The Effects of 5-year Etanercept Therapy on Cardiovascular Risk Factors in Patients with Psoriatic Arthritis

Rabia Agca, Maaike Heslinga, Eva L. Kneepkens, Carlo van Dongen, and Michael T. Nurmohamed

ABSTRACT. ***Objective.*** To investigate the effects of etanercept (ETN) on lipid metabolism and other known cardiovascular disease (CVD) risk factors in patients with psoriatic arthritis (PsA).

Methods. In an observational cohort of 118 consecutive patients with PsA, CVD risk factors were assessed over 5 years. Mixed-model analyses were performed to investigate the effects of ETN therapy on CVD risk factors over time.

Results. Disease Activity Score in 28 joints, C-reactive protein (CRP), and erythrocyte sedimentation rate decreased during therapy with ETN. There was an increase in total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), and low-density lipoprotein cholesterol. The TC/HDLc ratio remained unaltered. The apolipoprotein B to apolipoprotein A-I (apoB/apoA-I) ratio decreased significantly. An increase in CRP was associated with an increase in the apoB/apoA-1 ratio.

Conclusion. Serum lipid concentrations showed small changes over a 5-year period of ETN therapy and were inversely associated with inflammatory markers. Other CVD risk factors remained stable. The apoB/apoA-1 ratio decreased over time and an increase in disease activity was associated with an increase in this ratio. However, this modest lipid modulation cannot explain the observed beneficial CV effects of ETN, and ETN likely exerts those effects through inflammation-related mechanisms. (First Release June 1 2017; J Rheumatol 2017;44:1362–8; doi:10.3899/jrheum.161418)

Key Indexing Terms:
CHOLESTEROL
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Psoriatic arthritis (PsA) is an inflammatory joint disorder (IJD) that occurs in about 14%–30% of patients who are affected by the skin condition psoriasis[1,2]. In the last decade, severe psoriasis, but also rheumatic diseases such as rheumatoid arthritis (RA), have been associated with an increased risk of developing cardiovascular disease (CVD)[3]. There is accumulating evidence that PsA should also be considered a disease accompanied by a heightened CVD risk[4,5]. However, literature about the underlying mechanisms that generate this increased risk is scarce. In all inflammatory arthropathies, including PsA, accelerated atherosclerosis is observed because of inflammatory mediators that are involved in the development and progression of these disorders, such as tumor necrosis factor-α (TNF-α). TNF-α is a powerful proinflammatory cytokine that induces inflammation not only in skin and joints, but also in the vascular endothelium, by which it directly influences vascular morphology[6]. Additionally, TNF-α is known to modify traditional risk factors for CVD, such as the lipid metabolism, insulin resistance, and body weight, presumably further increasing CVD risk[7]. Indeed, an increased prevalence of lipid disorders, hypertension (HTN), and obesity has been reported in both psoriasis[8] and PsA[3,9,10]. Yet hyperlipidemia, an important and modifiable CVD risk factor, is rarely observed in its "classic" form in IJD[11]. Generally, inflammation induces a decrease in all serum lipids and this is usually reversed by effective antiinflammatory therapy, though conflicting literature exists. It is suggested that other lipid measurements, such as apolipoprotein B (apoB) and the ratio between apolipoprotein B and apolipoprotein A-I (apoB/apoA-I ratio), might be better predictors of CVD risk in these patients because conventional lipid profiles are difficult to interpret in the context of high-grade inflammation[12,13].

From the Department of Rheumatology, Amsterdam Rheumatology and Immunology Center | VU University Medical Center, Amsterdam, the Netherlands.

R. Agca, MD, Department of Rheumatology, Amsterdam Rheumatology and Immunology Center | VU University Medical Center; M. Heslinga, MD, Department of Rheumatology, Amsterdam Rheumatology and Immunology Center | VU University Medical Center; E.L. Kneepkens, MD, PhD, Department of Rheumatology, Amsterdam Rheumatology and Immunology Center| Reade; C. van Dongen, MD, Department of Rheumatology, Amsterdam Rheumatology and Immunology Center| Reade; M.T. Nurmohamed, MD, Professor, Department of Rheumatology, Amsterdam Rheumatology and Immunology Center | VU University Medical Center.

Address correspondence to Dr. M. Heslinga, Amsterdam Rheumatology and Immunology Center| Reade, Dr. Jan van Breemenstraat 2, 1056 AB, Amsterdam, the Netherlands. E-mail: m.heslinga@reade.nl

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Optimal antiinflammatory therapy is thought to reduce CVD risk in all IJD and this might be mediated by favorable changes in CV risk factors (e.g., the lipid profile)[14]. However, the longterm effects of antiinflammatory treatment, especially of biological agents, on CVD risk and CVD risk factors in patients with PsA have not yet been adequately investigated. Etanercept (ETN), a potent inhibitor of TNF-α, has beneficial effects on CVD risk in patients with RA, an effect thought to be partially mediated by favorable effects on the lipid profile[15]. For PsA, literature on the association between disease activity and lipid levels is limited, although it is assumed that lipids are also modified by inflammation in PsA[16]. Thus far, longterm effects of ETN on lipid levels and other CVD risk factors in PsA are unknown. Therefore, we investigated the effects of ETN therapy on cardiovascular (CV) risk factors, with special focus on lipid profiles, in a cohort of patients with PsA with extended followup.

MATERIALS AND METHODS

Study population. There were 118 consecutive patients diagnosed with PsA and scheduled to receive their first ever prescription of ETN who were recruited for an observational cohort at the Department of Rheumatology in the Jan van Breemen Institute in Amsterdam, the Netherlands, between April 2004 and February 2014. The diagnosis of PsA was made by a rheumatologist. All patients started ETN according to the consensus statement on initiation of treatment with biologicals. Treatment was with subcutaneous administration of ETN alone, either 50 mg once a week or 25 mg twice a week, or with concomitant methotrexate (MTX) and/or prednisone. The study was conducted in compliance with the Declaration of Helsinki and approved by the local Medical Ethics Committee of Slotervaart Hospital (approval number: P0538). Written informed consent was obtained from all patients.

Study design. Patients visited the rheumatology outpatient clinic at the Jan van Breemen Institute for study assessments at baseline and 1, 3, 6, and 12 months, and every following year up to 5 years of ETN therapy. Disease activity was measured with the Disease Activity Score in 28 joints (DAS28), the Psoriasis Area and Severity Index (PASI), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Prior and current medication use, systolic and diastolic blood pressure, and body mass index (BMI; kg/m^2) were recorded at each visit. Triglycerides (TG) and total cholesterol (TC) were assessed using an enzymatic colorimetric test. High-density lipoprotein cholesterol (HDLc) was measured using polyethylene glycol–modified enzymes. Low-density lipoprotein cholesterol (LDLc) was calculated using the Friedewald formula when TG were lower than 4.5 mmol/l. TC/HDLc ratios were calculated. In a subpopulation of 81 patients, apoA-I and apoB were measured with an immunoturbidimetric assay. All blood samples were determined batch-wise.

Statistical analysis. Data are presented as mean ± SD in case of normal distribution, and otherwise as median and interquartile range or numbers and percentages. Log transformations were done if necessary. Mixed-models analyses were performed to assess the changes in CV risk factors over time and their relation to disease activity variables such as DAS28, CRP, and ESR, because this method is designed for analyzing cohort data with missing values. The unstructured random covariance type was used. Patients were included in the analysis only if study assessments were performed at baseline and at least at 1 other visit during followup. The univariate models were adjusted for potential confounders, including age, sex, disease duration, concomitant MTX, prednisone, nonsteroidal antiinflammatory drugs, antihypertensives, and statin use. A p value < 0.05 was considered statistically significant. All data were analyzed with SPSS version 20.0.

RESULTS

The study population consisted of 118 patients with a mean age of 47 ± 13 years, and a nearly equal proportion of men (n = 58) and women (n = 60). The baseline characteristics are presented in Table 1. Patients had a median psoriasis duration of 13 years (5–22) and a median arthritis duration of 6 years (2–13). Twelve patients had previously been treated with adalimumab and 1 with infliximab. Fifty-three patients were receiving MTX and 9 patients were treated with prednisone concomitantly with ETN. The median duration of ETN treatment was 4 years (2–5).

Changes in inflammatory variables. Study assessments were performed at baseline, 4, 16, 28, 52, 104, 156, 208, and 260 weeks. ESR, CRP, and DAS28 decreased significantly over time, with the greatest decrease in the first month after the start of ETN treatment (Figure 1). DAS28 remained high in patients who discontinued therapy after 28 weeks (3.13 ± 1.65 vs 1.98 ± 1.08, p = 0.003) and 52 weeks (2.86 ± 1.45 vs 1.62 ± 0.94, p = 0.001). CRP and ESR were significantly elevated in the patients who discontinued therapy after 28 weeks (ESR 9, 3–30 vs 4, 2–8, p = 0.028 and CRP 2, 1–12 vs 2, 1–3, p = 0.049) and 52 weeks (ESR 19, 5–39 vs 4, 2–7, p = 0.009 and CRP 5, 2–10 vs 1, 1–2; p = 0.003). In the mixed-models analysis, patients who discontinued therapy had higher DAS28 in comparison with patients who continued ETN treatment over 5 years (β 0.56, 95% CI 0.12–0.99, p = 0.013). The PASI did not differ among these patients (data not shown). The reasons for discontinuing therapy were remission (n = 8), failure (n = 11), adverse events (n = 10), migration or nonresponse (n = 9), pregnancy wish (n = 1), and other unknown reasons (n = 3).

Changes in CVD risk factors over time during ETN therapy. At baseline, 39.8% of the patients had HTN, 74.6% had dyslipidemia, and 56.8% was overweight. TC/HDLc ratio was above 3.5 in 56.4% of the patients and 6.8% had diabetes.

The mixed-models analysis showed a significant increase in TC, HDLc, and LDLc over 5 years after correction for age, sex, disease duration, concomitant MTX, prednisone, and statin use. ApoA-I and apoB measurements were available in a subpopulation of 81 patients. The apoB/apoA-I ratio decreased significantly over 5 years, while the TC/HDLc ratio remained stable (Table 2). Blood pressure, BMI, creatinine, and TG remained stable over the years (Table 2). The mean lipid levels per visit are shown in Figure 2.

Relationship between CVD risk factors and disease activity. In the mixed-models analyses, changes in DAS28 were associated with changes in diastolic blood pressure, TC, HDLc, and TG (Table 3). One point increase in DAS28 was associated with an increase in diastolic blood pressure, a decrease in TC and TG. This association was still significant after adjustment for age, sex, disease duration, and concomitant medication use (Table 3). There was a trend for an increased apoB/apoA-I ratio with a 1-point increase in

Table 1. Baseline characteristics. Values are mean ± SD, median (interquartile range), or n (%).

Characteristics	Value
Demographics, n = 118	
Age, yrs	47 ± 13
Female	60 (50.8)
PsA-related factors	
Psoriasis duration, yrs	13 (5–22)
Arthritis duration, yrs	6 (2–13)
Psoriasis Area and Severity Index	0 (0–2)
Disease Activity Score 28	4.36 ± 1.39
Swollen joint count	5 (2–10)
Tender joint count	7 (3–15)
ESR, mm/h	16 (6–28)
CRP, mg/l	6 (2–14)
VAS disease activity	59 ± 24
Health Assessment Questionnaire	1.0 (0.5–1.6)
Antiinflammatory medication use	
Use of previous biologics	13 (11.0)
Concomitant methotrexate use	53 (44.9)
Methotrexate dose, mg/week	19.0 ± 7.5
Concomitant prednisone use	9 (7.6)
Prednosine dose, mg/day	7.2 ± 3.6
Use of other DMARD	11 (9.3)
NSAID use	58 (49.2)
CVD-related factors	
Current smoking	15 (12.7)
Body mass index, kg/m^2	27 ± 6
Obesity	67 (56.8)
Systolic blood pressure, mmHg	130 ± 22
Diastolic blood pressure, mmHg	81 ± 10
Hypertension	47 (39.8)
Diabetes mellitus	8 (6.8)
Antihypertensive use	28 (23.7)
Statin use	11 (9.3)
Creatinine, umol/l	75 ± 18
Lipid profile	
TC, mmol/l	5.31 ± 1.24
HDLc, mmol/l	1.43 ± 0.43
LDLc, mmol/l	3.21 ± 1.05
LDL ≥ 2.5*	88 (74.6)
Triglycerides, mmol/l	1.29 (0.85–1.87)
TC/HDLc ratio	3.99 ± 1.37
ApoA-I, g/l**	1.55 ± 0.42
ApoB, g/l**	0.89 ± 0.27
ApoB/apoA-I ratio**	0.6 ± 0.2

* Sulfasalazine, hydroxychloroquine, leflunomide, dyslipidemia. ** Apolipoproteins were available for a subgroup of 81 patients. PsA: psoriatic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; CVD: cardiovascular disease; TC: total cholesterol; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B.

DAS28 (p = 0.057). A point increase in DAS28 was associated with an increase in HDLc. However, this was not significant after correction for the above-mentioned variables. The TC/HDLc ratio did not change significantly with changes in DAS28. When patients were split into responders versus nonresponders, patients with a DAS28 above 2.6 had lower TC and TG than patients with a DAS28 under 2.6, while the HDLc was increased (Table 4). An increase in CRP was associated with a decrease in TC (β –0.09, 95% CI –0.16 to –0.02, p = 0.02) and an increase in the apoB/apoA-I ratio (β 0.03, 95% CI 0.004–0.05, p = 0.02). There was a trend for a decrease in TG (β –0.04, 95% CI –0.08 to 0.003, p = 0.07) and in apoA-I (β –0.05, 95% CI –0.09 to 0.01, p = 0.077) after adjustment for the above-mentioned confounders.

DISCUSSION

ETN therapy effectively reduced DAS28, CRP, and ESR as markers of disease activity in patients with PsA, with the greatest reduction of disease activity at 6 months. This reduction persisted until 5 years of therapy in those who continued treatment. At baseline, a substantial proportion of the patients had HTN (39.8%), dyslipidemia (74.6%), and was overweight (56.8%). In addition, 56.4% of the patients had an elevated TC/HDLc ratio and 6.8% had diabetes. This is consistent with previous reports of an increased prevalence of traditional CVD risk factors in patients with PsA[3,9]. Interestingly, the majority of patients showed nearly normal TC, HDLc, and TG values at baseline. Over a 5-year period of ETN therapy, patients with PsA showed a significant increase in TC, HDLc, and LDLc. In RA, it has been reported[11] that during times of active inflammation, LDLc and HDLc decrease. Antiinflammatory treatment, for example with TNF inhibitors, can reverse this decrease. There is a nonlinear relationship between lipid levels and CVD risk in IJD (most data are available for RA). A decrease in lipid levels (i.e., TC, LDLc, and TG) is often seen in patients with active inflammation, while their CVD risk is increased. During treatment with antiinflammatory agents, lipid levels increase in these patients, leading to a normalization of lipid levels. In our study, we demonstrated that this phenomenon also holds true for PsA, i.e., treatment with ETN increases lipid levels. This increase in lipids should probably be considered as a normalization of serum lipid levels and a reflection of effective antiinflammatory therapy rather than an adverse effect of ETN. To avoid misinterpretation of CV risk status in these patients, measurement of lipid levels for the purpose of CV risk estimation should preferably be performed when disease activity is stable or in remission. The other CVD risk factors, i.e., blood pressure, BMI, creatinine, and TG remained stable over the years, although there was a trend for an increase in BMI in these patients (p = 0.07). Increases in BMI with TNFi treatment have been described previously in patients with psoriasis[16,17,18] and PsA[18]. Further, the TC/HDLc ratio remained stable over 5 years, which is to be expected because these lipid values generally change in the same direction during inflammation and suppression of inflammation with therapy[17]. Normally, this would indicate that the CVD risk remains stable over 5 years.

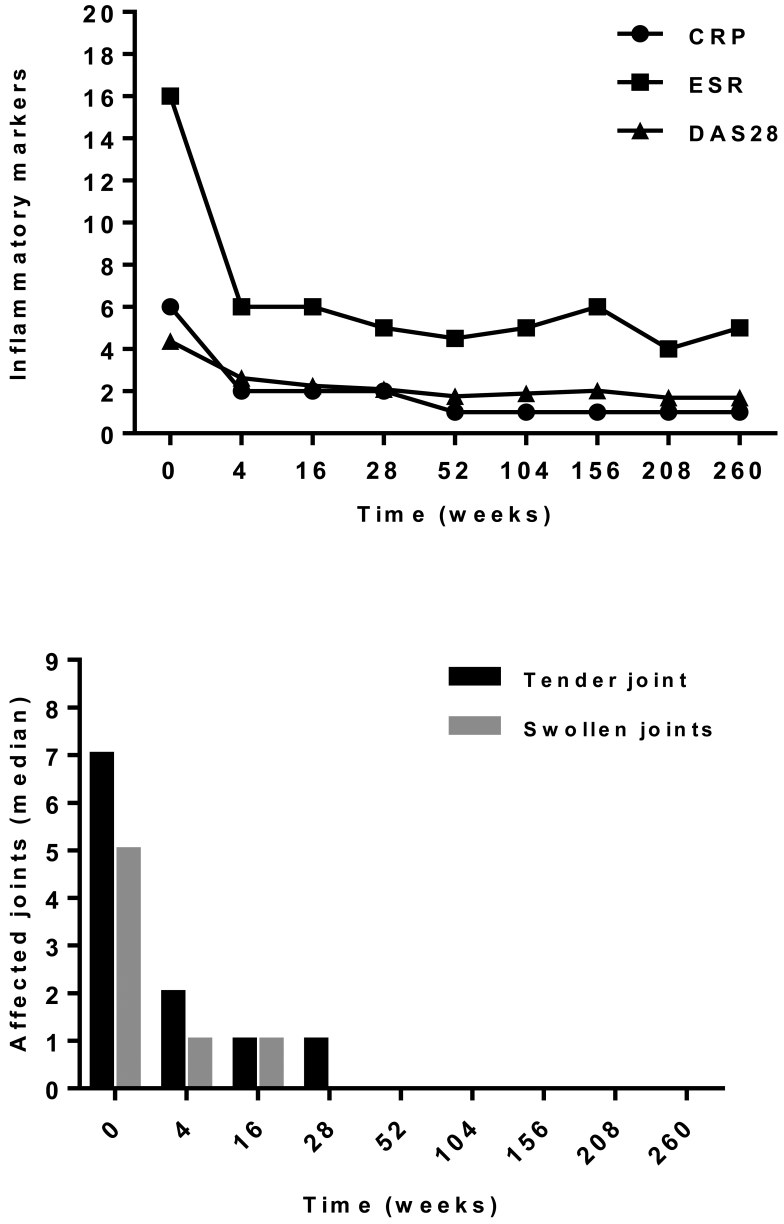

Figure 1. Disease activity variables. CRP and ESR are presented as median (interquartile range), and DAS28 is presented as mean ± SD. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score in 28 joints.

However, there was a significant decrease in the apoB/apoA-I ratio over time, which could reflect a decrease in CVD risk. A previous study showed that the apoB/apoA-I ratio is associated with an increased risk of fatal myocardial infarction in men and women (relative risk 1.23, 95% CI 1.18–1.27; and 1.38, 95% CI 1.25–1.52, respectively)[18]. Intriguingly, elevated disease activity markers, i.e., DAS28 and CRP, were associated with an unfavorable lipid profile, i.e., lower TC and TG, but an increase in the apoB/apoA-I ratio (β 0.03, 95% CI 0.004–0.05), a possible reflection of an increase in CVD risk. Also, there was a trend for a decrease in apoA-I, the cardio-protective component of HDLc, with a 1-point increase in CRP. In line with this, over time an increase in DAS28 was associated with a small increase in diastolic blood pressure (0.56 mmHg per point increase in DAS28) and there was a trend for an increased HDLc and apoB/apoA-I ratio per point increase in DAS28 ($p = 0.057$). This might seem surprising because HDLc is known as cardio-protective and most studies report a decrease in HDLc during inflammation, although these studies have focused on RA and not on PsA. These "conflicting" results may indicate that a raise in HDLc does not necessarily translate into a

Table 2. Mixed-models analysis of changes in CVD-related factors over 5 years. Values are mean ± SD or median (interquartile range) unless otherwise specified.

Variable	Mean	β	95% CI	p
Systolic blood pressure	130 ± 20	–0.001	–0.02 to 0.02	0.92
Diastolic blood pressure	81 ± 11	0.002	–0.01 to 0.01	0.66
BMI	27 ± 5	0.002	–0.0001 to 0.004	0.07
Creatinine	75 ± 17	–0.003	–0.01 to 0.01	0.55
TC	5.38 ± 1.12	0.0008	0.0001–0.001	0.03
Adjusted*		0.0008	–0.0001 to 0.002	0.02
HDLc	1.34 ± 0.45	0.0005	0.0001–0.001	< 0.01
Adjusted*		0.0005	0.0002–0.001	< 0.01
LDLc	3.19 ± 0.98	0.0008	–0.0001 to 0.002	0.03
Adjusted*		0.0009	–0.0001 to 0.002	0.02
Triglycerides	1.37 (0.96–2.00)	–0.00003	–0.0005 to 0.0005	0.99
TC/HDLc ratio	4.01 ± 1.30	0.0006	–0.0006 to 0.002	0.31
ApoA-I^	1.59 ± 0.34	0.00001	–0.0005 to 0.0005	0.98
ApoB^	0.89 ± 0.24	–0.0001	–0.0004 to 0.0001	0.34
ApoB/apoA-I ratio^	0.58 ± 0.20	–0.0002	–0.0005 to 0.00001	0.06
Adjusted*		–0.0003	–0.0005 to –0.00005	0.02

* Adjusted for age, sex, disease duration, concomitant methotrexate, prednisone, and statin use. ^ Subanalysis of 81 patients at baseline with apoA-I and apoB measurements available. CVD: cardiovascular disease; BMI: body mass index; TC: total cholesterol; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B.

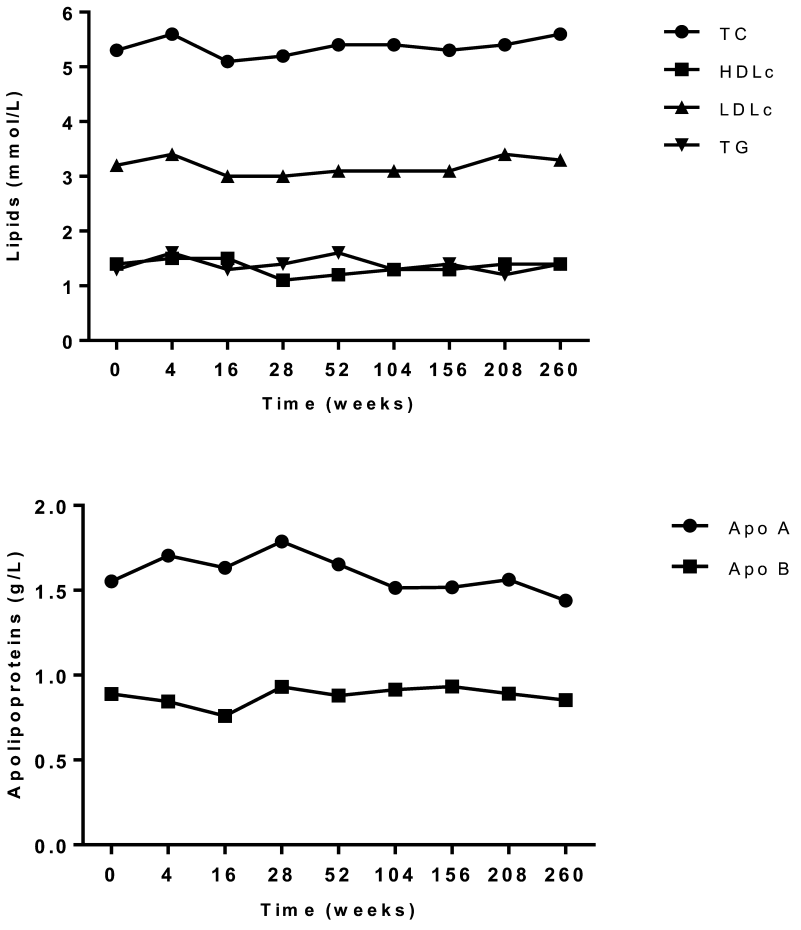

Figure 2. Changes in lipids and apolipoproteins over a 5-year period. Values are mean ± SD. TC: total cholesterol; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol; TG: triglycerides; apo A: apolipoprotein A; apo B: apolipoprotein B.

Table 3. Association between DAS28 and CVD-related factors over 5 years. Values are mean ± SD or median (interquartile range) unless otherwise specified.

Variable	Mean	β	95% CI	p
Systolic blood pressure	130 ± 20	0.43	–0.41 to 1.28	0.31
Diastolic blood pressure	81 ± 11	0.64	0.12–1.17	0.02
Adjusted*		0.56	0.03–1.09	0.04
BMI	27 ± 5	–0.001	–0.099 to 0.097	0.98
Creatinine	75 ± 17	–0.18	–0.76 to 0.39	0.53
TC	5.38 ± 1.12	–0.05	–0.09 to –0.007	0.02
Adjusted*		–0.05	–0.09 to –0.01	0.02
HDLc	1.34 ± 0.45	0.04	0.01–0.06	0.007
Adjusted*		0.03	0.000001–0.05	0.05
LDLc	3.19 ± 0.98	–0.02	–0.06 to 0.03	0.47
Triglycerides#	1.37 (0.96–2.00)	–0.03	–0.05 to –0.01	0.006
Adjusted*		–0.03	–0.06 to –0.01	0.008
TC/HDLc ratio	4.01 ± 1.30	–0.04	–0.11 to 0.02	0.21
ApoA-I^	1.59 ± 0.34	–0.0008	–0.03 to 0.03	0.96
ApoB^	0.89 ± 0.24	0.009	–0.008 to 0.03	0.29
ApoB/apoA-I ratio^	0.58 ± 0.20	0.01	–0.003 to 0.03	0.11
Adjusted*		0.014	–0.0004 to 0.03	0.057

* Adjusted for age, sex, disease duration, concomitant methotrexate, prednisone, nonsteroidal antiinflammatory drugs, antihypertensives, and statin use. # Log-transformed. ^ Subanalysis of 81 patients at baseline with apoA-I and apoB measurements available. DAS28: Disease Activity Score in 28 joints; CVD: cardiovascular disease; BMI: body mass index; TC: total cholesterol; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B.

Table 4. CV risk factors in DAS28 > 2.6 versus DAS28 < 2.6 over 5 years. Values are mean ± SD or median (interquartile range) unless otherwise specified.

Variable	Responder	Nonresponder	β	95% CI	p
Systolic blood pressure	128 ± 19	133 ± 20	2.01	–0.65 to 4.67	0.14
Diastolic blood pressure	80 ± 10	82 ± 12	1.27	–0.37 to 2.92	0.13
BMI	25.9 ± 3.8	28.7 ± 5.8	–0.27	–0.55 to 0.004	0.05
Creatinine	76 ± 14	74 ± 21	–0.80	–2.26 to 0.66	0.28
TC	5.45 ± 1.02	5.29 ± 1.25	–0.16	–0.29 to –0.02	0.03
Adjusted*			–0.017	–0.31 to –0.03	0.02
HDLc	1.31 ± 0.45	1.38 ± 0.45	0.11	0.04–0.18	0.004
Adjusted*			0.08	0.009–0.16	0.03
LDLc	3.23 ± 0.92	3.15 ± 1.07	–0.06	–0.20 to 0.07	0.35
Triglycerides**	1.37 (0.99–2.04)	1.38 (0.95–1.90)	–0.09	–0.16 to –0.01	0.02
Adjusted*			–0.09	–0.16 to –0.01	0.02
TC/HDLc ratio	4.01 ± 1.26	4.03 ± 1.34	–0.08	–0.27 to 0.11	0.41

* Adjusted for age, sex, disease duration, concomitant methotrexate, prednisone, antihypertensives, and statin use. ** Log-transformed. CV: cardiovascular; DAS28: Disease Activity Score in 28 joints; BMI: body mass index; TC: total cholesterol; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol.

favorable lipid and CVD risk profile in patients with high disease activity because HDL composition, rather than its levels, determine its function[19].

HDLc, which is normally considered antiatherogenic, could change into a proatherogenic molecule because of modification of HDLc subcomponents under inflammatory conditions. In our study, the decrease in apoA-I (trend) and the increase in apoB/apoA-I ratio, with elevation of inflammatory markers, suggest a change in the HDLc molecule to a more proatherogenic HDLc under high-grade inflammation. Thus, we consider the higher TC and TG in patients with low DAS28 scores in our study a normalization of serum lipid levels and a reflection of effective antiinflammatory therapy. Conversely, the patients with high DAS28 who had lower TC and TG and higher HDLc are considered to have a worse CVD risk profile, also in accordance with existing literature on this subject.

Several limitations should be considered. The changes in lipid levels were small in our study and the clinical relevance of such small changes is probably limited. Additionally,

apolipoprotein values were only available in a subpopulation of patients. Therefore, mixed models were used because they are designed to analyze this type of data. However, we expect that these findings will be even more significant in a larger group of patients because we have already found significant differences in apolipoproteins in this small group of patients with PsA.

Nevertheless, our study demonstrates stable CVD risk factors, especially a stable lipid profile in a heterogeneous population of patients with PsA over a 5-year period of ETN therapy. To our knowledge, no other study has described changes in CVD risk factors over an extended period in patients with PsA receiving TNFi therapy, although a beneficial effect of TNFi on surrogate markers of atherosclerosis (i.e., carotid intima-media thickness) in PsA has been reported[20]. Further, significant changes in apoB/apoA-I ratio, BMI, and diastolic blood pressure were found over time during ETN therapy, reflecting a possible beneficial effect on lipid subcomponents, blood pressure, body composition, and consequently CVD risk in these patients. However, these changes were only small and require further study. Modulation of lipids and other known CVD risk factors probably only partially explains the favorable effects of anti-TNF therapy on CVD risk. Hence, the presumed beneficial effects of TNFi on CVD risk in PsA appear to be mediated by other mechanisms, likely related to inflammation.

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