Major cardiovascular adverse events by baseline cardiovascular risk stratification in patients with ulcerative colitis treated with tofacitinib: data from the OCTAVE clinical program

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Introduction

- Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of UC
- The risk of ASCVD in the general population increases with age.[1] In comparison with the general population, patients with IBD have an increased risk of ASCVD[2,3]
- A higher risk of adjudicated MACE with tofacitinib vs TNFi was observed in ORAL Surveillance (NCT02092467), an open-label, randomized, prospective, post-authorization safety study in patients aged ≥50 years with RA and ≥1 additional CV risk factor (IR 0.98 with all tofacitinib doses vs IR 0.73 with TNFi)[4]

Objective

- To evaluate the occurrence of MACE stratified by baseline (BL; first tofacitinib exposure) CV risk in the tofacitinib UC OCTAVE clinical program

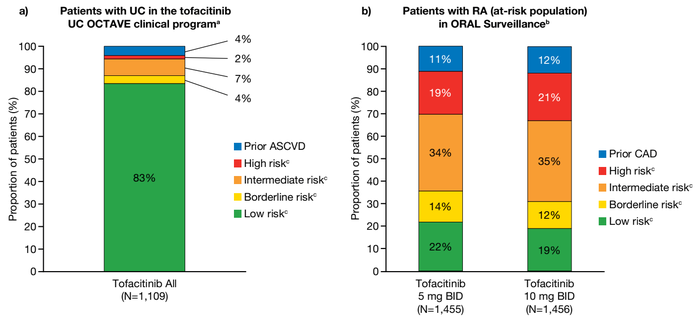
Methods

- In total, 1,157 patients (median treatment duration 623 [range 1–2,850] days; 2,814.4 PY of exposure) who received ≥1 dose of tofacitinib 5 or 10 mg BID in a Phase 2 induction study (NCT00787202) and Phase 3 studies (OCTAVE Induction 1 and 2 [NCT01465763; NCT01458951], OCTAVE Sustain [NCT01458574], and OCTAVE Open [NCT01470612]) were included
- Proportions and IRs of adjudicated MACE were stratified by BL CV risk profile:
  - Firstly, patients were categorized by prior history of ASCVD, defined as a history of any CAD (including MI), cerebrovascular disease (including stroke), or peripheral artery disease
  - Secondly, patients without prior ASCVD were categorized by 10-year ASCVD risk score using the ASCVD-PCE risk calculator recommended by the ACC (risk score categories: high ≥20%; intermediate ≥7.5–<20%; borderline ≥5–<7.5%; low <5%)[5]

Results

- In comparison to ORAL Surveillance, only very few patients in the tofacitinib UC OCTAVE clinical program had a high ASCVD BL risk (**Figure 1**)
- MACE IRs were numerically lower in patients with a low/borderline risk of ASCVD vs patients with a high/intermediate risk and were generally numerically lower in the overall cohort of patients in the tofacitinib UC OCTAVE clinical program vs ORAL Surveillance[6] (**Figure 2**)
- Eight patients had an adjudicated MACE (Table), and the majority occurred in patients with intermediate/high ASCVD risk (**Figure 3**):
  - One event (2.5%) occurred among 40 patients with prior ASCVD
  - Five events (5.2%) occurred among 97 patients from intermediate/high BL ASCVD risk categories
  - Two events (0.2%) occurred among 901 patients from the low BL ASCVD risk category

Figure 1. Low proportions of patients in a) the tofacitinib UC clinical program with high/intermediate risk, compared with b) ORAL Surveillance in each baseline cardiovascular risk category



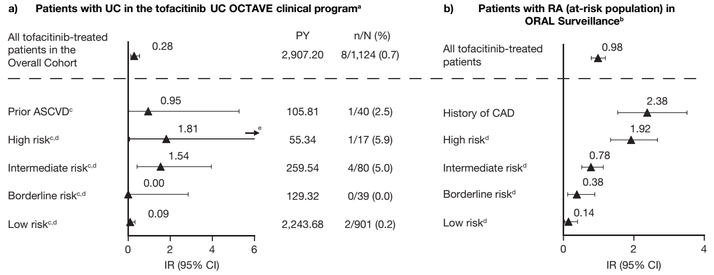
[a]Patients without a prior ASCVD were categorized according to their 10-year risk of ASCVD; BL was defined as first tofacitinib exposure; includes data for patients with prior ASCVD or patients for which BL CV risk could be determined who received ≥1 dose of tofacitinib 5 mg or 10 mg BID (N=1,109); BL CV risk was missing in 48 patients due to missing components; [b]Post-authorization safety study in patients with RA aged ≥50 years with ≥1 additional CV risk factor (current cigarette smoker, hypertension, HDL-c <40 mg/dL, diabetes mellitus, family history of premature CHD, extra-articular RA, or history of CAD); patients without a history of CAD were categorized according to their 10-year risk of ASCVD; data were missing from 17 and 19 patients in the tofacitinib 5 mg BID and tofacitinib 10 mg BID treatment groups, respectively; [c]Risk score categories: high ≥20%; intermediate ≥7.5–<20%; borderline ≥5–<7.5%; low <5%

Table. Demographics and baseline characteristics of patients with MACE in the tofacitinib UC OCTAVE clinical program

MACE / Adjudicated event Preferred Term	Induction BL age, (years); Sex	Day of onset;[a] PD tofacitinib[b]	Average partial Mayo score; Average total Mayo score	Smoking status	Relevant medical history (eg, diabetes, hypertension; Yes / No)[c]	Relevant medication history (eg, aspirin, statins; Yes / No)[d]	Elevated serum lipids at BL; Last recorded[e]
MI / Acute coronary syndrome	66; Male	28;[f] 5 mg BID	4.0; 8.0	Ex-smoker	Yes	Yes	HDL-c; None[j]
MI / Acute MI	64; Male	1,540;[g] 5 mg BID	1.6; 3.2	Never smoker	No	Yes	None; None[j]
MI / MI	74; Male	142;[h] 5 mg BID	1.2; 5.5	Ex-smoker	Yes	Yes	None; None[k]
CV death / Aortic dissection	39; Male	31;[f] 10 mg BID	5.0; 9.0	Never smoker	No	No	TC, LDL-c; NR[l]
CV death / Cardiac arrest	67; Male	1,725;[g] 10 mg BID	0.7; 3.1	Ex-smoker	Yes	Yes	None; TC[m]
Stroke / Hemorrhagic stroke	55; Female	148;[h] 10 mg BID	3.4; 7.5	Never smoker	Yes	Yes	None; TC[n]
Stroke / Cerebrovascular accident	56; Male	857;[g] 10 mg BID	1.4; 4.3	Current smoker	Yes	Yes	TC, TG, LDL-c; TG[o]
Stroke / Cerebellar hemorrhage	55; Male	1438;[g] 5 mg BID	0.8; 2.3	Never smoker	Yes	Yes	TC, LDL-c; TC, LDL-c[p]

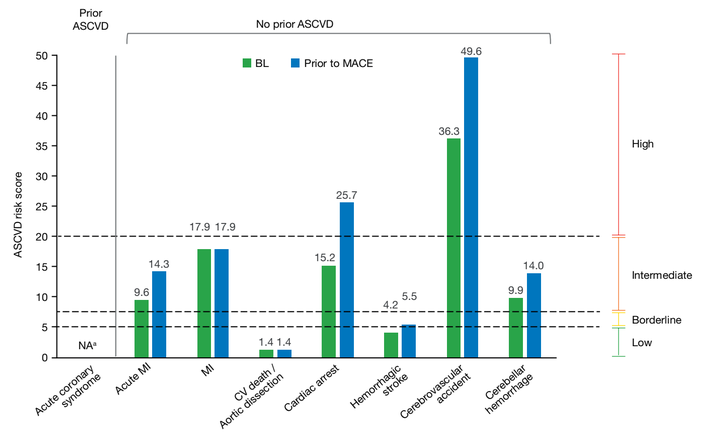
[a]Study onset day in relation to first day of tofacitinib exposure; [b]Patients were categorized based on the average daily dose of tofacitinib (placebo exposure was not included): PD tofacitinib 5 mg BID (average total daily dose <15 mg) and PD tofacitinib 10 mg BID (average total daily dose ≥15 mg); [c]Includes angina pectoris, arrhythmia, deep vein thrombosis, diabetesmellitus,dyslipidemia, hypercholesterolemia, hypertension, left ventricular hypertrophy, myocardial infarction, or pulmonary embolism; [d]Includes aspirin, amlodipine, atorvastatin, enalapril, glimepiride, metformin, perindopril, rosuvastatin, simvastatin, verapamil, or warfarin; [e]Measurement is from the last recorded study timepoint. Reference ranges: TC, 130–200 mg/dL; TG, 45–250 mg/dL; HDL-c, 40–80 mg/dL; LDL-c, 0–130 mg/dL; [f]Event onset during OCTAVE Induction 1 or 2; [g]Event onset during OCTAVE Open; [h]Event onset during OCTAVE Sustain; [i]BL values for this patient were TC: 192, HDL-c: 112, LDL-c: 59, TG: 105; LR study timepoint values were TC: 151, HDL-c: 65, LDL-c: 70, TG: 82; [j]BL values for this patient were TC: 167, HDL-c: 59, LDL-c: 92, TG: 80; LR study timepoint values were TC: 151, HDL-c: 51, LDL-c: 82, TG: 88; [k]BL values for this patient were TC: 161, HDL-c: 63, LDL-c: 71, TG: 134; LR study timepoint values were TC: 172, HDL-c: 44, LDL-c: 96, TG: 159; [l]BL values for this patient were TC: 309, HDL-c: 80, LDL-c: 189, TG: 194; serum levels were not assessed at LR study timepoint for this patient; [m]BL values for this patient were TC: 172, HDL-c: 39, LDL-c: 103, TG: 150; LR study timepoint values were TC: 214, HDL-c: 54, LDL-c: 128, TG: 159; [n]BL values for this patient were TC: 183, HDL-c: 63, LDL-c: 94, TG: 132; LR study timepoint values were TC: 205, HDL-c: 71, LDL-c: 111, TG: 117; [o]BL values for this patient were TC: 230, HDL-c: 39, LDL-c: 132, TG: 297; LR study timepoint values were TC: 181, HDL-c: 56, LDL-c: 73, TG: 258; [p]BL values for this patient were TC: 216, HDL-c: 34, LDL-c: 150, TG: 161; LR study timepoint values were TC: 282, HDL-c: 51, LDL-c: 191, TG: 194

Figure 2. Incidence rates of MACE in a) the tofacitinib UC clinical program and b) ORAL Surveillance, stratified by baseline cardiovascular risk category



Analyses were performed for all patients receiving ≥1 dose of tofacitinib 5 or 10 mg BID in either the UC clinical program (Overall Cohort) or ORAL Surveillance; [a]Events that occurred >28 days after the last dose of study drug were excluded. Patients without prior ASCVD were categorized according to their 10-year risk of ASCVD, per the ASCVD-PCE risk calculator (as recommended by the ACC); includes patients with prior ASCVD and patients for which BL CV risk could be determined; [b]Post-authorization safety study in patients with RA aged ≥50 years with ≥1 additional CV risk factor; patients without a history of CAD were categorized according to their 10-year risk of ASCVD; [c]Excludes data from the Phase 2 study, therefore N=1,077; [d]Risk score categories: high ≥20%; intermediate ≥7.5–<20%; borderline ≥5–<7.5%; low <5%; [e]Upper CI value: 10.07

Figure 3. ASCVD risk scores at baseline and prior to MACE for patients with MACE in the tofacitinib UC OCTAVE clinical program



ASCVD risk scores at BL and prior to MACE in 8 patients with MACE. Risk score categories: high ≥20%; intermediate ≥7.5–<20%; borderline ≥5–<7.5%; low <5%; [a]ASCVD risk scores were not calculated as this patient had prior ASCVD

Limitations

- Interpretation of these post hoc analyses was limited by the small sample size in several ASCVD subgroups, the low number of MACE, and short median treatment duration in respect to assessment of long-latency events
- Prior history of CV disease was defined differently in the UC OCTAVE clinical program and RA ORAL Surveillance (history of ASCVD and history of CAD, respectively)
- Clinically relevant abnormalities detected by ECG were included as exclusion criteria for all studies included in this analysis
- The ASCVD-PCE tool is recommended to assess 10-year ASCVD risk in individuals aged 40–75 years who are being evaluated for CV disease prevention

Conclusions

- **The overall occurrence of MACE was infrequent in the tofacitinib UC OCTAVE clinical program**
- **In contrast to ORAL Surveillance, most patients had a low risk of ASCVD, which suggests it is important to consider the background risk of the patient population when treating patients with tofacitinib**
- **This analysis shows a potential association between baseline CV risk and MACE incidence in patients with UC receiving tofacitinib, emphasizing the importance of continuously assessing and addressing CV risk profiles when treating patients with UC**

Abbreviations

ACC, American College of Cardiology; **ASCVD**, atherosclerotic CV disease; **ASCVD-PCE**, ASCVD Pooled Cohort Equations; **BID**, twice daily; **BL**, baseline; **CAD**, coronary artery disease; **CHD**, coronary heart disease; **CI**, confidence interval; **CV**, cardiovascular; **ECG**, electrocardiogram; **HDL-c**, high-density lipoprotein-cholesterol; **IBD**, inflammatory bowel disease; **IR**, incidence rate (unique patients with events per 100 PY of exposure); **LDL-c**, low-density lipoprotein-cholesterol; **LR**, last recorded; **MACE**, major adverse CV events; **MI**, myocardial infarction; **N**, total number of patients; **n**, number of patients in each category; **NA**, not applicable; **NR**, not reported; **PD**, predominant dose; **PY**, patient-years; **RA**, rheumatoid arthritis; **TC**, total cholesterol; **TNFi**, tumor necrosis factor inhibitor; **TG**, triglycerides; **UC**, ulcerative colitis.

References

1. Arnett D et al. Circulation 2019; 140: e59-e646.
2. Cainzos-Achirica M et al. J Am Coll Cardiol 2020; 76: 2895-2905.
3. Agrawal T et al. AM J Prev Cardiol 2021; 6: 100171.
4. Ytterberg SR et al. N Engl J Med 2022; 386: 316-326.
5. American College of Cardiology, American Heart Association. ASCVD Risk Estimator. Available at: https://tools.acc.org/ldl-ascvd_risk_estimator/index.html#!/calculate/estimator/estimator. Accessed August 01, 2022.
6. Buch MH et al. Ann Rheum Dis 2022; 81 (Suppl 1): Abstract 1182.
7. DeTora LM et al. Ann Intern Med 2022; 175: 1298-1304.

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