Combination cyclosporine and (hydroxy)chloroquine in rheumatoid arthritis

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ABSTRACT
Antimalarials are attractive candidates for combination therapy. In vitro experiments have revealed a synergistic mode of action of cyclosporine and chloroquine which could not, however, be confirmed in a clinical trial.

Introduction
In the treatment of rheumatoid arthritis (RA), a rationale for combination therapy with two or more disease modifying anti-rheumatic drugs (DMARDs) has emerged from the failure of monotherapy with a single DMARD to provide remission in most patients. The administration of two or more DMARDs can overcome this problem if the DMARDs have different toxicity patterns to avoid cumulative toxicity (1).

For this reason, the antimalarials are attractive candidates for combination therapy, since most other DMARDs are nephrotoxic or hepatotoxic. Another goal of combination DMARDs is to use drugs with mechanisms of action that can potentiate each others’ efficacy (i.e., that are synergic) (2).

In this paper two studies of the combination of cyclosporine plus (hydroxy)-chloroquine are described: first an in vitro study, followed by a clinical study.

In vitro synergy of (hydroxy)chloroquine and cyclosporine
The intracellular mechanism of action of cyclosporine is known in detail, making this drug an attractive partner for use in combination with other agents with unknown modes of action (3).

Therefore, investigations were performed of the in vitro effects of the combination of chloroquine and cyclosporine in defined cell populations. This combination had been shown to inhibit in a synergistic manner the in vitro proliferation of peripheral blood mononuclear cells (4, 5) and the production of interferon gamma by rheumatoid synovial tissue-derived cloned T cells (6).

On these results, a mechanism of action of chloroquine on T cells was proposed, as well as a theory concerning the synergy of the drug interaction. T cell proliferation was used as an indicator for the effects of the combination of cyclosporine and chloroquine on T cells. Chloroquine appeared to inhibit T cell proliferation following activation by way of the T cell receptor (7). At least two mechanisms could be identified: (i) chloroquine inhibited the internalization and subsequent degradation of the interleukin-2 (IL-2) receptor complex, processes known to be important in post-membrane intracellular signaling by way of IL-2, without interfering with IL-2 receptor expression; and (ii) the production of IL-2 was inhibited by chloroquine, at the levels of both transcription and protein release (7).

The synergistic mode of action of cyclosporine and chloroquine on activated T cells in vitro could be explained as follows: cyclosporine primarily inhibits IL-2 production at the transcriptional level, while chloroquine primarily inhibits the responsiveness of T cells to IL-2 (7). The final result is the synergistic inhibition of IL-2 production and T cell proliferation (7).

Combining chloroquine and cyclosporine in early RA
Studies from the mid-1980s and the 1990s have documented that cyclosporine at a dosage of 2.5 - 5 mg/kg/day can alleviate the symptoms of inflammation in patients with RA (8). Later studies indicated that cyclosporine also inhibits radiologic progression (9). Since there was doubt as to whether cyclosporine alone could maintain an acceptable long-term clinical response in patients with RA, studies of combination therapy with cyclosporine have been conducted, including the successful combination of cyclosporine and methotrexate (10). Based on in vitro data, we decided to study the combination of chloroquine...
and cyclosporine (11). The study population consisted of patients with recent-onset RA who were treated initially with chloroquine for 16 weeks. Thereafter, patients with a suboptimal clinical response to chloroquine monotherapy were randomly assigned to the double-blind addition of either placebo or low-dose cyclosporine (1.25 mg/kg/day or 2.50 mg/kg/day) for a further 24 weeks. During the double-blind period - between entry and week 24 - all groups showed improvement in most efficacy parameters. The patients treated with cyclosporine showed a significantly larger decrease in the tender joint count than both of the other groups after 24 weeks, while no other between-group differences were statistically significant. The most common adverse events were gastrointestinal complaints, seen in about 20% of the patients with similar patterns in each group. However, a temporary increase in serum creatinine occurred more often in the cyclosporine groups, especially in the 2.5 mg group, than in the patients receiving placebo.

Conclusions regarding treatment with chloroquine plus cyclosporine
The promising synergy seen in vitro between cyclosporine and chloroquine was not observed to the same extent in the clinical study. The results of the study were influenced by the placebo patients who continued - unexpectedly - to improve after randomization. Moreover, one could question whether the design of the study (step-up, 3 arms) might have influenced the results. Furthermore, the study was influenced by toxicity, especially gastrointestinal toxicity and nephrotoxicity. In particular, an unacceptable increase of > 30% occurred more frequently in the 2.5 mg cyclosporine group than was expected on the basis of previous studies (12).

It is possible that the combination of hydroxychloroquine with cyclosporine may be less toxic, since chloroquine unfavorably influences renal function in contrast to hydroxychloroquine (13). Indeed, several small preliminary studies suggest efficacy for the combination of cyclosporine and hydroxychloroquine (14, 15), although formal studies to compare monotherapy with either drug are not available. Future studies of the combination of cyclosporine and antimalarials might be performed using hydroxychloroquine, since there does not appear to be a place for the combination of cyclosporine with chloroquine.

References