Simultaneous Platelet P2Y$_{12}$ and P2Y$_{1}$ ADP Receptor Blockade Are Two Better Than One?

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Human platelets possess 3 purinergic receptors (P2Y$_{12}$, P2Y$_{1}$, and P2X$_{7}$), which collectively orchestrate key steps leading to platelet activation and aggregation (Figure). Until now, the selective blockade of the platelet P2Y$_{12}$ ADP receptor, combined with the inhibition of thromboxane production by aspirin, has remained the backbone of pharmacotherapy for patients presenting with acute coronary syndrome or undergoing percutaneous coronary intervention.

Despite significant progress in the attenuation of excess platelet activity in these high-risk settings, percutaneous coronary intervention–related thrombotic complications, including stent thrombosis, and severe bleeding continue to be major sources of morbidity and mortality. Early after acute coronary syndrome, patients may experience delayed or variable metabolism of orally administered antiplatelet agents. Young, immature platelet fractions are increased in acute coronary syndrome and confer excess platelet hyperactivity and thrombotic risk. Despite adequate inhibition of traditional platelet targets, other unprotected surface receptors and intracellular signaling pathways may continue to be activated. As such, there remains an enduring need for fast-acting, potent, and safe antiplatelet agents in contemporary clinical practice.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Gremmel et al explore a novel approach to ADP antagonism that would, in theory, overcome these hurdles and provide more complete and consistent platelet inhibition. The investigators studied GLS-409, a modified nucleotide analog of diadenosine tetraphosphate, leveraging its inherent biologic antiplatelet properties in simultaneously blocking the P2Y$_{12}$ and P2Y$_{1}$ receptors. In a series of elegantly designed, small, successive experiments, the investigators further our understanding of the pharmacokinetic and pharmacodynamic properties of this prototypical agent. In the first of these studies, in vivo administration of GLS-409 resulted in robust inhibition of platelet aggregation in rats. Next, GLS-409 was demonstrated to improve certain indices of coronary blood flow, albeit at the expense of prolonging bleeding time, in a canine model of recurrent coronary thrombosis. Finally, GLS-409, when added in vitro to blood samples from healthy human volunteers, showed comparable platelet aggregability to cangrelor alone and to the combination of cangrelor and a selective P2Y$_{1}$ inhibitor; these effects were retained even after addition of high-dose aspirin.

Although the cardiovascular safety of this novel compound was supported by the relative stability of rat and canine hemodynamics in this study, further clinical studies will be mandatory given our limited experience with the adjunctive inhibition of the P2Y$_{1}$ receptor. Given the tenuous balance between thrombosis and bleeding, diadenosine tetraphosphate analogs will need to prove to be clinically efficacious in reducing ischemic risk, while minimizing bleeding and maintaining an overall acceptable safety profile. In addition to bleeding complications, patients should be monitored for potential nontarget effects, given the broad distribution of P2Y$_{1}$ receptors beyond the platelet surface alone.

The pharmacological profile of this novel class of platelet antagonists (intravenously administered, rapidly acting, reversible) is intuitively attractive for patients at high risk for coronary thrombosis and major bleeding. These properties closely resemble those of cangrelor, a potent intravenous P2Y$_{12}$ ADP antagonist that recently garnered approval for use during percutaneous coronary intervention in the United States and Europe. We look forward to the ongoing preclinical and clinical development of GLS-409 and other diadenosine tetraphosphate derivatives to ensure the efficacy, safety, practical application, and incremental value of these agents.

Disclosures

Dr Bhatt discloses the following relationships: advisory board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; chair: American Heart Association Get With The Guidelines Steering Committee; data monitoring committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, http://www.ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME steering committees); other: Clinical Cardiology (Deputy Editor); research funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi.
Aventis, The Medicines Company; site co-investigator: Biotronik, Boston Scientific, St. Jude Medical; trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda.

References

Key Words: Editorial ■ acute coronary syndrome ■ blood platelets ■ pharmacology ■ platelet aggregation inhibitors ■ thrombosis
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*Arterioscler Thromb Vasc Biol.* 2016;36:427-428
doi: 10.1161/ATVBAHA.115.307097

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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