Abstract: P1930

Pharmacodynamic effects of vorapaxar as an add-on antiplatelet therapy in patients with and without diabetes mellitus: the optimizing anti-platelet therapy in diabetes mellitus (OPTIMUS)-5 study

Authors:
F Franchi1, F Rollini1, V Kairouz1, J Rivas1, A Rivas1, M Agarwal1, M Briceno1, M Wali1, A Nawaz1, G Silva1, Z Shaikh1, D Soffer1, MM Zenni1, TA Bass1, DJ Angiolillo1, 1University of Florida College of Medicine - Jacksonville - United States of America,

Topic(s):
Antiplatelet Drugs

Citation:
The study was supported in part by an investigator initiated study grant from Merck

Background: Vorapaxar (Vora) is a protease-activated receptor (PAR)-1 inhibitor which when added to dual antiplatelet therapy (DAPT) in patients with a history of myocardial infarction (MI) or with peripheral arterial (PAD) reduces thrombotic cardiovascular events at the expense of increased bleeding. The efficacy of Vora is enhanced in patients with diabetes mellitus (DM) compared to non-DM. However, the differential pharmacodynamic (PD) effects of Vora in DM vs non-DM patients are unknown. Moreover, although withdrawal of aspirin has emerged as a strategy to reduce bleeding when adjunctive antithrombotic therapies are used, the PD effects of Vora after stopping aspirin in DAPT treated patients is unknown.

Purpose: To assess the PD effects of Vora in addition to standard DAPT as well as in combination with clopidogrel following aspirin withdrawal in patients with and without DM.

Methods: This was a prospective parallel-design PD study conducted in post-MI or PAD patients with and without DM. Patients on DAPT with aspirin (81mg/qd) and clopidogrel (75mg/qd) were divided in two groups according to DM status. Each cohort was treated with Vora (2.5mg/qd) in addition to DAPT (i.e., triple therapy) for 30 days and afterwards stopped aspirin and maintained treatment with Vora plus clopidogrel (i.e., dual therapy) for other 30 days. PD testing using 5 different assays was conducted at 3 time-points: baseline (while on DAPT); after 30 days of triple therapy; after 30 days of dual therapy. The primary endpoint was the non-inferiority of CAT (Collagen-ADP-TRAP)-induced aggregation, a marker of global platelet reactivity, of Vora plus clopidogrel (dual therapy) vs Vora plus DAPT (triple therapy).

Results: The PD population was composed of a total of 64 patients (DM, n=30; non-DM, n=34). Although adding Vora to DAPT significantly reduced CAT-induced aggregation, stopping aspirin was associated with an increase in CAT-induced aggregation in both DM (mean difference=12; 95%CI: 3 to 21; p=0.010) and non-DM (mean difference=10; 95%CI: 4 to 16; p=0.003), thus not meeting the primary endpoint of non-inferiority (Figure). The magnitude of such increase was higher in DM compared with non-DM (p=0.036). Although Vora abolished TRAP-induced aggregation in both DM and non-DM patients, it did not affect markers of clot kinetics including speed of thrombin generation. Aspirin withdrawal was associated with a marked increase in makers sensitive to cyclooxygenase-1 (COX-1) blockade; markers of P2Y12 signaling were higher in DM compared to not DM after aspirin withdrawal.

Conclusion: Adjunctive treatment with Vora reduces platelet-mediated thrombogenicity without affecting clot kinetics in both DM and non-DM patients while on DAPT. However, platelet-mediated thrombogenicity is increased after aspirin withdrawal, a phenomenon which is enhanced in DM patients underscoring the pivotal contribution of the COX-1 signaling pathway in these high risk patients.
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