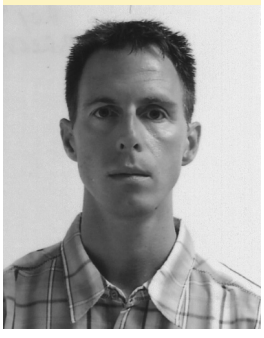
RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune disease that has as its primary target the synovial tissues.[1]



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A prevalence of 0.5 - 1% is reported in diverse populations worldwide.[2] The disease is more common and has an earlier onset in women, frequently beginning in the childbearing years.[1] Twin concordance data suggest the disease has a multifactorial aetiology with a significant contribution from both genetic and environmental factors.[2]

PATHOGENESIS

Specific CD4+ T-cells are involved in the induction of the immune response in RA, probably as a response to an unknown exogenous or endogenous antigen. Consequently, recruited monocytes, macrophages and fibroblasts produce cytokines such as tumour necrosis factor alpha (TNF-alpha) and interleukin-1 within the synovial cavity. These cytokines are central to a damaging cascade, ultimately triggering the production of matrix metalloproteinases and osteoclasts, which results in irreversible damage to soft tissues and bones. The occurrence of B-lymphocyte dysregulation is suggested by the association of erosive disease with the presence of rheumatoid factor, which mediates further damage through complement fixation.[3]

CLINICAL FEATURES AND EVALUATION

Making a diagnosis of RA depends on an accurate description of the patient's illness. Diffuse symmetrical joint pain and swelling affecting the small peripheral joints are the commonest presenting symptoms. These symptoms are often associated with difficulty making a fist and morning stiffness of variable duration.

Joint inflammation

The key signs of joint inflammation in RA are those of tenderness and swelling. These may be associated with local heat, but erythema is not a feature of rheumatoid inflammation. A joint is considered 'active' if it is tender on pressure or painful on passive movement with stress (i.e. when a joint at the limit of its range of movement is nudged a little further) and/or if there is soft-tissue swelling.

Joint damage and destruction

Joint destruction may be assessed clinically or radiologically. Clinical observations associated with joint disruption include a reduction in the range of movement, collateral instability, malalignment, subluxation or bone-on-bone crepitus.

The information obtained from the clinical evaluation will reveal which joint structures are affected by inflammation, which are damaged and to what extent function is impaired.

Extra-articular features

Extra-articular features that should be looked for include the presence of rheumatoid nodules, Raynaud's phenomenon, digital infarcts, scleritis/episcleritis, peripheral neuropathy and leg ulcers. One should also check for anaemia, splenomegaly, pleuritis or pericarditis and the sicca syndrome.

Early, progressive and late disease

Early disease describes patients who as yet exhibit no clinical evidence of joint damage or radiological signs of cartilage loss or bone erosion. Prognostic fac-

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tors should be sought (see later). Some patients show a progressive course from the outset. They have unrelenting, continuous disease activity despite treatment. Late disease describes patients whose disease has led to definite joint damage and in most cases the disease is of many years' duration.

Patterns of presentation and clinical course

RA begins predominantly as an articular disease. It may also start with an extra-articular or non-articular presentation, such as a local bursitis or tenosynovitis, or as a systemic presentation with diffuse polyarthralgia or polymyalgia. The commonest presentation is polyarticular, with a gradual onset of disease affecting small peripheral joints. Less common is a slow monoarticular presentation affecting larger joints such as the shoulders or knees. Less frequently, RA presents as an abrupt acute polyarthritis and rarely as an acute monoarthritis resembling septic arthritis or gout.

Individual joints

Joint involvement in RA is symmetrical. While wrists, fingers, knees and feet are the most commonly affected joints, severe disease is associated with larger joints that contain more synovium, such as the shoulders, elbows and knees.

Hands

Symmetrical swelling of the metacarpophalangeal (MCP) joints and fusiform swelling of the proximal interphalangeal (PIP) joints are typical of RA. MCP joint involvement, with the development of volar subluxation and ulnar drift, is a characteristic deformity. Three deformities due to lack of collateral ligament support characterise PIP joint involvement:

- the boutonnierre (PIP joint flexion and DIP joint hyperextension)
- the swan-neck (MCP joint flexion, PIP joint hyperextension and DIP joint flexion)
- the unstable PIP joint.

Synovitis in the PIP joint can produce any of these deformities. Thumb deformities include the flail interphalangeal (IP) joint and the boutonnierre thumb (MCP flexion and secondary IP hyperextension).

Wrists

Symmetrical disease of the wrists is almost invariably present. Attenuation of the weak triangular ligament allows volar displacement.

Shoulders

Synovitis leads to erosion and damage of the humeral head and the glenoid fossa. The rotator cuff is also lined with synovium and may show inflammation and destruction.

Acromioclavicular joint disease is frequently found in RA and may be the prime source of shoulder pain.

Cervical spine

The neck is an important target in RA, particularly at the C1 - C2 level. Atlantoaxial subluxation may occur.

Ankle and foot

The ankle joint is not as frequently involved as the subtalar and midtarsal joints. Disease of the metatarsal heads is common in RA. Forefoot deformity starts with synovitis of the metatarsophalangeal (MTP) joints. Clawing of the toes and dorsal dislocation of the MTP joint results.[4]

Systemic involvement

The major clinical features reflecting systemic involvement in RA include fever, malaise and weight loss.

Subcutaneous nodules occur in 20% of seropositive RA patients and rarely in seronegative patients.

Haematological abnormalities may also occur. Anaemia is multifactorial in origin and includes iron deficiency anaemia and the anaemia of chronic disorders. Thrombocytosis is a frequent finding in active RA. Thrombocytopenia is rare except when related to drug treatment or Felty's syndrome, a severe subset of seropositive RA complicated by granulocytopenia and splenomegaly.

Pulmonary involvement in RA is frequent, although the clinical features may be subtle. Manifestations include interstitial pneumonitis/fibrosis and pleural effusions.

RA may lead to **cardiac** involvement, with pericarditis being the most common manifestation.

The most common **ocular** involvement in RA is keratoconjunctivitis sicca. Other manifestations include episcleritis, scleritis and corneal ulceration and keratolysis. Drugs used to treat RA can also affect the eyes, including steroids and chloroquine.

RA may also be complicated by **neurological** manifestations. Peripheral entrapment neuropathies such as carpal tunnel syndrome correlate with the degree of local synovitis. Atlantoaxial subluxation may cause a cervical myelopathy. Neuropathies, especially mononeuritis multiplex, may occur in the setting of rheumatoid vasculitis.

Muscle weakness in RA is usually due to muscle atrophy secondary to joint inflammation. An inflammatory myopathy may also occur.

Secondary **amyloid** may develop as a result of longstanding active inflammation.

Rheumatoid vasculitis may occur in patients who have longstanding disease. Small-vessel vasculitis commonly involves the skin and causes nail-fold infarcts and leg ulcers. The more ominous manifestations are the appear-

ance of digital tip infarcts and multiple neuropathies.[5]

EARLY DIAGNOSIS AND TREATMENT

Joint damage occurs early in the course of RA[1] – 75% of patients with early RA develop erosions and most of these develop within the first 2 years.[6] Initiation of therapy with disease-modifying antirheumatic drugs (DMARDs) within 3 months after the diagnosis of RA is crucial. A delay of as little as 3 months in the introduction of these medications results in substantially more radiographic damage at 5 years.[1]

There are several challenges to early and effective intervention in RA. Among these are a lack of definitive criteria, delays in seeking medical attention, and difficulties identifying who is likely to have persistent RA or risk factors for severe disease.[7] The inherent problem with the treatment of early RA is the long lag time between the onset of the disease and referral to a rheumatologist for accurate diagnosis and specific treatment. Because diagnosis of early RA is often difficult, the diagnostic lag time is the major contributor to the overall delay in treatment. The median lag time to diagnosis has been found to be 18 weeks.[8] A useful goal is to have all patients evaluated by a rheumatologist within 3 months after the onset of symptoms, so that essentially all patients will be receiving DMARDs by the time they have had symptoms for 3 months.[1] There are differences between rheumatologists and non-rheumatologists in initiating the use of DMARDs. Non-rheumatologists generally delay treatment, which can result in substantial differences in the long-term outcome of the disease.[8]

The diagnosis of RA is aided by the use of 7 criteria – the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA.[1] The criteria are:

- the presence of morning stiffness (of at least 1 hour in duration)
- arthritis of 3 or more of 14 possible joint areas
- arthritis of the hand joints
- symmetrical arthritis
- rheumatoid nodules
- elevated levels of rheumatoid factor
- radiographic changes (erosions or juxta-articular osteopenia).[9]

Many other syndromes, including self-limiting viral conditions lasting several weeks, mimic RA. Therefore, the first 4 criteria must be present for a minimum of 6 weeks before a diagnosis of RA can be made.[1] When the 1987 ACR criteria are used to evaluate patients who have been ill for less than 1 year, the sensitivity decreases from 91% overall to 81%.[7]

The diagnosis cannot be established by a single laboratory test.[1] Most patients with inflammatory rheumatic diseases have an elevated ESR and/or CRP, but a normal ESR has been found in up to 40% of patients with active RA and a normal value does not exclude an inflammatory rheumatic disease.[10]

Rheumatoid factor is found in about 70 - 90% of patients with RA, while 10 - 30% remain seronegative. However, of those who ultimately do become seropositive, rheumatoid factor is detected in only 60% during the first 6 months of the disease. Based on the prevalence of the disease and the prevalence of a positive test in normal people, the likelihood of having RA if the test is positive is 1/2 and 1/1.5 in the presence of joint pain.[10]

Antibodies to a peptide called cyclic citrullinated peptide (anti-CCP antibodies) have a high specificity for RA. In patients with early arthritis, IgM rheumatoid factor > 40 IU/ml or anti-CCP antibody > 50 U/ml predicts the clinical diagnosis of RA with a sensitivity of 55.4% and a specificity of 96.7%.[11]

Early referral recommendation for early RA

Rapid referral to a rheumatologist is advised if there is a clinical suspicion of RA, which may be supported by the presence of any of the following:

- ≥ 3 swollen joints
- MTP/MCP joint involvement (squeeze test positive)
- early morning stiffness ≥ 30 minutes.[8]

MANAGEMENT

The goals in managing RA are to prevent or control joint damage, prevent loss of function and decrease pain. The ultimate goal is to strive for remission (no joint symptoms) in all patients.[1,12]

The initial evaluation should document symptoms of active disease (joint pain, duration of early morning stiffness, fatigue), functional status, objective evidence of disease activity (synovitis), mechanical joint problems (crepitus, malalignment, deformity), the presence of extra-articular features and the presence of radiographic damage. The presence of co-morbid conditions should also be assessed.[12]

Selection of the treatment regimen requires an assessment of prognosis. Poor prognostic factors include rheumatoid factor positivity, raised CRP/ESR, involvement of large joints, relatively high joint counts and erosions on X-ray.[7,8,12]

DRUGS USED FOR RA

Medications are divided into 3 main classes: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids (GCS) and DMARDs.

NSAIDs

NSAIDs provide partial relief of pain and stiffness. These drugs do not slow the progression of the disease and should be used together with DMARDs in longer-term care.[1]

GCS

Low-dose GCS (≤ 10 mg prednisone daily) are highly effective at relieving symptoms in patients with active RA, with improvement occurring within days.[12] Doses above 10 mg per day are rarely indicated for joint disease.[1] GCS also retard radiological progression[13] and evidence suggests that they are potent disease-modifying anti-rheumatic drugs.[14] The symptomatic effect tends to wane after about 6 months,

but the disease-modifying effect persists even when treatment is stopped. Some advocate high-dose induction therapy[13] and others favour low-dose maintenance therapy, e.g. 7.5 mg prednisone daily for at least 2 years in early disease.[13,15] Controversy does however continue about the exact place of GCS. They are effective as bridge therapy when starting DMARDs. One should strive for the lowest dose that controls the disease.[1]

DMARDs

DMARDs are defined as drugs that retard or halt progression of the disease (demonstrated radiographically). Methotrexate is the synthetic DMARD that is most likely to induce a long-term response and is therefore most often selected for initial therapy. It has a long-term track record of acceptable toxicity and low cost. Concomitant administration of folic acid decreases many toxic effects. Safe administration requires careful monitoring, including regular liver function tests. Methotrexate should not be used in patients who have underlying liver disease, who consume alcohol or who do not want to undergo regular laboratory monitoring. Sulfasalazine has an efficacy similar to that of methotrexate. Antimalarial drugs (chloroquine and hydroxychloroquine) are less effective, but the best tolerated. Leflunomide is a newer synthetic DMARD with an efficacy similar to that of sulfasalazine or moderate-dose methotrexate. Biological products that inhibit the actions of TNF-alpha, infliximab and etanercept, are now available to treat RA.[1]

MANAGEMENT APPROACH

Controversy remains over whether to initiate DMARD therapy in a sequential step-up approach in patients with persistently active disease in whom single agents have failed, or whether to initiate combination therapy early in the disease course and then apply a step-down approach once adequate disease control is attained.[12] Other unanswered questions include which drug to use first and whether we should try to induce rapid disease suppression with GCS or TNF inhibitors.[1] Several trials have shown that combination DMARD therapy is superior to therapy with a single DMARD. The triple combination of methotrexate, sulfasalazine and hydroxychloroquine has been found to be superior to the double combination of methotrexate and sulfasalazine or to methotrexate alone.[1,12]

Most rheumatologists select methotrexate as the initial therapy for most patients. The drug is started at a dose of 7.5 - 15 mg given orally once weekly. If patients continue to have active disease, the dose should be increased in 5 mg increments each month or two to 25 mg per week. As oral absorption may be highly variable, a trial of subcutaneous methotrexate may be indicated if the response is suboptimal. If active disease persists despite optimal methotrexate therapy, other DMARDs should be added and the initial choice should be sulfasalazine, chloroquine or both. If active disease persists after 3 months of these DMARD combinations, leflunomide or a TNF inhibitor should be added to methotrexate.

Whether to start a course of low-dose GCS initially along with the chosen DMARD is controversial. Many clinicians start treatment with prednisone at 5 - 7.5 mg per day as bridge therapy until the slower-acting DMARDs have a chance to work. Once the DMARD begins working, many rheumatologists will taper the GCS.

If DMARD therapy is started within 3 months after the onset of symptoms and escalated with the goal of achieving remission, the majority of patients will have the disease well controlled within a year while taking conventional single or combination DMARD therapy.[1]

CO-MORBID CONDITIONS

Estimates of survival suggest an average shortening of lifespan of 3 - 18 years in RA patients. The excess mortality is predominantly due to increased coronary artery atherosclerosis. The systemic inflammation associated with RA predisposes to premature atherosclerosis. Risk factors should be addressed, including cessation of smoking, maintenance of physical activity and dietary fat modification.[16]

The incidence of osteoporosis is doubled in patients with RA. Baseline bone mineral density studies should be performed in all patients, especially those who will receive GCS. Bisphosphonate therapy should be considered.[1]

The other co-existing illness which has an effect on morbidity and mortality in RA is infection, especially pulmonary infection.[1]

CONCLUSION

Structural joint damage occurs early in the course of RA. Effective management of active RA requires early diagnosis and early DMARD treatment to improve the long-term outcome of the disease.[8]

References available on request.

IN A NUTSHELL

Joint damage occurs early in RA.

Initiation of disease-modifying therapy within 3 months of onset is crucial.

Patients with suspected RA should be evaluated by a rheumatologist within 3 months of onset of symptoms.

Low-dose glucocorticoids are very effective at relieving symptoms of RA.

Disease-modifying antirheumatic drugs retard or halt radiographic progression of the disease.

Methotrexate is most often selected for initial therapy.

Important co-morbid conditions in RA patients are coronary artery disease and osteoporosis.