Disease-Modifying Antirheumatic Drugs
Potential Effects in Older Patients

Gregory Gardner¹ and Daniel E. Furst²

1 Division of Rheumatology, University of Washington, Seattle, Washington, USA
2 Virginia Mason Research Center and Medical Center, Section of Immunology, and Division of Rheumatology, University of Washington and Seattle, Washington, USA

Summary

Disease-modifying antirheumatic drugs (DMARDs) are frequently used in rheumatoid arthritis. A number of physiological changes occur in the elderly which may modify the use of these medications.
The most commonly used DMARDs are antimalarial drugs (particularly hydroxychloroquine), sulfasalazine and methotrexate. The principal mechanism of action of the antimalarials relates to the fact that they change intracellular pH, which downregulates numerous immune functions. Hydroxychloroquine is metabolised to 3 metabolites and has a very low clearance. It is moderately effective in dosages up to 6.4 mg/kg/day. While it is not the most effective of the DMARDs, it is the least toxic.

Sulfasalazine is a prodrug which is enzymatically split in the bowel to form sulfapyridine (the principal active metabolite) and 5-aminosalicylic acid. The metabolism of sulfasalazine is complex and, to some extent, genetically determined. The mechanism of action of the drug is not well understood, but involves decreased production of cytokines and decreased proliferative response of lymphocytes. It may slow the rate of bony damage associated with rheumatoid arthritis. Nearly 50% of the patients who are prescribed sulfasalazine continue to receive the drug for up to 4 years. Sulfasalazine is not as well tolerated as hydroxychloroquine. Gastrointestinal toxicity, in particular, seems to be a problem in elderly patients taking this medication.

Methotrexate is presently the most popular of the DMARDs for the treatment of rheumatoid arthritis. Methotrexate inhibits dihydrofolate reductase and adenosine release and has a secondary effect on cytokines and polymorphonuclear chemotaxis. It is highly metabolised within cells and remains there for prolonged periods. Up to 70% of patients who are prescribed methotrexate continue treatment for 5 years. Methotrexate treatment is associated with gastrointestinal, hepatic, cutaneous and, possibly, pulmonary adverse effects.

The use of azathioprine, penicillamine and gold compounds is briefly reviewed in this article. Elderly patients have an increased incidence of rashes when using penicillamine, relative to young patients. There are no age-related differences in the efficacy and tolerability of azathioprine or gold therapy.

The poor absorption and renal toxicity associated with cyclosporin, the new 'salvage' therapy in rheumatoid arthritis, make it generally unsuitable for use in the elderly, except under specialists' supervision.

Over the last decade it has been recognised that earlier treatment with disease-modifying antirheumatic drugs (DMARDs) or second-line agents may be warranted as rheumatoid arthritis is not the benign disease it was once thought to be and much of the disability in rheumatoid arthritis occurs early in the disease. Although some have advocated multidrug therapy at the outset, most practising rheumatologists have not adopted such an aggressive strategy and are waiting until further data on tolerability and efficacy are available. Nevertheless, patients are receiving second-line agents earlier than in the past and combination therapy is under intense scrutiny. Whether this will modify the poor long term outcome of rheumatoid arthritis remains to be demonstrated.

During the last 2 decades, the number of DMARDs available for the treatment of rheumatoid arthritis has increased and their uses have evolved. In addition to intramuscular gold, antimalarials, penicillamine and azathioprine, sulfasalazine and methotrexate have been rediscovered for the treatment of rheumatoid arthritis. Although still experimental, cyclosporin is also being increasingly used in this disease.

Is rheumatoid arthritis different in older patients? There are findings which suggest that rheumatoid arthritis in the elderly may be more persistently ac-