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Introduction

The choice of, and the decision to apply, disease modifying drugs

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Although rheumatoid arthritis (RA) is recognised to be a systemic illness, frequently the only manifestation is an inflammatory polyarthritis in which synovitis causes joint destruction. Extra-articular or systemic features include vasculitis which, when present, may be the cause of potentially serious or fatal manifestations. The aetiology remains unknown, although immunological disturbances are certainly involved in the perpetuation of the disease. The formation of immune complexes within the joint is probably responsible for the release of chemical mediators of inflammation.

The natural history of the disease is variable, ranging from a brief episode of polyarthritis which resolves spontaneously, to a rapidly progressive arthritis with widespread systemic features.

The evidence for an immunological disturbance arises from:

(1) the presence of serum and synovial fluid autoantibodies—rheumatoid factors;
(2) the presence of other serum antibodies, for example antinuclear antibodies;
(3) the histology of the synovium which includes infiltration with plasma cells and lymphocytes;
(4) reduced synovial fluid complement levels in actively inflamed joints;
(5) the presence of immune complexes in synovial fluid;
(6) reduced serum complement levels in patients with active systemic disease;
(7) amyloid deposition.

The first line of treatment always consists of the use of non-steroidal anti-inflammatory analgesics, in full dosage, to achieve both pain relief and some reduction of the inflammatory component of the synovitis. There is, however, no evidence that these drugs influence the natural history of the disease, and therefore further drugs are continually being sought which will modify the disease process and suppress the synovitis and vasculitis in particular. Such drugs which are available at present are potentially toxic and have not been shown predictably to halt the progression of the disease. Thus their use, in a disease which is usually not fatal, depends on the careful assessment of the course of the disease in the individual patient and on the making of a balanced judgement between the likely effect of the disease, if not suppressed, and the possible toxicity of the treatment.

The decision to use a drug which may suppress the disease, drugs which are also known as 'slow-acting', 'long-acting' or 'second-line' agents, depends on a definite diagnosis with evidence that the disease is progressing. Evidence of such progression may be demonstrated by some or all of the following features:

(1) persistent active synovitis
    —prolonged morning stiffness
    —pain, warmth and tenderness of joints
    —clinical synovitis;
(2) deteriorating functional capacity owing to active inflammatory synovitis;
(3) increasing number of affected joints;
(4) rheumatoid factor tests
    —becoming positive
    —increasing titre;
(5) radiological erosions
    —development or increase in number;
(6) development of extra-articular features, for example nodules, vasculitis, etc.

The group of suppressive drugs consists of seven different classes of agents:

(1) gold salts;
(2) antimalarials—chloroquine preparations;
(3) 'immunosuppressives' (cytotoxic: anti-metabolic agents);

(4) penicillamine;
(5) levamisole;
(6) dapsone;
(7) sulphasalazine.

Of these, the first four are well established in the treatment of RA. Levamisole has been shown to be effective in a majority of patients but is considered by many to produce too high an incidence of toxic effects to be considered for routine treatment.[98 116 209 229] The effectiveness of dapsone and sulphasalazine remains debatable.[135-137]

Historically gold salts are the most firmly established form of suppressive treatment of RA, having been introduced over 50 years ago by Forrestier. It was not until controlled trials were conducted by Fraser[70] and the Empire Rheumatism Council[63] that its effectiveness was demonstrated. Nevertheless, its mode of action remains uncertain, prediction of both benefit or toxicity in the individual patient is not possible and measurement of serum levels has not been proved to be a useful method of monitoring gold therapy.[100 188]

The chloroquine group of drugs were added next, initially being used empirically but later being shown to be effective in controlled trials,[87 139 180] but less effective than gold or azathioprine.[56]

The first report of the use of a cytotoxic agent in the management of RA was in 1951, when Jimenez-Diaz[106] treated nine patients with nitrogen mustard on the basis that it was appropriate to treat proliferative synovitis with an antiproliferative agent. There followed other reports of the use of this agent, but by 1964 interest had moved to the so-called immunosuppressives, in particular azathioprine, chlorambucil and cyclophosphamide. The rationale for the use of these agents was that if an immunological disturbance plays an important part in the pathogenesis of RA, then it would be beneficial for this immunological overactivity to be suppressed. Thus, by 1972 there were 25 published trials of azathioprine in 350 patients, nine trials of chlorambucil in 330 patients, and 12 trials of cyclophosphamide in 370 patients, and an additional 235 patients had been treated in trials with aminopterine, 6-mercaptopurine or methotrexate. The majority of these trials were uncontrolled.[14] However, there have now been many controlled trials, mainly of azathioprine and cyclophosphamide, which have demonstrated their efficacy and their toxicity, which have compared them one with the other and also with gold salts, chloroquine and penicillamine, and which have compared different dosage schedules.[5 18 34 35 38 56 84 89 95 124 143 224 225 237 239] Nevertheless, it has not been convincingly demonstrated that immune responses are suppressed *in vivo*. Of particular concern is the debate on the possible oncogenic effect of the immunosuppressive cytotoxic agents,[5] although to date a large follow-up survey has only revealed a small increase in the number of non-Hodgkin's lymphomata in patients who are not organ transplant recipients.[115]

Most recently penicillamine has been studied, the results of the first series of 21 patients being published by Jaffe in 1965.[103] Although the mode of action of penicillamine remains unknown, controlled trials have shown it to be effective and it has been subjected to trials of different dosage regimens and in comparison with other suppressive agents. This drug too is potentially toxic.[18 48 97 99 133 155]

None of the agents available at present provides a complete answer to the need to suppress RA, in that approximately 75% of patients respond to treatment and certainly a complete cure is not effected. The measurement of efficacy depends on clinical response, improvement in laboratory parameters of disease activity and, possibly most importantly, the demonstration of a reduction in progressive joint damage. Only the 'immunosuppressive' cytotoxic agents have been shown possibly to reduce the progression of radiological erosive change,[34 38] and a histological study of the effect of chlorambucil on active synovitis did not reveal any significant improvement.[5]

This symposium, therefore, aims to re-examine our present state of knowledge of the effectiveness and toxicity of the drugs currently available which may modify the rheumatoid process, and of the 'immunosuppressive' cytotoxic agents in particular.

Questions which may be posed are:

(1) May these drugs be considered to modify the progression of the disease by:
   (a) suppressing the activity of the inflammatory component of rheumatoid arthritis?
   (b) reducing or preventing the progression of erosive joint damage?
   (c) suppressing the laboratory measurements of inflammation and immunological overactivity?
(2) What is the long term toxicity of these agents?
(3) What is the comparative efficacy and toxicity of the different agents?
(4) What are appropriate dosage schedules?
(5) What are their modes of action?

We shall consider both clinical and laboratory data and hope for a wide-ranging discussion between the speakers and the audience.