LONG-TERM USAGE AND SIDE-EFFECT PROFILE OF SULPHASALAZINE IN RHEUMATOID ARTHRITIS

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SUMMARY
In a cohort of patients with early rheumatoid arthritis, sulphasalazine (SASP) was mainly given as a first-choice second-line agent. SASP resulted in a significantly better survival rate compared with hydroxychloroquine, which is also given as a first-choice agent. When the survival rate of SASP was compared with that of aurothioglucose, both given as second-choice agents, again, a statistically significant better survival rate was found for SASP. In 9% of the patients, SASP could be withdrawn as a complete remission was obtained. Adverse reactions occurred mainly during the first 3 months of treatment, and in 20% of patients these were severe enough to stop treatment. Gastrointestinal adverse reactions were most frequently observed, and all adverse reactions were completely reversible after treatment withdrawal. Treatment was started with a standard dose of 2000 mg/day. However, in ~30% of the patients, this dose was increased up to 3000 mg/day and, in another 30%, the dose was decreased to 1500 or 1000 mg/day.

KEY WORDS: Rheumatoid arthritis, Sulphasalazine, Hydroxychloroquine, Aurothioglucose, Survival.

SULPHASALAZINE (SASP), a conjugate of 5-aminosalicylic acid (5-ASA) and sulphapyridine, was synthesized in the 1940s as a drug to treat both rheumatoid arthritis (RA) and inflammatory bowel diseases [1]. As a result of conclusions based on a badly designed study, and the spectacular results of the use of corticosteroids in the treatment of RA, SASP fell out of favour for the treatment of RA and for many years was used mainly in the treatment of inflammatory bowel diseases [2]. In the late 1970s, the drug was rediscovered for the treatment of RA by McConkey et al. in the UK [3]. Since then, SASP is increasingly being used, particularly in Europe, as a first-choice second-line agent for the treatment of RA. In this article, we will review our experiences with SASP in the treatment of RA over the last 10 yr.

PATIENTS AND METHODS
Since 1985, all patients with RA with a disease duration of <1 yr, who have never been treated before with a second-line agent, have been included in a prospective cohort study. In general, treatment with second-line agents is considered if the disease is active despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for 2–4 weeks. During the early years of this cohort study, SASP and hydroxychloroquine (HQ) were agents of first choice. The choice of agent was dependent on the rheumatologist treating the disease. Since 1988, due to the results of the double-blind trial comparing SASP with HQ, SASP was almost exclusively used as a first-choice second-line agent [4, 5]. The dosing schedule of SASP consists of a starting dose of 500 mg/day, which is increased weekly by 500 mg to the standard dose of 2000 mg/day. In cases of mild/moderate adverse reactions, the dose can be reduced to 1500 or 1000 mg/day, and in cases of lack of efficacy, the dose is increased up to 3000 mg/day. To date, 240 patients have been included in this cohort study.

Statistics
Kaplan-Meier product limit estimates of drug survival were used. The following endpoints were used: ineffectiveness, adverse drug reactions and treatment withdrawal for different reasons (patient’s initiative, non-compliance, etc.). Data were censored to allow for patients lost to follow-up, death and drug withdrawal for remission. The log-rank test was used for comparison of survival curves.

RESULTS
To date, 186 patients have been treated with SASP; in 76% of the patients, it was given as a first-choice, second-line agent. As a result, at the start of SASP treatment the median disease duration of the patients was only 1 yr and the radiographic damage was minimal. The demographic data and clinical characteristics of these patients are shown in Table I.

The standard dose of SASP at the start of treatment was 2000 mg/day. However, as a result of adverse reactions and lack of efficacy in 32% of the patients, the dose was increased during the follow-up to 2500 or 3000 mg/day, while in another 30% of patients the dose was decreased to 1500 or 1000 mg/day. About 50% of the patients in whom the dose was increased were still using SASP 20 months later (Fig. 1).

During the first 2 yr of SASP treatment, there was a gradual decrease in the drug survival curve due to drop-out because of lack of efficacy and toxicity. After 2 yr, a flattening of the curve was observed (Fig. 2).

Following a comparison of patients who were treated with SASP as a first-choice second-line agent (n = 130) with 45 patients who were treated with HQ as
TABLE I
Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>186</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>122:64</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>1</td>
</tr>
<tr>
<td>RF positive (%)</td>
<td>84</td>
</tr>
<tr>
<td>Disease activity score</td>
<td>4.34</td>
</tr>
<tr>
<td>Ritchie articular index</td>
<td>11</td>
</tr>
<tr>
<td>ESR</td>
<td>40.5</td>
</tr>
<tr>
<td>Radiographic damage</td>
<td>5</td>
</tr>
<tr>
<td>SASP as first choice (%)</td>
<td>76</td>
</tr>
<tr>
<td>RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; SASP, sulphasalazine.*</td>
<td></td>
</tr>
</tbody>
</table>

the first-choice agent, a statistically significant difference in favour of SASP was seen with respect to the drug survival in the first 2 yr \( (P = 0.0001 \); Fig. 3). As it has been shown that the rank order of second-line agents influences drug survival, we also compared the survival of patients receiving SASP as a second-choice agent with patients who were treated with aurothioglucose as a second-choice agent [6]. A statistically significant improvement in drug survival was seen in patients treated with SASP, mainly as a result of the high drop-out rate due to adverse reactions in the aurothioglucose-treated group \( (P = 0.04 \); Fig. 4).

Withdrawals

In 47 patients, SASP had to be stopped due to adverse reactions. Gastrointestinal side-effects, such as nausea and vomiting, were most frequently observed, followed by adverse reactions, such as rash, fever and leucopenia (Table II). The majority of the withdrawals took place during the first 3 months of treatment and, after 1 yr, a plateau in the drug survival curve was observed (Fig. 5). Patients over 60 yr of age were more frequently withdrawn due to adverse reactions than patients under the age of 60 \( (P < 0.05)\).

In 17 patients, treatment could be stopped due to the absence of disease activity (‘remission’). During the follow-up period, eight patients had to start again with a second-line agent; in seven of these patients, SASP was re-instituted. Six patients responded again (one achieved a remission again) and one patient did not respond.

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CONCLUSIONS

In this cohort of patients with early RA, SASP was given mainly as a first-choice second-line agent. The drug survival curve of SASP compared with HQ, both given as first-choice agents, was significantly better for SASP. After 2 yr, 50% of the patients on SASP and only 20% on HQ were still using the drug. The survival curve of SASP, if given as a second-choice agent, was also significantly better compared with that for aurothioglucose. After 1 yr, 60% of those on SASP and 40% on aurothioglucose were still receiving this treatment.

Adverse reactions severe enough to stop treatment occurred in ~20% of the patients. All reactions were reversible after stopping treatment; adverse reactions reappeared in only eight of the 17 patients in whom a rechallenge was performed.

The higher survival rates of SASP in this study are superior to those of Situnayake et al. [7]. One of the reasons for this discrepancy might be caused by the adjustment of the SASP dosage, as only about one-third of the patients were treated with the standard dose of 2000 mg/day.

REFERENCES