Tumor Necrosis Factor-α Inhibitor Use Is Not Associated with Lipid Changes in Rheumatoid **Arthritis**

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ABSTRACT. Objective. To determine the association of use of tumor necrosis factor- α (TNF- α) inhibitors with differences in lipid levels in patients with rheumatoid arthritis (RA).

> Methods. We studied 807 patients with incident RA to compare differences in lipid levels in TNF-α inhibitor users versus nonusers, with adjustment for relevant covariables.

> Results. TNF-α inhibitor use was not associated with differences in levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides, LDL:HDL, or TC:HDL compared to nonusers.

> Conclusion. Use of TNF- α inhibitor was not associated with differences in lipid levels in patients with RA. (First Release April 1 2012; J Rheumatol 2012;39:946-8; doi:10.3899/jrheum.111093)

Key Indexing Terms:

RHEUMATOID ARTHRITIS

LIPIDS

TUMOR NECROSIS FACTOR-α INHIBITORS

Patients with rheumatoid arthritis (RA) are at risk for cardiovascular disease due to the underlying inflammation and the presence of comorbidities such as dyslipidemia¹. The most common lipid abnormality reported in RA is low high-density lipoprotein (HDL) and increased atherogenic index [ratio of total cholesterol (TC) to HDL]². Evidence suggests that disease activity may affect lipid levels in patients with RA², thus strong modulators of inflammation such as tumor necrosis factor-α (TNF-α) inhibitors should be expected to improve lipid profiles in these patients. However, TNF- α inhibitors in patients with RA have been reported to have a variable effect on lipids in small studies of short duration. In addition, most of these studies evaluated the effects of infliximab exclusively^{3,4,5,6,7,8,9,10,11,12}; studies of etanercept or adalimumab, the TNF inhibitors used most commonly in the United States¹³, are sparse 14,15,16 . The purpose of our study was to examine the association of the TNF- α inhibitors as a group, and etanercept compared to monoclonal anti-TNF-α antibodies (adalimumab or infliximab) in particular, with lipid levels in a large retrospective cohort of patients with incident RA, adjusting for other important covariates that may influence these levels.

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MATERIALS AND METHODS

Data were extracted by the Geisinger Health System (GHS) information technology department from the electronic health records (EPIC®). All adult individuals with incident RA within the GHS between January 1, 2001, and December 31, 2009, were identified (n = 1881). RA was defined as a diagnosis with International Classification of Diseases (ICD)-9 code of 714.0 at ≥ 2 outpatient encounters with a GHS rheumatologist. Only patients with a primary care physician at GHS and at least 1 lipid level test post-RA diagnosis were included (n = 807), 68% of whom had repeated lipid tests.

Outcomes. The primary outcome was the level of low-density lipoprotein (LDL; Cobas[®], Roche/Hitachi Diagnostics, Indianapolis, IN, USA) in TNF-α inhibitor users versus nonusers. Secondary outcomes were levels of TC, HDL, triglycerides (TG; Cobas®, Roche/Hitachi Diagnostics), and atherogenic indices (LDL:HDL and TC:HDL) in TNF-α inhibitor users versus nonusers¹⁷.

Statistical analysis. The 6 outcomes (LDL, HDL, TC, TG, LDL:HDL, TC:HDL) were modeled using repeated-measures multivariable regression models with first-order autoregressive covariance to account for within-patient correlation. The primary predictor was TNF-α inhibitor use (time-varying, whether taking or not taking the medication at lipid measurement date). Time from RA diagnosis to lipid result was included in every model, and nonlinear time trends were checked and included if significant interactions between TNF-α inhibitor use and time were also checked for each of the models. Covariates as shown in Table 1 were added and adjusted for in regression models with the exception of erythrocyte sedimentation rate (ESR); this variable was not included in the model because of its association with TNF-α inhibitor use and its possible mediator effect. Results are presented as average fixed-effects estimates for the primary predictor, TNF-α inhibitor use. Subgroup analysis with predictor etanercept or monoclonal anti-TNF- α antibodies (adalimumab or infliximab) was also carried out with the same principles. A sensitivity analysis on each of the 6 final models was performed on the subgroup of patients with RA who were not receiving statins and subsequently on a subgroup of patients not receiving statins nor having diabetes, to evaluate a cleaner cohort, given the strong influence of both covariates on the lipid levels. Statin use was evaluated as low, medium, and high potency according to published classification 18. Comorbidities were defined as follows: diabetes = ICD-9 250 (diabetes) or hemoglobin A1c > 6.5

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Table 1. Patient characteristics by tumor necrosis factor- α inhibitor use. Data are number of patients (%) or median (interquartile range).

Characteristic	Overall, n = 807	Never Used, $n = 629$	Ever Used, n = 178	p*
Male	247 (31)	187 (30)	60 (34)	0.282
White	775 (96)	607 (96)	168 (94)	0.194
Hypertension	541 (67)	425 (68)	116 (65)	0.508
Diabetes	270 (34)	220 (35)	50 (28)	0.065
Positive rheumatoid factor (known = 662)	505 (76)	394 (76)	111 (77)	0.932
Medication use (ever)				
NSAID	386 (48)	290 (46)	96 (54)	0.078
Steroids	542 (67)	415 (66)	127 (71)	0.197
Hydroxychloroquine	237 (29)	194 (31)	43 (24)	0.062
Methotrexate	369 (46)	260 (41)	109 (61)	< 0.001
Etanercept	98 (12)	_	98 (55)	
Adalimumab	59 (7)	_	59 (33)	
Infliximab	27 (3)	_	27 (15)	
Statins	343 (43)	264 (42)	79 (44)	0.634
Statin potency				
Low	44 (5)	35 (6)	9 (5)	0.792
Medium	171 (21)	135 (21)	36 (20)	0.721
High	152 (19)	114 (18)	38 (21)	0.331
Other lipid lowering	76 (9)	57 (9)	19 (10)	0.698
Age at RA diagnosis, yrs	60.0 (51–71)	62.0 (53-71)	55.0 (48-63)	< 0.001
BMI (known = 783)	29.8 (26–35)	29.8 (26-34)	29.9 (26-36)	0.178
BMI maximum	32.5 (28–38)	32.5 (28–38)	32.4 (28–39)	0.640
BMI closest to RA diagnosis	29.8 (26–35)	29.8 (26–35)	29.7 (26–35)	0.834
Initial LDL	105 (82–130)	118 (91–144)	118 (97–140)	0.515
Initial HDL	53 (43–65)	57 (47–69)	60 (49–71)	0.129
Initial triglyceride	134.5 (97–199)	154 (112–219)	168 (118–249)	0.134
Initial total cholesterol	190 (165–219)	204 (173–237)	201 (185–231)	0.394
ESR (known = 673)	23.5 (12–41)	25 (12.5–42.5)	22 (10.7–34)	0.018

^{*} Chi-square tests (frequencies) or Wilcoxon's test (medians). NSAID: nonsteroidal antiinflammatory drugs; RA: rheumatoid arthritis; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ESR: erythrocyte sedimentation rate.

or ever-use of hypoglycemic/diabetic medications; hypertension (HTN) = 2 outpatient visits within 2 years with ICD-9 code 410 (HTN) or 2 consecutive measurements of systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg.

RESULTS

Patient characteristics are shown in Table 1. In this cohort of 807 patients with incident RA, the TNF-α inhibitor users had greater RA duration, lower median ESR over observation, and were more likely to have been treated with methotrexate. The 807 patients contributed a total of 3210 lipid measurements, of which 13.0% occurred while exposed to a TNF-α inhibitor (7% etanercept and 6% monoclonal antibodies). The median duration of exposure to TNF-α inhibitors was 1.3 (interquartile range 0.6–3.7) years. Results of the regression modeling are shown in Table 2. When adjusting for demographics, RA features, and RA and lipid-lowering medication use, TNF-α inhibitor use was not associated with statistically significant differences in LDL, HDL, TC, TG, LDL:HDL, or TC:HDL.

In the RA subgroup that never used statins, etanercept use was associated with a 25.54 mg/dl (95% CI 4.38, 46.70) increase in TG levels (p = 0.02) and a trend toward increased

TC 9.06 mg/dl (95% CI 0.07, 18.06) compared to nonusers of TNF- α inhibitor (p = 0.05). However, after excluding patients who were statin users or had diabetes, the increase of TG or TC in patients receiving etanercept was no longer significant [0.79 mg/dl (95% CI –20.02, 21.61; p = 0.9) and 3.44 mg/dl (95% CI –6.13, 13.00; p = 0.5), respectively].

DISCUSSION

The published studies on the association of TNF-α inhibitors with lipid changes in RA report inconsistent results, likely due to small sample size, variable study duration, and lack of adjustment for covariables such as age, comorbidities, and relevant disease-modifying antirheumatic medications; very few include a comparator group of patients not using these biologic modifiers. Most of the studies exclusively examined the relationship between infliximab use and changes pre-drug and post-drug exposure, and they invariably showed an increase in TC with treatment; the majority also showed an increase in HDL but no changes in TC:HDL^{4,5,6,7,8,9,10,11,12,13,14,15,16}. Other reports including patients receiving etanercept and adalimumab show either an increase in HDL or no changes in

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Table 2. Final adjusted longitudinal model* estimates for tumor necrosis factor- α (TNF- α) inhibitor use status. Values are median (interquartile range).

	Total on TNF-α Inhibitors			
	All	No Statins	No Statins or Diabetes	
Total cholesterol (TC)	1.55 (-2.93, 6.04)	3.45 (-3.17, 10.07)	0.33 (-6.93, 7.59)	
HDL	0.42 (-0.94, 1.78)	1.48 (-0.75, 3.70)	1.47 (-1.17, 4.10)	
LDL	-1.73 (-5.52, 1.99)	-2.18 (-7.52, 3.16)	-0.62 (-6.67, 5.43)	
Triglyceride	9.11 (-1.56, 19.77)	13.31 (-2.45, 29.08)	2.43 (-13.77, 18.62)	
TC/HDL	0.004 (-0.12, 0.13)	-0.01 (-0.19, 0.16)	-0.06 (-0.26, 0.14)	
LDL/HDL	-0.03 (-0.12, 0.07)	-0.05 (-0.18, 0.08)	-0.05 (-0.20, 0.10)	

^{*} Adjusted for sex, age at RA diagnosis, race, body mass index (time-varying), rheumatoid factor (yes/no), diabetes, hypertension, and use (time-varying) of steroids, nonsteroidal antiinflammatory drugs, methotrexate, hydroxychloroquine, statins (classified as none, low, medium, high potency), and other lipid-lowering medications. HDL: high-density lipoprotein; LDL: low-density lipoprotein.

lipids 14,15 , but the results were not reported specifically for each TNF- α inhibitor except for 1 study 16 . We observed no association of either etanercept or monoclonal TNF- α inhibitor use versus nonuse with lipid levels in patients with RA. The increase in TG in the subgroup of RA patients treated with etanercept that were never treated with statins disappeared after adjustment for concomitant diabetes, indicating this was an association with diabetes rather than etanercept.

Limitations of our study include the possibility of confounding by indication and absence of information on family history of dyslipidemia, measures of functional status, and physical activity. However, our study used a large cohort of patients with incident RA in whom a number of relevant covariables could be accounted for in our regression analyses. This analysis approach may be the reason for our reassuring findings, in contrast to those in previous reports.

In this large study of a retrospective cohort of patients with incident RA, TNF- α inhibitor use was not associated with differences in individual lipid levels or the atherogenic index. Further prospective studies are needed to determine the effect of individual TNF- α inhibitors on lipids in patients with RA.

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