Does sulphasalazine cause drug induced systemic lupus erythematosus? No effect evident in a prospective randomised trial of 200 rheumatoid patients treated with sulphasalazine or auranofin over five years

Margaret-Mary Gordon, Duncan R Porter, Hilary A Capell

Abstract

Background—Sulphasalazine (SSZ) has been reported to cause drug induced systemic lupus erythematosus (SLE), but diagnosis of this complication in the context of rheumatoid arthritis (RA) is difficult.

Objective—To determine prospectively: (1) if patients become seropositive for antinuclear antibodies (ANA) during prolonged treatment with SSZ without clinical evidence of SLE; (2) if ANA positive patients develop more adverse reactions than ANA negative patients; (3) if drug induced SLE was identified in this cohort.

Methods—200 patients enrolled in a randomised prospective trial of SSZ and auranofin (AUR) were followed up for five years. Baseline and annual ANA results were collected along with information on drug toxicity and reasons for discontinuation of treatment.

Results—Over five years 24 patients stopped taking SSZ and 49 AUR because of side effects. Of the features common to SLE, rash developed in nine SSZ patients and 11 AUR treated patients and mouth ulcers in three and four patients respectively. Six SSZ treated patients and three treated with AUR developed leucopenia, which promptly resolved with drug withdrawal. No adverse event was ascribed to drug induced SLE. Of the 72 SSZ treated patients who were ANA negative or weakly positive at outset, 14 (19%) became strongly ANA positive compared with 11 (14%) of 80 AUR patients. Patients ANA positive at baseline or who became ANA positive were not more likely to develop drug toxicity or to withdraw from treatment than those ANA negative throughout.

Conclusion—ANA positivity is common in patients with RA, but the presence or development of ANA did not increase the likelihood of withdrawing from treatment. No case of drug induced SLE was seen over five years in this study.

Systemic lupus erythematosus (SLE) is a multifactorial disease. Since the 1970s, almost 50 drugs have been reported to be associated with drug related lupus.1 Hydralazine, penicillamine and procainamide are most commonly implicated, and several case reports have also established sulphasalazine (SSZ) as a causative agent.2–4 Diagnosis in the context of rheumatoid arthritis (RA) is difficult as the side effects of several disease modifying drugs (DMARDs) share features of SLE. In addition, “overlap” between RA and SLE is occasionally reported.

Antinuclear antibodies (ANAs) may develop during long term treatment with a number of drugs, and ANAs are invariably detected in those who progress to develop a drug induced lupus syndrome.9–11 While the occurrence of antibodies is common, (detected in 50–90% of patients treated), the frequency of associated disease is rare. The exact incidence of drug induced lupus and of asymptomatic serological abnormalities has not been clearly established.

The aim of this study was to determine if treatment with SSZ is associated with: (1) the development of ANA; (2) clinical evidence of drug induced SLE; (3) if there is a relation between ANA status and drug toxicity.

Methods

Two hundred patients with RA considered to require second line treatment were enrolled in a prospective, randomised trial comparing SSZ and auranofin (AUR) and followed up for five years. One hundred patients were randomised to each group. If the patient had previously been taking SSZ (25 patients) or AUR (four patients), they were allocated to receive the other drug. SSZ was started at 500 mg/day and increased if tolerated to a target dose of 40 mg/kg/day. AUR was introduced at 3 mg twice daily, increasing to 3 mg thrice daily if necessary.

Patients were assessed at weeks 0, 12, 24, 48 and then annually until year 5. Full blood count, erythrocyte sedimentation rate, C reactive protein, biochemistry were performed at each visit with measurements of Ritchie articular index, pain score on 10 cm visual analogue scale and morning stiffness. Baseline and annual ANA results were collected with information on drug toxicity, concomitant medication and reasons for withdrawal from treatment.

Results

There was no significant difference between the groups with regard to patient details, with a
Sulphasalazine and drug induced SLE

The development of drug related SLE developing on a background of RA may be difficult, as many of the signs, symptoms and serological abnormalities reported in these patients may be a natural consequence of the underlying disease, rather than the drug. This may be particularly true in disease developing in the context of RA treated with SSZ.

SSZ is a commonly used DMARD in RA and other inflammatory joint diseases that has a relatively low risk of toxicity.13 RA results in polyarthritis and malaise, and extra-articular features such as pleurisy or pericarditis, or both, are not infrequent manifestations. RA and SLE may rarely coexist but it is more common for ANAs to be found in RA alone in 10–70% of patients.14 15 The development of ANAs or dsDNA antibodies should not necessitate withdrawal from treatment, although careful follow up will be required. These antibodies develop in 5–15% of patients taking SSZ for RA, without clinical symptoms of SLE.16 The most useful diagnostic criteria for drug induced SLE is the rapid improvement of clinical features after withdrawal of the drug, thus providing evidence that the lupus

**Table 1** Proportion of patients continuing treatment over the five years

<table>
<thead>
<tr>
<th>Year</th>
<th>SSZ</th>
<th>AUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>19</td>
</tr>
</tbody>
</table>

**Table 2** Adverse events over the five years

<table>
<thead>
<tr>
<th>Event</th>
<th>SSZ</th>
<th>AUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>33*</td>
<td>56*</td>
</tr>
</tbody>
</table>

* Led to discontinuation of treatment in 24 SSZ and 48 AUR treated patients.

**Table 3** Antinuclear antibodies: % ANA positive at baseline and at time of discontinuation or after five years of treatment

<table>
<thead>
<tr>
<th></th>
<th>% ANA positive at baseline</th>
<th>% ANA positive after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSZ</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>AUR</td>
<td>20</td>
<td>31</td>
</tr>
</tbody>
</table>

There was no significant difference between the groups. Patients who were ANA positive at baseline or who became ANA positive during follow up were not more likely to develop drug toxicity or to withdraw from treatment than those who were negative throughout. Antihistone and anti-dsDNA antibodies were not measured in all the patients.

**Discussion**

Although the exact aetiology is unclear, SLE is a multifactorial disease in which both genetic and environmental factors, including drug treatment, are involved. Drug induced lupus is a well recognised but uncommon disease entity that occurs with treatment with any of a number of drugs. It differs from idiopathic disease in that malaise and musculoskeletal symptoms predominate, while renal and central nervous system involvement are rare or absent.17

The diagnosis of drug related SLE developing on a background of RA may be difficult, as many of the signs, symptoms and serological abnormalities reported in these patients may be a natural consequence of the underlying disease, rather than the drug. This may be particularly true in disease developing in the context of RA treated with SSZ.
syndrome is induced by SSZ rather than unmasked by it. Failure to recognise this complication may lead to delay in withdrawing the offending drug or inappropriate treatment.

In one review of SSZ induced SLE, 88% had arthralgia, 33% had fever and 25% had rash.17 18 Leucopenia, anaemia, vasculitis and pneumonitis have also been reported although serious renal disease has not been reported.2 7 ANAs often develop, but dsDNA antibodies, which are highly specific for SLE, are rarely found in drug induced lupus.19

Serological abnormalities are often found, but the frequency of drug induced lupus is low. ANAs may be detected in as many as 50–90% of patients depending on the drug, dose and duration of treatment.1 The development of ANAs suggests a drug induced autoimmune phenomenon, resulting in other antibodies than the classic antihistones. The true incidence and prevalence has never been clearly elucidated, but it remains that more patients develop ANAs but remain asymptomatic than develop clinical symptoms.

SSZ is reduced in the colon to 5-aminosalicylic acid and sulphapyridine. 5-ASA is mostly unabsorbed and sulphapyridine is acetylated. Genetically determined variation in acetylation leads to variation in rates of metabolism. Sixty per cent of the British population in acetylation leads to variation in rates of metabolism. Slow acetylators and are more likely to experience adverse effects from either SSZ or AUR. Baseline ANA should be determined before treatment to provide answers about uncommon side effects from either SSZ or AUR. Baseline ANA status should be determined before treatment with any of the drugs known to be incriminated in the development of drug induced lupus and patients should be observed carefully for signs and symptoms of SLE. Indeed, as so many drugs have been implicated to date, all patients starting DMARD treatment for inflammatory arthritis should have baseline ANA checked.

In conclusion, ANAs are common in patients with RA. Side effects of commonly used DMARDs share features with signs and symptoms of SLE. In this study, 11–14% of patients became strongly ANF positive during follow up, but the presence or development of ANAs did not correlate with clinical disease or increase the likelihood of withdrawing from treatment. Larger cohorts followed up prospectively are being studied to elucidate the relevance of this effect in long term use of SSZ.

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