Short Term Effects of Infliximab on the Lipid Profile in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Cardiovascular morbidity and mortality appear to be enhanced in rheumatoid arthritis (RA), which might be due to an increased prevalence of cardiovascular risk factors such as dyslipidemia. It was recently shown that effective disease modifying antirheumatic drug treatment had a favorable influence on the lipid profile in patients with active RA. As infliximab markedly reduces disease activity in RA, we investigated the effects of infliximab on the lipid profile.

Methods. Infliximab was administered at baseline and at 2 and 6 weeks in patients with active RA. Total cholesterol and HDL-cholesterol concentrations were measured and their ratio, the atherogenic index (an important cardiovascular risk factor indicator), was assessed.

Results. Sixty-nine patients were enrolled. The Disease Activity Index score (DAS-28) was 5.9 (SD ± 1.4) at baseline and decreased to 4.6 (± 1.4) after 2 weeks and further to 4.1 (± 1.5) after 6 weeks. Total cholesterol level was 5.2 mmol/l at baseline and increased to 5.7 mmol/l ($p < 0.001$) at 2 weeks, and was 5.6 mmol/l ($p < 0.001$ vs baseline) at Week 6. For HDL-cholesterol these values were 1.5, 1.6 ($p < 0.001$), and 1.6 mmol/l ($p < 0.001$ vs baseline), respectively. Changes in disease activity were significantly inversely associated with changes in total cholesterol and HDL-cholesterol levels. The atherogenic index, however, remained constant. Corticosteroid use at baseline was associated with significantly higher total cholesterol and HDL-cholesterol levels and a lower (more favorable) atherogenic index at baseline.

Conclusion. Infliximab treatment was associated with a significant increase of both total cholesterol and HDL-cholesterol levels, which correlated with decreasing disease activity. However, this was not accompanied by a favorable effect on the atherogenic index. The favorable effect of infliximab on cardiovascular comorbidity might not be mediated by effects on lipid metabolism, but longterm investigations are needed to confirm this. (J Rheumatol 2005;32:252–5)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | DISEASE ACTVITITY | INFLIXIMAB
LIPID PROFILE | CHOLESTEROL | ATHEROGENIC INDEX

Mortality appears to be increased in patients with rheumatoid arthritis (RA) compared to the general population, and cardiovascular disease is the most important cause of death[1]. Theoretically, this increased cardiovascular morbidity and mortality in RA patients could be caused by factors such as (1) an increased prevalence of classical risk factors for cardiovascular disease such as dyslipidemia, diabetes mellitus, hypertension, body mass index, physical fitness, and smoking habits; 2) RA itself through the underlying inflammatory process, or decreased functional capacity, or related therapy with disease modifying antirheumatic drugs (DMARD); and (3) under-treatment of cardiovascular comorbidity. This increased cardiovascular risk is also evidenced by an increased prevalence of subclinical atherosclerosis as assessed by increased carotid intima-media thickness in patients with RA in comparison with healthy controls[2,3].

We previously reported that active RA is associated with an unfavorable lipid profile, i.e., decreased total cholesterol and relatively more depressed HDL cholesterol concentrations in comparison with age and sex matched RA patients in remission[4]. This so-called atherogenic index, i.e., the ratio between total cholesterol and HDL cholesterol, which is an important cardiovascular risk factor indicator, tended to normalize upon antirheumatic treatment. This normalization occurred more rapidly in combination treatment with methotrexate (MTX), sulfasalazine, and corticosteroids compared with treatment with sulfasalazine alone[4]. Ultimately, these favorable alterations of the lipid profile

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could result in a lower cardiovascular risk. The beneficial effects of antirheumatic treatment in that investigation[4] could be mediated through either a direct effect of corticosteroids or indirectly by influencing the disease activity.

Reports on the effect of treatment with anti-tumor necrosis factor (TNF) blocking agents on the lipid profile in RA patients with active disease are scarce. Only one group investigated the effect of anti-TNF in a very limited number of patients with RA and psoriatic arthritis. They found that the lipid profile changed to a more atherogenic profile during treatment with infliximab[5].

We prospectively investigated the effects of the anti-TNF therapy infliximab, a drug with no known direct effects on the lipid profile, in a large cohort of patients with active RA.

MATERIALS AND METHODS

Consecutive patients with active RA (defined as a Disease Activity Index 28 Joint Score, DAS-28[6], of at least 3.2) who were referred to the Slotervaart Hospital for treatment with infliximab were included. All patients fulfilled the American College of Rheumatology 1987 criteria for RA[7]. Infliximab (3 mg/kg) was administered at 0, 2, and 6 weeks. All blood samples (nonfasting) were collected in the morning, prior to each infusion and stored at –70°C for a maximum of 6 months until lipid determinations. Total cholesterol and HDL-cholesterol concentrations were measured and their ratio calculated to assess changes in lipid profiles.

At each visit erythrocyte sedimentation rate, C-reactive protein, a visual analog scale for general health, and number of swollen and tender joints were assessed to determine disease activity (DAS-28 score). Changes in medication were recorded at each visit.

Total cholesterol and HDL-cholesterol determinations. Total serum cholesterol (normal 5.0–6.4 mmol/l) was measured by an enzymatic method in an autoanalyzer; HDL-cholesterol (normal > 0.9 mmol/l for men, > 1.1 mmol/l for women) was determined enzymatically with polyethylene glycol-modified enzymes.

Although the classical (chemical) reference value considers a total cholesterol value of 6.4 mmol/l as the upper limit of normal, for interpretation of results we chose 5.0 mmol/l as the upper limit in view of recommendations by national and international consensus committees[8,9]. These guidelines were made in view of increasing evidence that "high-normal" total cholesterol serum levels already imply an increased cardiovascular risk.

Statistical analysis. Total cholesterol, HDL, and the total cholesterol/HDL ratio (the atherogenic index) at 2 and 6 weeks were normally distributed and therefore compared to baseline with paired t tests. To investigate the association between the changes in lipid profiles (outcome variables) and changes in disease activity, linear regression analyses were performed for the period from 0 to 2 weeks and the period 0 to 6 weeks. Two analyses were done: one crude without adjustments and one adjusted for age, disease duration, sex, and change in prednisone dose. All analyses were carried out with SPSS (version 11.0).

RESULTS

Patients. A total of 69 consecutive patients were enrolled, with the following baseline characteristics (Table 1): 55 (80%) women, mean age 55 (13) years, mean disease duration 12 years (range 0–59), and 48 (70%) were rheumatoid factor positive. At entry, 90% (n = 62) of patients used MTX (mean dose 15.8 mg/week) and 5 patients used other DMARD (Table 1).

Thirty-two patients used corticosteroids at the start of the study (mean prednisone dose 10.6 mg/day) and 19 of these patients maintained a stable dose, whereas in the other 13 patients the dose was decreased because of a good response to infliximab. DAS-28 score was 5.9 (1.4) at baseline and decreased to 4.6 (1.4) after 2 weeks ($p < 0.001$), and further to 4.1 (1.5) after 6 weeks ($p < 0.001$; Table 2).

Table 1. Baseline characteristics of the 69 patients with RA.

Baseline Characteristics	
Age, yrs	
Median	58
Range	24–80
Female, n (%)	55 (80)
Rheumatoid factor positive, n (%)	48 (70)
Mean duration of disease, yrs (range)	12 (0–59)
DAS-28 at baseline, mean (SD)	5.9 (1.4)
Treatments	
Steroids, n (%)	32 (46)
Mean dose, mg (range)	10.6 (2.5–30)
Methotrexate, n	62 (90)
Mean dose, mg (range)	10.8 (2.5–30)
Other DMARD, n	
D-penicillamine	1
Azathioprine	3
Cyclosporine	1
Hydroxychloroquine	5

Total cholesterol and HDL-cholesterol. Total cholesterol and HDL-cholesterol levels were 5.17 mmol/l and 1.47 mmol/l at baseline, respectively. Total cholesterol and HDL-cholesterol levels were significantly higher at baseline in the steroid-user group than in the patients without steroid treatment: 5.52 vs 4.86 ($p < 0.001$) and 1.72 vs 1.25 ($p < 0.001$), respectively. This resulted in a more favorable atherogenic index in the steroid-user group at baseline: 3.41 vs 4.10 ($p < 0.05$), respectively. Age, sex, and disease activity were not significantly different between these groups.

Total cholesterol increased from 5.17 to 5.70 mmol/l ($p < 0.001$ vs baseline) at 2 weeks and was 5.52 mmol/l ($p < 0.001$ vs baseline) at Week 6. The values for HDL-cholesterol were 1.47, 1.60 ($p < 0.001$ vs baseline), and 1.59

Table 2. DAS-28, ESR, total cholesterol, HDL-cholesterol, and atherogenic index (cholesterol/HDL-cholesterol) levels during the 6 week treatment.

	Baseline	2 Weeks	6 Weeks
DAS-28	5.9 (1.4)	4.9* (1.4)	4.1* (1.5)
Total cholesterol, mmol/l (SD)**	5.17 (1.06)	5.7* (1.17)	5.52* (1.24)
HDL-cholesterol, mmol/l (SD)***	1.47 (0.43)	1.60* (0.47)	1.59* (0.50)
Atherogenic index	3.8 (1.2)	3.7 (1.1)	3.7 (1.2)

* $p < 0.001$ compared to baseline. ** Normal < 5.0 mmol/l. *** Normal > 0.9 mmol/l for men, > 1.1 mmol/l for women.

mmol/l ($p < 0.001$ vs baseline), respectively. The atherogenic index, however, remained constant during the 6 weeks of infliximab treatment (Table 2).

To assess whether changes in the lipid profile were associated with a change in disease activity we performed linear regression analyses. The changes in HDL-cholesterol and total cholesterol from 0 to 2 weeks showed no significant association with changes in DAS-28. However, changes in DAS-28 from 0 to 6 weeks were significantly inversely associated with changes in both total and HDL-cholesterol levels (Table 3). This association remained after adjusting for changes in prednisone dose, age, sex, and disease duration. Although the mean atherogenic index did not change, changes in DAS-28 were significantly associated with changes in the atherogenic index in the period from 0 to 2 weeks. However, this association disappeared when considering the whole study period (from 0 to 6 weeks; Table 3).

As prednisone had a significant confounding effect in our model, we performed the same regression analyses for the change in prednisone dose. Changes in prednisone dose were significantly associated with the changes in HDL and were inversely associated with the atherogenic index from 0 to 6 weeks ($B = 0.031$, $p = 0.005$, and $B = 0.0453$, $p = 0.047$, respectively). This association remained after adjusting for the change in disease activity. No other relations between changes in prednisone and lipid profile were found at either of the intervals.

DISCUSSION

We found slightly elevated total cholesterol concentrations and normal HDL-cholesterol concentrations in RA patients with active disease at baseline. Treatment with infliximab induced a significant increase in levels of both total cholesterol and HDL-cholesterol. However, these changes did not alter the atherogenic index, which is an important prognostic marker for future cardiovascular disease. The increases in cholesterol levels were significantly associated with a decrease in disease activity. Whether a further decrease of disease activity beyond this period results in a further increase of lipid levels remains to be established.

The lipid profile found at baseline in this study differs from the lipid profile in our previous investigation[4]. The differences between these 2 investigations might be due to differences in storage duration (HDL decreases with the length of storage) or different disease activity in the study groups.

The stable atherogenic index over the study period contrasts with findings in early RA cohorts[4,10]. One trial in patients with early RA investigating combination DMARD therapy (including corticosteroids) indicated a favorable effect on the atherogenic index. The explanation could be that rheumatoid cachexia[11], with accompanying low cholesterol levels and relatively lower HDL-cholesterol levels, is more prominent in early RA than in established RA, which might be because disease activity in early RA is higher than in established RA. This higher disease activity is accompanied with a higher TNF level, an important factor for the development of rheumatoid cachexia[12].

The other study demonstrated decreasing HDL-cholesterol levels during treatment with infliximab, leading to a less favorable atherogenic index[5]. However, in this latter investigation only 7 RA and 8 psoriatic arthritis patients were studied, hence a chance finding cannot be excluded.

The results of this study indicate that use of corticosteroids was, at baseline, associated with increased total

Table 3. Results of linear regression models to evaluate the association between changes in lipid profile and changes in DAS-28 from 0 to 2 weeks and 0 to 6 weeks. The corrected model gives the results of the studied relation after correction for age, sex, disease duration, and changes in prednisone dosage.

	Coefficient B	Significance p	95% CI Lower	95% CI Upper
Changes in HDL from 0 to 2 weeks				
Changes in DAS-28	–0.04	0.13	–0.083	0.011
Corrected	–0.04	0.14	–0.084	0.012
Changes in HDL from 0 to 6 weeks				
Changes in DAS-28	–0.06	0.01	–0.099	–0.014
Corrected	–0.05	0.01	–0.093	–0.012
Changes in total cholesterol from 0 to 2 weeks				
Changes in DAS-28	0.02	0.77	–0.125	0.168
Corrected	0.01	0.88	–0.1	0.157
Changes in total cholesterol from 0 to 6 weeks				
Changes in DAS-28	–0.15	0.02	–0.27	–0.025
Corrected	–0.16	0.01	–0.28	–0.042
Changes in atherogenic index from 0 to 2 weeks				
Changes in DAS-28	0.14	0.01	0.04	0.245
Corrected	0.13	0.02	0.03	0.238
Changes in atherogenic index from 0 to 6 weeks				
Changes in DAS-28	0.05	0.23	–0.03	0.140
Corrected	0.04	0.41	–0.05	0.121

cholesterol levels and, to a relatively greater extent, increased HDL-cholesterol levels. Consequently, a lower atherogenic index in prednisone users in comparison to nonusers was observed at baseline. Lowering the prednisone dose was associated with a decreasing HDL-cholesterol level and an increase of the atherogenic index. Whether this favorable effect of corticosteroids on the lipid profile, at baseline, is ultimately offset by other cardiovascular side effects of corticosteroid use, e.g., hypertension or hyperglycemia, remains to be determined. The effect of lowering prednisone attenuates the effect of a decreasing disease activity (by infliximab) on the atherogenic index, and could explain the observation that the atherogenic index did not change during the study period.

Overall, our study shows that short term treatment with infliximab increases both total cholesterol and HDL-cholesterol, and that this was associated with a decrease of disease activity. However, the atherogenic index remained constant, which might be related to lowering the prednisone doses.

Hence the favorable effect of infliximab on cardiovascular comorbidity observed in the literature might not be mediated by effects on lipid metabolism[13], but longterm investigations are needed to confirm this hypothesis.

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