The South African Rheumatism and Arthritis Association (SARAA) recommendations for The use of biologic disease modifying anti-rheumatic drugs

October 2022

Section A

1. Introduction:

The biologic disease modifying anti-rheumatic drugs (bDMARDs) and more recently the biosimilar biologic DMARDs (bbDMARDs) and targeted synthetic DMARDs (tsDMARDs), all collectively known as biologic therapy or biologics, are important advances in the treatment of several rheumatic diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), spondyloarthritis (SpA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) as well as connective tissue and auto-immune diseases. In the case of inflammatory arthritis, these diseases cause damage to joints with resultant pain and loss of function. All of these diseases are also associated with significant morbidity and at times a higher mortality due to complications of the disease, associated co-morbidities or adverse effects of the medications used. Early diagnosis and aggressive treatment, including the use biologics, has been shown to improve patient outcome. At present they are used after failure of conventional treatment. The choice of a bDMARD, bbDMARD or tsDMARD is determined by clinical factors such as co-morbidities, poor prognostic factors, patient preference with regard to route of administration, registered indications of the drugs and knowledge of the possible risks associated with use. Once a patient has commenced a biologic therapy, he or she should be monitored for clinical response at regular intervals and should only continue if an adequate response is achieved and maintained. The use of another biologic therapy may be necessary in patients who do not achieve or maintain a clinical response. It is not recommended to continue therapy if the patient has not responded.

It is recommended that biologics be prescribed by rheumatologists experienced in the diagnosis and treatment of these diseases as well as the use of these therapies and knowledge of their possible adverse events. This includes the assessment of disease activity and functional disability using validated quantitative response measures. Furthermore, where therapy requires infusion, this should be administered in a facility with the necessary monitoring and resuscitation equipment, by suitably qualified staff.

These recommendations provide a guide, but treatment needs to be tailored to the individual patient.

The field of rheumatology is dynamic and is constantly being expanded. New data that may become available after the current revision of these recommendations should be taken into account when using the drugs.

2. The South African Rheumatism and Arthritis Association (SARAA) biologics registry:

The biologics registry was established by SARAA with the aim of capturing information about the use and safety of biologics in South Africa . The biologics registry plays a pivotal role in the continued access to these new therapies for patient with rheumatic diseases in South Africa.

Applications for biologic therapy use are evaluated by the SARAA Biologics Advisory Peer Review Panel (Panel) that consists of at least 6 rheumatologists, who voluntarily review applications for individual patients for eligibility according to the SARAA

recommendations (see Policy document and Standard operating procedure for the SARAA Biologics Advisory Peer Review Panel at www.saraa.co.za). Applications are either recommended or declined by at least 2 of the Panel members. The Panel can also make comments pertaining to an application. The identity of the patient and prescribing rheumatologist is not available to panel members.
The panel only reviews applications for the use of biologic drugs for licensed indications. Where an application is made for an unlicensed indication, such as for the treatment of a connective tissue disease, the treating rheumatologist is still, however, encouraged to send patient information to the registry so that information about all biologic therapy use can be captured.

3. Application process for biologic DMARD therapy in South Africa

Information is entered onto the biologics registry platform.
Patient demographic and clinical information must be submitted to the registry for all patients.
Patients must complete and sign the SARAA patient informed consent form.
A signed consent form from the prescribing rheumatologist should be submitted.
All initial applications sould be accompanied by proof of screening tests for the presence of latent tubeculosis infection.
Clinical progress reports should be submitted at least annually or more frequently.
The registry should be notified of any adverse events or change in therapy

References:
1.Tuberculosis and targeted synthetic or biologic DMARDs, beyond TNFi. Therapeutic Advances in musculoskeletal diseases. G Evangelatos et al. June 22,2020
2. Points to consider for treatment of immune-mediated inflammatory diseases with Janus Kinase inhibitors; a consensus statement. P Nash et al. Annals of Rheumatic Diseases 2021(80)71-87

Recommendations for the use of biologics in South Africa with regards to Tuberculosis (TB)

Due to the high background prevalence of TB in South Africa and the increased risk for reactivation of latent TB and new TB infection in patients on biologics, recommendations for the use of biologics with regards to TB have been drawn up in consultation with various experts in this field.

Testing for Latent TB infection

- Regardless of the underlying rheumatic condition or choice of biologic, all prospective biologic users must be screened for latent TB infection (LTBI). This only needs to be done with the initial application and is not needed when an application is made to switch therapy.
- LTBI should be tested by means of a PPD (Tuberculin Skin Test: TST) or an IGRA test. Skin induration of > or = 5mm is regarded as a positive TST, irrespective of a previous Mantoux. The IGRA tests should always be performed before or at the same time as the TST test to exclude sensitisation and a false positive IGRA. A TST should also not be repeated as it will cause a false positive TST in the future. Patients who have had a negative TST in the past should be stratified for risk as above, as further LTB tests are unreliable.

- All patients should be sent for a chest X-ray, not longer than 3 months prior to commencing biologic therapy.
- Results of testing and x-ray report should be sent to the registry.
- Testing for LTBI with IGRAs or TST is not reliable in very high risk patients. It is still requested that these tests should be done for the purpose of data on the registry and that they should should receive treatment as outlined.
- Patients that have a lower risk of TB exposure, may be considered for 2 IGRA tests (Quantiferon and TB spot) sequentially if the first test is negative, and a TST test. This regime has a higher likelihood of detecting LTB.

Treatment of LTBI

- LTBI detected by means of a positive TST or IGRA test, may be treated with:
  - 9 months of isoniazid (INH) 300 mg/daily
  - INH 300mg/daily and rifampicin 600mg/d for 3 months.
  - Supplementation with pyridoxine 25mg daily
- Biologic therapy may be commenced 1 month after LTB treatment is initiated.
- Repetition of the LTBI course may be necessary if a patient has been exposed to TB or if their exposure risk has changed, irrespective of LTBI tests.

TB infection with the use of biologics

- TB infection can occur in patients on biologics and there is no specific diagnostic test that will make the diagnosis of the infection.
- Regular clinical evaluation for any possible TB infection. Note that IGRA and TST is not to be used to evaluate patients with suspected active TB.
- Up to half of patients will have extra-pulmonary TB and the diagnosis needs to be made on the clinical presentation and the use of appropriate investigations
- Some biologics, such as the tumour necrosis factor α inhibitors (TNF-i), whether original or biosimilar, are known to play a specific role in TB infection and confer a greater risk of infection than other non-TNF-i biologics. JAK inhibitors have a similar risk.
- Even if a patient switches from a biologic with a higher risk for TB biologic to a low risk agent, vigilance for TB must remain high for the duration of biologic therapy.
- Vigilance for TB must continue for at least 6 months after discontinuation of a biologic
- When there is a suspected TB case, chest x-rays and sputum PCR for TB, as well as evaluation for extra-pulmonary disease should be done.
- If TB not confirmed, involve a multidisciplinary team in order to expedite the diagnosis.
- Low dose corticosteroids ≤10mg/d as well as conventional DMARDs may be used for the control of arthritis during TB treatment, although prednisone is a risk factor for the development for TB in patients with rheumatic disease.
- Recommencement of a biologic therapy should be done in consultation with the multidisciplinary team.
- A safer biologic should be chosen if possible.

Add P20

Reactivation of LTBI

- Latent TB infection can be reactivated in patients on biologics.
- This occurs within months of the commencement of the bDMARD.
- This risk is greatly reduced by the treatment of LTBI with the regime described above.

Risk of acquired TB infection

- Given the very high risk of TB exposure in SA (40-1000 cases/100 000 population) most patients are at an intermediate to high risk of exposure to TB infection. The higher the risk of exposure, the higher the risk of possible infection. Assessment of the risk of TB exposure remains of great importance and is also the crux of biologic therapy choice in a patient.
- Biologic prescribers should know how to assess risk based on the current guidelines and educate the patients how to keep their risk low.

TB exposure risk assessment Caution is advised when prescribing JAKi in patients with VTE risk, CVS risk factors, smokers, patients older than 65y who are not recommended to use ongoing INH prophylaxis.

-
    - Although South Africa is a country with a very high background risk of TB exposure, the risk of TB is even higher in the following settings:
        - Close contact with known or suspected TB cases.
        - Persons working or resident in an area with a high TB incidence, or a person who works or spends a significant amount of time in such an area.
        - Residents or employees of congregate settings such as correctional facilities, care facilities, shelters, schools, universities and colleges or any congregation of people, especially where there is poor ventilation.
        - Health care workers
        - Drug or alcohol abusers
        - Persons reliant on public transport such as taxis, buses and trains.

Recommendations for use of biologics including tsDMARDs in patients with high TB risk in specific diseases

- Rheumatoid arthritis
    - The tumour necrosis factor α inhibitors (TNF-i), whether original or biosimilar, are known to play a specific role in TB infection and confer a greater risk of infection than other non-TNF-i biologics. Because of this a non-TNF-i should be considered in these patients. The risk of TB infection on a JAK inhibitor is similar to the risk in a TNFi.
    - If a TNF-i or JAK inhibitor is used the following is recommended:
      Isoniazid prophylaxis (INH) for the duration of the TNF-i therapy.
      Patients older than 65 years should not use long term INH due to hepatic vulnerability.
      Caution is advised when prescribing JAKi in patients with VTE risk, CVS risk factors, smokers, patients older than 65y who are not recommended to use ongoing INH prophylaxis.

- Spondyloarthritis
    - A non-TNF-i, such as Secukinumab, Il-17A inhibitor (Cosentyx) and Ustekinumab, IL-12 and IL-23 inhibitor, seem to have similar safety to other non-TNF-i bDMARDs with regards to TB safety and are recommended with higher TB exposure risk.

Recommendations for the use of biologics in patient with lower TB risk

- Individuals who that are not necessarily at higher risk of exposure, taking into consideration the background rate of TB infection in South Africa.
- If LTBI is present treatment should be given.
- Despite a perceived lower risk, these patients be need to be made aware of any possible symptoms or signs of TB and be evaluated on a frequent basis for active TB or LTBI.

4. General considerations for the use of biologic DMARDs

4.1. Infection risk:

The use of all biologics is associated with an increased risk of serious infection. They should be discontinued if an infection occurs and only recommenced once the infection is clinically resolved.

The decision to restart a biologic, switch or discontinue after a serious infection is a clinical decision taking into consideration patient factors such as increasing age, any comorbidity, concomitant medication and concomitant csDMARD

Biologic DMARDs should be used with caution in the following circumstances:

- Chronic infected leg ulcers
- Septic arthritis in a native joint within the 12 months prior to commencing treatment
- Septic arthritis of a prosthetic joint within 12 months prior to treatment or indefinitely if the joint is retained
- Persistent or recurrent respiratory tract infections or bronchiectasis
- Indwelling urinary catheter
- Hypogammaglobulinaemia

Viral infections:

- Patients should be screened for Hepatitis B virus before starting a TNF-I as reactivation of chronic infection can occur.
- Patients who are Hepatitis B positive can be treated with biologic agents provided they are on antiviral agents. Consultation with a hepatologist is advised if patients are Hep B or Hep C Positive either before or during biologic therapy.
- All patients should be screened for HIV

4.2. Use of biologics with surgery

- There may be an increased risk of peri-operative infections with patients on biologics, although this is probably small.
- Most guidelines are based on expert opinion due to small studies or low quality evidence.
- It is recommended that surgery should be planned to be done at the end of a dosing cycle for the specific biologic.
- Restart the biologic when wound healing has occurred and staples or sutures have been removed and there is no evidence of infection.

- Biologic therapy should be withheld for at least one month pre- and post prosthetic joint replacement.
- Tocilizumab should be withheld for longer than the recommended time where possible due to delayed wound healing and increased risk of infection.

Drug	**Dosing interval**	**Time to plan surgery**
Adalimumab	Every 2 weeks	Week 3
Infliximab	6 – 8 weekly	Week 5/7/9
Etanercept	Weekly	Week 2
Golimumab	Monthly	Week 5
Rituximab	6 Monthly	Month 7 (4 – 7)
Actemra IV	Monthly	Week 5
Actemra SC	Weekly	Week 2 or preferably 3
Abatacept IV	Monthly	Week 5
Abatacept SC	Weekly	Week 2
Secukinumab	Every 4 weeks	Week 5
Ustekinumab	Every 12 weeks	Week 13

4.3. The use of biologics in pregnancy

European League Against Rheumatism (EULAR) Overarching principles:
A) Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy.
B) Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the foetus/ child to no harm.
C) The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the foetus or child.
D) The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynaecologist/obstetrician and the patient, and including other healthcare providers when appropriate.

Use of specific biologics during pregnancy and lactation

- Infliximab:
  - Current evidence indicates no increased rate of congenital malformations;
  - Infliximab can be continued up to gestational week 20
  - If indicated, it can be used throughout pregnancy
  - Infliximab is compatible with breast feeding
- Adalimumab:
  - Current evidence indicates no increased rate of congenital malformations;
  - Adalimumab can be continued up to gestational week 20
  - If indicated, it can be used throughout pregnancy
  - Adalimumab is compatible with breast feeding

- Golimumab:
  - Current evidence does not indicate an increased rate of congenital malformations;
  - Because of limited evidence, alternative medications should be considered for treatment throughout pregnancy
  - Golimumab is compatible with breast feeding
- Etanercept:
  - Current evidence indicates no increased rate of congenital malformations;
  - Etanercept can be continued up to gestational week 30–32
  - If indicated, it can be used throughout pregnancy
  - Etanercept is compatible with breast feeding
- Rituximab:
  - Current evidence indicates no increased rate of congenital malformations; in exceptional cases it can be used early in gestation
  - With use at later stages of pregnancy clinicians should be aware of the risk of B cell depletion and other cytopenias in the neonate
  - No data exist regarding rituximab in breast milk, therefore rituximab should be avoided in breast feeding
- Tocilizumab:
  - No statement can be made in regard to safety during pregnancy due to scarce documentation; treatment with tocilizumab is therefore best avoided
  - No data exist regarding tocilizumab in breast milk, therefore tocilizumab should be avoided in breast feeding
- Abatacept:
  - No statement can be made in regard to safety during pregnancy due to scarce documentation; treatment with abatacept is therefore best avoided
  - No data exist regarding abatacept in breast milk, therefore abatacept should be avoided in breast feeding
- Ustekinumab:
  - Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy
  - No data exist regarding ustekinumab in breast milk, therefore ustekinumab should be avoided in breast feeding
- Secukinumab:
  - Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy
  - No data exist regarding secukinumab in breast milk, therefore ustekinumab should be avoided in breast feeding
- JAK inhibitors:
  - Safety in pregnancy for mother and foetus has not been established and use should be avoided in women wanting to fall pregnant. Contraception is advised during use. Use in breast feeding should be avoided.

4.4. Vaccinations:

- Initial evaluation of any patient for proposed biologic therapy should include a review each patient's vaccination exposure before the start of immunosuppressive therapy.

- *Haemophilus influenzae b*
- Hepatitis A
- Hepatitis B
- Human papilloma virus (HPV)
- Influenza
- *Neisseria meningitides*
- Rubella (for women of childbearing age)
- *Streptococcus pneumoniae*
- Tetanus toxoid

- Vaccination against viral infections can be given during biologic DMARD treatment, although the antibody response might be decreased.
- Vaccinations against common infections, such as influenza and pneumococcal disease are recommended in patients on biologics.
- Vaccinations other than yearly ones, should be carried out before commencing biologic therapy.
- Vaccination with live, attenuated viruses (nasal influenza virus, herpes zoster and yellow fever) is contraindicated during biologic DMARD therapy and should be considered before starting treatment. Patients needing to travel to countries where yellow fever is endemic may ask for a waiver for their travel documents if on a biologic DMARD.
- Avoid live vaccines for 3 months after stopping abatacept and tocilizumab
- Use of biologics should be stopped at 32 weeks pregnancy so that neonate can receive live vaccines.

Recommended vaccinations:			
	Whom?	When?	What?
pneumococcal	all patients receiving or planning to start bDMARDs	≥2 weeks before the start of bDMARD Esp for rituximab, abatacept, tocilizumab. 5-yearly	*13-valent pneumococcal vaccine (PCV13)* PLUS ≥8 weeks later *23-valent pneumococcal polysaccharide vaccine (PPSV23)*
influenza	All patients	Annually	
Hepatitis A virus	If no antibodies and risk eg travel		Two-dose series (better seroprotection rates)
Hepatitis B virus	If no antibodies and risk eg occupational or		Recombivax HB three-dose schedule at 0, 1, and 6 months

	lifestyle risk factors		or Engerix-B two doses of 20 mcg/mL administered simultaneously on a four-dose schedule at 0, 1, 2, and 6 months
Tetanus toxoid	As indicated	10-yearly	

Live Vaccines			
BCG vaccination	Contraindicated and ineffective in adults Contraindicated in neonates of mothers using TNFi		
herpes zoster	All patients ≥50 yrs	≥4 weeks before bDMARD	*live attenuated vaccine* single dose, lasts only 10 years risk of dissemination OR *recombinant (non-live) glycoprotein E vaccine* 2 doses spaced 4 weeks apart no risk of developing disseminated disease ? risk of ↑ autoimmune disease activity
varicella	Post exposure prophylaxis		*live VZV vaccine* if on mild i/s OR *VZV immune globulin* (VariZIG) and/or acyclovir prophylaxis
yellow fever	not recommended	? vaccinate a patient likely to travel to a high-risk yellow fever area prior to commencing biologic therapy	

4.5. Switching:

Switching between different biologic therapies is appropriate in patients where there is lack of efficacy or the occurrence of side effects on a specific biologic DMARD.

When switching from TNF inhibitors, abatacept or tocilizumab, the new drug can be started when the next dose of the previous drug would have been given.

With the use of rituximab, it is recommended to initiate treatment:

- ≥ 4 weeks after etanercept treatment
- ≥ 8 weeks after infliximab of adalimumab treatment

When switching from rituximab – it is recommended that the next biologic is initiated 6 months after the last dose of rituximab.

4.6. The use of concomitant methotrexate

- In clinical trials, the use of all biologic therapies in combination with methotrexate showed better efficacy than biologic monotherapy. Patients intolerant to methotrexate can use leflunomide.
- Some biologic DMARDs are registered for monotherapy use and can be used without concomitant methotrexate.
- In patients who cannot use Methotrexate or other csDMARDS as comedication, the use IL6i or tsDMARDS as monotherapy may have advantages.
- Methotrexate can be used at 7.5mgs-10mg weekly dose to provide added efficacy to in particular TNFi, and intolerance at these low doses is rare.
- Methotrexate at low dose has been shown to reduce antidrug antibodies.
- Biologics can be effectively combined with other csDMARDS such as Leflunomide.

The use of biologic DMARDs in combination with multiple conventional DMARDs have not been shown to improve clinical response.

Section B: Biologic and biosimilar DMARDs

1. The TNF inhibitors (TNF-i)

1.1 General

Trade names:

Currently available TNF inhibitors are:

- Infliximab (Revellex®)
- Etanercept (Enbrel®)
- Adalimumab (Humira®)
- Golimumab (Simponi®)

Mode of action:

Inhibition of tumour necrosis factor alpha (TNF)

- Although these drugs have the same target, there are differences in, pharmacokinetics and method of administration.
- Etanercept is a soluble receptor of TNF, wheras the others are monoclonal antibodies to TNF.

Registered indications:
They are registered in South Africa for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis in patients in patients with active, moderate to severe disease failing to respond to conventional therapy. See disease specific guidelines.

Dosage and mode of administration:

- Infliximab: 3mg/kg intravenously every 6-8 weeks is recommended for RA and PsA, and 5mg/kg for AS every 6 – 8 weeks
- Etanercept 50 mg weekly or 25mg twice weekly subcutaneously
- Adalimumab 40 mg every second week subcutaneously
- Golimumab 50mg every 4 weeks subcutaneously

Interval to response to treatment:

- 2 – 4 weeks, with significant response by 12 – 24 weeks.

1.2 Safety of the TNF inhibitors:

Infections:

- Tuberculosis (TB): Patients with immune mediated inflammatory diseases are at greater risk for the development of TB and those on TNF inhibitors can have a markedly increased risk. LTBI can be reactivated or the patient can develop a new infection. LTBI usually occurs in the first few months following the initiation of treatment while new infections can be seen at any time. About half of the infections will be extra-pulmonary. The risk of reactivation of TB can be minimised following the treatment of LTBI. Rates of TB reactivation have been higher in patients using adalimumab and infliximab. All patients should be monitored on an on-going basis for the development of TB and the monitoring should continue for at least 6 months after stopping treatment.
- Opportunistic infections: infections with fungi, particurly histoplasmosis, listeria and non-tuberculous mycobacteria have been reported.
- Bacterial infections: Patients are at greater risk of serious infections requiring hospitalisation.
- Viral infections: Patients should be screened for hepatitis B virus before starting a TNF inhibitor as reactivation of chronic infection can occur. If hepatitis B infection is found to occur during treatment, prophylactic antiviral treatment can be given.

Autoimmune-like syndromes:

- Autoantibody formation is common, but is usually not clinically significant. Drug induced lupus and anti-phospholipid antibody syndrome may occur.

Cardiovascular:

- The use of the TNF inhibitors is contraindicated in NYHA class III/IV heart failure as there is an association with greater morbidity and mortality.

Haematological:

- There have been reports of pancytopaenia and aplastic anaemia.

Liver function abnormalities:

- Modest ALT and AST elevations have been seen in patients on adalimumab and infliximab, usually not more than twice the upper limit of normal. Worsening of alcoholic hepatitis has been seen.

Injection site reactions and infusion reactions:

- Injection site reactions are usually mild. Acute infusion reactions can occur with intravenous infliximab, but can usually be treated with corticosteroids and antihistamines and by slowing the infusion rate.

Malignancies:

- The risk of lymphoma and solid tumours does not seem to be increased, but there may be an increased risk of non-melanoma skin tumours.
- Treatment with a TNF inhibitor should be avoided in patients with a history of malignancy in the preceding 5 years.
  Patients should be regularly screened for skin cancers (including melanoma).

Neurological disease:

- There have been reports of rare cases of central and peripheral demyelinating syndromes including multiple sclerosis, optic neuritis and Guillain-Barré syndrome. These tend to occur within the first 5 – 8 months of use. Use of a TNF inhibitor is contraindicated if there is any history of demyelinating disease.

Pulmonary disease:

- Acute, severe exacerbation of interstitial lung disease has been reported. TNF inhibitors are not recommended in patients with interstitial lung disease.

Skin disease:

- Rashes, particularly psoriasis, rarely Steven's-Johnson syndrome, vasculitis and erythema multiforme have been reported. They may subside with a switch from one TNF inhibitor to another.

2 Rituximab

2.1 General

Trade name: MabThera®

Mechanism of action:
Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes CD20 positive B-cells.

Registered indications:

- Use of rituximab is indicated for the treatment of moderate to severe, active RA in patients with inadequate response or intolerance to TNF inhibitors.
- Rituximab may be considered for first line biological DMARD therapy in certain patients:
  - Patients with a high risk of TB infection
  - Previous lymphoma
  - Interstitial lung disease
  - Vasculitis

Dosage and mode of administration:

- Pretreatment Neutrophil counts and IgG levels should obtained prior to each infusion, or in the event of serious infections.
- Rituximab is given as 2 intravenous infusions of 1000mgs 14 days apart, in an infusion room with adequate monitoring and resuscitation
- Premedication with IVI methyl prednisolone 100-125mgs, oral Paracetamol and antihistamine is given 30 minutes prior to reduce infusion reactions.
- Infusion reactions are most common during the first infusion, are usually mild. They may be managed by slowing the infusion rate and administration of fluids
- Infusion should be ceased should anaphylaxis occur(< 10%)
- Retreatment is recommended at 6 months or when the disease flares. Better clinical efficacy was shown in patients treated at regular 6 monthly intervals compared to treatment on demand.
- Retreatment with a lower dose is possible in those with a good response.
- Patients with a partial response to the first cycle may respond more fully to the second cycle.

- Rituximab is given in combination with methotrexate, or if not tolerated, leflunomide.
- The response to rituximab is greater in rheumatoid factor positive or anti-cyclic citrullinated peptide (ACPA) positive patients. In sero-negative patients an alternative treatment should be considered.

Time interval to response to treatment:

- Time to response is usually 8 – 16 weeks.

2.2 Safety of Rituximab

Infections:

- There is an increase in the rate of serious infections. This is higher in patients with decreased IgG levels below 5g/l.
- Tuberculosis:
    - The risk of TB is lower than with other biologics, but the usual TB surveillance measures should be applied.
- Viral hepatitis: Hepatitis B reactivation can occur. Screening for HBsAg and anti-HBc antibodies should be done in patients before treatment.

Haematological side effects:

- There have been reports on neutropaenia in oncology patients, but this seems to be rare in patients with autoimmune diseases, but may be associated with increased infection rate.

Infusion reactions:

- Infusion reactions occur most commonly with the first infusion. Pre-treatment with methylprednisolone is given to reduce the risk and severity of reactions.

Malignancies:

- There is no evidence that rituximab is associated with an increased incidence of solid tumours or lymphoma.

Neurologic syndromes:

- Cases of progressive multifocal leucoencephalopathy have been seen in patients on rituximab.

Skin reactions:

- There have been reports of psoriasis and vasculitis on rituximab treatment

3. Abatacept

3.1 General

Name of drug: abatacept
Trade name: Orencia®

Mode of action:

- Abatacept is a soluble fusion protein to CTLA-4 that acts as a T-cell co-stimulation modulator inhibiting T-cell stimulation. It prevents CD28 from binding to its counter-receptor, CD80/CD86, due to its higher affinity for CD80/CD86. This prevents the suppression of T reg activity and prevents increased T effector cell activity

Registered indications:

- It is indicated as a treatment for active, moderate to severe RA either after failure to respond to adequate treatment of csDMARDs or a biologic DMARD. It can be used as a monotherapy or in combination with methotrexate or leflunomide.
- Treatment of juvenile idiopathic
- Psoriatic arthritis

Dosage and mode of administration:

- 750mg or 1000mg given IVI every 4 weeks with a loading dose of 3 doses given at weeks 0, 2 and 4 or
- 125mg weekly SC.
- Patients whose disease is well-controlled on long-term IV abatacept can switch to receiving the medication by SC administration while maintaining clinical efficacy and without increased safety issues.

Time interval to response

- Response can be within 2 – 4 weeks, but most patients respond within 12 – 16 weeks.

3.2 Safety of abatacept

Infections:

- There is an increased rate of serious infections
- Cases of TB were seen in clinical trial patients, but the risk of reactivation of LTBI with abatacept is not known.

Malignancies:

- There has been no reported increased incidence of lymphoma or solid malignancies in patients with RA in clinical trials on abatacept or from registry data.

Pulmonary disease*:*

- An increased rate of serious lower respiratory tract infections was seen in patients with chronic obstructive pulmonary disease (COPD) and abatacept should be given with caution in these patients.

General: Avoid live vaccines within 3 months of stopping abatacept

4. Tocilizumab

4.1 General

Name of the drug: tocilizumab
Trade name: Actemra®

Mode of action:
- Tocilizumab is a humanised anti-IL-6 receptor monoclonal antibody.

Registered indications:
- Moderate to severe, active RA failing traditional DMARDs or biologic DMARDs.
- Juvenile idiopathic arthritis

Dosage and mode of administration:
- It is administered as an intravenous infusion, given over 1 hour, every 4 weeks.
- The recommended dosage is 4 -8 mg/kg to a maximum of 800 mg per infusion.
- Use with methotrexate is recommended, but it can be used as monotherapy.

4.2 Safety of tocilizumab

Infections
- There was an increase in the rate of serious infections in clinical trials on tocilizumab compared to patients on placebo which was similar to the rates seen with other biologic DMARDs. The drug should not be when the patient has an active infection.
- Tocilizumab decreases CRP levels through IL-6 inhibition and CRP levels may not increase as would normally be seen in an acute infection, limiting the use of CRP as a diagnostic indicator for infection.
- Cases of TB and opportunistic infections (cancidiasis, aspergillosis and pneumocyctis) have been reported in patients on tocilizumab.
- Viral infections: As with treatment with other biologic DMARDs, herpes zoster infection can occur. The risk of reactivation of hepatitis B or C is not known

Gastrointestinal
- Gastrointestinal adverse events, including generalised peritonitis, lower gastrointestinal perforation, fistulae and intra-abdominal abscesses occurred with an incidence rate of 0,26/100 patient years in clinical trials with tocilizumab compared with placebo. It should be used with caution in patients with a history of intestinal ulceration and diverticulosis.
- Severe liver damage has been reported
    - If used incombination with leflunamide there is a higher chance of raised AST, ALT

Haematological

- Neutropaenia was seen in clinical trials with decrease to < 1000 polymorphs/ml, rarely < 500/ml. This was usually transient and was not associated with an increased rate of infections. A downward dose adjustment to 4mg/kg is necessary should the neutropaenia persist.
- Decreased platelet count has been reported

Infusion reactions:

- Serious infusion reactions to tocilizumab are uncommon, but can occur.

Lipid levels:

- Increases in plasma lipid levels are seen in 20 – 30% of patients and should be monitored and treated,
- To date, an increase in cardiovascular incidents has not been seen in clinical trials.

Liver enzyme and bilirubin elevations:

- Liver enzyme elevations are seen in some patients on tocilizumab treatment. No incidences of hepatic failure have been documented, but dose reduction is recommended if on-going transaminase or bilirubin increase is found and liver function should be monitored regularly.

Malignancies

- There has been no increased incidence of malignancies in clinical trials on tocilizumab.

Skin

- Erythroderma has been described related to tocilizumab.

General: Avoid live vaccines within 3 months of stopping tocilizumab

5. Ustekinumab

Name of drug: Ustekinumab
Trade name(s): Stelara®

Mechanism of action: Human IgG1κ monoclonal antibody binds to the p40 protein subunit used by IL-12 and IL-23 cytokines.

Registered Rheumatological Indications:

- Adult patients with:
- Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy.
- Active psoriatic arthritis (PsA), alone or in combination with methotrexate.
- Moderately to severely active Crohn's disease (CD) who have failed or were intolerant to treatment with immunomodulators or corticosteroids, and/or one or more TNF blockers.
- Adolescent patients (12 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Dosage and mode of administration:

- 45 mg SC at Weeks 0 and 4, then q12 weeks thereafter
- For patients >100 kg with co-existent moderate-to-severe plaque psoriasis,

- Iincrease dose to 90 mg SC at Weeks 0 and 4, then q12 weeks thereafter

Time interval of response to therapy:

- Response to therapy can be seen as early as 8 weeks, but a full response is assessed at week 24. (6 months)

5.1 Safety Profile:

Infections:

- >10% Upper respiratory infection
- 1-10% Nasopharyngitis,

Other side effects seen in 1 – 10% of patients

- Back pain, Cellulitis, Depression, Diarrhoea, Fatigue, Headache

Less common side effects:

- Injection site erythema, Myalgia, Fatigue, Nasal congestion, Urticaria, Rash, Pruritus

Other uncommon side effects:

- Antibody formation <1% (selected) Severe infection, Malignancy, Reversible posterior leukoencephalopathy syndrome

Pregnancy:

Limited data on ustekinumab use in pregnant women to inform a drug associated risk

Special points of interest/caution:

Data are not available on the presence of ustekinumab in human milk, effects on the breastfed infant, or effects on milk production

Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ustekinumab and any potential adverse effects on the breastfed child from ustekinumab or from the underlying maternal condition

5. Secukinumab

Name of drug: secukinumab

Trade name(s): Cosentyx®

Mechanism of action: Inhibitor of Interleukin 17A

Registered Rheumatological Indications:

Indicated to the treatment of the following diseases after failure of csDMARDs or bDMARDs with or without methotrexate.

- Ankylosing spondylitis (AS)
- Plaque psoriasis
- Psoriatic arthritis (PsA)

Dosage and mode of administration:

Dosing is for subcutaneous dosing

- For AS or PsA
    - Loading dose of 150mg sc per week at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter
    - Without a loading dose 150mg every 4 weeks sc
- Plaque psoriasis
    - With loading dose 300mg sc at weeks 0, 1, 2, 3, 4 and every 4 weeks thereafter
    - Without loading dose 300mg every 4 weeks

Time interval of response to therapy:

Safety Profile:

Infections:

- Increased risk of infections, particularly upper respiratory tract infections
- Muco-cutaneous candida infections

Pregnancy:

Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy.

No data exist regarding secukinumab in breast milk, therefore ustekinumab should be avoided in breast feeding

6. Biosimilar DMARDs

6.1 General

A biosimilar is a biological agent that is a similar version of an already approved original biological agent (reference product) that is intended to be used in the treatment of the same diseases as the reference product. Before they are approved, biosimilars must undergo a rigorous development process, comparing them with the original biological drug on which it is based, to establish that the biosimilar has highly similar physicochemical characteristics, biological activity, equivalent efficacy and no clinically meaningful differences in safety and immunogenicity as the originator reference product. After approval, biosimilars must comply with the same pharmacological practices for biological drugs. Several biosimilar disease-modifying antirheumatic drugs (bsDMARDs) based on the tumour necrosis factor inhibitors adalimumab, etanercept and infliximab have been approved for use in patients with rheumatic diseases around the world. An important potential benefit of the bsDMARDs is that cost savings can be made if bsDMARDs are used.

6.2 Position statement on the use of biosimilar DMARDs

SARAA is committed to maintaining the highest standard of care for patients with rheumatologic disease against the background of a country, which is resource constrained. To this end we welcome the registration of the bsDMARDs in South Africa and hope that the reduction in price for treatment will mean that more patients that are in need of treatment, will be able to access it. The decision to give any bDMARD or bsDMARD is a shared decision between the treating rheumatologist and the patient based on what is the most appropriate treatment for that patient. There is data to support non-medical switching to a biosimilar, but this still should be a shared decision and should not be a switch between an originator of one class of biologic being switched to another class.

7. Targeted synthetic DMARDs (tsDMARDs)

The JAK inhibitors are the most recent class of therapies for various auto-immune and immune mediated inflammatory diseases, collectively known as the targeted synthetic disease modifying drugs (tsDMARDs). They are small-molecule oral treatments that have comparable efficacy to biologics. They target the Janus kinases that are protein tyrosine kinases found intracellularly that mediate responses to cytokines by cells. There are 4 isoforms of JAKs: JAK1, JAK2, JAK3 and TYK2 that are found in pairs. Different JAK inhibitors target different JAK isoforms, but the overall effect and side effect profile of these drugs is very similar. Indications for the use of JAK inhibitors are rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthritis, systemic lupus erythematosus and other inflammatory disorders (eg, inflammatory bowel disease, atopic dermatitis, alopecia areata, vitiligo). They are also used in the management of certain hematologic disorders such as myelofibrosis, polycythaemia vera and graft-versus-host disease.

Trade names and dosing of the available JAK inhibitors in South Africa are:

Tofacitinib: Xeljanz® Dose is 5mg twice daily
Baricitinib: Unamity® Dose is 4mg daily
Upadacitinib: Rinvoq® Dose is 15mg daily

Safety profile:

- Infections: Most commonly reported infections are not serious, but there is a risk of serious infection similar to that seen with biologics. There is a greater risk for herpes zoster infection than seen with biologics. TB and opportunistic infections have been reported.
- Gastrointestinal: nausea and diarrhoea are seen most commonly, but intestinal perforation has been reported. Liver enzymes may be raised, particularly with concomitant methotrexate use.
- Increased muscle enzymes occur, but are not usually associated with symptoms.
- Cardiovascular risk: An increased risk of venous thromboembolism has been observed with tofacitinib and baricitinib, but patients should be evaluated for thrombotic risk factors before prescribing a JAK inhibitor. Dyslipidaemia is seen in patients, but is probably not clinically relevant. Cardiovascular risk was seen to be increased in a phase IV trial of tofacitinib compared to etanercept in patients with cardiovascular risk, there was an increased risk of myocardial infarction and stroke in the tofacitinib group.

- Haematologic: Neutropenia and lymphopaenia that is not clinically significant can occur with the use of all JAK inhibitors. More rarely a neutropaenia of <1000/ cells/ml and lymphopaenia of <500 cells/ml has been seen without an associated increase in infection risk. Treatment should be temporarily interrupted in patients with low neutrophils or lymphocytes and dosing can be reduced if needed depending on whether treatment is continued.
- Malignancy: There was no increase in malignancy risk in JAK inhibitor trials, but in the same trial that showed increased cardiovascular risk they also reported an increased malignancy risk, although the details as to which malignancies is still not clear.

Section C: Specific inflammatory joint diseases

1. Rheumatoid arthritis

Rheumatoid arthritis (RA) can be a devastating disease due to progressive damage to the joints with loss of function and disability as well as the development of co-morbid conditions such as cardiovascular disease which can result in increased mortality. It is important to make a diagnosis as soon as possible after the patient presents with symptoms and to start treatment with traditional DMARDs. Signs of early RA may not be typical as seen in established disease, but a patient seen with tenderness over the metacarpophalangeal joints or metatarsophalangeal joints, palpable synovitis in more than 3 joints and early morning stiffness for more than 30 minutes may well have early RA.

1.1 Diagnosis of RA

The diagnosis of RA is made on a combination of the clinical picture as well as serology and inflammatory markers. The ACR/ EULAR 2010 classification criteria for rheumatoid arthritis is used for classification of patients on the SARAA registry.

1.2 Indicators of poor prognosis:

Certain features indicate a poorer prognosis:

- Seropositivity: Either a high titre rheumatoid factor or antibodies to cyclic citrullinated peptides (ACPA)
- High markers of inflammation: ESR or CRP
- Development of erosions on x-rays within the first 2 years of disease
- Functional disability
- Extra-articular disease

1.3 Treating RA to a defined target of remission or low disease activity

The target of response to treatment of RA is to get the disease into remission or at least low disease activity, as soon as possible. The patient should initially be re-evaluated and therapy adjusted every 1 – 3 months until the target of low disease activity or remission is achieved Thereafter patients can be evaluated 3 to 6 monthly. Low disease activity should be maintained throughout the course of the disease

1.4 Assessment of disease activity and function

To assess the activity of disease in a patient and the impact of disease on function, he or she should be evaluated using a validated score. The Simplified Disease Activity

Index (SDAI) is the composite score used most commonly in South Africa. This has been well validated and is a practical measure to assess disease activity

The SDAI is made up of the sum of the:

- Tender joint count (28 Joint count)
- Swollen joint count (26 joint count)
- Patient's global assessment on a visual analogue scale of 0 -10cm
- Physician's global assessment on a visual analogue scale of 0-10cm
- CRP in mg/dl

SDAI ≥ 26 represents high disease activity
SDAI 12- 26 represents moderate disease activity
SDAI 3.4 – 11 represents low disease activity
SDAI ≤ 3.3 represents remission

The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is used to measure the level of function with a range of 0 - 3.

1.4 SARAA Eligibility Criteria for the use of biologic therapies

- Commencement of further treatment with either a biologic should be considered in patients who have an inadequate response to csDMARDs ie have moderate to severe disease activity despite being on adequate treatment with csDMARDs, where this is defined as:
  - Moderate to severe disease activity (SDAI >12)
  - All patients must have a history of use of at least 2 conventional DMARDs used serially or in combination over a 3 - 6 month period at therapeutic or maximum tolerated doses. Use of a biologic can be considered earlier than 6 months if the patient has signs of poor prognosis.
  - Methotrexate should be one of the conventional DMARDs used, unless contra-indicated, at an adequate dose of preferably 20mg weekly.
- Use of a biologic can be considered earlier than 6 months if the patient has signs of poor prognosis as defined above.
- A letter of motivation should accompany any application for biologic in a patient not fulfilling the SARAA eligibility criteria.

1.5 Choice of therapies including bDMARD, biosimilar bDMARDs or targeted synthetic DMARDs

- First line biologic therapy should be based on the clinical context of the patient and the discretion of the treating rheumatologist.
  - bDMARDs or biosimilar bDMARDs or JAK inhibitors
- No difference between biologic therapy use in outcomes, irrespective of their target based on head-to-head trials, meta-analyses, and results of systemic literature reviews.
- Rituximab should be considered as first line therapy in special circumstances:
  - Past lymphoma;
  - Demyelinating disorders;
  - Past TB infection, LTB, or high TB risk.
  - Previous malignancy

- Non-TNF inhibitors can be considered as first-line biologics because of the high risk of TB with TNF inhibitors.

1.6 Continuation of biologic:

Patients should be assessed 3 months after commencing biologic therapy to assess the response.
It is recommended that treatment should be continued only if there has been an adequate response to continuous treatment for 6 months.

Adequate response to treatment is defined as:

- Improvement in SDAI score of 50% or
- Achievement of low disease activity state: SDAI score < 11

Patients with inadequate response or intolerance should be switched to another biologic or should discontinue treatment.

Response to treatment should be monitored regularly.

Dose adjustment:

- Increasing the dose or reducing the dosing interval of infliximab may provide increased benefit.
- Increasing the dose of etanercept has not shown increased benefit.
- No data is available on increasing the dose of adalimumab.
- Rituximab may be used in a dose of two 500mg infusions
- Tocilizumab can be used at a dose of 4mg/kg

- There is no evidence that any one biologic is more effective than another.
- Loss of response may occur.
- Inadequate response to one TNF inhibitor does not preclude response to another, but consideration can also be given to using a biologic with another mode of action.
- Primary inadequate responders are less likely to respond to a second TNF inhibitor.

1.6 Discontinuation of treatment

In patients who have achieved sustained remission, tapering of the biologic therapy may be done by increasing the intervals between dosing.

2. Ankylosing spondylitis (AS) and axial spondyloarthritis (AxSpA)

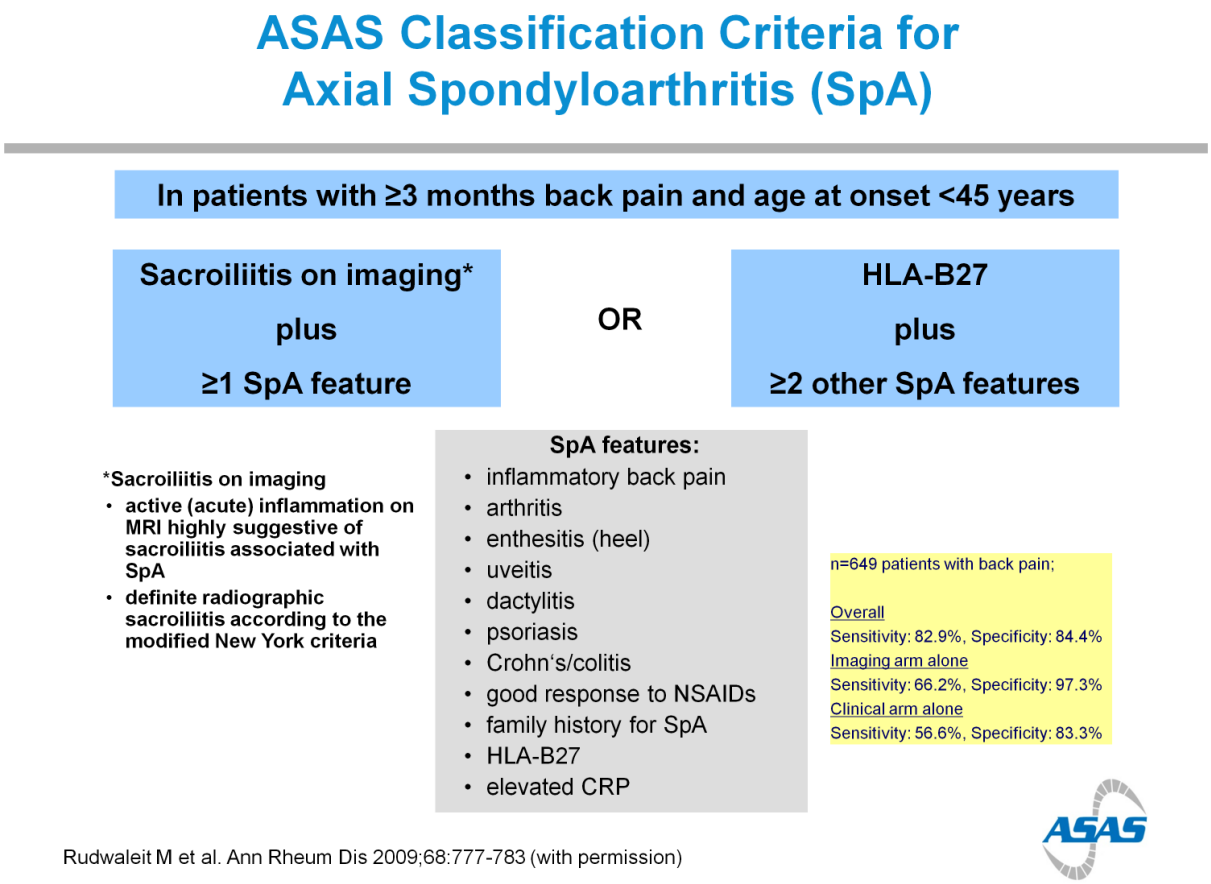
Patients with AS or SpA may have axial disease, peripheral arthritis or enthesitis, which respond to different treatment approaches.

- Axial disease seldom responds to treatment with csDMARDs, but NSAIDs are usually beneficial.

- NSAIDs, sulphasalazine and intra-articular corticosteroid injection are indicated for peripheral arthritis.
- Local corticosteroid injections are indicated for treatment of enthesitis, although corticosteroid injections must not be given into tendons as it can cause weakening of the tendon with a greater chance of tendon rupture.

2.1 Diagnosis

The diagnosis of AS is made using the ASAS criteria for axial SpA.



2.2 Assessing disease activity

Disease activity should be assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS). This has been shown to have good discriminatory capacity and sensitivity to change and incorporates an objective measure of disease activity such as CRP or ESR. It incorporates questions found on the BASDAI score, but also uses a marker of inflammation; either CRP or ESR.

The score is calculated using a calculator that can be obtained online or as an Application for a hand held device. It is made up of the patient reported outcomes relating to the level of disease in the week prior to the evaluation:

- Spinal pain VAS 0 – 10
- Peripheral arthritis 0 – 10
- Duration of morning stiffness 0 – 10
- CRP mg/l

Cut-offs:

- Inactive disease <1.3
- Moderate disease activity 1.3–2.0
- High disease activity 2.1–3.5
- Very high disease activity >3.5

2.3 Target for treatment

Target for treatment in treating Axial SpA and AS should be to a target of :

- ASDAS inactive disease <1.3

2.4 Treatment with biologics therapies:

Treatment with a bDMARD is indicated for treatment of active axial SpA or AS failing conventional treatment if:

- There is a diagnosis of definite AS or axial SpA according to ASAS criteria
- There has been active moderate to high disease activity disease for at least four weeks defined by:
  - A sustained ASDAS score of > 2.1 and
  - Spinal pain VAS of at least 4
- Presence of refractory disease
  - Failure of at least two NSAIDs during a 4 week period
  - Failure of intra-articular steroids if indicated
  - Failure of sulfasalazine or other cDMARD such as methotrexate in patients with peripheral arthritis.
- Refractory enthesitis, uveitis or other extra-articular manifestations

  There is no evidence to support the obligatory use of cDMARDs before or concomitant with TNF-inhibitor treatment in patients with axial disease.

2.5 Response to treatment

- Assessment of response should be carried out after 12 weeks of treatment.
- Major improvement 50% or delta 2.
- Clinically important improvement is delta 1.1
- Continue treatment if delta ASDAS is at least 1.1

2.6 Biologics for treatment of Axial SpA and AS

The biologic therapies registered for use of treating Axial SpA and AS in South Africa are the TNF-I, biosimilar TNF-I and Cosentyx, an interleukin 17 inhibitor.

3. Psoriatic arthritis

3.1 Diagnostic criteria

The diagnosis of psoriatic arthritis is made using the Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria classification criteria.

The CASPAR criteria for psoriatic arthritis (PsA) consist of inflammatory articular disease (joint, spine, or entheseal) with ≥ **3 points** from the categories below. The sensitivity is 98.7% and the specificity is 91.4%.

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis **(2 points)**
    1. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
    2. 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 health care provider.
    3. 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 **(1 point)**
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist **(1 point)**
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot **(1 point)**

3.2 Assessing disease activity:

Disease activity is assessed using the DAPSA disease activity score.

3.2 Indication for biologic therapy

Biologics should be considered for the following patients:

- Active PsA despite 2 csDMARDs indicated for the use in treatment of PsA: methotrexate, sulphasalazine of leflunamide, at maximal doses over 3 months. Given sequentially or in combination.
- In patients with polyarthritis with at least 3 tender and 3 swollen joints who have failed treatment with at least 2 conventional DMARDs (maximal dosages over 12 weeks, sequentially or in combination)e.g. leflunomide, methotrexate or sulfasalazine,
- For patients failing 1 cDMARD particularly where there is evidence of adverse prognostic factors:
    - 5 or more swollen joints
    - Elevated CRP persisting for more than 3 months
    - and/or structural joint damage due to disease,
- In patients with severe persistent oligoarthritis (less than 3 tender/swollen joints) that has a major demonstrable influence on well-being of the patient that has failed treatment with at least 2 csDMARDs and appropriate intra-articular therapy
- In patients with active axial psoriatic disease recommendation for ankylosing spondylitis should be followed

Response criteria- using the PsARC criteria

Response is defined as

- Improvement in two factors (with at least one being a joint score) with worsening of none of the following four factors

1. Patient global assessment (1-5 on a Likert scale- improvement defined as a decrease of 1)
2. Physician global assessment (as above)
3. 68 Tender joint count (improvement is a 30% decrease)
4. 66 Swollen joint count (Improvement 30% decrease)

A partial response is defined by some improvement in swollen and tender joint score and no worsening in physician or patient global score. If there has been a partial response, consideration should be given to a further 12 weeks of therapy.

In the case of failure of a TNF-i, either due to inefficacy or toxicity, an alternative TNF inhibitor should be considered

Eligibility criteria for biologic treatment of psoriatic arthritis

- Biologic therapies should be considered for the following patients:
    - In patients with polyarthritis with at least 3 tender and 3 swollen joints who have failed treatment with at least 2 conventional DMARDs (maximal dosages over 12 weeks, sequentially or in combination)e.g. leflunomide, methotrexate or sulfasalazine,
    - For patients failing 1 cDMARD particularly where there is evidence of adverse prognostic factors:
        - 5 or more swollen joints
        - Elevated CRP persisting for more than 3 months
        - and/or structural joint damage due to disease,
    - In patients with severe persistent oligoarthritis (less than 3 tender/swollen joints) that has a major demonstrable influence on well-being of the patient that has failed treatment with at least 2 cDMARDs and appropriate intra-articular therapy
    - In patients with active axial psoriatic disease recommendation for ankylosing spondylitis should be followed

Enthesitis/dactylitis

After failure of local and systemic anti-inflammatory therapy, and taking into account quality of life consequences, bDMARD may be indicated. There is no effect of csDMARDS on enthesitis. Must be unequivocal diagnosis supported by imaging. Studies have shown that IL17i and IL23i may be superior to anti-TNFi but all can be effective. Physicians need to apply good clinical judgment with respect to avoiding overuse of bDMARD in this scenario.

Indicated biologic drugs:

- TNFi : Adalimumab 40mg s/c eow, Etanercept 50mg s/c weekly, Infliximab IV 5mg/kg 8 weekly, Golimumab s/c 50mg monthly are all approved for the treatment of Psoriatic Arthritis.
- IL12/23i : Ustekinumab (45mg s/c week 0, 4 then 12 weekly thereafter).
- IL 17i: Secukinumab (150mg s/c week 0,1,2,3,4 and then 4 weekly thereafter. For TNFi inadequate responders, and those with moderate to severe plaque psoariasis, dose is 300mg in the same regime)

- Apremilast (30mg BD)

bDMARDS may be used in any order. Choice is left to the physician after consideration of costs, co-morbidities, route of administration, patient preference, Tuberculosis risk and skin involvement. Effect on joints is equivocal amongst available agents. There are possible different efficacies with respect to skin and enthesitis. Apremilast to be reserved for milder disease (oligo- or mono-arthritis, limited skin involvement or when other bDMARD not appropriate).

Combination therapy-
Methotrexate + TNFi or non- TNFi may have a role. Most studies suggest combination does not improve clinical symptoms beyond monotherapy. Some registry studies show increased drug survival with Methotrexate in combination with Infliximab.

Treatment Target
Should be MDA (Minimal Disease activity) or VLDA (Very low disease activity. A patient is in MDA if they fulfil 5/7 of the following criteria:

- TJC ≤1(68), SJC≤1(66), PASI≤1 or BSA <3%, Patient pain VAS ≤15, Patient global disease ≤20, HAQ≤ 0.5 and tender entheseal points≤1.

VLDL achieved with 7/7 criteria fulfilled.

DAPSA assesses TJC (68), SJC (66), Patient global VAS, Patient pain VAS, and CRP. Range 0-164.

- Remission is 0-4
- Low disease Activity 5-14
- Moderate disease activity 15-28
- High disease activity ≥ 28
- Response to treatment-
- Minor change 50%
- Moderate change 75%
- Major change 85%

Response to treatment

- Response is defined as
    - Improvement in two factors (with at least one being a joint score) with worsening of none of the following four factors
        - Patient global assessment (1-5 on a Likert scale- improvement defined as a decrease of 1)
        - Physician global assessment (as above)
        - 68 Tender joint count (improvement is a 30% decrease)
        - 66 Swollen joint count (Improvement 30% decrease)

    - A partial response is defined by some improvement in swollen and tender joint score and no worsening in physician or patient global score. If there has been a partial response, consideration should be given to a further 12 weeks of therapy.

- In the case of failure of a bDMARD , either due to inefficacy or toxicity, an alternative bDMARD should be considered including switching to another anti-TNF agent.

4 Role of Biologic therapies in the connective tissue diseases

Biologic therapies are reserved for severe, organ or life-threatening manifestations of connective tissue diseases (CTDs); or as 3rd or 4th line alternatives in treatment refractory disease. The use of biologics in the various CTDs is off-label, with the exceptions of Belimumab for adult and paediatric SLE, Rituximab in GPA and MPA, and Tocilizumab in GCA.

1. Systemic lupus erythematosus (SLE)

Goals of therapy include:-

- Remission of disease signs and symptoms
- Prevention of damage accrual
- Minimisation of drug side effects
- Overall improvement of quality of life

Useful measures of disease activity and damage in clinical practice

- SLEDAI
- SLICC Damage Index
- Physician's Global Assessment (PGA)

Definitions of remission in SLE:

- Complete remission – absence of clinical activity with no use of glucocorticoids (GCs) or immunosuppressive drugs (IS).
- Low disease activity states – SLEDAI ≤ 3 on antimalarials; or SLEDAI ≤ 4, PGA ≤ 1 with GCs ≤ 7.5mg of prednisone and well tolerated IS agents.

Definitions of remission in LN:

- Partial renal remission - ≥ 50% reduction in proteinuria to sub-nephrotic levels and serum creatinine within 10% baseline (aim to achieve in 6-12 months)
- Complete renal remission – proteinuria < 500mg/24 hours and serum creatinine within 10% of baseline (aim to achieve in 12 – 24 months)

Outline of therapy:

First-line therapy

- Antimalarials (Chloroquine (CQ)/hydroxychloroquine) – all patients barring contraindications
- Glucocorticoids – rapid reduction in signs and symptoms of disease activity

Second-line therapy (Immunomodulatory drugs)

Drug	**Indications**
Methotrexate	skin manifestations, arthritis, myositis, serositis
Azathioprine	skin manifestations (cutaneous vasculitis), myositis, haematological, pregnancy, maintenance in mild renal disease

Cyclophosphamide	severe manifestations of major organ involvement especially renal, CNS and cardio pulmonary, alternatively in refractory non-renal lupus
MMF	renal, skin, serositis, haematological, myositis
Cyclosporin/Tacrolimus	renal and haematological
Leflunomide	arthritis and renal

Third-line therapy – Biologics

- Belimumab (anti-BLyS therapy):
    - The only FDA/EMA approved biologic drug therapy for the management of SLE.
    - Not yet licenced for use in South Africa. Requires section 21 application via SAHPRA.
    - Indications would be ongoing activity on CQ with/without additional IS and inability to taper GC < 7.5 mg/day
    - Use is limited to mild to moderate cutaneous, musculoskeletal and serological manifestations, with currently no role in LN.

- Rituximab:
    - Off-label use in refractory renal or extra-renal manifestations of SLE.
    - In the case of renal lupus - only after failing MMF/CYP or in severe renal flares.
    - Extra-renal uses: severe diffuse neuropsychiatric manifestations, cardio-pulmonary and haematological disease if refractory to at least one IS drugs. Can be used as first-line treatment in severe autoimmune thrombocytopenia and haemolytic anaemia.
    - There is also benefit of combination CYP/Rituximab regimens for severe TTP or renal-limited TMA.
    - Recommended dose regimens:
        - 500mg/dose at Day 1 and Day 14
        - 1000mg/dose at Day 1 and Day 14, based on severity of disease or therapeutic response.
        - Dosing can be repeated at 6 month intervals dependent on therapeutic response.

2. Systemic Sclerosis (SSc)

Systemic sclerosis disease manifestations are a result of inflammation, vasculopathy and fibrosis, with IS therapies and biologic agents reserved for inflammatory manifestations of SSc.

Therapeutic options for SSc according to the EULAR treatment recommendations 2016 are MTX (skin and joint), CYP (skin and lung), or MMF (skin and lung) and in selected patients, autologous stem cell transplantation.

Biologic therapy use in SSc is reserved for severe or refractory skin, lung and joint involvement.

As there is no cure for SSC, management is aimed at retarding disease progression.

Outcome measures include:-

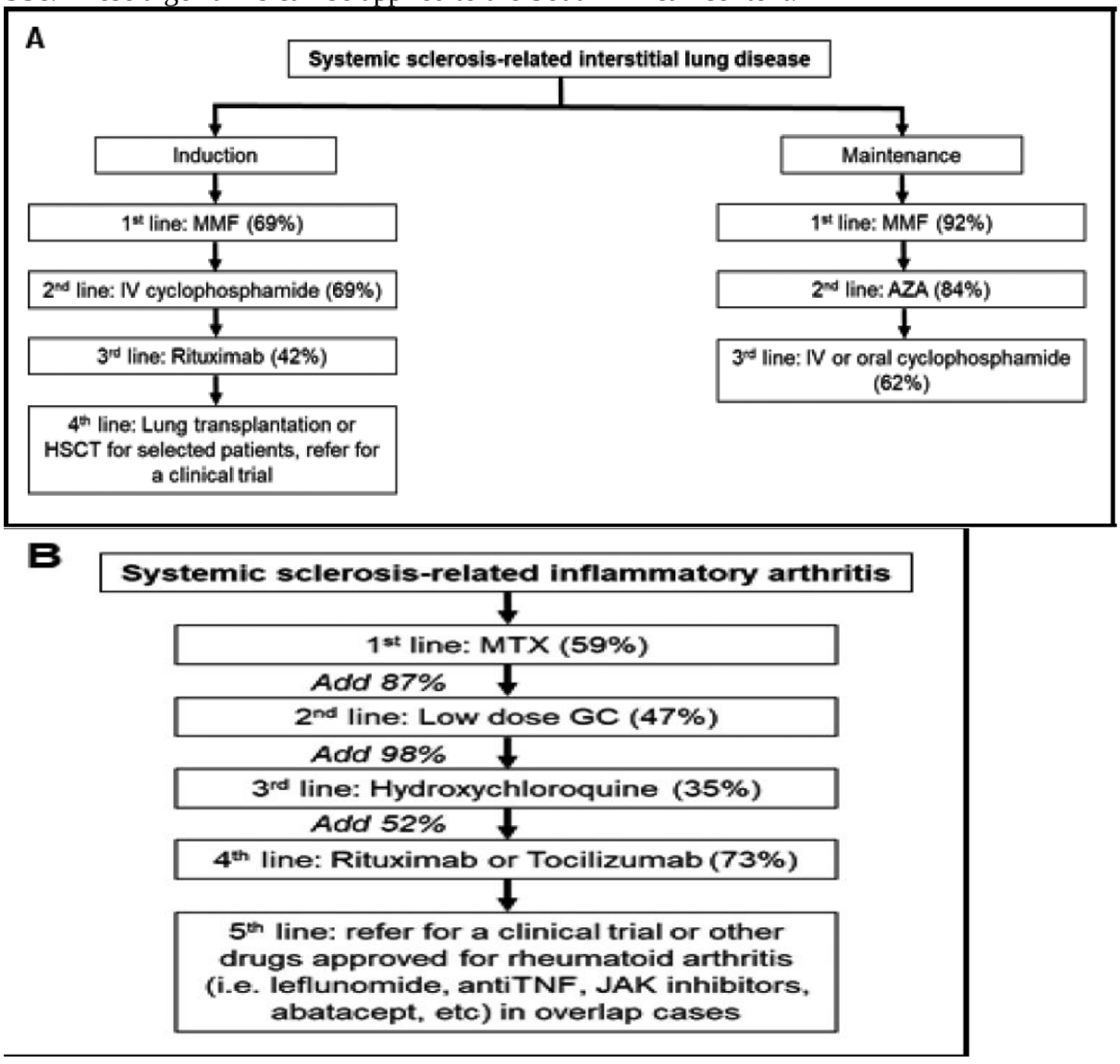
- Skin: modified Rodnan skin score (mRSS)

- Lung: Pulmonary function tests, namely forced vital capacity (FVC) and diffusion capacity (DLCO) and high-resolution CT-scan (HRCT) of the lungs to define the extent of pulmonary involvement.
- Patient assessment tools: HAQ-DI and patient global assessment

Biologics in SSc

The Scleroderma Algorithm Group, made up of leading experts on SSc, reached consensus on algorithms for treating the various manifestations of SSc. Biologic use was limited to SSc-related ILD and arthritis.

Figure 1 below describes the approach to treatment of ILD and inflammatory arthritis in SSc. These algorithms can be applied to the South African context.



- Rituximab in SSc:
  - Most widely studied biologic drug in SSc
  - Benefits seen in severe skin disease, ILD and arthritis, with the most convincing data shown with SSc-associated ILD.
  - Use for skin alone is not recommended.
  - Results from a large RCT for Rituximab use in CTD-associated ILD is still pending.

- Dose regimens commonly used include the 2 weekly regimen (500 or 1000 mg) at 6 monthly intervals depending on response.

- Tocilizumab in SSc:
  - Reserved for severe refractory joint involvement as an alternative to Rituximab, having failed conventional DMARD therapy.
  - Some anti-fibrotic effects demonstrated in in-vitro and animal studies
  - There is some evidence, however limited, showing improvement in skin scores.

3. Inflammatory myopathies (IIM)

There are no standardized therapeutic guidelines for treatment of IIM, particularly due to the lack of randomized controlled trials and the rarity of the disease. Therefore, the therapeutic approach is mainly guided by expert opinion and case series.

Glucocorticoids (GCs) remain first-line therapy in treatment of IIM, with IS drugs introduced early as adjunctive therapy for efficacy and for their steroid sparing effects. Choice of IS is based on the patient's clinical characteristics and main organ involvement. Failing this, biologic treatments can be used for refractory disease manifestations in IIMs.

3.1. Rituximab in myositis

Rituximab is the most commonly used biologic therapy in the IIMs, with the following indications:

- Severe refractory myositis after failing first and second line agents i.e. MTX, AZA, combination therapy and MMF. Despite not meeting its primary endpoints, Rituximab showed a considerable steroid-sparing effect in the large RCT, Rituximab in Myositis, RIM trial.
- Myositis-associated ILD failing standard therapies including MMF and CYP
- Severe skin involvement
- Refractory joint disease

Greatest benefit is seen in patients with myositis-specific antibodies, in particular anti-ARS, anti-Mi2 and anti-SRP antibodies.

RTX is usually prescribed with two 1g infusions 2 weeks apart and may be repeated after 6months.

3.2. Other biologics in myositis

There is very limited data on the role of other biologics in IIM. Studies with anti-TNF therapies have shown disappointing results, and are not recommended for use in IIMs.

Tocilizumab has shown positive results in 2 case reports suggesting a potential role as 4^{th} line therapy in refractory muscle and joint disease. There are ongoing trials exploring the efficacy of TCZ in refractory myositis.

Potential benefit with the use of Abatacept in refractory myositis was demonstrated in a single small randomised open-label study.

4. ANCA-associated vasculitis (AAV)

The AAVs include granulomatosis with polyangitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangitis (EGPA). Rituximab is licenced for use in AAV.

Indications for rituximab (RTX) in AAV

- Remission induction of new-onset organ-threatening or life-threatening AAV in combination with GCs, as an alternative to CYP.
- Major relapse of organ-threatening or life-threatening disease in combination with GCs.
- Remission maintenance in combination with low-dose GCs as an alternative to either azathioprine, methotrexate or mycophenolate mofetil (MMF) in GPA or MPA. This should be continued for at least 24 months after achieving sustained remission.

Evidence supporting the use of RTX

- Two RCTs, RAVE (Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis) and RITUXVAS (comparing RTX regimen with standard CYP/AZA regimen in the treatment of active, 'generalised' ANCA associated vasculitis), showed non-inferiority over CYP, and was more effective in relapsing disease in RAVE.
- The rituximab dose in both studies was 375 mg/m2 of body surface area, once a week for four infusions.
- The MAINRITSAN trial compared low-dose RTX in GPA/MPA (at a fixed 500 mg dose) to tapering dose of AZA for remission maintenance after induction with CYP. RTX use was associated with significantly fewer relapses and no renal relapses.
- Evidence for use in EGPA is less than for GPA or MPA.

Additional considerations

- In patients who wish to preserve their reproductive potential, RTX is preferred over CYP.
- Hypoimmunoglobulinaemia has been noted with RTX and testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection is recommended.

5. Large vessel vasculitis (LVV)

The LVVs include Takayasu's arteritis (TA) and giant cell arteritis (GCA).
Rapid diagnosis and treatment is essential in these conditions to avoid potentially irreversible complications, including blindness in GCA and aortic aneurysm in TA.
These severe acute presentations warrant treatment with potent immunomodulatory therapy, including biologic therapy.

5.1. Giant-cell arteritis (GCA)

- The cornerstone of treatment is high dose GCs (40-60mg Prednisone), and a substantial number of patients can be managed with GC monotherapy.
- Adjunctive use of TCZ or MTX should be considered for selected patients.
    - Refractory or relapsing GCA
    - The presence or increased risk of developing GC-related adverse effects or complications
- Two high-quality randomised controlled clinical trials in patients with GCA have shown that adjunctive administration of TCZ reduces the risk of relapse and cumulative GC exposure compared with GC monotherapy.

- There are no head-to-head trials comparing TCZ and MTX in GCA, however based on a meta-analysis of studies, TCZ provides a higher confidence in achieving clinically relevant treatment effect.
- There is no data on long term efficacy and safety of TCZ in GCA, and the duration of treatment, as well as dose reductions should be decided on an individual basis.
- The target for treatment is sustained remission i.e. absence of signs and symptoms and normal acute phase reactants.
- Considerations before initiating TCZ include the risk of treatment-related complications in an elderly population with underlying comorbidities e.g. intestinal perforation.

5.2. Takayasu arteritis (TA)

- Non-biological disease modifying agents (DMARDs) should be given in combination with GCs in all patients with TA early on in disease. This is due to the high relapse rates and the risk of new vascular lesions. These drugs include MTX, MMF, AZA, CYP and Leflunomide.
- TCZ or anti-TNF drugs are used as second-line therapy, in cases of relapsing or refractory disease despite conventional DMARDs.
- Two RCTs showed a non-significant lower relapse rate and treatment response in TCZ over conventional DMARDs.
- Efficacy of anti-TNFs in TA has been reported in one prospective and several retrospective open-label uncontrolled studies/case series.
- There is no high-quality evidence showing superiority of biologics over conventional (DMARDs) in TA. As such, the choice of IS agent should be based on patient comorbidities or contraindications.
- Due to lack of long term data, duration of treatment must be decided on an individual basis.

Figures 2 & 3 summarise the 2018 EULAR recommendations for the management of GCA and TA which can be used as a model to treat patients with LVV.

References:

1. Smolen JS,Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs.*Ann Rheu Dis* 2010;**69**:964 – 975
2. Furst DE, Keystone E, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases.*Ann Rheu Dis* 2011;**70**:(Suppl 1):i2 – i36.
3. Buch MH, Smolen JS, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis.*Ann Rheu Dis;* 2011;**70**:909-920.
4. Van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis *Ann Rheu Dis*;**70**:905-908.

5. British Society for Rheumatology. Principles for Biologic Prescribing – December 2010. http://www.rheumatology.org.uk/resources/guidelines/bsr_guidelines.aspx
6. British Society for Rheumatology. RA guidelines on eligibility criteria for the first biological therapy. http://www.rheumatology.org.uk/includes/documents/cm_docs/2010/r/2_ra_guidelines_on_eligibility_criteria_for_the_first_biological_therapy.pdf
7. National Institute for Health and Clinical Excellence. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. http://www.nice.org.uk/
8. National Institute for Health and Clinical Excellence. Tocilizumab for rheumatoid arthritis. http://guidance.nice.org.uk/TA198
9. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. **2008** Recommendations for the Use of Nonbiologic and Biologic DMARDs in RA**:** American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59:762–84.
10. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis.*Clin Exp Rheumatol*. 2005 Sep-Oct;**23**(5 Suppl 39):S100-8
11. Gaujoux-Viala C, Mouterde G, Baillet A, Claudepierre P, Fautrel B, Le Loët X, Maillefert JF, Evaluating disease activity in rheumatoid arthritis: Which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of DAS28, SDAI and CDAI. *Joint Bone Tocilizumab for the treatment of rheumatoid arthritisSpine*.2011 Jun 14.
12. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F, Hawker G. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8.
13. Coates LC et al. BSR & BHPR guidelines for the treatment of Psoriatic arthritis with biologics. doi:10.1093/rheumatology/ket187
14. J Braun, T Pham, J Sieper, J Davis, Sj van der Linden,M Dougados,D van der Heijde,for the ASAS Working Group. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003;62:817-824 doi:10.1136/ard.62.9.817
15. Courvoisier N, Dougados M, Cantagrel A, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 2008; 10:R106
16. Reid V et al. Harmonised Biologics Pathway for Ankylosing Spondylitis and Psoriatic Arthritis. Dec 2014. Gmmg.nhs.uk/html/pathways.html