Conference proceedings

Do drugs alter the course of rheumatoid arthritis?*

The proliferation of nonsteroidal anti-inflammatory agents (NSAIA) for the treatment of rheumatic diseases has been matched in recent years by a proliferation of drugs that are claimed to have a disease modifying action in rheumatoid arthritis. Early contenders for this claim (aurothiomalate, hydroxychloroquine, and D-penicillamine) were discovered by serendipity. The search for novel compounds that might have comparable therapeutic action without side effects requires a critical evaluation of assessments that might be of use in measuring disease modifying action, and some workers remain unconvinced that such claims are valid even for established drugs such as aurothiomalate.

Against this background the 3rd Annual Day Conference on ‘Growing points in the treatment of rheumatic diseases’ was devoted to whether drugs might alter the course of rheumatoid arthritis and how we might show they do. It was held in Harrogate on 1 April 1982, organised by Dr Howard Bird, and attracted a multidisciplinary audience of almost 100.

Biochemical, cellular, and immunological aspects

Dr N. Hall (Bath) discussed biochemical assessments with particular reference to serum sulphhydryl measurements. NSAIAAs caused little change in serial sulphhydryl reactions, though antirheumatoid drugs including clozic and levamisole and some drugs conventionally classified as NSAIAAs (benoxaprofen and fenclofenac) caused an increase. By contrast cyclophosphamid, which slowed radiological progression, caused no change. It was postulated serum–SH groups might have a protective role against excess superoxide dismutase activity. The relevance of macrophage function in chronic inflammation was discussed by Dr W. Dawson (Lilly Research Centre, Windlesham). Indomethacin had no effect on antigen-dependant lymphocyte proliferation, but D-penicillamine was active, albeit only at very high dose. Studies were in progress on anti-inflammatory compounds that might have anti-rheumatoid action.

Dr R. Clague (Manchester) described his work with autoimmunity to native type II collagen in rheumatoid arthritis. Conventional second-line therapy (with the exception of azathioprine) failed to lower the humoral immune response in this model on a small number of patients assessed serially. By contrast prednisolone did reduce humoral response, though some felt this was not experienced with other antibodies when prednisolone was given at this dose. Dr L. Holt (Manchester) described morphological changes seen with the electron microscope in up to 10% of lymphocytes from patients on oral gold therapy. The nature and significance of these required further clarification. They might represent pinocytosis, though Professor Cooper (Leeds) felt this was unlikely; they had been observed in dying cell populations. Dr B. Coughlan (Guy’s Hospital, London) described immunological changes resulting from oral gold. Over 4 months IgM and IgG did not change, but there was a fall in C-reactive protein (CRP) and rheumatoid factor in a controlled trial.

A lively panel discussion debated whether biochemical tests are related to fundamental disease activity. A single test was unlikely to predict an ‘anti-rheumatoid’ action of all novel drugs even if such a serological concept was valid in isolation from radiological change and clinical response. Professor Panayi (Guy’s Hospital, London) questioned whether we had evidence that a direct action on the hepatocyte with subsequent reduction in CRP (which might be an action of D-penicillamine) was synonymous with arrest of rheumatoid disease.

Clinical aspects

Dr H. Berry (King’s College Hospital, London) described a controlled single blind trial of chloroquine and benoxaprofen. Comparable clinical improvement occurred with both drugs; there was perhaps a tendency to rebound with benoxaprofen. Dr K. Grindulis (Birmingham) reviewed his experience with aurothiomalate in rheumatoid arthritis in a provocative paper that showed only 25% of patients were able to continue treatment for more than one year. Most came off with adverse reactions, and at 2 years only 14% remained on the drug with success. The optimum use of gold still required clarification. In a vigorous discussion Dr J. Kirwan (London Hospital, London) questioned many aspects of conventional trial design in the light of his recent questionnaire sent to clinicians in an attempt to define how they defined ‘response’.

* Report prepared by H. A. Bird and V. Wright, Clinical Pharmacology Unit, Royal Bath Hospital, Harrogate, North Yorkshire.
Objective assessments

Technetium scanning in rheumatoid arthritis was reappraised by Dr D. Lewis (Glasgow). A new summated index was described using scans of 5 joint areas and advocated as a neglected method, even though results did not always correlate closely with observed clinical change. The audience remained uncertain what this and comparable techniques such as thermography actually measured. Two papers then considered conventional x-ray assessment of rheumatoid progression. Dr J. Hunter (Glasgow) described observations on erosions at the proximal interphalangeal joints, metatarsophalangeal joints, distal end of radius, and distal end of the ulna. There were major procedural problems, including different interpretation by observers. However, the audience felt the value of radiology deserved perseverance, and Dr A. Rushton (ICI Ltd, Alderley Edge) described a radiological assessment of clozic. There were far fewer withdrawals in the clozic groups (50 mg/day and 200 mg/day) compared with a placebo group, and in spite of difficulties in methodology (not least the withdrawal of the drug in mid-study) a significant halting of erosion progression was found by 2 independent groups of observers on blind scoring.

Dr C. Buckland-Wright (Guy's Hospital, London) described his work with microfocal radiography. Initially developed for the study of bone density and osteopenia, this method detected erosions long before they could be detected by conventional radiography. The earliest erosions were seen at the site of synovial attachment to bone, and the method was particularly suited to the hands, which were involved early in rheumatoid disease. It might be applicable to crystal deposition disease. The presentation provoked controversy among radiological delegates.

Future trends

In this session contributions considered early work in areas of therapeutic innovation. Two papers moved away from joint disease to consider drug treatment of systemic disease involving the blood vessels. Dr D. G. I. Scott (Birmingham) described his work with intravenous cyclophosphamide and methyl prednisolone in rheumatoid vasculitis, which produced improvement in an uncontrolled series. The audience favoured the use of 'pulse therapy,' and the choice between oral and intravenous cyclophosphamide was discussed. Dr B. McConkey (Birmingham) mentioned his own work with pulse methyl prednisolone therapy in rheumatoid arthritis and his slight anxiety about a possible risk of avascular necrosis at the hip. An alternative approach might be the use of prostaglandin E1, and microvascular changes produced by this drug were described by Dr M. Martin (Leeds). After an initial transient exacerbation of arthralgia, symptomatic improvement occurred and some ulcers improved. Methods borrowed from diabetes mellitus research might clarify changes in small vessels and were at present under study.

Finally Dr Roberts (Roche Products Ltd, Welwyn Garden City) reviewed the expanding interest in the use of retinoic acid derivatives in arthritis. Etretinate (Ro10–9359; Tigason), which was effective in healing the skin lesions of psoriasis, had been claimed in 3 uncontrolled trials to give some improvement to the joint lesions in psoriatic arthropathy. In one study this had been confirmed by joint scanning as well as by clinical assessments. The novelty of a compound that healed both skin and joints in this condition prompted a review of possible mechanisms. The retinoic acids had been implicated in immunosuppression, immunostimulation, cartilage metabolism, inhibition of collagenase released from synovial cells in culture, and inhibition of free oxygen radical release.

Although the conference failed to reach a unanimous opinion on whether drugs alter the course of rheumatoid arthritis, conventional assessments were given a full airing, and some exciting new trends emerged which will be the subject of further discussion at the day conference to be held on Thursday 7 April 1983.
Do drugs alter the course of rheumatoid arthritis?

*Ann Rheum Dis* 1982 41: 549-550
doi: 10.1136/ard.41.5.549

Updated information and services can be found at:
http://ard.bmj.com/content/41/5/549.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/