A RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL OF SULPHASALAZINE COMBINED WITH PULSES OF METHYLPRÉNDISOLONE OR PLACEBO IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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SUMMARY
Thirty-eight patients with rheumatoid arthritis meeting American College of Rheumatism (ACR) criteria were entered in a randomized controlled trial (RCT) with a 6-month follow-up. Disease activity was defined according to the presence of at least three of the following criteria: (1) the presence of three or more swollen joints; (2) the presence of six or more tender joints; (3) morning stiffness greater than 45 min; (4) erythrocyte sedimentation rate (ESR) greater than 20 mmHg in the first hour. All the patients had to be 18 yr or older and could not have used any DMARDs in the past 2 months. In addition, they should not have any contraindication to the use of SSZ or i.v. MP pulse therapy. Only patients classified as functional class I, II and III according to the Steinbrocker criteria were eligible for inclusion in this study. Patients who presented any associated renal, liver or lung disease, as well as diabetes mellitus and moderate or severe hypertension, were excluded from the study. Patients with RA who were using prednisone (daily dose up to 5.0 mg/day or equivalent) and NSAIDs should have been on a stable dose of these drugs for at least 4 weeks. NSAIDs and corticosteroids (CE) were kept in a stable dose throughout the study period.

Patients were considered eligible only if they had failed to respond adequately to NSAIDs and at least one second-line agent. All eligible patients were randomized to receive SSZ (2 g/day) and pulses of MP (5 mg/kg), or SSZ (2 g/day) and pulses of saline (SA). A single infusion over 2 h was carried out in both groups for a total of three times (0, 1 and 2 months). Patients and rheumatologists were blinded to the treatment group.

KEY WORDS: Sulphasalazine, Methylprednisolone, Combination therapy, Rheumatoid arthritis.

RHEUMATOID arthritis (RA) is a chronic inflammatory disease that affects mainly the joints and related tissues. It has been suggested that patients with RA should be treated early in the course of their disease with a combination of medications to control inflammatory synovitis and prevent joint destruction [1, 2]. Pulse treatment with methylprednisolone (MP) could be used for a limited period of time in combination with disease-modifying anti-rheumatic drugs (DMARDs), thereby accelerating the clinical improvement until the sustained benefit due to DMARD is achieved [3, 4].

Sulphasalazine (SSZ) is one of the DMARDs that has been frequently used over the past 10 yr in the treatment of RA and several studies have demonstrated its efficacy in the treatment of this disease [5–7].

The objective of this study was to assess whether monthly treatment with i.v. MP (first 3 months) accelerates the efficacy of SSZ.

MATERIAL AND METHODS
Thirty-eight patients with RA meeting American College of Rheumatology (ACR) criteria [8] in an active phase of the disease, selected from the rheumatic disease out-patient clinic at Escola Paulista de Medicina, entered a randomized controlled trial (RCT) with a 6-month follow-up. Disease activity was defined according to the presence of at least three of the following criteria: (1) the presence of three or more swollen joints; (2) the presence of six or more tender joints; (3) morning stiffness greater than 45 min; (4) erythrocyte sedimentation rate (ESR) greater than 20 mmHg in the first hour. All the patients had to be 18 yr or older and could not have used any DMARDs in the past 2 months. In addition, they should not have any contraindication to the use of SSZ or i.v. MP pulse therapy. Only patients classified as functional class I, II and III according to the Steinbrocker criteria were eligible for inclusion in this study. Patients who presented any associated renal, liver or lung disease, as well as diabetes mellitus and moderate or severe hypertension, were excluded from the study. Patients with RA who were using prednisone (daily dose up to 5.0 mg/day or equivalent) and NSAIDs should have been on a stable dose of these drugs for at least 4 weeks. NSAIDs and corticosteroids (CE) were kept in a stable dose throughout the study period.

Patients were considered eligible only if they had failed to respond adequately to NSAIDs and at least one second-line agent. All eligible patients were randomized to receive SSZ (2 g/day) and pulses of MP (5 mg/kg), or SSZ (2 g/day) and pulses of saline (SA). A single infusion over 2 h was carried out in both groups for a total of three times (0, 1 and 2 months). Patients and rheumatologists were blinded to the treatment group.

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Patients were interviewed every 2 months and examined by the same attending rheumatologist. The following outcome measures were recorded at baseline, 2, 4 and 6 months: (1) joint count, recorded according to the ACR co-operating clinics criteria; (2) morning stiffness (minutes); (3) grip strength evaluated by a sphygmanometer inflated to 20 mmHg; the pressure at the level maintained by squeezing was recorded and the mean of three measurements was calculated; (4) pain was evaluated through the use of a numerical rating scale from 0 to 10 (10 = extreme pain); (5) functional ability was assessed by the interviewer-administered Portuguese version of the Health Assessment Questionnaire (HAQ) [9]; and (6) ESR (Westergreen). In addition, urinalysis and serial routine blood studies were performed every 2 months on all patients. These included a complete blood count, differential white cell and platelet count, SGOT (AST), SGPT (ALT), LDH, alkaline phosphatase, blood urea nitrogen and serum creatinine. The occurrence of adverse effects was assessed at each follow-up visit.

Compliance with treatment drugs was evaluated every 2 months by pill count. The trial research proposal was reviewed and approved by the local ethical committees of the participating centre. All patients gave written informed consent prior to enrolment.

Statistical analysis
Descriptive statistics were performed to summarize clinical and demographic characteristics of each patient group. Efficacy analysis was performed using the paired and unpaired Student's t-test for comparison of mean values of continuous variables both within and between the two groups in follow-up, respectively. A priori, for the purpose of comparing the efficacy of the two treatment regimens, we defined joint count as the primary outcome measure. The level of statistical significance was set at \( P < 0.05 \).

RESULTS
The demographic characteristics of the patients in both groups were similar (Table I). Seventy-five per cent or more of our out-patient clinic are women and the few eligible men refused to take part in this particular study. Eighty per cent of the patients in the SSZ + MP group were taking corticosteroids compared to 75% of the patients in the SSZ + SA group. The mean daily dosage was 4.5 mg/day in the SSZ + MP group and 5.0 mg/day in the SSZ + SA group.

The two groups were comparable at baseline regarding their demographic and clinical characteristics (Table II). The functional capacity evaluated by the HAQ was also similar in both groups. The mean value of this particular study. Eighty per cent of the patients in the SSZ + MP group were taking corticosteroids compared to 75% of the patients in the SSZ + SA group. The mean daily dosage was 4.5 mg/day in the SSZ + MP group and 5.0 mg/day in the SSZ + SA group.

The two groups were comparable at baseline regarding their demographic and clinical characteristics (Table II). The functional capacity evaluated by the HAQ was also similar in both groups. The mean value (S.D.) was 1.422 (0.493) for the SSZ + MP group and 1.357 (0.553) for the SSZ + SA group.

![FIG. 1.—Change in joints (swollen and tender) across the 6 months of treatment by group.](image)
TABLE IV  
Between-group comparison of the improvement observed in each outcome measure in patients who completed the study. Values are presented as means.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>SSZ + MP (n = 15)</th>
<th>SSZ + SA (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness (min)</td>
<td>-112.0</td>
<td>-98.9</td>
<td>NS</td>
</tr>
<tr>
<td>Grip strength (mm Hg)</td>
<td>23.2</td>
<td>21.7</td>
<td>NS</td>
</tr>
<tr>
<td>Joint count (0–66)</td>
<td>-17.2</td>
<td>-17.8</td>
<td>NS</td>
</tr>
<tr>
<td>Pain (0–10)</td>
<td>-2.1</td>
<td>2.6</td>
<td>NS</td>
</tr>
<tr>
<td>HAQ* (0–3)</td>
<td>-0.519</td>
<td>-0.635</td>
<td>NS</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>-21.0</td>
<td>24.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Health Assessment Questionnaire.

Twenty-nine patients completed the study. All outcome measures improved significantly in both treatment groups (P < 0.001) (Table III). Evaluation at each follow-up visit showed no significant differences between treatment groups in any of the outcome measures (Fig. 1).

Table IV presents the comparison of the improvement observed in patients who completed the study. There were no statistically significant differences between the two groups according to the clinical and laboratory parameters.

Nine patients were withdrawn from the study: five from the SSZ + MP group and four from the SSZ + SA group. Adverse effects attributable to SA/MP pulse therapy were rare and mild. Lack of efficacy was observed in three patients (one patient in the SSZ + MP group and two in the SSZ + SA group).

Very good compliance with the treatment regimens, as assessed by pill count, was observed in both treatment groups. Only 3.7 and 5.0% of the SSZ tablets were not taken by the SSZ + MP and SSZ + SA patients, respectively.

**DISCUSSION**

A combination of two or more DMARDs might have advantages compared with treatment with a single drug in the management of RA. Potential advantages with the combination therapy, in relation to additive and/or synergistic effects, have been postulated by some authors: faster onset of effect and a greater response rate when compared with treatment with a single DMARD [10–13].

The efficacy of SSZ as a disease-modifying drug in the management of RA has been known for more than 10 yr [14, 15].

Although the efficacy of steroids in the treatment of RA has been known for a long time, their use has been limited because of side-effects after long-term therapy (facial flushing, palpitation, psychological disturbance, hypertension, sudden death, cardiac arrhythmias, and so on) [16]. However, short-term usage of low-dose steroids seems to be safe and effective. They have been used in the treatment of acute exacerbation of arthritis and to improve short-term remission in patients being started on DMARDs [17].

In addition, some studies have shown that cortisol deficiency may contribute to the development of chronic arthritis in murine streptococcal cell wall (SCW) arthritis [18]. Investigations of the hypothalamic–pituitary–adrenal (HPA) axis in patients with RA have confirmed that they have suboptimal corticosteroid responses to stress when compared with normal controls [19].

Choy et al. [20], in a randomized double-blinded placebo-controlled trial, have studied 41 patients with RA who were taking sodium aurothiomalate (SAT) and who were randomized to receive three doses of either 500 mg MP orally and placebo injection or 120 mg of i.m. depot methylprednisolone acetate (MPA) and oral placebo tablets at 4 weekly intervals. Disease activity was evaluated by clinical and laboratory parameters. They concluded that 120 mg i.m. depot MPA was more effective at inducing improvement in disease activity than 500 mg of oral MPA in RA patients starting on SAT therapy. They recommended the use of 120 mg of i.m. MPA at 0, 4 and 8 weeks during the induction phase of chrysotheraphy.

Gough et al. [21], based on the positive findings of the study of Choy et al., examined in a randomized double-blind fashion the effect of corticosteroid supplementation in addition to SSZ in early disease. Patients were randomized to receive either 120 mg i.m. MP or an equivalent volume of normal saline at 0, 4 and 12 weeks. All patients commenced Salazopyrin at 500 mg daily, increasing to 2 g daily over the first month. Clinical and laboratory assessment was made at 0, 1, 2, 8, 12, 25 and 52 weeks. This study did not show any significant benefit from the addition of i.m. MP to SSZ in this group of patients with early RA.

In these two previous studies, the patients were excluded if they were on oral steroids or had received any form of steroid within the preceding 2 months.

These two previously randomized studies of combination treatments are controversial in their results and fail to settle whether MP used in combination with another DMARD is a good association or not. In this study, at the end of the follow-up period the two groups showed a significant improvement in the variables of disease activity. However, the study did not show any significant benefit from the addition of a pulse of MP to SSZ when compared with the placebo group.

As can be observed, the improvements in all outcome measures were very similar. It is unlikely, therefore, that a type II error has occurred in this trial due to the small sample size studied. The small difference in improvement observed in the outcome measures between the two groups was also definitely not clinically important.

In the present study, the association of SSZ with i.v. MP therapy was based on our previous study of a comparative dose of i.v. MP in patients with RA [3]. Thirty-nine patients with RA, in an active phase of the disease, were submitted to a 6 week double-blind randomized controlled trial that compared 5 mg/kg i.v. MP with 10 mg/kg i.v. MP, given as a single pulse...
during a 2 h period. At the start of the study, both groups were comparable for demographic variables and outcome measures, like number of swollen joints, grip strength, morning stiffness, pain, HAQ and erythrocyte sedimentation rate, were evaluated immediately prior to and at 1, 3 and 6 weeks infusion. A statistically significant improvement in the clinical variables was observed in both groups. However, no statistically significant difference between the two groups was found at any time in any of the outcome measures. This fact justified the choice of the lowest dosage of MP (5 mg/kg) as the one selected to be studied.

The incidence of adverse reactions among the patients studied was very low and also in accordance with previous studies. The most frequent side-effects were nausea, vomiting and gastrointestinal upset [22-25].

Recently, Farr et al. [26] have studied the speed of action of SSZ compared with penicillamine (Pen) in a 1 yr study. Clinical and laboratory assessments were carried out at 0, 1, 2, 3, 6, 9 and 12 months. The authors verified that at 1 month there was a significant improvement with SSZ in seven indices (ESR, IgA, active joint, swelling and clinical scores, morning stiffness and grip strength), but none with Pen. At 2 months, 13 indices had improved with SSZ compared with six with Pen. At 12 months, a similar number of parameters in each group showed response. They concluded that SSZ had a more rapid effect with greater efficacy at 1 and 2 months, and both drugs produced a similar degree of effect over 1 yr. These findings may justify the similar improvement at 3 months in our study in both groups, since the two groups were taking SSZ, despite the administration of MP in one of the groups.

The percentage of pills not taken by the patients was very low and similar in both groups. We may attribute this to the fact that the patients received the SSZ pills regularly and monthly, and were in both groups encouraged to follow the trial recommendations strictly. Also, the clinical improvement observed in both groups at the end of the first 2 months may have acted as a stimulus for the patients to take the pills regularly.

In view of the findings of this and the previous study of Gough et al., we do not recommend the use of MP during the induction phase of SSZ therapy.

REFERENCES


