

South African Rheumatism and Arthritis Association 2024 guidelines for the use of biologic and targeted synthetic disease-modifying antirheumatic drugs

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Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) target a specific pathway of the immune system, and are usually prescribed after failure of conventional synthetic disease-modifying antirheumatic drug therapy. The choice of b/tsDMARD depends on the disease profile and comorbidities, patient preference, registered indications of the drugs, and risks associated with therapy. It is recommended that b/tsDMARDs for immune-mediated inflammatory rheumatic diseases are prescribed by a rheumatologist, and all patients must be included in the South African Rheumatism and Arthritis Association biologic registry. Knowledge of and vigilance for adverse events, particularly infections, associated with b/ts DMARD therapies are of paramount importance.

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Disease-modifying antirheumatic drugs (DMARDs) are immunosuppressive and immunomodulatory agents used to treat immune-mediated inflammatory rheumatic diseases. Biologic DMARDs (bDMARDs) were introduced in the early 1990s, and came into use in South Africa (SA) in the 2000s. These therapies target a specific pathway of the immune system. The bDMARDs include original (boDMARDs) and biosimilar DMARDs (bsDMARDs), and are monoclonal, chimeric humanised fusion antibodies, or receptors that have been fused to a part of the human immunoglobulin (Tables 1 and 2). More recently, the targeted synthetic DMARDs (tsDMARDs) have been developed, including the Janus kinase inhibitors (JAKis) (Table 3).

Biologic/targeted synthetic DMARDs are usually prescribed after failure of conventional synthetic DMARD (csDMARD) therapy. The choice of b/tsDMARD depends on factors including disease profile and comorbidities, patient preference regarding route of administration, registered indications of the drugs, and risks associated with therapy. Patients treated with b/tsDMARDs should be monitored at regular intervals and should only continue if an adequate response is achieved and maintained. The use of an alternative b/tsDMARD may be necessary in patients who do not achieve or maintain a clinical response or who have an adverse event. It is not recommended to continue therapy if the patient has not responded.

It is recommended that b/tsDMARDs only be prescribed by rheumatologists experienced in the diagnosis and management of immune-mediated inflammatory rheumatic diseases, with adequate knowledge of these therapies and their possible adverse events. The management of patients using b/tsDMARD therapy 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 guidelines provide a guide, but treatment needs to be tailored to the individual patient's needs. The field of rheumatology is dynamic and is constantly expanding. New data that may become available after the current revision of these guidelines should be considered when using the drugs.

South African Rheumatism and Arthritis Association biologic registry

The South African Rheumatism and Arthritis Association (SARAA) biologic registry was established with the aim of capturing information about the use and safety of b/tsDMARDs in SA. Before commencing b/tsDMARD therapy, clinical details of prospective patients must be submitted to the registry and approval must be obtained from the SARAA Biologics Advisory Peer Review Panel. This panel, consisting of at least six rheumatologists, reviews applications of individual patients for eligibility for b/tsDMARDs according to the SARAA guidelines (see policy document and standard operating procedure for the SARAA Biologics Advisory Peer Review Panel at www.saraa.co.za). Applications need to be approved by at least two panel members. The identity of the patient and the prescribing rheumatologist is not available to panel members.

The panel only reviews applications for the use of b/tsDMARDs for licensed indications. Details of use for an unlicensed indication, such

Summary of SARAA Eligibility Criteria for b/tsDMARD therapies

SARAA eligibility criteria for b/tsDMARD therapies in rheumatoid arthritis

- MDA/HDA (CDAI >10)
- Failed MTX + another csDMARD × 3/12
- Refractory extra-articular disease (e.g. RA-ILD)

SARAA eligibility criteria for b/tsDMARD therapies for axial spondyloarthritis

- Objective evidence of inflammation:
 - ↑CRP/MRI demonstrating active sacroiliitis/MSUS demonstrating inflammation in joint/enthesitis/dactylitis
- High Disease Activity (sustained for two visits at least 4 weeks apart):
 - ASDAS >2.1 and spinal pain VAS ≥4
- Failure of standard treatment:
 - at least two NSAIDs during a 4-week period
 - if peripheral arthritis, failure of sulfasalazine
- Refractory enthesitis, uveitis or other extra-articular manifestations

SARAA eligibility criteria for b/tsDMARD therapies for psoriatic arthritis

- Polyarthritis/persistent oligoarthritis failed MTX + another csDMARD × 3/12
- Axial disease with poor response to NSAIDs
- Refractory dactylitis, enthesitis or extra-articular disease

SARAA eligibility criteria for b/tsDMARD therapies for other spondyloarthritis (including reactive arthritis, inflammatory bowel disease-associated arthritis, and undifferentiated spondyloarthritis)

- Failure of conventional therapy for peripheral arthritis, enthesitis, dactylitis, axial spondyloarthritis or severe extra-articular disease

SARAA = South African Rheumatism and Arthritis Association; b/tsDMARD = biological/targeted synthetic disease-modifying antirheumatic drug; MDA = XXX AUTHOR: PLEASE COMPLETE; HDA = XXX; CDAI = Clinical Disease Activity Index; MTX = methotrexate; csDMARD = conventional synthetic DMARD; RA = rheumatoid arthritis; ILD = interstitial lung disease; CRP = C-reactive protein; MRI = XXX; MSUS = musculoskeletal ultrasound; ASDAS = xxxxx; VAS = xxxxx; NSAID = non-steroidal anti-inflammatory drug.

as treatment of a connective tissue disease, should still be submitted to the registry so that information about all b/tsDMARD therapy use can be captured.

Application process for b/tsDMARD therapy in SA

Information is entered onto the SARAA biologic registry website (<https://saraa.phoenixx.app>), including patient demographic and clinical information. Patients must complete and sign the SARAA patient informed consent form agreeing to inclusion on the registry. Clinical progress reports should be submitted to the registry annually, or more frequently if necessary. The registry must be notified of any adverse events or change in therapy.

General considerations for the use of b/tsDMARDs

Infection

- The use of all b/tsDMARDs is associated with an increased risk of serious infection.^[1-3] The b/tsDMARD should be discontinued if a serious infection occurs and only recommenced after the infection has resolved.
- The decision to restart a b/tsDMARD, switch or discontinue after a serious infection is a clinical decision made after taking into consideration patient factors such as age, comorbidities, concomitant medication and csDMARD use.
- b/tsDMARDs should not be initiated in the presence of serious infection.

In the following circumstances, b/tsDMARDs should be used with caution because of the high risk of infection:^[4]

- 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
- Immunosuppressed patients, including those with HIV infection with a low CD4 count.

Tuberculosis

SA has a very high prevalence of tuberculosis (TB), and patients with autoimmune rheumatic diseases have an increased risk for reactivation of latent TB and new TB infection.^[5] This risk is further increased with b/tsDMARD therapy, particularly tumour necrosis factor inhibitors (TNFis).^[6] The risk of reactivation of latent TB infection (LTBI) is greatly reduced by screening for and treating LTBI.

Risk of TB infection

Given the very high risk of TB exposure in SA (40 - 1 000 cases per 100 000 population), most SA patients are at an intermediate to high risk of exposure to TB. The higher the risk of exposure, the higher the risk of infection. The following are among those considered at very high risk of TB exposure:

- Healthcare workers
- Residents or employees of congregate settings such as correctional facilities, care facilities, shelters, schools, universities and colleges, or any congregation of people
- Persons reliant on public transport such as taxis, buses and trains
- Close contact with known or suspected TB cases
- Persons working or resident in an area with a high TB incidence
- Drug or alcohol abusers.

Screening for LTBI

- Regardless of the underlying rheumatic condition or the choice of b/tsDMARD, all prospective b/tsDMARD users must be screened for LTBI. This only needs to be done when commencing therapy and is not needed when switching therapy.

Table 1. Details of TNFis for immune-mediated inflammatory rheumatic diseases available in South Africa

Biologic	Mechanism of action	Drug name	SAHPRA-approved indications	Loading dose	Maintenance dose
Etanercept	TNF receptor blocker	Enbrel	RA, axSpA, PsO, PsA	-	50 mg SC weekly
		Erelzi	JIA, paed PsO		OR 25 mg SC twice weekly (3 - 4 days apart)
Adalimumab	Human anti-TNF mAb	Humira	RA, axSpA, PsA, PsO, CD, fistulising CD, UC	CD & UC: 160 mg SC at week 0, 80 mg SC at week 2, then start maintenance (40 mg EOW) at week 4	40 mg SC EOW
		Amgevita	Uveitis, HS, JIA, paed CD, paed PsO, paed uveitis	Plaque PsO and uveitis: 80 mg SC then start maintenance (40 mg EOW) at week 2 HS: 160 mg at week 0, then 80 mg SC at week 2, then start maintenance (40 mg EOW) at week 4	
Infliximab	Mouse/human anti-TNF mAb	Revellex	RA, axSpA, PsO, PsA, CD,	RA: 3 mg/kg IVI (weeks 0, 2 and 6) axSpA, PsA, PsO, IBD: 5 mg/kg IVI (weeks 0, 2 and 6)	RA: 3 mg/kg IVI every 8 weeks Inadequate/loss response: administer 3 mg/kg every 4 weeks or increase dose stepwise by 1.5 mg/kg (maximum 7.5 mg/kg) every 8 weeks axSpA, PsA, PsO, IBD: 5 mg/kg IVI every 8 weeks Inadequate response: Administer 5 mg/kg every 4 weeks or increase dose to 10 mg/kg every 8 weeks
		Remsima	UC, fistulising CD		
		Remiflix	Paed CD, paed UC		
Golimumab	Human anti-TNF mAb	Simponi	RA, axSpA, PsO, PsA, UC JIA	For IVI: 2 mg/kg at weeks 0, 4 then every 8 weeks	50 mg SC every 4 weeks 2 mg/kg IVI every 8 weeks

TNFi = tumour necrosis factor inhibitor; SAHPRA = South African Health Products Regulatory Authority; TNF = tumour necrosis factor; RA = rheumatoid arthritis; axSpA = axial spondyloarthritis (radiographic and non-radiographic); PsO = psoriasis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; paed = paediatric; SC = subcutaneous; mAb = monoclonal antibody; CD = Crohn's disease; UC = ulcerative colitis; EOW = every other week; HS = hidradenitis suppurativa; IBD = inflammatory bowel disease; IVI = intravenous infusion.

- All patients require a chest radiograph, not longer than 3 months prior to commencing b/tsDMARD therapy.
- LTBI is tested for with either a tuberculin skin test (TST) (e.g. the Mantoux test performed with purified protein derivative) or an interferon-gamma release (IGRA) test (e.g. QuantiFERON-TB Gold).
- For the TST, a skin induration ≥ 5 mm is regarded as a positive result.
- IGRA tests should always be performed before or at the same time as the TST to exclude sensitisation and a false-positive IGRA result induced by the TST.
- Repeating an IGRA test or performing a TST may be useful when the initial IGRA result is indeterminate, borderline or invalid.
- Testing for LTBI (IGRA or TST) is not reliable in very high-risk patients, and clinicians must use clinical judgement.^[7]
- LTBI detected by means of a positive TST or IGRA test may be treated with one of three regimens:
 - 9 months of isoniazid (INH) 300 mg daily
 - 3 months of INH 300 mg daily and rifampicin 600 mg daily
 - 12 once-weekly doses of INH (15 mg/kg) and rifapentine (900 mg, if < 50 kg 750 mg).^[8]
- Supplementation with pyridoxine 25 mg daily is recommended.
- Liver function tests must be monitored, with caution in patients aged ≥ 65 years.
- b/tsDMARD therapy may be commenced 1 month after LTBI treatment is initiated.

Choice of b/tsDMARD in patients at very high TB risk

Some b/tsDMARDs, such as TNFis, whether original or biosimilar, confer a greater risk of TB reactivation/infection than non-TNFi biologics. A non-TNFi should therefore be considered as first-line therapy in patients with very high risk of exposure or patients with previous TB.^[9] If a TNFi is used in very high-risk patients, INH prophylaxis for the duration of the TNFi therapy is recommended regardless of LTBI results. Similarly, other comorbidities may influence the choice of b/tsDMARD (Table 4).

Treatment of LTBI

- It is imperative to rule out active TB disease in all persons prior to initiating treatment for LTBI.

Table 2. Details of non-TNFi biologic disease-modifying antirheumatic therapies for immune-mediated inflammatory rheumatic diseases available in South Africa

Biologic	Mechanism of action	Drug name	SAHPRA-approved indications	Loading dose	Maintenance dose
Rituximab	Mouse/human anti-CD20 mAb	Mabthera Ristova Blitzima	RA, ANCA-associated vasculitis Haematological malignancies: NHL, CLL	-	High dose: 2 g IVI 6-monthly (1 000 mg day 1 and day 15) Low dose: 1 g IVI 6-monthly (500 mg on day 1 and day 15)
Tocilizumab	Humanised IL-6 receptor mAb	Actemra	RA Systemic JIA, polyarticular JIA GCA	-	IVI: 4 - 8 mg/kg monthly (max. 800 mg per infusion) SC: <100 kg: 162 mg SC every 2 weeks >100 kg: 162 mg SC weekly
Abatacept	Receptor fusion protein inhibiting T-cell costimulation	Orencia	RA JIA	SC: single IVI dose with the first 125 mg SC dose IVI: loading dose of 3 doses given at weeks 0, 2 and 4	SC: 125 mg SC weekly +/- IVI loading dose IVI: 10 mg/kg (500 mg, 750 mg or 1 000 mg) every 4 weeks <60 kg: 500 mg; 60 - 100 kg: 750 mg; >100 kg: 1 000 mg
Ustekinumab	IL-12/23 mAb	Stelara	PsO, PsA, CD	<100 kg: 45 mg SC at weeks 0 and 4 >100 kg: 90 mg SC at weeks 0 and 4	<100 kg: 45 mg SC every 12 weeks >100 kg: 90 mg SC every 12 weeks
Guselkumab	IL-23 mAb	Tremfya	PsO, PsA	100 mg SC at weeks 0 and 4	100 mg SC every 8 weeks; can increase to 100 mg SC every 4 weeks
Sekukinumab	Humanised IL-17A mAb	Cosentyx Scapho	PsO, PsA, axSpA Paed PsO	PsA, axSpA: 150 mg at weeks 0, 1, 2, 3 and 4 Plaque PsO: 300 mg at weeks 0, 1, 2, 3 and 4	PsA, axSpA: 150 mg SC every 4 weeks, if uncontrolled 300 mg SC every 4 weeks Plaque PsO: 300 mg SC every 4 weeks
Ixekizumab	Humanised IL-17A mAb	Copellor	PsO, PsA, axSpA Paed PsO	axSpA, PsA: 160 mg at week 0 Plaque PsO: 160 mg SC at week 0 then 80 mg at weeks 2, 4, 6, 8, 10 and 12	axSpA, PsA, plaque PsO: 80 mg SC every 4 weeks

TNFi = tumour necrosis factor inhibitor; SAHPRA = South African Health Products Regulatory Authority; mAb = monoclonal antibody; RA = rheumatoid arthritis; ANCA = anti-neutrophilic cytoplasmic antibody; NHL = non-Hodgkin's lymphoma; CLL = chronic lymphocytic lymphoma; IVI = intravenous infusion; IL = interleukin; JIA = juvenile idiopathic arthritis; GCA = giant cell arthritis; SC = subcutaneous; PsO = psoriasis; PsA = psoriatic arthritis; axSpA = axial spondyloarthritis (radiographic and non-radiographic); paed = paediatric.

Table 3. Details of targeted synthetic disease-modifying antirheumatic therapies and phosphodiesterase 4 inhibitor for immune-mediated inflammatory rheumatic diseases available in South Africa

Biologic	Mechanism of action	Drug name	SAHPRA-approved indications	Dose
Tofacitinib	JAKi (JAK1, 2 and 3)	Xeljanz	RA, PsA, UC (AS, JIA)	RA, PsA: 5 mg PO BD UC: 10 mg PO BD
Baricitinib	JAKi (JAK1 and 2)	Olumiant	RA, COVID-19	4 mg PO daily Age ≥5 years and history of chronic or recurrent infections: 2 mg once daily
Upadacitinib	JAKi (JAK1)	Rinvoq	RA, PsA, axSpA, UC, AD	15 mg PO daily (AD dose can be increased to 30 mg if inadequate response)
Apremilast	PDE4i	Otezla	PsO, PsA	30 mg PO BD Initial dose titration: day 1: 10 mg daily; day 2: 10 mg BD; day 3: 10 mg mane/20 mg nocte; day 4: 20 mg BD Reduce to 30 mg once daily if eGFR <30 mL/min/1.73

SAHPRA = South African Health Products Regulatory Authority; JAKi = Janus kinase inhibitor; JAK = Janus kinase; RA = rheumatoid arthritis; PsA = psoriatic arthritis; UC = ulcerative colitis; AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; PO = per os; BD = two times a day; axSpA = axial spondyloarthritis; AD = atopic dermatitis; PsO = psoriasis; PDE4i = phosphodiesterase 4 inhibitor; eGFR = estimated glomerular filtration rate.

Table 4. Safety of DMARDs and immunosuppressants

	NSAID	GC	csDMARD	TNFi	Rituximab	Abatacept	IL-6i	IL-17i	IL-12/23i;		PDE4i
									IL-23i	JAKi	
High infection risk		Avoid		Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution
High TB risk		Avoid		Avoid	Caution	Caution	Caution	Caution	Caution	Caution	Caution
CV risk	Avoid				Caution						Avoid
Obesity		Avoid									
Active hepatitis B			Caution	Caution	Avoid			Caution	Caution		Caution
HIV + low CD4		Caution	Avoid	Avoid							Caution
NAFLD		Caution	Caution								
Previous malignancy				Caution		Avoid		Caution	Caution		Caution
MS/demyelinating disease				Avoid							
Depression/anxiety											
Severe heart failure		Caution						Caution	Caution		Caution
Risk for VTE	Avoid	Caution		Avoid							Avoid
Diverticulosis											Avoid

DMARD = disease-modifying antirheumatic drug; NSAID = non-steroidal anti-inflammatory drug; GC = glucocorticoid; csDMARD = conventional synthetic DMARD; TNFi = tumour necrosis factor inhibitor; IL-6i = interleukin 6 inhibitor; IL-17i = interleukin 17 inhibitor; IL-12i = interleukin 12 inhibitor; IL-23i = interleukin 23 inhibitor; JAKi = janus kinase inhibitor; PDE4i = phosphodiesterase 4 inhibitor; TB = tuberculosis; CV = cardiovascular; NAFLD = non-alcoholic fatty liver disease; MS = multiple sclerosis; VTE = venous thromboembolism.

Active TB infection

- Reactivation of LTBI usually occurs within months of commencement of the b/tsDMARD, but TB infection can occur at any time, and patients and healthcare workers need to remain vigilant for symptoms and signs of TB infection. This vigilance for TB must continue for at least 6 months after discontinuation of a b/tsDMARD.
- When TB is suspected, chest radiographs and sputum polymerase chain reaction testing for TB, as well as evaluation for extrapulmonary disease, should be done. Of note, extrapulmonary TB is common.
- IGRA tests and TSTs are *not* useful to evaluate patients with suspected active TB.
- A multidisciplinary team should be consulted if TB is suspected but microbiological or histological evidence is lacking.
- If TB is diagnosed or a decision is made to commence empirical TB therapy, b/tsDMARDs should be discontinued. Patients should be treated as per national guidelines with a multidrug anti-TB regimen, with clinical, radiological and microbiological follow-up, and monitoring for TB drug toxicity with consultation with the local infectious disease specialists.
- Low-dose corticosteroids (CSs) (≤10 mg/d) as well as csDMARDs may be used during TB treatment.
- There are no clear guidelines as to when b/tsDMARDs can be safely restarted. This decision should be made in consultation with the multidisciplinary team. If possible, a safer b/tsDMARD should be chosen.

Viral infections

- All patients should be vaccinated (Table 5).
- Patients should be screened for hepatitis B virus (HBV) before starting b/tsDMARD therapy, as reactivation of chronic infection can occur. This is particularly important before rituximab therapy, where hepatitis B core antibody (HBcAb) must be checked.^[10] Patients who are HBV positive can be treated with b/tsDMARDs provided they are on antiviral agents. Consultation with a hepatologist is advised if patients are hepatitis B or C positive before or during b/tsDMARD therapy.
- All patients should be screened for HIV and treated appropriately if HIV positive. b/tsDMARDs should be avoided in HIV-positive patients with low CD4 counts because of the risk of opportunistic infections. In HIV-positive patients with normal CD4 counts, b/tsDMARDs appear relatively safe.
- The risk of herpes zoster (HZ) and HZ-related complications is increased in patients with rheumatic diseases, and particularly those treated with b/tsDMARDs (especially JAKi), so HZ vaccination is recommended.^[11]

Vaccinations (Table 5)

- All patients should be vaccinated, ideally before commencing csDMARD therapy and definitely before b/tsDMARD therapy.
- Initial evaluation of any patient for proposed b/tsDMARD therapy should include a review of each patient’s vaccination exposure before the start of immunosuppressive therapy. These include *Haemophilus influenzae* type B, hepatitis A and B, human papillomavirus, *Streptococcus pneumoniae*, influenza, *Neisseria meningitidis*, tetanus toxoid, rubella (for women of childbearing age), COVID-19 and adjuvanted recombinant zoster vaccine.^[12-15]
- Vaccination with inactivated vaccines can be given during b/tsDMARD treatment, although the antibody response may be decreased. Vaccination should be offered 2 weeks before rituximab therapy for this reason.

Table 5. Vaccinations for patients using biologic/targeted synthetic disease-modifying antirheumatic therapies

Type	Organism	Recipients	Timing	Comments
Inactivated vaccines	<i>Streptococcus pneumoniae</i>	All patients receiving or planning to start bDMARDs	≥2 weeks before the start of bDMARD, esp for rituximab, abatacept, tocilizumab	PCV13 PLUS ≥8 weeks later PPSV23 If the cost of giving both vaccines is a concern, then PPSV23 alone is an alternative
	Influenza	All patients	Annually	
	Hepatitis A virus	If no antibodies and risk, e.g. travel		Two-dose series (better seroprotection rates)
	Hepatitis B virus	If no antibodies and risk, e.g. occupational or lifestyle risk factors		Recombivax HB: Three-dose schedule at 0, 1 and 6 months OR Engerix-B: Two doses of 20 µg/mL administered simultaneously on a four-dose schedule at 0, 1, 2 and 6 months
	Tetanus toxoid	As indicated	10-yearly or post exposure as indicated	
	COVID-19	All patients	Annually	If possible, delay commencement of any DMARD treatment, but particularly rituximab, by 2 weeks after completing vaccination to enhance the vaccine efficacy Abatacept and JAKi should be omitted for 1 week (only if disease is well controlled) after each vaccine dose to enhance the vaccine efficacy
	Herpes zoster	All patients ≥50 years	2 doses, 2 - 6 months apart	Adjuvanted RZV (Shingrix): No risk of developing disseminated disease
	BCG vaccination	Contraindicated and ineffective in adults		
	Herpes zoster	Contraindicated during DMARD therapy	≥4 weeks before DMARD	LZV (Zostavax) Single dose, lasts 10 years
	Live vaccines	Varicella	Contraindicated during DMARD therapy	
Yellow fever		Contraindicated during b/ tsDMARD therapy	Vaccinate a patient likely to travel prior to commencing b/tsDMARD or offer travel waiver document	

bDMARD = biologic disease-modifying antirheumatic drug; PCV13 = 13-valent pneumococcal vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; DMARD = disease-modifying antirheumatic drug; JAKi = Janus kinase inhibitor; RZV = recombinant zoster vaccine; LZV = live attenuated zoster vaccine; VZV = varicella zoster virus; b/tsDMARD = biologic/targeted synthetic DMARD.

- Vaccination with live attenuated viruses (HZ and yellow fever) is contraindicated during b/tsDMARD therapy. Patients using b/ tsDMARDs who need to travel to countries where yellow fever is endemic may ask for a waiver for vaccination.
- Live vaccines should be avoided for 3 months after stopping abatacept and tocilizumab.

Perioperative management

There may be an increased risk of perioperative infections in patients on b/tsDMARDs, although this is probably small.^[16] Most guidelines are based on expert opinion owing to small studies or low-quality evidence. Surgery should be scheduled at the end of a dosing cycle for the specific b/tsDMARD (Table 6). When wound healing has occurred and staples or sutures have been removed (typically after 14 days) and there is no evidence of infection, the b/tsDMARD can be restarted.

In the case of joint replacement surgery, b/tsDMARDs should be withheld for at least 1 month before and after surgery. Tocilizumab should be withheld for longer than the recommended time where possible owing to delayed wound healing and increased risk of infection.

Serious infections: b/tsDMARD interruptions

b/tsDMARDs should only be interrupted for serious infections. Clinicians must be aware that non-serious infections are common, and that continuation of therapy generally does not prolong or worsen infection. Stopping therapy may worsen inflammation and may necessitate glucocorticoid therapy – which is likely to worsen infection. For severe infections (hospitalisation required, fever or low cell counts), all DMARDs should be temporarily discontinued and restarted only when the infection has resolved.

Table 6. b/tsDMARDs and recommended timing of surgery

Drug	Dosing interval	Time to plan surgery
Adalimumab	Every 2 weeks	Week 3
Infliximab	Every 8 weeks	Week 9
Etanercept	Weekly	Week 2
Golimumab	Every 4 weeks	Week 5
Rituximab	6-monthly	Month 7 (possibly 4 - 7)
Tocilizumab IV	Every 4 weeks	Week 5
Tocilizumab SC	Weekly	Week 2 or preferably 3
Abatacept IV	Every 4 weeks	Week 5
Abatacept SC	Weekly	Week 2
Secukinumab	Every 4 weeks	Week 5
Ustekinumab	Every 12 weeks	Week 13
Baricitinib	Daily	Day 4
Tofacitinib	Daily or twice daily	Day 4
Upacitinib	Daily	Day 4

b/tsDMARD = biologic/targeted synthetic disease-modifying antirheumatic drug; IV = intravenous; SC = subcutaneous.

Pregnancy

Family planning should be addressed in all patients of reproductive age, with adjustment of therapy before a planned pregnancy. Decisions on drug therapy during pregnancy and lactation should be based on agreement between the patient, rheumatologist and obstetrician.

Use of specific b/tsDMARDs preconception, and during pregnancy and lactation

TNFis

- Current evidence indicates no increased risk of congenital malformations.^[17,18]
- The TNFi should be stopped at 32 weeks so that the neonate can receive live vaccines (e.g. BCG and live oral poliovirus vaccine). Alternatively, the TNFi can be continued throughout pregnancy, and then neonatal vaccines delayed for 6 months. Consultation with a paediatrician is advised. TNFi therapy is safe while breastfeeding.^[19,20]

Rituximab

- Currently there is not enough evidence to support use during pregnancy and breastfeeding: some evidence indicates no increased rate of congenital malformations, so in exceptional cases it can be considered early in gestation.^[20,21] There may be a risk of B-cell depletion and other cytopenias in the neonate if used at later stages of pregnancy.^[22] Consultation with a paediatrician is advised.

Tocilizumab, abatacept, ustekinumab, secukinumab, guselkumab, JAKis

- Safety in pregnancy for mother and fetus has not been established, and use should be avoided in women wanting to fall pregnant.^[19,20]

Background csDMARD therapy

- In RA clinical trials, the use of all bDMARDs in combination with methotrexate (MTX) showed better efficacy than biologic monotherapy.^[23,24] Therefore, bDMARDs should be co-prescribed with MTX in RA.^[25] In spondyloarthritis (SPA) (axial or peripheral), there is less evidence that co-prescription of MTX adds efficacy.^[26-28] MTX can be used at low doses (7.5 - 10 mg weekly), and intolerance at these low doses is rare. Patients intolerant to MTX can use leflunomide. Tocilizumab and JAKis are registered for monotherapy use and can be used without co-prescription of MTX.^[25]

- Multiple csDMARDs in combination with a b/tsDMARD have not been shown to improve clinical response.
- Prednisone should not be used in combination with b/tsDMARDs and should be weaned if possible.

Switching b/tsDMARDs

- Switching between different b/tsDMARD therapies is appropriate in cases where there is lack of efficacy or occurrence of side-effects on a specific b/tsDMARD.^[25,29,30]
- When switching from a TNFi, abatacept, tocilizumab, secukinumab or ustekinumab, the new drug can be started when the next dose of the previous drug would have been given.
- When switching from a TNFi to rituximab, it is recommended to initiate treatment ≥ 4 weeks after etanercept discontinuation, and ≥ 8 weeks after infliximab or adalimumab discontinuation.
- When switching from rituximab, it is recommended that the next b/tsDMARD is initiated 6 months after the last dose of rituximab.

Biosimilar DMARDs

A biosimilar is a copy of a biologic (bio-originator) made by a different manufacturer from the original innovator of the biologic agent that is no longer protected by patent. The biosimilars have undergone rigorous assessment in comparison with the reference product and have been approved by a regulatory agency (e.g. the South African Health Products Regulatory Authority (SAHPRA)). Direct comparison of the bsDMARDs with the boDMARDs shows that efficacy and side-effects are similar.^[31-33]

The SARAA is committed to maintaining the highest standard of care for patients, against the background of a country that is resource constrained. To this end we welcome the registration of the bsDMARDs in SA and hope that the reduction in the price of treatment will improve access to therapies. There are data to support switching from a boDMARD to a bsDMARD, but this must be a shared decision between the treating rheumatologist and the patient.^[34]

Cost-effectiveness

Inflammatory joint diseases incur high individual, medical and societal costs.^[35-37] The cost-effectiveness of good disease control has been clearly demonstrated, with low disease activity or remission incurring lower healthcare costs.^[38] For patients with inflammatory joint disease (and certain connective tissue diseases) with an inadequate response to csDMARDs or immunosuppressives, b/tsDMARDs offer

improved control of disease activity. However, b/tsDMARDs are substantially more expensive per year than csDMARDs. A systematic review showed that most cost-effective approach in the case of RA (but this is likely to pertain to other inflammatory joint diseases) is to offer csDMARD treatment early in the course of disease, escalating to combination csDMARD therapy in the case of non-response, and finally adding a bDMARD if the non-response continues.^[39] Of note, this systematic review was conducted in high- or upper middle-income countries. Cost-effectiveness studies and meta-analyses have shown mixed results, often pertaining to specific therapies and their costs, and to specific patient characteristics.^[40-44] There are no published cost-effectiveness studies of DMARD therapies in SA, and few from low- or middle-income countries.^[37,44-47] These studies highlight the expense of bDMARDs, but show improved disease control in patients failing csDMARD therapy.

Cost-effectiveness, expressed as the effect on health divided by the costs of an intervention, can be improved by either increasing effectiveness or reducing costs. Recently, strategies to improve cost-effectiveness of b/tsDMARDs have been proposed, including biosimilar or generic drug use, avoidance of dose loading where possible, initiating therapy at a lower dose with escalation only if required, utilising the cheapest route of administration, minimising drug wastage, encouraging medication adherence, and drug tapering where possible.^[48] The advent of bDMARDs has led to significant cost savings driven by price competition among the reference products, and improved patient access to optimise disease management without a massive cost burden for healthcare systems is anticipated.^[49]

Role of biologic therapies in the connective tissue diseases

Biologic therapies are reserved for severe organ- or life-threatening manifestations of connective tissue diseases, or as third- or fourth-line options for severe refractory disease. The use of biologics in the various connective tissue diseases is off-label, with the exceptions of rituximab in anti-neutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV), tocilizumab in giant-cell arteritis (GCA), and belimumab (not currently available in SA) for adult and paediatric systemic lupus erythematosus (SLE).

SLE

Belimumab (anti-B-lymphocyte stimulator (BLyS)) therapy, not yet licensed for use in SA is the only Food and Drug Administration/European Medicines Agency approved biologic drug therapy for the management of SLE. Rituximab may be useful (off-label) in severe neuropsychiatric, cardiopulmonary or haematological manifestations or refractory nephritis or arthritis.^[50]

Systemic sclerosis

Biologic therapy use in systemic sclerosis (SSc) is reserved for severe or refractory skin, lung and joint involvement.^[51] Rituximab is beneficial in severe skin disease, interstitial lung disease (ILD) and arthritis, with the most convincing data shown with SSc-associated ILD. Use for skin disease alone is not recommended. Tocilizumab may be used for severe refractory joint involvement or as an alternative to rituximab, in patients who have failed csDMARD therapy.

Inflammatory myopathies

Biologic treatments can be used for refractory disease manifestations in inflammatory myopathies (IIMs). The greatest benefit is seen in patients with myositis-specific antibodies, in particular anti-ARS, anti-Mi2 and anti-SRP antibodies. Studies with TNFi therapies have

shown disappointing results and they are not recommended for use in IIMs. JAKis and abatacept may have a role in refractory disease.^[52,53] Rituximab is the most commonly used biologic therapy in the IIMs, with the following indications:

- Severe refractory myositis failing first- and second-line immunosuppressants, i.e. MTX, azathioprine, mycophenolate mofetil or calcineurin inhibitors as monotherapy or in combination
- Myositis-associated ILD refractory to standard therapies
- Severe skin involvement
- Refractory joint disease failing csDMARD therapy.

Anca-associated vasculitis (AAV)

The AAVs include granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. Rituximab is licensed for use in AAV, with the following indications:

- Remission induction of new-onset organ-threatening or life-threatening AAV in combination with CS, as an alternative to cyclophosphamide^[54]
- Major relapse of organ-threatening or life-threatening disease in combination with CS
- Remission maintenance in combination with low-dose CS as an alternative to immunosuppressive therapy. This should be continued for at least 24 months after achieving sustained remission.

Large-vessel vasculitis

Tocilizumab or a TNFi should be considered for selected patients with refractory or relapsing GCA. The risk of treatment-related complications in an elderly population with underlying comorbidities, e.g. intestinal perforation, must be carefully considered.^[55]

Behçet's disease

Apremilast is effective for refractory oral ulcers. TNFis, interleukin 1 (IL-1) inhibitors, ustekinumab, secukinumab and tocilizumab may be considered for refractory disease.^[56]

Details of individual b/tsDMARDs

1. TNFis

Currently available TNFis are infliximab, etanercept, adalimumab and golimumab. Although these drugs have the same target, there are differences in the pharmacokinetics and method of administration. Etanercept is a soluble receptor of TNF, and infliximab, adalimumab and golimumab are monoclonal antibodies to TNF.

Mechanism of action: Inhibition of TNF- α .

Registered indications:

- Treatment of RA, SpA and juvenile idiopathic arthritis (JIA) with inadequate response to csDMARDs
- Only monoclonal antibodies to TNF (infliximab, adalimumab and golimumab) and not receptor blockers (etanercept) are effective for inflammatory bowel disease (IBD) and uveitis. In SpA with concomitant IBD, a monoclonal TNFi rather than etanercept should be selected.

Dosage and mode of administration:

- Infliximab (after loading dose): RA: 3 mg/kg intravenous (IV) infusion every 6 - 8 weeks; axial SpA (axSpA), psoriatic arthritis (PsA): 5 mg/kg every 6 - 8 weeks
- Etanercept 50 mg weekly subcutaneously (SC) or 25 mg twice weekly
- Adalimumab 40 mg every 2nd week SC
- Golimumab 50 mg every 4 weeks SC.

Time to response to treatment: 2 - 4 weeks, with significant response by 12 - 24 weeks.

Safety of TNFis

Infections

- TB (see ‘Tuberculosis’ under ‘General considerations for the use of b/tsDMARDs’ above): TNFis confer the highest risk of TB reactivation or infection, and screening for LTBI, with vigilance for infection, are mandatory. In high-risk patients, INH prophylaxis should be considered regardless of LTBI screening results.
- Opportunistic infections: Infections with fungi, particularly histoplasmosis, listeria and non-tuberculous mycobacteria have been reported.
- Bacterial infections: Patients are at increased risk of serious infections requiring hospitalisation.
- Viral infections: Patients should be screened for HBV before starting a TNFi, as reactivation of chronic infection can occur.

Autoimmune-like syndromes

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

Cardiovascular

- Use of TNFis is contraindicated in New York Heart Association class III/IV heart failure, as there is an association with increased morbidity and mortality.

Haematological

- There have been reports of pancytopenia and aplastic anaemia.

Liver function abnormalities

- Modest liver transferase enzyme elevations have been seen in patients on adalimumab and infliximab, usually not more than twice the upper limit of normal. Deterioration of alcoholic hepatitis has been observed.

Injection site reactions and infusion reactions

- Injection site reactions are usually mild. Acute infusion reactions can occur with IV infliximab, but can usually be treated with CSs and antihistamines and by decreasing the infusion rate.

Malignancies

- An increased risk of lymphoma and solid tumours has not been observed, but there is a possible increased risk of non-melanoma skin tumours. Patients should therefore be screened regularly for skin cancers.

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 treatment. A TNFi is contraindicated if there is a history of demyelinating disease.

Pulmonary disease

- Acute, severe exacerbation of ILD has been reported, and TNFis are not recommended in patients with ILD.

Skin disease

- Rashes, particularly psoriasis (PsO), rarely Stevens-Johnson syndrome, vasculitis and erythema multiforme have been reported. They may subside with a switch from one TNFi to another.

2. Rituximab

Mode of action: A chimeric anti-CD20 monoclonal antibody that depletes CD20-positive B cells.

Registered indications:

- Moderate to severe active RA with inadequate response to csDMARDs.
- AAV.

The response to rituximab is greater in rheumatoid factor-positive or anti-cyclic citrullinated peptide-positive RA patients. In seronegative RA patients, an alternative treatment should be considered. Rituximab may be considered as the first choice of b/tsDMARD therapy in certain RA patients:

- Patients with a high risk of TB infection
- Previous lymphoma
- ILD
- Vasculitis.

Dosage and mode of administration:

- Rituximab is given as two IV infusions of 1 000 mg or 500 mg 14 days apart, by staff trained in the use of these drugs, in an infusion room with adequate monitoring and resuscitation equipment available.
- Premedication with an IV infusion of methylprednisolone 100 - 125 mg, oral paracetamol and an antihistamine given 30 minutes prior to the rituximab to reduce infusion reactions.
- First infusion given over 4 hours; subsequent infusions given over 2 - 4 hours.
- Infusion reactions are most common during the first infusion and are usually mild. They are managed by decreasing the infusion rate, with fluid administration.
- Infusion should be stopped if anaphylaxis occurs (<10%).
- Retreatment is recommended at 6-monthly intervals or when the disease flares. Better clinical efficacy was shown in patients treated at regular intervals compared with 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 MTX, or if not tolerated, leflunomide.
- Consider checking pretreatment neutrophil counts and immunoglobulin G (IgG) levels prior to each infusion, or in the event of serious infections.

Time to response to treatment: Usually 8 - 16 weeks.

Safety of rituximab

Infections

- There is an increased risk of serious infections. This is higher in patients with decreased IgG levels (<5 g/L).
- 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 hepatitis B surface antigen (HBsAg) and HBcAb should be done before treatment. Reactivation of resolved hepatitis B (HBsAg-, HBcAb+) occurs in 5 - 10%. Patients with chronic and inactive hepatitis B (HBsAg+) should either not receive rituximab, or must receive concomitant antiviral prophylaxis (lamivudine, other).

Immunisations

- Response to T-cell-independent antigen vaccines (influenza, pneumococcal, COVID-19) is severely decreased if given after rituximab. Vaccination should therefore be done 2 - 4 weeks before or 6 months after infusion. Tetanus vaccination is not impaired.

Haematological

- There have been reports of neutropenia in oncology patients. This seems to be rare in patients with autoimmune diseases, but may be associated with an increased infection rate.

Infusion reactions

- Infusion reactions occur most commonly with the first infusion. Premedication reduces the risk and severity of reactions.

Malignancies

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

Neurological syndromes

- Cases of progressive multifocal leucoencephalopathy have been reported.

Skin reactions

- There have been reports of PsO and vasculitis on rituximab treatment.

3. Abatacept

Mode of action: Soluble fusion protein to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a T-cell co-stimulation modulator, thus inhibiting T-cell stimulation. It prevents CD28 from binding to its counter-receptor, CD80/CD86, owing to its higher affinity for CD80/CD86.

Registered indications:

- Treatment of RA, JIA and PsA with inadequate response to csDMARDs.

Dosage and mode of administration:

- SC: 125 mg SC injections weekly +/- IV loading dose
- IV infusion: 10 mg/kg (500 mg, 750 mg or 1 000 mg) every 4 weeks with IV loading dose
- 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
- Prescribed as monotherapy or in combination with MTX or leflunomide.

Time to response to treatment: Within 2 - 4 weeks, but most patients respond within 12 - 16 weeks.

Safety of abatacept**Infections**

- The rate of serious infections is increased. Cases of TB were reported in clinical trial patients, but the risk of reactivation of LTBI with abatacept is not known. Avoid live vaccines within 3 months of stopping abatacept.

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, and abatacept should be given with caution in these patients.

4. Tocilizumab

Mode of action: Humanised anti-interleukin 6 (IL-6) receptor monoclonal antibody.

Registered indications:

- RA with inadequate response to csDMARDs
- JIA
- GCA.

Dosage and mode of administration:

- IV infusion, given over 1 hour, every 4 weeks (4 - 8 mg/kg to a maximum of 800 mg per infusion)
- SC: 162 mg every week (if >100 kg); 162 mg every other week (if <100 kg), can be increased to weekly dose if inadequate response
- Use with MTX is recommended, but it can be used as monotherapy.

Safety of tocilizumab**Infections**

- There is an increase in the rate of serious infections. The drug should not be used during an active infection.
- Of note, because tocilizumab decreases C-reactive protein (CRP) levels through IL-6 inhibition, CRP levels may not increase in an acute infection, limiting the use of CRP as a diagnostic marker for infection.
- Cases of TB and opportunistic infections (candidiasis, aspergillosis and pneumocystis) have been reported.
- Viral infections: As with treatment with other b/tsDMARDs, HZ infection can occur. The risk of reactivation of hepatitis B or C is not known.
- Avoid live vaccines within 3 months of stopping tocilizumab.

Gastrointestinal

- Generalised peritonitis, lower gastrointestinal perforation, fistulas and intra-abdominal abscesses are described. Tocilizumab should be used with caution in patients with a history of intestinal ulceration and diverticulosis.
- Severe liver damage has been reported. If used in combination with leflunomide, there is an increased chance of raised transaminases. Dose reduction is recommended if there is ongoing transaminase or bilirubin increase.

Haematological

- Neutropenia was seen in clinical trials with a decrease to <1 000 polymorphs/mL, rarely <500/mL. This was usually transient and was not associated with an increased rate of infections. A downward dose adjustment to 4 mg/kg is necessary should the neutropenia persist.
- Thrombocytopenia has been reported.

Infusion reactions

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

Dyslipidaemia

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

Malignancies

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

Skin disease

- Erythroderma has been described related to tocilizumab.

5. Ustekinumab

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

Registered indications:

- PsA with inadequate response to csDMARDs, alone or in combination with MTX
- Patients with plaque PsO (adult and paediatric) who are candidates for phototherapy or systemic therapy
- Patients with active Crohn's disease who have failed or were intolerant to treatment with immunomodulators or CSs, and/or one or more TNFi.

Dosage and mode of administration:

- 45 mg SC at weeks 0 and 4, then 12-weekly thereafter
- For patients >100 kg with moderate to severe plaque PsO, 90 mg SC at weeks 0 and 4, then 12-weekly thereafter
- Can be combined with a csDMARD (e.g. MTX).

Time to response to treatment: Response can be seen as early as 8 weeks, but a full response is assessed at 6 months.

Safety of ustekinumab**Infections**

- Upper respiratory infection, particularly nasopharyngitis, seen in 1 - 10%.

Less common side-effects

- Injection site erythema, myalgia, fatigue, nasal congestion, urticaria, rash, pruritus
- Back pain, cellulitis, depression, diarrhoea, fatigue, headache
- Antibody formation <1% (selected)
- Malignancy (non-melanoma skin cancers), reversible posterior leucoencephalopathy syndrome.

6. Interleukin 17A inhibitors

Currently available interleukin 17A (IL-17A) inhibitors are secukinumab and ixekizumab.

Mechanism of action: Inhibitor of IL-17A.

Registered indications:

- axSpA, plaque PsO (adult and paediatric) and PsA with inadequate response to csDMARDs.

Dosage and mode of administration:

- Can be combined with a csDMARD (e.g. MTX).

Secukinumab:

- axSpA or PsA: Loading dose of 150 mg SC per week at weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter. Can be used without a loading dose.
- Plaque PsO: Loading dose 300 mg SC at weeks 0, 1, 2, 3 and 4 and every 4 weeks thereafter. Can be used without a loading dose.

Ixekizumab:

- 80 mg SC every 4 weeks after loading dose (axSpA, PSA: 160 mg

week 0 then 80 mg every 4 weeks; plaque PSO: 160 mg week 0 then 80 mg weeks 2, 4, 6, 8, 10 and 12).

Safety of ustekinumab and secukinumab

- Increased risk of infections, particularly upper respiratory tract infections
- Mucocutaneous candida infections^[57]
- Development and/or exacerbation of IBD has been reported.^[58]

7. Guselkumab

Mechanism of action: Human monoclonal antibody against IL-23.

Registered indications:

- Plaque PsO
- PsA with inadequate response to csDMARDs.

Dosage and mode of administration:

- 100 mg SC at weeks 0 and 4, followed by followed by maintenance dose of 100 mg every 8 weeks.

Safety of guselkumab

- May increase risk of infection
- Serious hypersensitivity reactions, including anaphylaxis, and liver enzyme elevations have been reported

8. Belimumab (anti-BLyS therapy)

Not yet licensed for use in SA: requires section 21 application via the SAHPRA. Use for mild to moderate cutaneous, musculoskeletal and serological manifestations with uncontrolled disease despite antimalarial therapy with/without additional immunosuppressive therapy and inability to taper CS <7.5 mg/day.

9. Targeted synthetic DMARDs**JAKis**

The JAKis are the most recent class of therapies for various autoimmune and immune-mediated inflammatory diseases, collectively known as the tsDMARDs. They are small-molecule oral treatments that have comparable efficacy to biologics. They target the Janus kinases (JAKs), which are protein tyrosine kinases (TYKs) found intracellularly that mediate responses to cytokines by cells. There are four isoforms of JAKs: JAK1, JAK2, JAK3 and TYK2, that are found in pairs. Different JAKis target different JAK isoforms, but the overall effect and side-effect profile of these drugs is very similar.

Names and dosing of the available JAKis in SA are:

- Tofacitinib, dose 5 mg twice daily
- Baricitinib, dose 4 mg daily
- Upadacitinib, dose 15 mg daily.

Indications for JAKis:

- RA, axSpA, PsA, JIA, SLE, and other inflammatory disorders (e.g. IBD, atopic dermatitis, alopecia areata, vitiligo)
- Also used in the management of certain haematological disorders including myelofibrosis, polycythaemia vera and graft-versus-host disease.

Safety of JAKis**Infections**

- Most commonly reported infections are not serious, but there is a risk of serious infection similar to that seen with bDMARDs.
- There is a greater risk for HZ infection than seen with bDMARDs.^[59]
- TB and opportunistic infections have been reported,^[60] and

screening for LTBI is mandatory prior to commencing JAKi therapy.

Cardiovascular risk

- Increased incidence of major adverse cardiovascular events (myocardial infarction and stroke) in recent trial tofacitinib-compared with etanercept-treated RA patients with cardiovascular risks.^[61] Avoid JAKis, particularly the higher doses, in patients with significant cardiovascular risks (smokers, previous cardiovascular events, age ≥ 65 years).
- Dyslipidaemia, but this is probably not clinically relevant.

Thromboembolic risk

- An increased risk of venous thromboembolism (VTE) has been observed with tofacitinib and baricitinib. JAKis should be avoided in patients with previous VTE, traditional risks for VTE and additional risks including advanced age, obesity, diabetes mellitus, hypertension, hyperlipidaemia and smoking.^[62]

Gastrointestinal

- Nausea and diarrhoea are seen most commonly, but intestinal perforation has been reported. Liver enzymes may be raised, particularly with concomitant MTX use.
- Increased muscle enzymes may occur, but are not usually associated with symptoms.

Haematological

- Neutropenia and lymphopenia that is not clinically significant can occur with the use of all JAKis. More rarely, neutropenia of $< 1\ 000$ cells/mL and lymphopenia of < 500 cells/mL have been seen without an associated increase in infection risk. Treatment should be temporarily interrupted in patients with low neutrophil or lymphocyte counts, and dosing can be reduced if needed depending on whether treatment is continued.

Malignancy

- There was no increase in malignancy risk in JAKi trials, but the same trial that showed increased cardiovascular risk also reported an increased malignancy risk, although the details as to which malignancies are still not clear.

9. Phosphodiesterase 4 inhibitors

Apremilast

Mechanism of action: Phosphodiesterase 4 inhibitor.

Registered indications:

Summary points pertaining to b/tsDMARD use

- b/tsDMARDs are prescribed after the failure of csDMARD therapy
- b/tsDMARDs to treat immune-mediated inflammatory rheumatic diseases should be prescribed by a rheumatologist
- Before commencing b/tsDMARD therapy, clinical details of prospective patients must be submitted to the registry and approval must be obtained from the SARAA Biologics Advisory Peer Review Panel
- All b/tsDMARDs are associated with an increased risk of serious infection necessitating screening, vaccination and vigilance for community-acquired and opportunistic infection including TB, viral hepatitis and HIV.

b/tsDMARD = biologic/targeted synthetic disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD; SARAA = South African Rheumatism and Arthritis Association; TB = tuberculosis.

- As monotherapy or in combination with other csDMARDs for active PsA not responding to other csDMARDs.

Dosage and mode of administration:

- Initially 10 mg twice daily, titrated over 5 days to a maintenance dose of 30 mg twice daily.

Safety of apremilast

- Common: Upper respiratory tract infections, insomnia, headache, cough, diarrhoea, nausea, vomiting back pain, fatigue
- Suicidal ideation, weight loss and gastric bleeding have been reported.

- Sepriano A, Kerschbaumer A, Bergstra SA, et al. Safety of synthetic and biological DMARDs: A systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2023;82(1):107-118. <https://doi.org/10.1136/ard-2022-223357>
- Vassilopoulos A, Shehadeh F, Benitez G, et al. The incidence of opportunistic infections in patients with psoriatic arthritis treated with biologic and targeted synthetic agents: A systematic review and meta-analysis. *Front Pharmacol* 2022;13:992713. <https://doi.org/10.3389/fphar.2022.992713>
- Adas MA, Allen VB, Yates M, et al. A systematic review and network meta-analysis of the safety of early interventional treatments in rheumatoid arthritis. *Rheumatology (Oxford)* 2021;60(10):4450-4462. <https://doi.org/10.1093/rheumatology/keab429>
- Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: A systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2020;79(6):760-770. <https://doi.org/10.1136/annrheumdis-2019-216653>
- World Health Organization. WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021 - 2025: Background document. 2021. https://cdn.who.int/media/docs/default-source/hq-tuberculosis/who_globalhblclistsb_2021-2025_backgrounddocument.pdf?sfvrsn=f6b854c2_9 (accessed 19 February 2024).
- Goletti D, Petrone L, Ippolito G, Niccoli L, Nannini C, Cantini F. Preventive therapy for tuberculosis in rheumatological patients undergoing therapy with biological drugs. *Exp Rev Anti Infect Ther* 2018;16(6):501-512. <https://doi.org/10.1080/14787210.2018.1483238>
- Zhou G, Luo Q, Luo S, et al. Interferon- γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: A systematic review and meta-analysis. *Lancet Infect Dis* 2020;20(12):1457-1469. [https://doi.org/10.1016/S1473-3099\(20\)30276-0](https://doi.org/10.1016/S1473-3099(20)30276-0)
- Tseng S-Y, Huang Y-S, Chang T-E, Perng C-L, Huang Y-H. Hepatotoxicity, efficacy and completion rate between 3 months of isoniazid plus rifampentine and 9 months of isoniazid in treating latent tuberculosis infection: A systematic review and meta-analysis. *J Chin Med Assoc* 2021;84(11):993-1000. <https://doi.org/10.1097/JCMA.0000000000000605>
- Tikly M, Hodkinson B, Dheda K. Biologic therapy for rheumatoid arthritis in developing countries – a place for non-TNF inhibitors as first-line treatment? *Rheumatology* 2015;54(2):208-209. <https://doi.org/10.1093/rheumatology/keu040>
- Hong X, Xiao Y, Xu L, Liu L, Mo H, Mo H. Risk of hepatitis B reactivation in HBsAg-/HBeAb+ patients after biologic or JAK inhibitor therapy for rheumatoid arthritis: A meta-analysis. *Immun Inflamm Dis* 2023;11(2):e780. <https://doi.org/10.1002/iid3.780>
- Winthrop KL, Tanaka Y, Lee EB, et al. Prevention and management of herpes zoster in patients with rheumatoid arthritis and psoriatic arthritis: A clinical review. *Clin Exp Rheumatol* 2022;40(1):162-172. <https://doi.org/10.55563/clinexp/rheumatol/cpu6r9>
- Jansen MH, Rondaan C, Legger GE, et al. EULAR/PRES recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases: Update 2021. *Ann Rheum Dis* 2023;82(1):35-47. <https://doi.org/10.1136/annrheumdis-2022-222574>
- Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020;79(1):39-52. <https://doi.org/10.1136/annrheumdis-2019-215882>
- Feldman C, Dlamini S, Richards GA, et al. A comprehensive overview of pneumococcal vaccination recommendations for adults in South Africa, 2022. *J Thoracic Dis* 2022;14(10):4150-4172. <https://doi.org/10.21037/jtd-22-287>
- Dagnev AF, Rausch D, Herve C, et al. Efficacy and serious adverse events profile of the adjuvanted recombinant zoster vaccine in adults with pre-existing potential immune-mediated diseases: A pooled *post hoc* analysis on two parallel randomized trials. *Rheumatology (Oxford)* 2021;60(3):1226-1233. <https://doi.org/10.1093/rheumatology/keaa424>
- Russell LA, Craig C, Flores EK, et al. Preoperative management of medications for rheumatologic and HIV diseases: Society for Perioperative Assessment and Quality Improvement (SPAQI) consensus statement. *Mayo Clin Proc* 2022;97(8):1551-1571. <https://doi.org/10.1016/j.mayocp.2022.05.002>
- Komaki F, Komaki Y, Micic D, Ido A, Sakuraba A. Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor- α use in females with immune mediated diseases: A systematic review and meta-analysis. *J Autoimmun* 2017;76:38-52. <https://doi.org/10.1016/j.jaut.2016.11.004>
- Hoxha A, Calligaro A, di Poi E, et al. Pregnancy and foetal outcomes following anti-tumor necrosis factor alpha therapy: A prospective multicentre study. *Joint Bone Spine* 2017;84(2):169-173. <https://doi.org/10.1016/j.jbspin.2016.03.014>
- 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* 2023;62(4):e48-e88. <https://doi.org/10.1093/rheumatology/keac551>
- Skorpen CG, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75(5):795-810. <https://doi.org/10.1136/annrheumdis-2015-208840>
- Perrotta K, Kiernan E, Bandoli G, Manaster R, Chambers C. Pregnancy outcomes following maternal treatment with rituximab prior to or during pregnancy: A case series. *Rheumatol Adv Pract* 2021;5(1):rkaa074. <https://doi.org/10.1093/rap/rkaa074>
- Das G, Damotte V, Gelfand JM, et al. Rituximab before and during pregnancy: A systematic review, and a case series in MS and NMOSD. *Neurol Neuroimmunol Neuroinflamm* 2018;5(3):e453. <https://doi.org/10.1212/NXI.0000000000000453>
- Emery P, Pope JE, Kruger K, et al. Efficacy of monotherapy with biologics and JAK inhibitors for the treatment of rheumatoid arthritis: A systematic review. *Adv Ther* 2018;35(10):1535-1563. <https://doi.org/10.1007/s12325-018-0757-2>

24. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41(9):1552-1563. [https://doi.org/10.1002/1529-0131\(199809\)41:9<1552::AID-ART5>3.0.CO;2-W](https://doi.org/10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W)
25. Smolen JS, Landewé RB, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82(1):3-18. <https://doi.org/10.1136/ard-2022-223356>
26. Fagerli KM, Lie E, van der Heijde D, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: Results from 440 patients included in the NOR-DMARD study. *Ann Rheum Dis* 2014;73(1):132-137. <https://doi.org/10.1136/annrheumdis-2012-202347>
27. Mease PJ, Collier DH, Saunders KC, Li G, Kremer JM, Greenberg JD. Comparative effectiveness of biologic monotherapy versus combination therapy for patients with psoriatic arthritis: Results from the Corrona registry. *RMD Open* 2015;1(1):e000181. <https://doi.org/10.1136/rmdopen-2015-000181>
28. Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: Primary results from a randomised, controlled phase III trial. *Arthritis Rheumatol* 2019;71(7):1112-1124. <https://doi.org/10.1002/art.40851>
29. Smolen JS, Keystone E, Emery P, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66(2):143-150. <https://doi.org/10.1136/ard.2006.061002>
30. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68(1):1-26. <https://doi.org/10.1002/art.39480>
31. Kim J-W, Jung J-Y, Suh C-H. Real-world observational study of biosimilars in inflammatory arthritis treatment: A systematic literature review. *Expert Opin Biol Ther* 2021;21(1):57-73. <https://doi.org/10.1080/14712598.2020.1812575>
32. Herndon TM, Ausin C, Brahmé NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. *PLoS ONE* 2023;18(10):e0292231. <https://doi.org/10.1371/journal.pone.0292231>
33. Tanaka E, Kawahito Y, Kohno M, et al. Systematic review and meta-analysis of biosimilar for the treatment of rheumatoid arthritis informing the 2020 update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis. *Mod Rheumatol* 2022;32(1):74-86. <https://doi.org/10.1080/14397595.2021.1899591>
34. Smolen JS, Goncalves J, Quinn M, Benedetti F, Lee JY. Era of biosimilars in rheumatology: Reshaping the healthcare environment. *RMD Open* 2019;5(1):e000900. <https://doi.org/10.1136/rmdopen-2019-000900>
35. Chiu YM, Lu YP, Lan JL, Chen DY, Wang JD. Lifetime risks, life expectancy, and health care expenditures for rheumatoid arthritis: A nationwide cohort followed up from 2003 to 2016. *Arthritis Rheumatol* 2021;73(5):750-758. <https://doi.org/10.1002/art.41597>
36. Birnbaum H, Pike C, Kaufman R, Maynchenko M, Kidolezi Y, Cifaldi M. Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin* 2010;26(1):77-90. <https://doi.org/10.1185/03007990903422307>
37. Bagepally BS, Kumar SS, Sasidharan A, Haridoss M, Venkataraman K. Household catastrophic health expenditures for rheumatoid arthritis: A single centre study from South India. *Sci Rep* 2023;13(1):15385. <https://doi.org/10.1038/s41598-023-42623-y>
38. Curtis JR, Fox KM, Xie F, et al. The economic benefit of remission for patients with rheumatoid arthritis. *Rheumatol Ther* 2022;9(5):1329-1345. <https://doi.org/10.1007/s40744-022-00473-6>
39. Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F. Cost effectiveness analysis of disease-modifying antirheumatic drugs in rheumatoid arthritis. A systematic review literature. *Int J Rheumatol* 2011;2011:845496. <https://doi.org/10.1155/2011/845496>
40. Kumar SS, Bagepally BS, Sasidharan A. Cost effectiveness of rituximab therapy for rheumatoid arthritis: A systematic review and meta-analysis of cost-utility studies. *Clin Drug Investig* 2023;43(2):97-108. <https://doi.org/10.1007/s40261-022-01238-3>
41. Kuwana M, Tamura N, Yasuda S, et al. Cost-effectiveness analyses of biologic and targeted synthetic disease-modifying anti-rheumatic diseases in patients with rheumatoid arthritis: Three approaches with a cohort simulation and real-world data. *Mod Rheumatol* 2023;33(2):302-311. <https://doi.org/10.1093/mr/roac038>
42. Gharabeh M, Bonafede M, McMorrow D, Hernandez EJM, Stolshek BS. Effectiveness and costs among rheumatoid arthritis patients treated with targeted immunomodulators using real-world U.S. data. *J Manag Care Spec Pharm* 2020;26(8):1039-1049. <https://doi.org/10.18553/jmcp.2020.26.8.1039>
43. Van de Laar CJ, Oude Voshaar MA, Fakhouri WK, et al. Cost-effectiveness of a JAK1/JAK2 inhibitor vs a biologic disease-modifying antirheumatic drug (bDMARD) in a treat-to-target strategy for rheumatoid arthritis. *Clinicoecon Outcomes Res* 2020;12:213-222. <https://doi.org/10.2147/CEOR.S231558>
44. Prawjaeng J, Leelahavong P, Budtarad N, et al. Cost-utility analysis of biologic disease-modifying antirheumatic drugs (bDMARDs), targeted synthetic DMARDs (tsDMARDs) and biosimilar DMARDs (bsDMARDs) combined with methotrexate for Thai rheumatoid arthritis patients with high disease activity. *BMC Health Serv Res* 2023;23(1):561. <https://doi.org/10.1186/s12913-023-09595-1>
45. Mittal G, Bisht M, Pai VS, Handu S. The cost-effectiveness of and adherence to disease-modifying antirheumatic drug (DMARD) therapy in rheumatoid arthritis patients in a tertiary care teaching hospital in Uttarakhand, India. *Cureus* 2023;15(2):e34664. <https://doi.org/10.7759/cureus.34664>
46. Fellous S, Rkain H, Ahid S, et al. One-year direct costs of biological therapy in rheumatoid arthritis and its predictive factors: Data from the Moroccan RBSMR registry. *Rheumatol Int* 2021;41(4):787-793. <https://doi.org/10.1007/s00296-020-04762-7>
47. Said SS, Kühl M-J, Fevang B-TS, Nystad TW, Johansson KA. Treating rheumatoid arthritis in Zanzibar: A cost effectiveness study comparing conventional, biologic, and targeted-synthetic disease modifying anti-rheumatic drugs. *medRxiv* 2023;2023.12.05.23299489. <https://doi.org/10.1101/2023.12.05.23299489>
48. Van der Togt CJ, van den Bemt B, Aletaha D, et al. Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: Results from an umbrella review and international Delphi study. *RMD Open* 2023;9(1):e002898. <https://doi.org/10.1136/rmdopen-2022-002898>
49. Smolen JS, Caporali R, Doerner T, et al. Treatment journey in rheumatoid arthritis with biosimilars: From better access to good disease control through cost savings and prevention of nocebo effects. *RMD Open* 2021;7(2):e001637. <https://doi.org/10.1136/rmdopen-2021-001637>
50. Panouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78(6):736-745. <https://doi.org/10.1136/annrheumdis-2019-215089>
51. Kowal-Bielecka O, Franssen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017;76(8):1327-1339. <https://doi.org/10.1136/annrheumdis-2016-209909>
52. Paik JJ, Casciola-Rosen L, Shin JY, et al. Study of tofacitinib in refractory dermatomyositis: An open-label pilot study of ten patients. *Arthritis Rheumatol* 2021;73(5):858-865. <https://doi.org/10.1002/art.41602>
53. Tjärnlund A, Tang Q, Wick C, et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: A randomised, phase IIb treatment delayed-start trial. *Ann Rheum Dis* 2018;77(1):55-62. <https://doi.org/10.1136/annrheumdis-2017-211751>
54. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis* 2024;83(1):30-47. <https://doi.org/10.1136/ard-2022-223764>
55. Kang L, Liu Y, Luo Z, et al. Systematic review and meta-analysis of the current literature on tocilizumab in patients with refractory Takayasu arteritis. *Front Immunol* 2023;14:1084558. <https://doi.org/10.3389/fimmu.2023.1084558>
56. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018;77(6):808-818. <https://doi.org/10.1136/annrheumdis-2018-213225>
57. Davidson L, van den Reek JM, Bruno M, et al. Risk of candidiasis associated with interleukin-17 inhibitors: A real-world observational study of multiple independent sources. *Lancet Reg Health Eur* 2022;13:100266. <https://doi.org/10.1016/j.lanepe.2021.100266>
58. Fauny M, Moulin D, d'Amico F, et al. Paradoxical gastrointestinal effects of interleukin-17 blockers. *Ann Rheum Dis* 2020;79(9):1132-1138. <https://doi.org/10.1136/annrheumdis-2020-217927>
59. Choy EH. Clinical significance of Janus kinase inhibitor selectivity. *Rheumatology* 2019;58(6):953-962. <https://doi.org/10.1093/rheumatology/key339>
60. Nash P, Kerschbaumer A, Dörner T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: A consensus statement. *Ann Rheum Dis* 2021;80(1):71-87. <https://doi.org/10.1136/annrheumdis-2020-218398>
61. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;386(4):316-326. <https://doi.org/10.1056/NEJMoa2109927>
62. Mori S, Ogata F, Tsunoda R. Risk of venous thromboembolism associated with Janus kinase inhibitors for rheumatoid arthritis: Case presentation and literature review. *Clin Rheumatol* 2021;40(11):4457-4471. <https://doi.org/10.1007/s10067-021-05911-4>

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