Effects of tofacitinib on cardiovascular risk factors and cardiovascular outcomes based on phase III and long-term extension data in patients with plaque psoriasis

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Background: Psoriasis is a systemic inflammatory condition that is associated with a higher risk of cardiovascular (CV) disease. Tofacitinib is being investigated as a treatment for psoriasis.

Objective: We sought to evaluate the effects of tofacitinib on CV risk factors and major adverse CV events (MACEs) in patients with plaque psoriasis.

Methods: Changes in select CV risk factors and the incidence rate (IR) of MACEs were evaluated in patients who were treated with tofacitinib.

Results: Tofacitinib treatment was associated with small, dose-dependent increases in total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, while the total/HDL cholesterol ratio was unchanged. There were no changes in blood pressure and glycated hemoglobin levels; C-reactive protein levels decreased. The IRs of a MACE were low and similar for both tofacitinib doses. Among 3623 subjects treated with tofacitinib, the total patient-years of exposure was 5204, with a median follow-up of 527 days, and the IR of MACEs was 0.37 (95% confidence interval, 0.22-0.57) patients with events per 100 patient-years.

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Limitations: There was relatively short follow-up time for patients who had MACEs.

Conclusions: While treatment with tofacitinib is associated with a small increase in cholesterol levels, the total/HDL cholesterol ratio does not change, there are no unfavorable changes in several CV risk factors, and the incidence of MACEs is low. (J Am Acad Dermatol 2016;75:897-905.)

Key words: cardiovascular outcomes; cardiovascular risk factors; major adverse cardiovascular events psoriasis; tofacitinib.

CAPSULE SUMMARY

- Tofacitinib is approved for the treatment of rheumatoid arthritis and is being investigated for the treatment of patients with moderate to severe plaque psoriasis.
- Lipid levels increased, but the total/high-density lipoprotein cholesterol and triglyceride/high-density lipoprotein cholesterol ratios did not change with tofacitinib treatment.
- The incidence of adverse cardiovascular events was not increased.

Psoriasis is a systemic inflammatory disease that affects 2% to 3% of the world's population.[1] Patients with severe disease are at increased risk for metabolic[2-7] and cardiovascular (CV) diseases.[2,4,8-14]

Tofacitinib is an oral Janus kinase inhibitor that is approved for the treatment of rheumatoid arthritis (RA)[15-17] and is also being investigated for the treatment of moderate to severe plaque psoriasis.[18-20] Lipid elevations, including increases in plasma levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, have been reported with tofacitinib treatment in patients with RA.[21] Data suggest that patients with active RA may have lower cholesterol levels because of an increase in cholesterol ester catabolism, and that tofacitinib treatment reduces cholesterol ester catabolism and thereby increases cholesterol to levels seen in healthy volunteers.[21]

Similar changes in cholesterol levels have been recently reported in phase II and III studies of tofacitinib in patients with plaque psoriasis.[18,22] These effects were dose-dependent and reversible upon drug discontinuation. Psoriasis itself is associated with dyslipidemia[23] and higher CV risk, and therefore it is important to better understand the effects of tofacitinib on CV risk factors in patients with psoriasis. We evaluated the effects of tofacitinib on lipid parameters, other clinically important CV risk factors, and on CV outcome in patients with plaque psoriasis who were enrolled in the tofacitinib phase II and III psoriasis studies.

METHODS

Subjects

Eligible patients with moderate to severe plaque psoriasis were enrolled in a phase II dose-ranging trial and 4 phase III trials for the assessment of tofacitinib therapy in the treatment of psoriasis. The patient entry criteria are described elsewhere.[18-20,22] In short, for phase III studies, patients were required to be ≥18 years of age, have had a diagnosis of plaque-type psoriasis for ≥12 months before the first study drug dose, have a Psoriasis Area and Severity Index score ≥12, have a Physician's Global Assessment of "moderate" or "severe," and have ≥10% of their body surface area affected by psoriasis.

Study design

All trials were conducted in compliance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines and were approved by the institutional review boards or independent ethics committees at each investigational center.

The study designs and dosing regimens for the Oral Treatment Psoriasis Trial (OPT) program (eg, OPT Pivotal 1 [NCT01276639], OPT Pivotal 2 [NCT01309737], OPT Compare [NCT01241591], and OPT Retreatment [NCT01186744] and the phase II dose ranging study [NCT00678210]) are described elsewhere.[18-20,22] The phase II trial investigated tofacitinib in doses of 2, 5, and 15 mg twice daily (BID) for 12 weeks. The phase III trials investigated 2 doses of tofacitinib (5 and 10 mg BID); OPT Pivotal 1 and OPT Pivotal 2 compared 5 and 10 mg doses BID versus placebo (16 weeks) followed by 36 weeks of blinded tofacitinib 5 and 10 mg BID; and OPT Compare assessed tofacitinib 5 and 10 mg BID versus placebo versus etanercept 50 mg twice weekly (12 weeks). OPT Retreatment assessed tofacitinib 5 and 10 mg BID for 24 weeks followed by variable duration withdrawal (4-16 weeks) and retreatment. The long-term extension (LTE) trial was available to patients who participated in 1 of the qualifying studies. Once patients enrolled into the LTE trial,