Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis

D N Kiortsis, A K Mavridis, S Vasakos, S N Nikas, A A Drosos

MATERIALS AND METHODS

Forty-five patients (28 with RA, 17 with AS) aged 19–74 years were studied. The patients with RA who were refractory or did not tolerate two disease modifying antirheumatic drugs (DMARDs) were treated with intravenous infliximab (3 mg/kg body weight) at 0, 2, and 6 weeks and every 8 weeks thereafter for a total period of 12 months. Rheumatoid patients also received prednisone (5 mg/day) and ciclosporin A or methotrexate. The dose of the drugs was stable during the study.

All patients with AS had axial disease, were receiving only non-steroidal anti-inflammatory drugs, and were treated with infliximab (5 mg/kg body weight) with the same protocol as above.

Patients were excluded from the study if they had (a) a history or presence of malignant disease; (b) known liver or kidney abnormalities or history of viral hepatitis B and C; (c) major complicating diseases such as amyloidosis or heart or lung disease; (d) diabetes mellitus; (e) endocrine or metabolic disorders; (f) drugs which might influence glucose metabolism; and (g) a positive tuberculin skin test or abnormal chest X-ray findings.

All participants reported no significant change in their body weight for at least 3 months before entry into the study. Apart from clinical assessment, a complete biochemical profile was performed before and after 6 months of treatment with infliximab. As a measure of insulin resistance the Homoeostasis Model Assessment (HOMA) Index was used and as a measure of insulin sensitivity the Quantitative Insulin Sensitivity Check Index (QUICKI) was used.

Statistical analysis was performed with the non-parametric Wilcoxon test and Spearman’s correlation coefficients.

RESULTS

The clinical response of patients with RA and AS has been reported previously.11,12 Body mass index and waist to hip ratio did not change significantly after 6 months of treatment. In the whole study, no significant changes of the HOMA Index or the QUICKI were seen. In the tertile of patients with the highest insulin resistance, a significant decrease of the HOMA Index and increase of the QUICKI was found (p<0.01 for both).

BACKGROUND: Tumour necrosis factor α (TNFα) may be an important mediator of insulin resistance. Infliximab is a chimeric monoclonal, high affinity antibody against the soluble and transmembrane TNFα, which can reduce markedly the biological activity of circulating and tissue TNFα and is used in the treatment of various autoimmune disorders. Very little information exists about the role of infliximab treatment on insulin sensitivity. Thus, we assessed the effects of infliximab infusions on insulin sensitivity in patients with RA and ankylosing spondylitis (AS).

MATERIALS AND METHODS

Forty-five patients (28 with RA, 17 with AS) aged 19–74 years were studied. The patients with RA who were refractory or did not tolerate two disease modifying antirheumatic drugs (DMARDs) were treated with intravenous infliximab (3 mg/kg body weight) at 0, 2, and 6 weeks and every 8 weeks thereafter for a total period of 12 months. Rheumatoid patients also received prednisone (5 mg/day) and ciclosporin A or methotrexate. The dose of the drugs was stable during the study.

All patients with AS had axial disease, were receiving only non-steroidal anti-inflammatory drugs, and were treated with infliximab (5 mg/kg body weight) with the same protocol as above.

Patients were excluded from the study if they had (a) a history or presence of malignant disease; (b) known liver or kidney abnormalities or history of viral hepatitis B and C; (c) major complicating diseases such as amyloidosis or heart or lung disease; (d) diabetes mellitus; (e) endocrine or metabolic disorders; (f) drugs which might influence glucose metabolism; and (g) a positive tuberculin skin test or abnormal chest X-ray findings.

All participants reported no significant change in their body weight for at least 3 months before entry into the study. Apart from clinical assessment, a complete biochemical profile was performed before and after 6 months of treatment with infliximab. As a measure of insulin resistance the Homoeostasis Model Assessment (HOMA) Index was used and as a measure of insulin sensitivity the Quantitative Insulin Sensitivity Check Index (QUICKI) was used.

Statistical analysis was performed with the non-parametric Wilcoxon test and Spearman’s correlation coefficients.

RESULTS

The clinical response of patients with RA and AS has been reported previously.11,12 Body mass index and waist to hip ratio did not change significantly after 6 months of treatment. In the whole study, no significant changes of the HOMA Index or the QUICKI were seen. In the tertile of patients with the highest insulin resistance, a significant decrease of the HOMA Index and increase of the QUICKI was found (p<0.01 for both).

CONCLUSIONS: The results suggest that infliximab treatment may have beneficial effects on insulin sensitivity in the most insulin resistant patients with RA and AS.

Abbreviations: AS, ankylosing spondylitis; CVD, cardiovascular disease; DMARDs, disease modifying antirheumatic drugs; HOMA, Homoeostasis Model Assessment; QUICKI, Quantitative Insulin Sensitivity Check Index; RA, rheumatoid arthritis; TNFα, tumour necrosis factor α.
insulin resistance, a significant decrease of the HOMA index and increase of the QUICKI was found (p<0.01 for both measures; table 1). No significant differences were seen for the two insulin action indexes between the patients with RA and those with AS. Moreover, no significant correlations were observed between the insulin action indexes and age, disease duration, or disease activity.

**DISCUSSION**

In this study a significant decrease in insulin resistance was seen after infliximab treatment in the most insulin resistant patients. The possibility cannot be completely excluded that other factors might have affected the insulin sensitivity in these patients. However, the lack of change in their body weight and their dietary habits, and the dose of steroids and DMARDs (both of which can considerably affect insulin resistance),13 14 indicate that the most probable cause of the improvement in insulin sensitivity was infliximab treatment. Only one small study has previously assessed the effects of infliximab on insulin resistance.15 The authors found no significant change in insulin sensitivity after three to five infusions of infliximab. However, owing to the very small number of patients included (10 subjects) they did not perform a separate analysis of the patients with the highest insulin resistance. In another study, the administration of another human anti-TNFα antibody (CDP571) did not considerably affect insulin sensitivity and glycaemic control in patients with type 2 diabetes mellitus.16 However, those subjects had long-standing diabetes mellitus (known duration of the disease averaging 9 years) and severe hyperglycaemia. In such patients, various other mechanisms may contribute to the insulin resistance, including hyperglycaemia, which has been shown to affect insulin signalling in a different way from TNFα.17

In conclusion, our results indicate that infliximab treatment may have beneficial effects on insulin sensitivity in the most insulin resistant patients with RA and AS. The improvement in insulin sensitivity may decrease the CVD risk in these patients. Further prospective studies are needed in larger groups, followed up for a long period of time, in order to assess the effects of infliximab treatment on cardiovascular risk.

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>After treatment</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA (n=14)</td>
<td>3.01 (0.48)</td>
<td>1.89 (0.35)</td>
</tr>
<tr>
<td>QUICKI (n=14)</td>
<td>0.30 (0.008)</td>
<td>0.35 (0.013)</td>
</tr>
</tbody>
</table>

All values are expressed as mean (SE).

**AUTHORS’ AFFILIATIONS**

D N Kiortsis, Laboratory of Physiology, Medical School, University of Ioannina, Ioannina, Greece
A K Mavridis, S Vasakos, Laboratory of Microbiology, General Hospital of Ioannina, Ioannina, Greece
S N Nikas, A A Drosos, Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

Correspondence to: Professor A A Drosos, Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece; adrosos@cc.uoi.gr

Accepted 1 September 2004

Published Online First 30 September 2004

**REFERENCES**