KEMENTERIAN KESIHATAN MALAYSIA

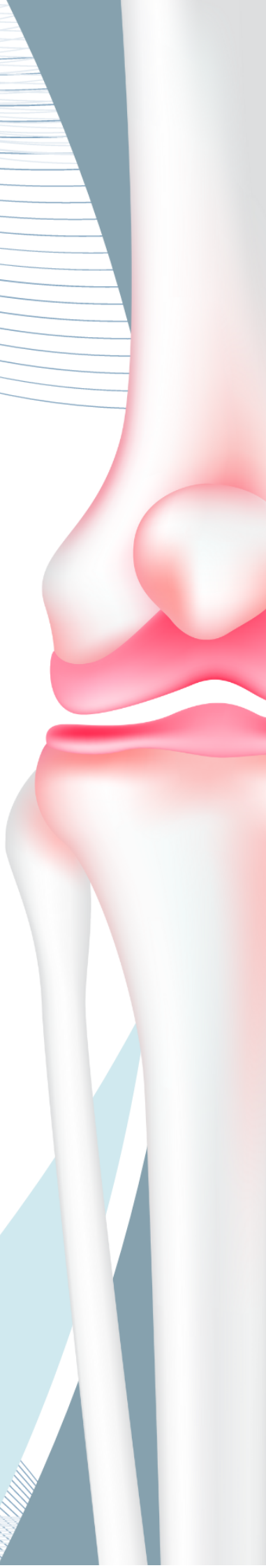
MSR MALAYSIAN SOCIETY OF RHEUMATOLOGY

CONSENSUS ON

ADVANCED THERAPY FOR INFLAMMATORY ARTHRITIS

Rheumatology Ministry of Health Malaysia

2023 Edition



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1. INTRODUCTION

Chronic inflammatory arthritis e.g., Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and axial Spondyloarthritis (SpA) including 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 are ranked third among diseases in females. The total drug expenditure in 2005 for the treatment of inflammatory and rheumatic diseases is RM50.7 million, ranking fifth as the most prescribed group of drugs and forms 7.8% of the top 40 prescribed drugs in Malaysia.[1]

The introduction of biologics and more recently, the targeted synthetic disease modifying anti-rheumatic drugs (tsDMARDs) and biologic DMARDs (bDMARDs) spawned a new therapeutic era in rheumatology transforming the treatment paradigm of the inflammatory arthritis. 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.

Admittedly, these drugs are more costly than conventional synthetic DMARDs (csDMARDs) in the short-term. However, cost-effectiveness analysis has shown that advanced therapy is more cost effective in the long-term taking into consideration other costs including hospitalisation and loss of productivity. The use of biologics in general is reported from various registries worldwide mainly from developed countries to be about 26%.[2] A recent publication reported that 50.7% RA patients in North America compared to 8.3% in the Chinese registry were treated with biological DMARDs.[3, 4] However, the report from the Malaysian National Inflammatory Arthritis and Malaysian Rheumatology Biologic Registry in 2020, quoted a rather low figure of 2.9% usage of biologics in the RA cohort.[5] The disparity in the usage as compared to the more developed countries is due to a lack of accessibility because of the high cost of these drugs among other reasons.

bDMARDs and tsDMARDs 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 these therapy especially tumour necrosis factor inhibitors (TNFi) and poses a public health concern in this country.

Currently, there are several classes of bDMARDs available in Malaysia which include TNFi, interleukin (IL) inhibitors (IL-6 inhibitor, IL-17 inhibitor, IL-12/23 inhibitor, IL-23 inhibitor) and B-cell depleting therapy. There are three tsDMARDs available which include Tofacitinib, Baricitinib and Upadacitinib. All of these agents have been approved for various inflammatory arthritis (refer to **Table 1** and **Table 2**). For the mechanism of action and pharmacokinetics of individual drugs, refer to **Appendix 1**.

The concept of treat-to-target (T2T) treatment strategy had resulted in better disease outcome in inflammatory arthritis. It includes a defined treatment target (clinical remission or at least low disease activity), shared decision making, assessment of disease activity and regular adjustment of treatment.

Therefore, there is a need to develop a Malaysian consensus on advanced therapy to address these issues in inflammatory arthritis. These recommendations are for rheumatologists in Ministry of Health to serve as a guide in their clinical practice.

Table 1. Approved Indications of BDMARDS for Inflammatory Arthritis in Malaysia

(as of July 2023)

bDMARDs	Rheumatoid Arthritis	Psoriatic Arthritis	Axial Spondyloarthritis
Tumour Necrosis Factor Inhibitors (TNFi)			
Infliximab	✔	✔	✔
Etanercept	✔	✔	✔
Adalimumab	✔	✔	✔
Golimumab	✔	✔	✔
Interleukin (IL) Inhibitors			
IL-6 inhibitor			
Tocilizumab	✔	✘	✘
IL-17 inhibitor			
Secukinumab	✘	✔	✔
Ixekizumab	✘	✔	✔
IL-12/23 inhibitor			
Ustekinumab	✘	✔	✘
IL- 23 inhibitor			
Guselkumab	✘	✔	✘
B-cell Depleting Therapy			
Rituximab	✔	✘	✘

Table 2. Approved Indications of TSDMARDS for Inflammatory Arthritis in Malaysia (as of July 2023)

tsDMARDs	Rheumatoid Arthritis	Psoriatic Arthritis	Axial Spondyloarthritis
Tofactinib	✔	✔	✘
Baricitinib	✔	✘	✘
Upadacitinib	✔	✔	✔

2. ADVANCED THERAPY IN RHEUMATOID ARTHRITIS

2.1 Indication

- **Persistent active disease**

Disease activity score (DAS) 28 at moderate and high disease activity (refer to **Appendix 1**)

AND

- **Failure to continue with standard therapy**

Failure to achieve target (remission or low disease activity) (refer to **Appendix 1**) with at least two csDMARDs e.g., Sulphasalazine (SSZ), Methotrexate (MTX), Leflunomide (LEF) or Hydroxychloroquine (HCQ) for at least six months, of which at least two months is at standard target dose.

OR

Withdrawal of csDMARDs due to intolerance or toxicity even if less than six months therapy.[6]

2.2 Types of Advanced Therapy

2.2.1 Tumour Necrosis Factor Inhibitors (TNF-i)

i. Infliximab (IFX)/Biosimilar IFX

- 3 - 10 mg/kg at week 0, 2, 6 and 8-weekly intravenous infusion (IVI). For administration of IFX, refer to **Appendix 2.**

ii. Etanercept (ETN)

- 50 mg/week subcutaneous (SC)

iii. Adalimumab (ADA)/Biosimilar ADA

- 40 mg 2-weekly SC

iv. Golimumab (GOL)

- 50 mg monthly SC or 2 mg/kg at week 0, 4 and 8-weekly IVI. For administration of IVI GOL, refer to **Appendix 3**.

2.2.2 Interleukin Inhibitor

i. Interleukin-6 Inhibitor

- **Tocilizumab (TCZ)**
  - 8 mg/kg IVI every 4 weeks. May be reduced to 4 mg/kg in certain dose-related laboratory changes including elevated liver enzymes, neutropenia and thrombocytopenia. Maximum dose is 800 mg per infusion. For administration of IV TCZ, refer to **Appendix 4.**
  - 162 mg SC weekly

2.2.3 B-cell Depleting Therapy

i. Rituximab (RTX)

- 1000 mg per infusion on day 1 and 15. For administration of IVI RTX, refer to **Appendix 5**.

2.2.4 Targeted Synthetic Disease Modifying Anti Rheumatic Drugs (tsDMARDs)

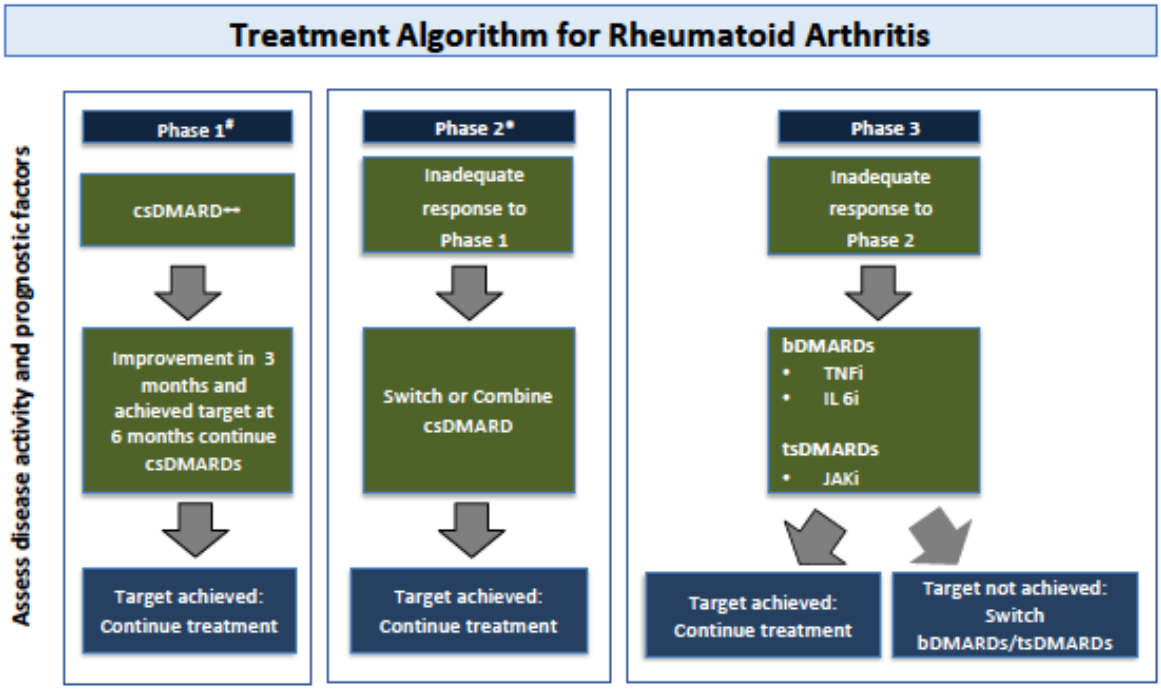
i. Janus Kinase Inhibitors (JAK-i)

- **Tofacitinib**
  - 5 mg BD oral (PO)

- **Baricitinib**
  - 4 mg OD PO or 2 mg OD PO for patients age ≥75 years or history of recurrent infection

- **Upadacitinib**
  - 15 mg OD PO

2.3 Treatment Algorithm



Combine with short-term glucocorticoids as bridging therapy

**The preferred csDMARDs: MTX over SSZ, LEF , HCQ

* In the presence of poor prognostic factors (high level rheumatoid factor/Anti-citrullinated peptide antibody, high disease activity, early joint damage), proceed to Phase 3

csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; MTX, methotrexate; SSZ, sulphasalazine; LEF, leflunomide; HCQ, hydroxychloroquine ;TNFi, tumour necrosis factor α inhibitors;IL-6i, Interleukin-6 inihibitor; JAKi, janus kinase inhibitors

3. ADVANCED THERAPY IN PSORIATIC ARTHRITIS

3.1 Indication

- **Persistent active disease**

Persistent polyarthritis [Disease Activity index for PSoriatic Arthritis (DAPSA) at moderate and high disease activity (refer to **Appendix 6**)] or mono/oligoarthritis with poor prognostic factors*.

Note: dactylitis counted as one active joint[7]
*Poor prognostic factors: structural damage; high inflammatory markers; dactylitis or nail involvement

AND

- **Failed standard therapy**

Failure to achieve target with at least two csDMARDs (SSZ, MTX, Cyclosporine (CSA), or LEF) for at least three months, of which at least two months is at standard target dose.

OR

Withdrawal of csDMARDs due to intolerance or toxicity even if less than three months therapy.

Note:
Advanced therapy for PsA with enthesitis - refer to treatment algorithm.
Advanced therapy for axial-only disease - follows guideline for axial SpA in adults.

3.2 Types of Advanced Therapy

3.2.1 Tumour Necrosis Factor Inhibitors (TNF-i)

i. Infliximab (IFX)/Biosimilar IFX
- 5 - 10 mg/kg at 0, 2, 6 weeks and 8-weekly IVI. For administration of IFX, refer to **Appendix 3**.

ii. Etanercept (ETN)
- 50 mg every week SC

iii. Adalimumab (ADA)/Biosimilar ADA
- 40 mg every 2 weeks SC

iv. Golimumab (GOL)
- 50 mg every 4 weeks SC or 2 mg/kg at 0, 4 weeks and 8-weekly IVI. For administration of IVI GOL, refer to **Appendix 3**.

3.2.2 Interleukin Inhibitors

i. Interleukin-17 Inhibitors
- **Secukinumab (SEC)**
  - with loading - 150 mg SC at week 0, 1, 2, 3, 4 then 4-weekly
  - without loading - 150 mg SC 4-weekly

  May consider increasing to 300 mg in persistent active disease, TNFi inadequate responders or coexistent moderate to severe plaque psoriasis.

- **Ixekizumab (IXE)**
  - 160 mg SC at week 0, followed by 80 mg 4-weekly
  - with coexisting moderate to severe plaque psoriasis - 160 mg SC week 0, 80 mg SC week 2, 4, 6, 8, 10, 12 followed by 80 mg 4-weekly

ii. Interleukin-12/23 Inhibitor
- **Ustekinumab (UST)**
  - ≤100 kg - 45 mg SC at week 0, 4 and then 12-weekly

- >100 kg - 90 mg SC at week 0, 4 and then 12-weekly

iii. Interleukin-23 Inhibitor

- **Guselkumab (GUS)**
  - 100 mg SC at Week 0, 4 and 8-weekly

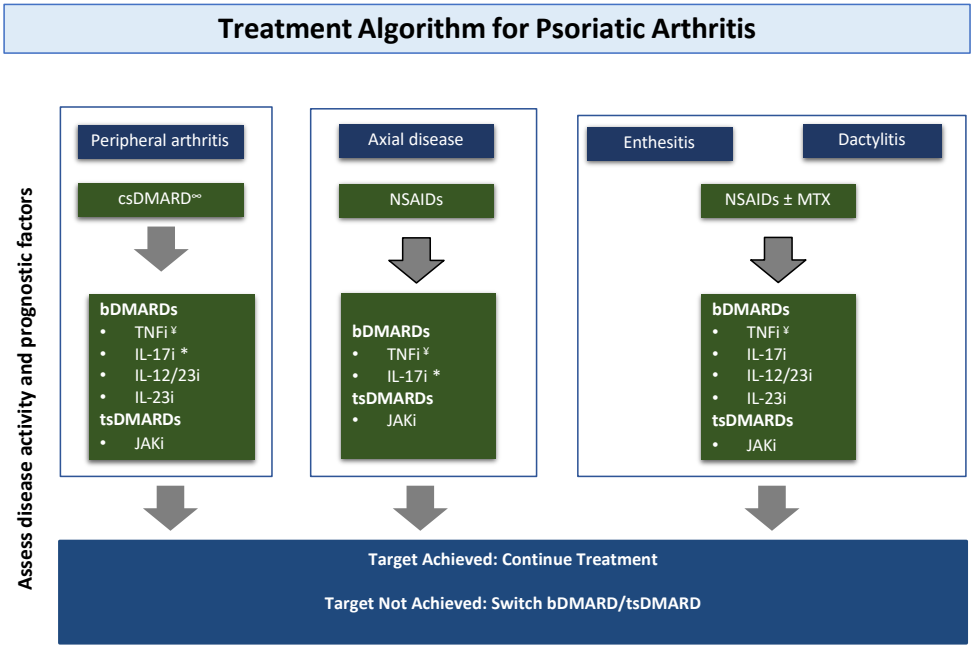
3.2.3 Targeted Synthetic Disease Modifying Anti Rheumatic Drugs

i. Janus Kinase Inhibitors (JAK-i)

- **Tofacitinib**
  - 5 mg BD PO

- **Upadacitinib**
  - 15 mg OD PO

3.3 Treatment Algorithm



∞The preferred csDMARDs: MTX, SSZ, LEF

¥If concomitant uveitis/ inflammatory bowel disease: TNFi (but not ETN)

*IL-17i is preferred in PsA with severe skin involvement

csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; MTX, methotrexate; SSZ, sulphasalazine; LEF, leflunomide; TNFi, tumour necrosis factor α inhibitors; ETN, etanercept; IL-17i, interleukin-17 inhibitors, IL-12/23i, interleukin-12/23 inhibitors, IL-23i, interleukin-23 inhibitors; JAKi, janus kinase inhibitors.

4. ADVANCED THERAPY IN SPONDYLOARTHRITIS (AXIAL SPA AND NON-RADIOGRAPHIC AXIAL SPA [NR-AXSPA])

4.1 Indication

Active spinal disease defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 or high disease activity with Ankylosing Spondylitis Disease Activity Score – C-reactive Protein [ASDAS-CRP] (preferred)/ASDAS-erythrocyte sedimentation rate [ASDAS-ESR] (refer to **Appendix 8**)

AND

No response with two consecutive non-steroidal anti-inflammatory drugs (NSAIDs) given at maximum doses for at least two weeks each OR incomplete response to two different NSAIDs over two months.[8]

4.2 Types of Advanced Therapy

4.2.1 Tumour Necrosis Factor Inhibitors (TNF-i)

i. Infliximab (IFX)/Biosimilar IFX

- 5 - 10 mg/kg at week 0,2 and 6, then every 6 to 8-weekly IVI. For administration of IFX, refer to **Appendix 2**.

ii. Etanercept (ETN)

- 50 mg/week SC

iii. Adalimumab (ADA)/Biosimilar ADA

- 40 mg 2-weekly SC

iv. Golimumab (GOL)

- 50 mg 4-weekly SC
- 2 mg/kg at 0, 4 weeks and 8-weekly IVI

For administration of IVI GOL, refer to **Appendix 3**.

4.2.2 Interleukin Inhibitors

i. Interleukin-17 Inhibitors

- **Secukinumab (SEC)**
  - With loading - 150 mg SC at week 0, 1, 2, 3, 4 followed by 4-weekly
  - Without loading - 150 mg SC 4-weekly

  May consider increasing to 300 mg in persistent active disease

- **Ixekizumab (IXE)**
  - Axial SpA - 160 mg SC at week 0, followed by 80 mg 4-weekly
  - nr-AxSpA - 80 mg SC 4-weekly

4.2.3 Targeted Synthetic Disease Modifying Anti Rheumatic Drugs

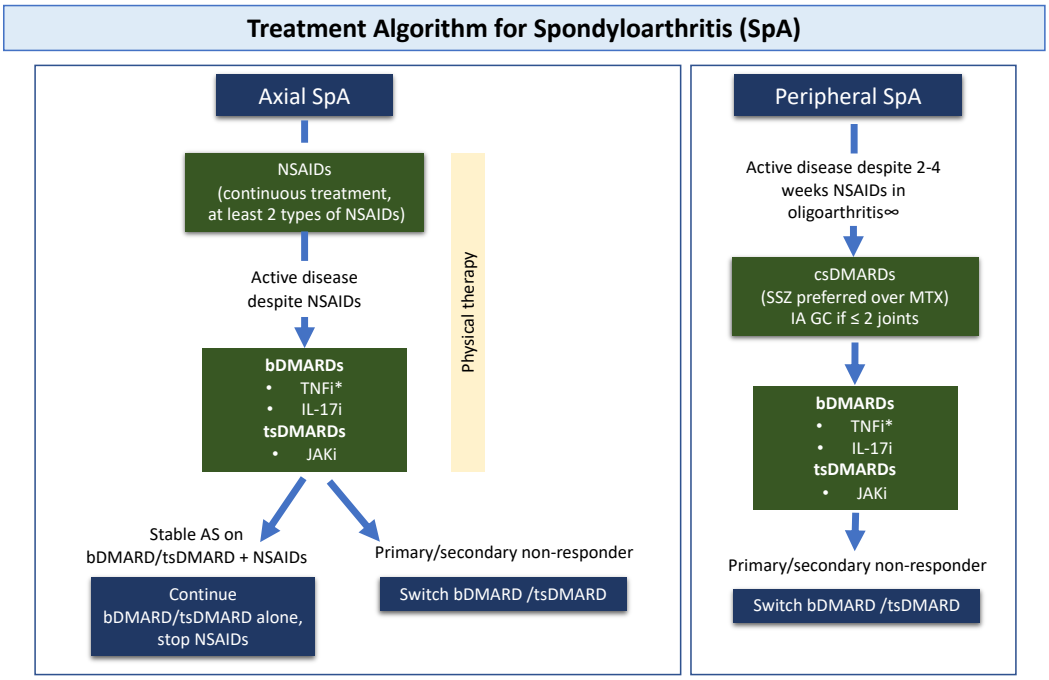
i. Janus Kinase Inhibitors (JAK-i)

- **Tofacitinib**
  - 5 mg BD PO

  FDA approved for ankylosing spondylitis, pending approval in Malaysia

- **Upadacitinib**
  - 15 mg OD PO

4.3 Treatment Algorithm



∞ in polyarthritis, to follow treatment algorithm for peripheral arthritis in PsA

*axSpA with uveitis or IBD, monoclonal antibody TNFi is preferred; For advanced hip arthritis, total hip arthroplasty is recommended.

csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; MTX, methotrexate; SSZ, sulphasalazine; IA GC, intra-articular glucocorticoids, TNFi, tumour necrosis factor α inhibitors; IL-17i, interleukin-17 inhibitors, JAKi, janus kinase inhibitors.

5. SWITCHING OF ADVANCED THERAPY

5.1 Switching Between Modes of Administration (MOA)/Types Of bDMARDs or tsDMARDs

If a bDMARD or tsDMARD has failed, treatment with another bDMARD or tsDMARD within the same or different MOA should be considered.[9]
Decision to switch within, or to another MOA should take into consideration treatment failure, intolerance and co-morbidities.

5.2 Timing of Switching Between Modes of Administration/Types of bDMARDs or tsDMARDs

Start new advanced therapy at the date scheduled for the next dose of the formerly used advanced therapy.[9]

6. CONVENTIONAL SYNTHETIC DISEASE MODIFYING ANTI RHEUMATIC DRUGS IN COMBINATION WITH ADVANCED THERAPY [10-15]

6.1 Tumour Necrosis Factor Inhibitors (Infliximab, Etanercept, Adalimumab, Golimumab)

- combination with MTX is preferred in RA. If MTX is contraindicated or patient is intolerant to it, other csDMARDs (SSZ or LEF) can be used as an alternative
- for PsA, can be used as monotherapy, or in combination with MTX. If MTX is

contradincated or patient is intolerant to it, other csDMARDs (SSZ or LEF) can be used as an alternative
- use as monotherapy in axial SpA

6.2 Interleukin Inhibitors

i. Interleukin-16 Inhibitor (Tocilizumab)
- use as monotherapy or in combination with other csDMARDs in RA

ii. Interleukin-17 Inhibitors (Secukinumab, Ixekizumab)
- use as monotherapy or in combination with other csDMARDs in PsA
- use as monotherapy in AS

iii. Interleukin-23 Inhibitor (Guselkumab)
- use as mono therapy or in combination with other csDMARDs in PsA

iv. Interleukin-12/23 Inhibitor (Ustekinumab)
- use as monotherapy or in combination with MTX in PsA

6.3 B-cell Depleting Therapy (Rituximab)

- preferably used in combination with MTX for better efficacy in RA. If MTX is contraindicated or patient is intolerant to it, other csDMARDs, especially LEF can be used as an alternative

6.4 Targeted Synthetic Disease Modifying Anti Rheumatic Drugs

- Janus Kinase inhibitors (JAK-i) (Tofacitinib, Baricitinib and Upadacitinib) can be used as monotherapy or in combination with MTX in RA.
- Tofacitinib and Upadacitinib can be used as monotherapy or in combination with csDMARDs in PsA.
- Upadacitinib is recommended as monotherapy in AS.

7. CONTRAINDICATIONS

These are contraindications for treatment:[16,17]
- Active serious infection
- Hypersensitivity to active substance
- Congestive cardiac failure with New York Heart Association (NYHA) grade 3 or 4*
- Multiple sclerosis or other demyelinating disorders
- Primary immunodeficiency states
- Bone marrow hypoplasia

* TNF-i only

8. PRECAUTION

Biologics should be used with caution in the following circumstances:
- Septic arthritis of a native joint within the last 12 months[18]
- Prosthetic joint sepsis within the last 12 months or indefinitely if the joints remain in situ[18]
- Family history of demyelination[19]
- Non-melanoma skin cancer (TNFi and UST, with concomitant psoralen ultraviolet A in

active psoriasis)[20]
Note: bDMARDs were previously thought to confer a higher risk of solid organ tumour. However, results from registries do not indicate that TNF-i alter the risk of cancer in RA patients[21]

- Previous history of intestinal ulceration or diverticulitis. There is an increased risk for gastrointestinal (GI) perforation if history of diverticulitis.[22]
- Older age and prednisolone use at >7.5 mg,[23] and major adverse cardiovascular event (MACE) if age >65 with other cardiovascular risk factors e.g. smoking in tsDMARDs.[24]

9. CRITERIA FOR TAPERING OR WITHDRAWAL OF BIOLOGIC OR TARGETED SYNTHETIC DISEASE MODIFYING ANTI RHEUMATIC DRUGS

Consider tapering when disease has been in remission for a minimum of 12 months for RA and may be considered for PsA, especially when bDMARD or tsDMARD is used concomitantly with a csDMARD.[25, 26]

10. SPECIAL SITUATIONS

10.1 Vaccinations

10.1.1 General

- Completion of all appropriate immunisations should be considered according to current immunisation guidelines.
- Patients who have never been exposed to hepatitis B infection [negative hepatitis B surface antigen (HBsAg)], antibody to hepatitis B core (anti-HBc) and antibody to hepatitis B surface protein (anti-HBs) should be considered for vaccination against hepatitis B.

10.1.2 Live Attenuated Vaccines

- is not recommended in patients on bDMARDs and tsDMARDs
- should be administered 2- 4 weeks **prior** to treatment initiation
- should be avoided during immunosuppression, with a possible exception of a cautious use of measles, mumps, rubella (MMR) booster and herpes zoster (HZ) vaccine under special circumstances.[27,28] However, if required, it can be given as shown in **Table 3**
- should be avoided during the first six months of life in newborns of mothers treated with bDMARDs during second-half of pregnancy[29]

Table 3. Timing of Live Attenuated Vaccine Administration for patients on bDMARD and tsDMARD

bDMARD	Timing after last dose*
TNF-i, IL-17, IL-12/23, IL-23	1 dosing interval
IL-6 inhibitors	1 dosing interval
Rituximab	6 months
JAK inhibitors	1 week

*Biologics should be withheld for 4weeks after administration of live attenuated vaccination

Source: Bass AR, Chakravarty E, Akl EA et al. 2022 American College of Rheumatology Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases. Arthritis Care Res

(Hoboken). 2023 Mar;75(3):449-464.

Table 4. American College of Rheumatology (ACR) Recommendations Update Regarding the Use of Vaccines in Patients with Rheumatoid Arthritis

Therapies	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumo-coccal	Influenza (intra-muscular)	Hepatitis B	Human Papilloma Virus	Herpes Zoster
Before initiating therapy					
TNF blockers	✔	✔	✔	✔	✔
Non-TNF blockers	✔	✔	✔	✔	✔
While already taking therapy					
TNF blockers	✔	✔	✔	✔	Not recommended
Non-TNF blockers	✔	✔	✔	✔	Not recommended

Source: Singh JA, Saag KG, Bridges SL Jr et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26.

10.2 COVID-19 Vaccination

General guidance:[30]

- There should be a shared decision between the clinician and patient regarding COVID-19 vaccination.
- Patients with autoimmune inflammatory rheumatic diseases (AIIRD) should be prioritized to receive COVID-19 vaccination. This is because they are at higher risk of severe COVID-19 infection with a worse outcome compared to the general population.
- The expected response to COVID-19 vaccination for patients on immunomodulatory treatment is likely to be blunted in its magnitude and duration compared to the general population.
- A theoretical risk for flare or disease worsening exists following vaccination.

Refer to the latest Ministry of Health Malaysia Clinical Guidelines on COVID-19 vaccination in Malaysia.

Table 5. Timing of COVID-19 Vaccine

Medication	Action
tsDMARDs Tofacitinib, Baricitinib, Upadacitinib	With-hold for 1 week after each vaccine dose; no modification to vaccination timing
bDMARDs Infliximab, Etanercept, Adalimumab, Golimumab, Tocilizumab, Secukinumab, Ixekizumab, Ustekinumab, Guselkumab	No modifications to either immunomodulatory therapy or vaccination timing
Rituximab	Vaccinate 4 weeks prior to next scheduled infusion; delay next infusion 2 - 4 weeks after second vaccine dose if disease activity allows

Source: Malaysia Ministry of Health. Clinical Guidelines on COVID-19 vaccination in Malaysia (Fourth Edition). Putrajaya: MoH; 2021

10.3 Pregnancy and Lactation

AIIRD often affects women in their reproductive years. Monoclonal antibodies (IFX, ADA, GOL) behave similarly to maternal immunoglobulin G (IgG) antibodies both in terms of active transplacental transfer and their persistence in neonatal circulation up to six 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 (ETN) due to its low affinity to neonatal IgG transporter.[31,32] Animal reproduction studies have failed to demonstrate a risk to the fetus.

With regards to tsDMARDs there are lack of data to determine its use in pregnancy and lactation as its small molecular size suggests transfer across the placenta and into breast milk.

- Women with AIIRD who plan to get pregnant should be started on pregnancy compatible medication.
- Women with AIIRD receiving medication that is incompatible with pregnancy should be switched to pregnancy compatible drugs prior to planned pregnancy.
- Pregnant women with active AIIRD that require medical therapy should continue or be switched to a pregnancy-compatible medication

The medications before and during pregnancy, and during lactation are shown in **Table 6**.

Table 6. Maternal Medication Use: Overview of Medication Use Before and During Pregnancy, and During Breastfeeding

Medication	Pre-conception	During pregnancy	Breastfeeding
TNF-i is considered compatible with pregnancy			
Infliximab	Yes	Yes[a]	Yes
Etanercept	Yes	Yes[b]	Yes
Adalimumab	Yes	Yes[c]	Yes
Golimumab	Yes	Yes[c]	Yes
Other bDMARDs (limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy)			
IL-6 inhibitors	Consider stopping at conception[d]	Severe disease if no alternatives[d,e]	Yes[f]
IL-17 inhibitors	Consider stopping at conception[d]	Severe disease if no alternatives[d,e]	Yes[f]
IL-23 inhibitors	No data	No data	No data
IL-12/23 inhibitors	Consider stopping at conception[d]	Severe disease if no alternatives[d,e]	Yes[f]
Rituximab	Consider stopping at conception[d]	Severe disease if no alternatives[d,e]	Yes[f]
JAK inhibitors	Stop ≥2weeks pre-conception	No	No

[a]-If low risk of disease flare and stopped by 20 weeks, full-term infants can have normal vaccination schedule.
[b]-If low risk of disease flare and stopped by 32 weeks, full-term infants can have normal vaccination schedule.
[c]-If low risk of disease flare and stopped by 28 weeks, full-term infants can have normal vaccination schedule.
[d]-May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.
[e]-If used in third trimester, avoid live attenuated vaccinations in infant vaccination schedule until 6 months of age.
[f]- limited evidence

Adapted: Russell MD, Dey M, Flint J et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2023 Apr 3;62(4):e48-e88.

10.4 Perioperative Management

Biologic DMARDs and tsDMARDs should be withheld close to one dosing cycle prior to

elective surgery and restarted after evidence of wound healing typically 14 days in the absence of infection and wound healing is complete.

Time of surgery scheduled in relation to the last dose of medication administered are listed in **Table 7.**

Table 7. Perioperative Management of bDMARDs and tsDMARDs in Patients with Rheumatic Diseases Undergoing Elective Surgery

Drugs	Schedule surgery (relative to last dose administered)[33]
SC Adalimumab/Biosimilar Adalimumab	Week 3
SC Etanercept	Week 2
SC Golimumab IVI Golimumab	Week 5 Week 9
IVI Infliximab/Biosimilar Infliximab	Week 5, 7 or 9 (depending on dosing interval of every 4, 6 or 8 weekly)
IVI Rituximab	Month 7
SC Tocilizumab IVI Tocilizumab	Week 2 Week 5
SC Secukinumab	Week 5
SC Ixekizumab	Week 5
SC Ustekinumab	Week 13
SC Guselkumab	Week 9
Tofacitinib	Day 4
Baricitinib	Day 4
Upadacitinib	Day 4

Source: Goodman SM, Springer BD, Chen AF et al. 2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Arthritis Care Res (Hoboken). 2022 Sep;74(9):1399-1408.

11. SCREENING PRIOR TO INITIATION OF ADVANCED THERAPY

11.1 Tuberculosis

The incidence of TB in Malaysia was reported at 92 per 100,000 population with 25,173 cases of the disease recorded in 2018.[34] National data on prevalence on latent tuberculosis infection (LTBI) is scarce. However, prevalence of LTBI among Malaysian health care

workers is 10.6%.[35] LTBI is defined as infection with mycobacterium TB complex, where the bacteria may be alive but in the state of dormancy and not currently causing any active disease or symptoms. LTBI patients have a 5 - 10% lifetime risk of progression to active TB and the risk is higher in immunosuppressed patients[36]. The reactivation tends to occur within the first two years after exposure.[37]

The overall risk of developing active TB whilst on TNFi is higher compared to general population.[38] Although less common, there is also a risk of TB reactivation with other classes of advanced therapy. Therefore, TB screening prior to commencing advanced therapy is strongly recommended to exclude active and latent TB.[39-41]

11.1.1 Tuberculosis Screening

Screening for LTBI or active TB infection must be done prior to starting advanced therapy (refer to **Appendix 9**).

The screening includes:

- Complete history, including prior TB treatment and contact with TB patients, and full physical examination.

AND

- Chest X-ray (CXR)
  CXR should be done within three months prior to initiation of advanced therapy. Patients with abnormal CXR and/or symptoms suspicious of TB should be investigated for active disease.

- Tuberculin Skin Test (TST)
  TST is one of the methods to determine whether a person is infected with *Mycobacterium tuberculosis*. Cut-off point for positive TST[42]
  - ≥10 mm for immunocompetent patient
  - ≥5 mm for immunosuppressed patient

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

OR

- Interferon gamma release assay (IGRA)[42] if available
  - QuantiFERON-TB Gold-In Tube (QFT-GIT) or
  - 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%, respectively)[42]

Once an TST/IGRA is positive, do not repeat the test as there is no clinical utility. If the TST/IGRA is negative, the decision to repeat TB screening will depend on clinician's assessment of patient's risk.

11.1.2 Chemoprophylaxis for Latent Tuberculosis Infection (LTBI)

Table 8. Anti-tuberculosis Regimens for LTBI in Adults

Drugs	Duration	Interval	Dosage
Isoniazid (INH)	6 - 9 months	Daily	5 mg/kg, max 300 mg
Isoniazid + Rifampicin (RIF)	3 months	Daily	INH: 5 mg/kg, max 300 mg RIF: 10 mg/kg, max 600 mg
Rifampicin	4 months	Daily	10 mg/kg, max 600 mg
Isoniazid + Rifapentine (RPT)*	3 months	Once weekly	INH: 15 mg/kg, max 900 mg RPT: <50 kg; 750 mg >50 kg; 900 mg

*Rifapentine is not currently registered in Malaysia. Its use should be restricted to those on directly observed therapy (DOT).
Note: Pyridoxine 10 mg/day should be given for all adult patients in INH and a higher dose of 30 mg/day for individuals at high risk of neuropathy.

Source:

1. Coates LC, Soriano ER, Corp N et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol. 2022 Aug;18(8):465-479.
2. World Health Organisation, WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment: Module 1: Prevention. Geneva: WHO; 2020

11.1.3 Timing of Biologic Therapy

- **Latent tuberculosis**

The ideal timing to initiate advanced therapy following chemoprophylaxis for latent TB has not been established. Preferably the initiation of advanced therapy should be about four weeks of TB chemoprophylaxis. However, if clinically indicated, treatment with advanced therapy can be commenced concurrently or earlier than four weeks.[41]

- **Previous tuberculosis prior to biologic therapy**
  - Previous completed or successful TB treatment
    Advanced therapy can be started if the patient had received previous completed TB treatment and active TB has been ruled out. These patients should be monitored clinically every three months and screened for active TB if necessary.

  - Previous incomplete TB treatment
    Patients who had incomplete 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 advanced therapy.

- **Active tuberculosis diagnosed prior to biologic therapy**

Ideally, advanced therapy should be delayed **until anti-TB treatment is completed**. However, if advanced therapy is required earlier, it **may be commenced after two months of intensive anti-TB treatment** and until the drug susceptibility profile is known and clinical improvement is evident (if positive cultures obtained).

11.2 Screening for Viral Hepatitis Infection

Advanced therapy poses a risk for hepatitis B virus (HBV) and hepatitis C virus (HCV) reactivation. Screening for these viruses prior to commencing treatment and subsequent risk stratification is important. Co-management with hepatologist for prophylactic anti-viral treatment especially in the setting of chronic HBV infection is recommended when necessary.

Recommended screening tests include:[41]

- Hepatitis B surface antigen (HBsAg)
- Antibody to hepatitis B surface protein (anti-HBs)
- Antibody to hepatitis B core antigen (anti-HBc)
- Antibody to hepatitis C virus (anti-HCV)

11.2.1 Hepatitis B Virus Screening and Prophylaxis

Patients who are at moderate or high risk of HBV reactivation should be considered for prophylactic anti-viral treatment (refer to **Table 9**).

Table 9. Risk of Hepatitis B Virus Reactivation According to Serologic Status of Chronic Hepatitis B and Type of Advanced Therapy

Medication	Chronic HBV infection [HBsAg (+)]	Resolved HBV infection [HBsAg (-)/ anti-HBc (+)]
bDMARDs		
TNF-α inhibitors	Moderate	Low
IL-6 inhibitors	Moderate	Low
IL-17 inhibitors	Moderate	Low
IL-12/23 inhibitors	Moderate	Low
Rituximab	Very high	High
tsDMARDs		
JAK inhibitors	Moderate	Low

Source: Koutsianas C, Thomas K, Vassilopoulos D. Reactivation of hepatitis B virus infection in rheumatic diseases: risk and management considerations. Ther Adv Musculoskelet Dis. 2020 Mar 16;12:1759720X20912646.

Based on professional society recommended guidelines patient with chronic hepatitis B should receive antiviral prophylaxis when starting advanced therapy. Patient with resolved hepatitis B infection (anti-HBs-negative and anti-HBc-positive) are recommended to receive antiviral prophylaxis.[43]

The ideal timing for commencing anti-viral prophylaxis especially in the setting of high baseline viral load is 1 - 2 weeks before starting immunosuppressive treatment. If delaying the start of advanced therapy is not feasible, anti-viral should be started as soon as possible

and continued for at least six months after the end of antirheumatic treatment (12 months if that treatment is RTX).[43]

11.2.2 Hepatitis C Virus Screening

Anti-HCV screening tests must be conducted for all patients commencing on advanced therapies, especially those starting on rituximab. There is no prophylactic treatment to prevent HCV reactivation.

HCV ribonucleic acid (RNA) must be evaluated in individuals found to be anti-HCV-positive. If HCV RNA is negative, the test should be repeated three months later. ALT and AST tests must be repeated once a month and HCV RNA test must be repeated once every three months in HCV RNA positive patients initiated biological drugs. In case of HCV reactivation (≥3 times increase in ALT level and ≥1 log increase in HCV RNA titer), discontinuation of the advanced therapy must be considered.[44 - 46]

11.3 Screening for Human Immunodeficiency Virus (HIV)

Screening test include anti-HIV antibody test. Management of HIV patients receiving advanced therapy includes co-management with an infectious disease specialist and careful monitoring of viral loads and CD4 counts.[44 - 46]

12. MONITORING DURING ADVANCED THERAPY

12.1 Baseline and Subsequent Investigations

Refer to **Table 10** and **Table 11** for baseline and subsequent investigations during advanced therapy.

Table 10. Baseline and Subsequent Investigations During Tumour Necrosis Factor Inhibitors, Interleukin Inhibitors and B-cell Depleting Therapy

<table>
<tr><th>Drug</th><th>Baseline investigation</th><th>Subsequent investigations</th><th>Frequency of monitoring</th><th>Additional monitoring</th></tr>
<tr><td>Adalimumab</td><td rowspan="5">• FBC
• LFT
• Serum creatinine
• Fasting glucose
• Fasting lipid
• Serology for HIV, HBsAg, anti-HBc and anti-hepatitis C antibody
• Urine pregnancy test (if indicated)</td><td rowspan="5">• FBC
• Serum creatinine
• ALT and/or AST
• ESR/CRP</td><td rowspan="4">At week 4 then 3-monthly</td><td rowspan="4">Signs and symptoms of demyelinating disorders</td></tr>
<tr><td>Etanercept</td></tr>
<tr><td>Infliximab/ IFX-biosimilar</td></tr>
<tr><td>Golimumab</td></tr>
<tr><td>Tocilizumab</td><td>8 weeks after initiation then 3-monthly</td><td>• Fasting lipid
• Monitor for sign and symptoms of gastrointestinal perforation</td></tr>
</table>

Rituximab	• TB screening (refer to **Appendix 10**)		During treatment and up to 12 months after treatment	• IgG level • Hepatitis B virus reactivation
Secukinumab			Monitor 2 to 3-monthly thereafter	Monitor for sign and symptoms of inflammatory bowel disease
Ustekinumab				
Guselkumab				

Adapted from: Malaysia Ministry of Health. Clinical Practice Guidelines on Management of Rheumatoid Arthritis. Putrajaya: MoH; 2019.

Table 11. Baseline and Subsequent Investigations During tsDMARDs Therapy

Drug	Baseline investigation	Subsequent investigations	Frequency of monitoring	Additional monitoring
Tofacitinib	• FBC • LFT • Serum creatinine • Fasting glucose • Fasting lipid • Serology for HIV, HBsAg, anti-HBc and hepatitis C virus • Urine pregnancy test (if indicated)	• FBC • Serum creatinine • ALT and/or AST • ESR/CRP • Fasting lipid • Albumin	At week 4 then 3-monthly	Monitor sign and symptoms of herpes zoster infection, major adverse cardiovascular event (MACE), veno-thrombo-embolism, gastrointestinal perforation and malignancy
Baricitinib	• TB screening (refer to **Appendix 10**)		4 - 8 weeks after initiation then 3-monthly	
Upadacitinib*				

Adapted from:
1. Malaysia Ministry of Health. Clinical Practice Guidelines on Management of Rheumatoid Arthritis. Putrajaya: MoH; 2019.
2. Product insert of the Rinvoq ® (Upadacitinib)

12.2 Tuberculosis Surveillance during bDMARD and tsDMARD Therapy

Obtain history suggestive of TB, history of contact with TB patients and perform a physical examination during periodic review. A repeat CXR is indicated if patient has symptoms and/or

contact with TB patient.

12.3 Tuberculosis Developing During Advanced Therapy

Patients who develop active TB while on advanced therapy should receive full anti-tuberculous treatment. Biologic DMARDs or tsDMARDs should be discontinued temporarily.

13. TYPES OF ADVANCED THERAPY

The mechanism of action and pharmacokinetics of the various advanced therapies are listed here according to their class. Refer to **Appendix 10** for dose adjustments in renal and liver impairment.

Certain common adverse effects e.g. infection, risk of malignancy, biochemical abnormalities may occur with any of the advanced therapies. The adverse effects relevant to the specific class of advanced therapies are listed in the tables.

13.1 Tumour Necrosis Factor Inhibitor (TNF-i)

Table 12. Tumour Necrosis Factor Inhibitors in Malaysia

DRUGS	MECHANISM OF ACTION/PHARMACOLOGY	HALF LIFE	ADVERSE EVENTS
Etanercept	Dimeric fusion protein that binds soluble and cell bound TNF, preventing interaction with cell surface TNF receptors	3 - 5 days	• Serious infections • Tuberculosis • SLE-like syndromes • Congestive cardiac failure • Demyelination and neurological complications • Pancytopenia • Malignancy
Infliximab/ Biosimilar Infliximab	Chimeric mouse/human monoclonal antibody (mAB) that binds soluble and cell bound TNF, preventing interaction with cell surface TNF receptors	8 - 10 days	
Adalimumab/ Biosimilar Adalimumab	Human mAb that binds TNF, preventing interaction with cell surface TNF receptors	10 - 14 days	
Golimumab	Human mAb that binds to soluble and transmembrane bioactive form of human TNF alpha, preventing interaction with cell surface TNF receptors	9 - 15 days	

13.2 Rituximab

Refer to **Appendix 5** on Administration of Rituximab.

Table 13. Rituximab

MECHANISM OF ACTION/ PHARMACOLOGY	HALF-LIFE	ADVERSE EVENTS
Humanised chimeric anti-CD20 with complement-mediated cytotoxicity; antibody-dependent cell-mediated toxicity and apoptosis	Approximately 3 weeks	**Infusion reactions:** About 30% after the first infusion*, less with the second infusion (9%). Severe infusion reactions may occur but are rare. Acute infusion reactions may occur within 30 minutes - 2 hours of the first rituximab infusion.[47, 48] These consist of fever, headache, rigors, flushing, nausea, rash, and upper respiratory tract infection (URTI) symptoms. Transient hypotension and bronchospasm are usually related to the infusion rate.[47, 48] If the patient experiences an infusion reaction[47] ○ 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. **Infections:** • There is a slight increase in infections compared with the placebo population, especially in patients with low IgG. • The reported incidence of any type of infection was 39% but mainly mild.* • Serious infection was reported as 2%.* The most common severe infections were pneumonia, cellulitis, and urinary tract infection. • Reactivation of Hepatitis B with fulminant hepatitis. • The occurrence of PML in rituximab-treated remains very rare. (<1 in 10,000)[#]

13.3 Tocilizumab

Refer to **Appendix 4** on Administration of TCZ.

Table 14. Tocilizumab

MECHANISM OF ACTION/ PHARMACOLOGY	HALF LIFE	ADVERSE EFFECT
Inhibits binding of IL-6 to its receptor	8 - 14 days	oral herpes simplex, herpes zoster, diverticulitis, gastrointestinal perforation, Steven-Johnson syndrome, dyslipidaemia, weight gain, hypertension

13.4 Interleukin-17 Inhibitors (Secukinumab, Ixekizumab)

Table 15. Interleukin-17 Inhibitors in Malaysia

DRUGS	MECHANISM OF ACTION/PHARMACOLOGY	HALF LIFE	ADVERSE EVENTS
Secukinumab	Fully human IgG1 mAb that selectively neutralizes the IL-17A	22 - 31 days	• URTI - Nasopharyngitis • Herpes simplex (Mucocutaneous) • Rhinorrhoea • Diarrhoea • Urticaria
Ixekizumab	Humanised IgG4 mAb that binds to IL-17A (both IL-17A & IL-17A/F)	13 days	• URTI • Injection site reactions • Tinea Infection • Oropharyngeal pain • Nausea

13.5 Interleukin-12/23 Inhibitors

Table 16. Interleukin-12 and Interleukin-23 Inhibitors in Malaysia

DRUGS	MECHANISM OF ACTION/PHARMACOLOGY	HALF LIFE	ADVERSE EVENT
IL-12 & IL-23			**1-10%:** • Headache (4.6%) • Injection site reactions (4.5%) • Arthralgia (2.7%) • Elevated liver enzymes (2.6%) • Diarrhoea (1.6%)
Ustekinumab	Fully human IgG1 mAb that binds to the p40 subunit of IL-12 & IL-23	15 - 32 days (median 3 weeks)	
IL-23			

Guselkumab	Fully human immunoglobulin G1 lambda (IgG1λ) mAb that blocks the p19 subunit of IL-23	15 - 18 days	• Gastroenteritis (1.3%) • Tinea infections (1.1%) • Herpes simplex infections (1.1%) **>10%:** • Infections (23%) • Upper respiratory tract infections (14.3%)

13.5.1 Interaction with Other Medicinal Products and Other Forms of Interaction

- **Interactions with CYP450 substrates**

In a Phase 1 study in subjects with moderate to severe plaque psoriasis, changes in systemic exposures (C_{max} and AUC_{inf}) of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant, indicating that drug interactions between guselkumab and substrates of various cytochrome (CYP) enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely. There is no need for dose adjustment when co-administering guselkumab and CYP450 substrates.

- **Concomitant immunosuppressive therapy or phototherapy**

In psoriasis studies, the safety and efficacy of Tremfya in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

13.6 Targeted Synthetic Disease Modifying Anti Rheumatic Drugs

13.6.1 Janus Kinase Inhibitors

Table 17. Janus Kinase Inhibitors (JAKi) in Malaysia

DRUGS	MECHANISM OF ACTION/ PHARMACOLOGY	HALF LIFE	ADVERSE EFFECT
Tofacitinib	JAK1/JAK3 >> JAK2/TYK2 inhibitor	0.8 - 1 hour	Lipid elevation, ALT increase, increase in phosphokinase, venous thrombosis, herpes zoster, cytopaenia, gastrointestinal perforation*, major adverse cardiovascular event**
Baricitinib	JAK1/JAK2 > TYK2 > JAK3	12 hours	
Upadacitinib	JAK1	8 -14 hours	

*use with caution in patients at increased risk for GI perforation (e.g. history of diverticulitis, older age and prednisolone use at >7.5 mg)[22]
**patients at greatest risk were older (age > 65) and had other cardiovascular risk factors (e.g., smoking)[24]

13.6.2 Drug-drug Interaction

i. Tofacitinib

- dose reduction to 5 mg OD
- potent CYP3A4 inhibitors e.g. ketoconazole, fluconazole

ii. Baricitinib

- dose reduction to 2 mg OD
- organic anion transporter 3 (OAT3) inhibitor e.g. probenecid

iii. Upadacitinib

- no recommendation for dose adjustment
- potent CYP3A4 inhibitors e.g. fluconazole (use with caution)
- strong CYP3A4 inducers e.g. rifampicin (monitor change in disease activity)

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APPENDIX 1

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)

SDAI	DISEASE ACTIVITY
>22	High
10 - 22	Moderate
<10	Low
<2.8	Remission

APPENDIX 2

ADMINISTRATION OF INTRAVENOUS INFLIXIMAB

Dosage:

Rheumatoid Arthritis

- 3 mg/kg IV given at weeks 0, 2, and 6 weeks and every 8 weeks thereafter

Ankylosing Spondylitis

- 5 mg/kg IV given at weeks 0, 2, and 6 weeks and every 8 weeks thereafter

Psoriatic Arthritis

- 5 mg/kg IV given at weeks 0, 2, and 6 weeks and every 8 weeks thereafter

Calculate the appropriate dose based on patient weight.

Administration of IV Infliximab

- Calculate the dose, total volume of reconstituted solution required, and the number of vials needed (1 vial contains 100 mg in 20 mls solution)
- Reconstitute each 100 mg vial with 10 ml of Sterile Water for injection to obtain a concentration of 10 mg/ml. Gently swirl the solution by rotating the vial. DO NOT SHAKE.
- Allow the reconstituted solution to stand for 5 minutes. The reconstituted solution should be colourless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein.
- Dilute the total volume of the reconstituted solution to 250 ml with sterile normal saline bottle/bag.
- Gently invert the bottle/bag to mix the solution. The resulting infusion concentration should range between 0.4 mg/ml (minim recommended concentration) and 4 mg/ml (maximum recommended concentration) of infliximab.
- Discard any unused portion of the reconstituted solution remaining the vials.
- The infusion should begin within 3 hours of reconstitution and dilution.
- Infuse the solution for at least 2 hours with an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 μm or less). Avoid concomitant infusion with other agents in the same IV line.

Source:

1. Janssen Immunology. Infliximab [Assessed on 24 September 2023] Available at: www.infliximab.com.
2. Remicaide® (Infliximab) Prescribing Information. www.accessdata.fda.gov. Revised 08/2017 (accessed on 24 September 2023).

APPENDIX 3

ADMINISTRATION OF INTRAVENOUS GOLIMUMAB

Dosage

2 mg/kg intravenous infusion over 30 minutes at Weeks 0 and 4, and every 8 weeks after.

Calculate the appropriate dose based on patient weight. Multiply weight in kg by 2 for total dose in milligrams (mg) Example: Patient weight in kg x 2 = total dose (mg).

Multiple the number of vials required by 4 for total volume to be withdrawn from the vials. Example: number of vials required X 4 = total volume to be withdrawn.

Administration of Intravenous Golimumab

- Dose: 2 mg/kg (vial contains 50 mg per 4 mls solution [12.5 mg od golimumab per ml]).
- Solution should be colourless to light yellow. Fine translucent particles may develop as golimumab is a protein. Do not use if opaque particles, discolouration, or other foreign particles are present.
- Dilute the total volume of golimumab solution with 100 ml normal saline (alternative solution: 0.45% sodium chloride). Gently mix and discard any unused solution remaining in the single-dose vials. Once diluted, the infusion solution can be stored for 4 hours at room temperature.
- Infuse the diluted solution over 30 minutes.

Source: Golimumab @ Simponi ARIA Dosing and Administration Guide for Adult Patients. www.simponiariahcp-v1.com/files/simponi_aria_dosing_and_admin_guide_new.pdf

APPENDIX 4

ADMINISTRATION OF INTRAVENOUS TOCILIZUMAB

Dosage

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

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

Administration of Intravenous Tocilizumab

- Dose: 4 - 8 mg/kg (vial contains 80 mg per 4 ml or 400 mg per 20 ml).
- Allow the solution to reach room temperature prior to infusion. Solution should be colourless. Do not use if discolorations or foreign particles are present.
- Dilute tocilizumab for infusion to a final volume of 100 ml using 0.9% sodium chloride with aseptic technique.
- To mix the solution, gently invert to avoid foaming.
- 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.
- 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.
- Premedication is not required.

Caution

- Haematological abnormalities - neutropenia, thrombocytopenia.
- Hepatic transaminases >1.5x ULN
- Hyperlipidaemia - elevated total cholesterol, triglyceride, LDL cholesterol

Source:

1. Actemra® (Tocilizumab) Prescribing Information. www.accessdata.fda.gov. Revised 08/2017 (accessed on 24 September 2023).
2. Tocilizumab. Drug Information. UpToDate 2014, Topic 10208 Version 70.0.

APPENDIX 5

ADMINISTRATION OF RITUXIMAB

Pre-medication Drugs

- 100 mg intravenous methylprednisolone or equivalent before infusions
- Paracetamol 1 gm P.O - 30 - 60 minutes prior to infusion
- Chlorpheniramine 4 mg P.O - 30 - 60 minutes prior to 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; first 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 first or second infusion.

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

Infusion Rate for DAY 1 Infusion

Time	mg/hour	ml/hour
First 30 minutes	50	25
Second 30 minutes	100	50

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

Infusion Rate for DAY 15 Infusion

Time	mg/hour	ml/hour
First 30 minutes	100	50
Second 30 minutes	200	100

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

If patients did not experience a serious infusion-related rection with their first or subsequent infusions of the standard dose of rituximab, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions. Initiate at a rate of 250 mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.

Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

Source: Rituximab Intravenous Infusion for Rheumatoid Arthritis (RA) and Vasculitis. Guideline number 792FM. Version 2.0. Effective date: March 2022. www.bucksformulary.nhs.uk/docs/Guideline_792FM.pdf. Accessed on 24 September 2023.

Example of Pre-Treatment Checklist

PRE-TREATMENT CHECKLIST

Patient's name:
Hospital number/ MRN/ IC:
Date:
Assessment performed by:

Temperature	: _____°C	Pulse	: _____bpm
Respiratory	: _____rpm	Blood Pressure	: _____mm/Hg
Urinalysis	: _____	(Optional)	

Is the patient pregnant/ breastfeeding? ☐ Yes ☐ No ☐ N/A

Any current infection e.g., URTI, dental abscess, UTI? ☐ Yes ☐ No

Any vaccinations in the last 4 weeks: ☐ Yes ☐ No

BLOOD TESTS RESULTS
Full blood count:
Liver function test:
Renal profile:
ESR/CRP:
Hepatitis B/C:

CHECKLIST	Yes	No
Does the patient have an information leaflet about Rituximab?		
Does the patient know details of first infusion? Date/Time: Venue:		
Does the patient know that any anti-hypertensive medication needs to be omitted on the morning of infusion?		
Does the patient know dates for second infusion second pre-treatment visit?		
Are the necessary medications prescribed ready for the infusion?		

Example of Administration of Rituximab Infusion Form

ADMINISTRATION OF RITUXIMAB INFUSION

PATIENT DETAILS
Patient Name:
MRN:
Ward:
Date:

Rituximab infusion (please circle): 1st | 2nd

CHECKLIST PRIOR TO COMMENCING INFUSION	Yes	No
1. Confirm patient identity.		
2. Blood test reviewed by doctor		
3. Pre-assessment review documented in notes		
4. Drug chart completed for rituximab, pre-infusion and pre-medications		
5. Baseline observation on arrival within normal parameters. 6. If yes, proceed as per guidelines		

Document all observations, infusion rates and any other information on the nursing record sheet.

NURSING OBSERVATION RECORD FOR RITUXIMAB INFUSION

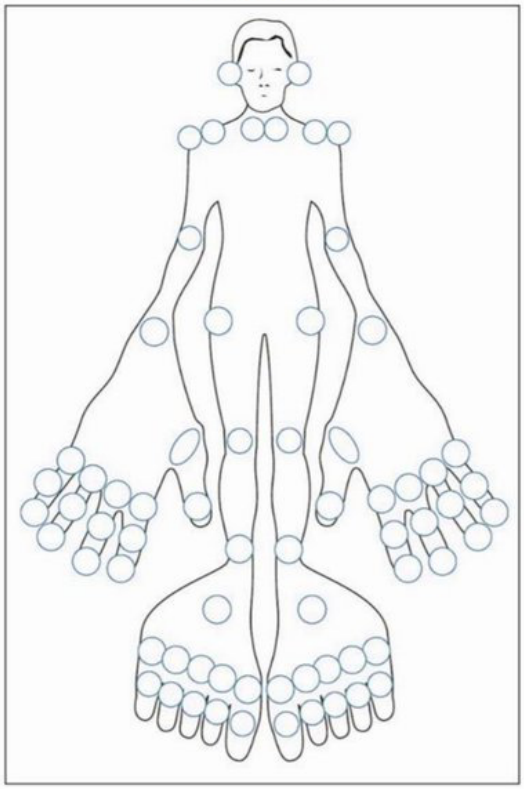
Date :
Name :
MRN :

Time duration of infusion	:_____	hr/mins
Rate of infusion	:_____	ml/hr
Blood pressure	:_____	mmHg
Pulse rate	:_____	bpm
Temperature	:_____	°C
Oxygen saturation	:_____	%
Any adverse reaction: (circle)	: Yes / No	

APPENDIX 6

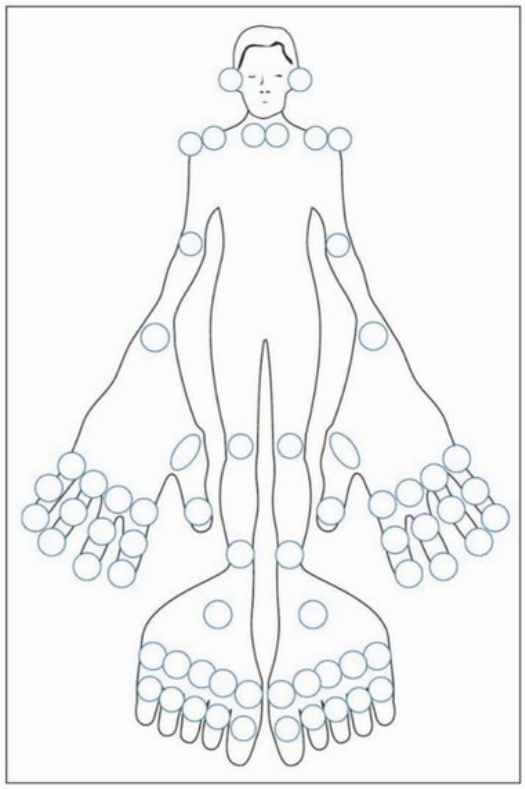
DAPSA (Disease Activity in PSoriatic Arthritis) Score

Tender Joints



1. Tender Joints Count (0-68), TJ: ☐☐

Swollen Joints



2. Swollen Joints Count (0-66), SJ: ☐☐

3. CRP (mg/dl): ☐☐☐

4. Patient's assessment of disease activity and pain

- How active was your rheumatic disease on average during the last week?

not active — 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10 — very active

- How would you describe the overall level of joint pain during the last week?

none — 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10 — very severe

DAPSA = TJ + SJ + CRP + Activity + Pain = ☐

Disease Activity: 0-4 Remission, 5-14 low, 15-28 moderate, >28 high Disease Activity

Source: Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010 Aug;69(8):1441-7.

APPENDIX 7

BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI)

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on an NRS

1. How would you describe the overall level of fatigue / tiredness you have experienced?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

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

none 0 1 2 3 4 5 6 7 8 9 10 very severe

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

none 0 1 2 3 4 5 6 7 8 9 10 very severe

4. How would you describe the level of discomfort you have had from an area tender to touch or pressure?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

5. How would you describe the level of morning stiffness you have had from the time you wake up?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

6. 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 hour 1 hour 2 or more hours

Calculation of BASDAI:
-Compute the mean of questions 5 and 6.
-Calculate the sum of the values of question 1-4 and add the result to the mean of questions 5 and 6.
-Divide the result by 5.

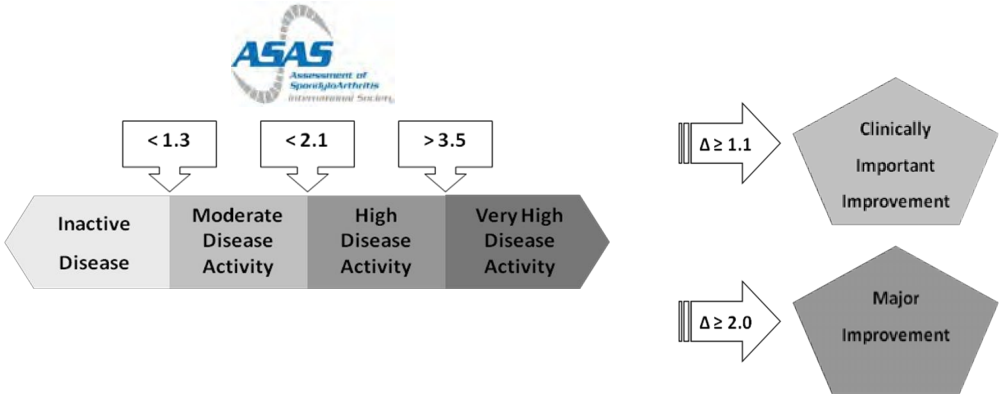
Alternatively, a VAS between 0 and 10 cm or 0 and 100 mm can be used. ASAS prefers to use a NRS.

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

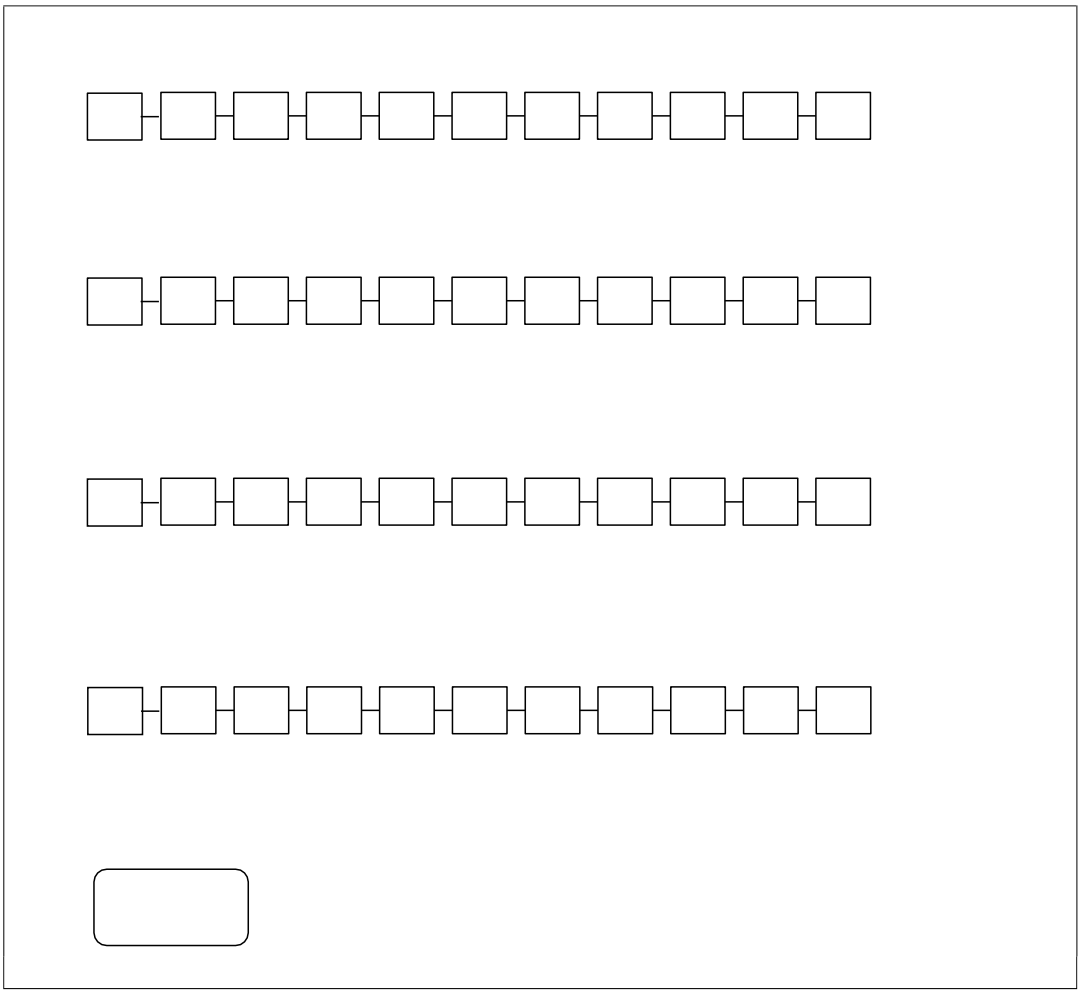
APPENDIX 8

ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE (ASDAS) FORMULAS: ASDAS-ESR AND ASDAS-CRP (PREFERRED)

Quick ASDAS*ESR Calculation Form



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

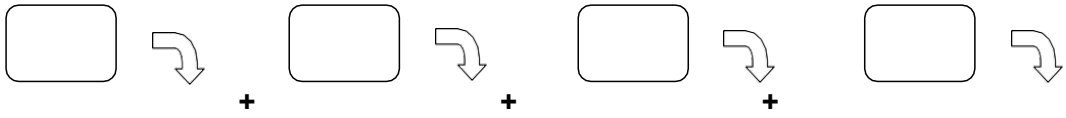


Back Pain	
0	**0,0**
1	**0,1**
2	**0,2**
3	**0,2**
4	**0,3**
5	**0,4**
6	**0,5**
7	**0,6**
8	**0,6**
9	**0,7**
10	**0,8**

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**

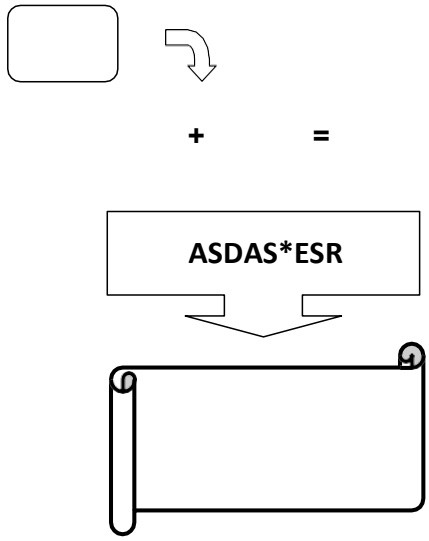
Patient Global	
0	**0,0**
1	**0,1**
2	**0,2**
3	**0,3**
4	**0,4**
5	**0,6**
6	**0,7**
7	**0,8**
8	**0,9**
9	**1,0**
10	**1,1**

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**

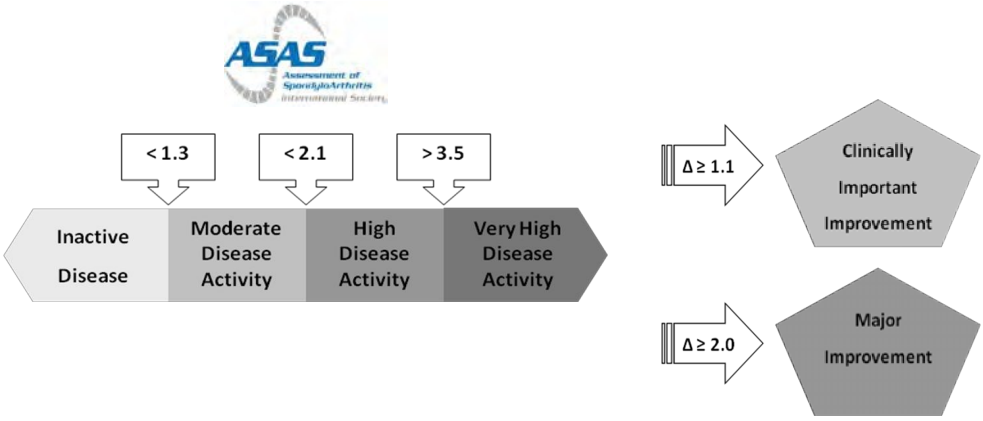


+ **+** **+**

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



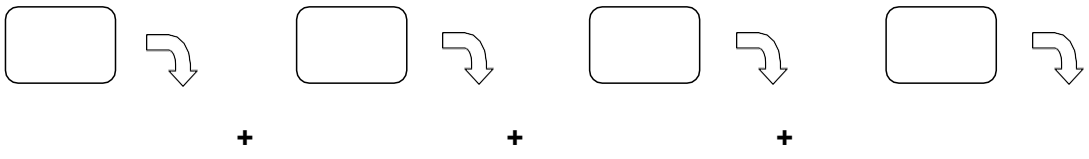
Name:_____ **Date:**_____/____/_____

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**

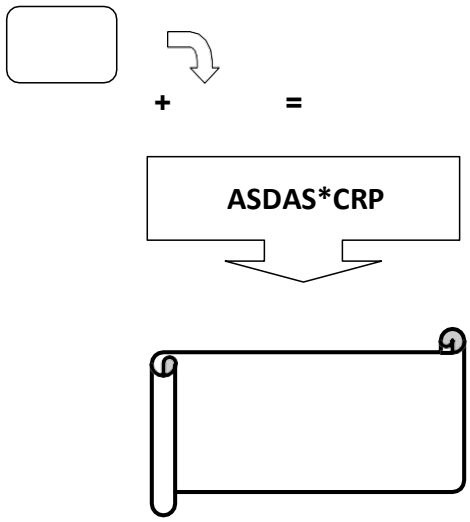
Morning Stiffness	
0	**0**
1	**0,1**
2	**0,1**
3	**0,2**
4	**0,2**
5	**0,3**
6	**0,4**
7	**0,4**
8	**0,5**
9	**0,5**
10	**0,6**

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**

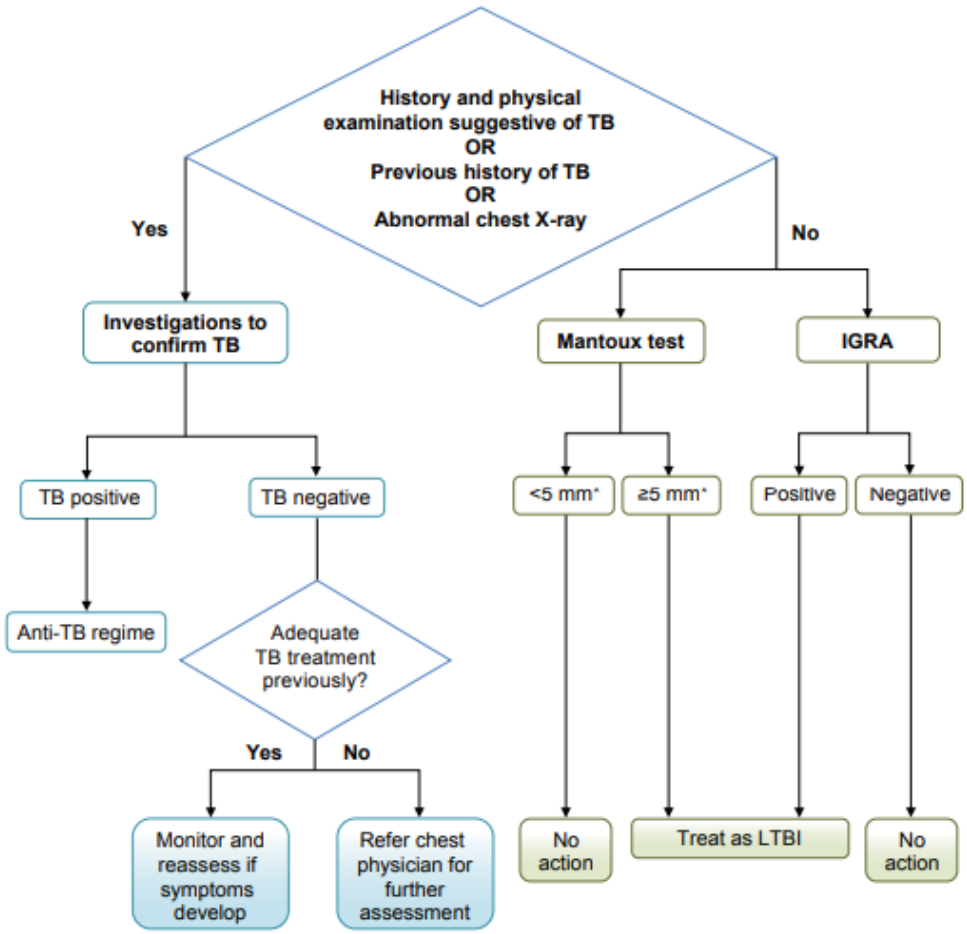


C*Reactive Protein (mg/L)							
0	**0,0**	14	**1,6**	60	**2,4**	130	**2,8**
1	**0,4**	15	**1,6**	65	**2,4**	135	**2,8**
2	**0,6**	16	**1,6**	70	**2,5**	140	**2,9**
3	**0,8**	17	**1,7**	75	**2,5**	145	**2,9**
4	**0,9**	18	**1,7**	80	**2,5**	150	**2,9**
5	**1,0**	19	**1,7**	85	**2,6**	155	**2,9**
6	**1,1**	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 9

TUBERCULOSIS WORKUP PRIOR TO TARGETED SYNTHETIC DMARDs AND BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS



IGRA: Interferon Gamma Release Assay
LTBI: latent tuberculosis infection
TB: tuberculosis

Adapted: Ministry of Health Malaysia. Management of Tuberculosis (3rd Edition). Putrajaya: MoH; 2012; Centers for Disease Control and Prevention. TB Elimination: Tuberculin Skin Testing. Atlanta: CDC; 2011

Source: Malaysia Ministry of Health. Clinical Practice Guidelines on Management of Rheumatoid Arthritis. Putrajaya: MoH; 2019.

APPENDIX 10

DOSE ADJUSTMENT IN RENAL AND LIVER IMPAIRMENT

DRUGS	RENAL ADJUSTMENT	LIVER ADJUSTMENT	OTHERS
Tumour Necrosis Factor Inhibitors	None	None	-
Rituximab	None	None	-
Tocilizumab (TCZ)	None	Liver enzyme abnormalities: • >1 - 3x ULN reduce to 4 mg/kg or interrupt dose until ALT/AST normalised • 3 - 5x ULN interrupt dose until <3x ULN and follow recommendation for >1 - 3x ULN • If persistent increase >3x ULN discontinue TCZ • >5x ULN discontinue TCZ	Low ANC: • ANC >1 - maintain dose • ANC 0.5 - 1 - interrupt TCZ dosing; when ANC >1 x 10^9/L resume TCZ at 4 mg/kg and increase to 8 mg/kg as clinically appropriate • ANC <0.5 - discontinue TCZ Thrombocytopaenia: • 50 - 100 - interrupt TCZ dosing • when platelet count is >100 x 10^3/µl resume TCA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate • <50 - discontinue TCZ
Secukinumab	None	None	
Ixekizumab	None	None	
Ustekinumab	None	None	
Guselkumab	None	None	
Tofacitinib	Mild (60 - 90 ml/min/1.73m2) • No dose adjustment Moderate (30 - <60 ml/min/1.73m2) • 5 mg OD	Mild (Child-Pugh Class A) • No dosage adjustment Moderate (Child-Pugh Class B) • 5 mg OD	Lymphopenia: • ALC 0.5 - <0.75 x10^9 cells/L - interrupt dosing; resume when ALC >0.75 x 10^9 cells/L • ALC <0.5 x 10^9 cells/L - discontinue dosing

DRUGS	RENAL ADJUSTMENT	LIVER ADJUSTMENT	OTHERS
	Severe (<30 ml/min/1.73m2) • 5 mg OD	Severe (Child-Pugh Class C) • Not recommended	Neutropenia: • Interrupt treatment, resume when ANC >1 x 10^9 cells/L • ANC <0.5 x 10^9 cells/L - discontinue Anaemia: • Interrupt treatment when Hb <8 g/L
Baricitinib	Mild (60 - 90 ml/min/1.73m2) • 2 mg OD Moderate (30 - <60 ml/min/1.73m2) • 1 mg OD Severe (<30 ml/min/1.73m2) • Not recommended	Mild (Child-Pugh Class A) • No dosage adjustment Moderate (Child-Pugh Class B) • No dose adjustment Severe (Child-Pugh Class C) • Not recommended	Lymphopenia: • ANC <0.5 x 10^9 cells/L interrupt dosing; resume when ANC >0.5 x 10^9 cells/L Neutropenia: • Interrupt treatment when ANC <1 x 10^9 cells/L; resume when ANC >1 x 10^9 cells/L Anaemia: • Interrupt treatment when Hb <8 g/L
Upadacitinib	None Limited data for use in severe renal impairment.	Mild (Child-Pugh Class A) • No dosage adjustment Moderate (Child-Pugh Class B) • No dose adjustment Severe (Child-Pugh Class C) • Not recommended	Lymphopenia: • ALC <0.5 x 10^9 cells/L interrupt dosing; resume when ANC >0.5 x 10^9 cells/L Neutropenia: • Interrupt treatment when ANC <1 x 10^9 cells/L; resume when ANC >1 x 10^9 cells/L Anaemia: • Interrupt treatment when Hb <8 g/L

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
RA	Rheumatoid Arthritis
PsA	Psoriatic Arthritis
SpA	Spondyloarthritis
AS	Ankylosing spondylitis
tsDMARDs	Targeted synthetic disease modifying anti-rheumatic drugs
bDMARDs	Biologic disease modifying anti-rheumatic drugs
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
TB	Tuberculosis
TNFi	Tumour necrosis factor inhibitors
IL	Interleukin
T2T	Treat-to-target
DAS	Disease activity score
SSZ	Sulphasalazine
MTX	Methotrexate
LEF	Leflunomide
HCQ	Hydroxychloroquine
CSA	Cyclosporine
JAKi	Janus kinase inhibitors
NSAIDs	Non-steroidal anti-inflammatory drugs
IVI	Intravenous infusion
IV	Intravenous
SC	Subcutaneous
IFX	Infliximab
ETN	Etanercept
ADA	Adalimumab
GOL	Golimumab
TCZ	Tocilizumab
RTX	Rituximab
BD	Twice daily
OD	Once a day
PO	Per oral
DAPSA	Disease Activity index for Psoriatic Arthritis
SEC	Secukinumab
IXE	Ixekizumab
UST	Ustekinumab
GUS	Guselkumab
nr-AxSpA	Non-radiographic axial spondyloarthritis
ASDAS	Ankylosing Spondylitis Disease Activity Score
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
NYHA	New York Heart Association
GI	Gastrointestinal
MACE	Major adverse cardiovascular event
HBsAg	Hepatitis B surface antigen
Anti-HBs	Antibody to Hepatitis B surface protein
Anti-HBc	Antibody to Hepatitis B core
MMR	Measles, mumps, rubella
HZ	Herpes zoster
COVID-19	Coronavirus disease 2019
AIIRD	Autoimmune inflammatory rheumatic diseases

IgG	Immunoglobulin G
LTBI	Latent TB infection
TST	Tuberculin skin test
QFT-GIT	QuantiFERON-TB Gold-In Tube
CXR	Chest X-ray
INH	Isoniazid
RIF	Rifampicin
RPT	Rifapentine
Anti-HCV	Antibody to Hepatitis C virus
RNA	Ribonucleic acid
HIV	Human Immunodeficiency virus
FBC	Full blood count
RP	Renal profile
LFT	Liver function test
ALT	Alanine transaminase
AST	Aspartate aminotransferase
SLE	Systemic lupus erythematosus
URTI	Upper respiratory tract infection

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