Journal of Clinical Lipidology (2017) 11, 1243–1256

Journal of Clinical Lipidology

Effect of tofacitinib on lipid levels and lipid-related parameters in patients with moderate to severe psoriasis

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KEYWORDS:
Tofacitinib;
Psoriasis;
Lipoproteins;
Lipid levels;
Lipid metabolism;
HDL function;
Cardiovascular risk

BACKGROUND: Psoriasis is a systemic inflammatory disease associated with increased cardiovascular (CV) risk and altered lipid metabolism. Tofacitinib is an oral Janus kinase inhibitor.

OBJECTIVE: The aim of the study was to investigate the effects of tofacitinib on traditional and nontraditional lipid parameters and CV risk markers in patients with psoriasis from a phase III study, OPT Pivotal 1.

METHODS: Patients with psoriasis were randomized to tofacitinib 5 or 10 mg twice daily (BID) or placebo BID. Serum samples were collected at baseline, week 4, and week 16. Analyses included serum cholesterol levels, triglycerides, lipoproteins, lipid particles, lipid-related parameters/CV risk markers, and high-density lipoprotein (HDL) function analyses.

RESULTS: At week 16, small concurrent increases in mean low-density lipoprotein cholesterol (LDL-C) and HDL cholesterol (HDL-C) levels were observed with tofacitinib; total cholesterol/HDL-C ratio did not change. There was no significant change in the number of small dense LDL particles, which are considered to be more atherogenic than large particles, and oxidized LDL did not increase. Paraoxonase 1 activity, linked to HDL antioxidant capacity, increased, and HDL-associated serum amyloid A, which reduces the anti-atherogenic potential of HDL, decreased. HDL capacity to promote cholesterol efflux from macrophages did not change. Lecithin–cholesterol acyltransferase activity, which is associated with reverse cholesterol transport, increased. Markers of systemic inflammation, serum amyloid A and C-reactive protein, decreased with tofacitinib.

CONCLUSION: While small increases in lipid levels are observed with tofacitinib treatment in patients with psoriasis, effects on selected lipid-related parameters and other circulating CV risk biomarkers are not suggestive of an increased CV risk [NCT01276639].

Funding: This study was funded by Pfizer Inc. Pfizer employees were involved in the study design, analysis, interpretation of the data, writing the report, and the decision to submit.

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Submitted December 12, 2016. Accepted for publication June 17, 2017.

http://dx.doi.org/10.1016/j.jacl.2017.06.012

Introduction

Psoriasis is a systemic inflammatory condition that is associated with an increased risk of cardiovascular (CV) disease.[1–3] Traditional risk factors for CV disease, including hypertension, obesity, metabolic syndrome, and dyslipidemia, are more prevalent in patients with psoriasis vs the general population[4,5] and likely contribute to increased CV risk in psoriasis. However, psoriasis is also associated with an increased risk of CV disease independent of these traditional risk factors,[1,2,6] which points to a role of psoriasis itself and the associated pathophysiology as an important element conducive to CV disease.[7,8]

A possible link between psoriasis and CV disease is the systemic inflammatory state.[9,10] Furthermore, chronic inflammatory diseases, including psoriasis, are associated with changes in lipid metabolism and may promote an atherogenic lipid profile.[11–15] Increased serum triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels, and reduced high-density lipoprotein cholesterol (HDL-C) levels, have all been reported in patients with psoriasis, with the extent of changes related to psoriasis severity.[11,13,14] These changes in lipid profile, that also may include abnormalities of lipid particle composition and function, can elevate the risk of atherosclerosis and contribute to the higher incidence of CV disease observed in patients with psoriasis vs the general population.[11,12,14]

Tofacitinib is an oral Janus kinase (JAK) inhibitor. It targets inflammation by reducing proinflammatory cytokine signaling and production. In pre-clinical models, tofacitinib preferentially binds to JAK1 and JAK3, and to a lesser extent JAK2, thereby blocking the effects of multiple cytokines, such as interleukin (IL)-2, IL-4, IL-6, IL-7, IL-9, IL-12, IL-15, IL-17, IL-21, IL-23, and interferon-γ, and disrupting T-cell proliferation and T helper cell differentiation.[16,17] Several of these cytokines are known to be involved in inflammatory conditions, such as psoriasis, rheumatoid arthritis (RA), inflammatory bowel disease, and atherosclerosis.[18] Given that inflammation leads to alterations in lipid metabolism, the treatment of these conditions may result in changes in lipid profile.[15]

Based on 4 phase III clinical studies, tofacitinib provides significant improvement in clinical signs and symptoms of moderate to severe plaque psoriasis.[19–21] Small dose-dependent increases in mean HDL-C and LDL-C levels were observed in patients with psoriasis within 1 month of tofacitinib initiation, with levels stabilizing thereafter.[19–21] Increases in HDL-C and LDL-C have also been reported in patients with RA treated with tofacitinib,[22] as well as with other JAK inhibitors, such as baricitinib,[23] decernotinib,[24] and peficitinib.[25] However, the impact of JAK inhibition on specific structural and functional lipid-related parameters has not been thoroughly investigated.

The current analysis investigated in more detail the effects of tofacitinib on traditional and nontraditional lipid parameters and other selected circulating CV risk biomarkers in patients from a phase III clinical study of tofacitinib in psoriasis, to further understand the effects of tofacitinib on lipid metabolism and CV risk.

Materials and methods

Study design

Analyses were based on data from patients enrolled in the OPT Pivotal 1 study (NCT01276639).[21] Briefly, OPT Pivotal 1 was a randomized phase III study. Patients with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index score $\geq$12; Physician's Global Assessment of "moderate" or "severe") were randomized 2:2:1 to tofacitinib 5 mg, tofacitinib 10 mg, or placebo twice daily (BID). At week 16, patients receiving placebo were rerandomized to tofacitinib 5 or 10 mg BID. All continuing patients were followed up to week 52. Patient inclusion and exclusion criteria have been described previously.[21]

Traditional lipid parameters included serum cholesterol levels (LDL-C, HDL-C, and TC), TGs, and lipoproteins, whereas nontraditional parameters included a variety of lipid-related parameters and lipid particle measurements.

During the OPT Pivotal 1 study, separate serum samples were collected and frozen for future measurement from all patients at baseline, week 4, and week 16. After the study was unblinded, patients were selected for this study based on stratified sampling from those with no missing values at these visits. Random samples were chosen without replacement separately from the tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo groups for each analysis in the following order: lipid particles, nontraditional lipid parameters, and selected CV risk markers (lecithin-cholesterol acyltransferase [LCAT], cholesteryl ester transfer protein [CETP] activity, oxidized LDL, lipoprotein-associated phospholipase A2 [Lp-PLA2], paraoxonase 1, HDL-associated serum amyloid A [HDL-SAA], lipoprotein (a) [Lp(a)], and circulating serum amyloid A [SAA]), and HDL function analyses. Samples for the lipid particle and nontraditional lipid parameter/CV risk marker analyses were selected from patients who had not received lipid-lowering treatment at baseline or during the study up to week 16 (lipid-lowering-therapy-naïve). Samples for the HDL function analysis were selected from both lipid-lowering-therapy-naïve patients and those who received lipid-lowering therapy. For analysis of traditional lipid parameters (TC, LDL-C, HDL-C, TGs, apolipoprotein [Apo] A-1, Apo B-100) and high-sensitivity C-reactive protein (hs-CRP), available samples at baseline, week 4, and week 16 from all OPT Pivotal 1 participants (including both lipid-lowering-therapy-naïve patients and those who received lipid-lowering therapy) were analyzed and data are presented for the overall study population.

This study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All

documentation was reviewed by the Institutional Review Board and/or Independent Ethics Committee at each investigational center. All patients provided written informed consent. Separate informed consent was provided by those patients who provided samples for this analysis.

Laboratory analyses

Separate analyses were done for each of the sets of measurements: lipid levels, lipid particles, lipid-related parameters/CV risk markers, and HDL function. LDL-C, HDL-C, TC, TGs, Apo A-1, Apo B-100, and hs-CRP were analyzed from fresh samples by Quintiles Inc (Durham, NC). Lipid particles were analyzed by LipoScience Inc (Raleigh, NC) using nuclear magnetic resonance (NMR) Lipoprofile® II, a validated and specific NMR spectroscopy method.[26] Samples for this assay were frozen at −80°C; these are known to be stable indefinitely (≥10 years) when frozen at −70°C. The samples (200 μL) were analyzed using a 400 MHz NMR analyzer, and the composite methyl signal appearing in each spectrum at approximately 0.8 ppm was deconvoluted to obtain individual lipid subclass signal amplitudes, which were then converted to concentrations. Lipid-related parameters and SAA were analyzed by PacBio Inc (Seattle, WA) using a validated and specific turbidimetric immunoassay method (Lp[a], Apo CIII),[27,28] colorimetric method (paraoxonase 1),[29] enzymatic method (LCAT activity),[30] enzyme-linked immunosorbent assay (Lp-PLA2, SAA, HDL-SAA, oxidized LDL),[31–33] or fluorometric method (CETP activity).[34] SAA was analyzed using whole unfractionated sample, whereas HDL-SAA was analyzed using an Apo E-rich HDL supernate isolated through precipitation with polyethylene glycol (PEG)-8000.[35] All assays were performed on samples that had been frozen at −70°C. The samples are known to be stable for >10 years (SAA), ≤3 years (Lp[a], Apo CIII, paraoxonase 1, Lp-PLA2, HDL-SAA, and oxidized LDL), ≤2.5 years (CETP activity), and ≤9 months (LCAT activity) (communication from PacBio Inc). HDL function was analyzed by Dr Alan R Tall et al. at Columbia University using an assay that measures the ability of HDL to promote cholesterol efflux from a cholesterol-loaded human cell line with monocytic properties cultured from pediatric leukemia patient (THP-1) human macrophages, as described previously.[36,37] In short, to obtain the HDL, 100 μL of plasma was added to 40 μL of 20% PEG in 200 mM glycine (pH 10) solution, causing the Apo B-containing particles to precipitate.[37] Three different volumes of PEG HDL (25, 50, and 80 μL) were incubated with THP-1 human macrophages. The TC in the medium was subsequently extracted and quantified using gas-liquid chromatography. The cholesterol efflux was determined by subtracting the cholesterol mass of the medium incubated with or without cells.[37]

Statistical analysis

The target sample sizes for the lipid particles and nontraditional lipid parameter/CV risk marker analyses were 70:70:50 (tofacitinib 5 mg BID: tofacitinib 10 mg BID: placebo). Sample sizes were determined by considering the acceptable level of precision of estimates. A sample size of 70 subjects for each of the tofacitinib groups would provide a margin of error of <10% for most endpoints considered. The target sample size for HDL function was 25 in each treatment group, which was considered adequate for this exploratory analysis based on previous studies using the same methodology.[36,37]

For comparison between treatment groups, an analysis of covariance model was used, with treatment as a fixed effect and baseline as a covariate. Difference between treatment groups was based on the least squares mean, and mean values (±standard error) are presented. Nominal *P* values are presented to provide guidance on interpreting the relative magnitude and consistency of the findings and are not adjusted for multiplicity. For selected endpoints in which the observed distribution was highly skewed, a rank-based *P* value is presented instead of one based on the original scale. Median values (and Q1, Q3) are presented for these parameters.

Results

Samples for this analysis were collected at baseline, week 4, and week 16 from randomly selected subsets of patients enrolled in the OPT Pivotal 1 study of tofacitinib for the treatment of moderate to severe plaque psoriasis. Of the 901 patients who received treatment in OPT Pivotal 1 (tofacitinib 5 mg BID, $n = 363$; 10 mg BID, $n = 360$; placebo, $n = 177$), 191 patients (21.2%) were included in the lipid particle analyses, 74 (8.2%) in the HDL function analysis, and 190 (21.1%) in the analysis of other lipid-related parameters and CV risk biomarkers.

Patient demographics and characteristics

Baseline characteristics for the total OPT Pivotal 1 study population have previously been reported.[21] For the additional analysis cohorts presented in this study, baseline characteristics were similar among treatment groups (Table 1). Most patients were male and White. Mean age ranged from 42.3 to 50.9 years, and mean body mass index from 28.5 to 30.1 kg/m^2. The proportion of patients with diabetes and hypertension tended to be higher in the HDL function analysis group than the other analysis groups. Baseline Framingham risk score was similar across groups.

Effect of tofacitinib on traditional lipid parameters

Concurrent increases from baseline in mean levels of LDL-C, HDL-C, and TGs were observed at week 4 with tofacitinib vs placebo; levels were relatively stable from week 4 to week 16 (Fig. 1). No further increase in mean

Table 1 Baseline demographics and characteristics for treatment groups and cohorts for analyses of lipid particles, lipid-related parameters, and cardiovascular risk markers, and high-density lipoprotein function

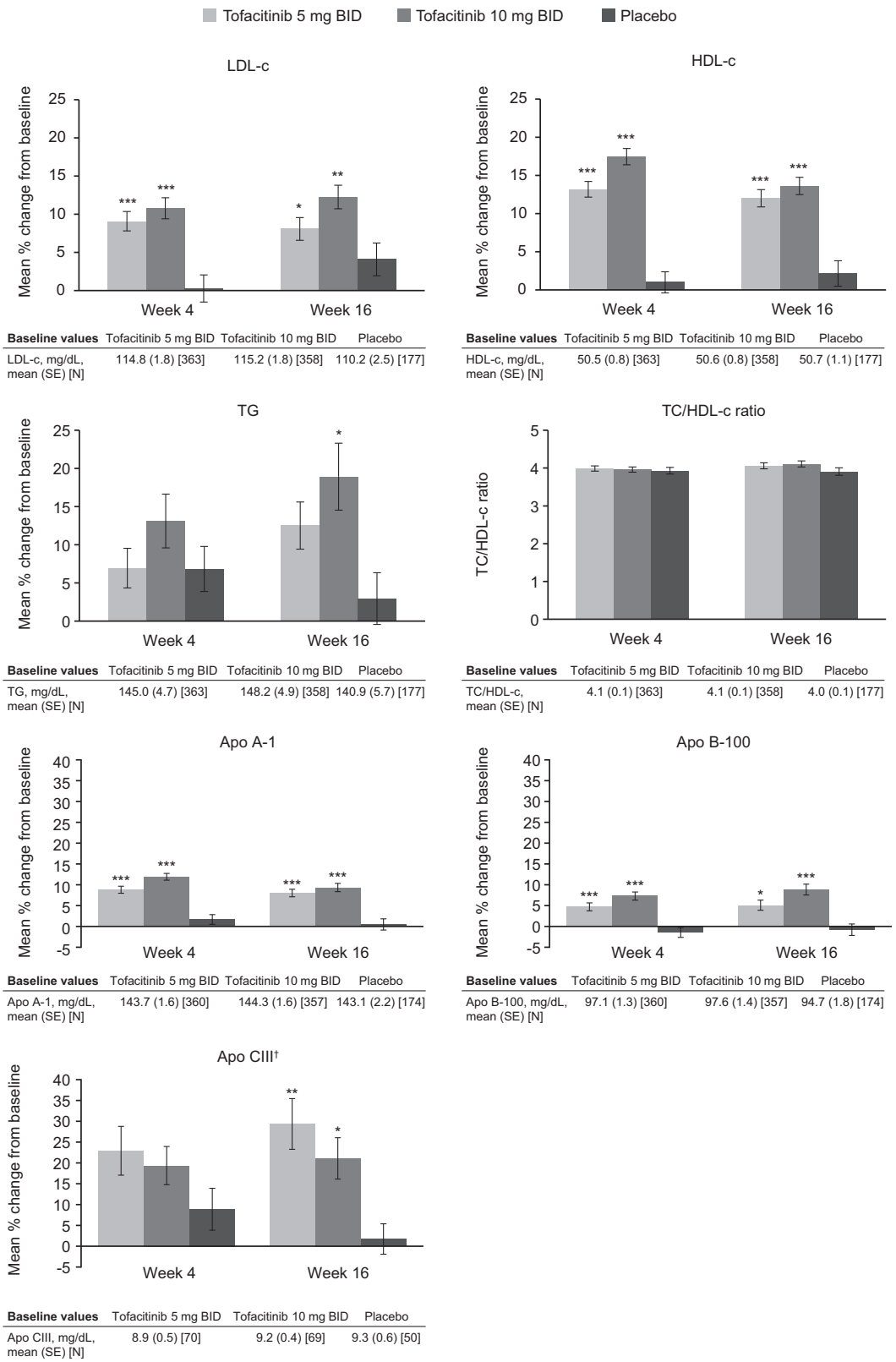
	Lipid particles			Lipid-related parameters and CV risk markers			HDL function		
Patient characteristics	Tofacitinib 5 mg BID (n = 70)	Tofacitinib 10 mg BID (n = 71)	Placebo (n = 50)	Tofacitinib 5 mg BID (n = 70)	Tofacitinib 10 mg BID (n = 70)	Placebo (n = 50)	Tofacitinib 5 mg BID (n = 25)	Tofacitinib 10 mg BID (n = 25)	Placebo (n = 24)
Demographics									
Age, years; mean (SD)	43.6 (12.7)	44.7 (12.3)	42.6 (12.5)	43.8 (14.6)	42.3 (12.9)	43.7 (12.2)	43.9 (9.0)	47.1 (13.3)	50.9 (11.1)
Male, n (%)	55 (78.6)	49 (69.0)	26 (52.0)	50 (71.4)	50 (71.4)	36 (72.0)	19 (76.0)	20 (80.0)	15 (62.5)
White, n (%)	55 (78.6)	56 (78.9)	45 (90.0)	64 (91.4)	63 (90.0)	49 (98.0)	23 (92.0)	24 (96.0)	22 (91.7)
BMI, kg/m^2; mean (SD)	30.1 (7.2)	28.5 (5.4)	30.1 (7.4)	30.1 (6.0)	30.1 (5.7)	29.2 (7.0)	28.5 (6.1)	28.6 (5.1)	29.2 (5.1)
Baseline disease characteristics									
Duration of psoriasis, years; mean (SD)	15.3 (10.5)	18.5 (12.7)	18.2 (10.6)	18.6 (12.3)	18.1 (11.6)	18.8 (11.7)	22.3 (10.3)	23.4 (14.1)	23.9 (13.9)
PASI score, n (%)									
<20	39 (55.7)	31 (43.7)	26 (52.0)	38 (54.3)	26 (37.1)	18 (36.0)	14 (56.0)	13 (52.0)	15 (62.5)
≥20	31 (44.3)	40 (56.3)	24 (48.0)	32 (45.7)	44 (62.9)	32 (64.0)	11 (44.0)	12 (48.0)	9 (37.5)
PGA									
Mild	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	63 (90.0)	65 (91.5)	48 (96.0)	62 (88.6)	58 (82.9)	47 (94.0)	23 (92.0)	23 (92.0)	24 (100.0)
Severe	6 (8.6)	6 (8.5)	2 (4.0)	8 (11.4)	12 (17.1)	3 (6.0)	2 (8.0)	2 (8.0)	0 (0.0)
hsCRP, n (%)									
<0.3 mg/dL	40 (57.1)	38 (53.5)	29 (58.0)	38 (54.3)	36 (51.4)	29 (58.0)	15 (60.0)	12 (48.0)	12 (50.0)
≥0.3 mg/dL	30 (42.9)	33 (46.5)	21 (42.0)	32 (45.7)	34 (48.6)	21 (42.0)	10 (40.0)	13 (52.0)	12 (50.0)
Baseline CV risk									
Metabolic syndrome*, n (%)	16 (22.9)	23 (32.4)	17 (34.0)	20 (28.6)	24 (34.3)	16 (32.0)	6 (24.0)	13 (52.0)	10 (41.7)
Diabetes†, n (%)	6 (8.6)	3 (4.2)	6 (12.0)	6 (8.6)	5 (7.1)	5 (10.0)	4 (16.0)	3 (12.0)	6 (25.0)
Hypertension‡, n (%)	13 (18.6)	18 (25.4)	10 (20.0)	16 (22.9)	15 (21.4)	16 (32.0)	9 (36.0)	12 (48.0)	10 (41.7)
Coronary heart disease, n (%)	0 (0.0)	1 (1.4)	2 (4.0)	1 (1.4)	1 (1.4)	1 (2.0)	1 (4.0)	1 (4.0)	1 (4.2)
Peripheral artery disease, n (%)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Framingham risk score, n (%)									
<10%	52 (74.3)	54 (76.1)	43 (86.0)	53 (75.7)	50 (71.4)	37 (74.0)	18 (72.0)	14 (56.0)	13 (54.2)
10% to ≤20%	15 (21.4)	15 (21.1)	7 (14.0)	16 (22.9)	18 (25.7)	13 (26.0)	7 (28.0)	10 (40.0)	9 (37.5)
>20%	3 (4.3)	2 (2.8)	0 (0.0)	1 (1.4)	2 (2.9)	0 (0.0)	0 (0.0)	1 (4.0)	2 (8.3)

BID, twice daily; BMI, body mass index; CV, cardiovascular; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; SD, standard deviation.

*Patients with at least 3 of the following conditions: waist circumference ≥102 cm (male) or ≥88 cm (female); triglycerides ≥150 mg/dL; HDL-C <40 mg/dL (males) or <50 mg/dL (females); systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg; fasting glucose ≥100 mg/dL.

†Patients with at least 1 of the following conditions: diabetes history/diagnosis; receiving diabetes treatment at baseline; baseline HbA1c ≥ 6.5%; if HbA1c was unavailable, baseline fasting plasma glucose concentration ≥7.0 mmol/L (≥126 mg/dL).

‡Patients with at least 1 of the following conditions: hypertension history/diagnosis; receiving hypertension treatment at baseline; at least 2 pre-dose records for systolic blood pressure ≥140 mm Hg or at least 2 pre-dose records for diastolic blood pressure ≥90 mm Hg.



Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
LDL-c, mg/dL, mean (SE) [N]	114.8 (1.8) [363]	115.2 (1.8) [358]	110.2 (2.5) [177]

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
HDL-c, mg/dL, mean (SE) [N]	50.5 (0.8) [363]	50.6 (0.8) [358]	50.7 (1.1) [177]

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
TG, mg/dL, mean (SE) [N]	145.0 (4.7) [363]	148.2 (4.9) [358]	140.9 (5.7) [177]

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
TC/HDL-c, mean (SE) [N]	4.1 (0.1) [363]	4.1 (0.1) [358]	4.0 (0.1) [177]

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Apo A-1, mg/dL, mean (SE) [N]	143.7 (1.6) [360]	144.3 (1.6) [357]	143.1 (2.2) [174]

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Apo B-100, mg/dL, mean (SE) [N]	97.1 (1.3) [360]	97.6 (1.4) [357]	94.7 (1.8) [174]

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Apo CIII, mg/dL, mean (SE) [N]	8.9 (0.5) [70]	9.2 (0.4) [69]	9.3 (0.6) [50]

Figure 1 Baseline values and percent change from baseline in traditionally measured lipid parameters and lipoproteins at weeks 4 and 16 for all patients in the OPT Pivotal 1 study. †Apo CIII data are reported from patients included in the lipid-related parameter analysis group; all other parameters are reported for the total OPT Pivotal 1 study population. *$P < .05$; **$P < .001$; ***$P < .0001$ vs placebo. Least squares means and corresponding SE and P values are derived from a mixed model with fixed effects for treatment, visit, treatment-by-visit interaction and baseline value, repeated measures for visit (nested within subject), and an unstructured covariance matrix Error bars represent ± SE. Apo, apolipoprotein; BID, twice daily; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, standard error; TC, total cholesterol; TG, triglycerides.

Table 2 Baseline values and percent change from baseline in lipid particles at week 4 and week 16

	Tofacitinib 5 mg BID (n = 70)			Tofacitinib 10 mg BID (n = 71)			Placebo (n = 50)		
Lipid particle	Baseline	Week 4 % CFB	Week 16 % CFB	Baseline	Week 4 % CFB	Week 16 % CFB	Baseline	Week 4 % CFB	Week 16 % CFB
Small very low-density lipoprotein particles (nmol/L) (VSP) [mean (SE)][†]	38.52 (2.62)	21.76 (7.87)	34.29 (11.55)	41.50 (2.60)	23.01 (12.53)	27.46 (11.41)	36.08 (2.55)	18.37 (13.48)	32.55 (19.69)
Very small low-density lipoprotein particles (nmol/L) (LVSP) [mean (SE)][†]	635.83 (30.89)	−2.38 (4.94)	−0.42 (6.30)	724.32 (40.86)	−9.48 (4.44)	1.63 (5.33)	590.84 (43.78)	19.03 (15.48)	−0.31 (8.19)
Low-density lipoprotein particles (nmol/L) (LDLP) [mean (SE)][†]	1219.57 (36.95)	2.66 (2.27)	3.56 (3.41)	1342.20 (50.85)	−0.66 (2.40)	**3.63 (2.53)***	1176.84 (43.33)	0.79 (3.10)	−1.53 (2.73)
Medium very low-density lipoprotein particles (nmol/L) (VMP) [mean (SE)][†]	27.14 (2.57)	113.78 (57.66)	171.28 (76.43)	26.54 (2.50)	71.58 (45.12)	79.20 (20.16)	24.89 (3.32)	101.61 (39.81)	99.75 (74.92)
Small low-density lipoprotein particles (nmol/L) (LSP) [mean (SE)][†]	799.09 (38.17)	−2.58 (4.79)	−1.14 (6.17)	906.96 (50.20)	**−10.15 (4.22)***	1.80 (5.12)	740.68 (55.03)	20.73 (15.30)	−1.54 (7.55)
Medium small low-density lipoprotein particles (nmol/L) (LMSP) [mean (SE)][†]	163.23 (7.93)	**−1.73 (4.73)***	−1.13 (6.17)	182.52 (9.65)	**−11.10 (4.24)***	4.02 (4.96)	149.80 (11.53)	36.64 (19.74)	−3.46 (6.55)
Large low-density lipoprotein particles (nmol/L) (LLP) [mean (SE)][†]	380.93 (25.13)	27.41 (7.95)	35.84 (12.13)	389.65 (20.80)	68.28 (27.60)	35.22 (15.41)	406.10 (28.22)	25.33 (14.57)	34.70 (13.98)
Intermediate-density lipoprotein particles (nmol/L) (IDLP) [median (Q1, Q3)][‡]	26.00 (10.00, 61.00)	−6.07 (−70.97, 83.33)	−13.75 (−73.24, 113.89)	33.00 (8.00, 74.00)	−21.84 (−83.33, 55.17)	**9.09 (−56.31, 100.00)***	22.00 (0.00, 47.00)	−10.00 (−60.78, 40.00)	−15.00 (−68.75, 83.33)
Very low-density lipoprotein size (nm) (VZ) [mean (SE)][†]	49.44 (1.09)	5.17 (2.03)	3.25 (2.16)	49.09 (1.17)	3.36 (2.10)	5.58 (2.42)	49.21 (1.39)	4.16 (2.49)	0.37 (2.17)
Low-density lipoprotein size (nm) (LZ) [mean (SE)][†]	20.83 (0.08)	0.93 (0.34)	0.93 (0.40)	20.77 (0.08)	1.46 (0.33)	0.57 (0.34)	20.97 (0.12)	0.26 (0.44)	0.89 (0.38)
High-density lipoprotein particles (nmol/L) (HDLP) [mean (SE)][†]	30.74 (0.83)	**11.74 (1.88)****	**12.88 (2.47)*****	30.06 (0.65)	**14.47 (2.19)*****	**13.10 (2.28)****	31.43 (0.74)	1.12 (2.08)	−0.57 (2.29)

Small high-density lipoprotein particles (nmol/L) (SHP) [mean (SE)][†]	21.94 (0.64)	6.53 (3.11)	**9.84 (3.46)***	21.78 (0.65)	12.78 (3.65)	**9.88 (3.35)***	21.20 (0.71)	6.43 (4.82)	−3.86 (3.36)
Medium high-density lipoprotein particles (nmol/L) (HMP) [mean (SE)][†]	2.81 (0.43)	109.94 (41.05)	268.95 (123.57)	2.42 (0.34)	347.76 (175.12)	190.26 (69.76)	2.86 (0.48)	37.22 (25.27)	53.41 (31.21)
Large high-density lipoprotein particles (nmol/L) (HLP) [mean (SE)][†]	5.99 (0.45)	22.22 (7.43)	25.11 (7.62)	5.87 (0.38)	32.94 (6.66)	20.92 (8.30)	7.38 (0.65)	9.26 (8.57)	23.82 (8.28)
High-density lipoprotein size (nm) (HZ) [mean (SE)][†]	8.83 (0.05)	0.49 (0.42)	0.34 (0.47)	8.79 (0.05)	1.03 (0.40)	0.47 (0.41)	8.96 (0.08)	−0.34 (0.47)	0.75 (0.41)
Very low-density lipoprotein and chylomicron triglycerides (total, calc.) (mg/dL) (NVCTG) [mean (SE)][†]	88.90 (8.86)	39.90 (11.29)	**45.46 (13.95)***	82.87 (6.37)	19.05 (9.56)	**57.89 (16.86)***	82.12 (8.97)	34.07 (19.36)	5.99 (9.48)
Very low-density lipoproteins and chylomicrons particles (nmol/L) (VLDLCP) [mean (SE)][†]	69.21 (4.27)	20.28 (7.38)	**29.99 (10.11)***	70.78 (4.67)	21.04 (13.94)	**30.69 (8.06)***	64.22 (5.36)	12.84 (8.38)	6.72 (8.07)
Large very low-density lipoproteins and chylomicrons particles (nmol/L) (VLCP) [median (Q1, Q3)][‡]	1.25 (0.30, 4.20)	22.50 (−18.75, 224.07)	**−3.13 (−58.82, 250.00)***	1.10 (0.20, 4.20)	0.00 (−50.00, 104.76)	**55.17 (−54.55, 300.00)****	1.45 (0.10, 5.50)	0.00 (−50.52, 89.71)	−29.52 (−75.40, 9.30)

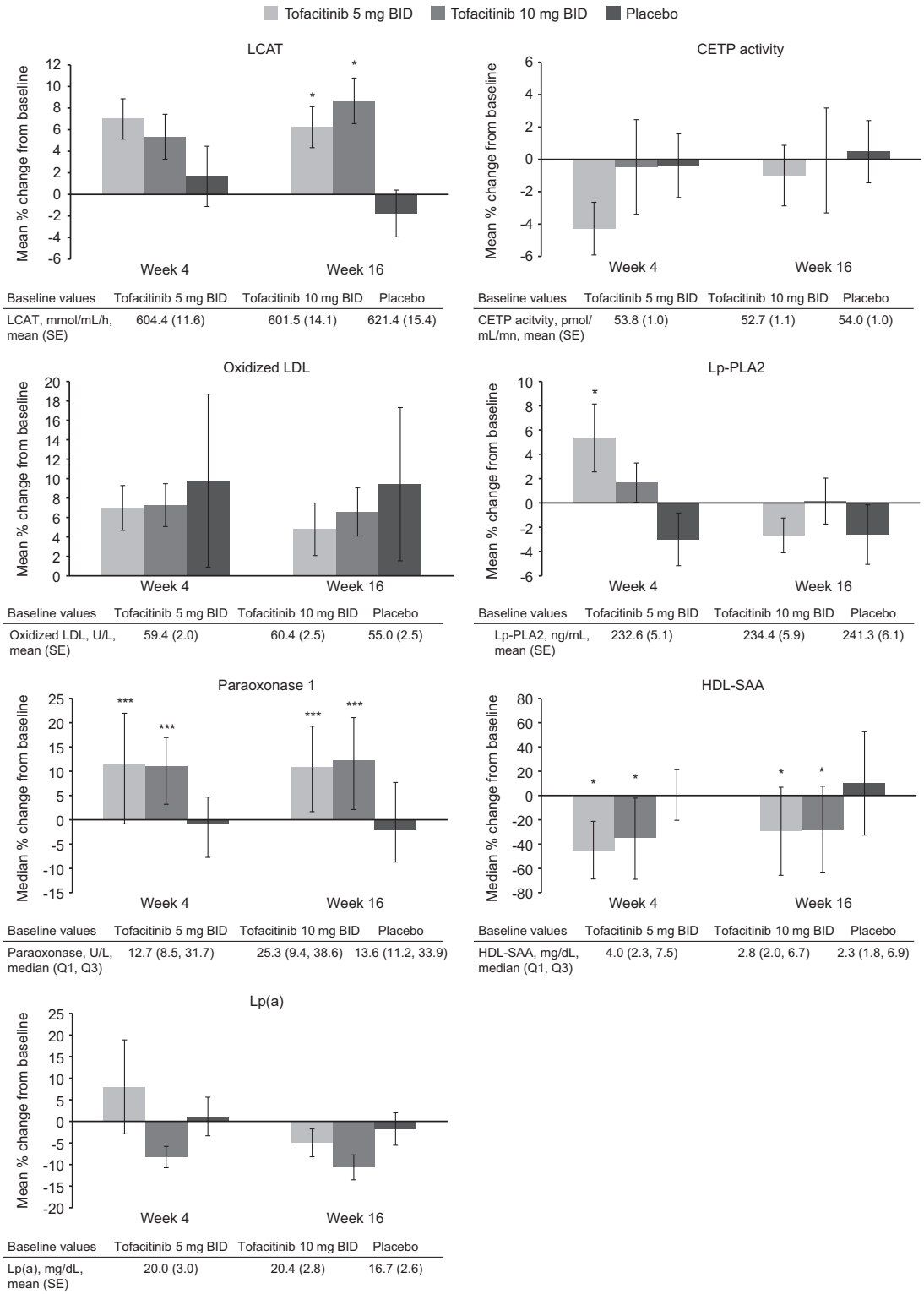
BID, twice daily; CFB, change from baseline; *n*, number of patients in treatment arm; SE, standard error.

Significant changes from baseline ($P < .05$) are highlighted in bold.

*$P < .05$; **$P < .001$; ***$P < .0001$ vs placebo.

†Results were obtained from an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline as a covariate.

‡*P* values were from ANCOVA models on normalized rank transformed data with treatment as a fixed effect and baseline (original scale) as a covariate.



Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
LCAT, mmol/mL/h, mean (SE)	604.4 (11.6)	601.5 (14.1)	621.4 (15.4)

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
CETP acitvity, pmol/mL/mn, mean (SE)	53.8 (1.0)	52.7 (1.1)	54.0 (1.0)

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Oxidized LDL, U/L, mean (SE)	59.4 (2.0)	60.4 (2.5)	55.0 (2.5)

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Lp-PLA2, ng/mL, mean (SE)	232.6 (5.1)	234.4 (5.9)	241.3 (6.1)

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Paraoxonase, U/L, median (Q1, Q3)	12.7 (8.5, 31.7)	25.3 (9.4, 38.6)	13.6 (11.2, 33.9)

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
HDL-SAA, mg/dL, median (Q1, Q3)	4.0 (2.3, 7.5)	2.8 (2.0, 6.7)	2.3 (1.8, 6.9)

Baseline values	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
Lp(a), mg/dL, mean (SE)	20.0 (3.0)	20.4 (2.8)	16.7 (2.6)

Figure 2 Baseline values and percent change from baseline in selected nontraditional lipid-related parameters at weeks 4 and week 16. *P* values for results presented as mean values were obtained from an ANCOVA model with treatment as a fixed effect and baseline as a covariate; *P* values for results presented as median values were from ANCOVA models on normalized rank transformed data with treatment as a fixed effect and baseline (original scale) as a covariate. $*P < .05$; $***P < .0001$ vs placebo. Error bars represent ± SE for mean values and ±Q1, Q3 for median values. ANCOVA, analysis of covariance; BID, twice daily; CETP, cholesteryl ester transfer protein; HDL-SAA, high-density lipoprotein serum amyloid A; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); Lp-PLA2, lipoprotein-associated phospholipase A2; SE, standard error.

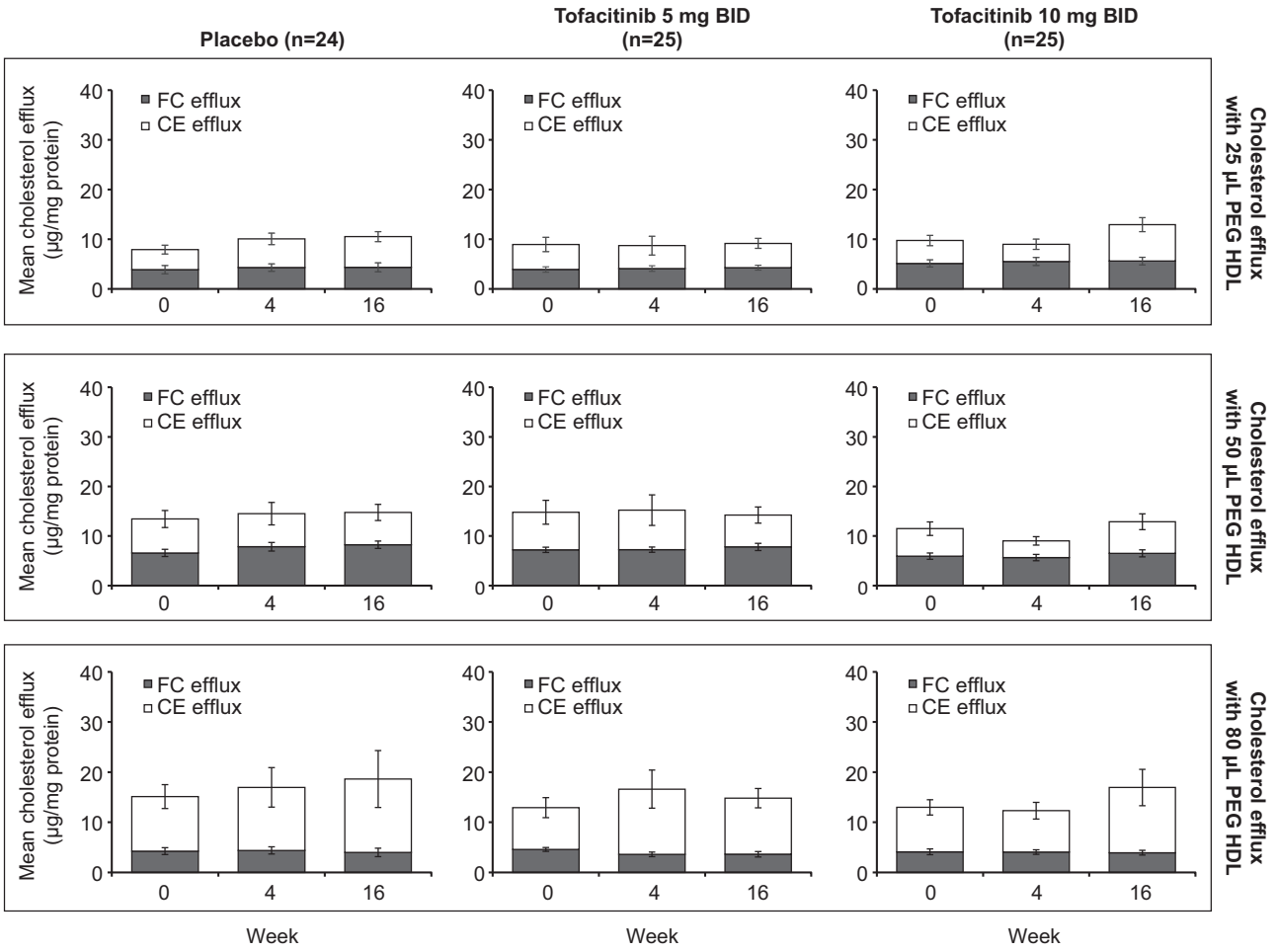


Figure 3 Comparison of cholesterol efflux (FC efflux and CE efflux) from human macrophages in placebo, tofacitinib 5 mg BID, and tofacitinib 10 mg BID patient groups using different PEG HDL volumes. Error bars represent ± SE. BID, twice daily; CE, cholesteryl ester; FC, free cholesterol; PEG HDL, polyethylene glycol high-density lipoprotein; SE, standard error.

lipid levels was observed with tofacitinib treatment over 52 weeks.[38] No changes from baseline were observed for TC/HDL-C ratio (Fig. 1) or LDL-C/HDL-C ratio (data not shown) for any treatment group. Mean levels of Apo A-1 and Apo B-100 increased from baseline with tofacitinib vs placebo by week 4 and were sustained to week 16. Mean levels of Apo CIII increased with tofacitinib vs placebo at week 16 (Fig. 1).

Effect of tofacitinib on lipid particles

To gain further insights into the effects of tofacitinib on lipid metabolism, changes in specific lipid particles and particle sizes were evaluated, as the number and composition of lipid particles have been suggested to be better markers of CV risk than serum cholesterol levels.[39] For example, smaller, more dense LDL particles are reported to be more atherogenic.[39,40]

Baseline values for lipid particles were similar among treatment groups (Table 2). A high degree of variability was seen in the levels of specific lipid particles at week 4 and week 16.

For LDL-related lipid parameters, changes from baseline were generally small and no consistent trend was seen between groups (Table 2). No significant differences were observed between tofacitinib and placebo in small very low-density lipoprotein particles, and very small LDL particles. There was no meaningful change in LDL particle size in any group.

Analysis of HDL-related particles revealed increases from baseline in HDL particles (HDLPs) at week 4 that were sustained at week 16 with both tofacitinib doses (Table 2). No change in HDLP was observed with placebo, and differences between both tofacitinib doses vs placebo were statistically significant at week 4 and week 16 ($P < .001$). In addition, an increase from baseline to week 16 was observed with tofacitinib for small high-density lipoprotein particles; this difference was statistically significant for both tofacitinib doses vs placebo ($P < .05$).

TG-related lipid parameters showed significantly greater increases from baseline with tofacitinib vs placebo at week 16, including very low-density lipoprotein and chylomicron TGs (NVCTG; $P < .05$), very low-density lipoproteins and chylomicrons particles (VLDLCP; $P < .05$), and large very

low-density lipoproteins and chylomicrons particles (VLCP; $P < .05$; Table 2).

Effect of tofacitinib on other nontraditional lipid-related parameters, including HDL-mediated cholesterol efflux

To evaluate whether tofacitinib alters lipid function in addition to altering overall lipid levels, selected parameters that are linked to lipid function and HDL capacity to promote cholesterol efflux from cholesterol-loaded human macrophages were evaluated. At baseline, all the measures were generally similar among treatment groups (Fig. 2).

A significant increase from baseline to week 16 in LCAT activity was observed with tofacitinib vs placebo ($P < .05$). No significant changes were seen in CETP activity in patients receiving tofacitinib or placebo (Fig. 2). No clinically meaningful changes from baseline in oxidized LDL, Lp-PLA2, or Lp(a) were observed at week 16 for patients receiving tofacitinib, and no statistically significant difference vs placebo was seen (Fig. 2).

At week 4 and week 16, greater increases from baseline in paraoxonase 1 and decreases from baseline in HDL-SAA were observed with both doses of tofacitinib vs placebo (Fig. 2; $P < .05$ for both time points and doses).

As expected,[36,37] in the HDL-mediated cholesterol efflux assay from a monocytic macrophage cell line, there was an apparent trend toward increased cholesteryl ester (CE) and TC (free cholesterol + CE) efflux with increasing PEG HDL volumes (Fig. 3). HDL capacity to promote free cholesterol efflux or CE efflux was not affected by either tofacitinib dose vs placebo at any of the HDL volumes assessed at week 4 or week 16 (Fig. 3).

Effect of tofacitinib on selected markers of systemic inflammation and CV risk

Significantly greater decreases from baseline in SAA were observed with both tofacitinib 5 and 10 mg BID vs placebo at week 16 (median % change from baseline [Q1, Q3]: −27.7 [−65.0, 30.0] and −25.8 [−58.7, 12.0] vs 3.3 [−18.2, 53.3], respectively; both $P < .05$). In addition, analysis of hs-CRP in the total OPT Pivotal 1 study population showed decreases from baseline to week 16 in patients who received tofacitinib 5 and 10 mg BID (median % change from baseline [Q1, Q3]: −54.7 [−76.7, −8.8] and −60.0 [−80.4, −24.2], respectively), but not placebo (4.8 [−33.3, 66.6]).

Discussion

In epidemiologic studies, higher LDL-C levels have been associated with increased CV risk and higher HDL-C levels with reduced CV risk.[41] Here, we observed small, concurrent increases in the mean levels of LDL-C, HDL-C, TC, and TGs with tofacitinib treatment, similar to previously reported findings from tofacitinib clinical studies.[19–21]

Other psoriasis therapies have also been associated with changes in lipid levels, including the oral systemic treatments methotrexate (increased LDL-C, HDL-C, and TC), acitretin (increased LDL-C, HDL-C, and TGs) and cyclosporine (increased TC and TGs).[42,43] However, there is little evidence to indicate whether these changes have a significant impact on CV risk in psoriasis. Although few studies of lipid changes with biologic treatments are available in patients with psoriasis, increased LDL-C, HDL-C, and TGs have been reported in patients with RA after treatment with biologic agents.[44]

Similar changes in lipid parameters as those observed in the present study have previously been reported in tofacitinib-treated RA patients[44] and the potential mechanism underlying effects of tofacitinib on circulating lipid levels has been evaluated in the RA patient population.[45] In RA patients, baseline HDL-C, LDL-C, and TC levels were lower than in healthy subjects and increased after 6 weeks of tofacitinib treatment to values approaching those in the healthy subjects. The CE fractional catabolic rate was greater at baseline in RA patients than in healthy subjects, and after tofacitinib treatment there was a decrease in the CE fractional catabolic rate and an increase in LCAT activity, with no change in CETP activity. These data suggest that low cholesterol levels in patients with active RA may be driven by increases in CE catabolism, which are reversed by tofacitinib; this leads to increases or "normalization" of cholesterol levels to those seen in healthy subjects.[45] In the present study, similar effects of tofacitinib on LCAT and CETP were observed, suggesting that the mechanisms underlying lipid changes associated with tofacitinib treatment are likely to be similar in psoriasis and RA. In addition, studies in patients with RA have indicated that increases in LDL-C as a result of tofacitinib treatment are readily reduced by statin therapy.[46] Although changes in some lipid levels can be related to changes in weight, an analysis of pooled data from 3 phase III studies, including OPT Pivotal 1, revealed only a slight increase in weight in patients with psoriasis who were treated with tofacitinib for up to 52 weeks.[38]

The concurrent increases in both LDL-C and HDL-C make the overall effect of tofacitinib on CV risk difficult to evaluate based on changes in these traditional lipid parameters alone. However, lipid ratios and nontraditional lipid parameters may be more indicative of CV risk, particularly in patients with chronic inflammatory diseases such as psoriasis.[47–49] Importantly, LDL-C/HDL-C and TC/HDL-C ratios did not change with tofacitinib treatment in the present study.

Although increased LDL-C is a risk factor for CV disease, the number and composition of LDL particles is thought to be a more accurate predictor of adverse CV events.[39] Similarly, although low HDL-C is an independent risk factor for atherosclerosis and CV disease,[50] HDLP number has been suggested to be a better marker than

HDL-C level.[51] The analysis of lipid particles presented here was therefore undertaken to understand any changes in the concentration or size of these particles with tofacitinib treatment. No increases were observed in small dense LDL particles, which are thought to be more atherogenic than large particles because of their greater propensity to enter the arterial wall and become oxidized.[39,52] Tofacitinib treatment was associated with sustained increases in some HDL-related particles, including HDLP and small HDLP, which may have an atheroprotective effect.[53] Increases in the TG-related parameters NVCTG, VLDLCP, and VLCP were observed with tofacitinib vs placebo, consistent with the slight increase in overall mean TG levels.

Despite an increase in absolute LDL-C levels, no effect of tofacitinib was seen on the level of oxidized LDL. Oxidized LDL promotes arterial inflammation by activating endothelial cells and circulating monocytes, thereby increasing the ability of monocytes to infiltrate the vascular wall, representing a primary stage in atherogenesis.[54] In addition, no changes were observed in Lp-PLA2. Circulating Lp-PLA2 is mainly associated with LDL, and hydrolyzes oxidized phospholipids on LDL particles, generating highly inflammatory mediators that lead to development of atherosclerosis.[55] A strong association has been observed between Lp-PLA2 levels and CV risk, including in subjects with normal LDL levels.[55]

The increase in HDL-C levels observed in this study could be interpreted as beneficial in reducing CV risk. However, recent evidence suggests that HDL function may be a key determinant of CV risk, even after adjustment for HDL-C level and particle size.[56] Analyses were therefore conducted to assess 2 important aspects of HDL function, that is, the ability to promote cholesterol efflux and antioxidant capacity.

Cholesterol efflux is part of reverse cholesterol transport, the process by which cholesterol from peripheral tissue (such as macrophages in atherosclerotic plaques) is removed to HDL and transported to the liver for excretion.[57] This process reduces the potential for atherosclerotic plaque formation, leading to protection against atherosclerotic disease.[58] In our study, tofacitinib maintained cholesterol efflux capacity of HDL vs placebo at both doses. In addition, similar to previous reports in tofacitinib-treated RA patients,[45] sustained decreases in HDL-SAA were seen with both tofacitinib doses. This may be interpreted as beneficial, since HDL-SAA reduces the anti-atherogenic profile of HDL by displacing the HDL major protein, Apo A1, which is required for activation of HDL cholesterol efflux pathways.[59] Increased LCAT activity was also observed with tofacitinib treatment. Increased LCAT activity is generally believed to be anti-atherogenic by promoting reverse cholesterol transport.[59,60] LCAT converts cholesterol into CEs that can be transferred to lipoproteins for transport to the liver.[61]

HDL-mediated antioxidant effects may also contribute to the anti-atherogenic effects of HDL.[62] For example, paraoxonase 1 is associated with HDL and prevents the formation of oxidized LDL.[63] In this study, paraoxonase 1 activity increased with tofacitinib treatment, suggestive of an increase in HDL anti-oxidant capacity.[64] Collectively, our data indicate a favorable effect of tofacitinib on HDL levels in psoriasis patients, without impairing cholesterol efflux capacity of HDL and with potential improvement in HDL antioxidant capacity.

High Lp(a) is a risk factor for early atherosclerosis, independent of other CV risk factors including increased LDL,[65] and Lp(a) is increased in patients with psoriasis and correlated with disease severity.[66] Although the exact physiological function of Lp(a) is unknown, there is evidence that it transports the more atherogenic, oxidized lipid particles into the arterial wall.[65] In this analysis, no difference in Lp(a) levels was observed with tofacitinib vs placebo.

Taken together, these data suggest that, while small increases in lipid levels are observed with tofacitinib, effects of tofacitinib on various lipid-related parameters do not indicate an increased CV risk. This is further supported by the observed decreases in circulating levels of SAA and hs-CRP, which are sensitive markers of systemic inflammation and CV risk.[67,68] Decreases in hs-CRP with tofacitinib have previously been reported in a phase II study in psoriasis[69] and are compatible with the anti-inflammatory effects of the drug.[70]

Consistent with the notion that tofacitinib treatment does not increase CV risk is the observation of low and non-dose-dependent incidence rates (IRs) of major adverse CV events (MACE) in the tofacitinib development programs. The IR (patients with event per 100 patient-years [PY] of tofacitinib exposure) for MACE (defined as a composite of myocardial infarction, cerebrovascular event, or CV death) in the psoriasis program across phase III and long-term extension studies (3623 patients; 5204 PY of tofacitinib exposure) was 0.37 (95% confidence interval: 0.22, 0.57).[38] In phase III studies in the RA development program (3800 patients; 3942 PY), the IR for MACE was 0.58 (0.39, 0.88), and in long-term extension studies in RA (4827 patients; 8699 PY), the IR was 0.37 (0.26, 0.52).[71] The IRs of MACE in the tofacitinib psoriasis clinical development program are comparable with those reported in untreated psoriasis patients[1,6,12] and patients receiving biologic and non-biologic systemic psoriasis treatments.[72]

A limitation of this study is that the analyses were conducted using samples taken from 3 different sub-sets of patients, and while patients whose samples were used in the lipid particle and nontraditional lipid parameter/CV risk marker analyses were naïve to lipid-lowering therapy, those in the HDL function analysis also included patients who had received lipid-lowering therapy. Therefore, although baseline demographics were similar across the analysis groups, any direct comparisons between groups should be made with caution. In addition, as only patients with no missing values who completed week 16 were eligible for these analyses, the samples may not be completely

representative of the total OPT Pivotal 1 population. Furthermore, although several markers of CV risk have been evaluated in the current analysis, it is not known how other markers of cardiometabolic disease would be modulated after treatment with tofacitinib. Finally, while the results indicate no unfavorable changes in lipid-related parameters as a result of tofacitinib treatment over 16 weeks, longer-term effects of tofacitinib on lipid metabolism have not been studied.

In conclusion, although small increases in TC, LDL-C, and TGs are observed with JAK inhibition by tofacitinib in patients with moderate to severe psoriasis, there is a concurrent increase in HDL-C, no change in the TC/HDL-C ratio, and effects of tofacitinib on several other lipid-related parameters and CV risk markers after 16 weeks of treatment are not suggestive of increased risk of adverse CV effects. This is in agreement with clinical data showing no increase in the incidence of MACE in tofacitinib-treated patients in relation to the expected rates in a psoriasis patient population.

Acknowledgment

The authors would like to thank the patients, investigators, and study teams involved in the OPT Pivotal 1 study. HDL efflux analyses were carried out by Dr Alan R Tall et al. at Columbia University, NY, USA. Medical writing support under direction from the authors was provided by Alice MacLachlan, PhD, and Carole Evans, PhD, on behalf of Complete Medical Communications, and was funded by Pfizer Inc.

Authors' contributions: R.W., S.L., M.K., and S.T. were involved in the conception and design of the study/analyses. S.L. performed the data and statistical analyses. R.W., E.J.A., P.R.H., B.T., S.L., A.M.T., M.K., and S.T. were involved in data interpretation and article drafting and reviewing.

Financial disclosures

R.W., S.L., A.M.T., and S.T. are employees and shareholders of Pfizer Inc. E.J.A. is a consultant/advisory board member to Abbott Vascular, Boston Scientific, Medtronic, Merck, Pfizer Inc, and Spectranetics. P.R.H. is a recipient of an unrestricted research grant from the LEO Foundation. B.T. has acted a consultant for Pfizer Inc and Valeant Pharmaceuticals. M.K. was an employee and shareholder of Pfizer Inc at the time of this analysis.

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