Intravenous anti TNF-α antibody therapy leads to elevated triglyceride and reduced HDL-cholesterol levels in patients with rheumatoid and psoriatic arthritis

Edmund Cauza¹, Karla Cauza², Ursula Hanusch-Enserer¹, Mehrdad Etemad¹, Attila Dunky¹, and Karam Kostner³

¹Department of Internal Medicine V, Department of Rheumatology, Wilhelminenspital, Vienna, Austria
²Department of Dermatology, University of Vienna, Vienna, Austria
³Department of Internal Medicine II, Department of Cardiology, University of Vienna, Vienna, Austria

Summary. Background & Aims: We investigated the effect of Infliximab, an anti TNF-α antibody, on plasma lipids and lipoproteins in patients with rheumatoid arthritis and psoriatic arthritis.

Methods: Five male and 10 female patients with a mean age of 56.7 years were included in this study. Seven of the patients were diagnosed with rheumatoid arthritis and 8 patients with psoriatic arthritis. All patients received infusions of 3mg/kg Infliximab (at week 0, 2 and 6). Lipids, lipoproteins and standard clinical parameters were assessed at baseline (0 week), after 2 weeks, and in 4 patients after 6 weeks.

Results: There was a significant increase in triglyceride levels during treatment with Infliximab (112±48 versus 133±53 mg/dl, p<0.01). In contrast, HDL-cholesterol levels were significantly lowered (56±12 versus 50±13 mg/dl, p<0.006) by the treatment. There was no significant difference in total cholesterol (209±25 versus 205±36 mg/dl) or in LDL-cholesterol (131±24 versus 118±43 mg/dl) before and after treatment. There was no significant change in plasma lipids and lipoproteins in patients with psoriasis arthritis.

Conclusion: This study shows that intravenous Infliximab therapy leads to changes in plasma lipid and lipoprotein profile in patients with rheumatoid and psoriatic arthritis and may result in a more atherogenic lipid and lipoprotein profile. Although larger patient numbers need to be studied to confirm our findings, these results suggest that lipid levels should be checked and monitored in patients receiving Infliximab therapy, particularly in patients with vascular disease.

Key words: Anti-tumor necrosis factor α, Infliximab, lipid metabolism, psoriatic arthritis, rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA), is a chronic disease of unknown cause and probably of autoimmune origin. Similar to RA, psoriatic arthritis (PsA) is considered a form of inflammatory arthritis. A new area in the treatment of
rheumatic diseases commenced with the development of anti-tumor necrosis factor-α (anti-TNF-α), a cytokine that plays an important role in inflammatory diseases and is considered a useful target for specific biological therapy in RA [1]. Tumor necrosis factor-α (TNF-α) is produced primarily by macrophages in response to pro-inflammatory stimuli, such as lipopolysaccharide (LPS), and is synthesized and expressed as a transmembrane protein that can be functional on the cell surface [2]. Intravenous Infliximab, a mouse-human chimaeric monoclonal antibody that binds and inhibits the activity of TNF-α [3], results in reduced expression of interleukins, chemokines and adhesion molecules in patients with RA [4]. TNF-α also plays an important role in lipid metabolism by decreasing the activity of 7 alpha-hydroxylase and lipoprotein lipase and by stimulating the liver production of triglycerides [5, 6]. Since it has also been reported that anti TNF-α treatment in rodents [7–9] leads to changes in their plasma lipoprotein levels, we were interested in the effects of intravenous infusions with Infliximab on plasma lipids and lipoproteins in humans.

**Patients**

Fifteen patients (5 male and 10 female patients with a mean age of 56.7 years, age range: 30–81), admitted to our division of rheumatology were studied. The subjects included 7 patients with RA according to the ARC criteria [10] and 8 patients with PsA (see Table 1). All patients with PsA fulfilled the currently accepted criteria for diagnosis [11]. Eight patients had been treated with methotrexate (MTX), 4 with DMARDs other than MTX, 2 patients only received NSAIDs and 5 corticosteroids. Two patients had hypertension and required drug treatment with calcium channel blockers. These medications were unchanged in all patients during Infliximab therapy. No patients fulfilled the diagnosis of diabetes mellitus, according to the WHO criteria. In four subjects a 2 hour 75 g oral glucose test was performed, however no patient fulfilled the criteria for impaired glucose tolerance (IGT), venous plasma glucose was ≤140 mg/dl or 7.8 mmol/l after 2 hours. The mean body mass index (BMI) in all patients was 25.3 ± 6.4 kg/m² and was calculated as weight divided by height squared.

**Methods**

Patients resistant to all other treatments received infusions of 3 mg/kg Infliximab (at weeks 0, 2, and 6). Standard clinical assessments were performed at baseline, and on weeks 2 and 6. Venous blood was drawn after overnight fasting (minimum 12 hours).

**Laboratory measurements**

All blood samples were collected in the morning prior to the first Infliximab infusions. In 11 patients, plasma lipids were measured after receiving one single infusion at day 14, and in the remaining 4 patients, after receiving 2 infusions at day 42. Citrated blood was centrifuged at 1500 g for 10 min at 4°C and the plasma was immediately stored at −20°C until use. For the analysis of Lp(a), a commercially available enzyme linked immunosorbent assay (ELISA), (Biopool, AB Umea, Sweden) was used. The amount of yellow colour developed, which results from the reaction of the horseradish peroxidase-labelled second antibody with the substrate orthophenylenediamine (OPD) and H₂O₂ and is proportional to the amount of Lp(a) present in the sample, was read on a spectrophotometer at 490 nm. The within-assay CV was 2.3% and the corresponding between-assay CV was 2.7%. No cross reactivity of the goat anti-Lp(a) antibody with LDL or plasminogen were found. The results were read as a mean of duplicate analysis. Cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol were measured by commercially available kits from Boehringer Mannheim (Mannheim, Germany).

**Statistical analysis**

The analysis of our data was performed using the Statistical Package for Social Sciences (SPSS/Mac+). For serum lipids, mean values ± standard deviation (SD) were calculated. P values below 0.05 were considered statistically significant. Student’s t-test was applied to assess significant differences of continuous variables among groups. Comparison of serum Lp(a) and triglycerides among groups was performed using the Wilcoxon test, due to its nonparametric distribution.

**Results**

15 patients were treated with Infliximab for an average of 3.06 weeks (range: 2 weeks – 6 weeks). Fifty per-

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>No. of remicade</th>
<th>Duration of disease (yr)</th>
<th>Steroids mg/d</th>
<th>DMARDs (without MTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>54</td>
<td>f</td>
<td>RA</td>
<td>2</td>
<td>11</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>CK</td>
<td>81</td>
<td>f</td>
<td>RA</td>
<td>2</td>
<td>30</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>SN</td>
<td>30</td>
<td>f</td>
<td>RA</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>DS</td>
<td>31</td>
<td>f</td>
<td>RA</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>GK</td>
<td>55</td>
<td>m</td>
<td>RA</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SK</td>
<td>62</td>
<td>f</td>
<td>RA</td>
<td>1</td>
<td>22</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>LF</td>
<td>68</td>
<td>f</td>
<td>RA</td>
<td>1</td>
<td>20</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>KJ</td>
<td>56</td>
<td>m</td>
<td>PsA</td>
<td>1</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>KG</td>
<td>76</td>
<td>f</td>
<td>PsA</td>
<td>1</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MH</td>
<td>59</td>
<td>f</td>
<td>PsA</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NG</td>
<td>53</td>
<td>f</td>
<td>PsA</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RA</td>
<td>54</td>
<td>f</td>
<td>PsA</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>HL</td>
<td>50</td>
<td>m</td>
<td>PsA</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SH</td>
<td>75</td>
<td>m</td>
<td>PsA</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DP</td>
<td>54</td>
<td>m</td>
<td>PsA</td>
<td>2</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion

To our knowledge, the present study is the first to report that intravenous anti TNF-α treatment leads to changes in plasma lipoprotein levels in humans. Plasma triglyceride levels were significantly increased and HDL cholesterol levels significantly decreased during treatment with Infliximab. LDL cholesterol and Lp(a) levels were not altered by the treatment. Changes in lipoproteins and plasma lipids in animals receiving anti TNF-α treatment have also been observed. Dessi et al. [8] and Carbo et al. [9] reported increased levels of triglycerides and free fatty acids in rodents after intravenous anti TNF-α treatment. The latter authors also reported an increased lipoprotein lipase activity in the treated animals. In contrast to this TNF-α was shown in another study to decrease the level of lipase in murine adipocytes in culture [12].

TNF-α plays an important role in lipid metabolism by decreasing the activity of 7 alpha-hydroxylase and lipoprotein lipase and stimulating the liver production of triglycerides [5, 6]. Type 2 diabetes and atherosclerotic cardiovascular disease have common antecedents and the plasma concentration of TNF-α also predicts insulin sensitivity with advancing age [13]. Levy et al. reported a significant correlation between TNF-α and plasma triglyceride levels in patients with cystic fibrosis [14]. Cytokines usually inhibit lipolysis and one would expect an anticytokine to have the opposite effect, however Dessi et al. could show that mice treated with an anti TNF alpha antibody also showed a triglyceride elevation [8]. The same authors also found an elevation of free fatty acids. We can only speculate about the mechanism of these changes, but anticytokines could activate lipoprotein lipase, a key enzyme of triglyceride metabolism. Since HDL exhibits anti-inflammatory properties, anti-inflammatory treatments could downregulate HDL production or increase metabolism.

To our knowledge, we are the first to report these changes in humans, particularly the decrease observed in HDL levels. At this stage we can only speculate about the mechanism of this decrease.

It is possible that the similarity of Infliximab and TNF-α is responsible for these changes, but it is more likely that Infliximab directly interferes with one or more steps in lipid metabolism. Further studies with larger numbers of patients are needed and may clarify the mechanism by which Infliximab may interfere with plasma lipid metabolism.

One limitation of the current study was the small number of patients studied, which is due to the fact that the treatment is expensive and few patients qualify for the treatment. Furthermore, blood samples were not taken at all time points in all patients. However this is just a preliminary report and we are currently undertaking a much larger study to address these issues.

In conclusion, we show that intravenous Infliximab therapy leads to elevated TG and decreased HDL levels in patients with RA and PsA, thus resulting in a more atherogenic lipid profile.

Our findings, if confirmed in larger patient numbers, suggest that lipid levels should be checked and monitored in patients receiving Infliximab therapy, especially in patients with vascular disease.

References

cholesterol and triglyceride metabolism in mice. Endocrinology 132: 2246–2253

Correspondence: Edmund Cauza, MD, Department of Internal Medicine V, Department of Rheumatology, Wilhelminenspital, Monteleartstraße 37, A-1160 Vienna, Austria, E-mail: edmund.cauza@akh-wien.ac.at

(Received February 28, 2002, accepted after revision October 2, 2002)