complexes of clinical symptoms are also found in systemic lupus erythematosus and systemic sclerosis.

To summarize: (i) our patients with MCTD were diagnosed only in the presence of anti-U1-RNP excluding the presence of anti-Sm; (ii) the clinical symptoms of MCTD are not the overlapping features of other connective tissue diseases; (iii) an internationally accepted classification of MCTD patients is required.

The authors have declared no conflicts of interest.

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Safety and efficacy of leflunomide and infliximab versus methotrexate and infliximab combination therapy in rheumatoid arthritis

Sir, There is little experience about the safety and efficacy of the combination of leflunomide with infliximab (LEF-INF) in rheumatoid arthritis (RA), and published data have shown some controversy [1–4]. We have read with interest the paper of Flendrie et al. [5], where they compare previous and concomitant LEF therapy plus INF with treatment with INF plus other DMARDs [5]. In order to provide further information in this field we present our results on the safety and efficacy of LEF plus INF in comparison with administration of methotrexate plus infliximab (MTX-INF).

Fifty patients with active RA defined by the ACR criteria [6], seen between December 1999 and September 2004, were divided into two groups according to the treatment received, i.e. LEF or MTX. They were matched for sex, age and duration of disease at the start of INF therapy and their records were analysed. At baseline and before each INF infusion, 28-joint disease activity score (DAS28), ANA and anti-double-stranded DNA (anti-dsDNA; tested by indirect immunofluorescence and with the Crithidia luciliae assay) were performed and any adverse event or drug modification was recorded. A titre ≥1/40 and 15 IU/ml was considered positive for ANA and anti-dsDNAs, respectively.

<table>
<thead>
<tr>
<th>Causes of INF withdrawal (n)</th>
<th>LEF-INF (n = 15)</th>
<th>MTX-INF (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Severe infusion reactions</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Surgery</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Exanthema and fever</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patient’s decision</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Categorical data were analysed using the χ² test and Student’s t-test. Drug survival analysis was done using Kaplan–Meier life curves. P < 0.05 was considered statistically significant. Informed patient consent was signed for all patients treated with infliximab.

Twenty three RA patients were included in the LEF-INF group and 27 in the MTX-INF group. Rheumatoid factor, DAS28 and mean number of DMARDs previously used were similar at baseline (Table 1). All patients on LEF started INF at least 6 months after beginning LEF therapy and 66.8% of these, had been treated with LEF for at least 1 yr. All patients except one had been treated previously with MTX and were switched to LEF mainly due to adverse events (73; 68%). In the MTX group all patients started treatment at least 1 yr before INF administration, and only six patients had received LEF before. Follow-up was 16.7 and 29 months in the LEF and MTX groups, respectively. There was no difference in efficacy measured by DAS28 between groups; DAS28 showed a moderate response (DAS28 was reduced 5.62 ± 1.12 vs 5.86 ± 1.41 at the start of INF therapy and before each INF infusion, 28-joint disease activity score (DAS28), ANA and anti-double-stranded DNA (anti-dsDNA; tested by indirect immunofluorescence and with the Crithidia luciliae assay) were performed and any adverse event or drug modification was recorded. A titre ≥1/40 and 15 IU/ml was considered positive for ANA and anti-dsDNAs, respectively.

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The authors have declared no conflicts of interest.
This study showed that patients in the LEF group had more severe infusion reactions leading to INF withdrawal. Other studies with the LEF-INF combination also reported an increase in the number of such reactions when compared with patients on INF alone [1]. This high number of adverse events has been partially explained by the concomitant initiation of the LEF and INF or the short interval between them [5]. In this study, all patients started LEF at least 6 months before INF. In agreement with Bingham et al. [4], we found high rates of positive ANA in the LEF-INF group, although the highest rates (100%) were reached by patients on MTX. Furthermore, none of our patients showed relevant clinical manifestations that could be attributed to this ANA production.

Flendrie et al. [5] did not find more discontinuations in patients on LEF. Differences in the study design or even genetic differences might account for this discrepancy.

Our study confirms that LEF might be a valid alternative in non-tolerant MTX patients, but we suggest monitoring these patients closely due to the potential increase in severe infusion reactions.

The authors have declared no conflicts of interest.

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