CONCISE REPORT

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

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Background: Tumour necrosis factor α (TNF α) may be an important mediator of insulin resistance. Infliximab is a chimeric monoclonal, high affinity antibody against the soluble and transmembrane TNF α , which can reduce markedly the biological activity of circulating and tissue TNF α and is used to treat various autoimmune disorders.

Objective: To assess the effects of infliximab infusions on insulin sensitivity in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Methods: 45 patients (28 with RA, 17 with AS) aged 19–74 years were studied. All patients were treated with intravenous infliximab. A complete biochemical profile was obtained before and after 6 months' treatment with infliximab. The Homoeostasis Model Assessment (HOMA) Index was used to measure insulin resistance and the Quantitative Insulin Sensitivity Check Index (QUICKI) to measure insulin sensitivity.

Results: In the whole study group, no significant changes of the HOMA Index or 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.

It is well established that there is increased risk for cardiovascular disease (CVD) in rheumatoid arthritis (RA).^{1,2} Several factors have been implicated, of which systemic inflammation is considered the major one.

Increased insulin resistance is an important risk factor for CVD.³ Patients with autoimmune connective tissue diseases have increased insulin resistance.⁴ Several factors have been implicated in the pathogenesis of insulin resistance. Tumour necrosis factor α (TNF α) is a proinflammatory cytokine that has a major role in the pathogenesis of autoimmune diseases and inflammatory disorders. Recently, many studies suggested that TNF α might be an important mediator of insulin resistance in animal models.^{5,6} Moreover, there is evidence that in insulin resistant patients TNF α overexpression occurs in adipose tissue and skeletal muscle.^{7,8} Weight loss in obese insulin resistant subjects results in a substantial reduction of TNF α expression and secretion, in association with a decrease in serum TNF α levels and a restoration of insulin sensitivity.⁹ Interestingly, administration of TNF α to healthy volunteers induced insulin resistance.¹⁰ Infliximab is a chimeric monoclonal, high affinity antibody against the soluble and transmembrane TNF α . It can reduce significantly the biological activity of

circulating and tissue TNF α and is used in the treatment of various autoimmune disorders.

Very little information exists about the role of infliximab treatment on insulin sensitivity.¹¹ 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 group as a whole. However, in the tertile of patients with the highest

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; TNF α , tumour necrosis factor α

Table 1 Effects of infliximab treatment on insulin resistance in the tertile of patients with the highest insulin resistance (n = 14)

	Before treatment	After treatment	p Values
HOMA	3.01 (0.48)	1.89 (0.35)	<0.01
QUICKI	0.30 (0.008)	0.35 (0.013)	<0.01

All values are expressed as mean (SE).

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-TNF α antibody (CDP571) did not considerably affect insulin sensitivity and glycaemic control in patients with type 2 diabetes mellitus.¹⁶ However, those subjects had longstanding 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 TNF α .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.

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