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Association of Tumor Necrosis Factor Inhibitor Treatment With Reduced Indices of Subclinical Atherosclerosis in Patients With Psoriatic Disease

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Objective. **To assess the effect of tumor necrosis factor inhibitors (TNFi) on subclinical cardiovascular disease in patients with psoriatic disease.**

Methods. **We performed a 2-stage study. In stage 1, carotid total plaque area was assessed in patients with psoriasis or psoriatic arthritis (PsA) (n = 319) by ultrasound at baseline and after 2–3 years. The annual progression rate of atherosclerosis was the outcome of interest. In stage 2, PsA patients receiving TNFi (n = 21) and age- and sex-matched PsA patients not receiving any biologic agent (n = 13) underwent ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography at baseline and 1 year to assess vascular inflammation, measured as target-to-background ratio (TBR). In both stages, multivariable regression analyses adjusted for cardiovascular risk factors and use of statins were performed.**

Results. **In stage 1, men had significantly higher atherosclerosis progression than women ($P < 0.001$). TNFi was associated with reduced atherosclerosis progression in men after controlling for cardiovascular risk and use of statins (adjusted β = −2.20 [95% confidence interval −3.41, −1.00], $P < 0.001$). There was no association between TNFi and atherosclerosis progression in women ($P = 0.74$). In stage 2, patients receiving TNFi had reduced TBR at 1 year ($P = 0.03$). Those not receiving TNFi had no significant change in TBR ($P = 0.32$). The improvement in aortic vascular inflammation in the TNFi group was independent of cardiovascular risk factors (adjusted β = −0.41 [95% confidence interval −0.74, −0.08], $P = 0.02$).**

Conclusion. **Our findings indicate that TNFi treatment is associated with reduced progression of carotid plaques in men and improvement in vascular inflammation in both men and women with psoriatic disease.**

Psoriasis is a chronic immune-mediated skin disease. Psoriatic arthritis (PsA) is an inflammatory arthritis that affects up to one-third of patients with psoriasis (1). Recent studies have highlighted the increased cardiovascular risk in patients with psoriasis or PsA, collectively termed psoriatic disease (2–5). This risk remains high even after accounting for traditional cardiovascular risk factors, supporting the notion that psoriatic disease is an independent risk factor for cardiovascular events (6,7).

The underlying shared mechanisms driving the accelerated atherogenesis in patients with psoriatic disease are varied and unclear. Psoriatic disease is associated with systemic inflammation that is not limited to the skin or the joints. Furthermore, it is widely accepted that atherosclerosis, the main cause of cardiovascular diseases, is an inflammatory disorder in which immune mechanisms interact with atherogenic lipid particles to initiate and propagate lesions in the vascular walls (8).

The innate and adaptive immune systems play a role in the development of atherosclerosis via the action of cytokines. Increased activity of Th1 cells and reduced activity of Treg cells, which lead to production of proinflammatory cytokines, such as tumor necrosis factor (TNF) and interferon-γ, are shared pathogenic pathways

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for the development of atherosclerosis, arthritis, and psoriasis (9,10). In addition, obesity and its related metabolic abnormalities, which are frequently found in patients with psoriatic disease, are strongly linked with systemic inflammation. The adipose tissue produces a variety of proinflammatory cytokines that have deleterious effects on multiple organs, including the vascular system (11). High serum levels of TNF may up-regulate cell-mediated immunity and promote inflammatory cell migration through the vascular endothelium, resulting in endothelial dysfunction leading to atherogenesis (12). Therefore, the suppression of inflammation by immunomodulating agents has evolved as a novel approach to treating these chronic inflammatory conditions and, subsequently, may represent a promising new target for the management of cardiovascular diseases in patients with chronic inflammatory conditions since the ensuing benefits may apply beyond the skin and joint disease (13).

There are limited and conflicting data regarding the impact of TNF inhibitors (TNFi) on cardiovascular events in psoriatic disease (14). Moreover, only a few small studies have assessed the effect of TNFi on subclinical indices of cardiovascular disease in psoriatic disease. While some studies showed improvement in vascular function and structural vessel wall abnormalities following TNFi therapy (15–18), others did not confirm this effect (19–21). Those studies were limited by their small sample size and short follow-up period. In this regard, ultrasound-guided carotid plaque measurement and ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET)/computed tomography (CT)–derived evidence of vascular inflammation are reliable indices of subclinical atherosclerosis (22,23).

The burden of atherosclerotic plaques in the carotid arteries, as measured by ultrasound, can serve as a surrogate measure for cardiovascular diseases. It can be used as a prognostic indicator of vascular risk, including coronary events, stroke, and death from cardiovascular causes in the general population and among patients with inflammatory arthritis (24–27). Uptake of ^{18}F-FDG in the arterial wall suggests the presence of vascular inflammation and correlates with macrophage activity within carotid plaques in human endarterectomy specimens (28). The presence of vascular inflammation in the major arteries is a surrogate measure of subclinical cardiovascular disease prior to cardiovascular events. Indeed, vascular inflammation by FDG-PET/CT predicts future cardiovascular events (23). Additionally, vascular inflammation is associated with high-risk morphology of carotid (29) and coronary plaques (30,31) and subsequent development of arterial wall calcification within the regions of focal arterial inflammation marked by high levels of ^{18}F-FDG uptake (32). Furthermore, vascular inflammation assessed by FDG-PET/CT has also been shown to be subject to modulation following first-line treatment modalities used for primary cardiovascular prevention, such as statins, providing utility in assessing treatment response (33,34).

Hence, in this 2-stage study, using these markers of subclinical atherosclerosis, i.e., carotid plaque assessment and vascular inflammation, as primary outcomes, we investigated the effect of TNFi on subclinical cardiovascular disease by comparing the extent of change in carotid atherosclerotic plaques and aortic vascular inflammation in patients with psoriatic disease treated with TNFi to that in untreated patients or patients treated with systemic nonbiologic antipsoriatic medications.

PATIENTS AND METHODS

Study design and participants. This was a 2-stage study comprised of 2 separate prospective cohorts of patients with psoriatic disease. All study patients had formal diagnoses of psoriasis alone or PsA confirmed by a dermatologist or rheumatologist, respectively. The study was approved by the University Health Network Research Ethics Board (Toronto, Ontario, Canada) and the Institutional Review Board of the National Heart, Lung, and Blood Institute (National Institutes of Health [NIH]) in accordance with the principles of the Declaration of Helsinki. All study participants in both cohorts provided written informed consent.

Stage 1 (Toronto cohort). Stage 1 was conducted in Toronto, Ontario, Canada and included a prospective cohort analysis of patients with psoriasis without arthritis and patients with PsA who were recruited from the University of Toronto PsA and psoriasis clinics from 2010 to 2015. Consecutive patients underwent an ultrasound of the carotid arteries to assess the extent of atherosclerotic plaques at baseline and after 2–3 years. The findings from stage 1 led us to create an inception cohort to assess the effect of TNFi on vascular inflammation in psoriatic disease.

Stage 2 (NIH cohort). In stage 2 of the study, we performed a nested cohort analysis of 34 PsA patients followed up prospectively at the NIH. These patients participated in an ongoing prospective study aimed toward investigating the relationship between psoriasis and cardiometabolic diseases. We assembled a cohort of 21 PsA patients who were receiving TNFi who were age- and sex-matched with 13 PsA patients who were not receiving any systemic antipsoriatic medications. The patients were assessed at baseline and after 1 year of follow-up. Patients were excluded if they had known cardiovascular disease, uncontrolled hypertension, HIV, internal malignancy in the past 5 years, active infection in the 72 hours before the baseline assessment, or major surgery in the past 3 months. Study patients underwent FDG-PET/CT scans to assess the degree of vascular inflammation in the aorta at baseline and at 1 year.

Data collection. In stage 1 (the Toronto cohort), patients were assessed every 6–12 months as clinically indicated, while in stage 2 (the NIH cohort), all patients were assessed at baseline and at 1 year of follow-up. In both stages, information

was collected about patient demographic characteristics, lifestyle habits, medications, and medical history. The following disease-related variables were recorded: tender and swollen joint counts, the number of clinically tender entheseal sites and dactylitic digits, and Psoriasis Area and Severity Index (PASI).

The presence of established cardiovascular risk factors was assessed by patient interview, review of medication history, physical examination, and blood tests. The following baseline variables were assessed: systolic blood pressure, use of antihypertensive agents, current smoking, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels, lipid-lowering therapy (at baseline or during study follow-up), and the presence of diabetes mellitus (as indicated by physician diagnosis or the use of glucose-lowering drugs).

TNFi therapy exposure. TNFi therapy was considered a binary variable. For both cohorts, TNFi therapy exposure was defined as treatment with any of the following TNFi agents for at least 50% of the follow-up period: infliximab, etanercept, adalimumab, golimumab, or certolizumab. For both cohorts, study patients were considered to be exposed to TNFi if they fulfilled the above criteria, even if the TNFi therapy was initiated prior to the baseline assessment. Patients receiving other biologic medications were excluded from the analyses.

Ultrasound assessment of carotid atherosclerosis. Ultrasound assessment was performed only in stage 1 (the Toronto cohort). Ultrasound assessment was performed using a high-resolution ultrasound system for carotid imaging (Esaote MyLab 70 XVision) by a single trained physician (LE) according to the study protocol (35). Scans of the left and right carotid arteries were obtained at baseline and after 2–3 years. All ultrasound scans were saved as video files for later reading. An atherosclerotic plaque was defined as the presence of focal wall thickening that was at least 50% greater than that of the surrounding vessel wall or as a localized intimal thickening exceeding 1 mm that protruded into the lumen and was distinct from the adjacent boundary (36).

Total plaque area (TPA), an independent predictor of clinical cardiovascular events (37), was measured as described

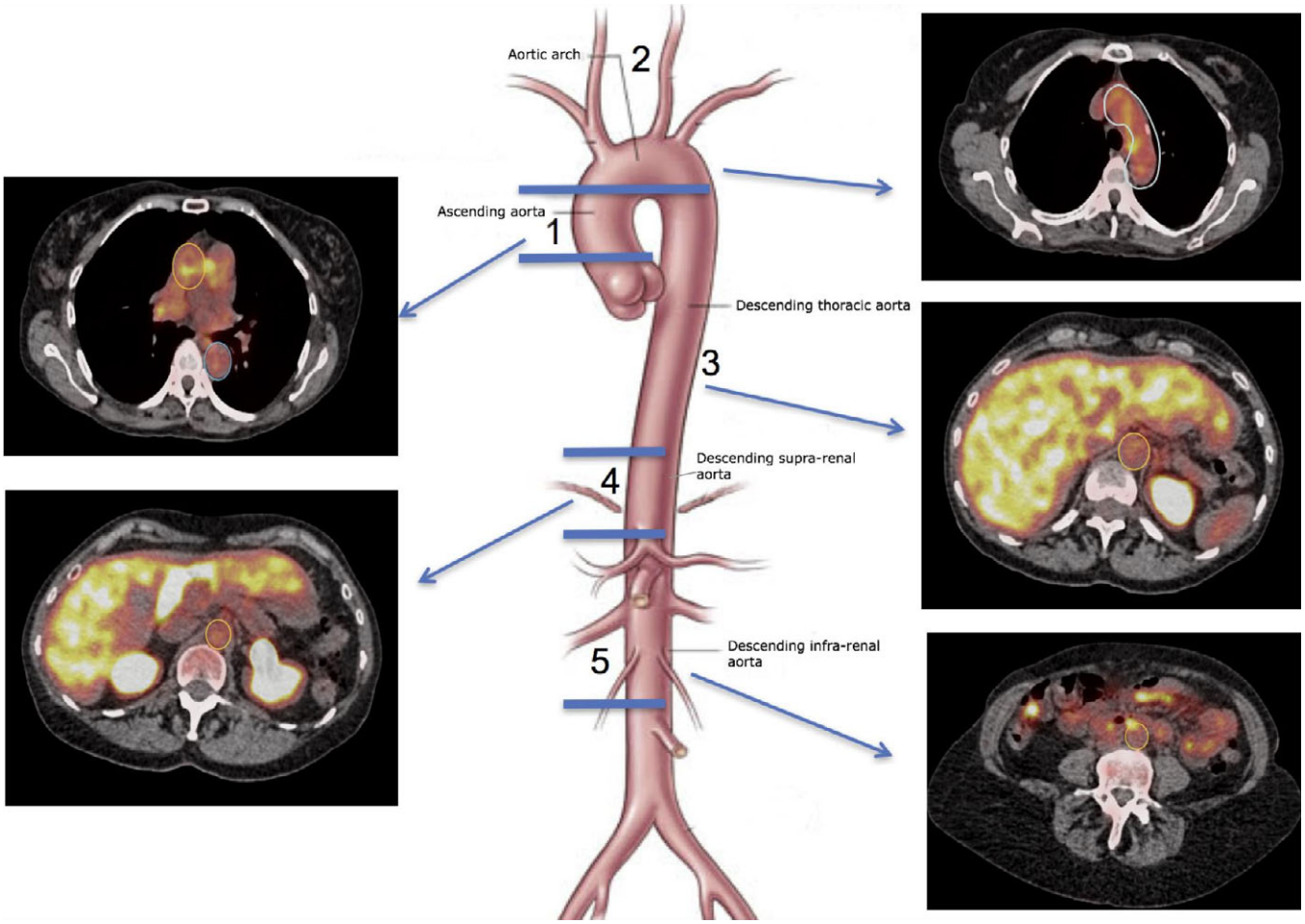

Figure 1. Schematic illustration of vascular inflammation analyses showing the aorta and accompanying ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography slices. Approximately 225 slices, each 1.5 mm thick, were obtained. The aorta was divided into 5 anatomic regions: ascending aorta, aortic arch, descending thoracic aorta, descending suprarenal aorta, and descending infrarenal aorta. Regions of interest were manually drawn on each slice to measure ^{18}F-fluorodeoxyglucose uptake in the artery.

by Spence (36). The plane for measurement of each plaque was chosen by reviewing the video of the scan to find the largest extent of plaque as seen on the longitudinal view. The image was then frozen, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The assessor then moved on to the next plaque and repeated the process until all observed plaques in the common, external, and internal carotid arteries were measured. TPA was recorded as the sum of the areas of all plaques in the right and left carotid arteries. Reading of the ultrasound scans obtained at baseline and follow-up was performed concurrently by a single reader (LE) who was aware of the temporal order of the images but was blinded with regard to the clinical data. The outcome of interest was the average annual progression rate of TPA, which was calculated by subtracting the baseline TPA from the follow-up TPA and then dividing by the number of years between the visits. The intraobserver intraclass correlation coefficient for TPA was 0.94 (35).

FDG-PET/CT image acquisition and analysis. FDG-PET/CT imaging was performed only in stage 2 (the NIH cohort). Patients underwent FDG-PET/CT following an overnight fast at baseline and after 12 months. Images were obtained ~60 minutes after administration of a 10 mCi dose of ^{18}F-FDG. All scans were completed using a 64-slice scanner (Siemens Biograph mCT PET/CT scanner), and 1.5-mm axial slices of the aorta were obtained. We analyzed the uptake of ^{18}F-FDG within the aorta using a dedicated PET/CT image analysis program (Figure 1) (Extended Brilliance Workspace; Phillips Healthcare) to measure vascular inflammation calculated as target-to-background ratio (TBR). The detailed methods applied in the calculation of TBR values have been discussed previously (38). TBR represents the extent of vascular inflammation in the aorta and predicts clinical cardiovascular events in the general population (23).

Statistical analysis. Summary statistics are presented as the mean ± SD for normally distributed variables, the median and interquartile range (IQR) for non-normally distributed continuous variables, and frequencies for categorical variables. In stage 1 of the study (the Toronto cohort), we assessed the impact of TNFi therapy (primary predictor) on carotid atherosclerosis progression. An interaction term of sex and TNFi therapy was added in a regression model. Due to a statistically significant interaction, we assessed carotid atherosclerosis progression for men and women separately. The initial linear regression model included TNFi therapy and baseline TPA as model covariates. A second model also included established cardiovascular risk factors, including age, systolic blood pressure, antihypertensive therapy, HDL cholesterol level, LDL cholesterol level, lipid-lowering therapy, diabetes mellitus, and current smoking. The final multivariable model included in addition the following psoriatic disease–related variables: PsA versus psoriasis alone, tender and swollen

Table 1. Baseline characteristics of the study participants*

	Stage 1 (Toronto cohort)			Stage 2 (NIH cohort)		
	TNFi treatment (n = 111)	Control (n = 208)	All (n = 319)	TNFi treatment (n = 21)	Control (n = 13)	All (n = 34)
Psoriasis alone, no. (%)	5 (4.5)	103 (49.5)	108 (33.9)	–	–	–
PsA, no (%)	106 (95.5)	105 (50.5)	211 (66.1)	21 (100.0)	13 (100.0)	34 (100.0)
Age, years	54.4 ± 11.4	54.6 ± 11.9	54.5 ± 11.5	49.6 ± 10.5	55.6 ± 9.9	51.9 ± 10.5
Sex, no. (%) men	65 (58.6)	113 (54.3)	178 (55.8)	12 (57.1)	6 (46.2)	18 (52.9)
Duration of psoriasis, years	26.1 ± 13.5	23.7 ± 15	24.6 ± 14.6	25.2 ± 12.1	24.3 ± 9.5	24.9 ± 11.0
Duration of PsA, years	15.5 ± 10.3	17.2 ± 12.2	16.4 ± 11.3	12.5 ± 10.7	19.5 ± 12.4	15.2 ± 11.7
Current smoker, no. (%)	13 (11.7)	26 (12.5)	39 (12.2)	3 (14.3)	1 (7.7)	4 (11.8)
Diabetes, no. (%)	9 (8.1)	19 (9.1)	28 (8.8)	3 (14.3)	2 (15)	5 (14.7)
Systolic blood pressure, mm Hg	123.5 ± 13.6	123.1 ± 15.4	123.3 ± 14.8	125.7 ± 10.9	119.9 ± 12.7	123.7 ± 11.9
Diastolic blood pressure, mm Hg	76.5 ± 8.6	77.7 ± 9.1	77.3 ± 8.9	74.0 ± 8.6	71.5 ± 8.9	73.0 ± 8.6
Antihypertensive medications, no. (%)	32 (28.8)	66 (31.7)	98 (30.7)	4 (19.0)	2 (15.4)	6 (17.6)
LDL cholesterol, mmoles/liter	3.1 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	2.6 ± 0.7	2.3 ± 1.0	2.4 ± 0.8
HDL cholesterol, mmoles/liter	1.4 ± 0.4	1.4 ± 0.3	1.4 ± 0.4	1.4 ± 0.3	1.7 ± 0.7	1.5 ± 0.5
Triglycerides, mmoles/liter	1.7 ± 1.2	1.5 ± 0.9	1.6 ± 1.0	1.1 (0.9–2.0)	1.0 (0.8–2.0)	1.1 (0.8–1.5)
Lipid-lowering agents, no. (%)†	29 (26.1)	68 (32.7)	97 (30.4)	9 (42.9)	4 (30.8)	13 (38.2)
BMI	29.1 ± 5.7	28.3 ± 5.1	28.6 ± 5.4	28.9 ± 5.3	28.6 ± 6.3	28.8 ± 5.6
Waist-to-hip ratio‡	0.94 ± 0.09	0.92 ± 0.08	0.93 ± 0.09	0.95 (0.91–0.98)	0.95 (0.91–1.02)	0.95 (0.91–0.99)
PASI	1.9 ± 2.6	3.5 ± 4.7	2.9 ± 4.1	7.4 ± 8.1	5.5 ± 4.3	6.68 ± 6.9
Tender joint count§	4.0 ± 6.2	3.0 ± 6.1	3.5 ± 6.2	7.8 ± 10.4	5.6 ± 11.6	6.9 ± 10.7
Swollen joint count§	1.1 ± 2.0	0.8 ± 2.1	1.0 ± 2.1	4.8 ± 9.2	3.1 ± 7.3	4.1 ± 8.8
NSAIDs, no. (%)†	37 (33.3)	50 (24.0)	87 (27.3)	8 (38.1)	3 (23.1)	11 (32.4)
Nonbiologic antipsoriatic medications, no. (%)†	52 (46.9)	68 (32.7)	120 (37.6)	3 (14.3)	3 (23.1)	6 (18)
Methotrexate, no. (%)†	46 (41.4)	47 (22.6)	93 (29.2)	2 (9.5)	2 (15.4)	4 (11.7)
Framingham Risk Score, %‡	11.8 ± 11.4	11.1 ± 9.8	11.4 ± 10.3	4 (2–6)	3 (1–4)	3 (1–6)

* Except where indicated otherwise, values are the mean ± SD. TNFi = tumor necrosis factor inhibitor; NIH = National Institutes of Health; LDL = low-density lipoprotein; HDL = high-density lipoprotein; BMI = body mass index; PASI = Psoriasis Area and Severity Index; NSAIDs = nonsteroidal antiinflammatory drugs.
† At baseline or follow-up.
‡ Values are the mean ± SD for stage 1 and the median (interquartile range) for stage 2.
§ Assessed only in patients with psoriatic arthritis (PsA).

Table 2. Atherosclerotic plaques at baseline and progression of plaques by treatment group in stage 1 (Toronto cohort) (n = 319)*

	Men			Women		
	TNFi therapy (n = 65)	No TNFi therapy (n = 113)†	All (n = 178)	TNFi therapy (n = 46)	No TNFi therapy (n = 95)†	All (n = 141)
Baseline TPA, mean ± SD mm^2	34.5 ± 47.7	21.1 ± 27.2	26 ± 36.5	15.9 ± 21.1	13 ± 21.7	13.9 ± 21.4
No. (%) with plaques at baseline	42 (64.6)	71 (62.8)	113 (63.5)	35 (76.1)	50 (52.6)	85 (60.3)
Annual progression rate of TPA, mean ± SD mm^2	1.6 ± 3.4	2.9 ± 5.1	2.5 ± 4.6	0.8 ± 3.3	0.8 ± 2.7	0.8 ± 2.9

* TNFi = tumor necrosis factor inhibitor; TPA = total plaque area.
† Patients receiving nonbiologic disease-modifying antirheumatic drugs or no systemic antipsoriatic medications.

joint count, PASI, use of nonbiologic antipsoriatic medications, and daily use of nonsteroidal antiinflammatory drugs. Finally, the control group was divided into patients receiving nonbiologic antipsoriatic drugs and those not receiving any systemic antipsoriatic medications. Carotid atherosclerosis progression was compared between the group receiving TNFi and each of these subgroups separately.

In stage 2 of the study (the NIH cohort), we assessed the impact of TNFi therapy on the change in vascular inflammation (as measured by TBR) from baseline to 12 months. Parametric variables were compared between groups at baseline and 1 year, by paired *t*-test. We conducted multivariable linear regression analyses to evaluate the association between TNFi therapy and change in TBR. These analyses were adjusted for traditional cardiovascular risk assessed by Framingham Risk Score, LDL cholesterol level, and lipid-lowering therapy. The effects of the model covariates were expressed as the regression coefficient (β) along with 95% confidence intervals (95% CIs) and *P* values. Only cases with complete data were analyzed.

RESULTS

Carotid atherosclerosis progression in stage 1 (Toronto cohort). The characteristics of the study participants are shown in Table 1. Stage 1 included 319 patients (55.8% men). Their mean ± SD age was 54.5 ± 11.5 years, and the mean ± SD duration of follow up was 2.9 ± 0.7 years. In general, the distribution of traditional cardiovascular risk factors was balanced between the TNFi group and the control group. A total of 198 patients (62.1%) had at least 1 carotid plaque at baseline. As expected, significantly higher baseline TPA ($P < 0.001$) and atherosclerosis progression rate ($P < 0.001$) were found in men than in women (Table 2). Additionally, higher baseline TPA was found in men receiving TNFi than in controls ($P = 0.04$) (Table 2).

Due to a statistically significant interaction between sex and TNFi ($P = 0.03$), atherosclerosis progression was assessed in men and women separately (Table 3). In the univariate analysis, TNFi therapy was associated with reduced atherosclerosis progression in men (adjusted β coefficient −2.09 [95% CI −3.32, −0.86], $P < 0.001$). This association remained statistically significant after controlling for cardiovascular risk factors and lipid-lowering drugs (adjusted β coefficient −2.20 [95% CI −3.41, −1.00], $P < 0.001$). Additionally, current smoking ($P = 0.02$) and LDL cholesterol level ($P = 0.008$) predicted atherosclerosis progression in men. In

Table 3. Association between TNFi treatment and the annual progression rate (mm^2) of atherosclerosis in stage 1 (Toronto cohort) in linear regression models*

	Men (n = 178)				Women (n = 141)			
	Univariate analysis†		Multivariable analysis		Univariate analysis†		Multivariable analysis	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
TNFi treatment	−2.09 (−3.32, −0.86)	<0.001	−2.20 (−3.41, −1.00)	<0.001	−0.04 (−1.05, 0.96)	0.93	0.17 (−0.86, 1.21)	0.74
Age (10-year increase)	0.25 (−0.33, 0.84)	0.39	0.19 (−0.40, 0.77)	0.53	0.21 (−0.25, 0.67)	0.37	0.29 (−0.24, 0.82)	0.28
Current smoker	1.78 (0.03, 3.52)	0.04	2.07 (0.39, 3.76)	0.02	0.86 (−0.68, 2.39)	0.27	0.76 (−0.80, 2.32)	0.34
LDL cholesterol	0.81 (0.11, 1.50)	0.02	0.98 (0.26, 1.69)	0.008	0.05 (−0.44, 0.54)	0.83	0.14 (−0.36, 0.65)	0.58
HDL cholesterol	1.74 (−0.20, 3.69)	0.08	1.54 (−0.33, 3.42)	0.11	−0.59 (−1.79, 0.59)	0.32	−0.78 (−2.02, 0.46)	0.21
Use of lipid-lowering agents	−0.03 (−1.32, 1.25)	0.95	0.55 (−0.77, 1.87)	0.41	0.05 (−1.11, 1.22)	0.93	−0.35 (−1.62, 0.91)	0.58
Systolic blood pressure (10-unit increase)	0.01 (−0.49, 0.47)	0.96	−0.15 (−0.63, 0.32)	0.53	−0.04 (−0.32, 0.24)	0.76	−0.14 (−0.41, 0.17)	0.38
Use of antihypertensive therapy	−0.04 (−1.38, 1.32)	0.96	−0.11 (−1.49, 1.26)	0.87	0.44 (−0.65, 1.53)	0.42	0.21 (−0.98, 1.41)	0.78
Diabetes mellitus	−0.86 (−3.02, 1.31)	0.44	0.17 (−2.03, 2.37)	0.88	1.54 (−0.16, 3.23)	0.08	1.68 (−0.15, 3.51)	0.07

* TNFi = tumor necrosis factor inhibitor; 95% CI = 95% confidence interval; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
† Adjusted for baseline total plaque area.

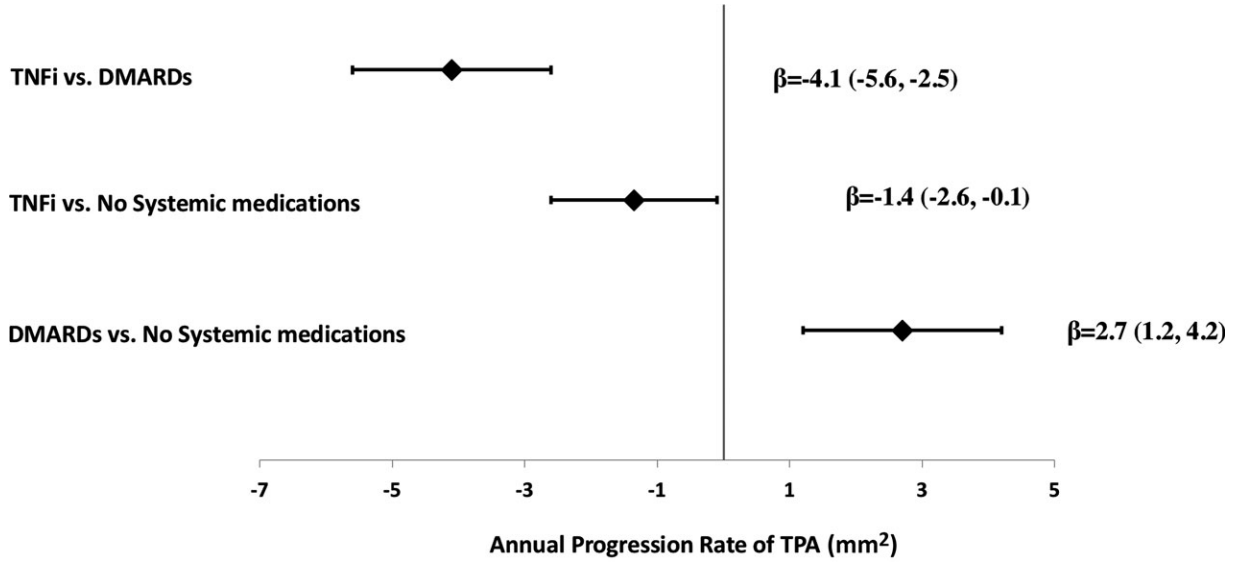

Figure 2. Association between classes of medications and the annual progression rate of the total plaque area (TPA) in men in a multivariable regression model adjusted for cardiovascular risk factors. Values are the adjusted β coefficient (95% confidence interval). TNFi = tumor necrosis factor inhibitors; DMARDs = disease-modifying antirheumatic drugs.

contrast, TNFi therapy was not associated with atherosclerosis progression in women in univariate analysis ($P = 0.93$) or multivariable analysis ($P = 0.74$).

We then divided the control group into patients who were receiving nonbiologic antipsoriatic medications and those not receiving any systemic antipsoriatic medications (Figure 2). In the fully adjusted multivariable regression model, TNFi therapy was associated with a reduced rate of atherosclerosis progression in men compared to nonbiologic antipsoriatic medications (adjusted β coefficient −4.1 [95% CI −5.6, −2.5], $P < 0.001$) and compared to no systemic antipsoriatic therapy (adjusted β coefficient −1.4 [95% CI −2.6, −0.1], $P = 0.03$). In contrast, the use of nonbiologic antipsoriatic medications was associated with increased atherosclerosis progression compared to no systemic antipsoriatic therapy (adjusted β coefficient 2.7 [95% CI 1.2, 4.2], $P < 0.001$).

Last, we assessed whether psoriatic disease–related factors, including measures of disease activity, confounded the association between TNFi and atherosclerosis progression. These variables were added to the fully adjusted regression model that included TNFi and cardiovascular risk factors. None of these variables significantly modified the association between TNFi and atherosclerosis progression (data not shown).

Vascular inflammation in stage 2 (NIH cohort). In stage 2 of the study, 34 patients with PsA were analyzed. The characteristics of the study participants are summarized in Table 1. The group that received TNFi comprised 21 patients and was predominantly male (55%). Their mean ± SD age was 49.6 ± 10.5 years, and their cardiovascular risk was low according to the Framingham Risk Score (median 4 [IQR 2–6]). These patients were age- and sex-matched with 13 patients who were not receiving any form of systemic antipsoriatic therapy and had low cardiovascular risk according to the Framingham Risk Score (median 3 [IQR 1–4]).

Vascular inflammation improved significantly at 1 year in the TNFi group (mean ± SD TBR 1.90 ± 0.28 versus 1.76 ± 0.24 at baseline; $P = 0.03$) as compared to the group not receiving any form of systemic therapy (1.86 ± 0.21 versus 1.89 ± 0.26 at baseline; $P = 0.32$). Furthermore, the 7.4% improvement in aortic vascular inflammation in the TNFi group was significant after adjustment for cardiovascular risk factors and lipid-lowering therapy (standardized β coefficient −0.41 [95% CI −0.74, −0.08], $P = 0.02$) (Table 4). No

Table 4. Association between TNFi treatment and vascular inflammation in stage 2 (NIH cohort) in linear multivariable regression analysis*

	Standardized β coefficient (95% CI)	*P*
TNFi treatment	–0.41 (–0.74, –0.08)	0.02
Framingham Risk Score	–0.28 (–0.63, 0.07)	0.14
Low-density lipoprotein	0.38 (–0.06, 0.82)	0.05
Lipid-lowering therapy	0.37 (0.02, 0.70)	0.04

* TNFi = tumor necrosis factor inhibitor; NIH = National Institutes of Health; 95% CI = 95% confidence interval.

sex-based interaction with vascular inflammation was observed over 1 year.

DISCUSSION

In this 2-stage study of well-characterized cohorts of patients with psoriatic disease, we presented the following major findings. At a mean follow-up of ~3 years, TNFi therapy was associated with reduced progression of carotid plaques independently of traditional cardiovascular risk factors. Furthermore, the association between TNFi and carotid plaque progression was stronger in men than in women. Finally, in stage 2 of the study, TNFi therapy was also associated with improvement in aortic vascular inflammation at the 1-year follow-up independently of traditional cardiovascular risk factors; however, no sex-based differences were found. We demonstrated that TNFi therapy in patients with psoriatic disease is associated with a reduction in subclinical atherosclerosis progression. To the best of our knowledge, this is the largest prospective study to assess the impact of TNFi on 2 different phenotypes of subclinical atherosclerosis in psoriatic disease.

In contrast to the strong evidence suggesting a potential beneficial effect of methotrexate and TNFi on cardiovascular risk in patients with rheumatoid arthritis (14), such information in psoriatic disease is limited and conflicting. While TNFi therapy was associated with a 50–72% reduction in the risk of developing cardiovascular events in 2 population-based studies (39,40), another large study from the US failed to demonstrate a significant difference in the rate of clinical cardiovascular events among psoriasis patients receiving TNFi (41). Moreover, reliable data on the effect of TNFi on subclinical measures of cardiovascular disease in patients with psoriatic disease are generally lacking.

The results of our study support the notion of a potential protective effect of TNFi on cardiovascular risk in psoriatic disease (39). Several small studies showed beneficial effects of TNFi on subclinical indices of atherosclerosis, including intima-media thickness, coronary flow reserve, and pulse wave velocity, in patients with psoriatic disease (15,17,18,42). However, to date, no study has investigated the impact of TNFi on atherosclerotic plaque, the end-stage structural lesion of atherosclerosis and a strong independent predictor of clinical cardiovascular events. Interestingly, the protective effect of TNFi as compared to nonbiologic antipsoriatic drugs was greater than that compared to no systemic therapy, and use of nonbiologic antipsoriatic medications was, in fact, associated with more atherosclerosis progression than lack of systemic therapy. These seemingly surprising results may be explained by the potentially milder disease (skin and joint inflammation) in the patients who were not receiving systemic drugs, which may explain their lower cardiovascular risk and slower progression of atherosclerosis.

Regarding the underlying mechanism linking TNFi and improved cardiovascular outcome, our results suggest that direct suppression of inflammation at the level of the vessel wall by TNFi may inhibit the formation and progression of atherosclerotic plaques and eventually lower cardiovascular risk. Although this is indirect evidence, as we did not evaluate the direct progression of vascular inflammation to atherosclerotic plaques, other studies have shown that higher ^{18}F-FDG uptake predicted subsequent arterial wall calcification within the same region (32), suggesting an accelerated atherosclerotic process identified by assessment of vascular inflammation. Furthermore, TNFi could potentially affect traditional cardiovascular risk factors, such as lipid profile and insulin resistance (43–45). However, we did not observe significant changes in the lipid profile, blood pressure, or glucose levels during follow-up (data not shown); thus, it is less likely that the effect of TNFi was mediated through modification of traditional cardiovascular risk factors.

The explanation for the different effects of TNFi on atherosclerotic plaque progression in men and women is elusive. Furthermore, we did not observe any sex-related differences in the effect of TNFi on vascular inflammation. It is possible that the lack of association between TNFi treatment and plaque progression in women was related to the low baseline levels and minimal progression rate of atherosclerotic plaques in this group. This may have resulted in reduced power to detect a similar effect that might have been detected during a longer follow-up period. Supporting this explanation is the lack of significant association between any of the established cardiovascular risk factors and atherosclerotic plaque progression in women. Another potential explanation for the observed sex-related differences in atherosclerotic plaque progression may be the possibility that TNFi therapy has a differential effect on atherosclerosis progression in women. There are notable differences in the pathogenic mechanisms involved in cardiovascular diseases and atherogenesis between the sexes (46). These differences may be related to the direct impact of sex hormones on the vascular system or to their indirect effect through traditional cardiovascular risk factors (e.g., a favorable lipid profile in premenopausal women) (47,48). Importantly, previous studies have shown differential effects of known cardiovascular risk factors on cardiovascular risk between sexes; thus, inflammation may have a

different impact on atherogenesis in males and females (47).

Our study had several limitations. First, since this is an observational study, the possibility of residual confounding cannot be completely ruled out. Despite our efforts to control for multiple potential confounding factors, it is possible that residual confounding may still exist and could potentially influence our results. Second, the assessment of vascular inflammation and plaque progression were performed in different cohorts. Therefore, we can only draw indirect conclusions regarding the impact of suppression of vascular inflammation and subsequent inhibition of atherogenesis. Furthermore, carotid ultrasound studies were not used for plaque measurements in the NIH cohort, limiting our ability to compare the findings from carotid and aortic imaging to determine if the changes were part of the same atherosclerosis process and if the changes demonstrated the same timeframe of atherosclerosis progression. Last, the majority of the patients started TNFi treatment prior to the initiation of the study; therefore, early effects on vascular inflammation and atherosclerosis progression could not be assessed.

However, our study also had several strengths. To our knowledge, this is the largest prospective study that assessed the impact of TNFi therapy on 2 different phenotypic features of atherosclerosis in psoriatic disease, providing insights about the effect of TNFi on early and late phases of atherogenesis. The study participants were well phenotyped with regard to established cardiovascular risk factors and measures of disease activity, which allowed us to control for multiple potential confounding factors. Despite lack of carotid ultrasound in the NIH cohort, our study is the first to apply multimodal imaging in 2 separate cohorts to examine the impact of TNFi on subclinical atherosclerosis. Furthermore, previous literature has demonstrated that carotid plaque measurement and vascular inflammation track with each other, thereby suggesting that carotid and aortic processes may imply the same level of atherosclerosis progression (49). The similar impact of TNFi on indices of atherosclerosis in 2 independent cohorts provides strong support for the protective effect of targeting this proinflammatory pathway on cardiovascular risk.

In conclusion, the results of this large prospective study support the potentially protective effect of TNFi on cardiovascular risk in patients with psoriatic disease. This effect is mediated by decreasing vascular inflammation, which may result in reduced progression of atherosclerotic plaques. Additional studies are needed to assess the impact of targeted biologic treatments on clinical and subclinical cardiovascular disease in patients with psoriatic disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Eder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Eder, Joshi, Dey, Cook, Siegel, Gladman, Mehta.

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