South African Rheumatism and Arthritis Association 2024 updated guidelines for the management of rheumatoid arthritis

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The management of rheumatoid arthritis (RA) requires early diagnosis and prompt initiation of therapy, together with lifestyle interventions, particularly smoking cessation. These guidelines recommend a treat-to-target strategy using a composite disease activity score at each visit, with frequent follow-up and escalation or switching of disease-modifying antirheumatic drug (DMARD) therapy until the goal of low disease activity is achieved. A stepwise algorithm for DMARD therapy is provided. Screening for comorbidities and vaccination is advised.

Keywords: South Africa, rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic incurable disease that interferes with physical function, work productivity, and health-related quality of life (HRQoL). Despite improvements in therapies over the past three decades, a third of RA patients report work disability within 5 years of RA diagnosis, and mental and physical HRQoL scores among RA patients are worse than those of patients with other chronic illnesses such as cardiovascular disease and diabetes.[1] Active disease can lead to irreversible joint damage, which is frequently associated with permanent functional disability, emphasising the importance of early aggressive therapy to control disease activity.[2,3] Monitoring and modification of therapy, including multiple successive therapies, may be required; up to 60% of patients will not meet treatment goals after their first disease-modifying antirheumatic drug (DMARD), and >60% of these will require at least a third DMARD course.[4] With optimal treatment strategies, remission or low disease activity (LDA) can be achieved in up to 80% of patients.[3] In poorly resourced areas, outcomes tend to be worse.[5]

Early diagnosis

Joint damage begins within the first 3 months of disease onset. There is a 'window of opportunity' where early aggressive therapy of RA can suppress inflammation before irreversible joint destruction has occurred.[6-8] Early diagnosis and initiation of DMARD therapy are therefore critical. The 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria are a useful reference (Table 1).[9,10] Recently, there has been recognition that some patients have joint symptoms but no clinically apparent synovitis. Patients with three or more of seven clinical features have an increased risk of progression to RA and are termed 'clinically suspect arthralgia' (CSA), and should be referred to a rheumatologist (Table 2).[11] A validation study showed that this test is useful, with a sensitivity of 84%.[12]

Assessment of RA

Assessing disease activity

A composite disease activity score should be performed at every visit. This score includes the number of tender and swollen joints (using 28 joint counts); global assessment of disease activity from the patient ('How has your arthritis been over the last week?'), scoring between 0 (very well) and 10 (very poor); and global assessment of disease activity by the physician, scoring between 0 (very well) and 10 (very poor), with or without a serum acute-phase reactant (Table 3). Disease activity can be classified into states of remission or low, moderate or high disease activity.[13] The three validated scores currently in use in South Africa (SA) are the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI) and the 28-joint Disease Activity Score (DAS-28).[14-16] The CDAI is the easiest measurement to perform, and the final score ranges from 0 to 76 (higher scores indicate higher disease activity).[16]

Disability

Physical disability can be measured with the Health Assessment Questionnaire-Disability Index (HAQ-DI).[17] This self-administered questionnaire should ideally be completed 6 - 12-monthly, and with motivation/remotivation for biologic therapy, work assessment and disability boarding.

Radiography

Baseline hand and feet radiographs should be performed for diagnostic (marginal erosions, joint space narrowing and juxta-

Table 1. 2010 ACR/EULAR RA classification criteria*

Criteria		Score†
Joints	1 large joint	0
	2 - 10 large joints‡	1
	1 - 3 small joints§	2
	4 - 10 small joints	3
	>10 joints	5
Serology	Negative RF *and* negative anti-CCP	0
	Low-positive RF *or* low-positive ACPA (≤3 times ULN)	2
	High-positive RF *or* high-positive ACPA (>3 times ULN)	3
Acute-phase reactants	Normal CRP and ESR	0
	Abnormal CRP or ESR	1
Symptom duration	<6 weeks	0
	≥6 weeks	1

ACR = American College of Rheumatology; EULAR = European Alliance of Associations for Rheumatology; RA = rheumatoid arthritis; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; ACPA = anti-citrullinated peptide antibody; ULN = upper limit of normal; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
*Patients must: (*i*) have at least 1 joint with definite synovitis (swelling), (*ii*) with the synovitis not better explained by another disease.
†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.

Table 2. Clinical features of joint pain suspicious for progression to RA ('clinically suspect arthralgia')*

History	Joint symptoms of recent onset (duration <1 year)
	Symptoms located in MCP joints
	Duration of morning stiffness ≥60 minutes
	Most severe symptoms present in the early morning
	Presence of a first-degree relative with RA
Physical examination	Difficulty with making a fist
	Positive squeeze test of MCP joints

RA = rheumatoid arthritis; MCP = metacarpophalangeal.
*Patients with a positive definition (≥3/7 parameters present) should be referred to a rheumatologist.

Table 3. Disease activity formulas and categories

Index	Formula	Remission	Low disease activity	Moderate disease activity	High disease activity
CDAI	TJC + SJC + PGA (cm) + MDGA (cm)	≤2.8	≤10	≤22	>22
SDAI	TJC + SJC +PGA (cm) + MDGA (cm) + CRP mg/dL	≤3.3	≤11	≤26	>26
DAS-28	0.56*√(TJC) + 0.28*√(SJC) + 0.7*ln (ESR) + 0.014*PGA (cm)	≤2.6	≤3.2	≤5.1	>5.1

CDAI = Clinical Disease Activity Index; TJC = tender joint count; SJC = swollen joint count; PGA = patient global assessment; MDGA = physician global assessment (0 = very good; 10 = very poor); SDAI = Simplified Disease Activity Index; CRP = C-reactive protein; DAS-28 = Disease Activity Score; ESR = erythrocyte sedimentation rate.

articular osteopenia) and prognostic purposes. These images are not sensitive enough to detect changes early in the disease, but are readily available, reliable and low in cost.

A chest radiograph is appropriate to exclude rheumatoid lung disease or tuberculosis (TB) prior to commencing therapy.

Musculoskeletal ultrasound

High-resolution musculoskeletal ultrasound (MSUS) is safe and relatively inexpensive, and allows accurate assessment of soft-tissue inflammation and joint erosions, and placement of intra-articular injections that is superior to clinical examination.[16,18] A trained and experienced rheumatologist or MSUS technician is required.

Magnetic resonance imaging

Magnetic resonance imaging (MRI), particularly contrast-enhanced MRI, is highly sensitive, demonstrating synovitis and tenosynovitis, and can detect erosions up to 3 years before they are evident on conventional radiographs. Bone marrow oedema may be seen on MRI in early RA, and is a strong predictor of bone damage.[19] Limited access to MRI scans together with cost limit the availability of this modality.

Imaging in the diagnosis and management of RA

While MSUS-detected tenosynovial hypertrophy with Doppler signal and MRI-detected tenosynovitis at the metatarsophalangeal joints are very specific for RA, recent studies have found that MRI and MSUS did not add value to the diagnosis of RA compared with the 2010 ACR/EULAR classification criteria. MSUS is useful when there is diagnostic doubt.[20] At present, MSUS and MRI scans are not part of routine diagnosis and should be used to visualise soft-tissue and bone lesions of a problem joint, or to confirm or exclude synovitis where there is clinical uncertainty.

Regular routine imaging of RA joints is not necessary: there is no evidence that follow-up assessments with either MSUS or MRI lead to better outcomes than clinical assessments, and they have the potential to lead to over-treatment.[21,22]

Prognostic features of RA

Poor prognostic factors include seropositivity, i.e. high titres of rheumatoid factor or anti-cyclic citrullinated peptide antibody; high inflammatory markers; erosions on radiographs within the first 2 years of disease; functional disability; extra-articular disease; cigarette smoking; and delayed diagnosis.[23]

Management principles

Patient information and decision-making

The aim of treatment is to maintain a good quality of life and physical function. A management plan should be developed based on shared decision-making between patients and clinicians, predicated on patients' values, goals, preferences and comorbidities. Patient education should include information about RA disease and complications, assessment of disease, treatment goals, medications and adherence.[24]

Self-management interventions, including medication management, physical activity, disease-related problem solving, emotional wellbeing, communication skills, and use of community resources including patient support groups, should be emphasised.[25] Lifestyle improvements complement medical treatment but do not replace it.

There is strong evidence that being cared for primarily by a rheumatologist improves outcomes for persons with RA.[26,27] All RA patients should ideally be seen by a rheumatologist, particularly those with diagnostic uncertainty, moderate or high disease activity, functional impairment, intolerance to DMARDs, and extra-articular disease.

Care of the RA patient requires a multidisciplinary holistic approach that may include an occupational therapist, podiatrist, physiotherapist, orthopaedic surgeon, psychologist and social worker. A rheumatology nurse can offer patient education and support, with positive effects on adherence to therapy and HRQoL.[28]

Lifestyle interventions

Adoption of a healthy lifestyle is of benefit to all RA patients.

Smoking cessation should be encouraged, as cigarette 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.[29]

Exercise (particularly supervised rehabilitation programmes) strengthens muscle, increases grip strength and functional capacity, and improves cardiovascular fitness, without worsening RA disease activity.[30] All RA patients should be encouraged to participate in regular aerobic and resistance exercise training.

Obesity is prevalent in early and established RA and is associated with poorer disease outcomes and with comorbidities.[31] Losing weight may improve RA disease activity.[32]

Comorbidities and extra-articular disease

The majority of RA patients have one or more comorbidity leading to premature mortality, poorer RA disease control, functional impairment and reduced HRQoL.[33,34]

Accelerated atherosclerosis leading to cardiovascular events, infections, non-steroidal anti-inflammatory drug (NSAID)-induced gastritis and osteoporosis are the major comorbidities in RA and need regular screening and evidence-based management.[34,35]

Extra-articular disease, particularly interstitial lung disease, and uncontrolled pain, fatigue, depression and anxiety need to be actively screened for and holistically managed.[36]

Screening for hepatitis B, hepatitis C, HIV and TB should be done at presentation. The vaccination status, pregnancy plans, and contraception and lactational status of the patient should be reviewed and discussed regularly.

Goal of therapy

The goal of therapy is to achieve at least LDA, i.e. CDAI ≤10.

Remission, or a state of no disease activity, may be defined by a composite disease activity score or by ACR/EULAR remission criteria.[37] While remission is a reasonable goal for patients with early disease, aiming for remission may not be realistic for all RA patients.

Treat-to-target strategy

Patients who achieve LDA/remission have a low risk of damage progression compared with those with moderate or high disease activity states, with better physical function, improved HRQoL, and fewer comorbidities including normalisation of cardiovascular risk factors, particularly when therapy is commenced in early disease.[38,39]

A treat-to-target strategy entails:

- Use of a composite disease activity score at each visit
- Escalation or switching of DMARD therapy until the goal of LDA is achieved
- Frequent follow-up every 1 - 3 months during the first 6 - 18 months of treatment or until LDA/remission is achieved.

Clinicians must aim to achieve LDA in all patients as soon as possible – aiming for 50% improvement in disease activity score within 3 months, and LDA at 6 months. Frequent evaluation is needed (every 1 - 3 months) in patients with active disease, with adjustment of therapy until LDA/remission is reached, after which time less frequent assessments (3 - 6-monthly) are acceptable.

DMARDs

These agents are divided into three broad groups: conventional synthetic (csDMARDs), biologic (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).

csDMARDs to treat RA include methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ) and antimalarials (AMAs) (Table 4).

bDMARDs may be either biologic original (boDMARDs) or biosimilar (bsDMARDs). Among the bDMARDs registered for use in RA in SA, four are tumour necrosis factor inhibitors (TNFis): receptor blockers (etanercept (original and biosimilar)) or monoclonal antibodies (infliximab (original and biosimilar)), adalimumab (original and biosimilar) and golimumab; and three non-TNFis: ritixumab (original and biosimilar), tocilizumab and abatacept.

tsDMARDs include the Janus kinase (JAK) inhibitors tofacitinib, baricitinib and upadacitinib.

Glucocorticoids

Side-effects limit the use of glucocorticoids (GCs) to short term and low dose (≤7.5 mg/day) in combination with DMARDs. Long-acting intramuscular methylprednisolone is an alternative to oral prednisone. GCs are not recommended as monotherapy for RA.

The risks associated with long-term GC use, especially at doses >5 mg/day, are considerable, including infection, vertebral and non-vertebral fracture, cardiovascular events, diabetes mellitus, obesity, cataracts, depressed mood, hypertension and dyspepsia.[40]

Short-term low-dose (<10 mg/day) GC 'bridging therapy' may be prescribed when initiating DMARD therapy for up to 3 months, after which the symptomatic effects seem to wane. Once DMARDs are fully effective, the GC should be tapered and stopped.[37,41]

Intra-articular GCs are useful for a mono- or oligoarticular flare of disease.

Table 4. Conventional synthetic DMARDs

	Indication	Dose	Side effects	Monitoring	Contraindications
MTX	First-choice DMARD as monotherapy or combination therapy Co-prescribed with biologic drugs	7.5 - 25 mg weekly orally or subcutaneously Co-prescribe with folic acid 5 - 10 mg/week, 24 hours after MTX	*Common:* nausea and vomiting, mucositis, alopecia, elevated liver enzymes, anaemia, neutropenia *Less frequent:* pneumonitis Teratogenic	Baseline CXR FBC and liver transaminase test within the first month of treatment, and thereafter 3 - 6-monthly	Pregnancy and breastfeeding, alcoholism, liver disorders, renal failure, bone marrow suppression Caution in HIV-positive patients with CD4 count <200 cells/μL
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), rash, elevated liver enzymes, myelosuppression	FBC and liver transaminase test within the first 1 - 2 months of treatment, and thereafter 3 - 6-monthly	Safe in pregnancy and breastfeeding
LEF	Monotherapy or in combination with MTX	10 - 20 mg/day orally	Nausea, vomiting, abdominal pain, diarrhoea, alopecia, elevated liver enzymes, skin rash Teratogenic in both males and females	FBC and liver transaminase test within the first month of treatment, and thereafter 3 - 6-monthly	Pregnancy and breastfeeding
AMA therapy, i.e. chloroquine	Mild RA or as part of combination therapy	Chloroquine 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	Ophthalmological assessments (OCT and visual field assessment) annually once the patient has used AMAs for ≥10 years	

DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; AMA = antimalarial; CXR = chest X-ray; FBC = full blood count; SSZ = sulfasalazine; LEF = leflunomide; RA = rheumatoid arthritis; OCT = optical coherence tomography.

Extra-articular disease, including scleritis, vasculitis and serositis, may require moderate to high doses of GCs in combination with DMARDs or other immunosuppressants[42] (Table 5).

Sequential DMARD therapy for RA

Initiation of DMARD therapy with escalation of therapy according to sequential steps is recommended if the LDA target is not reached (Table 6). If patients are taking a GC to remain at target, escalation of DMARD therapy is recommended over continuation of the GC.[37]

First-line therapy: MTX monotherapy

MTX is the most widely prescribed csDMARD, has been used to treat RA for more than 50 years, and is the 'anchor' drug in RA. MTX is initiated at 7.5 - 15 mg weekly, orally or subcutaneously, with rapid dose escalation according to response and tolerability to a maximum of 25 mg weekly.[37] Co-prescription with folate (5 - 10 mg weekly) is recommended.[43] Patients with an inadequate clinical response to oral MTX may benefit from switching to subcutaneous MTX. A split dose of oral MTX over 24 hours, or subcutaneous MTX, may be prescribed for patients who do not tolerate oral weekly MTX.[44] If MTX is not tolerated or is contraindicated, SSZ or LEF can be considered.[37,44]

MTX has an excellent safety profile, and although mild elevation of liver enzymes is not infrequent, this is usually transient, and cirrhosis is rare.[45,46] A modest alcohol intake (1 unit per day) is acceptable for patients using MTX, provided that liver function remains normal.

A large proportion of patients (25 - 40%) improve significantly with MTX monotherapy, and in combination with GCs, almost half of patients can attain LDA or remission in early RA, a rate similar to that achieved with bDMARDs.[47] In treatment-naive patients, biologic/targeted synthetic DMARDs (b/tsDMARDs) are not recommended as first-line therapy, as no bDMARD + MTX trial has shown superiority over MTX + GC in MTX-naive patients.[41]

An AMA such as chloroquine may be used as monotherapy for mild RA.

Second-line therapy: Combination csDMARD therapy

Patients who fail MTX monotherapy should be treated with combination csDMARDs.[48] The most commonly prescribed combination treatment is 'triple therapy' MTX + SSZ + CQ. Alternatively, MTX + LEF may be effective. Another approach is to switch to an alternative csDMARD monotherapy.

Third-line therapy: MTX plus b/tsDMARD

South African Rheumatism and Arthritis Association (SARAA) eligibility criteria for b/tsDMARD therapies in RA are as follows:

- Moderate or high disease activity, i.e. CDAI >10 or SDAI >11

Table 5. Suggestions for RA patients with comorbidities or extra-articular disease

Clinical problem	Potential issues with DMARDs/GCs	DMARD therapy of choice
Rheumatoid nodules	If progressive on MTX, change to non-MTX DMARD or reduce MTX dose	AMA, discontinue smoking, rituximab
Interstitial lung disease	MTX may be used: beware of risk of acute pneumonitis	Rituximab, tocilizumab, abatacept or mycophenolate mofetil
HIV positive, CD4 >200 cells/μL	Nil	All DMARDs safe
HIV positive, CD4 <200 cells/μL	Avoid MTX and bDMARDs because of risk of opportunistic infections	SSZ, AMA
Pregnancy	MTX/LEF contraindicated	SSZ, AMA, low-dose GC
	Insufficient data on non-TNFi tsDMARD	TNFi: discontinue in 3rd trimester or delay neonatal vaccines (BCG, rotavirus)
NAFLD	Avoid MTX, LEF and TNFi if elevated liver enzymes/extensive fibrosis Consider low-dose MTX or TNFi for patients with normal liver enzymes and no evidence of advanced liver fibrosis who have moderate to high disease activity	Rituximab, AMA, minimise GC if possible
Hepatitis B	Hepatitis B reactivation risk	If HBsAg positive, co-prescribe antiviral with any b/tsDMARD If prescribing rituximab and HBcAb positive (regardless of HBsAg result), co-prescribe antiviral
Hepatitis C	Deterioration of liver function if underlying liver disease	Consider non-hepatotoxic DMARDs (SSZ or AMA) Rituximab may be bDMARD of choice
Active TB	Treat TB Monitor liver function if co-prescribing MTX with TB treatment	Non-TNFi bDMARD
Latent TB or high risk for TB	Latent TB prophylaxis	Non-TNFi b/tsDMARD
Dyslipidaemia	Avoid tocilizumab, tsDMARDs	
Lymphoproliferative malignancy/other previous malignancy	Avoid b/tsDMARDs for 5 years	Rituximab
Heart failure	Avoid TNFi if severe heart failure	Non-TNFi b/tsDMARD
Serious infection in past 12 months or high risk of serious infection	Avoid GCs Avoid b/tsDMARDs	csDMARDs, rituximab, abatacept
Demyelinating disorders	Avoid TNFi	Rituximab
Pyoderma gangrenosum		Calcineurin inhibitor

RA = rheumatoid arthritis; DMARD = disease-modifying antirheumatic drug; GC = glucocorticoid; MTX = methotrexate; AMA = antimalarial; bDMARD = biologic DMARD; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumour necrosis factor inhibitor; tsDMARD = targeted synthetic DMARD; NAFLD = non-alcoholic fatty liver disease; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; b/tsDMARD = biologic/targeted synthetic DMARD; TB = tuberculosis; csDMARD = conventional synthetic DMARD.

Table 6. Stepwise algorithm for DMARD therapy in RA

	Standard strategy	Alternative strategy	Inadequate response within 3 months
First-line therapy	MTX monotherapy	Other csDMARDs if MTX not tolerated or contraindicated	Proceed to second-line therapy
Second-line therapy	Combination csDMARD	Non-MTX monotherapy	Proceed to third-line therapy
Third-line therapy	b/tsDMARD + MTX	If MTX not tolerated, consider tocilizumab or tsDMARD	Proceed to fourth-line therapy
Fourth-line therapy	Alternative b/tsDMARD		Alternative b/tsDMARD
De-escalation	After sustained remission × 6 months, consider slow taper of b/tsDMARD, maintain csDMARD		Restart b/tsDMARD if flares

DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; MTX = methotrexate; csDMARD = conventional synthetic DMARD = b/tsDMARD: biologic/targeted synthetic DMARD; tsDMARD = targeted synthetic DMARD.

- A 3-month trial of at least two csDMARDs used serially or in combination (including MTX at a dose of at least 20 mg weekly unless contraindicated, or at least at the maximum tolerated dose)
- b/tsDMARDs may be considered earlier for severe refractory extra-articular disease (e.g. RA-interstitial lung disease).

All b/tsDMARDs have greater efficacy if co-prescribed with MTX or LEF to improve efficacy and reduce immunogenicity of bDMARDs.[47,49] If MTX and other csDMARDs are poorly tolerated or contraindicated, bDMARDs showing good efficacy as monotherapy (tocilizumab) or tsDMARDs are the most appropriate choices.[37]

The use of combination b/tsDMARDs is not recommended at present.

All b/tsDMARDs should be initiated by a rheumatologist. All patients with a rheumatic disease on b/tsDMARDs must be included, with patient consent, in the SARAA biologic registry (https://www.saraa.co.za).

Before commencing b/tsDMARD therapy, screening and treatment for latent TB, hepatitis B, hepatitis C and HIV, in addition to vaccination, should be done.

Choice of b/tsDMARD

Clinical trials and clinical experience have demonstrated the efficacy of all currently available therapies. All bDMARDs have similar response rates in RA: LDA is achieved by up to 40% of patients. Response rates decrease with increasing previous drug experience.[50]

The choice of which b/tsDMARD is offered depends on the safety profile, contraindications, comorbidities, patient preference, cost, and rheumatologist's opinion. There are special circumstances where a particular agent may be preferred (Table 5). For example, rituximab should be considered as the initial bDMARD if there is a history of past lymphoma or other malignancy; any demyelinating disorder; or previous TB infection, latent TB, or a high risk of TB.[44]

Fourth-line therapy: Switching b/tsDMARDs

A b/tsDMARD that has not resulted in an adequate clinical response (LDA, i.e. CDAI ≤10, SDAI ≤11) after 3 months of treatment should be withdrawn, and an alternative b/tsDMARD should be prescribed. Any b/tsDMARD may be considered: evidence shows that administering a TNFi after another TNFi has failed can be as efficacious as using a drug with another mode of action.[50] The choice of which b/tsDMARD is offered therefore depends on the safety profile, contraindications, patient preference, cost, and rheumatologist's opinion.

De-escalation of therapy

As noted above, GCs should be reduced and discontinued as soon as possible, ideally within 3 months, or once LDA is achieved.

For patients who have maintained persistent LDA/remission without a GC for at least 6 - 12 months, DMARD tapering may be cautiously considered. Discontinuation of all DMARDs may be associated with disease flares, so at least one tolerated csDMARD at the lowest dose should be continued.[51] No difference in outcomes has been shown in terms of whether the csDMARD or b/tsDMARD is tapered first, and based on cost, safety and availability, the b/tsDMARD should be tapered first.[52] Tapering (dose reduction and/or interval increase), or even discontinuation of the b/tsDMARD, can be attempted but is frequently associated with disease flares. Reassuringly, most patients (>80%) will achieve target again once the bDMARD is restarted.[53]

Analgesics and anti-inflammatory drugs

Analgesics should be prescribed and taken on an 'as needed' basis for pain control. Paracetamol is a very effective analgesic, and doses of up to 4 g daily can be prescribed. Opioid analgesics should be limited to short-term use because of toxicity.[54]

NSAIDs are effective in controlling pain and stiffness, but are purely symptomatic therapies in RA and offer no disease-modifying action. NSAIDs should be used at the lowest effective dose and for the shortest possible duration of time, and withdrawn once disease activity is controlled with DMARDs. The toxicity of these drugs should not be underestimated, and all NSAIDs should be used with caution. Many patients with RA have risk factors for NSAID-induced gastrointestinal tract events, including older age (>60 years), as well as co-prescription of GCs and aspirin. There should therefore be a low threshold for co-prescribing a proton pump inhibitor for gastroprotection, or for considering a cyclo-oxygenase-2 (COX-2) selective agent.[55] In addition, all NSAIDs, both non-selective agents and selective COX-2 inhibitors, confer an increased risk of thrombotic events (stroke and acute coronary syndrome), and should be used with caution in patients with cardiovascular risk factors.[56] Other side-effects of NSAIDs, including hypertension, renal and liver dysfunction, should not be forgotten.

Summarised principles of rheumatoid arthritis therapy

- *Early diagnosis*
- *Prompt initiation of disease-modifying antirheumatic drug therapy*
- *Frequent monitoring with a composite disease activity score and escalation of therapy until low disease activity or remission achieved*
- *Low dose GC (≤7.5mg daily) as "bridging therapy" for 1-3 months when initiating DMARDs, then GC should be reduced and discontinued.*
- *Screening and management of comorbidities is essential.*

Monitoring of RA patients on therapy

There is no indication for 'routine' liver biopsy in patients on MTX therapy. Biopsy may be indicated in a patient with persistently elevated liver enzymes (greater than three times the upper level of normal) after DMARD discontinuation.[57] Measurement of serum creatinine is recommended at baseline and annually, unless more frequent monitoring is indicated. Annual metabolic blood tests (fasting glucose, glycated haemoglobin, lipogram) are appropriate. Baseline bone mineral density measurements are recommended in postmenopausal females with high fracture risk assessment tool (FRAX) scores 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, and 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 a b/tsDMARD requires prompt investigation for TB.

Economic considerations

RA is a chronic incurable disease with both direct costs (medication, hospitalisation, diagnostic or therapeutic interventions, professional fees, rehabilitation and mechanical aids for the patient, physiotherapy) and indirect costs (e.g. sick leave, disability). These costs escalate as functional disability and comorbidities increase.[58,59]

Early aggressive therapy before irreversible disability occurs reduces both direct and indirect costs. Treating patients to remission with combination csDMARDs or b/tsDMARDs reduces overall annual all-cause and RA-related total costs, including outpatient visit costs.[60]

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