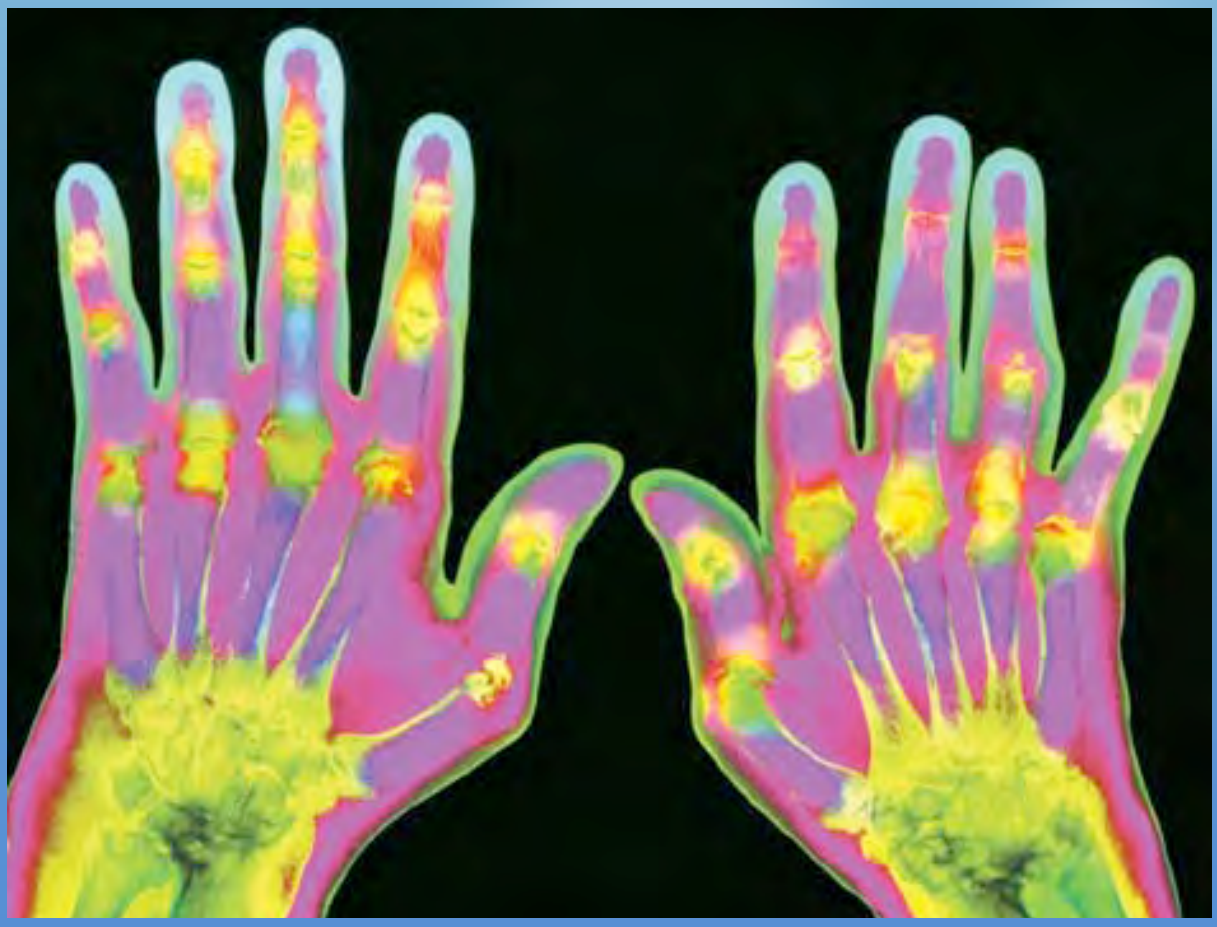
# Inflammatory Arthritis and Biologic Therapy – Malaysian Consensus



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### Introduction

Chronic inflammatory arthritis 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 biologics 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 National Inflammatory Arthritis Registry in 2010, 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. Tuberculosis (TB) is one of the potentially serious adverse effects of biologic therapy especially anti-TNF and will pose a public health concern in this country.

Currently, there are 3 classes of biologics available in the country which include anti-tumour necrosis factor (anti-TNF), interleukin 6 (IL-6) inhibitor and anti CD20 monoclonal antibody. These agents have been approved for various inflammatory arthritis (Table 1).

Table 1. Appoved indication of biologics in Malaysia

| Biologic agents | RA | PsA | AS |
|---|---|---|---|
| **Anti TNF** | | | |
| Infliximab | √ | √ | √ |
| Etanercept | √ | √ | √ |
| Adalimumab | √ | √ | √ |
| Golimumab | √ | √ | √ |
| **Anti CD 20 monoclonal antibody** | | | |
| Rituximab | √ | X | X |
| **Interleukin-6** | | | |
| Tocilizumab | √ | X | X |

Therefore, there is a need to develop a Malaysian consensus on biologic 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 biologic therapy in inflammatory arthritis with the emphasis on TB screening prior to commencing and surveillance whilst on biologic therapy.

These recommendations are for rheumatologists in Ministry of Health to serve as a guide in their clinical practice.

## 1.0 ANTI-TUMOUR NECROSIS FACTOR

Tumour necrosis factor (TNF) is a pro-inflammatory agent which is formed in the macrophages and T cells and is responsible for joint destruction and synovitis.[3] There are two cell-surface TNF receptors, p55 and p75, which mediate the activity of TNF on effector cells. The effects of anti-TNF are partially dependant on synovial TNF-a expression and infiltration by TNF-a producing inflammatory cells. Introduction of anti-TNF has revolutionised inflammatory arthritis treatment options.

Table 2: Currently available anti-TNFs in Malaysia

| **Anti-TNF** | **Etanercept** | **Infliximab** | **Adalimumab** | **Golimumab** |
|---|---|---|---|---|
| Specificity | Soluble and membrane- bound TNF and lymphotoxin alpha | Soluble and membrane-bound TNF | Soluble TNF | Soluble and membrane bound |
| Structure | Dimeric fusion protein : human TNF receptor connected to Fc portion of human IgG1 | Chimeric mouse / human monoclonal antibody to TNF | Human monoclonal antibody to TNF | Human IgG1k monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology |
| Mechanism of action | Binds soluble and cell bound TNF, thereby inhibiting the interaction of TNF with cell surface TNF receptors | Binds soluble and cell bound TNF, preventing interaction with cell surface TNF receptors | Binds TNF, thereby interaction with cell surface TNF receptors | Binds to both the soluble and transmembrane bioactive forms of human TNF-alpha |
| Half life | 3 days | 8-10 days | 10-14 days | 9-15 days |

## 1.1 Indications for anti TNFs

### 1.1.1 Indications in Rheumatoid Arthritis (RA):

**1.** Fulfils ACR 1987 RA classification or 2010 ACR/EULAR RA Classification Criteria (appendix 1A, 1B)

AND

2. Persistent active disease
   DAS 28 at high disease activity (appendix 1C) on 2 separate reviews, 1 month apart

AND

3. Failure to continue with standard therapy
   a) Failure to respond to 2 or more of the standard Disease Modifying Anti Rheumatic Drugs (DMARDs) such as Sulphasalazine (SSZ), Methotrexate (MTX), Leflunomide or Hydroxychloroquine 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 maximum tolerable dose.

   b) Withdrawal of DMARDs due to intolerance or toxicity even if less than 6 months therapy.(4)

### 1.1.2 Indications in Psoriatic Arthritis (PsA):

1. Adult PsA patients (fulfils Moll and Wright criteria with psoriasis and negative Rheumatoid factor or CASPAR with peripheral joints involvement with or without axial involvement) (appendix 2A, 2B)

   AND

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)(5)

   AND

3. Failed standard therapy
   a) Failure to respond to 2 or more of the standard DMARDSs (SSZ, MTX,

Cyclosporine, or Leflunomide) for at least 6 months, of which at least 2 months is at adequate maximum tolerable dose.

b) Withdrawal of drug due to intolerance or toxicity even if less than 6 months therapy

**Note**: anti-TNF-therapy for PsA with axial-only disease follows the treatment guideline for ankylosing spondylitis in adults

### 1.1.3 Indications in Ankylosing Spondylitis (AS):

1. Fulfils modified New York criteria for AS (appendix 3A) or the ASAS criteria for axial Spondyloarthritis (SpA) (appendix 3B)

   AND

2. Active spinal disease defined as BASDAI (appendix 4A) ≥ 4 and spinal pain VAS (last one week) ≥ 4 cm on two occasions, or high disease activity with ASDAS(appendix 4B) ,at least 4 weeks apart without any change of treatment.

   AND

3. Failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated or recommended dosage for ≥ 4 weeks.(6)

**Note**: ASAS criteria can be used to diagnose early AS (appendix 3B)

### 1.2 Contraindications to anti-TNF therapy:

- Active infection (includes active tuberculosis)
- HIV
- Acute Hepatitis B and C
- Untreated chronic Hepatitis B or treated chronic hepatitis B with Child-Pugh class B and higher(7)
- 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

- Congestive cardiac failure (CCF) with NYHA grade 3 or 4
- Multiple sclerosis or other demyelinating disorders
- Malignancy[7]

  - treated solid malignancy ≤ 5 years ago or treated non-melanoma skin cancer ≤ 5 years ago

  - skin melanoma
- Lymphoproliferative disorders

### 1.2.1 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
  - treated chronic Hepatitis B (Child-Pugh class A)
  - hepatitis C[#]
- 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 5 years[7]
  - 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 cyclosporine for at least a year (at risk for non melanoma skin cancer)
- Mild CCF
- Lung fibrosis
- History of uveitis[8]

[#] etanercept could potentially be used in RA patients requiring treatment[7]

## 1.3 Special considerations

### 1.3.1 Vaccination[4,7]

Vaccination may be beneficial for patients prior to starting DMARDs and biologics. There are 2 major categories of vaccine available: live and inactivated. A general rule is that inactivated vaccines can be administered safely to immunosuppressed individuals. However, the efficacy of these vaccines may be lower due to their immunosuppressive state.

Live attenuated vaccination is not recommended in patients on biologics. However, if required, it can be given as below:

- 4/52 prior to commencing anti-TNF
- 6/12 after last infusion of infliximab
- 2-3 weeks after last dose of etanercept
- 10 weeks after last dose of adalimumab
- no data are currently available regarding golimumab but the long half life should be taken into consideration
- stop tocilizumab for at least 70 days (5X the half-life), re-treatment is 2 weeks at least and 4 weeks ideally.

Table 3. ACR recommendations update regarding the use of vaccines in patients with RA[7]

| | Killed vaccines | | | Recombinant vaccine | Live attenuated vaccine |
|---|---|---|---|---|---|
| | Pneumococcal | Influenza (intramuscular) | Hepatitis B | Human papillomavirus | Herpes Zoster |
| Before initiating therapy | | | | | |
| Anti TNF biologics | √ | √ | √ | √ | √ |
| Non anti TNF | √ | √ | √ | √ | √ |

| | | | | | |
|---|---|---|---|---|---|
| biologics | | | | | |
| While already taking therapy | | | | | |
| Anti TNF biologics | √ | √ | √ | √ | Not recommended |
| Non anti TNF biologics | √ | √ | √ | √ | Not recommended |

### 1.3.2 Surgical procedures

There is inadequate evidence presently regarding the optimal timing for the use of biologics perioperatively. General consensus suggest to stop anti-TNF at least 1-2 treatment cycles prior to elective surgery.[9]

- etanercept – withhold 1 week prior
- infliximab – withhold 6-8 weeks prior
- adalimumab - withhold 2 weeks prior
- golimumab – no data available but the long half life should be taken into consideration prior to planned surgery [10]

Anti-TNF may be restarted post-operatively if there is no infection and wound healing is complete.

### 1.3.3 Pregnancy

Monoclonal antibodies (Infliximab, Adalimumab, Golimumab) behave similarly to maternal IgG antibodies both in terms of active transplacental transfer and their persistence in neonatal circulation up to 6 months postpartum. As the transplacental transfer does not notably start until the end of the second trimester, the fetus is not exposed during the first trimester, and hence the risk for teratogenicity is very low. There is limited placental transfer for fusion protein (Etanercept) due to its low affinity to neonatal IgG transporter.[11,12] Animal reproduction studies have failed to demonstrate a risk to the fetus. However, sporadic adverse events in humans have been reported but insufficient to determine toxicity or safety.

- For planned pregnancy, discontinue anti-TNF prior to conception wherever possible given the limitations of the available data and the uncertainties regarding the risk of congenital malformation. There is no recent data to support the optimal timing to stop anti-TNF prior to conception. Anti-TNF should be discontinued as soon as pregnancy is recognized.

- If warranted by the maternal disease and the benefit outweighs the risk, the monoclonal antibodies can be continued until the end of the second trimester (i.e should be discontinued before gestational week 30 [12].

### 1.3.4 Lactation

There is insufficient data to support safety of anti TNF in breastfeeding.

### 1.3.5 Tuberculosis (TB)

The incidence of TB in 2011 was reported at 71.35 per 100,000 population.[13] However, there is no data on latent TB infection (LTBI) which is defined as infection with mycobacterium TB complex, where the bacteria maybe alive but in the state of dormancy and not currently causing any active disease or symptoms. These LTBI patients have a 5-10% lifetime risk of progression to active TB and the risk is higher in immunosupressed patients. This reactivation tends to occur within the first 2 years after exposure.[14]

The overall risk of developing active TB whilst on anti-TNF is higher compare to general population.[15-17] Therefore, TB screening prior to commencing anti-TNF is strongly recommended to exclude active and latent TB [18, 19]

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

1. Complete history, including prior TB treatment and contact with TB patients, and a

full physical examination.

AND

2. Tuberculin Skin Test (TST) or Mantoux test

A study conducted in a rheumatology centre in Malaysia revealed that 60% of RA cohort with a history of BCG vaccination had an anergy Mantoux test[20]. Hence, patients with negative Mantoux test, a two-step tuberculin skin test should be considered. This is performed by repeating the TST (on the opposite forearm) one to four weeks after the first test. The induration observed with the second test is the baseline that should be used for subsequent evaluation of skin test conversion[21]. Cut-off point for positive TST[22, 23]

- o ≥ 10mm for immunocompetent patient
- o ≥ 5mm for immunosuppressed patient

Note: Measurement of less than the cut off point does not exclude TB

OR

3. Interferon gamma release assay (IGRA)[24] if available

a) QuantiFERON-TB Gold-InTube (QFT-GIT )

OR

b) T-SPOT. TB test

IGRAs have specificity >95% for diagnosis of latent TB infection. The sensitivity for T-SPOT.TB appears to be higher than for QFT-GIT or TST (approximately 90, 80, and 80 percent, respectively)[25]

The TST may boost subsequent IGRA results[26]. Therefore, if an IGRA test is needed to confirm a TST result, it has been suggested that blood be drawn for IGRA within three days of TST placement.

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 a physical examination.

**Chemoprophylaxis for latent TB [22]**

Table 4: Anti TB Regimens for LTBI in adults

| Drugs | Duration | Interval | Completion criteria |
|---|---|---|---|
| Isoniazid | 6 - 9 months | Daily | - 180 doses in 9 months (6-month regimen)<br>- 270 doses in 12 months (9-month regimen) |
| Isoniazid + rifampicin | 4 months | Daily | - 120 doses within 6 months |
| Rifampicin | 4 months | Daily | - 120 doses within 6 months |
| Isoniazid and rifapentine* | 3 months | Once weekly | - 12 doses |

*Rifapentine is not currently registered in Malaysia. Its use should be restricted to those on DOT (Directly observed therapy)

(Adapted from Centers for Disease Control and Prevention. Treatment Options for Latent Tuberculosis Infection. Available at http:www.cdc.gov/tb/publications/factsheets/treatment/LTBItreatmentoptions.htm)

**Timing of anti-TNF therapy[19]**

Active TB found prior 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 of intensive anti TB therapy** and until the drug susceptibility profile is known and clinical improvement is evident (if positive cultures obtained).

Previous TB prior anti-TNF therapy

(a) Previous adequate treatment

Anti TNF can be started if the patient had received previous adequate TB treatment and active TB has been ruled out prior to starting anti TNF. These patients should be monitored clinically every 3 months and screen for active TB if necessary.

(b) Previous inadequate treatment

Patients who had inadequate therapy for TB previously should be screened. If active TB has been ruled out, chemoprophylaxis for TB is recommended as the risk of TB reactivation is high. Ideally, chemoprophylaxis for TB in this category of patients should be completed before starting anti-TNF treatment.

Patients with latent TB

The ideal timing to initiate anti TNF following chemoprophylaxis for latent TB has not been established. Preferably the initiation of anti TNF should be about 4 weeks of TB chemoprophylaxis. However, if clinically indicated, treatment with biologic can be commenced concurrently or earlier than 4 weeks [7, 19]

TB developing during anti-TNF treatment

Patients who develop active TB while on anti-TNF treatment should receive full antituberculosis chemotherapy. Anti-TNF therapy should be discontinued temporarily.

## 1.4 Dosage

- Infliximab infusion
  - RA 3-10mg/kg @ 0, 2, 6 weeks and every 8 weekly thereafter
  - PsA 5-10mg/kg @ 0,2, 6 weeks and every 8 weekly thereafter
  - AS 5 -10mg/kg @ 0,2, 6 weeks and every 6 weekly thereafter
- Etanercept 25mg 2x/wk or 50mg/wk (subcutaneous)
- Adalimumab 40mg every 2 weeks (subcutaneous)
- Golimumab 50mg every 4 weeks (subcutaneous)

## 1.5 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 (ESR) or 2.7 (CRP) after 6 months of therapy
  - PsA - failure to achieve the PsARC response within 6 months of treatment. (appendix 5)
  - AS - failure of the BASDAI to improve by 50% or to fall by ≥ 2; and/or, for the spinal pain VAS to reduce by ≥ 2 cm, or failure of ASDAS to improve by 1.1 after 3 months of therapy.
- severe intercurrent infection (temporary withdrawal)
- pregnancy (temporary withdrawal)

## 1.6 DMARDs in combination with anti-TNF therapies

- Infliximab is co-prescribed with methotrexate or leflunomide in RA and PsA[27, 28]
- Adalimumab and Etanercept – preferably used in combination with methotrexate. If methothrexate is contraindicated, other DMARDs can be used as alternative.[7, 29]
- Golimumab should be administered in conjunction with methotrexate in rheumatoid arthritis; may administer with or without methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs) in psoriatic arthritis or ankylosing spondylitis.[10]
- Anti -TNF is generally given as monotherapy in AS.[30]

### Potential adverse effects

- Serious infections
- Tuberculosis
- 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
- Congestive cardiac failure
- Demyelination and neurological complications
- Haematological complications – pancytopenia
- Malignancy (no evidence for an increased risk of solid tumours or lympho-proliferative disease) - stop treatment if malignancy confirmed whilst on anti-TNF [31, 32]

## 2.0 ANTI CD20 AGENT (RITUXIMAB)

Rituximab is a genetically engineered chimeric mouse / human antibody. It targets the CD20 molecule, which is expressed on the surface of B cells from pre-B-cell through memory B-cell stages but not on stem cells and pro B cells nor on plasma cells/blasts.[33,34] Rituximab causes a selective transient depletion of the CD20+ B-cell subpopulation in the blood and only partial depletion in the bone marrow and synovial tissue. [35,36]

B cell targeted therapy for rheumatoid arthritis (RA) was developed with the objective of removing B cell clones responsible for the production of pathogenic autoantibodies. A specific objective was to induce sustained remission from short-term B cell depletion, based on the hypothesis that autoantibodies could not only produce tissue pathology but might be expected to drive their own production through a vicious cycle.

Rituximab was first licensed for the treatment of Non-Hodgkin Lymphoma and subsequently it has been approved for treatment of RA in Malaysia.

### 2.1 Indications

1. Fulfills ACR criteria for RA [appendix 1A, 1B]

   **AND**

2. Persistent active disease by -
   DAS 28 or Simplified Disease Activity Index (SDAI, >11) or Clinical Disease Activity Index (CDAI, >10)

   **AND**

3. Have had an inadequate response or intolerance to one or more TNF inhibitors.[37]

## 2.2 Contraindications[37]

- Hypersensitivity to Rituximab or other murine proteins
- Active acute or chronic infection
- Severe heart failure NYHA Class IV
- Pregnancy
- Safety and efficacy in children has not been established [38-44]

## 2.3 Caution[35]

- chronic or recent co-morbidity such as cardiovascular and pulmonary disease
- recurrent infections
- Hepatitis B screen[45]

  - patients tested negative for hepatitis B virus (HBV), hepatitis B surface antigen (HBsAg), but positive for antibodies against hepatitis B core (HBc) antigen were allowed rituximab therapy if negative for HBV DNA.
- Hepatitis C screen

Note: Routine Mantoux test is not required[46]

## 2.4 Dosage and Co-medication

### 2.4.1 Regime

Rituximab use is licensed at a dose of 1000 mg per infusion on days 1 and 15.[47]

### 2.4.2 Initiating in TNF failure patients:[47,48]

| | |
|---|---|
| Etanercept | - 4 weeks after the last dose |
| Adalimumab and Infliximab | - 8 weeks after the last dose |

Weekly methotrexate to increase efficacy (if tolerated)

Other DMARD (especially leflunomide) may be used as an alternative

### 2.4.3 Pre-medication drugs

- 100 mg intravenous methylprednisolone or equivalent before infusions [34,49]
- Paracetamol 1gm P.O– 30 - 60 minutes prior to infusion
- Chlorpheniramine 4 mg P.O – 30 - 60 minutes prior to infusion

### 2.4.4 Administration of infusion

**Pre infusion**

- Advise patients to omit any oral anti-hypertensives for 12 hours prior to infusion (Rituximab may cause hypotension during infusion).
- Administer pre-infusion medications, commencing 60 minutes before Rituximab

**Administering the infusion:**

- First infusion may take between 6-7 hours to complete (i.e. IV Methylprednisolone 30 minutes; interval 30 minutes; 1st infusion minimum 4 hours 15 minutes) or longer if the patient has any adverse reaction.
- The second infusion can be completed more quickly (Rituximab minimum of 3 hours 15 minutes) if the patient had no adverse effects during the first infusion.
- The rate of the infusion will depend on the concentration of the Rituximab and whether it is the 1st or 2nd infusion.

The following regime is based on a concentration of 2mgs/ml i.e. 1000mgs in 500mls.

**Infusion rate for DAY 1 infusion**

| Time | Mgs/hour | Mls/hour |
|---|---|---|
| 1st 30 minutes | 50mg/hour | 25mls/hour |
| 2nd 30 minutes | 100mg/hour | 50mls/hour |

Thereafter the rate can be increased by 50mg/hour (25mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) *providing no adverse reactions occur.*

**Infusion rate for DAY 15 infusion - if the patient had no reaction to the first infusion**

| Time | Mgs/hour | Mls/hour |
|---|---|---|
| 1st 30 minutes | 100mg/hour | 50mls/hour |
| 2nd 30 minutes | 200mg/hour | 100mls/hour |

Thereafter the rate can be increased by 100mg/hour (50mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) *providing no adverse reactions occur.*

## 2.5 Evaluation of response

Rituximab may take up to 16 weeks from the first infusion to reach a response, hence any evaluation of response should wait until at least 16weeks.[47,48,50]
IV glucocorticoid pre-medication may produce an early (usually temporary) effect for up to 8 weeks.

### 2.5.1 Definition of response

Minimum improvement of DAS 28 of 1.2 or greater or equivalent measure.

### 2.5.2 Repeated treatment

Repeated treatment should be considered after at least 24 weeks,[48,49] this should be considered in patients who do not reach remission or at least low disease activity.[51]

## 2.6 Adverse events[52]

### 2.6.1 Infusion reactions

30–35% after the first infusion; less with the second infusion.
Severe infusion reactions may occur but are rare.
Acute infusion reactions may occur within 1-2 hrs of the first Rituximab infusion.

These consist of fever, headache, rigors, flushing, nausea, rash, and URTI symptoms.
Transient hypotension and bronchospasm are usually related to the infusion rate.

If the patient experiences an infusion reaction

- STOP the infusion and treat the symptoms.
- The infusion should be restarted at half the previous rate only when the symptoms have resolved.

Note: in the case of extravasation, Rituximab is not an irritant and no special action is needed

### 2.6.2 Serious infection

Slight increase in infections compared with placebo population, especially in patients with low IgG. Cases of PML have been reported (~1:20 000).

## 2.7 Practical considerations

### 2.7.1 Vaccination[53,54]

Any patient considered for rituximab therapy should receive all indicated vaccines at least 4 weeks before rituximab therapy.

## 3.0 INTERLEUKIN-6 INHIBITOR (TOCILIZUMAB)

Tocilizumab is a recombinant humanised anti-human interleukin-6 receptor (anti-IL-6R) monoclonal antibody that binds both soluble and membrane bound IL-6 receptor.[55]

Interleukin-6 (IL-6) is a key cytokine that acts as a biochemical messenger between cells that play a role in regulating acute and chronic inflammation throughout the body.[56] IL-6 leads to inflammation in the joints and systemic manifestation such as anaemia, fatigue and increased cardiovascular risk.[56]

**Half-life**: Concentration-dependent apparent half-life is 11 days for 4 mg/kg and 13 days for 8 mg/kg.[55]

### 3.1 Indications:

1) Persistent active rheumatoid arthritis (RA) of moderate to severe disease
   AND
2) Failure or inadequate response or intolerance to 3 or more of the standard DMARDs individually or in combination for at least 6 months
   OR
3) Inadequate response or intolerance to at least one TNF-α inhibitor or Rituximab (under certain conditions).[57]

It may be used as monotherapy or in combination with methotrexate or other DMARDs.

### 3.2 Contraindication:

Specific contraindications have not been determined.[58]

- Hypersensitivity to tocilizumab.
- Active infection.

- Hepatitis B or C
- HIV
- Hepatic transaminases > 5x ULN
- Pregnancy / breast feeding

### 3.2.1 Caution:

- Previous serious infections – TB, invasive fungal infection, opportunistic infections
- Previous history of intestinal ulceration or diverticulitis
- Demyelinating disorders – multiple sclerosis, chronic inflammatory demyelinating polyneuropathy
- Live and attenuated vaccines should not be given concurrently
- Haematological abnormalities – neutropenia, thrombocytopenia.
- Hepatic transaminases > 1.5x ULN
- Hyperlipidaemia – elevated total cholesterol, triglyceride, LDL cholesterol.

TB screening and surveillance prior to starting and during tocilizumab therapy – (refer to screening and surveillance as for anti TNF).

### 3.3 Dosage:

4mg /kg intravenous infusion dilute to 100 ml normal saline over 1 hour every 4 weeks. May be increased to 8 mg/kg based on clinical response[58]. Maximum dose is 800 mg per infusion.[58]

No premedication is required. No dose adjustment in elderly and mild renal impairment.[55]

### 3.3.1 Children

The recommended dose of tocilizumab is [59]

• 12 mg/kg for patients < 30 kilograms (kgs)

• 8 mg/kg for patients ≥ 30 kilograms (kgs)

Initiating Tocilizumab in TNF-α inhibitor failure patients:[60]

Etanercept - ≥ 2 weeks after the last dose

Adalimumab - ≥ 8 weeks after the last dose

Infliximab - ≥ 8 weeks after the last dose

### 3.3.2 Dosing adjustment for toxicity:

Table 5: Liver enzymes abnormalities [55]

| Lab value | Recommendation |
|---|---|
| > 1 to 3x ULN | Dose modify concomitant DMARDs if appropriate.<br><br>For persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT/AST have normalized.<br><br>Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate. |
| 3 to 5x ULN<br><br>(confirmed by repeat testing) | Interrupt tocilizumab dosing until < 3x ULN and follow recommendations above for > 1 to 3x ULN. For persistent increases > 3x ULN , discontinue tocilizumab. |
| > 5x ULN | Discontinue tocilizumab |

Table 6: Low absolute neutrophil count (ANC)[55]

| Lab value<br><br>(cells x $10^9$/l) | Recommendation |
|---|---|
| ANC > 1 | Maintain dose |
| ANC 0.5 to 1 | Interrupt tocilizumab dosing.<br><br>When ANC > 1 X $10^9$/l resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. |
| ANC < 0.5 | Discontinue tocilizumab |

Table 7: Low platelet count [55]

| Lab value<br><br>( cells x $10^3$ /µl) | Recommendation |
|---|---|
| 50 to 100 | Interrupt tocilizumab dosing.<br><br>When platelets count is > 100 x $10^3$/µl resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. |
| < 50 | Discontinue tocilizumab. |

Monitoring parameters:[59]

- Sign and symptoms of infection (prior to and during therapy) e.g active tuberculosis.
- FBC (prior to and every 4-8 weeks during therapy).
- ALT/AST (prior to and every 4-8 weeks during therapy).
- Lipid panel (prior to, at 4-8 weeks following initiation, and every 6 months during therapy).
- Signs and symptoms of CNS demyelinating disorders.

### 3.4 Safety and efficacy:

The most common adverse effects were infections, gastrointestinal disorders, infusion reactions, elevations in ALT, increase in total cholesterol and neutropenias.

Table 8: Potential adverse reactions:[55]

| System Organ Class | Very Common | Common | Uncommon |
|---|---|---|---|
| Infections and infestations | Upper respiratory tract infections | Cellulitis, Oral herpes simplex, Herpes zoster | Diverticulitis |
| Gastrointestinal Disorders | | Abdominal pain, Mouth ulceration, Gastritis<br>Hepatic transaminase increased | Stomatitis, Gastric ulcer, GIT perforation,<br>Total bilirubin increased |
| Skin and subcutaneous tissue disorders | | Rash, Pruritis, Urticaria | |
| Nervous system disorders | | Headache, Dizziness | |
| Vascular disorders | | Hypertension | |
| Blood and lymphatic system disorders | | Leucopenia, Neutropenia | |
| Metabolism and nutrition disorders | | Hypercholesterolaemia<br>Weight increased | Hypertriglyceridemia |
| General disorders and administration | | Peripheral oedema, Hypersensitivity reaction | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| Respiratory | | Cough, Dyspnoea | |
| Renal disorders | | | Nephrolithiasis |
| Endocrine disorders | | | Hypothyroidism |

### 3.5 Administration of intravenous tocilizumab

1. Dose : 4-8 mg/kg (vial contains 80mg per 4ml or 400mg per 20 ml).
2. Allow the solution to reach room temperature prior to infusion. Solution should be colourless. Do not use if discolorations or foreign particles are present.
3. Dilute tocilizumab for infusion to a final volume of 100 ml using 0.9% sodium chloride with aseptic technique.
4. To mix the solution, gently invert to avoid foaming.
5. The infusion should be administered over 60 minutes. Do not administer IV push or IV bolus. Do not infuse concomitantly in the same intravenous line with other drugs.
6. Monitor vital signs prior, during and after infusion.
   If BP falls <100/60 mmHg, HR>120/min. SpO2 < 95% on room air, stop infusion and inform doctor immediately. Recheck the vital signs while waiting for doctor's review.
7. Premedication is not required.

## Appendix 1A

### ACR 1987 criteria for Rheumatoid Arthritis[61]

| Criteria | Definition |
|---|---|
| 1. Morning stiffness | Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement |
| 2. Arthritis of 3 or more joint areas | 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 |
| 3. Arthritis of hand joints | At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint |
| 4. Symmetric arthritis | 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) |
| 5. Rheumatoid nodules | Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician |
| 6. Serum rheumatoid factor | Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects |
| 7. Radiographic changes | 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) |

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of 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 [(62)]**

| | |
|---|---|
| **Target population (Who should be tested?): Patients who**<br>**1) have at least 1 joint with definite clinical synovitis (swelling)***<br>**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)‡** | |
| **A. Joint involvement§** | |
| 1 large joint. | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints (with or without involvement of large joints)# | 2 |
| 4-10 small joints (with or without involvement of large joints) | 3 |
| >10 joints (at least 1 small joint)** | 5 |
| **B. Serology (at least 1 test result is needed for classification)††** | |
| Negative RF and negative ACPA | 0 |
| Low-positive RF or low-positive ACPA | 2 |
| High-positive RF or high-positive ACPA | 3 |
| **C. Acute –phase reactants (st least 1 test result is needed for classification)‡‡** | |
| Normal CRP and normal ESR | 0 |
| Abnormal CRP or abnormal ESR | 1 |
| **D. Duration of symptoms§§** | |
| < 6 weeks | 0 |
| > 6 weeks | 1 |

* 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 assessments.*

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 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 1C**

**DAS 28 Disease Activity**

| DAS28 CRP | DAS28 ESR | Disease activity |
|---|---|---|
| >4.1 | >5.1 | High |
| 2.7-4.1 | 3.2-5.1 | Moderate |
| <2.7 | <3.2 | Low |
| <2.3 | <2.6 | Remission |

SDAI Disease Activity

| SDAI | Disease Activity |
|---|---|
| >26 | High |
| 11 – 26 | Moderate |
| <11 | Low |
| <3.3 | Remission |

CDAI Disease Activity ( without CRP)

| CDAI | Disease Activity |
|---|---|
| >22 | High |
| 10 – 22 | Moderate |
| <10 | Low |
| < 2.8 | Remission |

**Appendix 2A**

**Moll and Wright criteria for psoriatic arthritis[63]**

---

- 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 2B

### The ClASsification Criteria for Psoriatic ARthritis (CASPAR)[64]

To meet the CASPAR criteria*, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. (2 points)
   Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
   A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified healthcare provider.
   A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (1 point)
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range. (1 point)
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiograph of the hand or foot (1 point)

* The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

**Appendix 3A**

**Modified New York Criteria for a Diagnosis of Ankylosing Spondylitis[65]**

---

- Radiologic criterion:
  Sacroiliitis ≥ 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 3B**

**Assessment of Spondyloarthritis International Society (ASAS) criteria for classification of axial spondyloarthritis (to be applied in patients with chronic back pain and age at onset < 45 years of age) [(66)].**

ASAS classification criteria for axial spondyloarthritis (SpA)
In patients with ⩾3 months back pain and age at onset <45 years

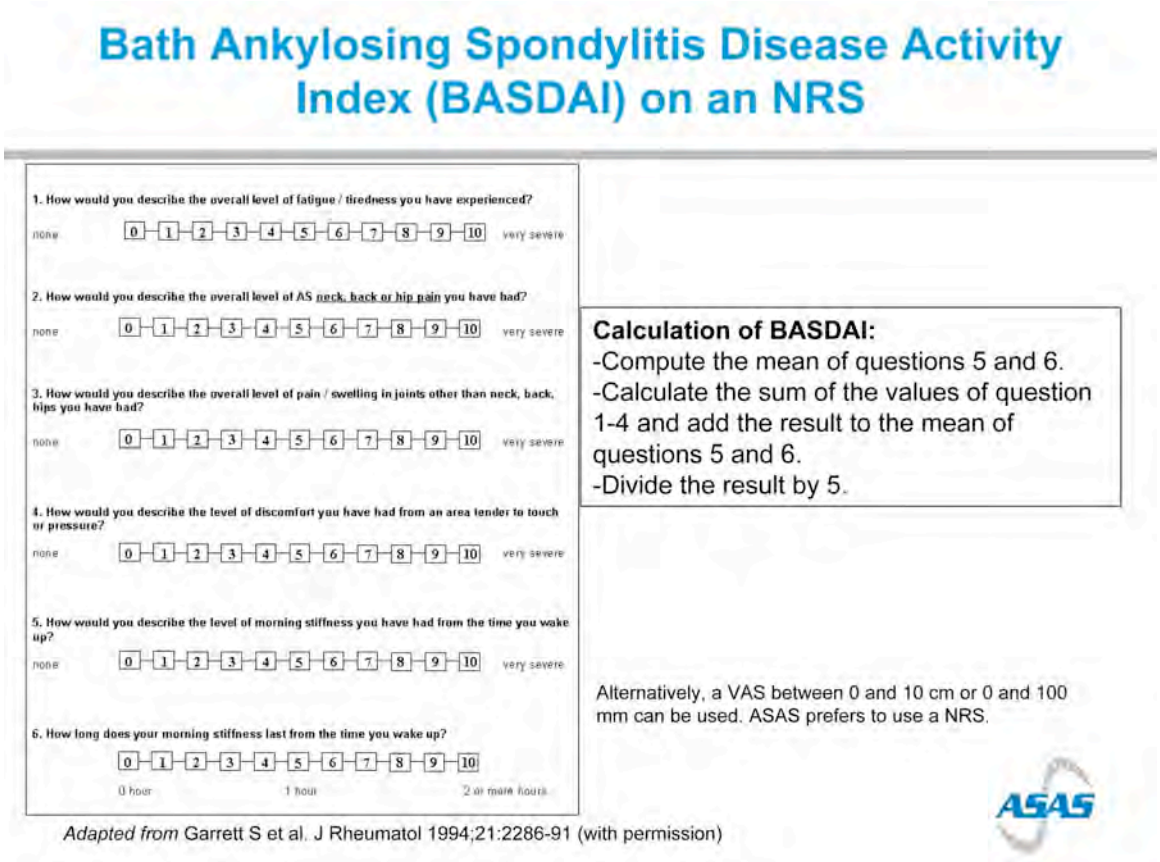
| | | |
|---|---|---|
| Sacroiliitis on imaging* plus ⩾1 SpA feature# | or | HLA-B27 plus ⩾2 other SpA features# |

#SpA features
- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

*Sacroiliitis on imaging
- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to mod NY criteria

## Appendix 4A

### Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[67]

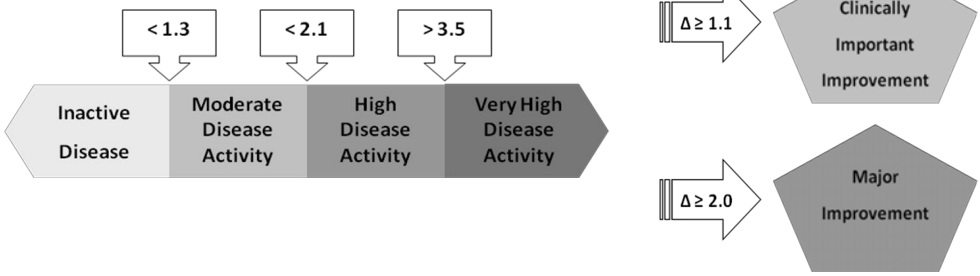



*Adapted from* Garrett S et al. J Rheumatol 1994;21:2286-91 (with permission)

## Appendix 4B

### Ankylosing Spondylitis Disease Activity Score (ASDAS) Formulas: ASDAS-ESR and ASDAS–CRP (preferred)

### Quick ASDAS-ESR Calculation Form




**Name : _____** **Date : ____ /____ /_____**

1) How would you describe the overall level of AS neck, back or hip pain you have had?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

None — Very severe

2) How long does your morning stiffness last from the time you wake up?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

0 — 1 — 2 or more hours

3) How active was your spondylitis on average during the last week?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

Not active — Very active

4) How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

None — Very severe

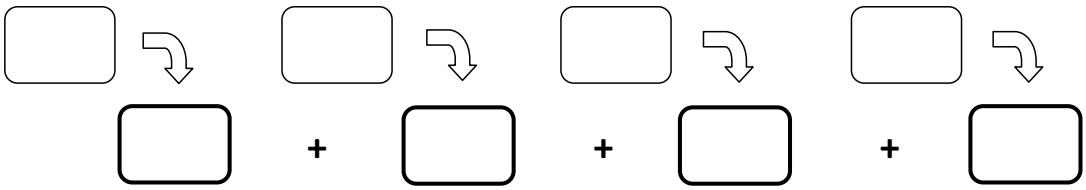
5) Erythrocyte sedimentation rate (mm/h)?

| Back Pain | |
|---|---|
| 0 | **0,0** |
| 1 | **0,1** |
| 2 | **0,2** |
| 3 | **0,2** |
| 4 | **0,3** |
| 5 | **0,4** |
| 6 | **0,5** |
| 7 | **0,6** |
| 8 | **0,6** |
| 9 | **0,7** |
| 10 | **0,8** |

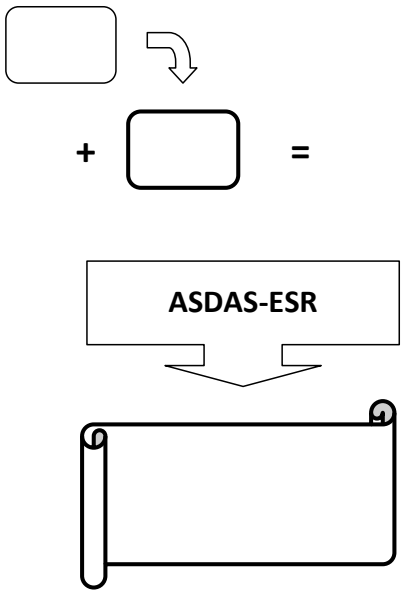
| Morning Stiffness | |
|---|---|
| 0 | **0,0** |
| 1 | **0,1** |
| 2 | **0,1** |
| 3 | **0,2** |
| 4 | **0,3** |
| 5 | **0,4** |
| 6 | **0,4** |
| 7 | **0,5** |
| 8 | **0,6** |
| 9 | **0,6** |
| 10 | **0,7** |

| Patient Global | |
|---|---|
| 0 | **0,0** |
| 1 | **0,1** |
| 2 | **0,2** |
| 3 | **0,3** |
| 4 | **0,4** |
| 5 | **0,6** |
| 6 | **0,7** |
| 7 | **0,8** |
| 8 | **0,9** |
| 9 | **1,0** |
| 10 | **1,1** |

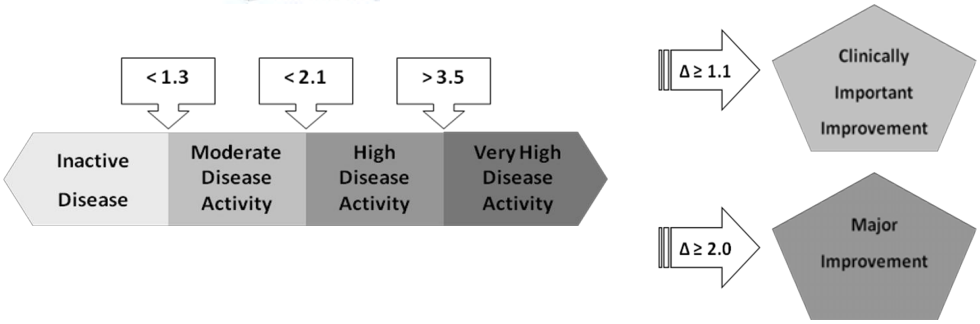
| Peripheral Pain/Swelling | |
|---|---|
| 0 | **0,0** |
| 1 | **0,1** |
| 2 | **0,2** |
| 3 | **0,3** |
| 4 | **0,4** |
| 5 | **0,5** |
| 6 | **0,5** |
| 7 | **0,6** |
| 8 | **0,7** |
| 9 | **0,8** |
| 10 | **0,9** |




| Erythrocyte Sedimentation Rate (mm/h) | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | **0,0** | 14 | **1,1** | 28 | **1,5** | 70 | **2,4** |
| 1 | **0,3** | 15 | **1,1** | 29 | **1,6** | 75 | **2,5** |
| 2 | **0,4** | 16 | **1,2** | 30 | **1,6** | 80 | **2,6** |
| 3 | **0,5** | 17 | **1,2** | 31 | **1,6** | 85 | **2,7** |
| 4 | **0,6** | 18 | **1,2** | 32 | **1,6** | 90 | **2,8** |
| 5 | **0,6** | 19 | **1,3** | 33 | **1,7** | 95 | **2,8** |
| 6 | **0,7** | 20 | **1,3** | 34 | **1,7** | 100 | **2,9** |
| 7 | **0,8** | 21 | **1,3** | 35 | **1,7** | 105 | **3,0** |
| 8 | **0,8** | 22 | **1,4** | 40 | **1,8** | 110 | **3,0** |
| 9 | **0,9** | 23 | **1,4** | 45 | **1,9** | 115 | **3,1** |
| 10 | **0,9** | 24 | **1,4** | 50 | **2,1** | 120 | **3,2** |
| 11 | **1,0** | 25 | **1,5** | 55 | **2,2** | 125 | **3,2** |
| 12 | **1,0** | 26 | **1,5** | 60 | **2,2** | 130 | **3,3** |
| 13 | **1,0** | 27 | **1,5** | 65 | **2,3** | 135 | **3,4** |



# Quick ASDAS-CRP Calculation Form




**Name : _____** **Date : ____ /____ /_____**

1) How would you describe the overall level of AS neck, back or hip pain you have had?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

None Very severe

2) How long does your morning stiffness last from the time you wake up?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

0 1 2 or more hours

3) How active was your spondylitis on average during the last week?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

Not active Very active

4) How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

None Very severe

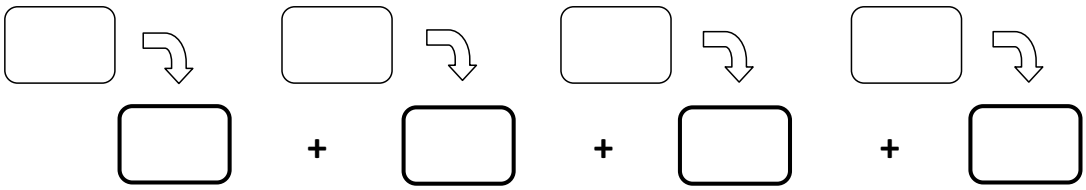
5) C-reactive protein (mg/L)?

| Back Pain | |
|---|---|
| 0 | **0** |
| 1 | **0,1** |
| 2 | **0,2** |
| 3 | **0,4** |
| 4 | **0,5** |
| 5 | **0,6** |
| 6 | **0,7** |
| 7 | **0,8** |
| 8 | **1,0** |
| 9 | **1,1** |
| 10 | **1,2** |

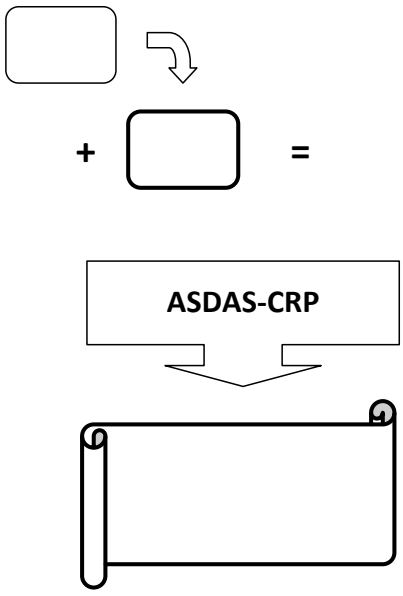
| Morning Stiffness | |
|---|---|
| 0 | **0** |
| 1 | **0,1** |
| 2 | **0,1** |
| 3 | **0,2** |
| 4 | **0,2** |
| 5 | **0,3** |
| 6 | **0,4** |
| 7 | **0,4** |
| 8 | **0,5** |
| 9 | **0,5** |
| 10 | **0,6** |

| Patient Global | |
|---|---|
| 0 | **0** |
| 1 | **0,1** |
| 2 | **0,2** |
| 3 | **0,3** |
| 4 | **0,4** |
| 5 | **0,6** |
| 6 | **0,7** |
| 7 | **0,8** |
| 8 | **0,9** |
| 9 | **1,0** |
| 10 | **1,1** |

| Peripheral Pain/Swelling | |
|---|---|
| 0 | **0** |
| 1 | **0,1** |
| 2 | **0,1** |
| 3 | **0,2** |
| 4 | **0,3** |
| 5 | **0,4** |
| 6 | **0,4** |
| 7 | **0,5** |
| 8 | **0,6** |
| 9 | **0,6** |
| 10 | **0,7** |




| C-Reactive Protein (mg/L) | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0 | **0,0** | 14 | **1,6** | 60 | **2,4** | 130 | **2,8** |
| 1 | **0,4** | 15 | **1,6** | 65 | **2,4** | 135 | **2,8** |
| 2 | **0,6** | 16 | **1,6** | 70 | **2,5** | 140 | **2,9** |
| 3 | **0,8** | 17 | **1,7** | 75 | **2,5** | 145 | **2,9** |
| 4 | **0,9** | 18 | **1,7** | 80 | **2,5** | 150 | **2,9** |
| 5 | **1,0** | 19 | **1,7** | 85 | **2,6** | 155 | **2,9** |
| 6 | **1,1** | 20 | **1,8** | 90 | **2,6** | 160 | **2,9** |
| 7 | **1,2** | 25 | **1,9** | 95 | **2,6** | 165 | **3,0** |
| 8 | **1,3** | 30 | **2,0** | 100 | **2,7** | 170 | **3,0** |
| 9 | **1,3** | 35 | **2,1** | 105 | **2,7** | 175 | **3,0** |
| 10 | **1,4** | 40 | **2,2** | 110 | **2,7** | 180 | **3,0** |
| 11 | **1,4** | 45 | **2,2** | 115 | **2,8** | 185 | **3,0** |
| 12 | **1,5** | 50 | **2,3** | 120 | **2,8** | 190 | **3,0** |
| 13 | **1,5** | 55 | **2,3** | 125 | **2,8** | 195 | **3,1** |



## Appendix 5

### The PsARC is a response criterion adapted from the Veterans Affairs Cooperative Study of Sulphasalazine[68]

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Response is defined as improvement in at least two of the following four measures, one of which must be the joint tenderness or swelling score with no worsening in any of the four measures.

1. Patient global assessment (on a 0–5 Likert scale)
2. Physician global assessment (on a 0–5 Likert scale);
   (improvement defined as a decrease by at least 1 unit; and worsening defined as increase by at least 1 unit)
3. Tender joint score
4. Swollen joint score
   (improvement defined as decrease of at least 30%; worsening defined as an increase of at least 30%).

**Appendix 6A**

**RITUXIMAB**

**PRE-TREATMENT CHECKLIST**

*Patient details label*

DATE:----------

ASSESSMENT PERFORMED BY:_____

Temp __ºC Pulse_____ bpm;  Resp_____ rpm; BP_____ mm/Hg

Urinalysis_____ (Optional)

IS THE PATIENT PREGNANT /BREAST FEEDING: YES / NO / NA

ANY CURRENT INFECTION
e.g. URTI, DENTAL ABSCESS, UTI YES / NO

ANY VACCINATIONS[£] IN THE LAST 4 WEEKS YES / NO

BLOOD TESTS RESULTS:  FBC, LFT, RP, ESR/CRP
Hep B /Hep C

_____

**CHECKLIST:**

Does the patient have an information leaflet about Rituximab? YES / NO

Does the patient know details of first infusion Date YES / NO

Time_____

Venue_____

Does the patient know that any anti-hypertensive medication needs to be omitted on the morning of infusion? YES / NO

Does the patient know dates for second infusion second pre-treatment visit YES / NO

Are the necessary medications prescribed ready for the infusion? YES / NO

**Appendix 6B**

**ADMINISTRATION OF RITUXIMAB**

PATIENT NAME:
MRN:
WARD:
DATE:

Rituximab infusion 1 / 2 (circle)

**Checklist prior to commencing infusion**[i]

| | |
|---|---|
| 1. Confirm patient identity | Y / N |
| 2. Blood tests reviewed by Dr | Y / N |
| 3. Pre- assessment review documented in notes | Y / N |
| 4. Drug chart completed for Rituximab, pre-infusion and pre- medications | Y / N |
| 5. Baseline observations on arrival within normal parameters | Y / N |

If **YES** proceed with Rituximab infusion as per guidelines
Document all observations and infusion rates on the record sheet and any other information on the nursing record sheet.

DATE_____

NAME _____

MRN_____

**Nursing Observations Record Sheet - Rituximab Infusions**

Time Duration of infusion ___hr/mins

Rate of infusion _____mls/hr

BP ____mm/Hg

Pulse __bpm

Temp___ ºC O2 saturation _____%

Any adverse reaction? YES / NO

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