Rheumatoid Arthritis-A Review

H S Howe,* *FAMS, MBBS, M Med (Int Med)*

Abstract

Rheumatoid arthritis, a common chronic inflammatory arthritis, tends to run a more benign course inpatients from the community than those seen at hospitals. The aetiology is unknown but the disease is postulated to result from the interaction between genetic and environmentalfactors. The strongest genetic association is with the major histocompatibility complex (MHC) Class II antigen HLA DR 4, although not more than 50% of the genetic susceptibility is due to MHC genes. In early disease the pathogenesis is thought to be T cell mediated whereas in late disease the mechanisms are T cell independent, with destruction contributed to by autonomous fibroblast like synoviocytes. The diagnosis is made on clinical grounds. Management is directed at controlling active synovitis so that joint damage is limited. The early use of a slow acting anti-rheumatic drug is now advocated, as studies have shown that they canpotentiallyprevent or limit the progression of disease. Biological therapies are still experimental but may hold promise for the future.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis which is occasionally associated with extra-articular manifestations. Although the first good clinical description was by Landre-Beauvais in 1800, the term rheumatoid arthritis was first used only in 1878 by Alfred Garrod.[1] In contrast, ankylosing spondylitis, osteoarthritis and gout have been diagnosed from skeletal manifestations as long as 4000 years ago. However, recent skeletal findings suggest. that RA may have existed in the New World as long as 5000 years ago.[2] Standardised criteria for diagnosis were not developed until 1958 by the American Rheumatism Association (now American College of Rheumatology). The prevalence of RA in adult Caucasian populations is usually stated as 1%.[3] The incidence in the UK using a prospective population based register has been calculated as 36/100 000 for women and 14/100 000 for men.[4] In Asians the prevalence has been estimated to be around 0.3%.[5-7] Females are 2 to 3 times more commonly affected than males. The disease onset in men is later than in women, with increasing incidence in the former after age 50 years compared with the mid 20s in the latter group. Both sexes have a broad peak in the 65 to 75 year age group.[8]

Aetiology

The aetiology of the disease is not known but is thought to be multifactorial, a result of environmental factor(s) interacting with one or more genes. The concordance rate in monozygotic twins is not more than 20%.[9] Although less than 50% of the genetic susceptibility is due to major histocompatibility complex (MHC) genes, studies have shown a clear association between HLA DR4 and rheumatoid arthritis in most populations.[10] The DR 4 subtype is *0401 and *0404 in Caucasians, *0405 in Chinese, Japanese, Koreans, Polynesians and Spanish." In a study of Singapore Chinese patients with RA, the association was also found to be with *0405 and this subtype was also more prevalent in those with extra-articular manifestations.[12] Where there is no DR 4 association, the DR association is with *0101 and *0102 (in Israeli Jews and Italians) and DR 1402.[13] The basis of these MHC Class II associations is a conserved epitope QKRAA(0401) and QRRAA (0101, 0102, 0404, 0405, 0408, 1402) spanning amino acid residues 67 to 74 in the third hypervariable region of the DRB1 gene in these alleles.[10] Some DQ and DR haplotypes are associated with extra-articular manifestations.[14] Although the DR association is not necessary for the development of RA its role in influencing disease persistence or severity is still under debate. Other MHC [tumour necrosis factor (TNF), heat shock protein (HSP)][15] and nonMHC genes such as the TCR *VB* genes may be involved.[16] The role of oral contraceptives, infection (Proteus, tuberculosis, mycoplasma, Epstein-Barr virus (EBV), parvovirus), diet

* *Consultant Rheumatologist*
Department of Rheumatology and Immunology
Tan Tock Seng Hospital
Address for Reprints: Dr Howe Hwee Siew, Department of Rheumatology and Immunology, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433.

and smoking in the causation of RA is not established.[17-19]

Pathogenesis

According to current concepts, inflammation and tissue destruction in RA result from complex intercellular interactions initiated by the interaction between antigen presenting cells and CD 4+ T cells. The antigen presenting cells display complexes of Class II MHC molecules and peptide antigens that bind to specific receptors on T cells. Macrophage activation ensues with secretion of proinflammatory cytokines such as IL1 and TNF. These cytokines then stimulate synovial fibroblasts and chondrocytes. The importance of T cells in the pathogenesis of RA has recently been questioned, as there is a paucity of antigen specific T cells and T cell cytokines such as IL2 and interferon gamma in the rheumatoid synovium and treatment with monoclonal antibodies directed against T cell specific subsets have been disappointing.[20-23]

Fibroblast like synoviocytes are transformed and autonomous aggressors that operate independently of T cell mechanisms[24] which have received increasing attention in the last decade. They predominate in rheumatoid pannus, express abundant adhesion molecules and secrete enzymes that destroy nearby tissue in response to proinflammatory cytokines. Their potentially malignant like behaviour and importance in established disease has been emphasised in several studies. Cartilage damage has been shown to require contact between fibroblasts and cartilage and the presence of macrophages.[25] It is possible that early in the course of RA the pathogenesis is T cell mediated but later events are T cell independent.[22] The pathological changes in the RA joint are well known and will not be described here.[26]

Clinical Features

The clinical features of RA can be classified as articular and extra-articular. Symmetrical polyarticular involvement is the norm with the small joints of the hands and feet affected in a characteristic pattern. Classically the temporomandibular joints, cervical spine, sternoclavicular joints, shoulders, elbows, wrists, metacarpophalangeal joints, finger proximal interphalangeal joints, hips, knees, ankles, subtalar joints, metatarsophalangeal joints and toe proximal interphalangeal joints are affected in established polyarticular disease. Redness of the overlying skin is uncommon, and its presence may be a clue to joint infection or crystals. Pain, early morning stiffness and functional limitation are typical of active disease. The presence of fever should always lead to a search for an infective or other cause. Typically the onset is insidious and the joints involved in an additive and progressive manner. Less commonly the onset can be oligo or monoarticular or palindromic. Rarely there may be an explosive acute onset with fever. This has been reported to occur more frequently with elderly onset RA (EORA).[27] Other uncommon presentations include syndromes that mimic polymyalgia, fibromyalgia and adult Still's disease, carpal tunnel syndrome, rheumatoid nodulosis, isolated tenosynovitis, mono or oligoarticular arthritis and cricoarytenoid arthritis. Extraarticular manifestations include constitutional symptoms and involvement of other systems. Loss of weight due to active disease may be marked leading to investigations for other causes. Involvement of other systems is well known.[28] There is racial variation in RA with less extra-articular involvement in Asian patients.[29] Nodular disease is rare in Oriental populations but may be seen in up to 30% of Caucasian patients.

Diagnosis

The diagnosis of RA is clinical, and based on the presence of recognised manifestations and exclusion of other conditions. The differential diagnosis of a symmetrical polyarthritis with predominant involvement of the small joints of the hands and feet include:

Acute presentation

Viral infection	: rubella, mumps, varicella, Epstein-Barr virus, cytomegalovirus, parvovirus B 19 and hepatitis B and C
Bacterial infection	infective endocarditis, gonococcal infection
Other infections	: chlamydia, mycoplasma
Neoplasms	: leukaemia, multiple myeloma

Subacute or chronic presentation

Connective tissue disease	: systemic lupus erythematosus, overlap syndrome, Sjogren's syndrome, vasculitis, osteoarthritis, calcium pyrophosphate deposition, polyarticular gout, psoriatic arthritis
Infection	: parvovirus B19, hepatitis C, tuberculosis
Metabolic conditions	: hypothyroidism, haemochromatosis

Therefore a full clinical examination is necessary in order to detect clues to the presence of these disorders. The American College of Rheumatology (ACR) classification criteria are useful for conducting studies or clarifying and comparing patients with RA.[30]

Investigations

Investigations at baseline should include a full blood count and platelet count, erythrocyte sedimentation rate (ESR) or C-reactive protein, serum creatinine, electro-

lytes, liver function tests, rheumatoid factor (RF), antinuclear antibody (ANA) and X-rays of the hands and feet. In active disease, a normochromic, normocytic anaemia, normal total white count and occasionally mild thrombocytosis or eosinophilia may be present. The RF (IgM RF unless otherwise stated) is positive in 60% to 80% at some stage of the disease. The ANA may also be positive, but in low titre. The serum creatinine, electrolytes and liver function tests are needed as baseline evaluation for drug therapy and may indicate the presence of an underlying systemic or metabolic disease. Liver function tests may show a mild elevation of the alkaline phosphatase and fall in the serum albumin in active disease.[31]

Management

The aim of management is to control active synovitis in order to prevent or limit joint damage. As RA is a chronic disease it is crucial for the patient to understand the rationale and goals of therapy so that she/ he can participate effectively in the treatment programme. Coordinated multidisciplinary care is used in the management of RA with input from nursing, physical therapy, occupational therapy, social work, health education, podiatry and surgical professionals.

In early disease, pain and functional limitation may be due solely to active synovitis, with its control returning the joint to normal. In late disease, structural damage may be the main cause of pain and functional limitation. In practice most patients have a mixture of both active synovitis and structural damage.

Published guidelines for the management of RA have been put forward by the ACR.[32] Periodic assessment of the disease activity, drug toxicity and efficacy as well as joint damage is essential. Active disease is present when there is early morning stiffness and joints involved by synovitis i.e. synovial thickening associated with signs of inflammation such as pain, increased warmth and stiffness. The duration of early morning stiffness is useful in distinguishing between synovitis and structural joint damage, with one hour or more of early morning stiffness being indicative of inflammatory joint disease. Most hospital-based RA patients develop erosions within the first two years of disease[33] thus the clinical evaluation of activity (potentially reversible) and damage (irreversible) should be done at every clinical visit. Active joint disease is often aggravated by physical activity, and periods of rest or time off from work may be necessary.

Typically the-patient is started on a non-steroidal anti-inflammatory drug (NSAID) first and evaluated two weeks later. The need for a NSAID should be carefully considered in elderly patients, especially those with co-morbid conditions. In this situation, low dose oral prednisolone may be a safer alternative. The large number of NSAIDs available reflect the absence of an ideal agent and a "gut sparing " NSAID has yet to be formulated. With the discovery of cyclooxygenase (COX) 2 preferential inhibitors (e.g. nabumetone) the gastrointestinal (GI) toxicity is reduced while COX 1 preferential NSAIDs (e.g. indomethacin, sulindac, piroxicam and especially meclofenamate) have a high incidence of GI toxicity.[34] There are exceptions to this general rule (e.g. ketorolac) and the GI toxicity of ibuprofen is dose dependent. If active synovitis is present but the patient's functional capacity is not severely limited then the dose of NSAIDs may be increased to the maximum tolerated dose or an alternative NSAID tried. Synovitis, effusion, malalignment, articular damage and capsular contracture all can cause functional limitation and effective treatment depends on determining which of these contributes most. The patient should then be reviewed in another two to three weeks and if synovitis is still active, a slow acting anti-rheumatic drug (SAARD), also known as disease modifying anti-rheumatic drugs (DMARDs) or disease controlling anti-rheumatic therapy (D-CART) should be started. While NSAIDs and steroids may provide symptom relief they do not prevent joint damage and its progression, although a recent study suggests that low dose steroids may have some effect on the rate of progression of joint damage.[35] SAARDs have the potential to prevent or reduce joint damage[36,37] and therefore should be used early i.e. not more than 3 months after a NSAID is started. If joint damage is already present then a SAARD is indicated. Some authors would say that a good response to a NSAID is an indication of reversibility and therefore an indication for the early use of a SAARD. SAARDs currently in use include hydroxychloroquine, sulphasalazine, methotrexate (MTX), gold salts, D-penicillamine and azathioprine. Cyclosporin is occasionally used when these SAARDs are ineffective.[38] Some studies show that minocycline and doxycycline, dapsone and gammalinolenic acid may be useful as SAARDs.[39-41] Whether SAARDs should be given in a sequential or additive manner is still under debate.[42] Most rheumatologists use a combination of SAARDs for patients who have a partial response to one SAARD or when the disease is refractory to different individual SAARDs. The SAARDs most commonly used in current practice are hydroxychloroquine (for mild disease where symptoms can be controlled with NSAIDs), sulphasalazine and weekly low dose methotrexate. Studies have shown that methotrexate is the drug most likely to be continued long term with the least drop out from adverse effects or loss of efficacy, with more than 50% on MTX continuing the drug beyond three years.[43] The 4-week onset of action is also the shortest of all the SAARDs which can take from one to six months to work. Studies also attest to its safety in long term use. Guidelines for monitoring SAARDs have been published by the ACR[44] and are also available from its website http:/ / www.rheumatology.org. The duration of SAARD use is

indefinite although in some patients they can ultimately be discontinued.[45] SAARDs should be continued at a maintenance dose as they control but do not cure RA. If disease remission occurs on SAARDs, regular intake of NSAIDs or oral steroids often is no longer required. Complete remission is defined as the absence of active inflammatory joint pain, morning stiffness, fatigue, synovitis on joint examination, progression of radiographic damage, and elevated ESR or CRP.[46]

The place of steroids in RA is mainly in providing symptomatic relief while waiting for the SAARDs to work. While this is the ideal situation in which steroids should be used patients sometimes cannot be weaned off completely. The dosage of daily oral steroid should not exceed 10 mg of prednisolone/day and often the maintenance dose can be reduced to as little as 2 mg to 4 mg a day. As RA itself is associated with osteoporosis, the daily use of steroids may compound this problem. Treatment strategies for steroid-induced osteoporosis have been described.[47] Intraarticular steroids are useful when one or two joints are slow to respond to SAARDs and other medication but should not be given more frequently than once in three months. Newer therapies such as oral tolerance, anticytokine therapy, regulation of T cell subsets, stem cell therapy and bone marrow transplantation are still experimental[48-50] but hold out promise for the treatment of RA in the future.

Common Problems in Management

Anaemia, a common problem in practice, can be evaluated using an algorithm.[51] Situations in RA where intervention is required include rupture of finger extensor tendons (prompt surgery), atlantoaxial subluxation with compression of the spinal cord (surgery), rupture of a popliteal cyst (aspiration and intra-articular steroid injection), persistent synovitis in one or two joints not responding to medication (aspiration and /or other evaluation to exclude infection or other causes), stress fractures (diagnostic evaluation), leg ulcers (exclusion of vasculitis) and entrapment neuropathy (surgery occasionally). As an estimated 19% to 70% of RA patients have atlantoaxial subluxation, often asymptomatic, those undergoing procedures which may involve manipulation of the neck should have preoperative flexion and extension views of the cervical spine to detect this complication.[52]

The place of surgery is mainly in correcting damage whether in the repair of ruptured tendons, carpal tunnel release or total joint replacement, arthrodesis or resection (metatarsal heads). Although synovectomy can be used for pain relief its effect is usually not permanent.

Course and Outcome

The course of RA as defined by the ACR diagnostic criteria is different between patients in the community and those seen at tertiary centres. Inflammatory polyarthritis conforming to ACR diagnostic criteria in the community often is a mild disease with a self-limited course.[53] RA managed at a hospital tends to be more severe disease that does not remit and is rapidly destructive early in its course especially in those with seropositive polyarthritis. Severity of disease is reflected by the haemoglobin level, ESR, tender joint count, swollen joint count and the presence of erosions on X-rays. Studies have shown that poor baseline functional status is predictive of earlier mortality, and the five variables of predictive value are higher age at onset, co-morbid cardiovascular disease, higher number of involved joints, measures indicating poor functional status and fewer years of formal education.[54] Patients die 10 to 15 years earlier than would be expected for age and sex matched individuals. The overall patterns of attributable causes of death do not differ from the general population, cardiovascular disease being the leading cause of death. Lymphoma, leukaemia and myeloma occur more commonly in the RA population.“” Mortality in rheumatoid arthritis has been compared with Hodgkin's disease.[56] The survival rates are 90% for patients with fewer than 20 involved joints (85% Stage I/II), 60% in patients with 21 to 30 joints (60% Stage III) and 40% to 50% in those with more than 30 joints or poor functional status (45% Stage IV disease).

Disability is generally accepted as the major area of impact of RA. The most important risk factor for subsequent disability is disability at the time when first obtained. Increasing age at onset is linked to increased rates of disability, partly because of increase of co-morbid conditions. Predictive factors for severe disease are symmetrical peripheral polyarthritis, with significant early morning stiffness, and early disability associated with persistently elevated ESR, strongly seropositive disease, vasculitis and other extra-articular manifestations.

A widely-held belief that RA in Oriental patients tends to be milder was not borne out in a study by Veerapen et al of Malaysia[57] who compared severity of disease in hospital outpatient clinics of Malaysia and Britain. The health assessment questionnaire (HAQ),[58] used widely to measure disease outcomes, has to be modified for use in different populations. Recently the HAQ, modified for local cultural differences, was validated in a pilot study on Singapore Chinese patients with RA.[59] It can be used as a quantitative evaluation of function/disability in following the course of disease in individual patients. Consistent treatment with SAARDs really does seem to improve functional outcome, although the great majority of patients tend to have persistently active disease, thus all patients should be followed up indefinitely.

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