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Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor☆,☆☆

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ABSTRACT

Objectives: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The implications of treatment with tofacitinib on cardiovascular (CV) risk in RA are unknown. Therefore, CV adverse events (AEs), and blood pressure and lipid level changes, in tofacitinib-treated patients with RA were evaluated.

Methods: Data were pooled from six Phase (P)3 studies (24 months) and two open-label long-term extension (LTE) studies (60 months) of tofacitinib in patients with RA and inadequate response to DMARDs. Tofacitinib was administered alone or with non-biologic DMARDs. CV events, including major adverse CV events (MACE: CV death and non-fatal CV events) and congestive heart failure (CHF), were assessed by a blinded adjudication committee.

Results: Overall, 4271 patients from P3 studies and 4827 enrolled from P2/P3 studies into LTE studies were evaluated, representing 3942 and 8699 patient-years of exposure to tofacitinib, respectively. Blood pressure remained stable over time across studies. The number of investigator-reported hypertension-related AEs in tofacitinib-treated patients was low in P3 studies (Months 0–3: 2.8%; Months 3–6: 1.4%; > 6 months: 2.8%). Across studies, lipid level increases were generally observed within 1–3 months of treatment and stabilized thereafter. Patients with events [incidence rate (IR)/100 patient-years) for MACE and CHF, respectively, were: 23 (0.58) and 9 (0.23) in P3 studies, and 32 (0.37) and 8 (0.09) in LTE studies; IRs were comparable with placebo (P3) and did not increase over time (LTE).

Conclusions: Tofacitinib was associated with a low incidence of CV events in a large Phase 3 program, including LTE studies. Further long-term studies are underway.

Abbreviations: AE, adverse event; ACR, American College of Rheumatology; Apo, apolipoprotein; BID, twice daily; BP, blood pressure; CHF, congestive heart failure; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DBP, diastolic blood pressure; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; IR, inadequate response; LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; MACE, major adverse cardiovascular events; MI, myocardial infarction; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; pt-yrs, patient-years; q2w, once every 2 weeks; RA, rheumatoid arthritis; RCT, randomized controlled trial; SAE, serious adverse event; SBP, systolic blood pressure; sc, subcutaneously; SD, standard deviation; TC, total cholesterol; TDD, total daily dose; TNFi, tumor necrosis factor inhibitor.

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Introduction

Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular (CV) disease and CV-related death compared with the general population [1–3]. CV events are reported to occur approximately a decade earlier in patients with RA compared with the general population [4,5], suggesting that RA is an independent risk factor for premature heart disease [2,6]. CV disease risk in older patients ($\geq$ 75 years) with RA was reported to be more than three-fold the Framingham-predicted risk for the general population [7], and female patients with RA have demonstrated a two-fold higher risk of myocardial infarction (MI) compared with female patients without RA [8].

The increased risk of CV disease in patients with RA appears to be linked to coronary atherosclerosis [9,10]. Studies have also suggested that the increased risk is not driven by traditional CV risk factors alone [6,11–13], and RA-associated inflammation and disease activity play a pivotal role [14,15]. The relationship between lipid levels, RA treatment, and CV risk in patients with RA is complex. Indeed, although the evidence is inconclusive, some data indicate that effective management of RA with disease-modifying anti-rheumatic drugs (DMARDs) is associated with a reduced risk of CV events, most likely due to inhibitory effects on inflammatory pathways [16,17].

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib has demonstrated efficacy and safety in patients with RA at doses of 5 and 10 mg twice daily (BID) in Phase 2 [18–22] and Phase 3 randomized controlled trials (RCTs) of up to 24 months' duration [23–28] and in long-term extension (LTE) studies with up to 72 months of observation [29,30].

During the Phase 2 studies, increases in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were observed in patients with active RA receiving treatment with tofacitinib [18,19,21,22,31]. Consequently, Phase 3 and LTE studies included adjudication of potential CV events and deaths.

The purpose of the current analysis was to evaluate the CV event rates and changes in blood pressure (BP) and lipid levels from pooled Phase 3 and open-label LTE studies of tofacitinib in patients with moderate to severe active RA.

Methods

Study design and treatment

The six double-blind, Phase 3 RCTs included in this analysis were of 6–24 months' duration, and pooled in a single data set (Table 1). Pooling was justified by the similarity of demographic and baseline disease characteristics of patients across the studies. The two open-label LTE studies (A3921024 [NCT00413699] and A3921041 [NCT00661661]) [29] (Table 1) enrolled eligible patients from two Phase 1, nine Phase 2, and six Phase 3 index studies of tofacitinib. Details on individual study designs have been published previously [23–28] and are summarized in Table 1. In all studies, patients were permitted to receive treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and oral glucocorticoids, that is, $\leq$ 10 mg/day prednisone or equivalent, consistent with rheumatology practice worldwide. Dosing of tofacitinib and background DMARD therapy was required to be stable in Phase 1, Phase 2, and 3 studies. In the LTE studies, dose adjustments of tofacitinib and background DMARD therapy were permitted based on the investigator's assessment of efficacy and safety. For the purpose of the current analysis, the average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of $<$ 15 mg/day and $\geq$ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.

All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. All patients provided written, informed consent. The final protocols, amendments and informed consent documentation were reviewed and approved by the Institutional Review Board and/or Independent Ethics Committee of each investigational site.

Patients

In Phase 3 studies, eligible patients aged $\geq$ 18 years with active moderate to severe RA were enrolled globally from North America, Europe, Latin America, Asia, and Australia. Patients eligible for enrollment in the LTE studies were aged $\geq$ 18 years (A3921024) or $\geq$ 20 years (A3921041). Key inclusion criteria are detailed in Table 1. Key exclusion criteria included: current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, metabolic, pulmonary, cardiac, or neurological disease; or a 12-lead electrocardiogram at screening that demonstrated clinically relevant abnormalities that might have affected patient safety or interpretation of the study results. The screening visit included an evaluation of vital signs, including blood pressure and heart rate, and fasting lipid profiles.

Cardiovascular events

Adjudicated major adverse CV events (MACE) and congestive heart failure (CHF) events were categorized and incidence rates calculated. The endpoint of MACE was defined as the composite of the following events: CV mortality (including coronary, cerebrovascular, cardiac, and non-cardiac vascular events), and non-fatal CV events (including MI and cerebrovascular events).

Measurement of lipid levels

Total cholesterol (TC), HDL-C, and triglyceride levels (fasting) were assayed using conventional analytical techniques in all studies. LDL-C levels were calculated using the Friedewald formula [32]. When triglyceride levels were $\geq$ 400 mg/dL, LDL-C was measured directly by ultracentrifugation. Plasma concentrations of apolipoprotein (Apo) A-1 and Apo B-100 were measured using immunophelometry.

Blood pressure and hypertension

For all studies, BP measurements were obtained at the screening, all study visits, and at follow-up, and were recorded to the nearest mmHg in the dominant arm after the patient had rested for $\geq$ 5 minutes. For recorded BP measurements, hypertension was defined using criteria specified in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [33]. By contrast, adverse events (AEs) related to hypertension were identified and reported by the investigators, then coded to preferred terms using MedDRA.

Statistical analyses

Data are reported through Month 24 for Phase 3 studies and through 60 months of observation for LTE studies. All data captured up to and including 10 April 2013 are included in this analysis. For Phase 3 studies, data are presented by Months 0–3 (placebo comparison phase), Months 3–6 (placebo advancement phase), and $>$ 6 months (tofacitinib-only phase). Data collection and analyses for LTE studies were still ongoing at the time of the