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Changes in Lipid Levels and Incidence of Cardiovascular Events Following Tofacitinib Treatment in Patients With Psoriatic Arthritis: A Pooled Analysis Across Phase III and Long-Term Extension Studies

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Objective. The risk of cardiovascular disease (CVD) is higher in patients with psoriatic arthritis (PsA) compared to the general population. Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. Because tofacitinib increases circulating lipid levels in some patients, we evaluated CVD risk factors and major adverse cardiovascular events (MACE) in patients with active PsA receiving tofacitinib 5 or 10 mg twice daily plus conventional synthetic disease-modifying antirheumatic drugs.

Methods. Data were pooled from 2 phase III studies (Efficacy and Safety of Tofacitinib in Psoriatic Arthritis [OPAL Broaden] and Tofacitinib in Patients with Psoriatic Arthritis With Inadequate Response to TNF Inhibitors [OPAL Beyond]) and 1 ongoing long-term extension (Open-Label Extension Study of Tofacitinib in Psoriatic Arthritis [OPAL Balance], data cutoff January 2017; database not locked). Outcomes included fasting lipid levels, blood pressure, hypertension-related adverse events (AEs; including hypertension, high blood pressure, and increased blood pressure), and MACE.

Results. Overall, 783 tofacitinib-treated patients were included. Percentage increases from baseline in low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) levels ranged from 9% to 14% for tofacitinib 5 mg and 10 mg at 3 and 6 months; no meaningful changes in LDL-c:HDL-c or total cholesterol:HDL-c ratios were observed. Blood pressure remained stable for 24 months. Fifty-eight patients (7.4%) had hypertension-related AEs; none were fatal (incidence rate [IR] per 100 patient-years 4.81 [95% confidence interval (95% CI) 3.65–6.22]). Five patients (0.6%) had MACE (IR 0.24 [95% CI 0.05–0.70]); 2 were fatal.

Conclusion. Serum lipid level increases at month 3 following tofacitinib treatment in PsA were consistent with observations in rheumatoid arthritis and psoriasis. The IR of hypertension-related AEs and MACE was low; long-term follow-up is ongoing.

INTRODUCTION

Psoriatic arthritis (PsA) is an immune-mediated systemic inflammatory disease with multiple disease manifestations, including peripheral arthritis, enthesitis, dactylitis, and spondylitis, together with skin and nail psoriasis (1). The risk of cardiovascular disease (CVD) and cardiometabolic disorders is higher in patients with PsA compared with the general population (2,3) and is considered comparable with rates in patients with rheumatoid arthritis (RA) and diabetes mellitus (4–7). Therefore, management of CVD risk factors is recommended (2,8,9). In addition, an association has been suggested between peripheral joint inflammation and lipid dysregulation in PsA (10).

Treatment options for PsA aim to achieve optimal control of disease activity through the suppression of inflammation (11). Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. The efficacy and safety of tofacitinib have been demonstrated in 2 phase III studies (Efficacy and Safety of Tofacitinib in Psoriatic Arthritis [OPAL Broaden] [12] and Tofacitinib in Patients with Psoriatic Arthritis With Inadequate Response to TNF Inhibitors [OPAL Beyond] [13]) and 1 ongoing long-term extension (LTE) study (Open-Label Extension Study of Tofacitinib in Psoriatic Arthritis [OPAL Balance] [14]).

The objective of this post hoc analysis was to better understand the changes in cholesterol levels and other selected CVD risk factors as well as to evaluate the incidence of major adverse cardiovascular events (MACE), a composite of CVD deaths, nonfatal myocardial infarction, and nonfatal stroke in patients with active PsA receiving tofacitinib 5 and 10 mg twice daily (BID) in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) using data from 2 phase III studies (OPAL Broaden [12] and OPAL Beyond [13]) and 1 ongoing LTE study (OPAL Balance [14]).

PATIENTS AND METHODS

Data were analyzed for patients who received ≥1 dose of tofacitinib 5 or 10 mg BID or placebo, pooled across 2 phase III studies and 1 LTE study of the 2 phase III studies in patients with active PsA. OPAL Broaden (12) was a phase III, 12-month, double-blind, placebo- and active-controlled parallel-group study in adult patients with active PsA who were naive to tumor necrosis factor inhibitors (TNFi), who were receiving 1 background csDMARD, and who had a prior inadequate response to ≥1 csDMARD. Patients were randomized 2:2:2:1:1 to tofacitinib 5 mg BID, tofacitinib 10 mg BID, adalimumab 40 mg subcutaneously every 2 weeks, placebo advancing to tofacitinib 5 mg BID after 3 months, or placebo advancing to tofacitinib 10 mg BID after 3 months. OPAL Beyond (13) was a phase III, 6-month, double-blind, placebo-controlled, parallel-group study in adults with active PsA who were receiving 1 background csDMARD and who had an inadequate response to ≥1 prior TNFi. Patients were randomized 2:2:1:1 to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo advancing to tofacitinib 5 mg BID after 3 months, or placebo advancing to tofacitinib 10 mg BID after 3 months. OPAL Balance (14) is an ongoing, open-label LTE study that enrolled patients who had participated in OPAL Broaden or OPAL Beyond. Data up to January 2017 (database not locked; data may change) were included in the current analysis, which included up to 3 years of tofacitinib exposure per patient. All patients received open-label tofacitinib 5 mg BID upon entry into OPAL Balance. The tofacitinib dosage could be increased to 10 mg BID at the investigator's discretion after 1 month, and could be decreased from 10 mg BID to 5 mg BID for safety reasons at any time. (For information on data sharing, see Supplementary Appendix 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23930/abstract.)

Patient eligibility and disposition. Eligible patients were age ≥18 years, had been diagnosed with PsA for ≥6 months prior to study participation, fulfilled the Classification criteria for Psoriatic Arthritis (15), and had active plaque psoriasis at screening and active arthritis (≥3 swollen and ≥3 tender/painful joints) at both screening and baseline (defined at the initiation of OPAL Broaden and OPAL Beyond) (12,13).

Assessments. Baseline demographics and patient characteristics from the corresponding qualifying study were used as baseline in the LTE. Pooled phase III data comprised phase III studies only and included placebo data up to month 3; pooled phase III and LTE data comprised tofacitinib data from the phase III and LTE studies (patients who were originally randomized to placebo were included, but only from the day that treatment with tofacitinib was initiated). Continuous

laboratory measurements such as fasting lipid levels and C-reactive protein (CRP) level analyses included pooled data from months 0 to 6 of phase III studies only (including tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo up to month 3 only). Blood pressure measurements and data on hypertension were pooled across the phase III and LTE studies using tofacitinib-exposed patients only and were identified using a Standardized Medical Dictionary for Regulatory Activities (MedDRA, version 19.1) query for hypertension (narrow). All hypertension-related events were reported as adverse events (AEs) and included the terms hypertension, high blood pressure, and increased blood pressure.

Table 1. Baseline demographics and characteristics from the phase III studies OPAL Broaden and OPAL Beyond*

Characteristics	Tofacitinib 5 mg BID (n = 238)	Tofacitinib 10 mg BID (n = 236)	Placebo (n = 236)
Baseline demographics			
Female, no. (%)	121 (50.8)	136 (57.6)	136 (57.6)
Age, years	49.5 ± 12.4	49.4 ± 11.7	48.4 ± 12.5
White, no. (%)	226 (95.0)	221 (93.6)	222 (94.1)
Body mass index, kg/m^2	29.8 ± 6.3	30.2 ± 6.3	29.2 ± 5.6
Smoking history, no. (%)			
Never smoked	139 (58.4)	140 (59.3)	158 (66.9)
Smoker	37 (15.5)	45 (19.1)	39 (16.5)
Ex-smoker	62 (26.1)	51 (21.6)	39 (16.5)
Baseline medical history, no. (%)			
Diabetes mellitus†	29 (12.2)	37 (15.7)	34 (14.4)
Hypertension‡	99 (41.6)	81 (34.3)	87 (36.9)
Dyslipidemia§	60 (25.2)	67 (28.4)	55 (23.3)
Metabolic syndrome¶	99 (41.6)	101 (42.8)	94 (39.8)
Lipid laboratory values			
HDL-c, mg/dl	55.7 ± 16.9	56.5 ± 19.6	55.7 ± 17.5
LDL-c, mg/dl	116.8 ± 32.4	119.1 ± 37.2	114.6 ± 33.1
Triglycerides, mg/dl	146.7 ± 93.9	144.2 ± 150.4	137.3 ± 74.6
Baseline disease characteristics			
Psoriatic arthritis duration, years	8.6 ± 7.9	7.5 ± 6.6	8.1 ± 7.5
Baseline PASDAS#	6.1 ± 1.2	6.2 ± 1.2	6.0 ± 1.2
Baseline HAQ DI	1.2 ± 0.7**	1.2 ± 0.6	1.2 ± 0.7
Baseline CPDAI with baseline BSA ≥3%††	10.0 ± 2.5	10.4 ± 2.7	9.8 ± 2.8
Baseline swollen joint count	12.5 ± 10.3	12.3 ± 9.8	10.9 ± 8.9
C-reactive protein, mg/liter	12.3 ± 20.5	12.0 ± 21.9	11.3 ± 20.2
Baseline total psoriatic BSA, mean % ± SD‡‡	10.0 ± 14.1	10.0 ± 12.6	12.0 ± 16.5
Relevant prior and concomitant medication, no. (%)			
Prior TNFi	131 (55.0)	132 (55.9)	132 (55.9)
Prior non-TNFi bDMARDs§§	11 (8.4)	14 (10.6)	11 (8.4)
TNFi naive	107 (45.0)	104 (44.1)	104 (44.1)
Concomitant methotrexate	186 (78.2)	180 (76.3)	193 (81.8)
Concomitant corticosteroid (day 1)¶¶	67 (28.2)	37 (15.7)	49 (20.8)
Concomitant NSAIDS (day 1)	144 (60.5)	125 (53.0)	132 (55.9)

* Values are the mean ± SD unless indicated otherwise. BID = twice daily; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; PASDAS = Psoriatic Arthritis Disease Activity Score; HAQ DI = Health Assessment Questionnaire disability index; CPDAI = Composite Psoriatic Disease Activity Index; BSA = body surface area; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug.
† Included patients who met ≥1 of the following criteria: diagnosis of diabetes mellitus recorded at screening; receiving any concomitant antidiabetic medication; glycosylated hemoglobin (HbA$_{1c}$) ≥6.5% at baseline, or baseline fasting plasma glucose ≥126 mg/dl, if HbA$_{1c}$ data were not available.
‡ Patients who were reported as having hypertension on the Cardiovascular Risk Factor case report form at baseline.
§ Defined as HDL-c <40 mg/dl (male) and <50 mg/dl (female) from baseline/screening data.
¶ Defined as patients with ≥3 components of the metabolic syndrome: obesity (waist circumference for male and female, respectively: US, Canada, Europe, Russia: ≥102 cm and ≥88 cm; Asian, including Japanese: ≥90 cm and ≥80 cm; ethnic central and South American: ≥90 cm and ≥80 cm); dyslipidemia: triglycerides ≥150 mg/dl, including patients receiving medications for lowering triglycerides, and HDL-c <40 mg/dl (male) and <50 mg/dl (female); elevated blood pressure: systolic ≥130 mm Hg or diastolic ≥85 mm Hg, including patients receiving antihypertensive medication; and fasting glucose ≥100 mg/dl, including patients receiving antidiabetic medication.
# For this subset of patients, n = 229, 230, and 231, respectively.
** n = 237.
†† For this subset of patients, n = 160, 147, and 166, respectively.
‡‡ For patients with BSA >0% at baseline.
§§ Patients who were treated with any non-TNFi bDMARD or both TNFi bDMARDs and non-TNFi bDMARDs were included in the prior non-TNFi bDMARDs category. For this subset of patients, n = 131, 132, and 132, respectively.
¶¶ Oral systemic corticosteroid use at baseline (maximum allowed dose of 10 mg/day of prednisone equivalent).

MACE were pooled across the phase III and LTE studies and were evaluated and classified by an external, independent adjudication committee, who were blinded to treatment; events were confirmed using prespecified criteria (see Supplementary Appendix 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23930/abstract).

Disease activity was measured using the Psoriatic Arthritis Disease Activity Score (PASDAS) (16), the Composite Psoriatic Disease Activity Index (CPDAI) (17), and the Disease Activity Index for Psoriatic Arthritis (18). In the pooled CVD event analyses across phase III and LTE studies, patients who received ≥1 dose of tofacitinib were considered as a single group (all tofacitinib doses). The average tofacitinib 5 mg BID treatment group consisted of patients with an average total daily dose of <15 mg from day 1 with tofacitinib; the average tofacitinib 10 mg BID treatment group consisted of patients with an average total daily dose of ≥15 mg from day 1 with tofacitinib.

Ethics approval. The institutional review boards and/or independent ethics committees approved the studies at each investigational center. Studies were conducted in compliance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written, informed consent.

Statistical analysis. Continuous data were summarized descriptively. In addition, changes from baseline in the CRP level were analyzed using a mixed model for repeated measures (MMRM), with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location, study, and baseline value; an unstructured covariance matrix was used and *P* values were unadjusted. Two separate MMRM analyses were performed, using data from week 2 to month 3, and for month 4 to month 6 using data from week 2 to month 6.

Discrete data were summarized using proportions and/or incidence rates (IRs) adjusted for person-time using the study drug. IR estimates (patients with events per 100 patient-years [PYs]) were calculated and included events occurring up to 28 days beyond the last dose (or to the data cutoff date for the ongoing LTE study). Exposure was defined as the total follow-up time calculated up to the day of the first event within the event counting period for patients who experienced the event or the last dose day plus an additional risk period of 28 days beyond the last dose (or to the data cutoff date for the ongoing LTE study, whichever was earlier) for patients without events. These definitions were chosen because the active reporting period for AEs was up to and including 28 calendar days after the last administration of the investigational product, and because reporting to the company safety database may occur at any time regardless of the time elapsed from the last administration of the study drug or since study completion. Inclusion of all events (numerator) without regard to elapsed time may inflate IR estimations, because the exposure time (denominator) is not similarly increased. Exact Poisson 95% confidence intervals (95% CIs, adjusted for PYs) are provided for the IR data (19,20).

RESULTS

Patients. Overall, 783 tofacitinib-treated patients were included in the analysis, pooled across the phase III and LTE studies. The total exposure to tofacitinib (all tofacitinib doses) was 1,237.9 PYs, with a median duration of exposure of 594.0 days (range 1–1,196 days). Baseline demographics and characteristics, including CVD risk factors, were generally similar between treatment groups in the phase III studies. Baseline demographics and characteristics from the pooled phase III studies are shown in Table 1. The mean age ranged from 48.4 to 49.5 years across treatment groups and the majority of patients were white (range 93.6–95.0%) and female (range 50.8–57.6%). At baseline, the duration of diagnosed PsA ranged from 7.5 to 8.6 years, and patients had high disease activity (PASDAS range 6.0–6.2; CPDAI range 9.8–10.4).
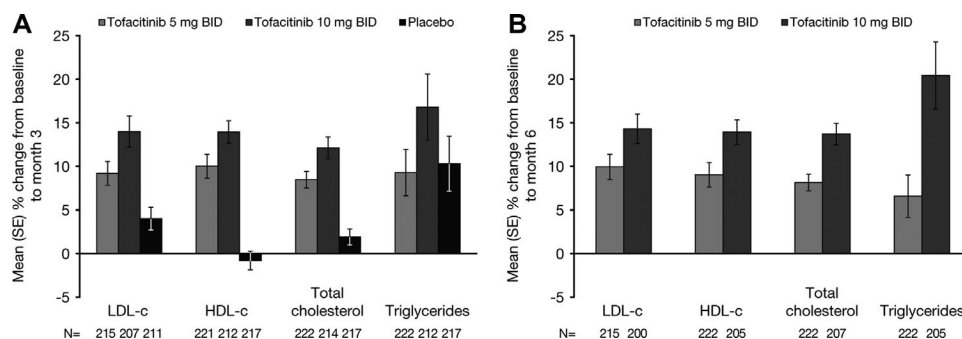
Figure 1. Mean percentage change from baseline in lipids at **A**, month 3 and **B**, month 6 (pooled phase III data), based on patients with a baseline and ≥1 postbaseline measurement. Patients randomized to placebo were advanced to tofacitinib 5 or 10 mg twice daily (BID) at month 3. LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; N = number of patients with value at the given time point.
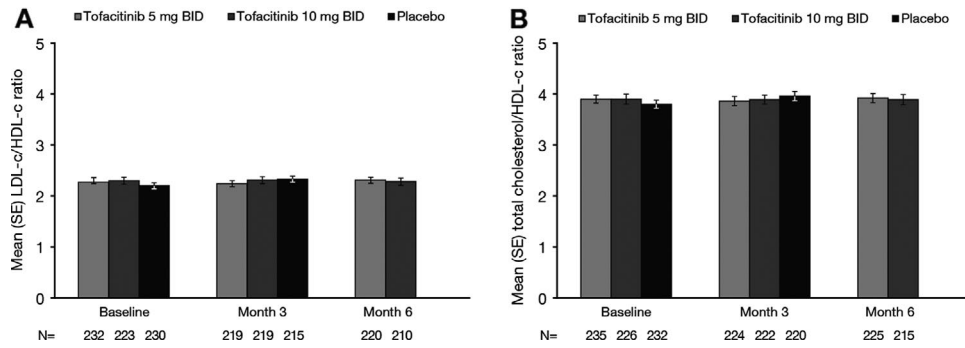
Figure 2. Mean lipid ratios at baseline, month 3, and month 6 for **A**, low-density lipoprotein cholesterol (LDL-c):high-density lipoprotein cholesterol (HDL-c) and **B**, total cholesterol:HDL-c (pooled phase III data), based on patients with a baseline and ≥1 postbaseline measurement. Patients randomized to placebo were advanced to tofacitinib 5 or 10 mg twice daily (BID) at month 3. N = number of patients with value at the given time point.

Outcomes. Mean percentage increases from baseline in low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) ranged from ~9% to 14% for tofacitinib 5 and 10 mg BID at 3 months (LDL-c 9.2% and 14.0%; HDL-c 10.0% and 14.0%, respectively) and stabilized through month 6 (LDL-c 9.9% and 14.3%; HDL-c 9.0% and 13.9%, respectively; pooled phase III data) (Figure 1). Percentage changes from baseline to month 3 or month 6 in LDL-c and HDL-c appeared to be greater with the 10 mg BID dose than the 5 mg BID dose. Similar mean percentage changes from baseline were also seen for total cholesterol and triglycerides at both time points (3 months: total cholesterol 8.5% and 12.1%; triglycerides 9.3% and 16.8%; 6 months: total cholesterol 8.2% and 13.7%; triglycerides 6.6% and 20.4%, respectively). No meaningful changes were observed in lipid ratios (3 months: LDL-c:HDL-c 2.2 and 2.3; total cholesterol:HDL-c 3.9 and 3.9; 6 months: LDL-c:HDL-c 2.3 and 2.3; total

cholesterol:HDL-c 3.9 and 3.9 for tofacitinib 5 mg and 10 mg BID, respectively) (Figure 2).

Treatment with tofacitinib 5 mg and 10 mg BID provided a significant least squares mean reduction in CRP levels from baseline versus placebo as early as week 2 (tofacitinib 5 mg –6.3 mg/liter; tofacitinib 10 mg –7.0 mg/liter; both $P < 0.001$ versus placebo [0.2 mg/liter]; pooled phase III data). Significant reductions from baseline in CRP level were also reported for both doses of tofacitinib versus placebo at month 3 (tofacitinib 5 mg –5.1 mg/liter; tofacitinib 10 mg –5.8 mg/liter; both $P < 0.001$ versus placebo [0.4 mg/liter]), and reductions were maintained to month 6 (tofacitinib 5 mg –6.4 mg/liter; tofacitinib 10 mg –8.3 mg/liter; no placebo comparison at month 6) (Figure 3). There was no dose response to tofacitinib treatment in terms of mean systolic and diastolic blood pressure over 24 months (pooled phase III and LTE data); neither dose of tofacitinib was associated with meaningful changes from baseline (Figure 4).
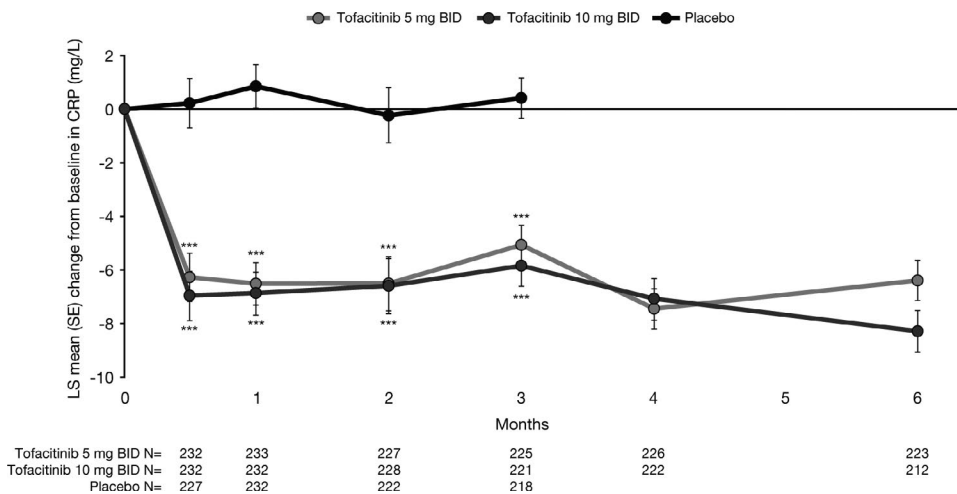
Figure 3. Least squares (LS) mean change from baseline in C-reactive protein (CRP) level over time (pooled phase III data). Two separate analyses were performed. A mixed model for repeated measures (MMRM) was used to generate results with data from week 2 to month 3, as well as results from week 2 to month 6. Each analysis was based on an MMRM with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location, study, and baseline value; an unstructured covariance matrix was used. BID = twice daily; N = number of patients with value at the given time point; *** = $P < 0.001$ versus placebo.
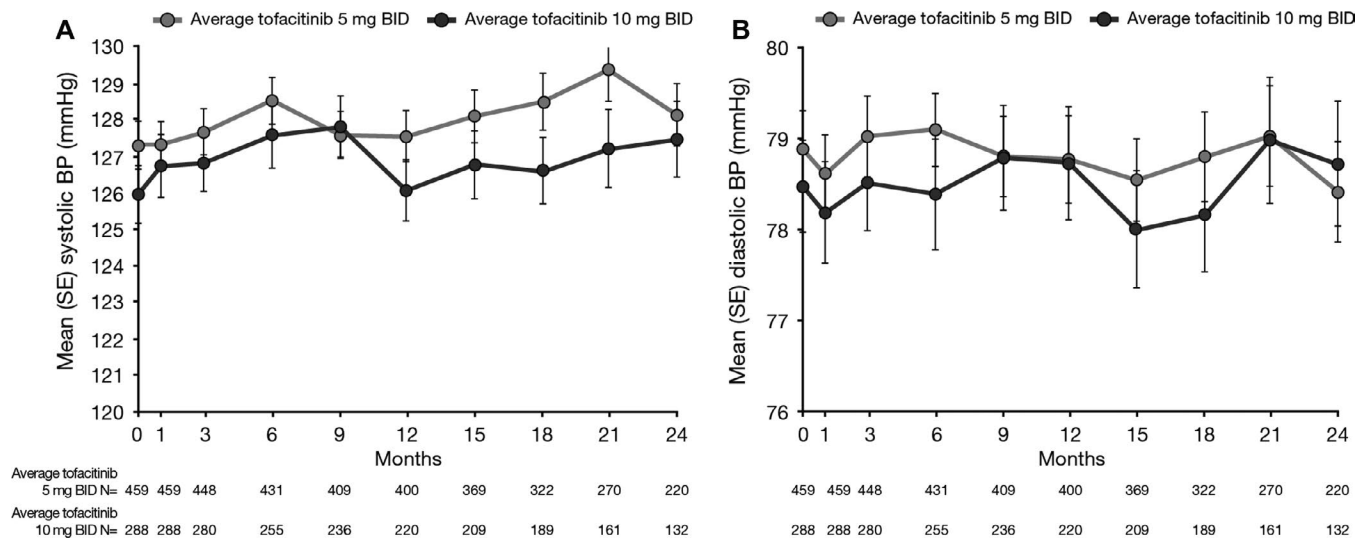
Figure 4. **A**, Mean systolic, and **B**, mean diastolic sitting blood pressure (BP) over 24 months (pooled phase III and long-term extension data). Includes all tofacitinib-exposed patients who had both a baseline and ≥1 postbaseline observation; baseline values are from the OPAL Broaden and OPAL Beyond studies. Average tofacitinib 5 mg twice daily (BID) comprised patients with an average total daily dose of <15 mg from day 1 using tofacitinib. Average tofacitinib 10 mg BID comprised patients with an average total daily dose of ≥15 mg from day 1 using tofacitinib. N = number of patients with value at the given time point.

Across the phase III and LTE studies, 58 patients with hypertension-related AEs (including the terms hypertension, high blood pressure, and increased blood pressure) were reported and none were fatal (Table 2). Of these, 2 hypertension events led to patient discontinuation (both receiving tofacitinib 5 mg). A further 2 events were classified as serious AEs (one each receiving tofacitinib 5 mg and 10 mg at the time of the event). When comparing doses, the IRs of hypertension events were similar between those patients receiving an average dose of tofacitinib 5 mg BID and those receiving 10 mg BID.

Table 2. Patients with hypertension-related AEs and treatment-emergent adjudicated MACE (pooled phase III and LTE data)*

	Pooled phase III data (0–3 months)			Pooled phase III and LTE data		
	Tofacitinib 5 mg BID (n = 238)	Tofacitinib 10 mg BID (n = 236)	Placebo (n = 236)	Average tofacitinib 5 mg BID (n = 482)	Average tofacitinib 10 mg BID (n = 301)	All tofacitinib (n = 783)
Total hypertension-related AEs, no. (%)	5 (2.1)	6 (2.5)	5 (2.1)	36 (7.5)	22 (7.3)	58 (7.4)
Exposure, PYs†	54.0	53.3	52.8	758.3	447.9	1,206.1
Total hypertension-related AEs‡	9.26 (3.01–21.61)	11.26 (4.13–24.50)	9.48 (3.08–22.12)	4.75 (3.33–6.57)	4.91 (3.08–7.44)	4.81 (3.65–6.22)
Total MACE, no. (%)	0	0	0	2 (0.4)	1 (0.3)	3 (0.4)
Ischemic stroke	0	0	0	0	1 (0.3)	1 (0.1)
Myocardial infarction	0	0	0	1 (0.2)	0	1 (0.1)
Sudden cardiac death§	0	0	0	1 (0.2)	0	1 (0.1)
Exposure, PYs†	54.6	54.4	53.7	788.6	469.8	1,258.44
Total MACE¶	0 (0–6.75)	0 (0–6.78)	0 (0–6.87)	0.25 (0.03–0.92)	0.21 (0.01–1.19)	0.24 (0.05–0.70)

* Values are the incidence rate (95% confidence interval) unless indicated otherwise. Hypertension-related adverse events (AEs; including the terms hypertension, high blood pressure, and increased blood pressure) were defined using a Standardized Medical Dictionary for Regulatory Activities query (version 19.1). All causalities included all defined events regardless of treatment relatedness. MACE = major adverse cardiovascular event; LTE = long-term extension; BID = twice daily; PYs = patient-years.
† PY exposure was the time to the day of the first hypertension-related AE, subject to an observation period of 28 days beyond the last dose or to the data cutoff date.
‡ Defined as the number of patients with events per 100 PYs.
§ Two additional events in the pooled phase III and LTE population, both in patients receiving tofacitinib 5 mg, were reported beyond the observation period and were not included in the incidence rate calculation.
¶ Defined as the number of patients with events per 100 PYs. Two additional events in the pooled phase III and LTE population, both in patients receiving tofacitinib 5 mg, were reported beyond the observation period and were not included in the incidence rate calculation.

In total, 5 patients (0.6%) experienced a MACE across the phase III and LTE studies (Table 2), of which 2 were fatal (both adjudicated to be unrelated to treatment) and 3 were non-fatal. In 2 patients, MACE (1 fatal and 1 nonfatal) were outside the 28-day observation period and were therefore not included in the IR calculation. The overall IR for MACE events, excluding the 2 patients where the event took place beyond the 28-day observation period, was 0.24 (95% CI 0.05–0.70) patients with events per 100 PYs. No patients had congestive heart failure. Further details of the fatal and nonfatal MACE can be found in Supplementary Appendix 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23930/abstract.

DISCUSSION

In the OPAL Broaden and OPAL Beyond phase III studies in patients with active PsA, dose-dependent increases in lipid levels of 10–15% were observed following treatment with tofacitinib 5 and 10 mg BID at month 3, with no appreciable further changes at month 6. HDL-c increased concurrently with other lipids, and no meaningful changes in LDL-c: HDL-c or total cholesterol:HDL-c ratios were observed. These changes are consistent with observations of lipid levels in other tofacitinib studies in patients with RA and psoriasis (21–24). Furthermore, both tofacitinib 5 and 10 mg BID provided significant and consistent reductions in CRP level from baseline compared with placebo over 3 months, and the proportion of patients reporting hypertension, as defined by the MedDRA Hypertension Standardized MedDRA Query, was similar between treatment groups, with comparable IRs. Although the risk of CVD and cardiometabolic disorders is higher in patients with PsA compared with the general population (2,3,25), and as lipid ratios, CRP levels, and blood pressure/hypertension are known CVD risk factors (26–28), taken together, this analysis showed no further increase in CVD risk following treatment with tofacitinib 5 or 10 mg BID. This conclusion is consistent with the observed IR of MACE, which was found to be generally consistent with that seen in a population-based longitudinal study of PsA (IR 0.57) (29), and in those patients receiving either secukinumab (IR 0.6) (30) or ustekinumab (IR 1.23) (31) for the treatment of PsA or psoriasis. In addition, IRs were similar to those observed in patients who received tofacitinib treatment in pooled analyses of patients with RA (IR range 0.19–0.58) (21,24) and psoriasis (IR 0.37) (22).

Suppression of circulating cholesterol levels in the setting of active systemic inflammation, such as in RA, has long been recognized (26,32–34). However, compared with controls, elevated LDL-c and triglycerides have been observed (35) in PsA, with rates of hypertriglyceridemia and metabolic syndrome higher in patients with PsA than in patients with RA (36). Dyslipidemia in PsA is possibly a consequence of skin and joint inflammation in

PsA associated with elevations of inflammatory cytokines such as TNF and interleukin-6 (37), which can induce hepatic synthesis of CRP (2). Other factors, such as obesity and diet, may also be involved. The insidious onset of PsA may also mean that patients with PsA are exposed to active disease for longer than patients with other inflammatory diseases, putting them at greater risk for lipid changes (36). In addition, the burden of systemic inflammation, along with oxidative stress and disease activity, have been demonstrated to play a role in increasing the risk of CVD and therefore MACE in patients with PsA (3,38). To further understand the link between lipids and CVD risk in patients with PsA, investigating nontraditional lipid risk factors such as HDL-associated paraoxonase 1 activity and HDL-associated serum amyloid A may be beneficial. Indeed, paraoxonase 1 activity has been found to be decreased in patients with PsA compared with healthy controls (38), and in patients with psoriasis, treatment with tofacitinib has been found to both increase paraoxonase 1 activity and decrease HDL-associated serum amyloid A (23).

Of note, both the US product information and European Union (EU) summary of product characteristics (SmPC) state that maximum increases in lipid parameters, including total cholesterol, LDL-c, and HDL-c, were generally observed within 6 weeks of treatment initiation. Furthermore, both the product information and SmPC recommend that lipid parameters should be assessed 8 weeks after starting treatment (and approximately 4–8 weeks thereafter in the US, or 8 weeks in the EU), and that patients should be managed according to clinical guidelines (39,40). Increases in total cholesterol and LDL-c associated with tofacitinib may be reduced to pretreatment levels with statin therapy (41).

Limitations of this analysis include the fact that comparisons with placebo were limited to the 3-month placebo-controlled portion of the phase III studies, and thus the overall extent and length of exposure to placebo was less than to tofacitinib. However, since the differences in lipid changes between 3 months and 6 months were minimal, the 3-month placebo-controlled period appears to be a sufficient duration for lipid evaluation. In addition, the evaluation of MACE and hypertension events over time was limited by the sample size and extent of exposure, and consequently, due to the long latency period of MACE, a study of this length may not provide sufficient data. However, when compared with the larger RA and psoriasis data sets of pooled data from randomized trials and LTE studies (6,300 patients with 21,886 PYs of exposure for RA [data cutoff April 4, 2016; database not locked, data may change]); 3,662 patients with 8,537 PYs of exposure for psoriasis [data cutoff May 10, 2016; database not locked, data may change]), the IRs were comparable. Furthermore, in a prospective, observational 5-year study, embedded within the US Corrona RA registry of patients with RA, rates of CVD, which included MACE as part of the definition, were comparable between patients initiating tofacitinib and patients initiating biologic DMARDs (42). Finally, caution should be applied when comparing studies due to different population

characteristics, capture and definition of events, and few events of interest in the PsA tofacitinib development program.

In patients with PsA, the magnitude and dose dependency of increases in lipid levels to month 6 were consistent with findings in tofacitinib studies in patients with RA and psoriasis. Because increases in LDL-c were paralleled by increases in HDL-c, no meaningful changes in total cholesterol:HDL-c ratio were observed. In addition, rates of hypertension were not affected by treatment dose, CRP levels decreased, and the incidence of MACE was low and similar to other PsA therapies. Of note, the incidence of MACE in patients with active PsA was within the range reported in prior tofacitinib studies in RA and psoriasis (21–24) and was generally consistent with data reported in the literature for other PsA treatments (29–31). In conclusion, there is no evidence at this time that treatment of PsA with tofacitinib is associated with increased CVD risk; however, longer-term follow-up is needed and is ongoing. Low numbers of patients with hypertension-related AEs and MACE were noted.

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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 submitted for publication. Dr. Gladman 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. Gladman, McInnes, Veale, Nurmohamed, Graham, Wang, Jones, DeMasi.

Acquisition of data. Veale.

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ROLE OF THE STUDY SPONSOR

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