EXTENDED REPORT

Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis

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Objective: Durable blockade of tumour necrosis factor-alpha (TNF-α) in patients with rheumatoid arthritis (RA) suppresses disease activity and its progression. Cardiovascular diseases are 1.5–2-fold more frequent in RA patients than in the general population. Although TNF-α has well-established effects on lipid metabolism, the long-term effects of TNF-α blockade on lipid pattern are still unclear. In the present study, we investigated the effects of 1-year therapy with anti-TNF on the lipid profile of RA patients.

Methods: Disease activity (DAS28) and plasma lipoproteins concentrations (total, HDL and LDL-cholesterol, triglycerides, ApoA, ApoB) were assessed in 55 RA patients and 55 controls. The whole RA group was followed up for 6 months, and 31 of the patients were followed up for 1 year.

Results: In RA patients, DAS28 decreased after 2 weeks from the start of therapy ($p<0.001$) and remained low during the entire study duration. Short-term effects of anti-TNF on plasma lipid concentrations seemed beneficial and anti-atherogenic. However, these changes did not persist: plasma concentrations of total and LDL-cholesterol and the atherogenic index increased after 6 months and 1 year from the start of therapy. During therapy, the changes in disease activity and inflammatory status were inversely correlated with changes in plasma total and HDL cholesterol levels and positively correlated with the variation of atherogenic index.

Conclusion: We conclude that one-year therapy with infliximab is likely to lead to a more pro-atherogenic pattern of the plasma lipids concentrations. However, the overall impact of these changes on the cardiovascular risk is more complex, considering the strong anti-inflammatory effects of anti-TNF drugs.

Rheumatoid arthritis (RA) is a chronic inflammatory disease of multifactorial aetiology. Cardiovascular diseases have been shown to occur 1.5–2 times more often in RA patients than in the general population, leading to increased mortality in this group of patients.[1] Among the traditional cardiovascular risk factors, the lipid profile in RA has often been described as ''pro-atherogenic'',[2] based on decreased HDL-cholesterol (HDL-C) and increased LDL:HDL-C ratio and lipoprotein (a) plasma concentrations in both active and treated RA.[2–4] Carotid artery intima-medial thickness, a surrogate marker of atherosclerosis severity, was found to be higher, while flow-mediated vasodilatation was lower in RA patients, suggesting a greater prevalence of sub-clinical atherosclerosis in RA.[5] Moreover, insulin resistance is more common in patients with RA than in the general population.[6] However, the increased incidence of cardiovascular events in RA patients cannot be entirely explained by these traditional risk factors.[7] Increased levels of inflammatory markers, including CRP and IL-6, have been shown to be associated with the risk of developing acute cardiovascular events in the general population.[8] Given these observations, chronic inflammation in RA seems to importantly contribute to the development of cardiovascular diseases in these patients.[9 10]

Tumour necrosis factor-alpha (TNF-α) is a pleiotropic cytokine with a pivotal role in triggering the host defense against micro-organisms. Besides this, TNF-α also contributes to atherogenesis through a series of mechanisms: it promotes the expression of adhesion molecules on endothelial cells, recruits and activates inflammatory cells, and initiates the inflammatory cascade within the arterial wall.[11 12] In addition, TNF-α interferes directly with the metabolic pathways of triglycerides and cholesterol.[13–15] Administration of TNF-α to humans results in an acute elevation of plasma triglycerides (TG) with decreased HDL-C concentrations.[16] TNF-α may also alter the composition of lipoprotein particles.[17] Overall, these changes produced by TNF-α are pro-atherogenic; and the persistence of these modified lipids in the circulation promotes the development of atherosclerotic lesions.

Given the effects of TNF-α on both inflammation and the lipid metabolism, one may expect TNF-α neutralisation to have two sets of effects that might lower cardiovascular risk: the anti-inflammatory effects and the anti-atherogenic effects on lipid pattern. Recently, a decrease in the incidence of cardiovascular events was reported in a large group of RA patients after a few years of anti-TNF therapy.[18] Moreover, endothelial function can be restored by anti-TNF agents in terms of improved flow-mediated vasodilatation and reduced expression of adhesion molecules.[19 20] However, the effects of lipid changes are less clear. We have previously shown that a short course of TNF-α blockade is followed by an improvement of lipids profile and insulin sensitivity on top of the diminished inflammatory status in RA patients receiving anti-TNF.[21 22]

The aim of the present study is to investigate the effects of long-term anti-TNF agents on the lipoprotein profile in patients with RA. We hypothesise that besides the downregulation of the pro-inflammatory status of RA, in which TNF-α is considered the pivotal cytokine, long-lasting blockade of the

Abbreviations: AI, atherogenic index; CS, corticosteroids; DAS, disease activity score; HDL-C, HDL-cholesterol; RA, rheumatoid arthritis; TC, total cholesterol; TG, triglycerides; TNF, tumour necrosis factor

pro-atherogenic effects of TNF-α on lipids metabolism will also occur.

PATIENTS AND METHODS

Patients and controls

In our study, we prospectively enrolled 67 consecutive patients with RA, who fulfilled the 1987 American College of Rheumatology criteria. All patients had an active disease (disease activity score (DAS) >3.2) at baseline and were about to start the therapy with a TNF-α blocker (infliximab). Patients taking lipid-lowering drugs were excluded. Patients were attending the outpatient clinic of Sint Maartenskliniek Nijmegen and entered the study after giving their written informed consent. The regional medical ethical committee approved the study. Infliximab (3 mg/kg) was given in infusions at baseline and at 2 weeks, 6 weeks and thereafter every 8 weeks. Changes in infliximab doses (5 mg/kg) or intervals of administration (6 weeks) were based on the patient's response to therapy and were made by the treating rheumatologist, irrespective of the aim of our study. Twelve patients who received treatment for less than 3 months were excluded because of the short-term therapy. In 55 patients, data were collected during a follow-up period of 6 months, whereas 31 patients were followed for 1 year. Stable dosages of disease-modifying antirheumatic drugs and oral corticosteroids (CS, prednisone <10 mg/day) were allowed during the study. Disease activity was measured regularly using the DAS28 score before each infliximab infusion.[23] Patients' disease duration, body-mass index (BMI), smoking status and other characteristics were recorded at baseline and presented in more detail in table 1. No change in the weight of patients was apparent during therapy. Besides the patients group, an age- and gender-matched healthy control group whose characteristics are presented in table 1 was also assessed.

Laboratory measurements

Blood samples were collected before each administration of infliximab. Fasting blood was collected in vacutainer tubes (Beckton & Dickinson, Rutherford, NJ) containing K3-EDTA (1 mg/ml), centrifuged at 3600 rpm for 8 min at 4°C, supplemented with saccharose as a cryoprotectant (final concentration 6 mg/ml) and frozen at −80°C until assay. Serum levels of plasma total cholesterol (TC), TG, and high-density lipoprotein cholesterol (HDL-C) were determined enzymatically on a Hitachi 747 analyser. The normal values for lipoproteins are: TC 4.7–6.5 mmo/l, HDL-C 0.95–1.50 mmol/l (for men) and 1.10–1.70 mmol/l (for women), TG 0.8–2.0 mmol/l. Low-density lipoprotein cholesterol levels were calculated according to the Friedewald formula, which provides reliable values up to a triglyceride concentration of 4.0 mmol/l. Apolipoprotein B (ApoB) and A-I (ApoA) concentrations were determined by immunonephelometry. The atherogenic index (AI) was calculated as the ratio between TC and HDL-C plasma concentrations.

Statistical analysis

Between healthy controls and RA patients at baseline, the comparisons were made using the Mann–Whitney test. For non-parametric values within the group, comparisons were made using the Wilcoxon signed rank test, while the paired Student's t test was use in the case the values were normally distributed. Correlations between inflammatory status markers and lipids were determined using Spearman test. Friedman's non-parametric test for related samples was used to test for changes in lipids concentrations from baseline during the follow-up period. Significance was set at the level of 0.05. Values are expressed as mean ± standard deviation (SD), unless stated otherwise.

Results

Characteristics of the patients at baseline and changes in disease activity

As shown in table 1, we found no important differences regarding the lipid profile between the whole group of RA patients and that of controls. However, male RA patients at baseline had lower HDL-C concentrations and a higher AI compared with male controls: 1.18 ± 0.32 mmol/l vs 1.61 ± 0.44 mmol/l, $p = 0.004$ and 4.53 ± 0.82 vs 3.75 ± 1.04, $p = 0.025$, respectively. In addition, females with RA at baseline had higher HDL-C levels than RA men: 1.44 ± 0.28 mmol/l vs 1.18 ± 0.32 mmol/l, $p<0.01$. This difference was observed at several time-points during the study period (not shown). Interestingly, there was no difference in the lipid pattern at baseline between CS users and non-CS users. As expected, the inflammatory markers were increased in the case of RA patients, but they did not correlate with any of the lipid

Table 1 Characteristics of control group and patients with RA at baseline

Parameters assessed	Rheumatoid arthritis (n = 55)	Controls (n = 55)	p value
General data			
Age (years) (SD)	56 (11)	56 (11)	NS
Gender (M/F)	16/40	16/40	NS
Disease duration (years) (SD)	9 (7)	–	–
Rheumatoid factor (+) (%)	64	–	–
DAS28 (SD)	5.26 (1.25	–	–
Medication			
Oral steroids (n)	9	–	–
Methotrexate (n)	34	–	–
Cardiovascular profile			
Ever smoking (%)	30	59	0.05
CAD history (%)	16	16	1.00
BMI (kg/m^2) (SD)	26.2 (5.2)	24.3 (3.7)	0.08
TC (mmol/l) (SD)	5.55 (0.99)	5.74 (0.79)	0.18
HDL(mmol/l) (SD)	1.37 (0.32)	1.44 (0.39)	0.52
LDL(mmol/l) (SD)	3.54 (0.83)	3.56 (0.72)	0.63
Atherogenic index (TC:HDL) (SD)	4.19 (1.10)	4.24 (1.28)	0.82
LDL:HDL (SD)	2.72 (0.82)	2.66 (0.99)	0.55
TG (mmol/l) (SD)	1.50 (0.65)	1.77 (0.83)	0.08
ApoA (mg/l) (SD)	1510 (350)	1537 (398)	0.46
ApoB(mg/l) (SD)	1024 (212)	1030 (219)	0.68

RA, rheumatoid arthritis; CAD, coronary artery disease; BMI, body mass index.

parameters, although a trend towards an inverse relation between ESR and total and HDL-C could be detected (not shown).

Anti-TNF therapy had an immediate inhibitory effect on the inflammatory status of the patients. After the first infliximab infusion, the DAS28 dropped significantly and thereafter remained stable throughout the entire follow-up period (table 2). According to the EULAR response criteria, 56% of our patients responded to therapy after 6 months, while in 21% an important improvement in disease activity could be recorded at this time point. These percentages did not change significantly after 1 year (60% and respectively 20%). Changes in infliximab doses and frequency of administrations occurred in both responders and non-responders patients, but they had little influence on the distribution of the patients between the two subgroups as assessed after 6 and 12 months of therapy.

Short-term changes in lipoproteins pattern during anti-TNF therapy

Two weeks after the first anti-TNF infusion, TC, LDL-cholesterol, HDL-C and ApoA increased significantly, while the AI remained unchanged (table 2). The 2-week changes on TC and TG were inversely correlated with changes in DAS28 over the same period: $r = -0.30$ ($p = 0.041$) and $r = -0.34$ ($p = 0.032$), respectively. To evaluate whether these initial effects are preserved also in the case of later infliximab infusions, lipid pattern was determined every 2 weeks between two consecutive infusions in a subgroup of 10 RA patients. However, no significant changes in lipid profile could be detected during this interval (not shown). Interestingly, after the first 2 weeks of anti-TNF therapy, CS co-medication significantly influenced TC and HDL-C levels, which increased more in these patients compared with those not receiving oral CS ($p<0.01$, between the two subgroups). In contrast, AI changes were not different between the two subgroups during the same interval.

Long-term changes in lipoproteins pattern during anti-TNF therapy

After 6 months of anti-TNF therapy, except for TG, no significant changes in plasma concentrations of lipids fractions assessed could be detected, compared with baseline (table 2). However, the AI increased significantly during this interval (Table2). In addition, the plasma concentration of TC, LDL-cholesterol and the AI increased after 1 year of therapy (Table2). Total-cholesterol, HDL cholesterol and AI significantly differ over the first 6 months compared with baseline using the Friedman non-parametric test ($p<0.002$, $p<0.001$ and respectively $p<0.024$). The same results regarding total and HDL cholesterol were observed in the 1-year follow-up group ($p<0.033$ and respectively $p<0.019$).

Interestingly, anti-TNF therapy had a more pronounced effect on lipids profile of male patients compared with female RA patients: in male, TC and LDL-cholesterol increased more markedly after 6 months and even after 1 year of therapy ($p<0.04$), and AI tended to increase (not shown). However, no trend in the total and LDL cholesterol increase in men during this period could be noticed. These changes were not related to either BMI or CS use.

Previous studies have reported the existence of a relation between plasma HDL concentrations and the inflammatory status in RA. In our study, the changes in HDL levels were inversely associated with the changes in ESR after 3 months ($p<0.001$, fig 1A), 6 months ($p<0.01$) and 9 months ($p<0.004$, fig 1C) of anti-TNF therapy, while only a tendency for the same relation between changes in DAS28 and HDL at the same time points could be detected (not shown). Plasma TC changes were negatively correlated with changes in ESR after 3 ($p<0.032$) and 6 months ($p<0.034$) of therapy and with changes in DAS28 after 1 year ($p<0.022$). Finally, changes in AI were found to be related to changes in ESR after 3 months ($p<0.03$, fig 1B), 9 months ($p<0.02$, Figure 1D) and 12 months ($p<0.03$), and with changes of DAS28 after 6 months ($p<0.03$) of therapy with infliximab. In addition, the AI had a tendency to increase more in non-responders compared with responders, after 6 months of anti-TNF therapy ($p = 0.089$). No differences could be seen in terms of long-term lipid pattern changes between those taking CS and/or methotrexate as co-medication and those not taking these drugs.

Discussion

In the present study, we show that TNF blockade with infliximab modifies plasma lipoprotein concentrations in RA patients. While short-term effects seem beneficial and anti-atherogenic, they are not sustained over longer periods. The overall decreases in disease activity and inflammatory status are accompanied by changes in lipoprotein profile in these patients.

Up to now, several studies have examined plasma lipid concentrations in RA patients compared with control groups. Total and LDL cholesterol levels of patients with RA were found to be elevated in some studies and reduced in others.[4 24–26] More constantly, decreased HDL-C levels were reported in active or untreated RA,[4 24 26] which might augment the cardiovascular risk. In our study, we also observed a slight decrease in HDL and TG levels in the group of RA patients compared with the control group. In addition, we did not find any important difference between RA and controls regarding the other lipid parameters evaluated. One possible explanation may be that the individuals enrolled in our control group were rigorously matched for age and gender, in contrast to other studies, where often the control group was younger. Alternatively, this discrepancy between studies regarding lipid pattern in RA

Table 2 Lipid changes during 1 year of anti-TNF therapy in patients with RA

	Baseline	Δ 2 weeks	Δ 6 months	Δ 12 months	P_1-value	P_2-value	P_3-value
TC (SD)	5.55 (0.99 mmol/l)	1.07 (0.12)	1.01 (0.14)	1.09 (0.16)	0.001	0.79	0.01
HDL (SD)	1.37 (0.32 mmol/l)	1.08 (0.14)	0.97 (0.15)	1.01 (0.31)	0.001	0.06	0.54
LDL (SD)	3.54 (0.83 mmol/l)	1.08 (0.14)	1.01 (0.18)	0.97 (0.38)	0.001	0.94	0.11
AI (SD)	4.19 (1.10)	1.01 (0.14)	1.09 (0.22)	1.04 (0.37)	0.84	0.02	0.05
LDL:HDL (SD)	2.72 (0.82)	0.99 (0.20)	1.06 (0.22)	1.10 (0.29)	0.88	0.10	0.15
TG (SD)	1.50 (0.65 mmol/l)	1.09 (0.33)	1.14 (0.37)	1.28 (0.63)	0.35	0.02	0.001
ApoA (SD)	1510 (350 mg/l)	1.07 (0.14)	0.99 (0.14)	1.00 (0.20)	0.02	0.40	0.06
ApoB (SD)	1024 (212 mg/l)	1.05 (0.12)	1.02 (0.15)	1.01 (0.23)	0.06	0.56	0.24
DAS28 (SD)	5.26 (1.25)	0.70 (0.21)	0.81 (0.30)	0.75 (0.30)	0.0001	0.0001	<0.0001

Results are presented as mean ± SD; 2-week, 6-month and 12-month results are expressed as percentages from baseline values (1.00 = 100%); P_1 compares baseline with 2 weeks levels; P_2 compares baseline with 6 months levels; P_3 compares baseline with 12 months.

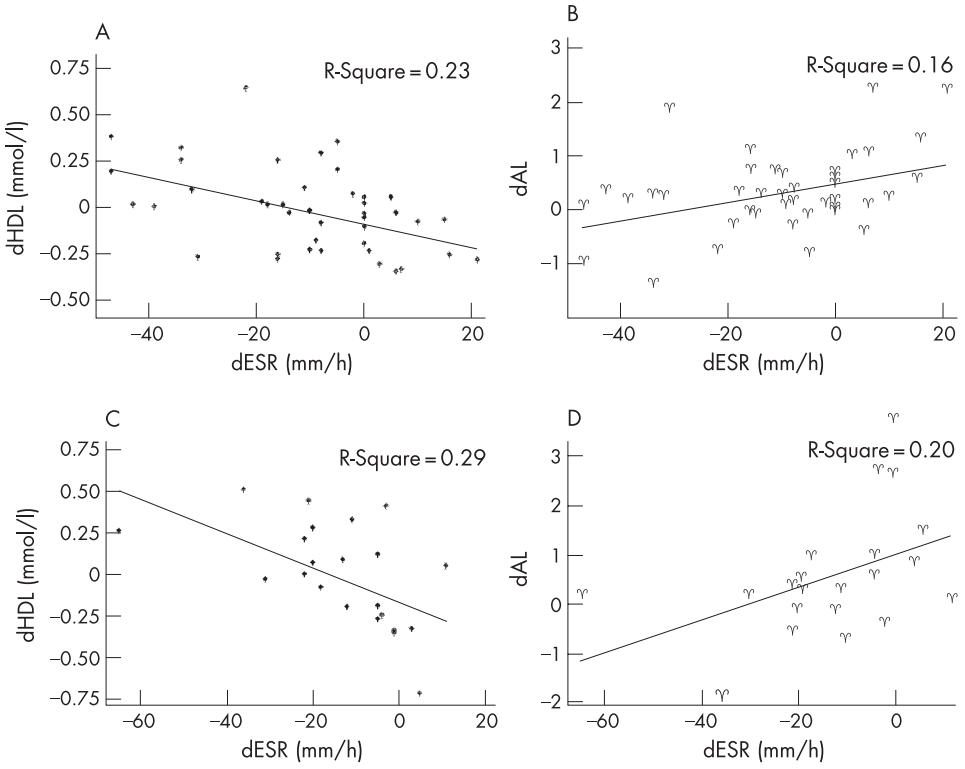

Figure 1 Correlations between changes in inflammatory status, as reflected by plasma ESR concentrations, and HDL-C (A,C) and AI (B,D) after 3 months (A,B) and 9 months (C,D) of therapy with infliximab.

patients might be due to the large heterogeneity between the groups of RA patients studied, in terms of number, disease duration and disease activity.

In the present study, short-term therapy with infliximab was followed by important changes in lipoprotein spectrum that were similar to those previously reported: increase in plasma HDL-C concentrations and no changes of AI during the first 2 weeks of anti-TNF therapy.[21 27] However, the short-term beneficial effects of TNF-α blockade were not sustained in time: total and LDL-cholesterol increased while plasma HDL-C concentrations did not change after 12 months of therapy. In addition, the AI and LDL:HDL-C ratio also increased during the same interval, suggesting a worsening of lipid pattern and an increase in the atherogenic risk in these patients. To date, few studies investigated lipids changes during long-term therapy with infliximab. Allanore *et al* and, more recently, Seriolo *et al* have found increased levels of total and LDL-cholesterol but also increased HDL-C concentrations and no modification of triglycerides, and the AI after approximately 6 months of anti-TNF therapy.[26 28] In another study, 6 months' therapy with infliximab was not accompanied by modification in cholesterol-rich lipoproteins, except for a slight increase in triglycerides concentrations.[29] Finally, after the same treatment period, Rantapää-Dahlqvist *et al* observed no changes in HDL-C levels but noticed an increase in TC, AI and LDL:HDL cholesterol ratio in RA patients receiving anti-TNF therapy.[3] However, the lipid profile present after 6 months of therapy did not change any further 1 year, even 2 years, after therapy with infliximab was initiated. Given these facts, the results of the present study add to the body of evidence that long-term effects of infliximab therapy do not lead to a more favourable lipoprotein pattern.

Previous studies have extensively described the capacity of TNF-α to decrease plasma concentrations of TC, LDL and HDL-C in humans.[13–16 30] Therefore, the neutralisation of TNF-α in patients with RA is likely to abolish these suppressive effects, leading to an increase in cholesterol-rich compounds as best seen in our study shortly after the start of therapy. In addition, the overall inflammatory status might also influence lipid spectrum in RA. This is sustained by studies showing that disease activity and inflammatory markers tend to have inverse relations with HDL-C levels in these patients.[31–33] This might explain the fact that the most significant changes in lipid profile, especially HDL levels, seen after the first 2 weeks from the start of the therapy parallel the most dramatic decrease in the inflammatory status,[21 26 27] while stable activity of RA as seen afterwards was often associated with minor or no changes in lipoprotein plasma concentration.[3 28 29] Eventually this was reflected in the correlations we found in our study at different time-points between changes in HDL-C concentrations or AI on one side and changes in ESR on the other side, which is in line with other reports.[3 26 28] Although recent studies reported weight-gain after TNF blockade in RA patients, this was not the case in our study.[34] Therefore, weight might not essentially contribute to the increase in cholesterol observed in our study. Finally, the use of corticosteroids is known to induce an increase in the levels of total and HDL-C.[3 27 29] However, in our investigated group of RA patients, we found no important differences in lipid changes during long-term TNF-α blockade between CS users and non-users. Therefore, the simultaneous use of oral CS was unlikely to produce the increase in TC and AI seen after 1 year. Nevertheless, total and HDL cholesterol increased more in CS users in the first 2 weeks after the start of therapy, which might be also explained by a decrease in IGF-1 levels as recently reported to occur in these patients during the same period.[35]

The lipid spectrum is among the most important determinants of cardiovascular risk, which is known to be increased in RA compared with the general population.[1] The present study indicates that long-term anti-TNF therapy may worsen the lipid profile, thereby augmenting the cardiovascular risk in these patients. However, as dyslipidemia is not the only risk factor present in RA that can be modulated by anti-TNF agents, the impact of lipids changes seen in the present study on the cardiovascular risk profile should be interpreted with caution. The increase in total and LDL cholesterol observed in the present study after 12 months was 7% (0.38 mmol/l or 14 mg/l)

and 8% (0.28 mmol/l or 11 mg/l), respectively. Therefore, although statistically significant, the changes in total and LDL-cholesterol plasma concentrations might have a limited contribution to increasing the cardiovascular risk in these patients.[7 36] In contrast, the inflammatory status was significantly and constantly depressed by anti-TNF agents, which is likely to diminish the cardiovascular risk.[7–10] In addition, several other studies have been indicated in which anti-TNF drugs could decrease homocysteine levels, improve endothelial function, increase insulin sensitivity and even reduce the incidence of cardiovascular events in a large cohort of RA patients.[19 20 22 37] These data suggest that anti-TNF therapy could either worsen or improve the cardiovascular risk factors in RA, and the net effect is difficult to evaluate only from the results obtained in the current study.

In conclusion, the results of the present study indicate that 1 year's therapy with infliximab is likely to lead to a more pro-atherogenic profile of the plasma lipid concentrations. However, the impact of these changes on the cardiovascular risk is complex and should be evaluated further in prospective studies with clinical endpoints.

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