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COMBINATION OF SULPHASALAZINE AND METHOTREXATE VERSUS THE SINGLE COMPONENTS IN EARLY RHEUMATOID ARTHRITIS: A RANDOMIZED, CONTROLLED, DOUBLE-BLIND, 52 WEEK CLINICAL TRIAL*


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SUMMARY

To compare the efficacy and safety of sulphasalazine, methotrexate, and the combination of both in patients with early rheumatoid arthritis (RA), not treated with disease-modifying anti-rheumatic drugs previously, we conducted a double-blind, double-dummy, controlled, clinical trial. One hundred and five patients with active, early RA, rheumatoid factor and/or HLA-DR1/4 positive were randomized between sulphasalazine (SSZ) 2000 (maximum 3000) mg daily, or methotrexate (MTX) 7.5 (maximum 15) mg weekly, or the combination (COMBI) of both, and were followed up by a single observer for 52 weeks. The mean change over time per patient, including all visits, in Disease Activity Score (DAS) was: SSZ: —1.6 (95% CI —2.0 to —1.2); MTX: —1.7 (—2.0 to —1.4); COMBI: —1.9 (—2.2 to —1.6); the difference week 0-week 52 (SSZ, MTX, COMBI respectively): DAS: —1.8, —2.0, —2.3, Ritchie articular index: —9.2, —9.5, —10.6, swollen joints: —9.2, —12.4, —14.3, erythrocyte sedimentation rate: —17, —21, —28. Nausea occurred significantly more in the COMBI group. The numbers of drop-outs due to toxicity were SSZ 9, MTX 2, COMBI 5. In conclusion, there were no significant differences in efficacy between combination and single therapy, only a modest trend favouring COMBI. The results of MTX and SSZ were very comparable. Nausea occurred more often in the COMBI group; the number of withdrawals due to adverse events did not differ significantly.

KEY WORDS: Combination therapy, Sulphasalazine, Methotrexate, Early rheumatoid arthritis.

The treatment of rheumatoid arthritis (RA) in its early phase relies on pharmacological means. Since RA is a disease which is often characterized by early occurring progressive and irreversible joint damage [1], and in the early phase the disease is probably the most responsive pharmacologically [2], drug treatment should be instituted early. The results of current therapy in early RA are not satisfactory due to lack of sufficient response. To overcome this, combinations of anti-rheumatic drugs have been proposed and used, analogous to anticancer treatment [3-6]. The general impression is that while definite conclusions cannot be drawn due to a lack of randomized controlled studies, there are some indications that combination therapy is more effective, but also more toxic. Which drugs to combine and how to use these combinations, e.g. to start with multiple drugs and taper them off, or to start with one drug and, when a satisfactory response is lacking, add another, is unclear.

The present study focuses on RA patients who had early and active disease, and who had not been treated with disease-modifying anti-rheumatic drugs (DMARDs) before. Participants had to have indications of a worse prognosis (rheumatoid factor positive and/or certain HLA types) in order to prevent overtreatment. Methotrexate (MTX) was chosen to be combined with sulphasalazine (SSZ) because both are likely to be superior to some other DMARDs with respect to efficacy and toxicity [7, 8]. Recently, we summarized the studies on this combination; the early impression was that the combination was effective, without a significant rise in toxicity, in patients who had already been treated with other second-line anti-rheumatic drugs [9].

In the present study, we tried to answer the question whether the combination of MTX and SSZ is superior to MTX or SSZ alone, and whether there is a difference between MTX and SSZ in the initial treatment of early RA patients.

PATIENTS AND METHODS

Patient selection

Patients with RA according to the ACR criteria who were aged ≥18 yr, and with symptoms attributable to RA with a duration of 12 months maximum, were included. They were selected from all consecutive patients who attended six peripheral and one academic clinic in a period of 18 months. A positive rheumatoid factor and/or HLA-DR4 and/or HLA-DR1 positivity had to be present. The arthritis had to be active: the Disease Activity Score (DAS) being ≥3.0 (see below). Preceding drug treatment for RA

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*On behalf of members of the STROZON research group.
other than analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) was not allowed. Patients with contraindications to the use of SSZ or MTX were excluded. Informed consent had to be obtained.

Study design

This was a randomized, controlled, double-blind 52 week trial with one observer. Patients were randomized in blocks of six between SSZ plus MTX-placebo, MTX plus SSZ-placebo and the combination of SSZ plus MTX. The study was approved by the ethical review board of each participating clinic.

Treatment

The patients were allocated to initial treatment with SSZ EC 500 mg twice daily increased to 1000 mg twice daily in 10 days, + MTX-matching placebo, 3 tablets/week; or MTX tablet 2.5 mg, 3 tablets in a single dose/week, taken together + SSZ-matching placebo in the same dose as above; or SSZ + MTX, the same dosages as above. All study tablets were prepacked in blister packages.

If a patient had the same or higher DAS (see below) and no prohibitive toxicity after 16 weeks of treatment with the study medication, the medication was changed as follows. The SSZ (or placebo) dose was increased to 6 tablets/day and the MTX (or placebo) dose was increased to 6 tablets/week. Once started, the high dose was continued throughout the study. If the higher dose was not effective after 8 weeks (as defined above), the patient was withdrawn. In the case of tolerable minor toxicity, the SSZ dose (or placebo) was lowered to 2 tablets/day and the MTX dose (or placebo) to 2 tablets/week. If a major severe adverse event (any event possibly related to the study medication causing hospitalization or death, or the possibility of such if the administration of the medication is continued) was suspected or occurred, the patient was immediately withdrawn.

All patients had a concomitant NSAID in a dose which was preferably not altered during the study period. No systematically administered corticosteroids were permitted. When local corticosteroids had to be employed, the treated joint was omitted from evaluation from the time of injection onwards.

Evaluation

The patients were evaluated 2-weekly for the first 4 weeks and 4-weekly thereafter until week 52, 14 visits in total. All clinical evaluations were made by one observer (CJH).

The primary evaluation criterion was the mean change in the DAS over time for each individual patient. The DAS consists of the Ritchie articular index, the number of swollen joints and the erythrocyte sedimentation rate (ESR) [10]. The mean change in DAS over time reflects all the changes relative to baseline and was calculated in the following way: the summation of 0.5 x DAS week 2, 0.5 x DAS week 4 (only 2-week intervals) and the DAS values of the next 12 visits (including week 52) divided by 13, minus the DAS of week 0 for each individual patient.

Secondary evaluation criteria were the number of patients with a good response according to the EULAR criteria [11], the mean change over the first 12 weeks (calculated in the same way as the primary efficacy variable, reflecting early changes) and week 0 and week 52 concerning: the DAS score, the number of painful joints (53 joints), the Ritchie articular index [12], the number of swollen joints (maximum of 44 joints, not graded), pain expressed by the patient on a visual analogue scale (VAS) ranging from 0 to 100 mm, general wellbeing expressed by the patient on a VAS of 0–100 mm, patient and physician global assessment of the actual disease activity (five-point ordinal scale) at each visit, the Health Assessment Questionnaire score and the degree of improvement of disease activity at the final evaluation (on a five-point ordinal scale), grip strength (kPa), the number of patients with an increase in dose, the number of joints having an intra-articular corticosteroid injection.

Compliance was checked by interviewing the patient and pill counting.

Laboratory evaluation, performed every 4 weeks, consisted of ESR, C-reactive protein (mg/l), haemoglobin content (mmol/l) and haematocrit, mean red cell volume (fl), WBC count with differential count, platelet count, alanine and aspartate aminotransferase (IE/ml), gamma glutamyl transferase (IE/ml), alkaline phosphatase (IE/ml) and creatinine in serum (µmol/l).

Toxicity was monitored every visit by interviewing the patients, physical examination and laboratory investigations.

Statistical analysis

All analyses were based on an intention to treat using end point analysis, i.e. the last observation carried forward. The primary evaluation criterion was the mean change in the DAS (see above), reflecting the area under the curve of the DAS corrected for the DAS at baseline. The difference in the values of this corrected area under the curve between the treatment groups was tested by analysis of covariance (ANCOVA).

Analysis of covariance was carried out to correct for differences in baseline values. Comparison of the three treatment groups at week 0 and changes between the week 0 and week 12 and week 52 values, and the mean changes over time of various variables, was made using ANCOVA, Kruskall–Wallis or χ² tests, as appropriate. Survival curves were analysed by the life table technique (log-rank test) using the frequencies together with the time to withdrawal.

A two-sided P value of 0.05 was considered to be statistically significant.

RESULTS

A total of 105 patients were included in the study: 34 in the SSZ group, 35 in the MTX group and 36 in the COMBI group. The baseline characteristics of the
patients are given in Table I. A total of 20 patients withdrew prematurely (before week 52) from the trial. Three patients in the SSZ group and one patient in the COMBI group were withdrawn before the end of their follow-up because of inefficacy. For reasons of toxicity, nine patients in the SSZ group, two in the MTX group and five in the COMBI group ended their participation (see also Table IV). The time to withdrawal was shorter in the SSZ group, compared to the other two treatment groups; the difference was significant \((P = 0.006)\).

The primary evaluation criterion, i.e. the mean change (95% confidence intervals) in DAS, by intention-to-treat analysis, was \(-1.6 \pm 2.0, -1.2\) in the SSZ group, \(-1.7 \pm 2.0, -1.4\) in the MTX group and \(-1.9 \pm 2.2, -1.6\) in the COMBI group. The differences were statistically not clinically significant. In Table II, the differences between the three groups are given using the adjusted means and these were tested by analysis of covariance to correct for the differences in baseline values. In Table III, the results (unadjusted numbers) of the primary and secondary evaluation criteria are given. The numbers of patients with a response according to the ACR criteria [13] at the end of study were 25 for SSZ, 25 for MTX and 28 for the COMBI. According to the EULAR definition [11], the numbers of patients with a good response at the end of study were 14 for SSZ, 15 for MTX and 14 for the COMBI. The distribution in time of good responders (EULAR definition) is depicted in Fig. 2. The time to good response among the good responders tended to be shorter in the SSZ group; a mean of 16.8 weeks compared to 27.2 weeks for MTX and 22.4 weeks for COMBI. In a life table analysis considering all patients, this difference was not statistically significant.

The numbers of patients judging their disease as moderately/much improved at the final assessment were 12/11 in the SSZ-treated group, 12/19 for MTX and 15/16 for COMBI (\(P = 0.0175\)). These numbers for the investigator's final assessment were: SSZ: 9/13; MTX: 15/16; COMBI: 9/22 (\(P = 0.06\)).

Compliance

The percentage of tablets taken was >90% in all patients in all subgroups.

Dose alterations

The dose of the medication was increased in 11 patients in the SSZ group, in 11 in the MTX group and in seven in the COMBI group (NS).

Concomitant medication (excluding the NSAIDs)

Twenty patients in the SSZ group, 15 in the MTX group and 28 of the COMBI patients had any con-

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSZ</th>
<th>MTX</th>
<th>COMBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>34</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.8 (13.0)</td>
<td>54.9 (13.2)</td>
<td>57.0 (12.2)</td>
</tr>
<tr>
<td>Female/male</td>
<td>21/13</td>
<td>23/12</td>
<td>24/12</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>3.1 (1.9)</td>
<td>3.0 (2.3)</td>
<td>2.6 (1.4)</td>
</tr>
<tr>
<td>Rheumatoid factor positive/negative</td>
<td>33/1</td>
<td>33/2</td>
<td>34/2</td>
</tr>
<tr>
<td>HLA-DR1, present/absent</td>
<td>10/24</td>
<td>10/25</td>
<td>10/26</td>
</tr>
<tr>
<td>HLA-DR4, present/absent</td>
<td>18/16</td>
<td>18/17</td>
<td>18/18</td>
</tr>
<tr>
<td>DAS</td>
<td>4.6 (0.8)</td>
<td>4.7 (0.9)</td>
<td>5.0 (0.8)</td>
</tr>
<tr>
<td>No. of painful/tender joints</td>
<td>20.8 (8.6)</td>
<td>20.6 (8.1)</td>
<td>24.8 (9.5)</td>
</tr>
<tr>
<td>Ritchie articular index</td>
<td>15.1 (6.0)</td>
<td>13.4 (6.4)</td>
<td>16.5 (6.3)</td>
</tr>
<tr>
<td>No. of swollen joints</td>
<td>17.0 (7.2)</td>
<td>19.9 (8.4)</td>
<td>20.8 (6.9)</td>
</tr>
<tr>
<td>ESR</td>
<td>50.7 (24.1)</td>
<td>50.3 (26.6)</td>
<td>55.3 (32.2)</td>
</tr>
<tr>
<td>HAQ score</td>
<td>0.97 (0.86)</td>
<td>0.92 (0.84)</td>
<td>1.20 (0.82)</td>
</tr>
<tr>
<td>Nodules present/absent</td>
<td>3/31</td>
<td>4/31</td>
<td>4/32</td>
</tr>
</tbody>
</table>

DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire.

<table>
<thead>
<tr>
<th>Variable</th>
<th>COMBI vs SSZ*</th>
<th>COMBI vs MTX*</th>
<th>MTX vs SSZ*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in DAS over all 52 weeks</td>
<td>0.1 (-0.3, 0.5)</td>
<td>0.04 (-0.4, 0.5)</td>
<td>0.06 (-0.3, 0.5)</td>
</tr>
<tr>
<td>Mean change in DAS over the first 12 weeks</td>
<td>-0.06 (-0.3, 0.2)</td>
<td>0.03 (-0.3, 0.3)</td>
<td>-0.09 (-0.4, 0.2)</td>
</tr>
<tr>
<td>Change in DAS week 52 - week 0</td>
<td>0.3 (-0.2, 0.8)</td>
<td>0.02 (-0.5, 0.6)</td>
<td>0.3 (-0.3, 0.8)</td>
</tr>
<tr>
<td>Change in RAI week 52 - week 0</td>
<td>0.6 (-1.7, 2.9)</td>
<td>-0.85 (-3.2, 1.5)</td>
<td>1.4 (-0.9, 3.8)</td>
</tr>
<tr>
<td>Change in no. of swollen joints, week 52 - week 0</td>
<td>1.8 (-0.9, 4.6)</td>
<td>1.1 (-1.5, 3.8)</td>
<td>0.7 (-2.0, 3.4)</td>
</tr>
<tr>
<td>Change in ESR, week 52 - week 0</td>
<td>8.7 (-6.5, 18.1)</td>
<td>4.2 (-5.1, 13.5)</td>
<td>4.6 (-4.9, 14.0)</td>
</tr>
</tbody>
</table>

*A positive value means an advantage for the first mentioned group, no significant differences.
†Analysis of covariance, baseline values as covariates.
‡The mean per patient of all changes from baseline to the individual time points (week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52; the values of week 2 and week 4 were divided by two).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean change over 52 weeks*</th>
<th>Mean change over the first 12 weeks</th>
<th>Change from baseline to week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSZ</td>
<td>MTX</td>
<td>COMBI</td>
</tr>
<tr>
<td>DAS</td>
<td>-1.6</td>
<td>-1.7</td>
<td>-1.9</td>
</tr>
<tr>
<td></td>
<td>(-2.0, -1.2)</td>
<td>(-2.0, -1.4)</td>
<td>(-2.2, -1.6)</td>
</tr>
<tr>
<td>No. of swollen joints</td>
<td>-7.9</td>
<td>-10.2</td>
<td>-11.3</td>
</tr>
<tr>
<td></td>
<td>(-10.1, -5.7)</td>
<td>(-12.5, -8.0)</td>
<td>(-13.5, -9.2)</td>
</tr>
<tr>
<td>Ritchie articular index</td>
<td>-8.6</td>
<td>-8.2</td>
<td>-9.4</td>
</tr>
<tr>
<td></td>
<td>(-10.7, -6.5)</td>
<td>(-10.1, -6.4)</td>
<td>(-11.1, -7.7)</td>
</tr>
<tr>
<td>No. of painful joints</td>
<td>-11.7</td>
<td>-13.0</td>
<td>-14.8</td>
</tr>
<tr>
<td></td>
<td>(-14.4, -9.0)</td>
<td>(-15.4, -10.5)</td>
<td>(-17.5, -12.0)</td>
</tr>
<tr>
<td>VAS general health (mm)</td>
<td>-14.1</td>
<td>-15.1</td>
<td>-16.6</td>
</tr>
<tr>
<td></td>
<td>(-22.6, -5.5)</td>
<td>(-22.0, -8.2)</td>
<td>(-22.4, -10.7)</td>
</tr>
<tr>
<td>VAS pain (mm)</td>
<td>-23.7</td>
<td>-19.3</td>
<td>-20.9</td>
</tr>
<tr>
<td></td>
<td>(-33.4, -14.0)</td>
<td>(-26.0, -12.5)</td>
<td>(-28.9, -12.9)</td>
</tr>
<tr>
<td>Grip strength (kPa)</td>
<td>14</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>(8.20)</td>
<td>(9.16)</td>
<td>(10.20)</td>
</tr>
<tr>
<td>HAQ score</td>
<td>-0.32</td>
<td>-0.46</td>
<td>-0.51</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>-17</td>
<td>-17</td>
<td>-23</td>
</tr>
</tbody>
</table>

MTX, methotrexate; COMBI, combination of methotrexate and sulphalsazine; SSZ, sulphalsazine; DAS, Disease Activity Score (see the text); HAQ, Health Assessment Questionaire.

*The mean per patient of all changes from baseline to the individual time points (week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52; the values of week 2 and week 4 were divided by two).
Acute events

The number of patients experiencing some kind of adverse event (Table IV) was not different among the treatments. All events were reversible on lowering the dose or stopping the medication. The adverse events possibly or probably related to the treatment occurred significantly more often in the COMBI-treated patients. This was due to the significantly higher incidence of mild nausea. One patient treated with SSZ withdrew due to anaemia. There were three patients with a serious adverse event according to the good clinical practice definition, all occurring in the SSZ group. Two patients had dyspnoea, one probably due to heart failure and the other due to a chronic obstructive lung disease, although a drug-induced pneumonitis could not be ruled out with certainty. The third patient was hospitalized for resection of the metatarsal heads.

**DISCUSSION**

In this double-blind, randomized, double-dummy controlled study of 105 early RA patients, we tried to answer the question whether the combination of SSZ and MTX is more effective than the single components, without a disproportional increase in toxicity, and whether there was a difference between SSZ and MTX. Although there was a slight trend that the combination was somewhat more potent than the individual components, the general conclusion is that the efficacy and toxicity are comparable in the three treatment groups. The differences between the combination therapy and the single components (Table II), although almost invariably in favour of the combination, were unimpressive and the relatively small confidence intervals make important differences less likely. Importantly, being the first double-blind direct comparison between SSZ and MTX, we did not observe any relevant differences in the mean change over time of the DAS between the two groups used. Interestingly, the time to good response tended to be shorter in the SSZ-treated patients compared to the MTX patients.

Given the current tendency to use higher doses of MTX, one could speculate on the implications for the results of the present study. Possibly, a difference...
would arise in favour of MTX over SSZ. The non-
significant differences between the COMBI and MTX
now present could disappear altogether with an
increasing contribution of MTX to the efficacy of the
combination.

The toxicity was not very different, notwithstanding
the statistically significant greater incidence of
mild nausea in the COMBI group. This is reflected in
the number of withdrawals, which did not differ sig-
ificantly, although there was a tendency for a higher
drop-out rate for the SSZ-treated patients, mainly
due to skin rashes. Whether the higher number of
concomitant drugs in the COMBI group could also
explain the greater toxicity remains speculative.

The place of this and other combinations of sec-
ond-line anti-rheumatic drugs in the therapy of RA is
still uncertain; theoretically, one can adopt various
strategies of combining [9], roughly divided into two
variants: to start combinations from the beginning
and taper them off when positive results are obtained
('step-down-bridge' approach [15]), and to add a
second anti-rheumatic drug once the first one is not
successful ('adding-on' or 'step-up' strategy). When
judging the results of the various studies concerning
the combination of SSZ and MTX, a picture emerges
of increased efficacy without additional toxicity when
the 'step-up' strategy is employed [9]. The only ran-
donized trial on the combination of MTX and SSZ
was carried out in patients with more advanced RA
[16]. Although it had an open design and some expec-
tation bias cannot be excluded with certainty, a clear
benefit was observed for the combination over MTX
alone, in patients who had insufficient efficacy of SSZ
alone. The majority of those patients initially had a
favourable response to SSZ, preceding the start of
the trial. The reaction to MTX alone (with a rela-
tively low dose) was modest in that study. So differ-
ences between the results of that study and the
present one might be explained by: another patient
population; early or more advanced RA; MTX help-
ing to overcome secondary resistance to SSZ. The
mechanism of this is unclear, but folate metabolism
is possibly involved [17, 18]. Another explanation for
the discrepancy between the results of the two studies
might be a ceiling effect in the present study: given
the large number of patients with a good response,
there is only a limited possibility for further improve-
ment, thus compressing the differences.

Another very recently published study on the com-
bination of SSZ, MTX, and also hydroxychloroquine
as a triple therapy in patients who failed on at least
one DMARD, reported an increased efficacy of the
triple therapy over the combination of SSZ and
hydroxychloroquine and over MTX alone, without
an increase in toxicity [19]. The results of SSZ in half
the usual dose combined with a full dose of hydroxy-
chloroquine were equal to MTX in a dose up to
17.5 mg. Controls using MTX with either SSZ or
hydroxychloroquine were lacking. It was surprising
that 79% of the MTX patients had a good response
after 9 months of treatment and no toxicity that
caused withdrawal, and subsequently ~60% of these
patients dropped out because of treatment failure
and/or toxicity, within 12 months. This seems con-
try to other experience with MTX, where, once a
good response is achieved, this is maintained for a
longer time [20].

The results of the present study, applying the 'step-
down-bridge' or 'parallel' strategy in early RA, do
not support the preliminary success of the combina-
tion of SSZ and MTX using the 'step-up' strategy [9].
Whether this is a result of the chosen strategy: the
'step-up' approach is more effective than the 'step-
down', or depends on the specific anti-rheumatic
drugs, will be clearer when other combinations of
anti-rheumatic drugs are tested in the same category
of patients.

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