# Combination of Cyclosporine and Leflunomide versus Single Therapy in Severe Rheumatoid Arthritis

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***ABSTRACT.*** ***Objective.*** This study assessed the efficacy and safety of combination (COMB) of cyclosporine (CSA) and leflunomide (LEF) versus each drug alone, in the treatment of severe rheumatoid arthritis (RA).

***Methods.*** One hundred six patients with active RA refractory to at least one disease modifying antirheumatic drug (methotrexate obligatorily) were entered into a 12-month open, prospective trial and were randomly allocated to receive either CSA 2.5 to 5 mg/kg/day, or LEF 20 mg/day, or the combination of both at the same initiating dose.

***Results.*** The American College of Rheumatology 50% (ACR50) response rates for the 3 groups were COMB 80%, CSA 40%, and LEF 42% (p = 0.001). Combination therapy was also significantly better than CSA and LEF at the more stringent 70% response rate (69% vs 34% vs 30%, respectively; p = 0.001). Comparable Disease Activity Score 28 reduction rates were noted at trial termination for all 3 treatment arms: COMB –2.74 vs CSA –2.53 vs LEF –2.28 (p nonsignificant). Discontinuation rates were more common in LEF vs CSA arm (p = 0.046). No unexpected or serious adverse drug effects were identified in the combination group during the 12-month period.

***Conclusion.*** The combination of CSA and LEF in patients with refractory RA provided statistically significant benefit in ACR50 and ACR70. Adverse events were not substantially increased. (J Rheumatol 2006;33:486–9)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS COMBINATION THERAPY CYCLOSPORINE LEFLUNOMIDE

Rheumatoid arthritis (RA) is a chronic autoimmune disease of the connective tissue, characterized by joint inflammation, joint damage, and articular destruction, associated with substantial morbidity and mortality. According to the most recent epidemiological study performed in Greece, the prevalence of RA in the adult population is 0.67%[1].

We compared the efficacy and safety of 2 established disease modifying antirheumatic drugs (DMARD), cyclosporine (CSA; Sandimmun Neoral®, Novartis) and leflunomide (LEF; Arava™, Aventis), and their combination (COMB), in patients with RA refractory to at least one DMARD [methotrexate (MTX) compulsorily].

## MATERIALS AND METHODS

This study was a 2-center, open randomized trial in a parallel design.

Dosage and monitoring of CSA and LEF was in accord with product labeling.

Clinical variables were assessed at baseline, at 2-week intervals for the first month, every month for Months 1–6, and every 2 months thereafter. The primary efficacy endpoint was the rate at which the patient cohort achieved 20%, 50%, and 70% improvement in American College of Rheumatology (ACR) criteria[2]. A secondary outcome variable was the index of the Disease Activity Score (DAS) in a 28-joint count (DAS28)[3].

To indicate the trend in the first 12 months of treatment, the mean percentage changes after 6 and 12 months are given together with their standard error of mean (SEM). Both changes after 6 and 12 months were compared among the 3 treatments by means of one-way ANOVA.

## RESULTS

Mean disease duration in COMB patients was 7.2 ± 6.3, in CSA 6.4 ± 6.2, and in LEF 7.3 ± 6.9 years (p nonsignificant).

Patient progression through the study is presented in Figure 1. Four patients in the combination group, 2 in the CSA group, and 9 in the LEF group were withdrawn from the study before reaching 12 months of therapy (5.7% in CSA vs 25% in LEF; p = 0.046). A Kaplan-Meier analysis (Figure 2) showed that overall discontinuations were not similar in the 3 treatment groups, since a significant difference existed in favor of CSA versus LEF (p = 0.008). Adverse events that led to treatment discontinuation are presented in Table 1. A 72-year-old female patient in the LEF group died after 20 weeks of therapy. The cause of death was thought to be acute myocardial infarction, a reason that probably was not correlated with LEF administration, since the patient had a known history of coronary heart disease.

Daily dose of CSA ranged from 2.5 to 4.6 mg/kg in the CSA group and from 2.5 to 4.3 mg/kg in the combination group; at 48 weeks the mean daily dose was 3.5 ± 0.9 mg/kg and 3.3 ± 0.9 mg/kg, respectively. The LEF daily dose was 20

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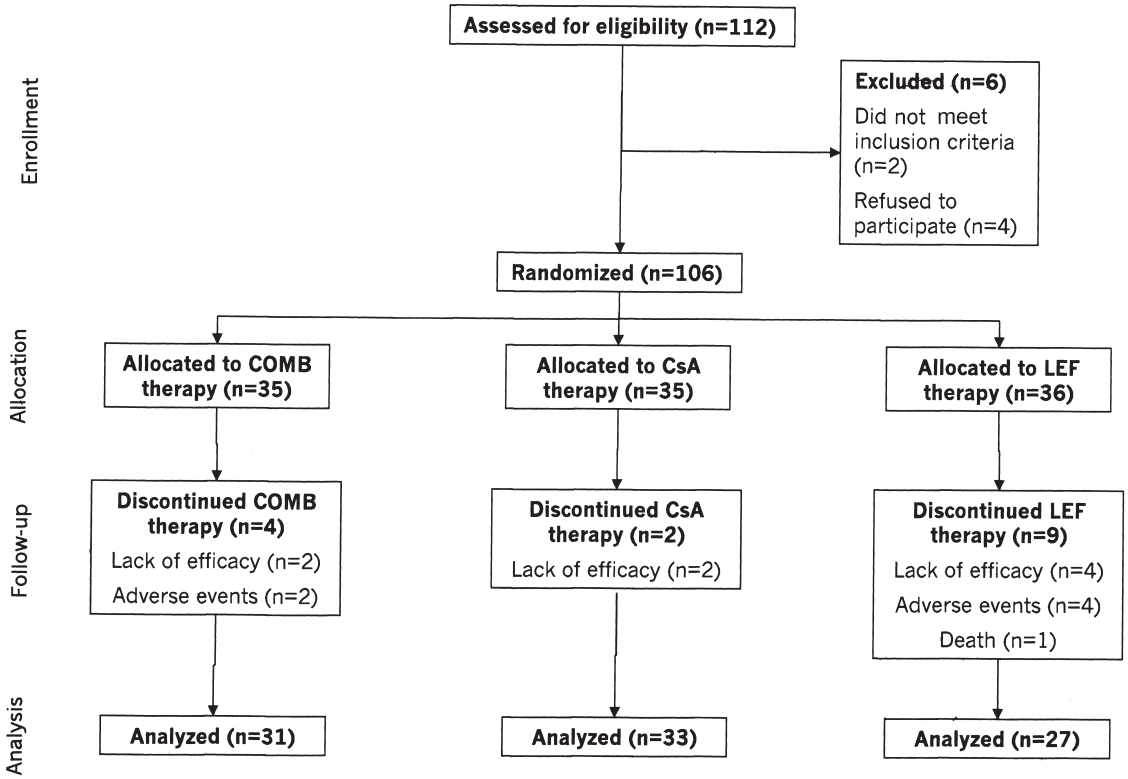


*Figure 1.* Allocation of 106 patients with RA to study arms.

mg in both groups. At Week 48, combination treated patients were taking less prednisolone than the CSA and LEF treated patients (3.8 ± 0.41 mg vs 5.2 ± 0.51 mg and 4.7 ± 0.39 mg, respectively; $p < 0.02$).

No difference was observed in ACR20 at the end of the study (COMB 82%, CSA 82%, LEF 69%; p nonsignificant), while the more stringent ACR50 and ACR70 response rates were in favor of the combination treatment group (80%, 40%, 42% and 69%, 34%, 30%, respectively; $p = 0.001$). All 3 therapeutic regimens showed significant reduction of DAS28 at the expiry of the trial (COMB –2.74 ± 0.22, CSA –2.53 ± 0.17, LEF –2.28 ± 0.22; p nonsignificant). Nevertheless, 10 combination treated patients achieved a DAS28 < 3.2, compared to 6 in the CSA group and 5 in the LEF group. Mean improvements in individual components of the ACR response criteria and other parameters are summarized in Table 2.

*Table 1.* All clinical adverse experiences by management arm and treatment withdrawals*.

| Adverse Event | COMB | CSA | LEF |
|---|---|---|---|
| Alopecia | 3 | 0 | 12 |
| Weight loss | 0 | 0 | 1 |
| Diarrhea | 3 | 0 | 2 (*1) |
| Erythema multiforme | 0 | 0 | 2 (*2) |
| Gingival hyperplasia | 0 | 2 | 0 |
| Headache | 3 | 2 | 2 (*1) |
| Herpes zoster infection | 1 (*1) | 0 | 0 |
| Hirsutism | 1 | 17 | 0 |
| Hypertension | 3 (*1) | 4 | 2 |
| Nausea | 5 | 0 | 1 |
| Oral ulcers | 2 | 0 | 1 |
| Paresthesia | 0 | 2 | 0 |
| Rash | 2 | 0 | 4 |
| Upper respiratory infection | 3 | 0 | 2 |
| Total | 26 | 27 | 29 |

The mean serum creatinine concentration increased from baseline to 12 months by 0.06 ± 0.04 mg/dl in the COMB group (p nonsignificant) and by 0.113 ± 0.03 mg/dl in the CSA group ($p = 0.007$). Overall, abnormal findings on liver function tests were reported in 4 patients in the combination group and 9 in the LEF group. In one COMB treated patient and 2 under LEF treatment, γ-glutamyl transferase elevation was remarkable (5 times the upper limit of normal). In all patients, this elevation was entirely reversible when the LEF dosage was reduced to 10 mg/day.

## DISCUSSION

Our data indicate that the combination of CSA and LEF considerably improved certain clinical variables as compared to monotherapy. Moreover, the combined treatment showed no unexpected or serious side effects.

It should be emphasized that in ACR20 and DAS28 indices no significant differences were found among treatment groups. This can be explained by the low sensitivity of the ACR20 index, and by the absence of all body joint evaluation as well as pain and physical function measurement in the DAS28. Therefore the combined treatment achieved statisti-

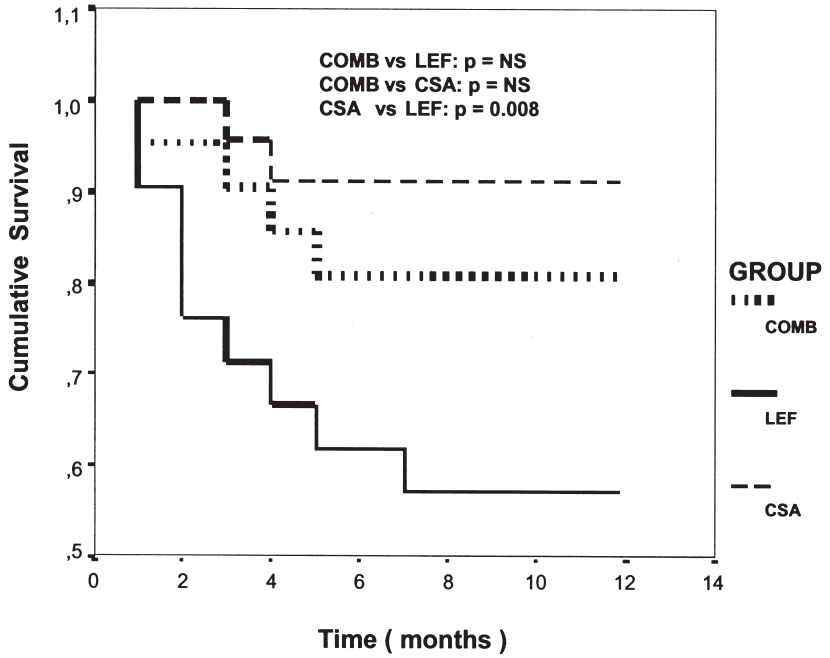


*Figure 2.* Kaplan-Meier analysis showing overall discontinuations in the 3 treatment groups.

*Table 2.* Mean improvements in individual components of the ACR response criteria and other clinical and laboratory parameters. Outcomes are given as percentages (SEM), after 6 and 12 months of treatment.

| Outcome Measures | COMB | | CSA | | LEF | |
|---|---|---|---|---|---|---|
| | 6 mo | 12 mo | 6 mo | 12 mo | 6 mo | 12 mo |
| No. of tender joints | –54.24 (2.9) | –81.35 (3.4) | –47.34 (2.1) | –76.73 (1.7) | –47.32 (3.1) | –66.8 (4.4) |
| No. of swollen joints | –51.84 (3.7) | –78.90 (3.9) | –44.31 (2.6) | –79.90 (2.9) | –40.65 (5.0) | –55.6 (5.4)***,## |
| Degree of disability | –53.1 (6.1) | –78.7 (6.5) | –51.5 (5.7) | –62.3 (5.9) | –58.2 (7.4) | –65.8 (7.3) |
| Morning stiffness | –84.3 (7.5) | –92.0 (9.8) | –78.1 (8.1) | –83.0 (8.4) | –80.6 (9.3) | –88.9 (9.2) |
| Pain | –50.0 (4.1) | –66.0 (4.5) | –45.0 (3.6) | –51.8 (3.9)* | –39.0 (3.1)* | –40.9 (2.8)*,# |
| Global (patient) | –63.4 (4.7) | –78.7 (6.5) | –53.1 (5.2) | –62.3 (5.9) | –59.8 (5.5) | –65.8 (7.3) |
| Global (physician) | –59.9 (5.1) | –77.8 (6.4) | –51.2 (5.3) | –59.8 (5.8) | –58.1 (5.4) | –64.8 (7.1) |
| Hemoglobin | 5.58 (4.0) | 16.5 (5.0) | –0.65 (1.3) | 1.7 (1.9)** | 3.0 (1.13) | 5.7 (1.8)* |
| ESR | –25.2 (9.6) | –31.7 (16.7) | –1.71 (8.9) | –2.4 (11.5)† | –26.3 (7.3) | –41.4 (8.0) |
| CRP | –12.4 (23.3) | –42.1 (25.5) | –18.3 (11.2) | –21.5 (29.3) | –23.4 (18.8) | –44.7 (11.6) |

* In favor of COMB (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). # In favor of CSA (# $p < 0.05$, ## $p < 0.001$). † In favor of LEF ($p < 0.05$). ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

cally significant improvement only in the more stringent response criteria (ACR50 and ACR70), suggesting that the clinical improvement was generalized and impressive. The alleviation of steroid dose was important in the group of patients under combined therapy, which also shows the effectiveness of the combination. A rational and simple interpretation of the good response in the combined therapy group is that both drugs were administered in relatively high doses. Moreover, CSA acts mainly at the T cell level, suspending the transcription of critical cytokine genes, while LEF inhibits uridine and pyrimidine generation and subsequent RNA and DNA synthesis.

It is encouraging that no serious unexpected short-term toxicity was reported. Although both drugs affect blood pressure, severe deterioration of preexisting hypertension was not noted in the COMB group, except in the case of one withdrawn patient. CSA was the unique therapy, the administration of which was not accompanied with dropouts due to adverse events. This is in accord with recently published studies showing low discontinuation rates of CSA due to adverse events in comparison with MTX or other DMARD[4,5]. Five patients showed serum creatinine concentration increasing to ≥ 30%; however this elevation was reversible by dosage reduction. However, it must be noted that in CSA treated patients, a sig-

nificant creatinine increase was recorded at the end of the trial. After appraising the longterm efficacy and safety of LEF, Kalden, *et al* suggested that upper respiratory tract infections and diarrhea were the most common adverse events[6]. In our study, the most frequent adverse effects were alopecia (33%) and rash (11%). The manifestation of erythema multiforme in 2 patients in this group was an unpredictable and potentially harmful adverse experience.

*Does combination therapy make a difference compared to single therapy.* Verhoeven, *et al* reviewed new developments in the combined drug treatment of RA and concluded that a step-down or parallel strategy in general shows more potential than a step-up strategy. Additionally, in late disease, patients with a suboptimal response to MTX improve clinically with the addition of CSA[7]. Going further, Hochberg, *et al* suggested that in patients with an incomplete response to MTX, the addition of CSA, etanercept, infliximab, or LEF was associated with a comparable ratio of ACR response[8]. Effectiveness of combined treatment in our study reached a level equivalent to that of the tumor necrosis factor-α antagonists or interleukin 1 receptor antagonists, in regard to ACR or DAS28 responses[9-12].

Biological therapies resulted in a significant evolution in management of RA over the last decade. However, not all patients can benefit from their use, while serious concerns regarding their longterm safety have been raised[13,14]. Our study indicates that the combination of 2 conventional immunosuppressive DMARD shows an excellent tolerability and safety profile and constitutes an alternative proposal for relief of severe RA. Controlled studies, designed in a double-blind manner, are needed to confirm the efficacy of this combination and to clarify the absence of potential delayed toxicity.

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