Modest But Sustained Increase of Serum High Density Lipoprotein Cholesterol Levels in Patients with Inflammatory Arthritides Treated with Infliximab

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ABSTRACT. ***Objective***. Tumor necrosis factor-α (TNF-α) is a key cytokine in the pathogenesis of chronic inflammatory arthritides, has proatherogenic effects, and may be positively correlated with impairment of the action of insulin. Patients with chronic inflammatory arthritides have an increased risk for cardiovascular diseases. We assessed whether anti-TNF-α treatment modifies the unfavorable lipid profile induced by chronic inflammatory arthritides.

Methods. Sixty patients (24 with rheumatoid arthritis, 26 ankylosing spondylitis, and 10 psoriatic arthritis) receiving infliximab because of ongoing disease activity despite disease modifying drugs (DMARD) were prospectively studied for 6 months. Lipid profile, total cholesterol/high density lipoprotein cholesterol (TC/HDL-C), and low density lipoprotein cholesterol (LDL-C)/HDL-C ratios, as well as disease activity indices (DAS28 and BASDAI), were assessed.

Results. A sustained increase of serum HDL-C was observed [mean increase (95% CI)] 5 (3–7) mg/dl, 3.5 (1–6) mg/dl, and 3 (1–5) mg/dl at 1, 3, and 6 months, respectively ($p < 0.01$). Compared to nonresponders, HDL-C increased significantly more in EULAR or BASDAI responders (0.8 vs 5.8 mg/dl; $p = 0.05$). Serum TC was significantly increased [11 (4–8) mg/dl; $p = 0.001$] only after the first month of treatment. TC/HDL-C and LDL-C/HDL-C decreased only after the first month [0.3 (0.1–0.4), $p < 0.01$, and 0.2 (0.1–0.4), $p < 0.01$, respectively]. For patients with baseline LDL-C > 130 mg/dl, LDL-C/HDL-C decreased ($p < 0.05$) during the whole study period and TC/HDL-C decreased ($p < 0.05$) at 1 and 3 months.

Conclusion. Anti-TNF-α treatment in patients with chronic inflammatory arthritides induces a modest, but sustained, increase in serum HDL-C levels, which may have a favorable effect in reducing the cardiovascular risk in these patients. (First Release Oct 1 2006; J Rheumatol 2006;33:2440–6)

Key Indexing Terms:
HDL CHOLESTEROL RHEUMATOID ARTHRITIS PSORIATIC ARTHRITIS
ANKYLOSING SPONDYLITIS INFLIXIMAB

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Supported in part by the AutoCure project and a grant from the Hellenic Rheumatology Society.

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Accepted for publication July 14, 2006.

Inflammatory cytokines like tumor necrosis factor-α (TNF-α) have a central role in the pathogenesis of rheumatoid arthritis (RA) and spondyloarthropathies[1-3]. Patients with RA have a significantly reduced life expectancy[4], while cardiovascular diseases (CVD) account for 35% to 50% of excess mortality[5]. Although there is some controversy, both traditional CVD risk factors as well as RA disease-related factors contribute to this excess risk. Although data for spondyloarthropathies are limited, it appears that patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) also have increased cardiovascular risk[6].

Although the pathogenesis of atherosclerosis is not completely understood, the current paradigm involves inflammatory interactions between plasma lipoproteins, immune cells (macrophages and T cells), vascular cellular components, and the extracellular matrix of the arterial wall[7]. Inflammatory cytokines such as TNF-α have a direct effect on lipoprotein

metabolism, by decreasing both low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), and increasing triglyceride (TG) serum levels[8]. Although LDL-C serum concentration decreases during inflammation, small dense LDL particles, which are believed to have atherogenic effects, increase[8]. Moreover, increased levels of TNF-α correlate with impairment of the action of insulin[9,10].

Patients with active RA have an unfavorable lipid profile, including a significant decrease of HDL-C, that can be reversed after aggressive disease modifying antirheumatic drug (DMARD) treatment[11]. Although less consistently, reports support a proatherogenic lipid profile in patients with PsA as well[12].

Anti-TNF-α agents are established for the treatment of patients with RA or spondyloarthropathies not responding to adequate treatment with DMARD[13]. Data assessing the longterm effect of anti-TNF-α on the lipid profile of patients with inflammatory arthritides are limited and have a limited followup[14-17]. We prospectively investigated for 6 months the effect of infliximab, an anti-TNF-α monoclonal antibody, on the lipid profile of a cohort of patients with RA, AS, and PsA.

MATERIALS AND METHODS

Patients and treatment. Sixty consecutive patients, receiving infliximab because of ongoing disease activity despite conventional treatment, were prospectively studied for 6 months. Patients with RA fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) for RA[18], while patients with a diagnosis of AS fulfilled the modified New York classification criteria[19]. Patients with PsA had skin psoriasis without rheumatoid factor and at least one of the following clinical subtypes of PsA[20,21]: polyarticular arthritis (absence of rheumatoid nodules), asymmetric peripheral arthritis, or AS-like arthritis. We had no patients with arthritis mutilans or pure distal interphalangeal joint involvement.

For patients with RA or PsA, infliximab was given at 3 mg/kg body weight at Weeks 0, 2, and 6, and every 8 weeks thereafter. Background DMARD and corticosteroids (< 10 mg/day) remained stable for the study period.

All patients with AS had axial disease and were treated with infliximab (5 mg/kg at 0, 2, and 6 weeks, and every 8 weeks thereafter). Moreover, no patient had a history of diabetes mellitus or was taking drugs that could interfere with lipid metabolism (statins, niacin, etc.). All subjects signed informed consent forms, and the University Hospital ethical committee approved the protocol.

Disease activity assessment. We applied the Disease Activity Score (DAS) 28 index based on 4 variables to assess disease activity of RA or PsA patients with peripheral disease. Response to treatment was assessed by the European League Against Rheumatism (EULAR) response criteria[22]. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was applied to assess AS disease activity or PsA patients with axial disease. An absolute decrease of 2 points (on a 0–10 scale) of the BASDAI was considered as a response of axial disease[23]. Patients were assessed for disease activity at baseline and at 3 and 6 months of treatment.

Laboratory investigations. Blood samples were taken the morning after 10 hours' overnight fasting. Glucose, high sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR) were measured. Serum concentrations of TC, HDL-C, and TG were measured using an automated chemistry analyzer (Olympus AU-600) with reagents from the same manufacturer. LDL-C was calculated according to the Friedewald formula. Hs-CRP was measured by immune nephelometry (BN II analyzer) and ESR was measured using an automated analyzer (Ves-matic 20). TG levels > 150 mg/dl, HDL-C < 40 mg/dl (for men) and < 50 mg/dl (for women), and LDL-C levels > 130 mg/dl were considered abnormal.

Statistical analysis. Values are expressed as mean ± SD. All p values are 2-tailed. A p value less than 0.05 was considered statistically significant. Paired samples t test was used for comparisons between subsequent visits. Paired differences are expressed as mean with 95% confidence interval (CI). Correlation between changes in inflammatory indices and HDL was assessed by Pearson's correlation (r).

RESULTS

Patients' characteristics. Patients with RA (n = 24) were older than both PsA (n = 10) and AS (n = 26) patients ($p < 0.001$). Of the study group, 55% were men and were significantly younger than women (45 ± 12 yrs vs 54 ± 16 yrs; $p < 0.05$), while patients with PsA had longer disease duration than those with RA ($p < 0.05$). Patients' demographics and diseases characteristics are shown in Table 1.

All patients with PsA had peripheral disease, while 6 out of 10 had concomitant axial involvement. The mean baseline DAS28 for patients with RA (6.9 ± 1.3) was higher compared to that of patients with PsA (5.1 ± 1.7; $p < 0.05$). BASDAI was comparable between AS and PsA patients with axial disease.

All but 2 of the patients with RA were taking concomitant DMARD [methotrexate (MTX: n = 21, mean dose 13 ± 3.5 mg/wk) or leflunomide (n = 3, mean dose 20 mg/day)], and 6 were taking steroids [mean 7 (5–10) mg/day]. Seven of the patients with PsA received MTX (12.8 ± 5.1 mg/week), while 11 of the patients with AS were taking MTX (11 ± 3.5 mg/wk). All patients treated with MTX received folic acid supplementation (7.5 mg/wk). Concomitant medications are shown in Table 2.

Lipid profile. Mean baseline values for TG (109 mg/dl) and HDL-C (49 mg/dl) were within normal range, while LDL-C

Table 1. Patients' demographics and disease characteristics.

Patients	Mean ± SD or No. (%)
AS (n = 26)	
Age, yrs	39.1 ± 8.1
Men	22 (85)
Duration, mo	17.9 ± 8.9
BASDAI	4.6 ± 1.8
RA (n = 24)	
Age, yrs	62.7 ± 10.1
Men	7 (29.2)
Duration, mos	14.1 ± 7.2
DAS28	6.9 ± 1.3
PsA (n = 10)	
Age, yrs	42.5 ± 12.8
Men	4 (40)
Duration, mos	10.3 ± 5.7
DAS28	5.1 ± 1.7
BASDAI (n = 6)	6.0 ± 1.6

AS: ankylosing spondylitis; RA: rheumatoid arthritis; PsA: psoriatic arthritis; BASDAI: Bath AS Disease Activity Index; DAS28: Disease Activity Score 28.

Table 2. Concomitant medications.

Patients	No. (%)
RA (n = 24)	
Prednisone	6 (25.0)
Methotrexate	21 (87.5)
Leflunomide	3 (12.5)
AS (n = 26)	
Methotrexate	11 (42.0)
PsA (n = 10)	
Prednisone	1 (10)
Methotrexate	7 (70)

(132 mg/dl) was slightly elevated (Table 3A). Eleven and 34 of the patients had abnormal baseline values for TG and LDL-C, respectively, while 19 men and 16 women had abnormal baseline HDL-C values. As expected, baseline HDL-C levels were lower in men than in women (42 ± 10 vs 58 ± 17 mg/dl, respectively; $p < 0.01$). No correlation between baseline lipid profile and disease activity (DAS28 or BASDAI) or inflammatory indices (ESR, CRP) was found, probably because of the small number of patients in each disease activity group. Baseline HDL-C levels were significantly higher in patients with RA (56 ± 16 mg/dl) compared to both PsA (45 ± 18 mg/dl; $p < 0.01$) and AS (44 ± 10 mg/dl; $p < 0.05$). In a linear regression analysis assessing the influence of diagnosis, age, and sex in baseline HDL-C levels, HDL-C levels were significantly associated only with sex (ß = 0.43, p = 0.002), while diagnosis was not an independent predictor of HDL-C values (ß = 0.059, p = 0.74).

A significant increase of serum HDL-C levels was observed at 1, 3, and 6 months [mean difference (95% CI): 5 (3–7) mg/dl, $p < 0.001$; 3.5 (1–6) mg/dl, $p < 0.01$; and 2.8 (1–5) mg/dl, p = 0.01, respectively].

Serum TC levels were significantly increased after 1 month [11.0 (4–18) mg/dl; p = 0.001], while at 3 and 6 months

Table 3A. Patients' lipid profile and inflammatory indices (mean ± SD).

	Baseline	1st Month	3rd Month	6th Month
TC, mg/dl	203 ± 39	214 ± 43***	210 ± 42	211 ± 45
HDL-C, mg/dl	49 ± 16	54 ± 14***	53 ± 15**	52 ± 15**
LDL-C, mg/dl	132 ± 33	136 ± 39	135 ± 38	138 ± 37
TG, mg/dl	109 ± 59	127 ± 96	116 ± 86	112 ± 59
TC-C/HDL-C	4.4 ± 1.3	4.2 ± 1.2**	4.2 ± 1.2	4.3 ± 1.3
LDL-C/HDL-C	2.9 ± 1.1	2.7 ± 1.0**	2.8 ± 1.0	2.9 ± 1.1
ESR, mm	41 ± 24	26 ± 22***	26 ± 21***	30 ± 23***
hs-CRP, mg/dl	2.38 ± 2.4	1.02 ± 1.3***	0.98 ± 1.1***	1.88 ± 2.5
DAS28	6.4 (1.7)		5.5 (0.8)*	5.3 (1.8)***
BASDAI	4.9 (1.9)		3.3 (1.7)*	2.6 (1.3)***

TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity C-reactive protein. * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Table 3B. Lipid profile modification according to response status. Responders n = 25, nonresponders n = 23 (mean ± SD).

	Baseline	1st Month	3rd Month	6th Month
Responders				
TC, mg/dl	200 ± 38	214 ± 40*	212 ± 31	220 ± 49
HDL-C, mg/dl	50 ± 19	55 ± 18**	55 ± 20**	56 ± 20***
LDL-C, mg/dl	128 ± 33	135 ± 39	134 ± 30	147 ± 40*
TG, mg/dl	108 ± 64	120 ± 78	124 ± 117	115 ± 71
TC/HDL-C	4.5 ± 1.6	4.2 ± 1.3*	4.3 ± 1.4	4.4 ± 1.7
LDL-C/HDL-C	2.9 ± 1.3	2.7 ± 1.2*	2.8 ± 1.2	3.0 ± 1.3
Nonresponders				
TC, mg/dl	215 ± 43	227 ± 50*	217 ± 51	214 ± 42
HDL-C, mg/dl	49 ± 13	54 ± 11*	52 ± 11	50 ± 10
LDL-C, mg/dl	142 ± 36	147 ± 44	143 ± 46	141 ± 34
TG, mg/dl	122 ± 57	149 ± 125	110 ± 51	116 ± 54
TC/HDL-C	4.6 ± 1.2	4.3 ± 1.2	4.3 ± 1.0	4.4 ± 1.0
LDL-C/HDL-C	3.1 ± 1.0	2.9 ± 1.0	2.9 ± 1.0	2.9 ± 0.8

TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity C-reactive protein. * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ compared to baseline.

no significant differences compared to baseline levels were found (Table 3). There were no significant differences of either TG or LDL-C serum concentrations during the followup period (Table 3A). For the whole study group, TC/HDL-C and LDL-C/HDL-C ratios decreased significantly only at the first month [0.3 (0.1–0.4), $p < 0.01$, and 0.2 (0.1–0.4), $p < 0.01$, respectively; Table 3A].

Interestingly, when patients with baseline LDL-C cholesterol levels above 130 mg/dl were analyzed separately (n = 32), the LDL-C/HDL-C index (3.4 ± 1.1 at baseline) was significantly decreased during the whole study period: mean difference (95% CI) 0.27 (0.06–0.48) at 1 month, 0.32 (0.03–0.6) at 3 months, and 0.26 (0.02–0.5) at 6 months ($p < 0.05$ for each timepoint). Comparably, TC/HDL-C index decreased significantly at 1 and 3 months [0.34 (0.09-0.59), $p < 0.01$, at 1 month, and 0.39 (0.06–0.72), $p < 0.05$, at 3 months, respectively]. When patients were analyzed separately according to diagnosis, significant differences were found in patients with AS and a trend for significance in patients with RA, as shown in Table 4. Loss of significance compared to the whole cohort is probably due to the smaller numbers of patients in each disease group.

No significant change of body weight was observed during the study.

Inflammatory indices and disease activity. ESR levels were significantly decreased at all visits [15 (10–20) mm, $p < 0.001$; 17 (12–23) mm, $p < 0.001$; and 13 (7–20) mm, $p < 0.001$, respectively], while hs-CRP levels were significantly decreased only at Months 1 and 3 [1.33 (0.75–1.92) mg/dl, $p < 0.001$; and 1.34 (0.64–2.05) mg/dl, $p < 0.001$; Table 3A].

A significant inverse correlation of ESR and HDL-C changes between baseline and both 3 and 6 months was found ($r = 0.3$ and 0.33; $p < 0.05$, respectively).

In reference to disease activity for patients with RA and PsA (n = 10), DAS28 improved significantly from 6.4 ± 1.7 at baseline to 5.3 ± 1.8 ($p < 0.001$) at 6 months (Table 3A). At 6 months a total of 17 out of 34 patients (50%) were responders according to the EULAR criteria (12/24 patients with RA and 5/10 with PsA). For axial disease activity, data at 6 months were available for 15 out of 26 patients with AS and for all 6 PsA patients with peripheral disease. BASDAI decreased significantly from 4.9 ± 1.9 at baseline to 2.6 ± 1.3 at 6 months ($p < 0.001$), while 47% (7/15) of patients with AS and 67% (4/6) of patients with PsA were responders (absolute decrease of at least 2 points).

We further analyzed modification of HDL-C levels according to disease activity (EULAR or BASDAI) response status. After 6 months of treatment, HDL-C levels increased significantly in EULAR or BASDAI responders [5.8 (3.0–8.6) mg/dl ($p < 0.001$)], while in nonresponders, although HDL-C levels increased, this was not statistically significant [0.8 (3.4–5) mg/dl ($p > 0.05$); Figure 1]. The modification of lipid profile according to response status is shown in Table 3B.

DISCUSSION

We found that medium-term treatment with infliximab in patients with inflammatory arthritides significantly raised serum HDL-C concentrations. These changes at 6 months correlated significantly with improvement of disease activity. The atherogenic indices TC/HDL-C and LDL-C/HDL-C were significantly decreased — for the whole group — for the first month of treatment. For patients with abnormal baseline LDL-C, both indices were significantly decreased up to the third month and LDL-C/HDL-C for the whole study period, indicating a more favorable effect in patients with impaired lipid profile. Major clinical trials of lipid-lowering agents have shown that even modest increases in HDL-C can reduce coronary event rates between 22% and 34%[24]. Thus, the effect of anti-TNF observed in our study could be clinically significant.

Studies with traditional DMARD have also shown a favorable modification of lipid profile. Hydroxychloroquine (HCQ) has been shown to reduce TC and LDL-C levels in patients with rheumatic disease[25]. After 6 months of treatment with HCQ, patients with RA increased HDL-C levels by approximately 7.7 mg/dl (from 46.1 to 53.8 mg/dl)[26]. A comparable effect was found in the COBRA trial. After 28 weeks of treatment (MTX, sulfasalazine, and corticosteroids), an increase of approximately 6.2 mg/dl of HDL-C was found[11]. Whether this

Table 4. Lipid profile modification according to diagnosis (mean ± SD).

	Baseline	1st Month	3rd Month	6th Month
Ankylosing spondylitis (n = 26)				
TC, mg/dl	201 ± 35	216 ± 47**	210 ± 48	205 ± 41
HDL-C, mg/dl	44 ± 10	50 ± 11***	48 ± 9*	45 ± 10
Rheumatoid arthritis (n = 24)				
TC, mg/dl	207 ± 40	214 ± 36	211 ± 33	220 ± 43
HDL-C, mg/dl	56 ± 17	60 ± 16†	59 ± 18	60 ± 17†
Psoriatic arthritis (n = 10)				
TC, mg/dl	198 ± 48	207 ± 52	212 ± 48	204 ± 61
HDL-C, mg/dl	46 ± 18	49 ± 15	51 ± 16	51 ± 15

TC: total cholesterol; HDL-C: high-density lipoprotein. * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; † $p = 0.08$ compared to baseline.

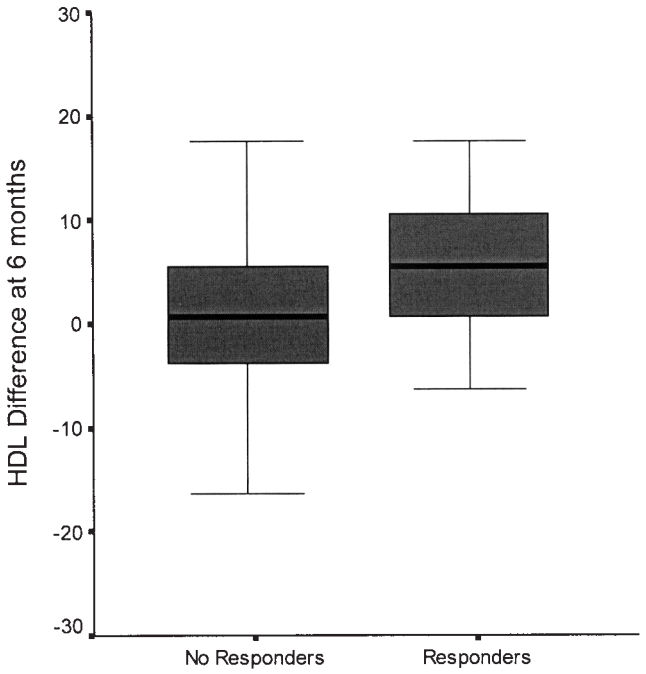

Figure 1. Changes in HDL-C levels in patients according to EULAR or BASDAI response status.

is an effect of DMARD, corticosteroid, or both is not clear, since it is well known that corticosteroids can increases HDL-C levels[27]. Safe comparisons between the aforementioned studies and ours cannot be done, mainly due to differences in baseline characteristics and ethnic background.

There are 3 small studies assessing the effect of short-term (2–6 weeks) anti-TNF-α treatment in lipid metabolism[14-16]. In 2 of them, an increase in HDL and TC levels was found with no changes in LDL. Vis, *et al*[15] found statistically significant increase of HDL-C by 3.7 mg/dl after 6 weeks of anti-TNF treatment, while Popa, *et al*[16] found an increase of 4.6 mg/dl after 2 weeks of treatment. These results are comparable to ours, showing an increase in HDL-C of 5 mg/dl after 1 month of treatment. Atherogenic indices were either not affected[15] or decreased[16]. In the third study, an unfavorable effect after only 6 weeks of infliximab treatment was found in a small and heterogeneous group of 7 patients with RA and 8 with PsA[14].

We confirmed a favorable and sustained effect of anti-TNF-α treatment on HDL-C in a cohort of 60 patients with chronic inflammatory arthritides. Interestingly, a more favorable effect was seen in patients with "borderline high" or higher baseline LDL-C levels, since atherogenic indices decreased for a longer period in this group of patients. Changes in HDL at 6-month levels were inversely correlated with changes in ESR. The correlation between changes in HDL-C and disease activity was further supported by the evidence that HDL-C levels increased significantly only in EULAR or BASDAI responders. Of note, response data were available for 58% (15/26) of patients with AS, but for all patients with RA and PsA. Vis, *et al* have also found an inverse relationship between HDL-C levels and DAS28[15]. Results for the correlation between differences in HDL-C and response status in patients with AS should be interpreted cautiously because of the limited response status (58%) in this group.

Recent results from an observational study have shown lower rate of first cardiovascular event in patients treated with anti-TNF agents compared to those treated with DMARD[28]. Although these data should be confirmed from other centers, they corroborate our data and results from the aforementioned studies, supporting a favorable effect of these agents on lipids, one of the risk factors for cardiovascular diseases.

Some of the changes in the lipid metabolism during inflammation are induced by gene transcription modification. Several nuclear hormone receptors, such as peroxisome proliferator-activated receptors (PPAR)-alpha, gamma, and beta/delta, liver X receptors (LXR)-alpha/beta, and farnesoid X receptors (FXR), that control certain steps in lipid homeostasis are downregulated by lipopolysaccharide, TNF-α, and other cytokines[29]. On the other hand, HDL-C exhibits its atheroprotective role by, among others, promoting reverse cholesterol transport. This pathway, in which excess cholesterol is transported from peripheral tissues to HDL-C and ultimately returned to the liver for excretion in the bile and feces, has recently attracted major interest[30]. To a large extent, it is dependent on the ability of LXR to activate the ABC superfamily of membrane transporters, namely the ABCA1, ABCG5, ABCG8, and ABCG1[31,32]. In mice, overexpression of ABCA1 leads to increased levels of HDL-C and apo A-I[33]. In humans, mutations of either ABCA1 or ABCG5 and ABCG8 are the cause of Tangier disease and sitosterolemia, respectively, and patients with either disease exhibit great reductions in HDL-C, increased atherosclerosis, and higher incidence of cardiovascular disease[34]. Inflammatory molecules like TNF-α downregulate LXR expression in the kidney and this is associated with a concomitant decrease in ABCA1 and ABCG5 expression[35]. In liver, TNF-α has been shown to depress LXR and concomitantly ABCG5 and ABCG8 expression, while in macrophages, TNF-α depressed ABCA1 and ABCG1[36]. Although it is reasonable to assume that downregulation of PPAR-alpha and PPAR-gamma by inflammatory molecules could explain the unfavorable effect in lipid profile, to our knowledge, there is no direct experimental proof. Nevertheless, the above data explaining the mechanisms of TNF-α involvement in lipid metabolism need further confirmation in humans.

On the other hand, the pathogenesis of atherosclerosis involves inflammatory interactions between plasma lipoproteins, immune cells (macrophages and T cells), vascular cellular components, and the extracellular matrix of the arterial wall, reactions where TNF-α, interleukin 1, and interferon-γ are actively involved[7,37]. Thus, any favorable effect of anti-TNF agents on the cardiovascular disease profile of patients

with RA can only partially be attributed to a favorable modification of lipid metabolism.

One of the limitations of our study is the heterogeneity of the group under investigation. Nevertheless, we consider grouping of these patients acceptable, although not ideal, because TNF-α, the target of our intervention, is a common pathogenetic cytokine to all 3 of these inflammatory arthritides. Moreover, although patients differed demographically, in linear regression analysis diagnosis was not an independent predictor of baseline HDL-C, TC, or LDL-C.

In summary, we found a modest but sustained effect on HDL-C after treatment with anti-TNF agents, which is probably more important in patients with impaired baseline LDL-C levels and which correlated with improvement in disease activity. The role of longterm treatment with anti-TNF agents in reducing cardiovascular events remains to be clarified by longitudinal, large-scale trials.

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