on immunosuppressive therapy, e.g. DMARD or biologic should be offered pneumococcal vaccine and influenza vaccination. Ideally, these should be administered at least 2 weeks prior to starting methotrexate or a biologic agent. However, treatment should not be delayed as a result of timing of immunisations. In these circumstances, the response rate to a non-live vaccine may be reduced. FRDU advocates patients being treated with immunosuppressant’s should be revaccinated against pneumococcus every five years.

The administration of live attenuated vaccines is contraindicated when administering biologic agents. There is no contraindication for the administration of live vaccines to relatives of patients on immunosuppressant drugs; close contacts should be fully immunised. Public Health England advise that to minimise the risk of infection in immunosuppressed individuals for whom live vaccines are contraindicated, their close contacts should be fully immunised according to the UK schedule, as a matter of priority. Close contacts of severely immunosuppressed individuals should also be offered vaccination against varicella and influenza. This will reduce the risk of exposure of vulnerable individuals to the serious consequences of vaccine-preventable infections.
On ceasing treatment with a TNF-inhibitor, live vaccination is permitted after a period of 3 months (1-2 months in the case of Etanercept). Biologic therapy must not be restarted for at least 2 weeks, preferably 4 weeks following administration of a live attenuated vaccine.

11.1 Herpes zoster (shingles) vaccination

The herpes zoster vaccination (shingles) is a live vaccine and is recommended to those aged 70 years (a catch-up programme is also being rolled out in those aged 70-79). The Green book has updated and it has defined when herpes zoster vaccination is contraindicated in certain immunosuppressed patients, dependent upon the degree of immunosuppression (see below). This means that some PsA patients may be eligible for the vaccine prior to commencing biologic therapy. In these patients, a period of 2 – 4 weeks should be delayed prior to starting biologic therapy.

The herpes zoster vaccine should not be given:

- those who are receiving or have received in the past 12 months biological therapy (e.g. anti-TNF therapy such as alemtuzumab, ofatumumab and rituximab) unless otherwise directed by a specialist - NB see statement above regarding live vaccines.
- those who are receiving or have received in the past 3 months immunosuppressive therapy including
  - short term high-dose corticosteroids (>40mg prednisolone per day for more than 1 week);
  - long term lower dose corticosteroids (>20mg prednisolone per day for more than 14 days)
  - non-biological oral immune modulating drugs e.g. methotrexate >25mg per week, azathioprine >3.0mg/kg/day or 6-mercaptopurine >1.5mg/kg/day

FRDU have agreed that patients on the following DMARD’s are not considered sufficiently immunosuppressed and eligible patients may receive the herpes zoster vaccination.

Herpes zoster vaccination is allowed in eligible patients treated with the following:
- Azathioprine (≤3mg/kg/day)
- Ciclosporin
- Hydroxychloroquine
- Prednisolone (≤20mg per day)
- Patients on combination therapy with 2, 3 or all of the following – hydroxychloroquine, sulphasalazine, methotrexate (≤25mg per week) and Prednisolone (≤20mg per day)
- Leflunomide
- Methotrexate (≤25mg per week)
- Myocrisin (IM gold)
- Patients in combination therapy with Azathioprine (≤3mg/kg/day) and prednisolone (≤20mg per day)

Herpes zoster vaccination is contraindicated in patients treated with the following:
- Any biologic therapy
- Combination therapy not mentioned above e.g. methotrexate and leflunomide
- Cyclophosamide
- Mycophenolate Mofetil (MMF)
- Tacrolimus
12. Outcome measure

The Psoriatic Arthritis Response Criteria (PsARC) with a 66-68 joint count is recommended as the clinical response criteria for peripheral PsA. A PsARC response is defined as improvement in two factors (with at least one being a joint score) with worsening of none of the following four factors:

- Patient global assessment (on a 0-5 Likert Scale)
- Physician global assessment (improvement is defined as decrease by ≥1 unit; worsening defined as increase by ≥1 unit.)
- Tender joint score
- Swollen joint score (improvement defined as decrease by ≥30%, worsening defined as increase ≥30%)

Although the PsARC will be the primary joint response. An ESR or CRP, a patient pain assessment (visual analogue score 0-10cm), will also be done and this will enable a Disease Activity Score (DAS) 28 to be calculated.

Low or minimal disease activity (MDA) is the ultimate goal of therapy. A patient with PsA is in MDA when they meet 5/7 of the following criteria:

- Tender joint count (≤ 1)
- Swollen joint count (≤ 1)
- PASI (≤ 1)
- HAQ (≤ 0.5)
- Tender entheseal points (≤ 1)
- Patient pain VAS (≤ 15)
- Patient global activity VAS (≤ 20)

13. Response criteria

Patients treated with anti-TNF therapy or ustekinumab will be assessed initially after 3 months of treatment. Treatment should be continued in patients who have responded. In the case of non-responders to anti-TNF, consideration will be given to a further 3 months of treatment if there has been a partial response and then continuing therapy if there has been a full response compared to baseline.

Patients on apremilast or secukinumab will be assessed initially after 4 months of treatment. If patient shows no evidence of therapeutic benefit after 16 weeks, therapy should be reconsidered. Treatment should be continued in patients who have responded. In the case of secukinumab, consideration will be given to a further 3 months of treatment if there has been a partial response and then continuing therapy if there has been a full response compared to baseline.

The Rheumatology nurse specialist or Rheumatology pharmacist will assess patients at 3 (or 4) months, and then again at 6 months. Their consultant will then review patients at 9 months following initiation of biologic therapy. Thereafter, patients will be reviewed regularly, at minimum frequency of annual review for stable patients.
If low or MDA is achieved and maintained, discussion can occur between clinician and patient to consider reducing the frequency of administration of biologic therapy. Failure to maintain response will result in increase in frequency of injections, to the previous dose.
References


13. Expert opinion from Dr Derek Sloan, Infectious Disease Consultant, NHS Fife.
