Diplopia on vorapaxar: An unexpected side effect emerging only at second glance

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Dual antiplatelet treatment (DAPT) with the cyclooxygenase inhibitor aspirin and an adenosine diphosphate (ADP) P2Y12 receptor inhibitor represents the mainstay of pharmacological treatment in both stable coronary artery disease and acute coronary syndromes patients undergoing an invasive management by percutaneous coronary intervention (PCI) (1). However, the residual risk of recurrent ischaemic complications especially among ACS patients undergoing PCI still remains high despite contemporary treatment strategies including DAPT. Keeping this in mind, the development of novel antiplatelet agents that target new and alternative platelet receptor pathways is still of great importance.

Vorapaxar (SCH 530348, Merck) is a novel orally active competitive and selective antagonist of the platelet thrombin receptor PAR-1 that potently inhibits thrombin-induced platelet aggregation. For administration on top of standard antiplatelet therapy, the US Food and Drug Administration (FDA) approved vorapaxar for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease on May 8, 2014. On January 19, 2015, the European Medicines Agency (EMA) granted approval for the reduction of atherothrombotic events in patients with a history of MI. Of note, the two large phase III trials conducted on vorapaxar, the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) (2) and the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P-TIMI 50) (3) trials showed a modest reduction in CV death, MI and stroke for the study drug groups during long-term follow-up. However, in both trials vorapaxar treatment was associated with a significant increase in severe bleeding events, including intracranial haemorrhage. Moreover, besides the observed but also expected increase in bleeding risk due to the co-administration of vorapaxar on top of standard antiplatelet therapy, there seem to be unexpected side effects to the drug as well that merit discussion and closer investigations.

In a Viewpoint Article in this issue of Thrombosis and Haemostasis, Serebruany et al. turn our attention to excess diplopia rates associated with vorapaxar within both phase III trials (4). As pointed out by the authors, there is FDA-confirmed evidence for overall 34 vorapaxar diplopia cases in TRACER (2) (13 vorapaxar vs 2 placebo cases; p = 0.010) and TRA 2P-TIMI 50 (3) (21 vs 8 cases; p = 0.018) versus all 10 cases in the placebo arm of the respective trials (p = 0.018) (5). However, both trial publications did not mention excess diplopia in their main publications or in their supplemental material. Interestingly, the very small – and most likely underpowered – ocular sub-study in 102 TRA 2P-TIMI 50 subjects, featuring spectral domain optical coherence tomography, visual acuity, retraction and fundus photography, was neutral in this respect (6). Because of the low incidence (1 case per 1,000 treated patients) and mostly transient nature of the events, FDA authorities did not recommend the addition of diplopia to the package insert yet. The authors of this Viewpoint paper suggest off-target PAR receptor mismodulation in the eye as a possible mechanism for excess diplopia associated with vorapaxar. However, no direct evidence for such a possible causal relationship is provided. Of note, Serebruany et al. have challenged the published data on vorapaxar and other novel antiplatelet agents several times so far (7–10). Encouraging such lively discussions is vital in modern days when numerous novel (antiplatelet) drugs enter the market. Thus, the authors are to be commended for this Viewpoint paper and for raising awareness for this important, so far underreported finding associated with vorapaxar. However, in interpreting the data, some issues and important aspects merit mentioning:

First, patients included in both trials represent a high-risk atherosclerotic patient population with significant co-medication. For example, 62% of TRACER patients had known hyperlipidaemia and 91% of TRA 2P-TIMI patients were on (non-specified) lipid-lowering agents. In addition, 31.5% of TRACER patients and 25.5% of TRA 2P-TIMI patients were suffering from diabetes mellitus, without further specification of medication even in the supplemental appendices. Of note, there is a published association between diplopia and statin use, which was first described in 2008 after reviewing spontaneous reports from the National Registry of Drug-induced Ocular Side Effects (Casey Eye Institute, Oregon Health & Science University, Portland, Oregon), the WHO and the FDA between 1988 and 2008 (11). Also for antidiabetic glitazones (rosiglitazone, pioglitazone), and for ivabradine, blurred vision and excess diplopia have been described after reviewing safety alerts issued on ocular adverse events by four health authorities between January 2005 and December 2014 (12). Without detailed information on co-medication of the different study groups, a confounding impact of co-medication on diplopia rates in these trials cannot be excluded and the
Current Controversies

observed clustering of diplopia in the vorapaxar study arms may simply be an epiphenomenon or even a play of chance.

Second, the excess diplopia rates in TRACER and TRA 2P-TIMI 50 might as well be attributable to the significantly increased bleeding risk in patients treated with vorapaxar, keeping in mind that no further imaging evaluation of the diplopia cases is reported for TRACER and TRA 2P-TIMI 50. It is known that cerebral microbleeds, usually attributed to hypertension, can cause transient diplopia and nausea due to internuclear ophthalmoplegia – and can only be diagnosed by cerebral MRI (13, 14). It is perfectly feasible that in a population prone to bleeding complications (particularly intracranial haemorrhage) yet undetected cerebral microbleeds are present. In addition, in such a scenario with excess intracranial haemorrhage rates, undiagnosed small cerebral bleeds might as well have caused cranial nerve palsy and subsequent diplopia, ptosis or ophthalmoplegia in some of the cases.

Finally, caution is advised on drawing too early conclusions on critical aspects of randomised trials like event adjudication for rare and unexpected events. Adjudicating rare events in such trials is very difficult due to their structural limitations: clinical trials in the premarketing phase of drug development do not expose millions of subjects to a medication, as is true for many drugs after they are marketed worldwide. In line, no diplopia cases were described in both phase II clinical trials on vorapaxar (15, 16) and first evidence on excess diplopia was found in the very large phase III trials – without justifying immediate addition of diplopia to the package insert yet as valued by the FDA reviewers. Importantly, true rare adverse events are generally more likely to be identified for recently approved drugs rather than during premarketing trials. A previous study found that half of drug withdrawals occur within two years after a market authorisation has been granted and that half of the major label changes (defined as drug withdrawal or black box warning inclusion) occur within seven years after drug approval (17).

Therefore, rigorous post-marketing surveillance is of utmost importance for safe adoption of novel therapeutic agents. As emphasised by this Viewpoint paper, clinicians need to be aware that vorapaxar-associated diplopia seems to exist. Thorough neurologic and ophthalmologic examination and, in some cases, MRI imaging for suspect cerebral microbleeds as well as ocular muscle enlargement and inflammation is advised when a patient seeks evaluation for possible vorapaxar-associated diplopia. Active post-marketing surveillance and awareness will help the scales fall from ours eyes when we see patients treated with novel agents that present with unexpected side effects – which possibly emerge only at second glance.

Conflicts of interest

DS reports having received speaker fees and honoraria for consulting from Eli Lilly, MSD, Daichi Sankyo, Bayer Vital, Astra Zeneca and Roche Diagnostics and research grants from Roche Diagnostics. LG declares that she has no conflicts of interest.

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References

7. Serebruany VL, Choi SY, Kim MH. The FDA review on data quality and conduct in vorapaxar trials: Much better than in PLATO, but still not perfect. Int J Cardiol 2016; 205: 13–16.