Effects of Infliximab Treatment on Lipoprotein Profile in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To investigate the longterm effects of the anti-tumor necrosis factor (TNF) therapy infliximab, a drug known to reduce disease activity in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Methods. Eighty-two patients (50 with RA, 32 with AS) aged 17-77 years were enrolled. All patients were treated with intravenous infliximab. Lipid profile was assessed at baseline and after 6 months of treatment.

Results. Disease activity significantly decreased in patients with RA and AS at the end of infliximab therapy. Infliximab treatment significantly increased total cholesterol from 206 to 216 mg/dl ($p < 0.05$) and triglycerides from 109 to 122 mg/dl ($p < 0.05$). The low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol did not change during treatment. Furthermore, the total cholesterol/HDL cholesterol and triglycerides/HDL cholesterol ratios did not change significantly.

Conclusion. The influence of infliximab treatment on lipid profile seems to be neutral, since neither LDL cholesterol levels nor total cholesterol/HDL cholesterol and triglycerides/HDL cholesterol ratios changed significantly during the 6-month therapy. Our findings suggest that the favorable effect of infliximab treatment on cardiovascular comorbidity may not be mainly mediated by the effects on the lipid profile, but further investigations are needed in order to confirm this hypothesis. (First Release Mar 15 2006; J Rheumatol 2006;33:921–3)

Key Indexing Terms:
INFLIXIMAB RHEUMATOID ARTHRITIS ANKYLOSING SPONDYLITIS
CHOLESTEROL TRIGLYCERIDES ATHEROGENIC INDEX

Coronary artery disease and the atherosclerotic process with which it is intimately associated constitute the major cause of death in Western Society. The World Health Organization, however, has predicted that cardiovascular disease will represent the major cause of morbidity and mortality worldwide before 2010. It has been reported that cardiovascular disease and mortality are increased in patients with rheumatoid arthritis (RA) compared to the general population[1]. Moreover, patients with RA have an increased prevalence of subclinical atherosclerosis as they exhibit increased carotid intima-media thickness as well as decreased arterial compliance[2,3].

Active RA is associated with an unfavorable lipid profile [decreased total cholesterol and relatively more depressed high density lipoprotein (HDL) cholesterol] in comparison with age and sex matched patients with RA in remission[4]. Deterioration of the atherogenic index (the ratio between total cholesterol and HDL cholesterol), which is an important cardiovascular risk factor indicator, tends to normalize upon antirheumatic treatment. This normalization occurs more rapidly in combination treatment with methotrexate (MTX), sulfasalazine, and corticosteroids compared with sulfasalazine treatment alone.

Infliximab, a chimeric monoclonal anti-tumor necrosis factor-alpha (TNF-α) antibody is used today for the treatment of RA, ankylosing spondylitis (AS), and other rheumatic diseases[5]. Effects of treatment with TNF blocking agents on the lipid profile of patients with RA are limited and only short term studies have been performed. However, atherosclerosis is a chronic inflammatory process leading to cardiovascular disease. Therefore, in this study we investigated the longterm effects of the anti-TNF therapy infliximab in a large cohort of patients with active RA and AS.

MATERIALS AND METHODS

Study patients. Consecutive patients with RA and AS who were followed in the outpatient rheumatology clinic of the University Hospital of Ioannina were included in the study. Patients with RA who were refractory or did not tolerate 2 disease modifying antirheumatic drugs (DMARD) received methotrexate (MTX) or cyclosporine-A and prednisone (5 mg/day). Drug

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dosage remained stable during the study. In patients with RA infliximab was administered (3 mg/kg body weight) at 0, 2, 6 weeks, and every 8 weeks thereafter for a period of 6 months. At each visit the number of tender and swollen joints was assessed, as well as the erythrocyte sedimentation rate and C-reactive protein (CRP). Disease activity was evaluated by the Disease Activity for 28 Joint Indices Score (DAS-28)[6], while clinical improvement was measured according to the American College of Rheumatology (ACR) response criteria[7].

Patients with AS had axial disease and received nonsteroidal antiinflammatory drugs (NSAID); 3 received MTX or sulfasalazine. In these patients infliximab was administered at 5 mg/kg body weight with the same protocol as above. Disease activity was evaluated according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[8], and clinical improvement was measured according to the Ankylosing Spondylitis Assessment Study Group (ASAS) response criteria[9].

Patients were excluded from the study if they had (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 and lipid metabolism; and (g) a positive tuberculin skin test or abnormal chest radiograph findings.

All participants reported no significant change in their body weight for at least 3 months before entry into the study. Furthermore, none of the participants reported a modification of dietary habits or experienced significant changes in body weight during the study.

All subjects gave informed consent and the study protocol was approved by the Institutional Ethics Committee.

Laboratory analysis. Apart from clinical evaluation, a complete biochemical profile was performed before and after 6 months of treatment with infliximab. Serum levels of total cholesterol, HDL cholesterol, and triglycerides were determined enzymatically in fasting state with techniques described[10]. Serum LDL cholesterol was calculated using the Friedewald formula (provided that triglycerides levels were lower than 400 mg/dl).

Statistical analysis. All statistical analyses were carried out with SPSS 12.0 (SPSS Inc., Chicago, IL). Continuous variables were tested for lack of normality using the Kolmogorov-Smirnov test. For parameters with normal distribution Student's t test was used. Otherwise the Wilcoxon test was used. Correlations were assessed with Pearson and Spearman correlation coefficients. A p value less than 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of our patients are shown in Table 1. There were 50 patients with RA and 32 patients with AS. None of the patients experienced a cardiovascular event during the study. Also, no significant change in body weight was observed during the study. All patients had active disease as evaluated by high DAS-28 for RA and high BASDAI for AS. Clinical response of patients with RA and AS has been reported[11,12]. In our study DAS-28 score in patients with RA significantly decreased from 5.03 (± 1.03) at baseline to 3.66 (± 1.09) at the end of infliximab treatment. Disease activity also significantly decreased in patients with AS (reduction of BASDAI score from 57.2 ± 18.5 to 20.1 ± 6). At baseline 43 patients had hypercholesterolemia (LDL cholesterol > 160 mg/dl) and 14 had hypertriglyceridemia (triglycerides > 150 mg/dl). Total cholesterol and HDL cholesterol levels were significantly higher at baseline in patients using steroids than in patients without steroid treatment: 214 versus 191 mg/dl ($p < 0.01$) and 53 versus 45 mg/dl ($p < 0.01$), respectively. Triglycerides and LDL cholesterol levels, atherogenic index, as well as disease duration and activity were not significantly different between these groups.

Table 1. Clinical characteristics of patients with RA and AS.

Clinical Features	RA	AS
N	50	32
Male/Female	12/38	31/1
Age, yrs, mean (SD)	52.8 (13.7)	42 (12.2)
Disease duration, yrs, mean (SD)	10.9 (6.3)	13 (8.4)
Disease activity score		
DAS-28, mean (SD)	5.3 (1.03)	—
BASDAI, mean (SD)	—	57.2 (18.5)
Current treatment		
NSAID, n (%)	—	32 (100)
MTX, n (%)	47 (94)	2 (6)
Cyclosporine, n (%)	3 (6)	—
Sulfasalazine, n (%)	—	1 (3)
Prednisone, n (%)	50 (100)	2 (6)
Dose, mg/day, mean (SD)	5	4

BASDAI: Bath ankylosing spondylitis disease activity score; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate.

Infliximab treatment significantly increased total cholesterol from 206 to 216 mg/dl ($p < 0.05$) and triglycerides from 109 to 122 mg/dl ($p < 0.05$). No significant change of LDL and HDL cholesterol was observed. Moreover, the TC/HDL-C ratio did not change significantly. Furthermore, the triglycerides/HDL cholesterol ratio, which is a marker of small dense LDL particles in plasma[13], did not change after treatment with infliximab. The increase of total cholesterol and triglycerides was similar between patients with RA and AS (Figure 1a, b). Moreover, changes in lipid profile did not differ between patients who received corticosteroids and those who did not. Changes of total cholesterol and triglycerides after the 6-month treatment were not correlated with changes in disease activity.

DISCUSSION

We investigated the longterm effects of infliximab on the lipid profile of patients with RA and AS. Infliximab treatment was associated with a significant decrease in disease activity and an increase of total cholesterol and triglycerides. However, total/HDL cholesterol and triglycerides/HDL cholesterol ratios did not change during the treatment period.

Previous reports of the influence of anti-TNF therapy on lipid profile were scarce and short term only. In the study of Popa, *et al* TNF neutralization with monoclonal anti-TNF antibodies increased HDL-cholesterol levels and decreased CRP and IL-6 levels after 2 weeks[14]. Cauza, *et al* reported that a 6-week intravenous infliximab therapy in patients with rheumatoid and psoriatic arthritis led to a significant increase in triglyceride levels, while HDL-cholesterol levels were significantly lowered. There was no significant difference in total cholesterol or in LDL-cholesterol before and after treatment[15]. Finally, Vis, *et al* mentioned that infliximab use was associated with a significant increase of both total cholesterol

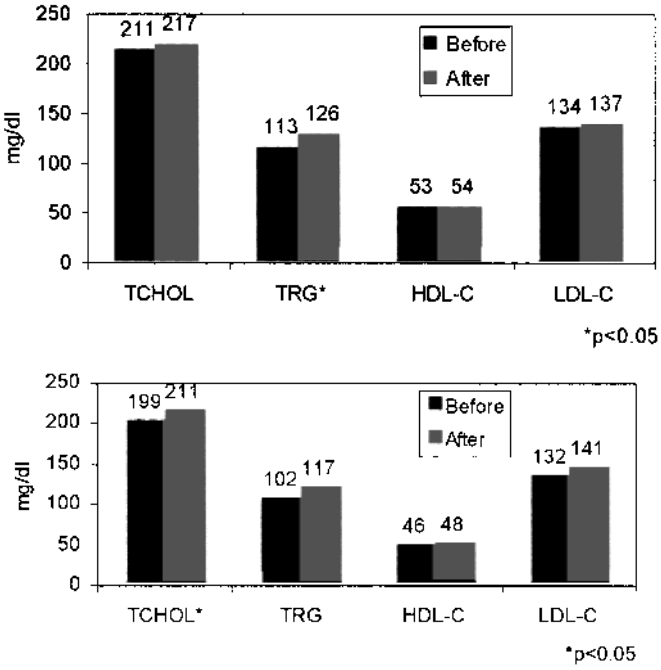

Figure 1. Lipid changes in (a) patients with RA and (b) patients with AS.

and HDL-cholesterol levels after 6 weeks of treatment, but this was not accompanied by a favorable effect on the atherogenic index[16]. The changes in lipid levels observed in these studies are probably due to short term effects of infliximab. Our study examined longterm effects of infliximab on lipid profile, which are more clinically important as atherosclerosis is a chronic process[17].

In our study the influence of infliximab treatment on lipid profile seems to be neutral, since neither the atherogenic LDL cholesterol levels nor total cholesterol/HDL cholesterol and triglycerides/HDL cholesterol ratios, which are major atherosclerotic risk indexes, changed during the 6-month therapy. These findings suggest that the probable favorable effects of infliximab treatment on cardiovascular morbidity[18] might not be mediated by the effects on lipid profile but other factors, such as improvement of endothelial function and insulin resistance, may play a significant role[19-21]. Further investigations are needed to define the possible protective mechanisms of infliximab treatment.

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