

Rheumatoid Arthritis

David Kill

Rheumatoid is a systemic inflammatory disease that commonly affects the synovial joints of the body to cause arthritis. This article will focus on the latter aspect of rheumatoid disease.

Rheumatoid arthritis (RA) usually affects the small joints of the hands and feet, but larger joints, such as the knees, may be affected and involvement of the upper neck may have particularly serious consequences. The distribution of affected joints is strikingly symmetrical.

The incidence of RA is around 1% in the UK. Most patients first present in their 30s or 40s and two-thirds are women. Children may be affected by juvenile RA.

RA is a disease predominantly of Anglo-Saxon populations and, like other diseases of autoimmune origin such as multiple sclerosis and Type 1 (insulin-dependent) diabetes, shows a definite decrease in prevalence from North to South.³ It is a multifactorial disease, but has a clear inherited component. In particular, disease severity is greater in patients positive for HLA-DR4.

RA causes considerable morbidity and significant mortality. Patients are usually affected during their most productive years and may require considerable time off work during disease flares. They may become disabled as the disease progresses and be unable to continue in work, sometimes requiring care from relatives or outside agencies. Life expectancy in sufferers is reduced by some seven years. It is worth pointing out that some of the morbidity and mortality is related to the treatment of RA and not the disease itself.

Rheumatoid has many systemic manifestations and mortality is higher in patients with extra-articular disease.⁴

It is generally believed that RA is initiated when an unknown insult triggers an autoimmune response that attacks the synovial joints and

other tissues. Unknown factors result in a perpetuation of this response and continuing joint destruction. Interested readers are referred to the recent comprehensive review of the disease process in RA by Choy and Panayi.⁵ In later stages of joint damage, osteoarthritis may complicate the picture.

The course of the disease is variable. The prognosis of acute onset (within 24 hours) RA is good, whereas that of insidious onset RA is poor. There is evidence that the initial sites of inflammation in the two classes of RA may be different.⁶

Diagnosis & assessment

Patients with RA suffer pain, disability and general ill health. The American Rheumatism Association (ARA), now the American College of Rheumatology¹³ (ACR), proposed diagnostic criteria for RA in 1956 and the revised criteria, published in 1987, are now used in clinical practice and as standard inclusion criteria for clinical trials.⁷ The criteria are:

- Morning stiffness in and around joints lasting at least one hour before maximal improvement.
- Soft tissue swelling (arthritis) of three or more joint areas observed by a physician.
- Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints.
- Symmetrical swelling (arthritis).
- Rheumatoid nodules
- Rheumatoid factor
- Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

RA is defined by the presence of four or more criteria for at least six weeks. Most trial protocols require patients to have had RA for at least six months in order to exclude patients with self-limiting disease.

Disease activity and severity are assessed by standard means that are common to the clinic and to clinical trials.

Articular pain is a major problem, perhaps the major problem, for patients and the



measurement of pain relief is probably the most important single assessment for all therapies. Pain intensity is usually assessed by means of a visual analogue scale. This consists of a plain horizontal 10cm line, the left end corresponding to "no pain" and the right end to "pain as bad as it could be." The patient is asked to mark the point on the scale corresponding to their level of pain by drawing a single line across the scale at that point. The pain intensity is taken to be the distance in millimetres from the left end of the scale to the line drawn by the patient.

Painful and swollen joints may be counted and scored. A number of articular indices have been described involving varying numbers of joints, but most studies now use the 28 joint index described by Fuchs et al.⁸ Scoring joints involves pressing on the joints and assessing the degree of discomfort experienced by the patient using a three-point scale, or assessing the degree of swelling using a similar scale.

The duration of morning stiffness is determined as an indicator of inflammation. It can be severe, and many patients take an anti-inflammatory analgesic drug on waking and then go back to bed for an hour or so until the stiffness wears off before beginning their daily activities. Morning stiffness is of great significance to patients and so is almost invariably assessed in clinical trials, but because of its variability it is not generally regarded as a useful outcome measure⁹.

Grip strength may be measured using a sphygmomanometer and a bag that the patient grips as tightly as possible. The pressure is read off the scale in mm Hg and the average of three readings for each hand recorded. This test seems to have gone out of favour in Phase III trials, but is of relevance to Phase IV and quality of life (QoL) work. The same may be said about measuring the time to walk a set distance.

Markers of the acute phase inflammatory response include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Many markers of bone turnover may also be useful, but are not such good measures of overall disease severity.

Anaemia of chronic disease is common in patients with RA, but they may also have anaemia due to bleeding from the gut as a

consequence of treatment with non-steroidal anti-inflammatories (NSAIDs).

Patient and physician global assessments of disease severity are almost always used. A five-point scale is often used, with grades 1 = asymptomatic, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe.

X-rays and MRI scans of the hands and feet are used to demonstrate the extent of bone erosions and any progression or regression during treatment. MRI is much more sensitive, but expensive. It is important that all images from clinical trial subjects are read centrally by experienced interpreters.

Core sets of data are gathered in the clinic for routine assessment of patients and for use in clinical trials. These include tender and swollen joint counts, pain intensity, ESR or CRP and physician global assessment. Brooks and Hochberg¹⁰ have recently compiled outcome measures for RA and other rheumatic disease.

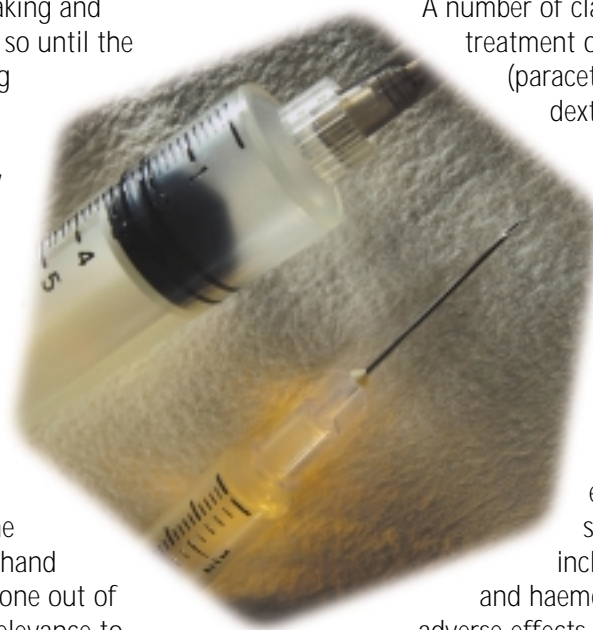
Treatment

A number of classes of drug are used in the treatment of RA including analgesics (paracetamol, alone or with

dextropropoxyphene: codeine),

NSAIDs, disease-modifying anti-inflammatory drugs (DMARDs), steroids and biological agents.

Simple analgesics may be useful in relieving pain, but an NSAID with analgesic and anti-inflammatory activity is usually required as well. NSAIDs are effective drugs, but may cause serious adverse reactions, including gastrointestinal ulceration and haemorrhage. The beneficial and adverse effects of NSAIDs result from their inhibition of the enzyme cyclo-oxygenase (COX), which exists in two isoforms. COX-1 is the constitutive enzyme, responsible for production of 'housekeeping' prostaglandins in the gastric mucosa and kidneys. COX-2 is an inducible enzyme that produces prostaglandins involved in inflammatory responses. An NSAID that inhibits both COX-1 and COX-2 (e.g. indomethacin, piroxicam) has a beneficial anti-inflammatory action, but also reduces the levels of protective prostaglandins in the stomach mucosa. Chronic use may result in mucosal ulceration and subsequent haemorrhage due to the latter effect. Peptic ulceration and its



complications due to NSAIDs are allegedly responsible for 2,000 deaths per year in the UK, mainly of elderly patients. The development of NSAIDs that preferentially (e.g. nabumetone, meloxicam) or selectively (e.g. celecoxib, rofecoxib) inhibit COX-2 should result in less morbidity.¹¹

DMARDs slow down the progression of RA by an effect on the disease process, usually a general 'dampening' effect on the immune system. They include:

- Anti-malarials (hydroxychloroquine).
- Gold, in injectible and oral forms.
- Sulphasalazine, originally developed for the treatment of ulcerative colitis.
- Methotrexate, originally developed for the treatment of cancer.

Steroids may be necessary, either in high-dose, short-term acute therapy of up to 60mg prednisolone/day, or for maintenance at a dose of 10mg or less of prednisolone a day once the disease is under control. Unfortunately, steroids may cause a large number of side-effects, including Cushingoid signs and symptoms and/or osteoporosis in long term use.

A huge breakthrough has been the finding that biological agents, such as agents active against

tumour necrosis factor (TNF), which is thought to play a pivotal role in the inflammatory process, can show dramatic effects in the treatment of RA and slow disease progression. Unfortunately these agents are very expensive. Long-term results are awaited and it may be that the inflammatory cascade bypasses the block, resulting in relapse, although this does not appear to be a problem at the moment. The major hazard with this therapy appears to be increased rates of infection.

Patients presenting with RA used to be treated just with NSAIDs, which damp down the inflammation, but do not affect the progress of the disease. Thus, symptoms and signs were relieved, while the underlying erosive process continued, resulting in joint damage. Patients often continued on NSAIDs for several years until progression of the disease resulted in referral to a rheumatologist. Treatment with DMARDs was then initiated, but much erosive damage to joints might have already occurred.

The understanding that significant erosive damage occurs in the early stages of the disease has led to more aggressive treatment of newly-diagnosed patients with DMARDs in an attempt to stop the disease in its tracks before the joints are permanently damaged. Rheumatologists now encourage colleagues in general practice to refer patients with suspected RA to them immediately, so that DMARD treatment may be initiated promptly if the diagnosis is confirmed. Many rheumatologists now run early arthritis clinics and, in the UK, a network of such clinics has been established to conduct research into this and subsequent phases of the disease. In many cases, DMARD treatment may be continued and monitored by GPs in close consultation with rheumatologists.

Rehabilitation of patients with RA is a sub-specialty in its own right and beyond the scope of this article. Interested readers are referred to the comprehensive textbook on the subject by Clarke et al.¹

Surgical replacement of damaged joints, including small joints of the hands, may eventually be necessary and stabilisation of the neck may be required in some cases.

Clinical trials

Patients with RA are frequently willing to participate in clinical trials, as none of the current treatments is entirely satisfactory and there is always the hope of something better. They also tend to be compliant with therapy, as

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this enables them to avoid pain and discomfort. Many are regular participants in trials and move from one into the next.

There is little excuse for a poorly-designed trial programme these days, as both the FDA and the CPMP have issued guidelines on clinical trials in RA, which are available on their websites. Until recently, the regulatory authorities have insisted on placebo controls in Phase III trials. The pros and cons of this approach have recently been reviewed by Stein and Pincus¹², who concluded that placebo control is not essential. In any case, many rheumatologists refuse to participate in placebo-controlled trials, arguing that once control of the disease is lost it may only be regained with difficulty, if at all.

Many rheumatologists now employ metrologists, who assess patients attending the clinic and who carry out most of the trial procedures. As they tend to know most of their patients well, they can be key to successful recruitment and retention of patients in a trial.

Many studies include a pharmacoeconomic element, which is often tagged on to a study primarily designed to assess efficacy and safety. However, this may not be appropriate and it is crucial to involve experts in pharmacoeconomics in the study design if meaningful results are to be obtained.

Conclusion

The recognition of RA as a serious, crippling and potentially fatal disease has led to early, aggressive treatment with agents able to bring the disease under control. However, keeping it under control and halting its progression remains difficult. It remains to be seen whether the promise of biologicals such as the anti-TNF and anti-IL-1 agents is borne out by clinical experience. The search for new compounds goes on, but there are now signs for hope and the next few years should be exciting ones for clinicians and their patients. However, the high cost of the new biological treatments is likely to be a major issue for some time.



David Kill is Senior Director, Central Planning & Control, Parexel International, a member of the Institute Board of Directors and Deputy Editor of Clinical Research focus.

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References

Book

- 1 Clarke A, Allard L, & Braybooks B (2001): "Rehabilitation Techniques in Rheumatology", Martin Dunitz.

Review

- 2 "Future Trends in the Management of Rheumatoid Arthritis." Rheumatology (1999) 38 (Suppl. 2)

Papers

- 3 Cimmino MA (1999): "Regional differences in the occurrence and severity of rheumatoid arthritis in Europe", CPD Rheumatology 1(1) p28-32.
- 4 Turesson C, Jacobsson L, & Bergstrom U (1999): "Extra-articular rheumatoid arthritis: prevalence and mortality", Rheumatology 38(7), p668-74.

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- 5 Choy EHS & Panayi GS (2001): "Cytokine pathways and joint inflammation in rheumatoid arthritis", *New England Journal of Medicine* 344(12), p907-16.
- 6 McGonagle D, Gibbon W, O'Connor P, et al (1999): "An anatomical explanation for good-prognosis rheumatoid arthritis", *Lancet* 353, p123-4.
- 7 Arnett FC, Edworthy SM, Bloch DA, et al (1988): "The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis", *Arthritis and Rheumatism* 31(3), p315-24.
- 8 Fuchs HA, Brooks RH, Callahan LF, & Pincus T (1989): "A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis", *Arthritis and Rheumatism* 32(5), p531-7.
- 9 Choy, E., personal communication
- 10 Brooks P & Hochberg M (2001): "Outcome measures and classification criteria for the rheumatic diseases. A compilation of data from OMERACT (Outcome Measures for Arthritis Clinical Trials), ILAR (International League of Associations for Rheumatology), regional leagues and other groups", *Rheumatology* 40(8), p896-906.
- 11 Bjarnason I (1999): "Prescribing NSAIDs: Intestinal toxicity and emerging safer anti-inflammatory drugs", *CPD Rheumatology* 1(1), p15-21.
- 12 Stein CM & Pincus T (1999): "Placebo-controlled studies in rheumatoid arthritis", *Lancet* 353, p400-3.
- 13 Hawkey CJ (1999): "COX-2 inhibitors", *Lancet* 353, p307-14.

Useful Websites

- American College of Rheumatology: www.rheumatology.org
- Arthritis Research Campaign: www.arc.org.uk
- British Society for Rheumatology: www.rheumatology.org.uk
- European League Against Rheumatism (EULAR): www.eular.org

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