CONCISE REPORT

Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study

J F Maillefert, B Combe, P Goupille, A Cantagrel, M Dougados

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Objective: To evaluate whether early combined therapy with methotrexate (MTX) and sulfasalazine (SSZ) during the first year in early rheumatoid arthritis (RA) induces long term beneficial effects, compared with monotherapy, when the further treatment strategy is a free choice.
Methods: Study design: five year multicentre prospective longitudinal trial. Participants: 146/205 patients with RA previously included in a one year prospective randomised trial comparing the effects of treatment with MTX, SSZ, or a combination of both. Criteria for inclusion: patients with early RA (≤1 year duration). Follow up: between the end of years 1 and 5, patients were followed up and treated by their own rheumatologist, who was allowed to indicate any treatment. Outcome measures: disease activity score (DAS), health assessment questionnaire (HAQ), and Sharp/van der Heijde radiological score at baseline and after five years of follow up. Analysis: comparison of the five year follow up DAS, HAQ, and radiological scores in patients given combined and single treatment during the first year.
Results: At the end of the five years of follow up, the patients primarily receiving single or combined treatment had similar mean DAS, HAQ, and radiographic scores.
Conclusion: Treatment of patients with early RA using combined therapy with MTX and SSZ during the first year did not influence the long term inflammatory status, or disability, or structural changes, compared with single disease modifying antirheumatic drug treatment.

It has been suggested that the efficacy of a combination of some disease modifying antirheumatic drugs (DMARDs) is better than DMARD monotherapy in rheumatoid arthritis (RA),[1–5] although negative results have been published.[6] Recently, Landewé *et al* suggested that use of intensive, short term combination treatment in patients with early rheumatoid arthritis (RA), according to the COBRA schedule[4] induces a sustained reduction in the rate of radiological progression.[7] Because this trial compared a combination of methotrexate (MTX), sulfasalazine (SSZ) and prednisolone with SSZ alone, it is difficult to assess whether the long term beneficial effects were due to MTX, prednisolone, or both.

A one year double blind randomised trial comparing MTX alone, SSZ alone, or the combination of both was conducted in patients with early RA.[6] Most of the patients included in this study were followed up prospectively for an additional four years, giving the opportunity to evaluate whether the early combined treatment with MTX and SSZ during the first year induces long term beneficial effects when the further treatment strategy is a free choice, such as observed with the combined therapy with MTX, SSZ, and corticosteroids.

PATIENTS AND METHODS

Study design

We carried out a five year multicentre, prospective, longitudinal follow up study

Participants

The participants comprised 146/205 patients with RA (American College of Rheumatology criteria) with disease duration of <1 year, who participated in a randomised, controlled, double blind 52 week clinical trial of a combination of SSZ and MTX compared with the single components. Criteria for inclusion have been previously described.[6] This study was conducted in three European countries. All patients included in France were subsequently prospectively followed up for four years. During these additional four years, the patients were treated by their own rheumatologists, who were allowed to indicate any treatment. All patients provided their informed consent. The study was approved by the ethics review board of Montpellier (France).

Assessment

The Health Assessment Questionnaire (HAQ), and the disease activity score (DAS) were collected during the randomised trial, and five years after inclusion. Hand, wrist, and foot radiographs were taken during the randomised trial and five years after inclusion. They were evaluated by a single observer unaware of the chronology of the films, according to the Sharp method modified by van der Heijde. The total damage score was obtained for each patient. The intraclass intraobserver coefficient of correlation was >0.85.

Statistical analysis

As a first analysis, the five year DAS, HAQ (analysis of variance (ANOVA)), and radiological score (Wilcoxon) of patients who had been primarily treated with combined therapy were compared with those of patients who had been treated with MTX or SSZ alone.

A second analysis compared the changes between baseline and five years in the DAS, HAQ, and radiological scores of patients who had been primarily treated with combined therapy, compared with those who had been treated with MTX or SSZ alone (ANOVA and Wilcoxon).

A third analysis compared the five year follow up DAS, HAQ, and radiological scores, and the changes between baseline and five years in these scores between three groups of patients (those primarily treated with combined therapy, those primarily treated with MTX, and those primarily treated with SSZ) (ANOVA and Wilcoxon).

Abbreviations: ANOVA, analysis of variance; DAS, disease activity score; DMARDs, disease modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; SSZ, sulfasalazine

Table 1 Treatments given during the five years in patients primarily randomised to be treated with single or combined DMARDs during the first year

	Single therapy	Combination therapy	p Value
Total duration of DMARDs during the 5 years (years), mean (SD)	4.5 (1.1)	4.4 (1.3)	0.5
Number of different DMARDs given during the 5 years of follow up (median)	2	2	0.4
Total duration of primary DMARD given (months), mean (SD)	28.9 (20.4)	31.9 (21.2)	0.4
Patients treated with corticosteroids between years 2 and 5 (%)	40.9	38.2	0.8
Duration of corticosteroids in treated patients (days), mean (SD)	249 (798)	170 (305)	0.6
Cumulative dose of corticosteroids in treated patients (g), mean (SD)	1.4 (2.3)	1.4 (2.4)	0.9

Table 2 Clinical and structural parameters observed at baseline and after five years' follow up in patients primarily randomised to be treated with single or combined DMARDs during the first year

	Single therapy	Combination therapy	p Value
Baseline DAS (mean (SD))	4.2 (0.7)	4.2 (0.8)	0.9
Baseline HAQ (mean (SD))	1.4 (0.7)	1.3 (0.8)	0.5
Baseline radiological score (median (25, 75% centiles))	0 (0, 3)	0 (0, 3)	0.7
5 Year DAS (mean (SD))	2.2 (1.1)	2.2 (1)	0.9
5 Year HAQ (mean (SD))	0.6 (0.6)	0.6 (0.7)	0.9
5 Year radiological score (median (25, 75% centiles))	8.5 (1.5, 17.2)	7.5 (1.1, 27.3)	0.7

Finally, confounding variables were evaluated using the intergroup comparison for treatments administered between the end of years 1 and 5 (ANOVA and the χ^2 test), and using three multivariate analyses in which the independent variables were age, sex, total duration of DMARD treatment during the five years, total duration of corticosteroid treatment between years 2 and 5, and early initiation of single compared with combined DMARD treatment. The dependent variables were the five years DAS, HAQ, and radiological score, respectively.

RESULTS

Two hundred and five patients were included in the one year trial, whose results have been previously reported.[6]

Among the 170 patients enrolled in the trial in France, 2 refused to participate in the follow up, 17 were lost to follow up, and 5 died. Thus, 146 (36 men, 110 women) with a mean (SD) age of 51.1 (14.2) years were prospectively followed up for an additional four years. Thirty eight had been primarily included in the combination group, while 53 were in the MTX and 55 in the SSZ groups (108 patients primarily included in a single treatment group).

Table 1 shows the treatments given during the five years. The mean (SD) duration of DMARDs was 4.5 (1.1) and 4.4 (1.3) years in the single and combination treatment groups, respectively. The total duration of the primary given DMARDs treatment was 28.9 (20.4) months (single therapy group) and 31.9 (21.2) months (combined treatment group) (p=0.4). During the follow up, 17/108 (16%) patients primarily included in a single treatment group were given combination therapy (MTX + SSZ in all), with a median and mean duration of combined treatment of 20 months (0 for the whole population of 108 patients) and 26.6 (16) months (4.2 (11.1) for the whole population of 108 patients).

At baseline, and after five years, there was no difference in the mean DAS, HAQ, and radiological score between patients included in a single DMARD group and those included in the combination group (table 2). At the end of the five years of follow up, 78 (62%; 20 missing values) patients were in remission, defined as a DAS score <2.6. On multivariate analysis, the five year DAS, HAQ, and radiological score were not related to age, sex, total duration of DMARDs and of corticosteroid treatment, or to the early initiation of single compared with combined DMARD treatment.

Similar results were obtained when the differences between the five year follow up and baseline scores were analysed, and when three groups (SSZ, MTX, combination) instead of two (single versus combined treatment) were compared (data not shown).

DISCUSSION

In this study, treatment of patients with early RA using combined MTX and SSZ therapy during the first year did not affect the long term inflammatory status, or disability, or structural changes, compared with single DMARD therapy.

This study might have had a selection bias: more than 20% of the patients primarily included in the one year trial were not followed up for four additional years. However, it is unlikely that such a bias would have influenced the results, because the difference is mostly due to the fact that only some centres involved in the trial participated in the follow up study.

Our results could be considered as surprising because several studies have suggested that some combinations of DMARDs have a better effect on disease activity, functional status, and structural changes than monotherapy.[1–5] However, except for the study by Landewé *et al*,[7] most previous studies did not evaluate the long term effects—that is, at least 3–4 years after completion of the trial.

Our results differ from those of Landewé *et al*.[7] Several hypotheses can be put forward to explain this discrepancy.

The inclusion criteria were similar in the two studies, but with some differences. Early RA was defined differently (<1 or 2 years). Our study recruited outpatients,[6] whereas in the other study we do not know whether patients were recruited from patients admitted to hospital or not.[4] No patients had previously been treated with DMARDs or corticosteroids in the present study, but in the other 20% had received antimalarial drugs.[4] The mean five year follow up DAS and radiological scores were higher in the COBRA study than in the present one, suggesting that the patients had a more severe disease. Our study focused on patients with rheumatoid factors and/or HLA-DR4/1 positive disease, whereas the COBRA study did not. Thus, although several factors suggest that patients included in the COBRA study might have had a more severe disease, this cannot be ascertained.

Secondly, differences in treatment during the follow up might explain the discrepancy. In the present study, there was no difference in the corticosteroid or DMARD treatments between groups, whereas in the COBRA study there was a slightly greater chance of being treated with MTX plus prednisolone, compared with the SSZ group. It is likely that such a moderate difference cannot explain discrepancies.

Finally, the difference in the five year follow up results might be due to differences in the initial treatment. The COBRA study did not include a MTX group alone. However, analysis of the present study showed similar results whether three groups (SSZ, MTX, combination) or two groups (combination therapy versus SSZ or MTX alone) were included. Thus, the most convincing explanation for the difference between the studies is the use of prednisolone in the COBRA study. Landewé *et al* suggested that prednisolone explained the sustained reduction in radiological progression, possibly through marked suppression of inflammation during the first year.[7] This hypothesis is reinforced by the results of this study. In the COBRA study combined therapy improved disease activity to a much greater extent than SSZ alone, with a decrease in the difference of clinical efficacy after prednisolone withdrawal.[4] On the contrary, our study did not demonstrate the superiority of combination therapy after one year.[6] The variation in the long term results between the two studies may be because of this difference in suppression of inflammation, mainly due to the use of prednisolone in the COBRA trial.

Authors' affiliations
J F Maillefert, Centre Hospitalier Universitaire Dijon, and INSERM/ERIT-M 0207, University of Burgundy, Dijon, France
B Combe, Fédération de Rhumatologie, Centre Hospitalier Universitaire Montpellier, and INSERM U475, Montpellier, France
P Goupille, Centre Hospitalier Universitaire Tours, Tours, France
A Cantagrel, Centre Hospitalier Universitaire Rangueil, Toulouse, France
M Dougados, Institut de Rhumatologie, Cochin Hospital, René Descartes University, Paris, France

Correspondence to: Professor M Dougados, Institut de Rhumatologie, Cochin Hospital, 27 rue du Fb St Jacques, 75679 Paris cedex 14, France; maxime.dougados@cch.ap-hop-paris.fr

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M Dougados, Institut de Rhumatologie, Cochin Hospital, René Descartes University, Paris, France

Correspondence to: Professor M Dougados, Institut de Rhumatologie, Cochin Hospital, 27 rue du Fb St Jacques, 75679 Paris cedex 14, France; maxime.dougados@cch.ap-hop-paris.fr

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