Guideline for the Prescribing of Biologic Therapy in adult patients (≥ 16 years) with severe active axial spondyloarthritis within NHS Fife

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1. Introduction

Axial SpA (axSpA) is a chronic inflammatory condition predominantly involving the spine and sacroiliac joints (SIJ), with or without extra-spinal manifestations including peripheral arthritis, enthesitis, iritis, psoriasis and IBD. Individuals with axSpA experience significant pain, stiffness and lack of function, which translates into important health care costs and increased mortality.

AxSpA can be classified into two subgroups: radiographic axSpA, commonly referred to as AS, and non-radiographic axSpA (nr-axSpA). The primary difference between these two subgroups is the presence or absence of defined structural changes in the SIJ as detected on plain radiography. A diagnosis of AS can be made according to the modified New York criteria when radiographs show at least grade 2 sacroiliitis bilaterally or grade 3 unilaterally, in the presence of appropriate clinical symptoms. In contrast, SIJ radiographs may be completely normal in nr-axSpA. The radiographic changes of AS may take 8 - 10 years to manifest, with a progression rate from nr-axSpA to AS of approximately 12% every 2 years, although some patients with nr-axSpA never develop AS.

The aims of treatment in axSpA are to reduce inflammation, relieve pain and stiffness, preserve spinal mobility and prevent the development of syndesmophytes.

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 axSpA disease is a challenge and will often require collaboration between rheumatology and other specialist departments within NHS Fife in many cases.

3. Eligibility for treatment with biologic therapy

Standard therapy is defined by BSR as two non-steroidal anti-inflammatory drugs (NSAIDs) for at least two weeks unless contraindicated.

Patients with severe active ankylosing spondylitis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

Patients with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI active non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

4. Treatment options

Where possible the biologic with the lowest acquisition cost will be used.

AS:

- TNF-alpha inhibitors: Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab
- Secukinumab
nr-axSpA:

- TNF-alpha inhibitors: Adalimumab, certolizumab pegol, etanercept and golimumab

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 aminotransminases and HBV DNA load during therapy)
- Patients with hepatitis C infection (monitor serum aminotransminases 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
6. Blood Monitoring during biologic therapy

<table>
<thead>
<tr>
<th>Biologic monotherapy:</th>
<th>Biologic plus concomitant cDMARD (if peripheral disease involvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FBC/CRP, U&amp;Es and LFTs one week prior to attending outpatient rheumatology clinic appointments for disease monitoring</td>
<td>• FBC/CRP, LFTs and U&amp;Es Refer to the blood monitoring requirements in the Shared Care Agreement for the particular oral DMARD</td>
</tr>
</tbody>
</table>
7. Biologic Treatment pathway

When a patient is eligible for biologic treatment, the choice of biologic will be agreed at the Virtual Biologics Clinic (VBC), taking into consideration previous treatment and co-morbidities. The VBC will be 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.

1st line biologic therapy:

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

2nd line biologic therapy:

- In the case of biologic failure, in patients not previously treated with Etanercept (Enbrel or Benepali), Etanercept in the form of Benepali will be considered as the next treatment option unless contraindicated/ not appropriate.

  OR

- Secukinumab in patients previously treated Etanercept (Enbrel) – not to be used in patients with IBD.

3rd line biologic therapy:

- An alternative mAB TNF-alpha inhibitor
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 breastfeeding 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.

- **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.

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>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>3 (approx. 70hours)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>14</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>14</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Golimumab</td>
<td>12 +/- 3 days</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>27 (ranging 18 – 46)</td>
<td>11 weeks</td>
</tr>
</tbody>
</table>

* From current Summary of Product Characteristics (available online at http://www.medicines.org.uk/emc/
** 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 to:

- 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.

Shingles vaccinations 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)

Shingles vaccinations contraindicated in patients treated with the following:

- Any biologic therapy

- Leflunomide
- Methotrexate (≤25mg per week)
- Myocrisin (IM gold)

- Patients in combination therapy with Azathioprine (≤3mg/kg/day) and Prednisolone (≤20mg per day)
• Combination therapy not mentioned above e.g. methotrexate and leflunomide
  • Cyclophosphamide
  • Mycophenolate Mofetil (MMF)
  • Tacrolimus

12. Outcome measure

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the spinal pain visual analogue scale (VAS) are used to assess clinical response. Bath Ankylosing Spondylitis Metrology Index is also performed.

Response to treatment is defined as:

• a reduction in the 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.

13. Assessment and monitoring

Patients treated with TNF-alpha inhibitor therapy will be assessed initially after 3 months of treatment, 4 months in the case of secukinumab. Treatment should only be continued if there is clear evidence of response. In patients with a partial response, consider continuing treatment and review patient at 6 months. Change biologic treatment in the case of non-response.

Treatment with another biologic drug 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.

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, every 6 months; then reduce to annual review for stable patients.

If response is maintained and there is no evidence of disease progression, 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


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