Reduction of Inflammation Drives Lipid Changes in Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To investigate the effects of changing inflammation on lipid levels in ankylosing spondylitis.
Methods. In a cohort of 230 patients, lipid levels were measured at baseline and after 52 weeks of treatment with tumor necrosis factor-α–blocking agents (anti-TNF).
Results. Total cholesterol (TC; +4.6%), low-density lipoprotein cholesterol (+4.3%), and high-density lipoprotein cholesterol (HDL-C; +3.7%) increased upon treatment. Changes were most evident in patients with substantial reduction in inflammatory levels (TC +8.2% vs +1.6% and HDL-C +8.3% vs +2.2% in patients with C-reactive protein ≥ 10 mg/l normalizing upon treatment vs CRP < 10 mg/l throughout treatment period).
Conclusion. Anti-TNF therapy results in lipid changes mostly when inflammation is appreciably modified. (First Release September 1 2015; J Rheumatol 2015;42:1842–5; doi:10.3899/jrheum.150193)

Key Indexing Terms:
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In the general population, high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) are well associated with atherosclerotic cardiovascular disease (CVD)[1]. In inflammatory diseases, such as ankylosing spondylitis (AS) and rheumatoid arthritis (RA), systemic inflammation induces secondary dyslipidemia with particularly lower levels of TC and HDL-C[2,3,4,5]. Effective antiinflammatory treatment with tumor necrosis factor–α–blocking therapy (anti-TNF) has been shown to reduce CVD risk, despite increases in lipid levels[6].

Extensive research on the effect of anti-TNF therapy on lipid levels has been performed in the last few years. However, it is still unclear whether lipid changes following anti-TNF therapy are due to reduced inflammation or are a treatment-specific effect of anti-TNF therapy[2]. In AS, C-reactive protein (CRP) levels are elevated in about half of the patients with high disease activity[7]. Therefore, AS is suitable to investigate the effect of anti-TNF therapy on lipid levels in patients with low versus high CRP levels (CRP ≥ 10 mg/l). The rarity of steroid use in patients with AS is another argument for investigating the effect of anti-TNF therapy in patients with AS, considering that research on the lipid-altering effects of anti-TNF therapy in RA might be obscured by simultaneous alterations in steroid use[8,9,10].

Understanding the complex relationship between inflammation and changes in lipid levels upon treatment is a key step toward correct CVD risk management. Hence, we investigated the effect of changing inflammation levels (i.e., decreasing CRP levels) as a result of anti-TNF therapy on the lipid profile in a large group of patients with AS.

MATERIALS AND METHODS

Patients. There were 230 consecutive patients enrolled with AS with an indication for subcutaneous anti-TNF therapy with etanercept (ETN) or adalimumab (ADA). All patients fulfilled the 1984 modified New York criteria for AS[11]. ETN dose was 50 mg subcutaneously once a week or 25 mg twice a week. ADA dose was 40 mg subcutaneously every 2 weeks. Patients treated with statins were excluded. Approval was obtained from the local ethics committee and all participating patients gave written informed consent.

Study design. Data were collected at baseline and after 52 weeks of treatment. Disease activity was measured with the Bath AS Disease Activity Index (BASDAI) on a 0–10 scale and serum CRP was measured at each visit. CRP was measured with a non-high–sensitive technique and about half of the patients had elevated CRP levels > 10 mg/l. A high inflammatory state was defined as CRP ≥ 10 mg/l[12].

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Assessments of lipids. Nonfasting lipid samples were collected. An enzymatic method using clinical chemistry analyzers (Roche Diagnostics) was used to measure TC. HDL-C was determined with poly(ethylene glycol)-modified enzymes. To determine LDL-C levels, the Friedewald formulas were used, but only if triglyceride levels were lower than 4.5 mmol/l. Apolipoprotein-A 1 (ApoA-1) and Apolipoprotein-B (ApoB) levels were measured with an immunoturbidimetric method using appropriate assays (Roche Diagnostics). The TC/HDL-C ratio and ApoB/ApoA-1 ratio were calculated.

Statistical analyses. Lipid levels at baseline and at 52 weeks were compared with the paired samples Student t test. Linear regression analyses were used to determine the association between changes in inflammation (i.e., CRP) and changes in lipid levels. Changes in lipids were normally distributed. A p value of < 0.05 was considered significant. All analyses were performed using SPSS Version 21.0.

RESULTS

Baseline characteristics of the 230 included patients are shown in Table 1. A total of 79 patients (34%) started treatment with ADA, and 151 patients (66%) started ETN. The mean (SD) age of included patients was 42 years (11), and 151 of the patients were men (66%). Median (interquartile range) disease duration was 7 years (2–14), mean BASDAI score at baseline was 5.7 (2.0), and 182 patients (79%) were HLA-B27–positive. After 52 weeks of treatment, lipid values were not available from 79 patients (34%) for several reasons: absence of cholesterol levels in 31 patients, loss to followup in 13 patients, and stopping of anti-TNF therapy in 35 patients because of side effects (n = 19), treatment failure (n = 13), or other reasons (n = 3).

Compared with baseline, median CRP levels decreased significantly upon treatment, from 8 mg/l (3–22) to 2 mg/l (1–6; $p < 0.01$). TC increased by 4.6% (Table 1), LDL-C increased by 4.3%, HDL-C increased by 3.7%, and ApoA-1 increased by 5.3%, while ApoB showed no significant difference. The lipid ratio ApoB/ApoA-1 decreased by 7.8%, while the TC/HDL-C ratio was not changed significantly after 52 weeks of anti-TNF therapy. Total body mass index (BMI) increased slightly over 52 weeks of treatment from 26.0 kg/m^2 (4.4) to 26.6 kg/m^2 (4.7; $p = 0.01$). A positive correlation was found between BMI and TC (r 0.255, $p < 0.01$) and a negative correlation between BMI and HDL-C (r –0.198, $p < 0.01$).

Regression analyses showed an inverse association between changes in CRP and changes in TC and HDL-C (Table 2), irrespective of baseline cholesterol levels. This means, for example, that for every decrease of 10 mg/l in CRP, TC increased by 0.10 mmol/l. Having divided the patients into 3 different treatment response categories (Table 3), significant changes in TC and HDL-C levels were seen only in patients with CRP levels greater than 10 mg/l at baseline reduced to < 10 mg/l after 52 weeks (Table 3, Group 2), with an increment of 8.2% in TC and 8.3% in HDL-C. The TC/HDL-C ratio did not change in any of the groups. No significant interaction was observed between the 3 groups

Table 1. Patient characteristics. Data are expressed as the mean (SD) or median (interquartile range) unless otherwise specified.

Characteristics		All, n = 230		
Demographic				
Age, yrs		42 (11)		
Male, n (%)		151 (66)		
Disease status				
Disease duration, yrs		7 (2–14)		
HLA-B27–positive, n (%)		182 (79)		
CRP, mg/l, n (%)		8 (3–22)		
CRP < 10 mg/l		130 (56)		
CRP ≥ 10 mg/l		100 (44)		
ESR, mm/h		18 (7–37)		
BASDAI		5.7 (2.0)		
NSAID, n (%)		166 (72)		
Lipid levels	t = 0	t = 52	%	p
TC, mmol/l	4.97 (0.93)	5.19 (0.99)*	+4.6*	0.002
HDL-C, mmol/l	1.34 (0.42)	1.39 (0.45)*	+3.7*	0.013
Triglycerides, mmol/l	1.27 (0.89–1.84)	1.38 (0.93–2.23)*	+8.6*	0.047
LDL-C, mmol/l	2.92 (0.82)	3.05 (0.83)*	+4.3*	0.022
ApoA-1, g/l	1.42 (0.32)	1.50 (0.34)*	+5.3*	0.002
ApoB, g/l	0.85 (0.22)	0.84 (0.21)	–1.2	0.335
TC/HDL-C ratio	4.03 (1.37)	4.07 (1.51)	+1.0	0.580
ApoB/ApoA-1 ratio	0.64 (0.22)	0.59 (0.19)*	–7.8*	0.001

* $p < 0.05$ compared with baseline. CRP: C-reactive protein; ESR: erythrocyte sedimentation rage; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NSAID: nonsteroidal antiinflammatory drugs; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA-1: apolipoprotein-A 1; ApoB: apolipoprotein-B.

Table 2. Relationship between changes in CRP and changes in lipid levels. Regression coefficients and standard errors estimated by regression analyses. The Δ for each lipid item are lipid level at 52 weeks minus lipid level at baseline. All analyses were adjusted for age and sex. Values are mean (SD) unless otherwise specified.

Variables	ΔCRP, × 10 mg/l	p
Δ TC, mmol/l	–0.104 (0.038)*	0.007
Δ HDL-C, mmol/l	–0.024 (0.012)*	0.041
Δ Triglycerides, mmol/l	–0.064 (0.060)	0.294
Δ LDL-C, mmol/l	–0.055 (0.029)	0.060
Δ ApoA-1, g/l	–0.027 (0.016)	0.085
Δ ApoB, g/l	–0.008 (0.006)	0.203
Δ TC/HDL-C ratio	–0.015 (0.043)	0.729
Δ ApoB/ApoA-1 ratio	+0.008 (0.007)	0.235

* p < 0.05. CRP: C-reactive protein; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA-1: apolipoprotein A 1; ApoB: apolipoprotein B.

(p = 0.198). Additional adjustment for changes in BMI showed no confounding effect of BMI changes on the relationship between changes in CRP and changes in lipid levels.

DISCUSSION

Having analyzed the complex relationship between inflammation and changes in lipid levels in patients with AS, the results can be summarized as follows: (1) anti-TNF therapy is associated with modest but broadly parallel increases in TC, LDL-C, and HDL-C; (2) the TC/HDL-C ratio is not appreciably altered by anti-TNF therapy; and (3) significant lipid changes following anti-TNF therapy were only seen in patients in whom CRP levels decreased below 10 mg/l, suggesting that the inverse association between inflammation and lipids is not a treatment-specific effect.

In AS, contrary to RA, disease activity is reflected by increased inflammatory markers (CRP) in only half of the patients[13]. Hence, by studying patients with AS, we had a unique opportunity to explore the effect of anti-TNF therapy in patients with high-grade inflammation (CRP ≥ 10 mg/l) and low-grade inflammation. In patients responding to anti-TNF therapy, as mirrored by a significant reduction in CRP levels, lipid levels changed significantly. On the other hand, lipid changes were negligible in patients with low levels of CRP at baseline, or in those without any change in CRP levels. This observation indicates that anti-TNF therapy results in lipid changes only when inflammation is appreciably modified.

In RA, various studies have shown that treatment with anti-TNF therapy results in a fast, absolute increase in lipid levels, after which the lipid levels seem to stabilize[14]. However, simultaneous tapering of steroids, frequently administered as bridging therapy, may confound these observed effects of anti-TNF therapy on lipid levels[8,9]. In AS, steroids are rarely used, which enabled us to examine the true effect of anti-TNF therapy on lipid levels[10]. In our study, we observed similar changes in TC and HDL-C following anti-TNF therapy, suggesting that the potential confounding involvement of steroids on lipid changes in RA is limited. With respect to CVD risk assessment, our data support the use of TC/HDL-C in accordance with the European League Against Rheumatism CVD risk management guideline because it appears to be the most stable marker[15].

The strengths of our study lie in the large group of homogeneous patients with AS included from a single hospital center. These were all patients with AS eligible for anti-TNF therapy, making it an excellent group to study the effects of inflammation and anti-TNF therapy on lipid levels. Further, current evidence of the effect from anti-TNF therapy on lipid levels in AS is derived from short-term studies with a limited number of patients, warranting the need for larger studies with a longer followup[3,16]. The longitudinal design of our study, however, requires careful consideration because dropouts and missing data may have led to biased results.

Lipid changes following anti-TNF therapy largely reflect an inflammatory suppression effect because these changes were seen only in patients with AS with decreasing inflam-

Table 3. Changes in lipid levels among 3 different treatment response categories during 52 weeks of TNF-α–blocking treatment. Patients with CRP levels increased to higher than 10 mg/l upon treatment (n = 3) and patients without CRP or lipid values at 52 weeks were omitted from this table (n = 81). Values are mean (SD) unless otherwise specified.

Groups	TC, mmol/l				HDL-C, mmol/l				TC/HDL-C Ratio			
	t = 0 Weeks	t = 52 Weeks	% Change (95% CI)	p	t = 0 Weeks	t = 52 Weeks	% Change (95% CI)	p	t = 0 Weeks	t = 52 Weeks	% Change (95% CI)	p
Group 1, low-low CRP	5.10 (0.97)	5.18 (0.94)	+1.6 (–1.8–4.9)	0.328	1.34 (0.45)	1.37 (0.47)	+2.2 (–1.5–6.7)	0.267	4.18 (1.50)	4.20 (1.67)	+0.5 (–5.6–6.2)	0.881
Group 2, high-low CRP	4.85 (0.91)	5.25 (0.96)*	+8.2 (3.5–13.0)*	0.001	1.33 (0.39)	1.44 (0.42)*	+8.3 (2.3–14.3)*	0.011	3.92 (1.34)	3.96 (1.39)	+1.0 (–4.8–6.9)	0.744
Group 3, high-high CRP	4.70 (0.87)	4.80 (1.05)	+2.1 (–11.3–15.5)	0.736	1.32 (0.36)	1.29 (0.36)	–2.3 (–9.1–3.8)	0.389	3.74 (1.31)	3.88 (1.24)	+3.7 (–5.9–13.4)	0.424

* p < 0.05 compared with baseline. TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; Group 1, n = 78: patients with CRP levels below 10 mg/l throughout the treatment period; Group 2, n = 54: patients in whom CRP levels dropped from ≥ 10 mg/l to below 10 mg/l; Group 3, n = 14: patients in whom CRP levels did not drop below 10 mg/l upon treatment.

mation levels. Because the TC/HDL-C ratio is essentially unaffected by inflammation or antiinflammatory treatment, this is currently the most appropriate marker to determine CVD risk in patients with an inflammatory condition. The clinical implications of increasing lipid levels through anti-TNF therapy on the overall CVD risk remain to be determined.

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