South African Family Practice 2014; 56(3):166–171
http://dx.doi.org/10.1080/20786204.2014.932547

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

Rheumatoid arthritis

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Immune-mediated inflammatory disorders include a clinically diverse group of conditions that share similar pathogenic mechanisms. Conditions such as rheumatoid arthritis (RA), psoriasis, spondyloarthropathy, inflammatory bowel disease and connective-tissue disease are characterised by immune dysregulation and chronic inflammation. This review will focus on immunopathogenic mechanisms, aspects of early disease, co-morbidity and therapy in RA.

Keywords: immune, inflammatory, rheumatoid arthritis, therapy

Introduction

Rheumatoid arthritis (RA) is the archetype of an immune-mediated inflammatory disorder. Numerous advances have been made in the understanding of the pathogenic mechanisms at molecular level, and this has facilitated the introduction of novel efficacious therapies. An understanding of these pathogenic mechanisms is imperative as therapies that target specific molecular and cellular components of the inflammatory response are being used successfully to treat a diverse group of other immune-mediated inflammatory diseases, such as psoriasis, spondyloarthropathy, inflammatory bowel disease and connective-tissue disease (CTD).[1]

Pathogenesis of rheumatoid arthritis

A normal immune response requires the innate and adaptive immune responses to work together to protect against foreign organisms. The innate immune system consists of cellular and molecular components, such as macrophages, neutrophils and complement, that interact with foreign antigens in an immediate and non-specific manner, and which also present the antigens to the adaptive immune response. The adaptive immune system acts with a more delayed, but specific response to eliminate or neutralise the effects of foreign antigens that are not managed completely by the initial response. The adaptive response consists predominantly of *T* and *B* cells that affect a response, depending on the inciting antigen, environmental and host factors. This usually results in an increase in antibody formation and molecular mediators of inflammation called "cytokines". Cytokines enable cross-talk between various components of the immunoinflammatory response. A host of cytokines, such as tumour necrosis factor (TNF) and interleukin (IL)-1, IL-6 and IL-17, promote inflammation, counterbalanced by cytokines such as IL-4 and IL-10[2] (Figure 1).

Immune dysregulation in RA results in a host of autoantibodies, such as rheumatoid factor (RF) and anticitrullinated peptide antibody (ACPA). The inciting antigen is unknown, with infective agents such as parvovirus B19 and an organism that causes gingivitis *(Porphyromonas gingivalis)*, being implicated as possible triggers.[3] Smoking has recently received much interest in the possible initiation of a chemical change in lung tissue, a process called "citrullination".[4] Citrullination involves a chemical change in certain peptides containing the amino acid, arginine, to citrulline. This citrullinated peptide is now exposed to the immune system and results in the generation of ACPA in genetically predisposed individuals. Citrullination also occurs in the rheumatoid synovium and interaction with these antibodies may not only trigger disease, but might also account for disease persistence.

Genetic factors play an important role in disease susceptibility. A specific amino acid sequence on certain human leukocyte antigens (HLA) has been found to be associated with RA. The HLA system is important for immune tolerance and response. For this reason, certain specific genetically determined amino acid sequences may be associated with certain diseases.[5] This sequence is termed the "shared epitope" in RA, and is found in approximately 80% of patients, particularly in those who are also ACPA-positive. The presence of the shared epitope varies in different ethnic groups. Some studies show a lower prevalence in African patients. However, a recent South African study found a similar percentage to that seen in Caucasians (83%).[6]

Once the immune system is activated, disease persistence is maintained by as yet unexplained mechanisms. Phenotypic changes in synovial cells, particularly synovial fibroblasts, may play a critical role.[7] These cells act in an autonomous, almost tumour-like fashion, generating proinflammatory cytokines which result in synovial proliferation and consequent local and systemic effects.[8]

Early rheumatoid arthritis

Immunological and biochemical changes occur even before the clinical onset of disease, with differing immunobiology before disease onset, in early disease and in established disease. Early disease represents a window of opportunity to obtain the best, most cost-effective results. This window seems to be within the first 2–3 years of disease. Most authorities advocate aggressive therapy aimed at disease control within 3–6 months of symptom onset.

The initial challenge is early diagnosis. The previous classification criteria (the 1987 American Rheumatism Association criteria) proved to be very insensitive to the diagnosis of early RA. The presence of rheumatoid nodules and radiographic changes were incorporated in these criteria, but these features are not seen in most patients with early disease. To this end, the new 2010 RA criteria allow a diagnosis to be made earlier, even in patients with a disease duration of less

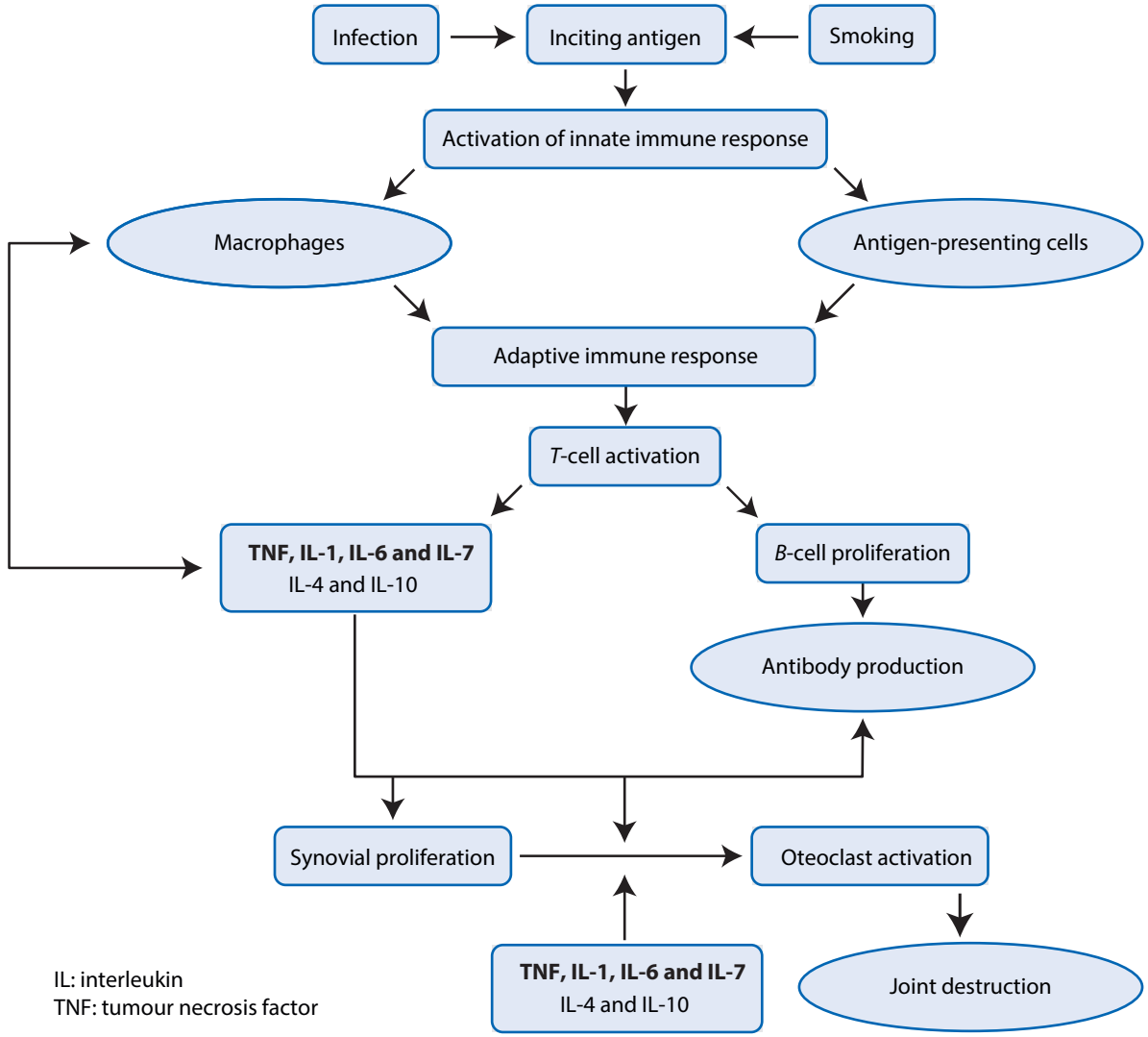

Figure 1: Schematic representation of mechanisms involved in the pathogenesis of rheumatoid arthritis

than six weeks[9] (Table I). These criteria are more sensitive and care needs to be taken to exclude viral infections, conditions such as osteoarthritis, psoriatic arthropathy and early CTDs.

Clinical features suggestive of early RA include morning stiffness that lasts for more than 30 minutes and which affects multiple joints and symmetrical joint involvement, particularly of the hands (Figure 2a) and feet (sparing the distal interphalangeal joints), as well as associated soft tissue swelling ("boggyness"), decreased range of motion (unable to make a fist), and metacarpal or metatarsal tenderness (the positive squeeze test). Characteristic deformities of RA are usually seen in patients with established, poorly controlled disease due to bone and soft tissue changes. Typical deformities in the hand include radial deviation at the wrist, ulnar deviation of the fingers, *Z* deformity of the thumb, and finger swan neck and Boutonniere deformities (Figures 2b and 2c). Tendon rupture may occur in early or late disease, and relates to tenosynovitis or attrition from adjacent bony deformities (Figure 2d). Viral aetiologies, such as hepatitis B, hepatitis C and human immunodeficiency virus infections, need to be excluded in patients with a disease duration of less than six weeks. Osteoarthris (OA) or psoriatic arthropathy should be considered in the presence of distal interphalangeal (DIP) joint involvement. Typical affected joints in OA (Figure 2e) are the DIP, proximal interphalangeal (PIP), first metacarpophalangeal (MCP) and first carpometacarpal joints of the hands, with associated bony swelling and morning stiffness of less than 10 minutes' duration. Patients with psoriatic arthritis may have inflammatory arthritis similar to RA, and often with DIP joint involvement. A systemic enquiry should include a family history of psoriasis and a search for characteristic nail and skin changes, noting that arthritic manifestations may precede skin involvement. Early CTD, such as systemic lupus erythematosus, may have similar articular features to RA. A systematic review is essential when searching for suggestive manifestations, such as malar or discoid rashes, photosensitivity, alopecia, recurrent oral ulceration, Raynaud's disease, serositis or major organ involvement.

Extra-articular manifestations are less common in early RA, and usually portend a poorer prognosis. Rheumatoid nodules occur in approximately 1% of patients. Typically, early disease is seen on the extensor surface of the forearm, just distal to the elbow. Ocular involvement includes dry eye syndrome and episclerits, and rarely scleritis and keratitis. Pulmonary fibrosis may occur from the disease or as a side-effect of the therapy. Neurological involvement usually relates to entrapment, such

as carpal tunnel syndrome and myelopathy from cervical spine subluxation.

Investigations

Full blood count

Anaemia of chronic disease is mediated by cytokines, such as IL-6, that inhibit iron transport and utilisation. Associated thrombocytosis may reflect an acute-phase response or gastrointestinal bleeding. A low white cell count may be seen in patients with a more severe form of RA, namely Felty's syndrome (RA, splenomegaly, chronic vasculitic leg ulcers and neutropenia).

Urea and electrolytes

Direct renal involvement in RA is rare, but it is important to monitor renal function at least annually as drug dosages may need to be adjusted or avoided altogether.

Liver function tests

Evidence of chronic liver disease may be apparent, but even if the liver function test is normal, viral hepatitis serology needs to be reviewed before starting therapy. Therefore, drug-related hepatitis may occur. Three- to four- monthly monitoring of aspartate transaminase or alanine transaminase is recommended.

Table I: 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis[9]

Classification criteria*	Score
A. Joint involvement	
• 1 large joint	0
• 2-10 large joints	1
• 1-3 small joints (with or without involvement of large joints	2
• 4-10 small joints (with or without involvement of large joints)	3
• > 10 joints (at least small joint)	5
B. Serology (at least one test result is needed for classification)**	
• Negative RF and negative ACPA	0
• Low positive RF or low positive ACPA	2
• High positive RF or high positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)	
• Normal CRP and normal ESR	0
• Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
• < 6 weeks	0
• ≥ 6 weeks	1

ACPA: anticitrullinated peptide antibody, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor

*Classification criteria for rheumatoid arthritis (score-based algorithm: Add the score of categories A-D. A score of ≥ 6/10 is needed to classify a patient as having definite rheumatoid arthritis

**Negative refers to IU values that are less than or equal to the upper limit of normal

Interpretation

A low positive refers to IU values that are higher than the upper limit of normal, but ≤ 3 times the upper limit of normal

A high positive refers to IU values that are > 3 times the upper limit of normal for the laboratory and assay

When the rheumatoid factor information or anticitrullinated peptide antibody is only available as a positive result, it should be scored as a low positive

Erythrocyte sedimentation rate and C-reactive protein

These non-specific measures of inflammation are usually, but not always, elevated in patients with active RA. Up to 40% of patients may have a normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) at presentation, despite active disease.[10] The ESR may be affected by multiple factors, such as age, anaemia and immunoglobulin concentration. The CRP may be more specific for inflammation, but elevation may relate to smoking and associated insulin resistance.[11]

Rheumatoid factor, anticitrullinated peptide and antinuclear factor antibodies

RF is an antibody to immunoglobulin G, seen in 80–90% of patients with established RA. It is seen in only 50–60% of patients with early RA. Patients with a positive RF factor tend to have more aggressive disease and extra-articular manifestations. The test is used for diagnostic purposes only, and has no role to play in monitoring response to therapy. Hence, if it is positive once, there is no need to repeat it. A false positive result may occur in the elderly and in numerous unrelated infective or inflammatory conditions, such as tuberculosis, hepatitis and interstitial lung disease.

ACPA has a specificity of approximately 98% for RA, but it is seen in only 50% of patients with early RF disease, and is used for diagnostic purposes only. ACPA positivity is associated with radiographic progression and a poorer prognosis. Testing for ACPA is appropriate if RF is negative in a patient with suspected RA, or if a false positive RF is probable, for example, in the elderly and in patients with hepatitis C.

Antinuclear factor antibodies are directed to nuclear antigens seen in a host of CTDs. Up to 30% of patients have a positive antinuclear factor, with no associated underlying CTD. The presence of ANF may be the clue to the presence of early CTD in patients who have the clinical features of RA and who are sero-negative (RF- or ACPA-negative). An ANF is considered to be positive if the titre is > 1/160. A positive test may reflect in 5% of the normal population. Therefore, the test should only be requested in the presence of suggestive clinical features and not for non-specific arthralgia.

Imaging

Plain radiographs of the hand and feet may reveal the presence of erosive disease and joint space narrowing. However, they are insensitive in early RA, as erosions are seen only after 1–2 years of disease. Newer imaging modalities, such as ultrasound and MRI, are able to detect synovitis and erosive disease very early in the course of the disease. Internationally, ultrasound is gradually being incorporated into routine rheumatological practice for diagnosis and sonar-guided infiltrations. Lack of expertise limits widespread use locally. MRI offers a more objective assessment of synovitis and bony involvement, but cost and accessibility limit its use in routine clinical practice.

Co-morbidity of chronic inflammation

Uncontrolled chronic inflammation results in the obvious local effects of joint destruction, deformity and consequent disability. However, inflammation can have systemic effects. RA has been found to be associated with premature atherosclerosis, osteoporosis and depression.

Proinflammatory cytokine levels are elevated in the systemic circulation in patients with RA, and this has several proatherogenic effects by affecting endothelial cell function, altering lipid metabolism and promoting insulin resistance. All of these result in RA being an independent risk factor for

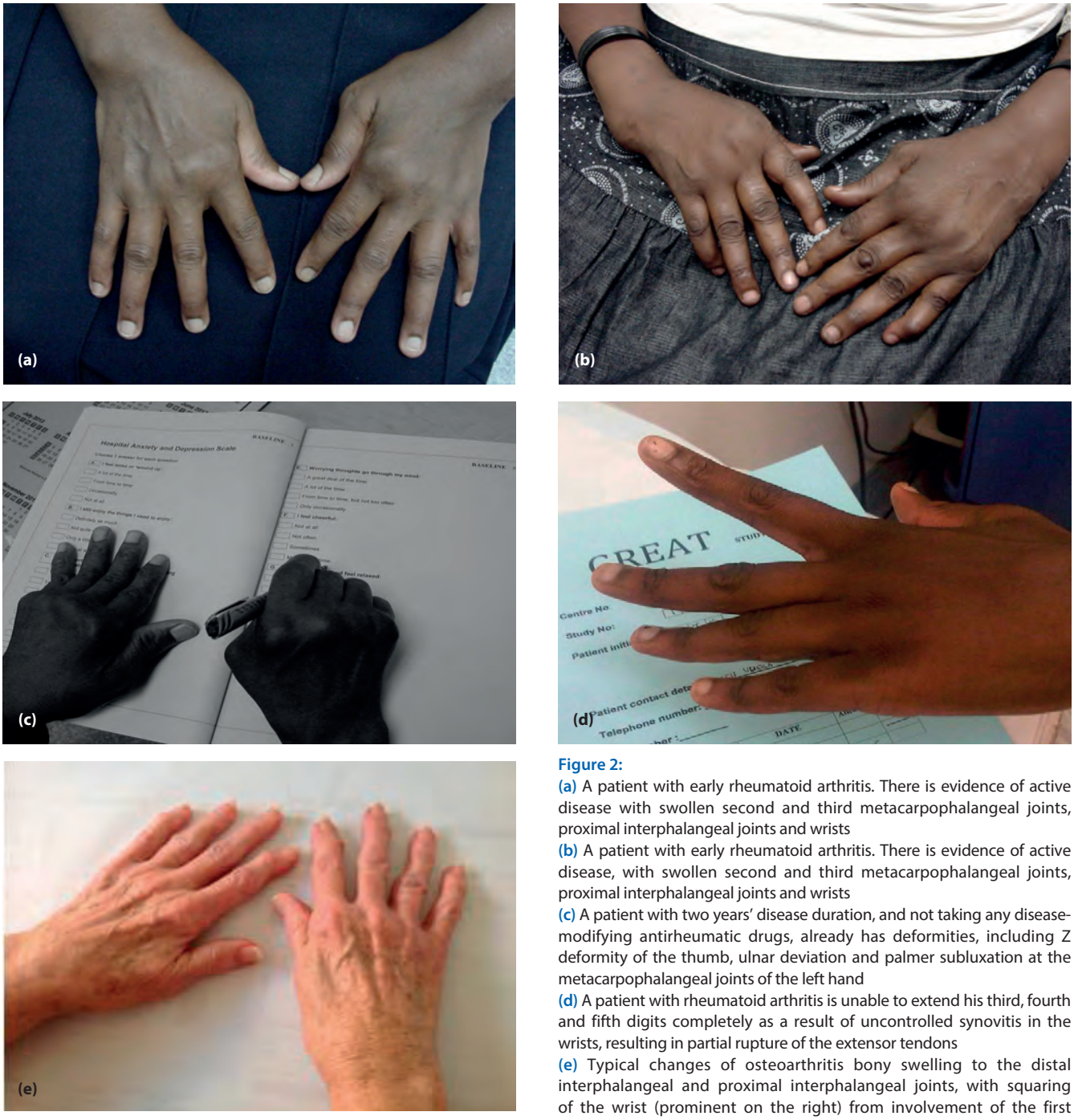

Figure 2:
(a) A patient with early rheumatoid arthritis. There is evidence of active disease with swollen second and third metacarpophalangeal joints, proximal interphalangeal joints and wrists
(b) A patient with early rheumatoid arthritis. There is evidence of active disease, with swollen second and third metacarpophalangeal joints, proximal interphalangeal joints and wrists
(c) A patient with two years' disease duration, and not taking any disease-modifying antirheumatic drugs, already has deformities, including Z deformity of the thumb, ulnar deviation and palmer subluxation at the metacarpophalangeal joints of the left hand
(d) A patient with rheumatoid arthritis is unable to extend his third, fourth and fifth digits completely as a result of uncontrolled synovitis in the wrists, resulting in partial rupture of the extensor tendons
(e) Typical changes of osteoarthritis bony swelling to the distal interphalangeal and proximal interphalangeal joints, with squaring of the wrist (prominent on the right) from involvement of the first carpometacarpal joint

ischaemic heart disease, comparable to the effect seen in type 2 diabetes.[12]

Synovitis results in erosive bony changes mediated by activated osteoclasts at the junction of bone and the proliferating synovium, called the pannus. Normal bone turnover is a dynamic process that maintains homeostasis with a balance between bone resorbing (osteoclast) and bone-forming cells (osteoblasts). The proinflammatory cytokine milieu, both locally and systemically, enhances osteoclastic activity, resulting in periarticular and generalised osteopenia.[13]

Patients with RA have a much higher prevalence of depression than the general population. Depression in RA is associated with disease activity, increased work disability and poor compliance. The effect of chronic disease plays a significant role, but abnormal proinflammatory cytokine profiles have also been demonstrated in patients with primary depression.[14]

Therapy

Disease control within 3–6 months, as well as aiming for remission or at least a low disease activity state, are key principles in the management of RA. An important pitfall in the management of patients with early RA is providing "reassurance" about disease control using pain management. Initially, many patients' symptoms improve significantly with pain management, especially if combined with corticosteroids, but often, a comprehensive review reveals ongoing disease activity. Ongoing disease activity is associated with joint damage, and studies in manual labourers with RA demonstrated loss of work ability within two years of disease onset. Thus, measuring disease activity is paramount to guiding

therapy in order to bring the disease under control within 3–6 months.

Measures of disease activity

Unfortunately, no single measure has been shown to correlate well with disease activity and consequent disease progression. The ESR and CRP are used as measures of activity in many inflammatory disorders, but have significant limitations as individual parameters in patients with RA. Composite disease activity measures have been validated to assess and monitor disease activity. These are various different scoring systems that incorporate responses to patient questionnaires on function and pain, clinical assessment of the number of swollen tender joints, the duration of morning stiffness and ESR or CRP. The Simplified Disease Activity Index (SDAI) is a practical scoring system advocated by many for routine clinical use.

The SDAI is a summation of:

- The number of swollen and tender joints count and an evaluation of bilateral shoulders, elbows, wrists, MCPs, PIPs and knees (28 joint count).
- Physician global assessment of activity, noted on a scale of 0–10 with "0" representing low activity and "10" high.
- A patient global activity score, also out of 10.
- The CRP in mg/dl.

A score of > 26 reflects high disease activity, > 11 ≤ 26 moderate disease activity, > 3 ≤ 11 low disease activity, and ≤ 3.3 remission. Ongoing disease activity is associated with radiographic progression, disability, morbidity and premature mortality. The objective is to achieve at least a low disease activity score, with remission being the desired goal. With recent advances in the pharmacological management of RA, this target is certainly achievable in the majority of patients.

Pharmacological therapy

Recommendations for the management of RA in South Africa have been published, and include an algorithm with appropriate therapies and appropriate timelines.[15] Disease-modifying antirheumatic drugs (DMARDs) remain the cornerstone of RA management. Tremendous advances in this class of drugs have revolutionised the management of RA, and also therapy across the spectrum of immune-mediated inflammatory disorders. Two subclasses have now been identified, namely synthetic DMARDs (sDMARDs) or biological DMARDs (bDMARDs).

sDMARDs, also sometimes referred to as "traditional DMARDs", include drugs such as choloroquine, salazopyrine, methotrexate and leflunomide. Methotrexate is the anchor drug in the management of patients with RA.

Methotrexate is a folic-acid antagonist that blocks purine and pyrimidine synthesis, required for nucleotide formation. Inhibiting nucleotide formation results in the prevention of cellular proliferation in predominantly rapidly dividing cells, which include cellular components of the immunoinflammatory response.[16] Inhibition of cellular proliferation also occurs in normal compartments, such as the gastrointestinal tract and bone marrow, and accounts for some of the side-effects seen, such as oral ulcers, diarrhoea and cytopenias. Co-administration of folic acid, 5 mg daily, decreases these side-effects, with only a minor impact on efficacy. Methotrexate exerts these effects only after undergoing an intracellular chemical change of polyglutamation. Polyglutamated methotrexate can remain active intracellularly for days, despite the drug being cleared from the systemic circulation within a few hours, hence the reason for the recommended weekly dosage. The usual initiating dose is 10–15 mg weekly, with a maximum dose of 25 mg weekly. Side-effects, including hepatitis, interstitial lung disease, mucositis, gastrointestinal disturbances and bone marrow suppression, must be monitored. Methotrexate should be avoided in patients with renal dysfunction, liver or pulmonary disease. It is teratogenic. Triple therapy, combined with chloroquine and salazopyrin, may be considered in patients with poor prognostic features.

Chloroquine and salazopyrin may be used as monotherapy in mild disease or if methotrexate is contraindicated. It is important to monitor retinal toxicity with yearly opthalmological assessments in patients on chloroquine. Salazopyrine has a sulphur moiety and should be avoided in patients with a sulphur allergy.

Leflunomide is a pyrimidine antagonist, similar to methotrexate in blocking cellular proliferation, and can be used as an alternative to methotrexate, but is commonly used after methotrexate failure. It has a long half-life and an enterohepatic circulation that results in elevated serum levels months after the drug has been stopped. This is an important consideration in females planning a pregnancy as special washout regimens need to be followed. Longer disease duration prior to starting sDMARD therapy is associated with a poorer response. However, 70–80% of patients will have an acceptable response to therapy with the appropriate use of DMARDs in early RA. Patients with an inadequate response will benefit from bDMARDs, albeit at a higher cost.

bDMARDs have changed the landscape of RA therapy, with marked improvement in up to 70% of patients who have failed the previously referred to therapy. These drugs target specific components of the immunoinflammatory response. Currently, available drugs in South Africa antagonise proinflammatory cytokines (TNF and IL-6), *T*-cell function and *B*-cell proliferation. bDMARDs are generally well tolerated. Specific precautions and patient screening are required to minimise side-effects, and most importantly infections, e.g. reactivation tuberculosis. Therefore, use of these agents is restricted to specialist care.

Despite the fact that pain management does not modify disease progression, it still remains an integral component in RA management. Pain management includes prudent use of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), using the lowest dose required, combined with gastroprotective agents in patients at high risk of peptic ulcer disease. NSAIDs should be avoided in patients with renal dysfunction and used with caution in patients with ischaemic heart disease, particularly if the patients are on aspirin. The protective effect of aspirin on ischaemia may be lost if combined with some NSAIDs as they compete with the same binding sites on platelets. If it is considered necessary to use the combination, then the dosage times must be separated by at least three hours. It is also essential to monitor changes in blood pressure when initiating an NSAID, as some patients may develop hypertension.

Corticosteroids play a dual role in RA management, with excellent relief of symptoms, especially in early disease, and modified disease progression to a limited extent. Corticosteroids are often given as a pulse, either intramuscularly or orally. If given orally, then use the lowest possible dose orally over a six-month period, and aim for complete weaning

thereafter. Corticosteroids that are used in early RA may mask ongoing disease and joint damage as they have the potential to delay appropriate therapy because their symptomatic effect is so great that patients' functionality markedly improves. Certainly, there is no role for corticosteroids as monotherapy for disease modification. Rather, they play an adjunctive role with other DMARDs.

Nonpharmacological therapy

A multidisciplinary approach to patients with RA is vital. Allied health disciplines, such as physiotherapists, occupational therapists, podiatrists and nutritionists, provide an important supportive role. Educating patients about their disease improves compliance and outcome. Specific counselling to deal with psycho-social matters and the cessation of smoking should be incorporated in the management plan.

Challenges to the management of rheumatoid arthritis in South Africa

Early diagnosis and management of patients with early RA, especially in the public sector is of concern. Hodkinson et al demonstrated a high disease burden on presentation in a recent study on 171 patients with early RA and attending public sector rheumatology clinics. Only 28% of the patients achieved a low disease activity state at 12 months under routine care. Over 60% of patients in this study experienced substantial functional disability and suboptimal mental health after one year of therapy.[17] As shown in this and other studies, a low level of schooling was identified as one of the poor prognostic features.

Socio-economic factors and access to health services are obvious challenges that affect the optimal management of RA. Biological therapies are expensive and may also predispose to specific infections, such as tuberculosis. The direct cost of biological therapies needs to be balanced with the potential for decreasing the social and economic burden that is passed to the public health system. Guidelines have been established for the appropriate use of DMARDs, including biological therapies in South Africa. Their use is steadily becoming available in the public sector.

Conclusion

RA is a chronic inflammatory disorder with considerable morbidity. Monitoring of co-morbidity, such as increased cardiovascular risk, needs to be incorporated into management strategies. Early diagnosis and aggressive therapy result in improved prognosis for most patients. The introduction of DMARD therapy early in the disease course, with frequent follow-up, while aiming for rapid and measurable disease control, is inexpensive and effective in most patients. The judicious use of biological therapies has given hope to patients with RA. *South African recommendations for the management of rheumatoid arthritis: an algorithm for the standard of care in 2013* is a recommended resource.[15]

Acknowledgement — Barbara English from the research office of the University of Pretoria's Faculty of Health Sciences is thanked for language editing.

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