Inflammatory Arthritis and Biologic therapy – Ministry of Health (MOH) Recommendations
Biologic Therapy for Inflammatory Arthritis – Ministry of Health Recommendations

Introduction

Chronic inflammatory arthropathies such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS) are associated with significant morbidity and disability. These may result in decreased quality of life, loss of productivity and increased health cost. According to Malaysian data on the burden of disease published in 2004, musculoskeletal disorders ranked 3rd among diseases in females. The total drug expenditure in 2005 for the treatment of inflammatory and rheumatic diseases is RM 50.7 million, ranking 5th as the most prescribed group of drugs and forms 7.8% of the top 40 prescribed drugs in Malaysia (1).

The introduction of anti-tumour necrosis factor (TNF) spawned a new therapeutic era in rheumatology. It has provided another treatment option in controlling disease activity, thus improving patients’ functional status and attenuating structural damage. This will result in potential long term benefits such as improved quality of life and increased prospect of remaining in work.

However, these drugs are expensive and will involve significantly higher demands on the drug budget. The preliminary report from the National Inflammatory Arthritis Registry quoted a 3.9% usage of biologics in RA cohort (2).

Biologics are potent immune modulators and may impact host immunosurveillance adversely, thus increasing susceptibility to infection, among other sequelae. Of particular note, tuberculosis (TB) is one of the potentially serious adverse effects of anti-TNF and will post a public health concern in this country where TB burden is moderately high.

Therefore, there is a need to develop a Malaysian guideline on anti-TNF therapy to address these issues. It is based on the British Society for Rheumatology (BSR) and American College of Rheumatology (ACR) recommendations on the use of anti-TNF therapy in Rheumatoid Arthritis with the emphasis on TB screening prior to commencing and surveillance whilst on anti-TNF.
These recommendations are for rheumatologists in MOH to serve as a guide in their clinical practice.

Currently available anti-TNF in Malaysia

<table>
<thead>
<tr>
<th>Anti TNF</th>
<th>etanercept</th>
<th>infliximab</th>
<th>adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Soluble and membrane-bound TNF and lymphotoxin alpha</td>
<td>Soluble and membrane-bound TNF</td>
<td>Soluble TNF</td>
</tr>
<tr>
<td>Structure</td>
<td>Dimeric fusion protein: human TNF receptor connected to Fe portion of human IgG1</td>
<td>Chimeric mouse/human monoclonal antibody to TNF</td>
<td>Human monoclonal antibody to TNF</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Binds soluble and cell bound TNF, thereby inhibiting the interaction of TNF with cell surface TNF receptors</td>
<td>Binds soluble and cell bound TNF, preventing interaction with cell surface TNF receptors</td>
<td>Binds TNF, thereby interaction with cell surface TNF receptors</td>
</tr>
<tr>
<td>Half-life</td>
<td>4 days</td>
<td>8-9.5 days</td>
<td>11-13.7 days</td>
</tr>
</tbody>
</table>
**Indications in RA (3):**

1. Fulfills criteria for RA (appendix 1A, 1B)

2. Persistent active disease

   DAS 28 > 5.1 (high disease activity) on 2 separate reviews

3. Inability to continue with standard therapy

   • Failure to respond to 2 or more of the standard DMARDs (SSZ, MTX, Leflunomide, HCQ) individually or in combination for at least 6 months, of which at least 2 months is at standard target dose and one of the drugs must include MTX in adequate dose – i.e. 20mg/wk

   • Withdrawal of drug due to intolerance or toxicity

**Indications in PsA (4):**

1. Adult PsA patients (fulfills Moll and Wright criteria with psoriasis and negative rheumatoid factor) with peripheral joint involvement, with or without axial involvement (appendix 2)

2. Persistent active disease

   Three or more tender joints and three or more swollen joints on two separate occasions at least 1 month apart, based on a 78-tender and 76-swollen joint count (note: dactylitis counted as 1 active joint)

3. Inability to continue with standard therapy

   • Failure to respond to 2 or more of the standard DMARDs (SSZ, MTX, cyclosporine or Leflunomide) individually or in combination for at least 6 months, of which at least 2 months is at standard target dose

   • Withdrawal of drug due to intolerance or toxicity
Note: Anti-TNF therapy for PsA with axial-only disease follows the treatment guideline for ankylosing spondylitis in adults

**Indications for Ankylosing Spondylitis (5):**

1. Fulfills Modified New York criteria for AS (appendix 3)
2. Active spinal disease defined as BASDAI of at least 4cm and spinal pain VAS (last one week) of at least 4 cm on two occasions, at least 4 weeks apart without any change of treatment
3. Failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated or recommended dosage for 4 weeks

**Contraindications:**

- active infection (includes active tuberculosis)
- HIV
- acute Hepatitis B and C
- chronic Hepatitis B or C infection (Child-Pugh class B or C)
- septic arthritis of a native joint within the last 12 months
- prosthetic joint sepsis within the last 12 months or indefinitely if the joints remain in situ
- CCF with NYHA grade 3 or 4
- multiple sclerosis or other demyelinating disorders
- malignancy and lymphoproliferative disorders
- breast feeding
Caution:

- high risk of infection
  - chronic leg ulcers
  - previous TB, unless completed a full course of anti-TB and measures taken to prevent reactivation
  - persistent or recurrent chest infections
  - indwelling urinary catheter
  - chronic Hepatitis B and C (Child-Pugh class A)

- high risk of malignancy
  - pre-malignant conditions (e.g. Barrett's oesophagus, cervical dysplasia and large bowel polyps)
  - previous history of malignancy with no recurrence for the past 10 years
  - possible history or strong family history of demyelination
  - patients with active psoriasis who have received >1000 joules cumulative PUVA dosage; especially those who have subsequently been treated with cyclosporin for at least a year (at risk for non melanoma skin cancer)

- mild CCF

- lung fibrosis
Special considerations

Vaccination

- primary and live attenuated vaccinations – patient on anti-TNF may not respond adequately
- live vaccines - to be given 4/52 prior to commencing anti-TNF if required
  - 6/12 after last infusion of infliximab
  - 2-3 weeks after last dose of etanercept
  - 10 weeks after last dose of adalimumab

Surgical procedures

- anti-TNF should be withheld 2-4 weeks prior to major surgical procedures
- anti-TNF may be restarted post-operatively if there is no infection and wound healing is satisfactory

Pregnancy

- safety unknown
- generally not recommended
- anti-TNF should be discontinued if a patient becomes pregnant while on treatment
- should discontinue Infliximab for 6/12 and Adalimumab for 5/12 before a female becomes pregnant or a male patient fathers a child

Tuberculosis

Malaysia has been classified by World Health Organization (WHO) as an intermediate burden country for Tuberculosis i.e Incidence Rate 25-100/ 100,000 populations (6).
However, there is no data on latent Tuberculosis which is characterized by exposure to \textit{mycobacterium tuberculosis} without clinical manifestations of active TB. This group of patients has 8-10% risk of progression to active TB in the first 2 years in non-immunosuppressed patients and the risk is higher in immunosuppressed patients(7).

The increased risk of TB reactivation in patients on biologics is a cause for concern. The risk of reactivation, whether pulmonary or extra pulmonary, is highest in the first 12 months with a median of 12 weeks after starting treatment. Therefore, TB screening prior to commencing anti-TNF is strongly recommended to exclude active and latent TB (8).

**TB screening prior to starting anti-TNF:**

1. History, including prior TB treatment and contact with TB patients, and a full physical examination.

2. Tuberculin Skin Test (TST or Mantoux test)
   - An anergy mantoux test is seen in 60% of a small RA population in Malaysia with a history of BCG vaccination (9). In these cases, two-step tuberculin skin test is suggested (10)
   - Cut-off point for positive TST (11)
     - ≥ 10mm for immunocompetent patient
     - ≥ 5mm for immunosuppressed patient
   - Measurement of less than the cut off point does not exclude TB

3. Interferon gamma release assay (IGRA) such as QuantiFERON-TB Gold (QFT-G) blood test if available (12)

4. CXR

Patients with abnormal chest x-ray and/or symptoms suspicious of TB should be investigated for active disease
**TB surveillance during Anti-TNF therapy**

Obtain history suggestive of TB, history of contact with TB patients and do a physical examination

**Chemoprophylaxis for latent TB (13)**

Isoniazid 5mg/kg/d (max 300mg/d) for 9 months (with an efficacy of 60%)

*Alternative regimens:*

Rifampicin 10mg/kg/d (max 600mg/d) for 4 mths (no efficacy studies on 4 mths therapy but efficacy of 40-50% on 3 mths therapy)

INH and Rifampicin for 3 months (with efficacy of 41%)

**Timing of anti-TNF therapy (14)**

**Active TB found prior to anti-TNF therapy**

Ideally, anti-TNF treatment should be delayed until anti tuberculosis treatment is completed.

However, if anti-TNF therapy is required earlier, it may be commenced after 2 months induction of anti TB therapy and until the drug susceptibility profile is known (if positive cultures obtained).

**Previous TB found prior to anti-TNF therapy**

(a) Anti-TNF can be started if the patient had received previous adequate TB treatment and active TB has been ruled out prior to starting TNF. These patients should be
monitored clinically every 3 months with a chest radiograph and sputum cultures, if respiratory symptoms develop.

(b) Patients who had inadequate therapy for TB previously should be referred to the respiratory physician before consideration for anti-TNF, as the risk of TB reactivation is high.

Patients with latent TB

These patients should receive TB chemoprophylaxis for at least 2 - 4 weeks prior to starting anti-TNF.

TB developing during anti-TNF treatment

Patients who develop active TB while on anti-TNF treatment should receive full anti-tuberculosis chemotherapy. If clinically indicated, anti-TNF treatment can be continued.

Dosage

- Infliximab infusion @ 0, 2, 6 weeks and every 8 weekly thereafter
  - RA 3-10mg/kg
  - PsA and AS 5-10mg/kg
- Etanercept 25mg 2x/wk or 50mg/wk (subcutaneous)
- Adalimumab 40mg every 2 weeks (subcutaneous)
**Criteria for withdrawal of therapy**

- development of drug-related toxicity
- inefficacy

RA - failure of DAS 28 score to improve by >1.2 or failure to reduce to a score of 3.2, after 6 months of therapy

PsA - failure to achieve the PsARC response within 6 months of treatment. (appendix 4)

AS - failure of the BASDAI to improve by 50% or to fall by ≥ 2 cm and/or for the spinal pain VAS to reduce by ≥ 2 cm after 3 months of therapy
- severe intercurrent infection (temporary withdrawal)
- pregnancy (temporary withdrawal)

**DMARDs in combination with anti-TNF therapies**

- Infliximab is co-prescribed with methotrexate in RA and PsA
- Adalimumab and Etanercept – combination with MTX is more efficacious but can be used as monotherapy
- Anti TNF is generally given as monotherapy in AS

**Potential adverse effects**

1. Serious infections
   - Anti-TNF should be discontinued in the presence of serious infections but can be recommenced once infection has completely resolved

2. Tuberculosis

3. SLE and autoimmunity
- SLE-like syndromes have been reported and anti-TNF should be discontinued if this occurs

- Development of ANA, anti-dsDNA or ACL do not increase the risk of clinical SLE

4. Congestive cardiac failure/cardiovascular disease

5. Demyelination and neurological complications

6. Haematological complications – pancytopenia

7. Malignancy (no evidence for an increase risk of solid tumour or lymphoproliferative disease) - stop treatment if malignancy is confirmed whilst on anti-TNF (15,16)
Algorithm for TB Screening Prior to Anti TNF Therapy

Hx and P/E suggestive of TB OR

Previous hx of TB OR

Abnormal CXR

YES

Ix to confirm active TB

YES

Anti TB regime

YES

Monitor and reassess if sx develop

NO

Adequate chemotherapy previously

≥10mm

≥10mm

Mantoux test

<10mm

Immunosuppressed

YES

LTBI if TST >5mm

No action

YES

Refer chest physician

Treat as Latent TB

NO

Exclude activity

YES
Appendix 1A

**ARA criteria for Rheumatoid Arthritis (17)**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement</td>
</tr>
<tr>
<td>2. Arthritis of 3 or more joint areas</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in &lt;5% of normal control subjects</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
</tr>
</tbody>
</table>

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.
### Appendix 1B

**The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis**

**Score**

Target population (Who should be tested?): Patients who

1) have at least 1 joint with definite clinical synovitis (swelling)*
2) with the synovitis not better explained by another disease†

Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of _6/10 is needed for classification of a patient as having definite RA)‡

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Joint involvement§</strong></td>
<td></td>
</tr>
<tr>
<td>1 large joint.</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (with or without involvement of large joints)#</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)**</td>
<td>5</td>
</tr>
<tr>
<td><strong>B. Serology (at least 1 test result is needed for classification)††</strong></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td><strong>C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡</strong></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>D. Duration of symptoms§§</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>
* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of < 6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment.

Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

. “Large joints” refers to shoulders, elbows, hips, knees, and ankles.

# “Small joints” refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 2

**Moll and Wright criteria for psoriatic arthritis (18)**

- Polyarticular, symmetric arthritis (rheumatoid arthritis-like)
- Oligoarticular (<5 joints), asymmetric arthritis
- Distal interphalangeal joint predominant
- Spondylitis predominant
- Arthritis mutilans

*To meet the Moll and Wright 1973 classification criteria for psoriatic arthritis, a patient with psoriasis and inflammatory arthritis who is seronegative for rheumatoid arthritis must present with 1 of the above 5 clinical subtypes. Moll and Wright specificity is 98% and sensitivity is 91%.*

Appendix 3

**Modified New York Criteria for a Diagnosis of Ankylosing Spondylitis (19)**

- Radiologic criterion:
  Sacroiliitis $\geq$ grade 2 bilaterally or grade 3 or 4 unilaterally

- Clinical criteria:
  Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
  Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
  Limitation of chest expansion relative to normal values correlated for age and sex.

*A definite diagnosis of ankylosing spondylitis requires the radiological criterion and at least one clinical criterion*
Appendix 4

The PsARC is a response criterion adapted from the VeteransAffairs Cooperative Study of sulphasalazine (20).

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 (as above) (improvement defined as decrease by at least 1 unit; worsening defined as increase by at least 1 unit)
- tender joint score
- swollen joint score (improvement defined as decrease of at least 30%; worsening defined as an increase of at least 30%).