While the treatment of RA has become more aggressive in recent years by the earlier use of second-line agents, remissions, as measured by the ACR [1], resulting from these therapies are rare. Concern has been expressed that the mortality risk in patients with RA is similar to that seen in Stage IV Hodgkin's disease or three-vessel coronary artery disease [2]. Certainly, the consideration of disability, joint destruction and functional loss in RA patients pleads for treatments with greater potential for disease modification or resolution.

One proposed method of improving treatment outcomes has been the use of combinations of second-line agents. There is some rationale for this strategy. The inflammatory process is remarkably complex and the use of two or more agents with different sites of action could result in more efficacy than any single agent alone. Alternatively, medications in combination could be used in lower doses with presumably less toxicity without loss of efficacy. Also, the success of the oncologist is intriguing. Multiple drug chemotherapy of the malignant lymphoproliferative malignancies has resulted in better survival and even eradication of some disease. RA has been called a 'non-malignant B-lymphoproliferative disease' [3] and a similar approach may prove beneficial. There have been isolated reports of RA patients treated for leukaemias or lymphomas with prolonged remissions of the RA after chemotherapy and another patient had a 2-year remission of RA following bone marrow transplantation for aplastic anaemia [4].

The major concern with combination second-line therapy is the possibility of synergism for the adverse toxic effects of the medications. There is a need to demonstrate safety as well as efficacy for any advocated combination of agents.

Selection of a combination of agents is empiric since the mechanism of action of most second-line drugs is not well understood. Even the presumed mechanism of action may not account for all the efficacy or toxicity of a given agent. While drugs with similar toxicity are often not used together, reports of many combinations have included drugs with overlapping toxicity and have shown reasonable tolerability.

Young and Scherbel used combinations of these drugs in their respective practices in the USA for several decades [5]. Apparently many patients achieved satisfactory results but these results were never reported or published. Use of a combination of second-line agents in treating resistant RA was first reported by Sievers and Hurri in 1963 [6]. These investigators studied an antimalarial (usually chloroquine) and parenteral gold in combination and singly. Major improvement or remission was reported in more patients receiving combination therapy than those receiving single drug therapy with either antimalarials or gold.

Increased enthusiasm for combination therapy developed in 1982 with the publication of a series of 17 patients treated by McCarty and Carrera [7]. These patients had progressive, erosive RA that was refractory to conventional therapy including gold injections. The patients were treated with hydroxychloroquine, followed by either cyclophosphamide or azathioprine. The alternate cytotoxic drug was then added. Disease suppression was seen in 14 of the 17 patients within 16 months with remissions reported in five patients. A follow-up study by this same group [8] on 31 patients revealed only one patient with a failure to respond. The three failures from the earlier study responded to longer treatment. Sixteen patients were ‘in remission’ within 24 months.

These dramatic results encouraged further study of combination therapy. At the 1993 ACR meeting in San Antonio, a concurrent session was devoted to combination therapy in RA [9–14]. The results presented in this session mostly mirror the results found in the literature. Combinations of more than two second-line agents have not been evaluated in randomized controlled clinical trials. Two drug combinations studied in open trials suggest that these combinations are efficacious with acceptable levels of toxicity. However, randomized double-blind trials of two drug combinations rarely demonstrate benefit of the combination in excess of that seen with at least one of the medications alone. The toxicity of combinations may be slightly increased over single drug therapy but is acceptable. Some investigators suggest that the failure of controlled trials to demonstrate a significant difference is a problem with sample size. Nevertheless, even a meta-analysis of controlled trials failed to demonstrate clear advantage of two drug combinations [9].

Why do the double-blind trials reach conclusions at variance with the open studies or clinical perception? The purpose of controlled studies is to investigate a specific treatment in specific and similar populations of patients. It is possible that the protocol restrictions select a patient population that does not reflect the population seen in open studies. However, review of these studies does not reveal readily identifiable differences in patient populations.

Another purpose of masking the treatments in a trial is to avoid conscious or unconscious bias on the part of the observer and the patient. Expectancy bias, either favouring or opposing a given therapy, is always present and can impact results. Perhaps the rationale for combination therapy makes the physician desire therapeutic success. Controlled trials are better suited to answering the question of comparable efficacies and tolerabilities although these answers may not be applicable to a specific patient or a more generalized patient population.

Two-drug combinations merit further study but the practicing rheumatologist should expect and require demonstration of efficacy to compensate for the slight but significant increase in toxicity. These answers are best obtained through randomized controlled trials of sufficient size and duration to give appropriate power to the results.
Similarly, multiple drug combination therapy have been suggested for early use in RA patients [15, 16]. These combinations appear promising but should also be submitted to the same scientific rigor if they are to be recommended for general use of the practicing physician. It is possible that multiple drug combinations will be more effective than two second-line agent combinations but it is also likely that the efficacy will be accompanied by greater toxicity.

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REFERENCES

ANNOUNCEMENTS AND CALENDAR FOR 1994

September 1  Closing date for the Margaret Holroyd Essay Prize.
September 5  MRCP Course, St Mary's Hospital, London.
September 16  Closing date for BSR Non-clinical Bursary.
September 22–23  Heberden Round (Prof. P. Maddison), Assembly Rooms, Bath.
October 12–13  BSR/BHRP Joint Meeting, Staffordshire.
October 28  Closing date for the Michael Mason Prize.
November 25  Closing date for the 1993 Senior Registrar Travelling Fellowship.

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