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). Based 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

1. FURST DE: Clinical pharmacology of combinaton DMARD therapy in rheumatoid arthritis. *J Rheumatol* 1996; 23 (S44): 86-90.
2. HARRIS JR ED: The rationale for combination therapy of rheumatoid arthritis based on pathophysiology. *J Rheumatol* 1996; 23 (S44): 2-4.
3. MORRIS R: Modes of action of FK 506, cyclosporin A and rapamycin. *Transplan Proc* 1994; 26: 3272-5.
4. DIJKMANS BAC, DE VRIES E, DE VREEDE TM: Synergistic and additive effects of disease modifying anti-rheumatic drugs combined with chloroquine on the nitrogen-driven stimulation of mononuclear cells. *Clin Exp Rheumatol* 1990; 8: 455-9.
5. VAN LOENEN HJ, DIJKMANS BAC, DE VRIES E: Effects of cyclosporine and chloroquine on the nitrogen-driven cell proliferation and Ig production of human mononuclear cells. *Agents Actions* 1990; 29: 103-4.
6. LANDEWÉ RBM, MILTENBURG AMM, BREEDVELD FC, DAHA MR, DIJKMANS BAC: Cyclosporine and chloroquine synergistically inhibit the interferon gamma production by CD4-positive and CD8-positive synovial T cell clones derived from a patient with rheumatoid arthritis. *J Rheumatol* 1992; 19: 1353-7.
7. LANDEWÉ RBM, MILTENBURG AMM, VERDONK MJA *et al*.: Chloroquine inhibits T-cell proliferation by interference with IL-2 production and responsiveness. *Clin Exp Immunol* 1995; 102: 144-51.
8. RICHARDSON C, EMERY P: Clinical use of cyclosporin in rheumatoid arthritis. *Drugs* 1995; 50 (S1): 26-36.
9. PASERO G, PRIOLO F, MARUBINI E *et al*.: Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporin. *Arthritis Rheum* 1996; 39: 1006-15.
10. TUGWELL P, PINCUS T, YOCUM D *et al*.: Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Eng J Med* 1995; 333: 137-41.
11. VAN DEN BORNE BEEM, LANDEWÉ RBM, GOEI THÉ HS *et al*.: Combination therapy in recent onset rheumatoid arthritis: A randomised double blind trial of the addition of low dose cyclosporine to patients treated with low dose chloroquine. *J Rheumatol* 1998: 25: 1493-8.
12. LANDEWÉ RBM, GOEI THÉ HS, VAN RIJTHOVEN AWAM, BREEDVELD FC, DIJKMANS BAC: A randomized, double-blind 24-week controlled study of low-dose cyclosporine versus chloroquine for early rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 637-43.
13. LANDEWÉ RB, VERGOUWEN MS, GOEI THÉ HS, VAN RIJTHOVEN AWAM, BREEDVELD FC, DIJKMANS BAC: Antimalarial drug induced decrease in creatinine clearance. *J Rheumatol* 1995; 22: 34-7.
14. SALAFFI F, CAROTTI M, CERVINI C: Combination therapy of cyclosporine A with methotrexate or hydroxychloroquine in refractory rheumatoid arthritis. *Scand J Rheumatol* 1996; 25: 16-23.
15. TIRRI G, LAMONTAGNA G, SALAFFI F *et al*.: Combination therapy with cyclosporin and hydroxychloroquine in early active severe rheumatoid arthritis. *Arthritis Rheum* 1997; 40: S97.