Rescue of combination therapy failures using infliximab, while maintaining the combination or monotherapy with methotrexate: results of an open trial

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Abstract

Objective. To assess the possible clinical and biological rescue of rheumatoid arthritis (RA) in 16 patients who were still active despite intensive combination therapy after receiving infliximab following the Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) schedule.

Methods. Sixteen patients who were still active despite combination therapy with optimal doses of methotrexate (MTX 15–17.5 mg/week) and cyclosporin A (CsA 2.5–3.5 mg/day) received infliximab. Ten received their combination plus infliximab (Combi), and six received infliximab plus MTX alone (Mono). The follow-up was carried out for 30 weeks in all patients and for 46 weeks in eight. Efficacy and safety were examined.

Results. At entry, the mean disease activity score (DAS) was 5.6 (all patients had a DAS >3.7). After therapy, eight of 10 patients in Combi and four out of six in Mono showed an improvement of >50% in the initial swollen joint count, yet only one patient reached 50% improvement in the initial DAS after 30 weeks, and one patient had a DAS <2.4 (low disease activity). Of the eight patients who reached 46 weeks of follow-up, three showed an improvement in DAS of 50% and two had a DAS <2.4. When considering the change over time, the difference between DAS at entry and at week 30 was statistically significant only in patients receiving MTX plus CsA, while it was not significant in those receiving MTX only. Two patients developed recurrent febrile upper respiratory infections in the Combi therapy group, while two had a single febrile infection in the MTX alone group. Two patients became strongly anti-cardiolipin positive (IgM >40 MPL) and one developed a coronary syndrome.

Conclusion. Infliximab can be added incrementally to MTX plus CsA, with favourable results in terms of efficacy and safety over time in severe rapidly aggressive and progressive RA. Finally, minor evidence emerged for a stronger efficacy of the Combi treatment compared with Mono.

KEY WORDS: MTX, CsA, Infliximab, Rapidly aggressive progressive rheumatoid arthritis.
this study we have addressed these issues. A group of RA patients who responded poorly to a combination of MTX plus CsA (Combi) were given infliximab, aimed at forcing the disease into remission.

Methods

Population

Sixteen patients with active RA, despite 6 months of combination therapy (MTX 15–17.5 mg/week plus CsA 2.5–3.5 mg/kg/day), were asked to receive infliximab.

Protocol

After obtaining their informed consent, all patients were given infliximab (3 mg/kg) following the schedule of the Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial. In all patients, MTX was given at a dosage of 15–17.5 mg/week. In 10 patients, CsA was continued in combination with MTX at the dosage of 2.5–3.5 mg/kg/day. At entry, all patients had an active disease defined as a swollen joint count (SJC) >6, a C-reactive protein (CRP) value >20 mg/l and a disease activity score (DAS) >3.7 (high activity) [11]. The protocol stated that when patients had not shown an improvement of at least 20% in SJC and CRP after 14 weeks, they were to be removed from the study unless their well-being and daily quality of living was sufficient to continue the infliximab treatment.

During the follow-up, all patients underwent biochemical and immunological assessment, including measurement of antinuclear antibodies (ANA), antibodies to DNA, antibodies to PL-anticardiolipin, and lupus anticoagulant and rheumatoid factor (RF) levels. In addition, possible infections were carefully evaluated at 2, 6, 14, 30 and 46 weeks of follow-up. In particular, nasal and throat swabs, urine cultures and sputum cultures were collected at any time-point to test for bacteria and fungi. A chronic, clinically relevant nasal or bronchial carriage was defined when a swab positive for bacteria and fungi. A chronic, clinically relevant nasal or bronchial carriage was defined when a swab positive for a high number of colonies (>1000) was documented in two consecutive samples, and was accompanied by a low grade fever [13–15]. These cases were defined as moderate infections and were treated with antibiotics or antimycotic drugs. All patients had been basally screened for previous tuberculosis infection. A tuberculin skin test (at 5 U) was conducted for all patients at entry into the study, with a 100% negative result.

Statistical analysis

Mean values, standard deviations and comparisons between values at the various time-points were calculated using the statistical package Prism-Graph Pad (Prism, San Diego, CA, USA). In particular, the Mann–Whitney U-test was used to compare mean values. A P-value <0.05 was considered to represent statistical significance.

Results

A single patient dropped out of the study after 14 weeks. The remainder were all available at 30 weeks. Eight patients have completed 46 weeks of follow-up. As shown in Table 1, all patients had highly active disease, defined according to CRP values, the DAS and the number of SJC. The mean DAS at entry was 5.6, and all participants had a DAS >3.7. Twelve out of 16 patients were RF positive (RF >20 IU/ml), seven were ANA positive (ANA >1/80), and one patient had a positive anti-DNA test (1/80) at entry, determined through the Chritidia luciliae test. One of the patients showed anti-cardiolipin positivity while no lupus anticoagulant was detected. During the follow-up, 12 patients demonstrated an improvement of >50% in the SJC, three patients showed a 20–50% improvement in the SJC, three patients showed no response at all, while CRP improved by >50% in eight patients out of sixteen.

At week 8, five patients had an improvement of >50% in SJC and CRP level compared with entry values. At week 30, nine patients still had a DAS >3.7 (high disease activity) and only one had a DAS <2.4. In particular, two out of six patients in monotherapy and five out of 10 in combination therapy reached a DAS <3.7 (moderate disease activity). Eight patients (four in Combi, four in Mono) had now been followed for 46 weeks; three had shown an improvement in DAS of >50%, but only two had a DAS <2.4 (low disease activity).

When studying patients who had received Combi (MTX plus CsA) compared with those who had received MTX alone, we observed that at 30 weeks, the change in DAS was statistically significant in the 10 patients who had received Combi, while in the six patients who had received only MTX the change over time was not statistically significant (Table 2). At week 30, eight out of 10 patients in the Combi group (80%) and three out of six in the monotherapy group (50%) had a >50% DAS improvement compared with entry values ($\chi^2 = 2.5$, a high number of colonies ($>1000$) was documented in two consecutive samples, and was accompanied by a low grade fever [13–15]. These cases were defined as moderate infections and were treated with antibiotics or antimycotic drugs. All patients had been basally screened for previous tuberculosis infection. A tuberculin skin test (at 5 U) was conducted for all patients at entry into the study, with a 100% negative result.

Table 1. Clinical, demographic and immunological data at entry

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number [mean, median] (95% confidence interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.8, 52 (40.2–57.5)</td>
</tr>
<tr>
<td>Sex (males/females) no.</td>
<td>2/14</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>14.4, 12 (8.8, 20.1)</td>
</tr>
<tr>
<td>RF + (%)</td>
<td>75</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>45.6, 34 (24, 57)</td>
</tr>
<tr>
<td>ANA + (%)</td>
<td>50</td>
</tr>
<tr>
<td>Ab-cardiolipin + (%)</td>
<td>6.25</td>
</tr>
<tr>
<td>Ab-DNA + (%)</td>
<td>0</td>
</tr>
<tr>
<td>SJC (n)</td>
<td>15, 14.5 (11, 19)</td>
</tr>
<tr>
<td>TJC (n)</td>
<td>26, 26 (20, 33)</td>
</tr>
<tr>
<td>DAS</td>
<td>5.6, 5.3 (5, 6)</td>
</tr>
</tbody>
</table>

SJC, swollen joint count; TJC, tender joint count; Ab-cardiolipin, a single patient with a low positivity of ACA-IgM at entry. This patient gave a normal value after the second infusion. The four consecutive numbers represent mean, median and confidence intervals respectively, the single number is the percentage.
Table 2. Basal and final values of the major clinical and biological parameters of the patients in the two subsets of patients with rapidly aggressive-progressive RA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Combi + infliximab (n = 10)</th>
<th>MTX + infliximab (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJC</td>
<td>Basal (mean ± s.d.)</td>
<td>Final (mean ± s.d.)</td>
</tr>
<tr>
<td>TJC</td>
<td>Basal (mean ± s.d.)</td>
<td>Final (mean ± s.d.)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>Basal (mean ± s.d.)</td>
<td>Final (mean ± s.d.)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>Basal (mean ± s.d.)</td>
<td>Final (mean ± s.d.)</td>
</tr>
<tr>
<td>VAS</td>
<td>Basal (mean ± s.d.)</td>
<td>Final (mean ± s.d.)</td>
</tr>
<tr>
<td>DAS</td>
<td>Basal (mean ± s.d.)</td>
<td>Final (mean ± s.d.)</td>
</tr>
</tbody>
</table>

*DAS, the change in DAS in the Combi treatment was the only significant intra-group difference (P < 0.05).

P = 0.1), while the SJC decreased by 50% in 80% of Combi and 66.6% of Mono patients, and CRP decreased in 50% of Combi and 50% of Mono patients.

With respect to the immunological parameters, no real changes were seen in RF levels. In the Combi recipient subset, basal RF values were $118 \pm 185$ compared with final values of $117 \pm 198$ IU/ml. In the monotherapy subset, basal RF values were $613 \pm 1299$ compared with final values of $410 \pm 883$ IU/ml.

ANA doubled the initial titre in four out of five initially positive patients, and ANA became positive in four out of 11 initially negative patients. Two patients became strongly anti-cardiolipin positive (ACA-IgM MPL > 40). None of the patients developed systemic lupus erythematosus-like disease or antiphospholipid syndrome during the follow-up period (Table 3). By the time the ACA-IgM appeared, one patient had had a coronary attack (an episode of stable angina never experienced before); specific treatment was started with heparin, aspirin and beta-blockers, and no new episodes manifested over the ensuing months while on aspirin plus beta-blockers. No allergic or renal side-effects were observed.

Two patients developed three febrile recurrent upper respiratory and lower urinary tract infections each (Candida albicans and Escherichia coli). All were in the Combi therapy subset. Two patients had a single febrile throat and urinary tract infection, respectively (Candida and Staphylococcus aureus). All were in the monotherapy subset.

All conditions were eradicated with specific antimycotic and antibiotic drugs.

Discussion

Anti-TNF-α therapy has certainly changed the potency of the therapeutic approach in rheumatology. The demonstration that it can arrest bone and structural damage, and that it reduces the activity of the disease in patients who respond poorly to MTX, has changed the face of the disease in several ways. We may now hope to genuinely offer our patients the possibility of regaining the ability to work.

Despite these promising results, we still do not know whether infliximab or other anti-TNF-α treatments allow rescue of combination therapy failures. In particular, no study has yet tried to clarify whether infliximab may really improve the clinical situation in patients with disease that is still active despite the combination of MTX plus SSZ or of MTX plus CsA. Furthermore, in these particular cases we do not know whether the combined drug should continue to be administered alongside the biological one, or whether one of the two must be stopped in order to avoid side-effects, and more specifically serious or mild recurrent infections. We addressed this issue in a small group of patients who still had an active disease despite treatment with MTX and CsA at optimal dosages. We chose to continue both drugs in 10 of our patients. The patients were comparable in terms of parameters of clinical and biological activity.

The results after 30 weeks show that patients undergoing Combi therapy had a small statistical advantage in terms of control of clinical activity, as measured using the DAS index. When using the number of swollen joints as the key parameter of clinical synovitis, eight out of 10 patients (Combi group) compared with three out of six (Mono group) had a 50% improvement at week 30. The first conclusion of this study is that combination therapy appears to allow a good level of control in these aggressive-progressive patients. However, only a single patient in the Combi therapy subset attained a DAS of <2.4 (the cut-off point for low disease activity) and none reached a DAS value consistent with remission.

Overall, the mean level of activity decreased in the majority of the patients, as shown by the number of patients improving by > 50% in the SJC and the level of CRP. If we consider the DAS score as a composite index to define the degree of improvement, we can see that even DAS improves in a statistically significant way, but no remission can be observed. These results improved in the subset of eight patients that we followed up to 46 weeks, with three patients attaining a 50% improvement in DAS. In these resistant cases, it is not known whether
a longer treatment period is required in order to see a major improvement. This means that patients who respond poorly to the combination of MTX and CsA do represent a real subset of aggressive-progressive patients, whose disease is highly active and resistant to infliximab, even in combination with MTX and CsA. A feeling of well-being was noted in the majority of patients, with one of the three who did not respond at all choosing to continue the drug despite the lack of clear-cut benefits. This was clearly because of the anti-fatigue effects of infliximab.

With respect to safety, we observed two cases of moderate infections that relapsed three times over the 30-week period in two patients of the Combi therapy subset. In the Mono group, we observed two cases of moderate infections in two patients; the episode only happened once in the 30-week time period. Overall, in patients who were responding poorly to the Combi therapy of MTX plus CsA, the addition of infliximab improved the number of swollen joints, considerably reduced CRP levels and reduced the composite index DAS to an even greater extent. The administration of Combi therapy instead of monotherapy with MTX alone appears to confer little clinical and biological advantage; however, patients on such a treatment regime represent real aggressive-progressive patients. Maintaining combination therapy seems to predispose patients to more episodes of moderate infections than with MTX alone plus infliximab. There is certainly a need to verify whether infliximab really can rescue patients who respond poorly to the various combination therapies available in the rheumatologic armoury and whether different anchor drugs might be adopted in selected cases.

References