Concise report

Benefits 8 years after a remission induction regime with an infliximab and methotrexate combination in early rheumatoid arthritis

Victoria Bejarano¹, Philip G. Conaghan¹, Mark A. Quinn¹, Benazir Saleem¹ and Paul Emery²

Abstract

Objective. To ascertain whether a 1-year remission induction therapy with an infliximab–MTX (INF–MTX) combination in patients with early RA provided sustained benefit after INF cessation compared with conventional treatment.

Methods. Twenty patients with poor prognosis RA of <1 year of disease duration were randomized to receive either INF and MTX or placebo infusions and MTX for 1 year. They then stepped down to MTX monotherapy and were treated according to standard clinical care. After 8 years, disease activity, function and quality of life (QoL) data were collected.

Results. At follow-up, data were available for 18 patients (1 in each group had died). Median 28-joint DAS was significantly lower in the INF–MTX group compared with placebo–MTX group (2.7 vs 4.3, \( P = 0.02 \)). Four patients in the INF–MTX group were in remission vs none in the placebo–MTX group. One patient in the INF–MTX group achieved drug-free remission. Both RAQoL and HAQ median scores were lower in the INF–MTX group; however, this did not reach statistical significance (median RAQoL 3 vs 8, \( P = 0.18 \); median HAQ 1.0 vs 1.5, \( P = 0.12 \)).

Conclusion. A remission induction regime with an INF–MTX combination for 1 year in early RA can improve long-term clinical outcomes. Larger studies will be required to confirm the implications of these findings.

Key words: Early rheumatoid arthritis, Anti-TNF, Infliximab, HAQ, Function, Methotrexate.

Introduction

The introduction of TNF blockade has revolutionized the treatment of RA. There is a large body of evidence supporting the effectiveness of these biological therapies when compared with conventional therapy for both established [1–3] and early [4–6] RA patients. However, the optimal protocol for cost-effective use of these agents in early disease has not been established. In particular, there are limited long-term data on the benefits of biological therapy when given for a fixed duration in early disease. We have previously reported the effects of a remission induction therapeutic regime in a cohort of 20 patients with RA of <1 year of disease duration, selected for poor prognosis [7]. They were randomized to receive either infliximab (INF; Schering-Plough, Kenilworth, NJ, USA) and MTX or placebo infusions and MTX for 1 year from the time of diagnosis. At the end of the year they continued MTX alone in a step-down protocol. Subsequently their treatment was tailored according to standard clinical care. One year after stopping INF, 70% of patients maintained disease control. While the 28-joint DAS (DAS-28) was similar between the treatment groups, function (as assessed by HAQ) and quality of life (QoL) (RAQoL questionnaire) percentage changes remained significantly better in the INF–MTX group. The aim of the present study was to ascertain whether the 1-year remission induction therapy with INF–
MTX in patients with early RA provided long-term benefit after 8 years.

Patients and methods
Twenty patients with RA according to the 1987 ACR classification criteria [8], of <1 year of disease duration, were selected according to poor prognostic factors such as RF positivity, possession of the shared epitope, raised CRP level, female gender and high HAQ score [9]. They were DMARD naïve. They were invited to participate in a randomized, double-blind, placebo-controlled study for 1 year and a further follow-up period of another year. During the double-blind phase all of them received MTX. The dose was rapidly increased up to 25 mg/week in the presence of remaining synovitis. They were randomized to receive either INF (3 mg/kg) or placebo infusions for 1 year. INF or placebo infusions took place at 0, 2, 6 weeks and 8 weekly thereafter. After the double-blind period they continued MTX therapy in a step-down protocol and were allowed further DMARDs as required. Standard clinical care consisted of a step-up regime with the addition of SSZ and HCQ before considering anti-TNF agents, at the discretion of the treating physician.

After 8 years they were followed up and standard clinical, laboratory, function and QoL data were collected. This included 28-joint tender and swollen counts, general health and disease activity visual analogue scale scores, CRP levels, RAQoL and HAQ scores. DAS-28 was calculated. Written consent was obtained from all the patients. The study was approved by the Leeds (West) Research Ethics Committee.

The primary outcome of this study was 8-year HAQ and RAQoL scores. A power calculation for this study was not performed as the number of patients was already predetermined by the previous study. DAS-28, HAQ and RAQoL scores were analysed with non-parametric tests. The rest of the variables were analysed using parametric or non-parametric tests depending on the presence of normal distribution or not, respectively. Analyses were reported for the intention to treat population.

Results
Eight years after randomization (median 8.1 years), data were collected for 18 patients (1 patient in each arm had died). Baseline demographics showed no difference between the groups (Table 1). This cohort of patients had early and severe disease (mean DAS-28 >6.5 and mean disease duration of 6.5 months). Baseline disease characteristics were similar between the groups except for the median RAQoL score, which was significantly lower in the INF–MTX group. At 8-year follow-up, HAQ and RAQoL scores were better in the INF–MTX group compared with placebo–MTX; however, this did not reach a level of statistical significance (median HAQ 1.0 vs 1.5, \( P = 0.12 \); median RAQoL 3 vs 8, \( P = 0.18 \)). Disease activity was significantly lower in the INF–MTX group (median DAS-28 2.7 vs 4.3, \( P = 0.02 \)). Furthermore, four patients in the INF–MTX group were in remission range (DAS-28 ≤2.6) vs none in the placebo–MTX group.

**Table 1** Baseline and 8-year follow-up data in both groups

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
<th>Demographics</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range), years</td>
<td>51 (41–55)</td>
<td>46 (40–63)</td>
<td>0.83</td>
<td>5 (5–11)</td>
<td>6 (5–12)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Gender: females, n (%)</td>
<td>6 (67)</td>
<td>6 (67)</td>
<td>0.72</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>RF+, n (%)</td>
<td>6 (67)</td>
<td>6 (67)</td>
<td>0.83</td>
<td>3 (33)</td>
<td>5 (55)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Disease duration, median (interquartile range), months</td>
<td>6 (3–12)</td>
<td>5 (3–11)</td>
<td>0.82</td>
<td>5 (3–18)</td>
<td>8 (5–27)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Disease assessment</td>
<td>CRP, median (interquartile range), mg/l</td>
<td>48 (15–66)</td>
<td>20 (11–55)</td>
<td>0.33</td>
<td>11 (9–21)</td>
<td>23 (14–26)</td>
<td>0.04</td>
</tr>
<tr>
<td>DAS-28, median (interquartile range)</td>
<td>6.3 (5.6–6.5)</td>
<td>6.9 (6.1–7.9)</td>
<td>0.09</td>
<td>1.3 (0.8–1.6)</td>
<td>1.4 (1.1–1.9)</td>
<td>0.66</td>
<td></td>
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<tr>
<td>QoL/function assessment</td>
<td>RAQoL, median (interquartile range)</td>
<td>11 (9–21)</td>
<td>13 (9–20)</td>
<td>0.04</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>0.91</td>
</tr>
<tr>
<td>HAQ, 0–3; median (interquartile range)</td>
<td>1.3 (0.8–1.6)</td>
<td>1.4 (1.1–1.9)</td>
<td>0.66</td>
<td>5 (55)</td>
<td>4 (44)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>BIORx, n (%)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>0.91</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONORx, n (%)</td>
<td>3 (33)</td>
<td>5 (55)</td>
<td>0.38</td>
<td>1 (11)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off Rx, n (%)</td>
<td>1 (11)</td>
<td>0</td>
<td>0.91</td>
<td>1 (11)</td>
<td>0</td>
<td></td>
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<tr>
<td>COMBIRx, n (%)</td>
<td>5 (55)</td>
<td>4 (44)</td>
<td>0.28</td>
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<td>PRED, n (%)</td>
<td>1 (11)</td>
<td>0</td>
<td>0.91</td>
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</tbody>
</table>

Significant P-values are given in bold. BioRx: use of biological agents; MonoRx: MTX monotherapy; Off Rx: off disease-modifying anti-rheumatic drug; CombiRx: use of a DMARD combination; Pred: use of prednisolone.
group. One patient in the INF–MTX group achieved drug-free remission. This was a 51-year-old male patient with a 3-month disease duration, seropositive, high disease activity (DAS-28 6.3) and functional impairment at presentation. He first achieved remission by Week 14 and maintained remission from Week 30 until his last assessment. He received the INF–MTX combination for 1 year and then stepped down to MTX 20 mg/week. He continued this treatment until 13 months ago when it was discontinued.

Discussion

To our knowledge this is the longest duration of follow-up of a cohort of patients with early RA who received a combination of INF–MTX therapy at the onset of disease. The group of patients who received 1 year of INF–MTX therapy had significantly lower levels of disease activity and nearly half of them were in remission. One patient achieved drug-free remission. They also had better function and QoL scores, though these did not reach statistical significance. Both arms had a protocol of rapid escalation of MTX until remission was achieved. It is relevant that after the first year of therapy, these patients were treated according to standard clinical care as opposed to the more stringent DAS-driven protocols. This reflects the standard of care that was considered appropriate at that time. Currently, there is strong evidence that DAS-driven protocols provide patients with better outcomes than the more traditional standard of care. Grigor et al. [10] reported better disease activity, function, QoL and radiographic progression in patients treated aiming for DAS-remission (intensive arm) when compared with routine care. The Behandel-Strategièn (BeSt) study group reported good disease control when using different treatment strategies that were DAS driven; however, there was a faster onset of action and less radiographic progression when using combination therapies from the cutset [11]. In that study at 4-year follow-up, 67% of patients had responded to an original combination of INF–MTX and 48% of the INF–MTX arm were able to withdraw INF without detriment to their disease control. Eighteen per cent of the INF–MTX arm continued a drug-free remission [12]. The fact that our patients had better disease control at follow-up after having received a remission induction regime despite subsequent routine care highlights the benefit from the initial INF–MTX combination therapy.

There are some limitations to this study. First, the sample size is small and the results need to be confirmed in larger cohorts. Secondly, there are no radiographic data. This would have added further weight to the data; however, the clinical benefit is relevant and after 8 years is likely to reflect the lack of damage better than at onset. Thirdly, this cohort did not follow a protocol of tight control after the first year of treatment, which may highlight even more benefit from the remission induction regime. Fourthly, there are no cost-effectiveness data. This is an important point to consider, as better disease control and function have the potential to reduce the direct and indirect costs attributable to RA. In conclusion, the use of a remission induction regime with INF–MTX for 1 year in early RA improved outcomes at an 8-year follow-up.

Rheumatology key messages

- One-year remission induction with INF–MTX in early RA can improve long-term outcomes compared with MTX.
- Better disease control, function and QoL were seen in the combination arm.

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References


