Combination therapy with methotrexate and sulfasalazine in rheumatoid arthritis—tolerance of therapy

The use of slow acting anti-rheumatic drugs (SAARDs) in patients with rheumatoid arthritis (RA) is often limited by lack of response or by side-effects.1 Combinations of SAARDs are increasingly being used where a single agent is ineffective or as an intensive first line approach to the treatment of RA, although the toxicity of combination therapy is uncertain. Life-table analysis of treatment outcomes and survival analyses allow an assessment of the probability of continuing therapy and provides important information about the clinical utility of SAARD treatment.4,5 We studied the reasons for cessation of combination therapy with methotrexate (MTX) and sulfasalazine (SSZ) in patients with RA, and report a life-table analysis of treatment episodes.

All patients with RA (American College of Rheumatology and validation criteria) managed in a single community based rheumatology practice (GOL), who received combined MTX and SSZ treatment over five years, were studied. There were 29 patients (22 females; seven males) with a mean age of 56-7 years (range 32-76) and disease duration of 11-6 years (range 1-38).

Cessation of therapy was arbitrarily defined if MTX was discontinued for more than one month or SSZ for more than two weeks. Restarting combination therapy was considered a new treatment episode. Kaplan-Meier survival curves were generated from the starting and cessation dates of treatment episodes. Causes of therapy cessation were classified as: 1) inefficacy, 2) toxicity, and 3) other. All patients started combination therapy because single agents were ineffective.

There were 31 treatment episodes in 29 patients (three females; seven males) with a median of 12-8 treatment episodes per patient. The median time from the start of therapy was 18-0 months (range 1-53). MTX was given as a single mean (SD) weekly dose [11·9 (2·6) mg; range 5·0–17·5 mg] and SSZ was given as divided mean (SD) daily doses [1740 (460) mg; range 500–3000 mg].

Ten treatment cessations occurred, seven due to inefficacy, one due to toxicity (severe nausea) and two others. Cessations for inefficacy occurred between three and eighteen months. The single cessation due to toxicity occurred in a patient in whom MTX was added to SSZ. Combination therapy was restarted six months later and was tolerated (follow up 3-6 months). Kaplan-Meier survival curves demonstrated a cumulative probability of continuing combination therapy of 80% and 62% at 12 and 24 months respectively (figure).

Laboratory investigations revealed macrocytosis (MCV>100 fL) in one patient receiving MTX before combination therapy.

**Macrocytosis (MCV>100 fL) before starting (t=0), after 12 months (t=12) and 24 months (t=24) of MTX and SSZ combination therapy in patients with RA.**

<table>
<thead>
<tr>
<th>Time (t)</th>
<th>Mean (SD) MCV</th>
<th>% of patients with MCV&gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>t=0</td>
<td>89 (6-5) fL</td>
<td>3%</td>
</tr>
<tr>
<td>t=12</td>
<td>92 (6-8) fL</td>
<td>24%</td>
</tr>
<tr>
<td>t=24</td>
<td>91 (6-7) fL</td>
<td>14%</td>
</tr>
</tbody>
</table>

The prevalence of macrocytosis increased within 12 months of starting combination therapy (table). A single patient developed neutropenia to a nadir of 1·7 × 10⁹/L during 34 months of combination therapy. Thrombocytopenia was not observed. Significantly abnormal liver function tests (greater than twice normal hepatic transaminases or alkaline phosphatase) were detected in one patient, three months after starting combination therapy but resolved spontaneously without withdrawal of therapy.

Both MTX and SSZ are folate antagonists and consequently have the potential for synergistic toxic effects.6,7 Bone marrow suppression, folate depletion and severe gastrointestinal toxicity has been reported.8,9 We found that toxicity is rarely sufficiently severe to require stopping combination MTX and SSZ therapy. The low rate of therapy cessation due to toxicity is not believed to be due to folic acid supplementation, as only six of the 29 patients received supplements. The cumulative probability of continuing combination therapy was comparable to that of single agent therapy with MTX and was greater than with use of SSZ alone, as reported in our previous life-table analysis of a similar community-based population.10 Toxicity usually occurs early in the course of treatment with SSZ, while toxic events causing cessation of combination treatment continued to occur throughout the duration of therapy.2 Thus a patient tolerating SSZ who has MTX added may not have the same outcome as one starting the two agents simultaneously. We found no difference in outcome attributable to the order of starting the drug. However the numbers in the two groups are small.

Although this is a small, open and observational study, we have reported important preliminary data on the utility of combination MTX and SSZ therapy in patients with RA. We conclude that combination MTX and SSZ therapy is not associated with unacceptable toxicity and has a probability of long term continuation comparable to that published for a single SAARD. Further larger prospective controlled trials will be necessary to define the efficacy and role of this combination.

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Is walking to the North Pole good for you?

On Saturday 24 April 1993, Nicky Cole embarked on a 100 mile expedition to become the first woman to walk to the North Pole. This involved significant physical and mental exertion in freezing conditions and she accomplished it within 10 days, with no apparent injury to herself or anyone who feels up to it? I put these questions to Nicky at the launch of her expedition at the Royal Geographical Society, and she suggested that I should try and answer them.

Physical examination before and after the walk confirmed that she was fit and well, although she was suffering from an irritable dry cough on her return. Routine investigations (full blood count, renal and liver function, creatinine kinase) showed little fluctuation and magnetic resonance imaging of her knees was also normal before and after the expedition. In this respect, this institute must claim a first in being the only group to persuade The Sunday Mirror to print an MRI of a woman in preference to a more anaesthetically appealing image.

Interestingly, Nicky’s general psychological health was below average five days before setting off, presumably associated with last minute stresses. Also, using a cyben Isokinetic machine to measure hamstring and quadriceps strength, power and endurance, a 5% reduction in quadriceps endurance was found at the end of the walk. This may represent early muscle damage, resulting from the calorie imbalance that invariably occurs on walking in these conditions. Furthermore, an increase in the overall T
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