South African recommendations for the management of rheumatoid arthritis: An algorithm for the standard of care in 2013

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As a South African Rheumatism and Arthritis Association (SARAA) initiative, these recommendations are offered with the aim of improving healthcare delivery and thereby enriching the quality of lives of those suffering from rheumatoid arthritis in South Africa.

Updated treatment recommendations for the therapy of rheumatoid arthritis (RA) in South Africa advocate early diagnosis, prompt initiation of disease-modifying anti-rheumatic drugs (DMARDs), and an intense treatment strategy where disease activity is assessed with a composite score such as the Simplified Disease Activity Index (SDAI). Frequent assessments and escalation of therapy are necessary until low disease activity (LDA) (SDAI ≤11) or ideally remission (SDAI ≤3.3) is achieved. Synthetic DMARDs may be used as monotherapy or in combination, and can be co-prescribed with low-dose corticosteroids if necessary. Biologic DMARD therapy should be considered for patients who have failed a 6-month trial of at least 3 synthetic DMARDs. All RA patients in SA are at increased risk of tuberculosis (TB), in particular patients using anti-tumour necrosis factor (TNF) biologic therapy. These recommendations provide practical suggestions for the screening and management of TB and other comorbidities, and offer an approach to monitoring of RA patients.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which, if treated inadequately, leads to irreversible joint damage, resulting in deformities, disability and premature mortality. The disease occurs worldwide and affects approximately 1% of the population.[1,2]

Recently, there have been major developments in the management of RA. These include (*i*) advances in the early diagnosis of the disease and evidence for the benefit of early therapy; (*ii*) better tools to assess response to therapy with the development of composite disease activity scores, allowing goal-directed therapy where the target is remission; and (*iii*) the emergence of biologic disease-modifying anti-rheumatic drugs (DMARDs). These strategies result in better control of inflammation, thus preventing joint damage and reducing disability. Against this background, the South African Rheumatism and Arthritis Association (SARAA) has proposed the development of an updated treatment strategy for the effective therapy of RA in South Africa (SA). These recommendations are aimed at all healthcare professionals managing RA, including rheumatologists, physicians, general practitioners, nurses and allied healthcare professionals.

SARAA adhered to the following ideologies when formulating these recommendations:

- They should be aimed at all healthcare professionals managing RA, including allied healthcare professionals, nurses, general practitioners, physicians and rheumatologists.
- There should be consultation with pivotal stakeholders in the final consensus of the document.
- They should be based on scientific evidence or, if unavailable, expert consensus.
- They should be recommendations and not a guideline. Management of RA is not cast in stone (and is likely to change again in the near future) and failure to adhere to them is not incriminating or negligent. They represent what SARAA, as a professional body, recommends and set a certain standard of care that should be aimed for, from the very basic management to the highly sophisticated. Should practitioners not be able to offer expertise where appropriate, they may consider referral to a centre that does.
- There are limitations to all recommendations and they cannot cover all clinical problems, but should be detailed enough to cover common circumstances, yet concise enough to be practical to the reader.
- SA is a multi-faceted society and thus a 'one size fits all' policy is not rational for all practitioners and patients, but these recommendations should be insightful to treating practitioners and stakeholders.
- These recommendations should be disseminated widely.

2. Scope

The treatment strategy is presented in the form of an algorithm (Fig. 1), and is accompanied by a more in-depth discussion of key management principles. This algorithm provides a step-wise approach to treatment, to enable health authorities and practitioners to develop and support the most effective method of achieving and maintaining remission in RA patients in both public and private health sectors. The purpose is not to remove the physician's autonomy, and physicians must select the most appropriate therapeutic option, taking into consideration the patient's preferences.

3. Methods

For this guideline to be widely accepted, the following methodology has been followed. Evidence from the literature and from RA guidelines developed elsewhere in the world has been reviewed. An online survey sent to all SA rheumatologists was performed to assess the level of agreement with key points relating to RA therapy. Various stakeholders including the Department of Health, medical funders, the Registrar of Medical Schemes, patient representative bodies (i.e. the Arthritis

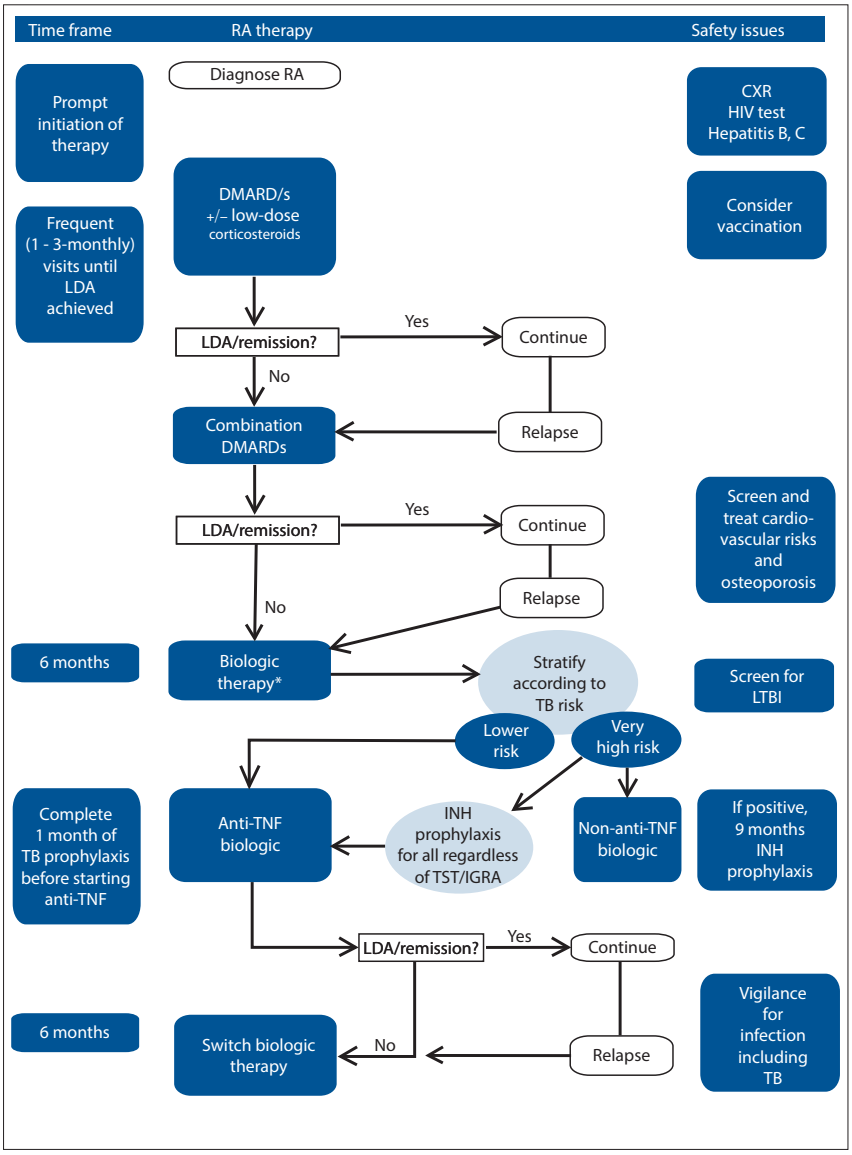

*Fig. 1. Algorithm for management of rheumatoid arthritis in SA. DMARD = disease-modifying anti-rheumatic drug; LDA = low disease activity (SDAI ≤ 11); CXR = chest X-ray; TB = tuberculosis; LTBI = latent TB infection; TST = tuberculin skin test; IGRA = IFN-γ release assay. * Biologic therapy should be considered in patients with high disease activity, or moderate disease activity in the presence of poor prognostic factor/s (seropositivity, early radiographic erosions, extra-articular disease or functional disability).*

Foundation) and academic departments have been consulted.

4. Key principles

4.1 Early diagnosis and treatment

Untreated RA results in severe disability and loss of health-related quality of life.[3] There is a direct relationship between the duration of uncontrolled inflammation and joint damage (as measured by bony erosions and joint space narrowing).[4] Joint damage begins within the first 3 - 6 months after disease onset and a narrow window of opportunity exists where early aggressive therapy of RA can suppress inflammation before irreversible joint destruction has occurred.[5-7] Thus, early diagnosis and prompt referral to a physician, or ideally to a rheumatologist, for initiation of DMARDs is critical. To this end, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) have developed updated criteria for the classification of RA (Table 1).[8] These new criteria may enable practitioners to make a much earlier diagnosis of RA than the previous ACR criteria.[9] Screening tools, such as the 'S-factor' developed by Arthritis Research UK and the Gait, Arms, Legs, and Spine (GALS) examination, may support primary healthcare workers in diagnosing inflammatory arthritis, promoting timeous referrals to specialists to initiate DMARDs (Table 2).[10,11]

4.2 Assessment

4.2.1 Disease activity

There have been significant advances in the methods of scoring disease activity in RA, where the clinical examination of tender and swollen joints, global assessments and laboratory investigations are combined in a composite disease activity score. The 3 validated scores currently in use in SA are the 28-Joint Disease Activity Score (DAS-28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) (Table 3).[12-14] These scores allow classification of the patient into a state of remission or low, moderate or high disease activity, providing a simple tool for assessing disease at each patient visit to guide therapeutic decisions.[15]

The results of clinical trials are expressed according to the percentage of patients achieving an ACR 20, ACR 50 or ACR 70 response. An ACR 20 response is defined by a ≥20% improvement in tender and swollen joint counts, and in 3 of the remaining 5 criteria.[16] The ACR 50 and ACR 70 represent a 50% or 70% improvement in these parameters, respectively. In general, the proportion of patients achieving an ACR 20 is higher than those achieving an ACR 50 or ACR 70.

4.2.2 Goal-directed therapy

In other fields of medicine, treatment targets have been defined and treatment aimed at achieving these targets has led to improved outcomes with less end-organ damage. Examples include HbA1c level in diabetes mellitus, blood pressure measurement in hypertension, and cholesterol level in dyslipidaemia. In RA, there is evidence that obtaining tight control of disease activity, with a pre-defined goal of low disease activity (LDA), or ideally, remission, to drive disease management decisions, allows better control of disease than routine clinic care. This intensive control strategy results in lower disease activity, better physical function and less structural damage, particularly when commenced in early disease.[17] For this reason, RA patients commenced on therapy may require evaluation as frequently as monthly, with calculation of a composite disease activity score at each visit, and escalation of DMARD therapy, until LDA (SDAI ≤11) or ideally remission (SDAI ≤3.3) is achieved, after which time, less frequent assessments (3 - 6-monthly) are acceptable. The target of LDA or remission should be maintained as long as possible, keeping in mind the individual patient's risk for drug-related complications or comorbid diseases.

4.2.3 Disability

Physical disability, with its negative consequences on personal care, employment and

social life, can be measured with a self-administered questionnaire, the Health Assessment Questionnaire - Disability Index (HAQ-DI).[18] In early disease, the HAQ-DI reflects joint inflammation and shows good correlation with clinical disease activity.[19] In established RA, physical function worsens annually as a consequence of irreversible joint damage.[20] The score ranges from 0 (no disability) to 3 (severe disability).

Table 1. 2010 ACR/EULAR RA Classification Criteria*

Criteria	Score†
A. Joints	
1 large joint	0
2 - 10 large joints‡	1
1 - 3 small joints§	2
4 - 10 small joints	3
>10 joints	5
B. Serology	
Negative RF **and** negative anti-CCP	0
Low-positive RF **or** low-positive ACPA¶	2
High-positive RF **or** high-positive ACPA‖	3
C. Acute phase reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1
D. Symptom duration	
<6 weeks	0
≥6 weeks	1

ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; RF = rheumatoid factor; CCP = cyclic citrullinated peptide; ACPA = anti-citrullinated peptide antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
*Patients who (*i*) have at least 1 joint with definite synovitis (swelling), (*ii*) with the synovitis not better explained by another disease.
†Add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA.
‡§'Large joints' refers to shoulders, elbows, hips, knees, and ankles.
§'Small joints' refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
¶≤3 times the upper limit of normal.
‖>3 times the upper limit of normal.

Table 2. 'S-factors' screening for early inflammatory arthritis (from Arthritis Care[10])*

Stiffness	Early morning stiffness lasting >30 min
Swelling	Persistent swelling of ≥1 joint, particularly hand joints
MCP squeeze test	Tenderness on squeezing across all 4 MCP joints
MTP squeeze test	Tenderness on squeezing across the metatarsal heads

MCP = metacarpophalangeal; MTP = metatarsophalangeal.
*Referral to a rheumatologist is recommended if ≥1 factor is present.

4.2.4 Radiography

Baseline radiographs of hands and feet should be performed for diagnostic and prognostic purposes. Erosions seen within the first 2 years of disease are markers of aggressive disease,[21] but normal X-rays do not exclude the diagnosis of RA. In addition, a chest X-ray (CXR) is appropriate to assess rheumatoid lung involvement, to exclude tuberculosis (TB) prior to commencing DMARDs and to provide a baseline in the event of pulmonary complications of therapy.

4.2.5 Sonar and MRI

Newer imaging modalities such as high-resolution ultrasound and magnetic resonance imaging (MRI) of peripheral joints allow detection of synovitis, joint space narrowing and erosions much earlier than is possible with conventional radiography.[22] Precise visualisation of anatomical structures allows more accurate diagnosis of joint and soft tissue pathology in the RA patient, and facilitates accurate placement of intra-articular injections, but these are not yet part of routine patient management.[23]

5. Therapy

5.1 Synthetic DMARDs

Methotrexate (MTX) is the most widely prescribed DMARD, and is recommended as first-line therapy in doses starting at 7.5 - 15 mg weekly, with rapid dose escalation according to response and tolerability to a maximum of 25 mg weekly. The drug has an excellent safety profile, and although mild elevation of liver enzymes is not infrequent, this is usually transient, and cirrhosis is rare.[24,25] There is no evidence that higher doses are more effective, and they may increase toxicity. Antimalarials (chloroquine (CQ) or hydroxychloroquine, which is not currently available in SA), may be used as monotherapy for mild RA, or in combination with MTX for moderate to severe disease. Sulphasalazine (SSZ) is effective as monotherapy, and is particularly useful in patients in whom MTX is contraindicated, or as part of combination DMARD therapy. Similarly, leflunomide may be prescribed as monotherapy or co-prescribed with MTX. A summary of the doses, major side-effects and recommendations for monitoring patients is presented in Table 4, and further details have been given in previous SA guidelines for RA.[26]

Patients who have failed MTX monotherapy should be treated with combination synthetic DMARDs. The most commonly prescribed combination treatment is MTX, SSZ and CQ.

5.2 Glucocorticoids

Glucocorticoids (GCs) rapidly reduce symptoms of RA and may inhibit development of erosions, particularly in early RA when used in combination with DMARDs.[27] However, side-effects limit their

Table 3. Disease activity formulas and categories

			Disease activity		
Index	**Formula**	**Remission**	**Low**	**Moderate**	**High**
SDAI	TJC + SJC + PGA (cm) + DGA (cm) + CRP (mg/dl)	≤3.3	≤11	≤26	>26
CDAI	TJC + SJC + PGA (cm) + DGA (cm)	≤2.8	≤10	≤22	>22
DAS-28	$0.56 * \sqrt{TJC} + 0.28 * \sqrt{SJC} + 0.7 * \ln(ESR) + 0.014 * PGA$ (mm)	≤2.6	≤3.2	≤5.1	>5.1

SDAI = Simplified Disease Activity Index; TJC = tender joint count; SJC = swollen joint count; PGA = patient global assessment; MDGA = physician global assessment; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; DAS-28 = 28-Joint Disease Activity Score; ESR = erythrocyte sedimentation rate.

Table 4. Synthetic DMARDs

	Indication	Dose	Side-effects	Monitoring	Contraindications
MTX	First choice DMARD as monotherapy or combination therapy	7.5 - 25 mg weekly orally or subcutaneously	**Common**: nausea and vomiting, mucositis, alopecia, elevated liver enzymes, anaemia, neutropenia	Baseline CXR; full blood count and liver transaminase test within the first month of treatment, and thereafter 3 - 6-monthly	Pregnancy and breast-feeding, alcoholism, liver disorders, renal failure, bone marrow suppression, interstitial lung disease
	Co-prescribed with biologic drugs	Co-prescribe with folic acid 5 - 10 mg/week, 24 hrs after MTX	**Less frequent:** pneumonitis, teratogenic		Caution in HIV-positive patients
CQ	Mild RA or as part of combination therapy	4 g/kg/day (generally 200 mg 3 - 5 times per week), orally	**Common:** gastrointestinal intolerance, skin hyperpigmentation, headache, dizziness **Less frequent:** retinopathy and myopathy	Annual ophthalmological assessments	
SSZ	Monotherapy if MTX not tolerated or contraindicated, or as part of combination therapy	1 - 3 g/day, orally	**Common:** gastrointestinal intolerance (anorexia, nausea, vomiting), skin rash, elevated liver enzymes, myelosuppression	Full blood count and liver transaminase test within the first 1 - 2 months of treatment, and thereafter 3 - 6-monthly	
Leflunomide	Monotherapy or in combination with MTX	20 mg/day orally, but 20 mg on alternate days can be used	Nausea, vomiting, abdominal pain, diarrhoea, alopecia, elevated liver enzymes, skin rash Teratogenic in both male and female patients	Full blood count and liver transaminase test within the first month of treatment, and thereafter 3 - 6-monthly	Pregnancy and breast-feeding, suspension is recommended 2 years before a possible pregnancy; alternatively, cholestyramine washout.

DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; CXR = chest X-ray; CQ = chloroquine; RA = rheumatoid arthritis; SSZ = sulphasalazine.

long-term use, and GCs are not appropriate as monotherapy. Low-dose oral prednisone (≤10 mg/day) is appropriate in combination with DMARDs in early RA (<2 year disease duration) for up to 6 months, after which the symptomatic effects seem to wane. In established RA, they may be used as 'bridging' therapy when DMARDs are initiated, and should be withdrawn once DMARDs have controlled the disease.[28,29] Intra-articular GCs are useful for a mono- or oligo-articular flare of disease. Long-acting intramuscular methylprednisolone may be used as an alternative to oral prednisone.

5.3 Biologic DMARDs

One of the most significant advances in the treatment of RA in recent years has been the development of biologic DMARDs, which are proteins directed against specific cytokines or their cell receptors. A wide choice of biologic DMARDs is now available in SA, with excellent efficacy in controlling RA in patients who have failed synthetic DMARD therapy. Clinical trials and post-marketing experience have shown that these DMARDs treat many aspects of RA disease: suppression of joint inflammation, prevention of radiographic progression, and improvement of physical function and health-related quality of life.[30] They may be classified into those inhibiting tumour necrosis factor (TNF) (i.e anti-TNF), and those targeting other cytokines or cells (non-anti-TNF). The ACR, EULAR and SARAA have developed recommendations for the use of these agents.[26,31,32] Biologic DMARDs are usually co-prescribed with MTX to improve efficacy and reduce antichimeric antibody production. The use of combination biologic DMARDs is not recommended. Table 5 summarises the biologics currently available, and provides details of dose and administration. Biologic DMARDs should be initiated by a rheumatologist, and information about patients on biologic therapy entered into a SARAA biologics registry.

5.4 Timing and choice of biologic therapy

In SA, commencement of biologic therapy after a 6-month trial of at least 3 synthetic DMARDs (including MTX, unless contraindicated) seems reasonable, given resource constraints, and given that up to one-third of patients will achieve LDA on synthetic DMARD therapy.[33,34] Indications for biologic therapy include an inadequate response to synthetic DMARD therapy, with high disease activity (SDAI >26), or moderate disease activity (SDAI 11 - 26) in the presence of poor prognostic factors (seropositivity, radiographic erosions within the first two years, extra-articular complications or functional disability). The efficacy of all currently available biologic drugs has been confirmed by clinical trials and by clinical experience, and the choice of drug depends on the safety profile

Table 5. Biologic DMARDs currently available in South Africa

Medication	Target	Type	Route	Dose	Half-life (days) *n*	Special comments
Anti-TNF						Extensive data from clinical trials and clinical experience; hence used as first-line biologics in most countries. Dose adjustment possible. These drugs confer increased risk of TB.
Infliximab	TNF-α	Mouse/human chimeric monoclonal antibody	IV	3 mg/kg every 8 weeks	8 - 10	
Etanercept	TNF-α	Soluble receptor fusion protein	S/C	50 mg weekly (or 25 mg twice weekly)	4	
Adalimumab	TNF-α	Human monoclonal antibody	S/C	40 mg every other week	10 - 20	
Non-anti-TNF						
Abatacept	T-cell co-stimulation	Receptor fusion protein	IV	Weight dependant 500 mg, 750 mg or 1 000 mg every 4 weeks	8 - 25	Useful where high risk of sepsis. Useful in heart failure.
Rituximab	$CD20^+$ B cells	Mouse/human chimeric antibody	IV	2 x 1 000 mg 14 days apart 6-monthly or at disease flare	19 - 22	Useful in seropositive patients. Long half-life, thus less flexibility if adverse effects or poor response.
Tocilizumab	IL-6 receptor	Humanised IL-6 receptor antibody	IV	8 mg/kg every 8 weeks	13	Useful for IL-6 driven disease anaemia, high CRP, fatigue.

DMARD = disease modifying anti-rheumatic drug; TNF = tumour necrosis factor; IV = intravenous; S/C = subcutaneous; IL = interleukin.

and on the patient's preferred route of administration. At present, the optimal sequence of biologics remains unclear. In future, biomarkers may assist in identifying the most appropriate biologic agent for an individual patient.[35]

A biologic DMARD that has not resulted in an adequate clinical response after 6 months of treatment should be withdrawn and another biologic DMARD should be prescribed.[36]

5.5 Analgesics and anti-inflammatory drugs

Analgesics should be prescribed and taken on an 'as needed' basis for pain control. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in controlling pain and stiffness, but are purely symptomatic therapies and offer no disease-modifying action. The toxicity of these drugs should not be underestimated. In RA, NSAIDs are often prescribed on a long-term basis, but should be used with caution as many patients have risk factors for NSAID-induced gastrointestinal tract events. Particularly at risk are older patients (age >60 years), as well as those who are co-prescribed corticosteroids and aspirin. Hence, there should be a low threshold for co-prescribing a proton pump inhibitor for gastroprotection, or for considering a COX-2 selective agent (coxib).[37] In addition, all NSAIDs, both non-selective agents and coxibs, confer an increased risk of thrombotic events, and should be used with caution in patients with cardiovascular risk factors.[38] Other side-effects of NSAIDs, including hypertension, renal and liver dysfunction should not be forgotten. Blood pressure should be checked within a month of initiating NSAID therapy. Ideally, NSAIDs should be used in the lowest effective dose and for the shortest duration of time, and withdrawn if possible once disease activity is controlled with DMARDs.

5.6 Extra-articular disease

Moderate to high-dose GCs, possibly combined with other immunosuppressant drugs, are used in severe extra-articular disease including serositis, vasculitis and scleritis.

5.7 Multidisciplinary team

Care of the RA patient requires a multidisciplinary approach with referral to an occupational therapist, podiatrist, physiotherapist, clinical psychologist and social worker, as appropriate. A rheumatology nurse can offer patient education and support, with positive effects on adherence to therapy and on health-related quality of life.[39] Adoption of a healthy lifestyle that includes regular exercise, loss of weight if overweight, and discontinuation of smoking is of benefit. Smoking has been shown not only to increase the risk of developing RA, but also to worsen the severity of joint disease, extra-articular complications and comorbidities of RA.[40]

Referral of the RA patient for orthopaedic surgery may be appropriate in certain circumstances. Importantly, surgical treatment of RA is only an adjunct to medical control of the disease with DMARDs. With modern aggressive therapy of RA, the number of patients requiring joint replacements and other surgical interventions is declining.[41]

6. Complications and safety issues

6.1 TB

All RA patients are at increased risk of TB, and this risk is increased by drugs used to treat RA including GCs, MTX and biologic drugs, in particular anti-TNF therapy.[42] The pro-inflammatory cytokine TNF plays an essential role in the containment of mycobacterial infection in granulomas, and inhibition of TNF may lead to reactivation of latent TB, or possibly to new TB infection.[43] This reactivation of TB generally occurs within the first 3 - 6 months of initiation of anti-TNF therapy.

The presentation may be atypical, with over half of cases reported as extra-pulmonary, and a high proportion of disseminated TB.[44]

Prior to initiation of therapy, each patient requires screening for latent TB infection (LTBI), and an assessment of the risk of TB infection/reactivation (risk stratification).

6.1.1 Screening for LTBI

The efficacy of screening for and treatment of LTBI before initiation of anti-TNF therapy has been well demonstrated, but the most appropriate test to detect LTBI is uncertain.[44-46] In a high prevalence setting such as SA, there is no reliable test for LTBI. The tuberculin skin test (TST) has traditionally been the primary tool for identifying LTBI, but limitations include false-negative results in immunocompromised patients (for example patients on immunosuppressive drugs such as MTX or corticosteroids[47]) and a false-positive test after BCG vaccination at birth, although this is not believed to be very significant amongst adults.[48] Other problems with the TST are the logistics of return visits for evaluation, and variations in administration and interpretation of the test.[49] Despite this, detection of LTBI by TST (defined as induration ≥5 mm) is highly effective. Recently, interferon (IFN)-γ release assays (IGRAs), which measure IFN-γ response to TB-specific antigens, have been introduced. While excellent performance and good cost effectiveness of these tests have been reported,[50] a negative IGRA does not exclude LTBI. In low-prevalence settings, the combination of TST and IGRA may be the best strategy.[51] Currently, there is little consensus on the most appropriate screening test in high-prevalence settings such as SA.[52]

A patient due to commence biologic therapy should have a TST, an IGRA test (if deemed appropriate by the clinician), and a CXR. An abnormal CXR suggesting active pulmonary TB clearly needs investigation, and treatment for the patient. A patient with a positive TST, and a normal CXR, should be given anti-TB chemoprophylaxis. Extrapolating from studies in HIV-positive patients, chemoprophylaxis may be either isoniazid (INH) for 9 months, or rifampicin combined with INH for 3 months.[53] The consensus is that anti-TNF therapy can be initiated after completion of a minimum of 1 month of chemoprophylaxis.

6.1.2 TB risk stratification

The incidence of TB in SA is amongst the highest in the world, with an estimated incidence of 808 per 100 000 in the general population.[54] In light of this, there are valid concerns regarding the safety of anti-TNF drugs, and all patients must be considered to be at relatively high risk of TB. In the absence of prospective data, recommendations must err on the side of caution.

The risk of developing active TB in RA patients treated with biologic DMARDs appears to depend on the background prevalence of LTBI. Factors associated with LTBI in the USA and in Hong Kong include older age, residence or travel in a TB-endemic area, high-risk occupation (healthcare or institution worker), previous TB infection, Felty's syndrome, and low socio-economic status.[55,56] Concomitant corticosteroid use and monoclonal rather than soluble anti-TNF drugs seem to confer a higher risk for TB.[46,57,58] Non-anti-TNF therapy appears to confer a much lower risk of TB, but cases have been reported.[59]

6.1.3 Very high-risk patients

Patients who are stratified as being at very high risk of LTBI and who require biologic therapy need careful consideration. This stratification is left to the physician's discretion, but would include healthcare workers, inmates or employees at institutions, patients who have had previous TB or who have a poor socio-economic background.

If such a high-risk patient is to commence anti-TNF therapy, a strategy offering 9 months of INH prophylaxis, regardless of TST/IGRA result, may be appropriate. Such a policy has been adopted in India because of the high incidence of TB.[60] Despite concerns of INH toxicity and of propagating INH-resistant TB, this strategy may be valid in high-risk settings such as SA. Longer-term chemoprophylaxis, continued for the duration of anti-TNF therapy, may be appropriate in very high-risk patients, but there are no prospective data.

Alternatively, non-anti-TNF drugs may be the safest choice of first-line biologic therapy in such patients. This is the current practice in Algeria and Morocco, and has been shown to be effective in high-risk patients in Germany.[61,62]

6.2 Other infections

There is an increased risk of infection amongst RA patients, particularly in patients treated with biologic therapy.[30] These include serious bacterial infections, as well as opportunistic fungal (histoplasmosis in particular), *Listeria* and non-tuberculous mycobacterial infections. Hence, biologic drugs should be used with caution in patients with chronic infected leg ulcers, septic arthritis in the preceding 12 months, septic arthritis of prosthetic joints, recurrent urinary or respiratory tract infections, an indwelling urinary catheter, or hypogammaglobulinaemia.

In the presence of active infection, administration of a biologic drug should be delayed. MTX does not increase the risk of sepsis or peri-operative complications in patients undergoing joint replacement surgery, and can be continued.[63] There may be a small risk of peri-operative infections in patients using biologic DMARDs, and it is recommended that these drugs are discontinued prior to surgery for a period of 3 - 5 times the half-life of the drug, and resumed after good wound healing.

6.3 HIV infection

In SA, the burden of HIV infection is amongst the highest in the world, with an estimated 33% of females between the ages of 25 and 29 years infected in 2010.[64] This pandemic has both diagnostic and therapeutic implications for the management of patients with concomitant inflammatory arthritis.[65]

HIV infection can cause, among other musculoskeletal syndromes, inflammatory polyarthritis mimicking RA.[66] Hence, an HIV test may be appropriate in a patient presenting with inflammatory arthritis.

There are several challenges in the management of RA patients who are HIV-positive. Information on the safety of using immunosuppressive drugs in an HIV-positive patient is limited. MTX and biologic drugs place patients at risk of opportunistic infections, and there is concern of added immunosuppression if prescribed in an HIV-positive patient.[67] For this reason, these therapies are not recommended and CQ (which may have antiviral properties[68]) or SSZ may be more appropriate choices. In addition, there are difficulties in the assessment of disease activity in HIV-positive patients due to the nonspecific increase in erythrocyte sedimentation rate (ESR) associated with HIV infection.[69] Little is known about the effect of antiretroviral therapy (ART) on RA disease, or the safety of biologic drugs in patients receiving ART. These are areas for future research.

6.4 Viral hepatitis

Hepatitis B reactivation can occur in hepatitis B surface antigen (HBsAg)-positive patients treated with MTX or biologic therapy (particularly rituximab). Thus, screening for viral hepatitis before starting treatment in high-risk patients is recommended.[70] Hepatitis B vaccination should ideally be offered to non-immune patients before commencing DMARD treatment. In hepatitis C-infected patients, anti-TNF therapy and rituximab is considered safe, and possibly beneficial.[71]

6.5 Vaccination

Patients with RA should receive killed vaccines based on age and risk, ideally at least 14 days before commencing DMARD or biologic therapy for optimal efficacy. These might include influenza, pneumococcal, hepatitis B and human papillomavirus vaccines. Live vaccines including herpes zoster and yellow fever vaccines are not recommended in RA patients on MTX or biologic therapy. It may, however, be appropriate to vaccinate a patient likely to travel to a high-risk yellow fever area, prior to commencing biologic therapy.

6.6 Cardiovascular events

Due to a combination of systemic inflammation and traditional cardiovascular risk factors, patients with RA have increased cardiovascular disease and risk of cardiovascular death, similar to that seen in patients with type 2 diabetes.[72] Traditional risk factors including smoking, hypertension, diabetes mellitus, and dyslipidaemia (most importantly low levels of high-density lipoprotein (HDL) cholesterol and resultant high total cholesterol to HDL ratio) need to be addressed.[73] In SA, treatment of dyslipidaemia is based on cardiovascular risk estimation using the Framingham Risk Score.[74] In the setting of RA that is seropositive, extra-articular or established (≥10 year disease duration), this percentage risk should be multiplied by 1.5.[73]

Uncontrolled severe joint inflammation, extra-articular disease, physical inactivity and corticosteroid use further contribute to the risk of cardiovascular events.[75] Improved disease control with therapy, such as MTX and anti-TNF therapy, has been shown to decrease cardiovascular risk in RA patients.[76,77]

6.7 Osteoporosis

Bone loss is an important consequence of long-standing RA, and patients may require co-therapy with osteoclast-inhibiting agents or osteoblast stimulators. The pathogenesis of osteoporosis in RA is multi-factorial and can be cumulative over time. In early disease, the predominant feature is localised, or juxta-articular, osteoporosis, which is a consequence of locally acting pro-inflammatory cytokines. It is not yet clear whether biologic DMARDs are capable of retarding or reversing bone loss in RA, but studies are under way to evaluate this. One recent study[78] failed to show a significant impact on bone density following anti-TNF therapy, but the sample size and duration may have meant that it was under-powered.

Generalised osteoporosis affecting the femur and lumbar spine is usually seen in long-standing RA, especially in post-menopausal women. The mechanism is likely to be due to a combination of immobilisation, age, menopause, GC therapy and inflammation due to RA. The dose of prednisone associated with bone loss is likely to be as low as 2.5 mg daily.[79] The ACR has recently published revised guidelines for the treatment of GC-induced osteoporosis, recommending that a lower threshold for intervention be used, since fractures in these patients may occur when the bone mineral density T-score is >-2.5 but <-1.0.[80] Calcium and vitamin D supplementations are recommended for routine use in all patients likely to receive GC therapy for longer than 6 months, irrespective of dose. Control of joint inflammation with DMARD therapy will help to maintain the bone density by improving physical activity.

6.8 Malignancy

Patients with RA are at increased risk of lymphoma, with the major risk being uncontrolled joint inflammation rather than DMARD therapy.[81] Neither synthetic nor biologic DMARDs seem to confer an increased risk of malignancy,[82,83] nor do they increase the chance of recurrence of a malignancy, or change the prognosis of cancers that occur in patients using biologic therapies.[84] The current recommendations are that biologic therapy be avoided in patients with a current or recent (<5 years) diagnosis of a malignancy.

6.9 Pregnancy

RA tends to improve during pregnancy. In general, because of potential risks to the fetus, DMARDs are not recommended, and low-dose GCs may be adequate to control symptoms. MTX and leflunomide are contraindicated in pregnancy and breastfeeding, but SSZ and CQ are considered relatively safe and may be useful in active disease. There is sparse evidence for the safety of biologic drugs in pregnancy or lactation and formal recommendations are that anti-TNF drugs and rituximab be stopped 3 months and 12 months, respectively, before conception. However, there are recent reports of successful pregnancies in patients using anti-TNF drugs, and many experts feel that these drugs can be safely continued during conception and the first 2 trimesters of pregnancy.[85]

7. Monitoring patients on therapy

Disease activity should be evaluated with an SDAI, and an intensive disease control strategy should be used with escalation of therapy if LDA or, ideally, remission is not achieved. Patients with moderate or high disease activity should be assessed frequently (1 - 3-monthly) until an LDA state is achieved, after which less frequent visits (3 - 6-monthly) are acceptable.

Monitoring for toxicity of DMARD therapy is summarised in Table 4. There is no indication for 'routine' liver biopsy in patients on MTX therapy. A biopsy may be indicated in a patient with persistently elevated liver enzymes (>3 times the upper level of normal) after DMARD discontinuation.[86] Annual serum creatinine and cholesterol tests are appropriate. Baseline bone mineral density measurements are recommended in post-menopausal women starting long-term GC therapy and should be repeated at 5-yearly intervals.

Because of the high risk of infection, including TB, RA patients and their physicians must remain vigilant for symptoms of infection. Patients should be advised to seek medical attention for any symptoms of possible infection, to allow for prompt assessment and treatment. Loss of weight, fever or lymphadenopathy in a patient on biologic therapy requires prompt investigation for TB, which might include a CXR, abdominal ultrasound and bone marrow aspiration.

8. SA rheumatologist survey

An online survey was sent to all SA rheumatologists to assess the level of agreement with 9 statements on management of RA. Rheumatologists were asked to score their agreement with each statement on a 10-point numerical scale (10 = agree completely; 0 = do not agree at all). The response rate to the survey was 46/81 (57%), and results are shown in Table 6. Importantly, there was strong support for an intensive control strategy involving frequent (1 - 3-monthly) visits, and calculation of a composite disease activity index with escalation of therapy if LDA is not achieved. In addition, there was excellent agreement regarding the selection of patients for biologic therapy. Of interest, the vast majority (83%) of SA rheumatologists concur that in patients at high risk of TB, non-TNF biologic therapy may be the more appropriate first-line therapy. There was moderate agreement (64%) with an approach giving INH prophylaxis to all high-risk patients starting anti-TNF treatment.

9. Economic aspects of therapy

The costs of therapy to treat RA, which may include the considerable expense of biologic drugs in patients who do not respond to synthetic DMARDs alone, need to be balanced against the consequences of uncontrolled disease with ensuing joint damage and disability. Loss of productivity in the home and workplace, loss of income, isolation from

Table 6. Level of agreement for online survey on issues of RA therapy sent to all SA rheumatologists (*N*=46)*

Statement regarding RA therapy	Agreement %
Use of a composite disease activity index	87
Frequent (1 - 3-monthly) assessments are appropriate until LDA or ideally remission is reached	91
Adjustment of therapy must be considered at any visit where LDA is not obtained	89
Low dose (≤10 mg/day) oral GC	
Early RA (≤12 months of symptoms): co-prescribed with DMARDs and for at least 6 months	72
In established disease as short-term 'bridging' when starting DMARD therapy	80
Biologic DMARD therapy should be considered when	
3 traditional DMARDs including MTX have been prescribed	83
6 months of traditional DMARD therapy has been completed	69
High disease activity	80
Moderate disease activity†	81
In a patient at high risk of TB, a non-anti-TNF biologic may be the most appropriate choice	83
IGRAs are superior to TSTs in diagnosing latent TB	49
Prophylactic therapy for latent TB in any patient at high risk of TB commencing anti-TNF therapy may be prudent regardless of TST or IGRA result	64
Vaccination, including pneumococcal and hepatitis B, is advisable in patients starting or already taking DMARD therapy	70

SA = South African; RA = rheumatoid arthritis; LDA = low disease activity; GC = glucocorticoid; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; TB = tuberculosis; TNF = tumour necrosis factor; IFN = interferon; TST = tuberculin skin test; IGRA = IFN-γ release assay; RF = rheumatoid factor.
*Participants were asked to rate their agreement with each statement on a scale of 0 - 10 (0 = do not agree at all; 10 = agree completely).
†In the presence of poor prognostic factors (high-titre RF positivity, nodules or other extra-articular disease, radiographic erosions, functional disability).

society and reduced recreational comforts, together with the negative psychosocial impact of the disease, have severe economic consequences for patients, their families, and to society.[87] The measures used to quantify these effects include the disability adjusted life-years (DALY) and the quality of life-years lost (QALY).

The costs of therapy will be relatively low in patients receiving non-biologic DMARDs, but will escalate when biologic DMARDs are added. When comparing different therapies for the treatment of RA, the number needed to treat (NNT) to achieve a response may be a useful reference. Such calculations will differ, depending on the tool used to measure response. Most studies base their calculations on achieving an ACR 50 response in a 70 kg subject. A recent meta-analysis of the cost-effectiveness of all biologics showed that the NNT varied between 2.8 and 5.7.[88]

A recent systematic review of the literature, which contributed to the EULAR recommendations, showed that the merits of effective control of RA outweigh the costs of therapy.[89] At disease onset, synthetic DMARDs should be initiated. If these fail, treatment escalations with biologic therapy are cost-effective, provided standard dosing schemes are used.

10. Areas for future research

There are several areas for future research to provide answers to optimal RA management in our unique SA situation. The most important issues revolve around TB, including the safety of biologic DMARDs, and the risk factors for development of TB. Contemporary epidemiological data on the prevalence and incidence of RA in SA are needed. Other areas for investigation include management of RA in HIV-positive patients, the burden of RA on productivity in SA, and local exploration of the cost-effectiveness of RA treatment.

Due to recent advances in RA therapies, it is suggested that these recommendations are updated every 2 years.

In summary, effective management of RA requires prompt diagnosis, early initiation of DMARD therapy, and an intensive control strategy with frequent assessments and rapid escalation of therapy. The aim should be to achieve LDA or ideally remission. Biologic drugs should be considered in patients who have shown inadequate response to synthetic DMARDs.

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