Modern management of rheumatoid arthritis – making a case for early aggressive medical treatment

Tikly M, FRCP, PhD (Wits)
Division of Rheumatology, Chris Hani Baragwanath Hospital and University of the Witwatersrand, Johannesburg
Correspondence to: Professor Mohammed Tikly, e-mail: tikly.mohammed01@gmail.com
Keywords: rheumatoid arthritis; early intervention; disease-modifying anti-rheumatic drugs

Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects approximately 1% of the adult population. Some 30 to 40% of patients experience work disability within five years of onset of the disease, but early aggressive medical treatment has vastly improved the long-term outcome of RA. The combination of simple clinical tools to measure disease activity, the use of traditional disease-modifying anti-rheumatic drugs (DMARDs) early in the course of the disease and the introduction of targeted biologic agents for DMARD-resistant disease has greatly reduced the risk of joint deformities, physical disability and premature death. The family practitioner, by suspecting RA early in its course and jointly monitoring efficacy and toxicity of DMARDs with the rheumatologist, plays a pivotal role in improving the care and outcome of the RA patient.

SA Fam Pract 2009;51(4):284-290

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterised by persistent inflammation of synovial joints that, if left untreated, results in joint deformity and destruction. The disease affects approximately 1% of the adult population, is three to five times more common in women, and has a peak age of onset of 40 to 60 years. Between 30 to 40% of patients experience work disability within five years of onset of the disease.[1] Life expectancy is also reduced by about 10 years, especially in patients with poorly controlled disease, mainly due to accelerated cardiovascular disease, infections and respiratory complications.[2]

The long-term outcome of RA has vastly improved in the past two decades.[3] Several factors have contributed to this change, ranging from advances in the fundamental understanding of the aetiopathogenesis of the disease and better clinical methods to assess disease activity and joint damage, to early initiation of disease-modifying anti-rheumatic drug (DMARD) therapy.

Underpinning this paradigm shift to early aggressive treatment in RA are observations in longitudinal studies that show that 1) self-remitting disease is rare; 2) joint destruction is a function of the disease duration and active inflammation (Figure 1)[4] and 3) tight control of inflammation, especially early in the course of the disease with DMARDs, reduces long-term morbidity and mortality.[3,5] This review will briefly cover aspects of the aetiopathogenesis, diagnosis, current approaches to the treatment of RA and monitoring response to therapy.

Aetiopathogenesis

The cause of RA remains elusive. The synovial inflammation of RA, as in the case of other autoimmune diseases, appears to be triggered by exposure to an exogenous/infectious agent(s) in the genetically susceptible individual. The major genetic risk factor, present in up to 90% of patients with RA, is the 'shared epitope', a common amino acid

Figure 1: Time course of inflammation and joint destruction in rheumatoid arthritis
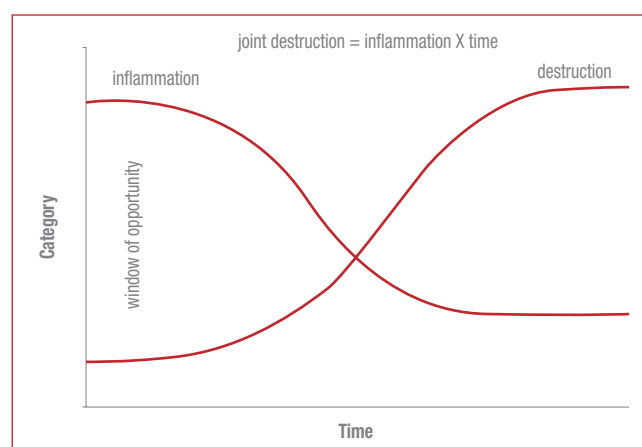
sequence (glutamine-leucine-arginine-alanine-alanine) found in positions 70–74 of the β chain of HLA-DR4 and DR1 alleles.[6] Mycoplasma species, the Epstein-Barr virus and the parvovirus are the microbes that have been most widely implicated as infectious triggers. Smoking increases both susceptibility and severity of RA.[7]

Synovial cell hyperplasia, resulting from infiltration of synovium by CD4 T-cells, macrophages and fibroblasts, together with angiogenesis and endothelial cell activation, are early pathologic events.[8] The exuberant proliferation of synovium, known as pannus, invades and destroys adjacent cartilage and bone, which on plain radiography manifests as joint space narrowing and marginal bone erosions respectively. Cartilage collagen and matrix destruction is mediated by matrix metalloproteinases and cathepsins. Abnormal production of numerous cytokines by synovial macrophages, especially TNF-α, interleukin (IL)-1 and IL-6, play a key role in bone destruction. B-lymphocytes produce autoantibodies such as rheumatoid factor (Figure 2).[9]

Figure 2: Pathways involved in inflammation and destruction in the rheumatoid joint
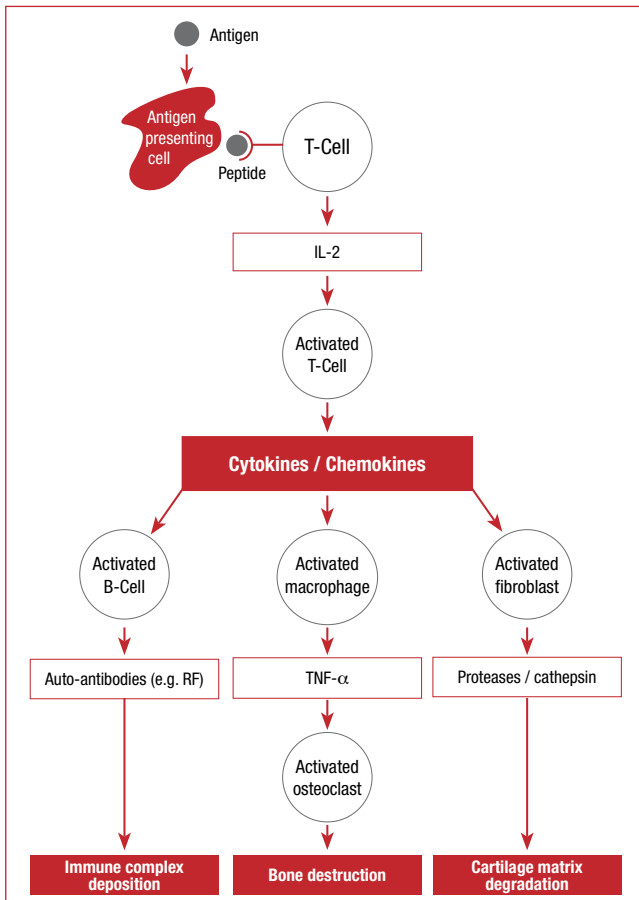
Clinical features and diagnosis

There is no single physical sign or laboratory test that is diagnostic of RA. Hence, the diagnosis of RA is based on the presence of a constellation of symptoms, signs, serological findings and radiographic abnormalities. Typically, RA presents as an insidious, progressive illness with pain, stiffness and swelling of the wrists, small joints of the hands, elbows, shoulders, knees, ankles and feet. Symptoms of malaise, fever and weight loss are common but non-specific. On examination, there is evidence of a symmetrical polyarthritis, manifesting as swelling and tenderness of the joints. Hand involvement invariably occurs sometime in the course of the disease. Indeed, the diagnosis of RA should not be made in the absence of synovitis of the wrists and/or small (metacarpophalangeal and proximal interphalangeal) joints of the hands. Subcutaneous nodules over the extensor surface of the elbows and fingers occur in about one-quarter of patients with established disease, more especially in smokers and in patients who are rheumatoid factor positive.[10] Systemic features of RA, such as vasculitis and serositis, are rare early in the course of the disease. About one-fifth of patients experience sicca symptoms of dry/gritty eyes and dry mouth.

Classification criteria for RA[11] (Table I) were developed primarily as a means of standardising patient populations for clinical research, but are widely used to diagnose RA in clinical practice. These criteria were originally developed on the basis of clinical features in a group of patients with established disease (mean disease duration > 7 years). Not surprisingly, these criteria are less useful in the setting of early RA and, hence, an expert group has proposed clinical guidelines for suspected early RA (Table II).

Table I: ACR classification criteria for rheumatoid arthritis[11]

The diagnosis of rheumatoid arthritis requires the presence of at least four of the following seven features:
1. Stiffness in and around the joint that lasts for one hour before maximal improvement.
2. Arthritis (soft tissue swelling or fluid) in three or more joint areas simultaneously (observed by physician).
3. Arthritis involving the proximal interphalangeal, metacarpophalangeal or wrist joints.
4. Symmetric arthritis.
5. Rheumatoid nodules (subcutaneous, over prominences or extensor surfaces).
6. Positive serum rheumatoid factor test.
7. Radiographic changes of rheumatoid arthritis (e.g. erosions, periarticular osteopaenia).

* The diagnosis of rheumatoid arthritis requires that four of the seven criteria be observed and that the first four (1 through 4) must be present for at least six weeks.

Table II: Clinical features suggestive of early rheumatoid arthritis[12]

- Early morning stiffness > 30 minutes
- ≥ 3 swollen joints
- Positive squeeze test (pain elicited on squeezing metacarpals or metatarsals)

Laboratory tests

Rheumatoid factor (RF) is an antibody, typically of the IgM class, directed against self-IgG. It is detectable in 70 to 80% of patients with established RA but less so in patients with early disease.[13] The test lacks specificity and can be positive in other chronic inflammatory and infectious diseases, such as systemic lupus erythematosus, tuberculosis, sarcoidosis, infective endocarditis and chronic liver disease. Low titres of RF are sometimes also detectable in apparently healthy individuals, especially in the elderly and smokers. The more recent discovery of antibodies to cyclic citrullinated peptide (anti-CCP) in RA has proved to be particularly helpful in the diagnosis of early disease.[14] The test has similar sensitivity to RF (70–80%), but its much higher specificity (> 95%) makes it especially useful in early disease where the diagnosis of RA is often in doubt. The antinuclear antibody test is positive in about 20% of patients, but, in general, is not indicative of an overlap connective tissue syndrome.

The acute phase reactants, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often elevated with active inflammation but are not specific diagnostic features of RA. Other features of active disease are a mild normochromic, normocytic anaemia and thrombocytosis.

Radiology

The typical radiographic features of RA are joint space narrowing, juxta-articular osteopaenia and marginal bone erosions. Erosions are rarely visible early in the course of the disease, but by two years more than 70% of patients will show evidence of erosive damage on plain radiographs.[15] Radiographs of both the hands and feet are necessary for

diagnostic purposes, bearing in mind that erosions are first evident in the metatarsophalangeal joints in about 40% of patients. It is unnecessary to X-ray other affected joints except to assess the extent of damage in a specific joint when surgery is being considered.

Management

The primary goals of treatment in RA are to 1) reduce pain and discomfort, and 2) prevent or minimise physical disability.[16] The principles of treatment are summarised in Table III.

Table III: Principles of medical management of rheumatoid arthritis

- Ensure diagnosis of RA is correct.
- Provide joint protection education.
- Discourage cigarette smoking.
- Early intervention with DMARDs for all patients with persistent synovitis.
- Adjunctive treatment with analgesics (e.g. paracetomol) and NSAIDs for pain control.
- Intra-articular steroids for the treatment of one or a few actively inflamed joints.
- Oral corticosteroids in low doses ($\leq$ 10 mg/day) as 'bridging therapy' in combination with DMARDs.
- Biologics for DMARD-refractory disease.

Symptom-modifying ('first-line') drugs

Simple analgesics, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs), including the selective COX-2 inhibitors (COXIBs), are effective in relieving pain and stiffness. Importantly, none of these drugs have any effect on the underlying disease process. These drugs are especially useful early in the course of the disease before the diagnosis of RA is confirmed, and for patients who have an inadequate response to DMARDs. At maximum therapeutic doses, all NSAIDs are roughly equipotent, but importantly, clinical response to any specific NSAID is highly variable in RA. Hence, failure to respond to the maximum therapeutic or tolerable dose of a particular NSAID after a trial of two to three weeks is an indication to change to another NSAID. Because of the potentially serious gastrointestinal, renal and cardiovascular side effects, NSAIDs should be used judiciously in the long term.[17] Guidelines to minimise NSAID toxicity are summarised in Table IV.

Traditional disease-modifying anti-rheumatic drugs

This class of drugs has the potential, either as monotherapy or in combination, to alter the underlying chronic inflammatory process. Since

Table IV: Strategies to minimise NSAID toxicity

- Prescribe only one NSAID at a time.
- Prescribe the lowest effective dose and for the shortest time.
- Educate the patient to take NSAID with meals.
- Alert the patient of warning symptoms of side effects such as epigastric pain, haematemesis, melaena stools and light-headedness.
- Avoid NSAIDs in patients with renal dysfunction, a history of peptic ulceration and GI bleeding, a history or significant risk factors for cardiovascular disease (ischaemic heart disease, stroke), cardiac failure, uncontrolled hypertension and a history of bleeding diathesis and those on anticoagulant therapy.
- In patients at high risk for GI complications, prescribe a COX-2 inhibitor or non-selective NSAID with a proton pump inhibitor. In the elderly, avoid long-acting non-selective NSAIDs and consider low dose prednisone as an alternative to NSAIDs for symptom relief.

the clinical effects of these drugs are only apparent after a period of a few weeks to months, they are sometimes referred to as 'slow-acting anti-rheumatic drugs'. They include methotrexate (MTX), sulphasalazine, chloroquine and leflunomide. Because of its superior efficacy, MTX is now the most widely prescribed DMARD worldwide. It is often prescribed as monotherapy, but is also very effective in combination with other traditional DMARDs. In general there have been two approaches to combination therapy. The 'step-up' approach is where one or two DMARDs are added to the 'anchor' DMARD for patients who have an inadequate response to DMARD monotherapy. The alternative approach is the more aggressive 'step-down' approach where triple DMARD therapy (often in combination with low-dose prednisone) is initiated early, with gradual reduction in the number of DMARDs and withdrawal of prednisone in patients who have sustained remission. The most effective combinations are those that include MTX as the 'anchor' drug. Chloroquine (or hydroxychloroquine, which is not registered in South Africa) has a synergistic effect with MTX in controlling rheumatoid synovitis. Adding sulphalasazine to this combination may confer further benefit in inadequate responders. Leflunomide, although effective as monotherapy, also works well in combination with MTX. Because of the potential serious side effects of all DMARDs, dosages, contraindications and regular blood monitoring need careful attention (Table V).

Corticosteroids

Corticosteroids (CS) are very effective in controlling inflammation in RA, but because of the risk of toxicity, especially osteoporosis, their use is restricted to low dose oral CS in low dose (prednisone $\leq$ 10 mg/day) as bridging therapy during the initial three to six months of DMARD therapy. Of note is that oral CS are never to be prescribed as monotherapy to control rheumatoid synovitis – they are only prescribed in combination with DMARDs in RA. Higher doses of oral CSs are sometimes necessary for extra-articular manifestations such as serositis and vasculitis. Intra-articular CS, either methylprednisolone, triamcinolone or betamethazone, have a major role in the local treatment of synovitis. In general, no more than four joints should be injected at any one time and no joint should be injected more than three to four times a year.

Biologics

The introduction of biologics, in particular the tumour necrosis factor -α (TNF-α) antagonists, just over a decade ago has been a major advance in the treatment of RA. These drugs have vastly improved the outlook for RA patients in industrialised countries,[18] but because these agents are so expensive, their use in the developing world is limited. Guidelines and indications for the use of biologics in South Africa are available on the South African Rheumatism and Arthritis Association website (http://www.saraa.co.za/Bio_guide001.asp).

TNF-α antagonists

There are presently three TNF-α antagonists registered in South Africa for the treatment of DMARD-refractory RA. They are all effective in reducing inflammation, improving functional disability and reducing the rate of joint destruction. Etanercept, a fusion protein of p75 TNF receptor linked to the Fc portion of human IgG, is administered subcutaneously (sc), 25 mg twice weekly or 50 mg weekly. Infliximab, a chimeric monoclonal antibody against TNF-α, is administered at doses of 3 mg/kg IV at weeks 0, 2 and 6 and then every four to eight weeks, and adalimumab, a recombinant human monoclonal antibody specific for human TNF-α, is administered sc, 40 mg every other week. All of these drugs are more effective when co-prescribed with MTX. There are no significant differences in efficacy between the three drugs.

Table V: Traditional disease modifying anti-rheumatic drugs

Drug	Dose	Adverse effects	Contraindications	Monitoring
Methotrexate	7.5–25 mg/week po/im/sc Folate 5 mg/week (at least 24 hours after MTX dose)	GI intolerance, mouth ulcers, headache, alopecia, bone marrow suppression, hepatoxicity, hypersensitivity pneumonitis, infections	Chronic liver disease, alcoholism, hepatitis B or C infection, advanced HIV infection, pregnancy	Baseline: FBC, LFT; Follow-up: FBC, AST/ALT every 2–4 weeks, then every 8–12 weeks.
Chloroquine	200 mg daily (4 mg/kg of chloroquine base)	GI intolerance, 'bulls eye' maculopathy, hyperpigmentation, neuromyopathy	Advanced age, renal dysfunction	Opthalmological examination at baseline and 6–12 months thereafter.
Sulphasalazine	2–3 g/day in two divided doses	GI intolerance, erythema multiforme, headache hepatotoxicity, thrombocytopaenia, agranulocytosis	Sulphasalazine-induced erythema multiforme-like rash	Baseline FBC, LFT; Follow-up: FBC, AST/ALT every 2–4 weeks, then every 12–16 weeks.
Leflunomide	10–20 mg daily	Diarrhoea, alopecia, nausea, LFT abnormality, rash, bone marrow suppression	Pregnancy	Baseline: FBC, LFT; Follow-up: FBC, AST/ALT every 2–4 weeks, then every 8–12 weeks.
Cyclosporine	2.5–4.5 mg/kg in two divided doses	Hypertension, nephropathy, gingival hyperplasia, hirsuitism, GI intolerance, hyperuricaemia	Nephropathy, uncontrolled hypertension, pregnancy	Baseline BP U & Cr ; Follow-up: BP and U & Cr every 8–12 weeks.
Azathioprine	1.5–2.5 mg/kg daily	GI intolerance, bone marrow suppression, LFT abnormalities	Known azathioprine hypersensitivity	Baseline FBC, LFT; Follow-up: FBC, AST/ALT every 2–4 weeks, then every 12–16 weeks.

GI – gastrointestinal; FBC – full blood count; LFT – liver function test; AST – aspartate aminotransferase; ALT – alanine aminotransferase; BP – blood pressure; U & Cr – urea and creatinine

TNF-α antagonists increase the risk of both common and opportunistic infections, especially disseminated tuberculosis (TB). Patients must be screened for latent or active TB before commencing TNF-α antagonists. Other reported adverse effects are demyelinating disorders (e.g. multiple sclerosis), lupus-like symptoms, aplastic anaemia, lymphoproliferative disorders and congestive heart failure.

Anti-B-cell therapy

The anti-CD20 monoclonal antibody, rituximab, which was initially developed for the treatment of B-cell lymphoma, is indicated for patients who have an inadequate response to TNF-α antagonists. Several novel biologics are currently being tested in clinical trials and some of them are likely to be registered shortly for clinical use in South Africa.

Non-pharmacological interventions

Joint protection education, with the help of the occupational therapist, aids in preventing joint deformities. Cigarette smoking should be strongly discouraged, as it both worsens joint inflammation and increases the risk of cardiovascular disease. Surgery is reserved for soft-tissue complications, like ruptures of the extensor tendons of fingers, and irreversible joint destruction of large joints like the knee and hip, in which case arthroplasty is indicated.

Monitoring response to therapy

Measuring disease activity in RA is critically important for two main reasons: 1) disease activity has direct bearing on the extent of irreversible joint damage and functional disability; 2) to assess response to DMARD therapy. There are several clinical and laboratory indicators of disease activity, including:

• Duration of early morning stiffness
• Severity of pain
• Number of tender and swollen joints
• Global assessment of disease activity by patient or physician
• Degree of functional disability
• Acute phase response (ESR/CRP)

Since no single indicator is sufficiently comprehensive to assess overall joint inflammation, composite scoring systems have been developed.[19] The 28 joint count disease activity score (DAS28) is widely used in clinical trials. The tender and swollen joint counts are best done with the aid of a homunculus (Figure 3). Simplified versions of the DAS[28], the simple disease activity index (SDAI) and clinical disease activity index (CDAI), have been validated for routine clinical practice. The CDAI differs from the SDAI in that it is computed without measuring CRP (Table VI). DMARD therapy is tailored to maintain at least a low disease activity state.

There is now convincing evidence that formally assessing disease activity and adjusting DMARD therapy accordingly have a significant impact on outcome. In the Tight Control of Rheumatoid Arthritis (TICORA) study, patients randomised to the 'intensive' treatment arm, where DMARD therapy was escalated to achieve a target low disease activity state, did significantly better with respect to functional outcome and radiological damage compared to patients in the 'routine' treatment arm, where disease activity scores were not measured and patients were managed at the discretion of the rheumatologist (Figure 4).[20]

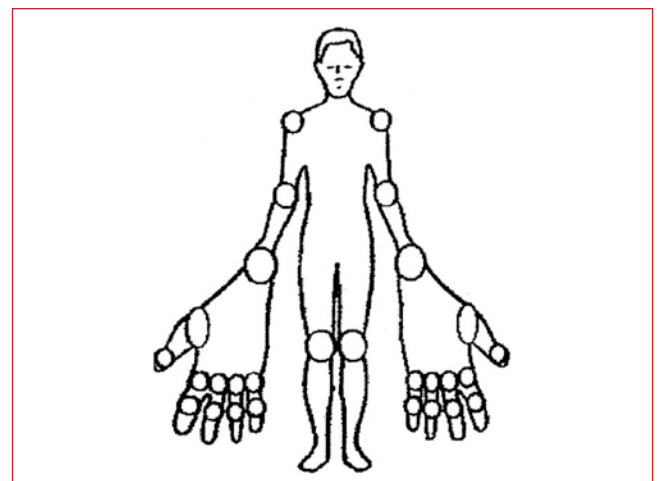**Figure 3: Homunculus used for the 28 joint count in rheumatoid arthritis**

Table VI: Rheumatoid disease activity indices

Component	SDAI	CDAI
Tender joint count*	0–28	0–28
Swollen joint count *	0–28	0–28
Patient global disease activity	0–10	0–10
(VAS in cm)		
Clinician global disease activity	0–10	0–10
(VAS in cm)		
CRP in mg/dL	0–10	-
Range of total index	0.1–86	0.1–76
Cut-off values for disease activity states		
Remission	≤ 3.3	≤ 2.8
Low disease activity	≤ 11	≤ 10
Moderate disease activity	≤ 26	≤ 22
High disease activity	> 26	> 22

SDAI – Simple disease activity index; CDAI – Clinical disease activity index; VAS – Visual analogue scale; *see homunculus (Figure 3).

Figure 4: The TICORA study showing superior outcome with intensive treatment compared to routine care in RA[20]
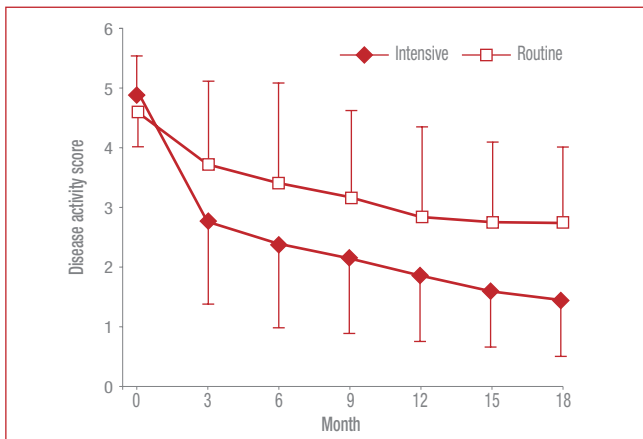
Functional disability

Because active RA has a profound effect on physical function, instruments designed to measure functional status are useful indicators of disease activity, especially in early RA. In late disease, physical disability is mainly an indicator of irreversible joint damage. The ACR classification of functional status in RA can be readily applied in routine clinical practice to assess severity and change in functional disability (Table VII).[21]

Table VII: ACR classification of functional status in rheumatoid arthritis[21]

Class	
Class I	Completely able to perform usual activities of daily living (self-care, vocational and leisure).
Class II	Able to perform usual self-care and vocational activities, but limited in leisure activities.
Class III	Able to perform usual self-care activities, but limited in vocational and leisure activities.
Class IV	Limited in ability to perform usual self-care, vocational and leisure activities.

Prognosis and co-morbidity

The long-term outcome is highly variable. Most patients with RA run a clinical course of exacerbations and remissions. Predicting the course of an individual case at disease onset remains difficult. The poor prognostic factors include[22,23]:

- Onset of disease before 30 years or at advanced age
- Large number of swollen joints
- Severe functional disability at presentation
- Extra-articular manifestations
- Joint erosions early in the course of the disease
- High ESR or CRP
- High titres of RF
- Presence of anti-CCP antibodies

Numerous studies have shown that RA patients are at increased risk of succumbing to cardiovascular complications (strokes and myocardial infarction).[2] General immune dysregulation in RA also predisposes patients to serious infections. The risk of TB is increased even in the absence of immunosuppressive drugs and TNF-α antagonists.[24]

Conclusion

Rheumatoid arthritis is now an imminently treatable condition. The combination of simple clinical tools to measure disease activity, the use of traditional DMARDs early in the course of the disease and the introduction of targeted biologic agents for DMARD-resistant disease have greatly reduced the risk of joint deformities, physical disability and premature death. The challenge for the family practitioner is to diagnose the condition early and to refer the patient to a rheumatologist for appropriate DMARD therapy.

References

1. Burton W, Morrison A, Maclean R, Ruderman E: Systematic review of studies of productivity loss due to rheumatoid arthritis. Occup Med (Lond) 2006, 56(1):18–27.
2. Naz SM, Symmons DP: Mortality in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007, 21(5):871–883.
3. Strand V, Singh JA: Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care 2008, 14(4):234–254.
4. Welsing PM, Landewe RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, Swinkels HL, van der Heijde DM: The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004, 50(7):2082–2093.
5. Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW: Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007, 66 Suppl 3:iii56–60.
6. Gorman JD, Criswell LA: The shared epitope and severity of rheumatoid arthritis. Rheum Dis Clin North Am 2002, 28(1):59–78.
7. Vittecoq O, Lequerre T, Goeb V, Le Loet X, Abdesselam TA, Klemmer N: Smoking and inflammatory diseases. Best practice & research 2008, 22(5):923–935.
8. Machold KP, Nell V, Stamm T, Aletaha D, Smolen JS: Early rheumatoid arthritis. Current opinion in rheumatology 2006, 18(3):282–288.
9. Muller-Ladner U, Pap T, Gay RE, Neidhart M, Gay S: Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheumatol 2005, 1(2):102–110.
10. Mikuls TR, Hughes LB, Westfall AO, Holers VM, Parrish L, van der Heijde D, van Everdingen M, Alarcon GS, Conn DL, Jonas B et al: Cigarette smoking, disease severity and autoantibody expression in African Americans with recent-onset rheumatoid arthritis. Ann Rheum Dis 2008, 67(11):1529–1534.
11. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS et al: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988, 31(3):315–324.
12. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS: Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis 2002, 61(4):290–297.
13. van Boekel MA, Vossenaar ER, van den Hoogen FH, van Venrooij WJ: Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res 2002, 4(2):87–93.
14. Niewold TB, Harrison MJ, Paget SA: Anti-CCP antibody testing as a diagnostic and prognostic tool in rheumatoid arthritis. QJM 2007, 100(4):193–201.
15. Boonen A, van der Heijde D: Conventional x-ray in early arthritis. Rheum Dis Clin North Am 2005, 31(4):681–698.
16. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 2002, 46:328–346.
17. Pham K, Hirschberg R: Global safety of coxibs and NSAIDs. Curr Top Med Chem 2005, 5(5):465–473.
18. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Sieper J, Emery P, Keystone EC, Schiff MH, Mease P et al: Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis 2007, 66 Suppl 3:iii2–22.
19. Dougados M, Aletaha D, van Riel P: Disease activity measures for rheumatoid arthritis. Clin Exp Rheumatol 2007, 25(5 Suppl 46):S22–29.
20. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004, 364(9430):263–269.
21. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F: The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1991, 35:498–502.
22. Morel J, Combe B: How to predict prognosis in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005, 19(1):137–146.
23. Kalla AA, Stanwix A, Gotlieb D, Asherson RA, Mody GM: Rheumatoid arthritis: clinical guideline 2003. S Afr Med J 2003, 93(12 Pt 2):991–1012.
24. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmarti R: Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003, 30(7):1436–1439.