Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study

S N Nikas, T I Temekonidis, A K Zikou, M I Argyropoulou, S Efremidis, A A Drosos

Rheumatoid arthritis (RA) is a chronic inflammatory disease which is characterised mainly by synovial inflammation and joint destruction, as well as extra-articular manifestations. Cytokines have a central role in the pathogenesis of this synovial inflammation. Tumour necrosis factor $\alpha$ (TNF$\alpha$) is one of the dominant cytokines. Many studies have shown that TNF$\alpha$ is present in biologically significant amounts in RA synovial tissue and fluids, and the amount seems to parallel the extent of inflammation and bone erosion.

Persistent inflamed monarthritis in patients with RA is difficult to treat. Usually it is treated with local patches, intra-articular injections of steroids, or even with chemical, radioactive, or surgical synovectomy. The introduction of anti-TNF$\alpha$ treatments, especially the infusion of infliximab, prompted us to investigate the effectiveness and safety of intra-articular injection of infliximab in patients with RA and resistant monarthritis.

METHODS AND RESULTS

Five patients who fulfilled the American College of Rheumatology criteria for RA were studied. All were receiving treatment with disease modifying antirheumatic drugs (DMARDs). They presented an active inflammatory monarthritis, resistant to local treatment with corticosteroids for a period of at least three months. Written informed consent was obtained from the patient, who were given intra-articular infliximab, 100 mg, in two consecutive injections at a 24 hour interval after local anaesthesia. The primary end point was to examine the efficacy and safety of intra-articular infliximab administration in patients with RA who had a partial response to DMARDs and exhibited signs and symptoms of persistent inflammation of one large joint. The current treatment was maintained during the study. The secondary end point was the comparison of magnetic resonance imaging (MRI) findings before and six weeks after infliximab administration. Patients with a history or presence of chronic infectious diseases, positive tuberculin skin test, or abnormal chest radiograph were excluded from the study.

Each patient had a complete physical and laboratory evaluation before and six weeks after treatment. The inflamed joint was examined and the following variables were evaluated: the degree of swelling and tenderness of the affected joint (mild 1+, moderate 2+, severe 3+), the pain score (visual analogue scale 0–10 cm), and the patient’s and doctor’s global assessment. In addition, a magnetic resonance (MR) examination of the inflamed joint was performed before and after treatment and the findings were read “blindly” and separately by two expert radiologists. The MR protocol consisted of sagittal short time inversion recovery scans and fat suppressed T1 weighted sagittal, coronal, and axial scans before and after intra-venous contrast injection (Gd-DTPA). Intra-articular fluid collection and synovial thickening with enhancement were considered as findings of synovial inflammation.

Finally, acute phase reactants such as C reactive protein and erythrocyte sedimentation rate were evaluated in all patients.

Three female and two male patients with a mean (SD) age of 52.2 (8.5) years and mean (SD) disease duration of 11.3 (2.2) years were studied. Three had positive IgM rheumatoid factor. Four of the five patients responded well after the intra-articular injection of infliximab as evaluated by the reduction in the swelling and tenderness, by the decrease in the pain score, and by the improvement of laboratory variables (table 1). This clinical and laboratory improvement was associated with the improvement of MRI findings, which showed reduction of synovial fluid and of the enhancing inflammatory tissue (fig 1). One patient did not respond to intra-articular injection of infliximab and the MRI findings did not show any improvement. This patient had a synovitis flare in many joints and was treated successfully with intravenous

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient 1 Before</th>
<th>Patient 1 After</th>
<th>Patient 2 Before</th>
<th>Patient 2 After</th>
<th>Patient 3 Before</th>
<th>Patient 3 After</th>
<th>Patient 4 Before</th>
<th>Patient 4 After</th>
<th>Patient 5 Before</th>
<th>Patient 5 After</th>
<th>p Value</th>
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<tbody>
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<td>Degree of swelling in the joint</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0.049</td>
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<td>Degree of tenderness of the joint</td>
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<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0.046</td>
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<tr>
<td>Pain score</td>
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<td>6.8</td>
<td>7.6</td>
<td>6.8</td>
<td>7.6</td>
<td>6.8</td>
<td>7.6</td>
<td>6.8</td>
<td>0.043</td>
<td></td>
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<td>Patient’s global assessment</td>
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<td>6.8</td>
<td>6.9</td>
<td>6.8</td>
<td>7.6</td>
<td>7.2</td>
<td>7.6</td>
<td>7.2</td>
<td>0.080*</td>
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<tr>
<td>Doctor’s global assessment</td>
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<td>6.6</td>
<td>6.5</td>
<td>6.5</td>
<td>6.7</td>
<td>6.6</td>
<td>6.7</td>
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<td>0.043</td>
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<td>Erythrocyte sedimentation rate</td>
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<td>58</td>
<td>75</td>
<td>60</td>
<td>75</td>
<td>60</td>
<td>75</td>
<td>60</td>
<td>75</td>
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<td>(mm/1st h)</td>
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<td></td>
<td></td>
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<tr>
<td>C reactive protein (mg/l)</td>
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<td>81</td>
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<td>81</td>
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<td>Remission follow up (months)</td>
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<td>6</td>
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<td>0.050</td>
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</table>

For the statistical analysis Wilcoxon test for pairs was used; *non-statistical change.
infusions of infliximab. No local or systemic adverse reactions were noted in our patients.

DISCUSSION

There is limited experience of intra-articular administration of infliximab in patients with RA. Dreher et al reported effectiveness with intra-articular infliximab in the local treatment of three patients with active RA, with an additional systemic effect. They noticed also a remarkable reduction of the daily cell count of the synovial fluid of one patient. Surprisingly, infliximab worked equally well in another patient with chondrocalcinosis, with immediate remission of clinical signs. Significant improvements were also seen by Lawless et al by injecting 1 mg of infliximab dorsally into the left wrist of a patient with monarticular erosive arthritis following silastic wrist prosthesis. On the other hand, Kellner et al published successful treatment of saccroiliitis in five patients with ankylosing spondylitis by intra-articular injection of 60 mg infliximab. Intra-articular administration of infliximab seems to be effective and safe in patients with RA with resistant monarthritis. Large, placebo controlled studies are required to validate our results.

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REFERENCES