COMBINATION THERAPY WITH CYCLOSPORIN IN RHEUMATOID ARTHRITIS

D. E. YOCUM
Department of Medicine, Arizona Arthritis Center, University of Arizona, Tucson, AZ 85724, USA

SUMMARY
The role of combination therapy in rheumatoid arthritis (RA) is increasing with the development of new treatment modalities. Past combinations of slow-acting anti-rheumatic drugs resulted in either excessive side-effects or lack of efficacy over single-agent therapy. However, refined methodology and a better understanding of the mechanism of action of newer agents have led to improved combinations, which appear more promising. In particular, in a 6 month, randomized, double-blind trial, the combination of cyclosporin (CyA) with methotrexate was found to be more efficacious than methotrexate alone, providing enhanced clinical benefit, without evidence of increased adverse events. The mean final dose of 2.97 mg/kg per day CyA in combination was lower than that required for CyA monotherapy. Further, a new formulation of CyA, with improved bioavailability, should provide enhanced efficacy and an acceptable safety profile, not only as monotherapy but also in combination with agents such as methotrexate. These developments offer new hope to patients with progressive RA, which is unresponsive to conventional therapy.

KEY WORDS: Rheumatoid arthritis, Combination therapy, Cyclosporin.

RHEUMATOID arthritis (RA) is a disease of unknown aetiology, which affects ~1% of the population worldwide [1], and is characterized by a chronic, proliferative and erosive synovitis that waxes and wanes over the lifetime of the affected individual. RA typically presents in the third and fourth decade of life, and is associated with significant morbidity and mortality, which result in major medical and social costs [2-4]. It is now possible to identify those patients destined to have aggressive disease with an accuracy of >80% [5], using biological and clinical predictors of severe, progressive disease, such as rheumatoid factor seropositivity, the shared genetic epitope (DR-β-1), persistent joint swelling and radiological erosions.

Despite the poor outcome associated with RA, little progress has been made in developing new treatments for this disease. Single-agent therapies have had limited success: typically, less than one-third of patients remain on an individual treatment after 1 yr [6], and although greater numbers of patients remain on methotrexate therapy beyond 1 yr, few achieve remission [7]. These poor results have provoked a major re-evaluation of treatment, and over the last 5 yr there has been a growing commitment to develop appropriate and effective combination therapy for RA. Many of the early combinations failed to take into account the underlying pathophysiology of RA and the specific characteristics of the therapies involved. However, lessons from oncology have taught physicians that by capitalizing on the strengths of the drugs, combination therapy can achieve more effective treatment with greater remissions, while minimizing the toxicities of the individual agents. The most logical combinations involve agents with dissimilar mechanisms of action and side-effect profiles.

EARLY COMBINATIONS
Early attempts at combination therapy in RA were somewhat limited in their success, with most trials using combinations of standard disease-modifying drugs [8-10]. Not only were many of these trials poorly designed, but the numbers of patients were inadequate, resulting in poor data, and most were reported only in abstract form with no clear conclusions. Nevertheless, these early trials demonstrated the importance of developing well-organized studies with appropriate numbers of patients and more specific drugs. Further combination studies with agents such as gold and D-penicillamine are unlikely to provide useful information, as the mechanisms of action of these agents are poorly delineated.

A variety of aggressive drug combinations have been tried in RA, most notably involving cytotoxic therapy. For example, an open, retrospective study was reported in 31 patients with severe refractory RA, who received a combination of cyclophosphamide, azathioprine and hydroxychloroquine, administered sequentially [11]. While over three-quarters of the patients either achieved remission or showed an extremely positive response, excessively high rates of neoplasia (4/31) and infection with death were observed. Hence, while cytotoxic combination therapies might be more effective than standard single-agent therapies in RA, the increased morbidity and mortality associated with such combinations is unacceptable.

RECENT COMBINATIONS
Methotrexate is considered by many rheumatologists to be the second-line drug of first choice for patients with RA [12], as it is capable of controlling clinical signs of inflammation, and its effects are sustained for longer...
than those of other slow-acting drugs [13, 14]. Consequently, the role of methotrexate in combination therapy for RA has been examined in a number of studies in recent years. The combination of methotrexate and azathioprine produced a 71% improvement in joint count in an open trial [15], although a double-blind trial found no difference between this combination and methotrexate alone at 24 and 48 weeks [15, 16]. However, other combinations involving methotrexate appear more promising [17, 18]. For example, the combination of methotrexate and sulphasalazine was found to be more effective than methotrexate alone, when given to patients who had failed on sulphasalazine [17]. Similarly, the combination of methotrexate plus sulphasalazine and plaquenil was more effective than both methotrexate as monotherapy, and the combination of sulphasalazine with hydroxychloroquine, in a double-blind trial [18].

CYCLOSPORIN AND METHOTREXATE
The two major cells involved in rheumatoid synovitis are the T cell and the macrophage. It has been suggested that activated T cells release lymphokines, which stimulate monocytes/macrophages to release a variety of monokines, growth factors and other inflammatory mediators [19]. Synoviocytes are then activated to form a pannus, endothelial cells are stimulated to proliferate and form new blood vessels, and osteoclasts are activated to erode bone. A logical approach to the treatment of RA, therefore, is to use a combination of drugs that will down-regulate the activities of both T cells and monocytes/macrophages. One such combination is that of methotrexate with cyclosporin (CyA); these agents work at different stages of the inflammatory pathway and via different mechanisms of action: methotrexate exerts its inhibitory effects on interleukin (IL)-1, macrophages and monocytes [20], while CyA inhibits IL-2 production and T-cell activity [21].

In addition to their potential combined biological effects [22, 23], there are a number of other reasons why methotrexate and CyA are suitable agents for combination therapy in RA. Both agents have complementary side-effect profiles and are beneficial as monotherapies, although while CyA appears to be disease modifying, methotrexate does not alter erosive disease (Fig. 1) [12, 24]. Further, true synergism between these agents was suggested by the results of a study in type II collagen arthritis in rats, in which the combination was shown to have marked efficacy [25].

Based upon this information, and a preliminary open study reporting efficacy in 20 RA patients [26], a multicentre, double-blind, randomized trial of low-dose CyA or placebo in combination with methotrexate was conducted in 148 patients with definite or classical RA [27]. Patients were required to have evidence of active inflammation, despite partial but substantial responses to prior methotrexate treatment, and were randomized to receive CyA or placebo for 6 months. After 6 months, patients on placebo were changed to CyA, and all patients were followed for an additional 6 months. The starting dose of CyA was 2.5 mg/kg per day, and was increased by 0.5 mg/kg per day, depending on clinical response and serum creatinine levels. The dose of methotrexate remained unchanged.

At the end of the 6 month, double-blind period, statistically significant improvements were observed in the combination group compared with the placebo group: tender and swollen joints counts \( (P = 0.02 \text{ and } 0.005 \text{ respectively}) \), physicians' global assessment of disease activity \( (P < 0.001) \), patients' global assessment of disease activity \( (P < 0.001) \), joint pain \( (P = 0.04) \) and degree of disability \( (P < 0.001) \). Thirty-six patients (48%) in the combination group, but only 12 (16%) in the placebo group, met the 1993 American College of Rheumatology criteria for improvement, i.e. improvement of >20% in the numbers of tender and swollen joints, and improvement in three of five other variables (Fig. 2) [27]. While there were increases in serum creatinine and diastolic blood pressure in the combination group, the number of adverse events resulting in patient drop-out was not significantly different between the groups. No unexpected adverse events were seen, and immunological evaluation demonstrated no adverse immune side-effects. [27] During the second 6 months, after open cross-over from placebo to CyA, patients achieved similar clinical results [28]. The mean final dose of CyA was 2.97 mg/kg per day in the combination group, which was lower than that in a previous placebo-controlled trial of CyA alone (3.8 mg/kg per day) [29].

Whether these results represent a true biological synergism remains to be tested. A drug such as CyA may, by reducing the glomerular filtration rate, increase the half-life of methotrexate. Yet if this were the case, an increase in methotrexate-associated side-effects might have been observed. However, the study size may be too
small to detect such an interaction. Pharmacokinetic interaction studies are now ongoing to evaluate this. Alternatively, the improved efficacy may reflect an effect of CyA on the minimal drug resistance of synovial cells, increasing their sensitivity to methotrexate. Future studies will help to confirm the underlying reasons for the greater efficacy of the combination.

**FUTURE COMBINATIONS**

A number of other combinations involving CyA may be effective in the treatment of RA. *In vitro* data on the combination of CyA and chloroquine suggest biological interactions [30, 31], although no studies have been performed. In addition, data from a preliminary trial of CyA in patients partially responsive to injectable gold appear encouraging [26], although the rationale for this combination is unclear.

A new micro-emulsion formulation of CyA is now available (Neoral®), which provides more predictable and reliable absorption without an increase in adverse reactions [32]. The improved pharmacokinetic profile and bioavailability of the new formulation suggest improved clinical efficacy at a lower dose and thus a reduced cost; the relative bioavailability of CyA from the new formulation is ~20% greater than that from the same dosage of standard formulation. The new formulation should expand the clinical potential of CyA, both as monotherapy and in combination with agents such as methotrexate.

The future of combination therapy in RA depends upon the development of new agents, a better understanding of the pathophysiology of this disease, the ability to identify patients with a poor prognosis at presentation, and the availability of funding to support controlled, long-term studies. In addition, it is important to avoid the inclusion of patients with different clinical presentations, different disease durations and different histologies, in the same multicentre study. The wide variability of response observed in such studies reflects the heterogeneity of the patients involved.

The development of monoclonal antibodies, especially the chimeric, humanized type, together with advances in molecular biology, have provided us with a wide array of potentially useful tools for use in combined therapy for RA. Recently developed examples include anti-CD5, anti-CD4, anti-major histocompatibility complex class II, anti-IL-2 receptor, anti-T cell receptor, pseudomonas exotoxin conjugates...
and the mass production of a variety of biological therapies [33, 34]. In addition, the number of immuno-modulatory drugs available has increased greatly; of these, agents such as rapamyacin may be of use in combination with CyA.

CONCLUSIONS

Combination therapy is a viable means of decreasing both symptoms and disease progression in RA. The potential for combined therapy in RA is vast, given the number of patients affected and the continuing development of new treatment modalities. One logical combination is that of methotrexate with CyA: both agents are effective as monotherapies, and they have distinct mechanisms of action, side-effect profiles and dosing schedules. In a recent double-blind, randomized study, patients with severe RA and only partial responses to methotrexate had clinically important improvement after combination therapy with CyA and methotrexate, without a substantial increase in adverse events. Long-term follow-up of patients receiving this combination is required, to determine whether the benefit is sustained, whether the agents might be discontinued temporarily or permanently, and whether long-term safety is maintained. Preliminary in vitro and in vivo data on CyA in combination with plaquenil or gold are also encouraging. To achieve greater success and stronger data, future trials should stage patients according to various clinical and immunological parameters. The development of successful combination therapy in RA could then be extended into a variety of other diseases such as scleroderma, systemic lupus erythematosus and multiple sclerosis.

REFERENCES

20. Kremer JM. Methotrexate (MTX) induces significant changes in IL-1, IL-2, IL-6 and IL-8 but not lymphocyte markers in patients (PTS) with rheumatoid arthritis (RA). Arthritis Rheum 1993;36(suppl.):S77 (abstract).


