Editorial

Targeting Glycoprotein VI for Thromboembolic Disorders
All Gain With No Pain?

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Voors-Pette et al1 report results of their first-in-human, phase one clinical trial using ACT017, a therapeutic antibody to platelet GPVI (glycoprotein VI). In healthy volunteers, ACT017 dose-dependently inhibited collagen-induced platelet aggregation without affecting template bleeding times. Combined with the absence of serious adverse events and consistent pharmacokinetic/pharmacodynamic properties, the road is paved for further clinical development of this promising antithrombotic drug.

See accompanying article on page 956

Platelet adhesion and activation at sites of vascular injury is a multistep process involving multiple platelet receptor-ligand interactions. GPVI plays a central role in this process, as it allows platelets to bind to exposed subendothelial collagen. The GPVI-collagen interaction subsequently induces intracellular signaling, ultimately leading to platelet activation.1 Intriguingly, despite an essential role in the formation of a stable platelet thrombus, no overt bleeding phenotype was observed either in GPVI deficient mice2 or in patients with a congenital GPVI deficiency.3 However, in some patients with anti-GPVI autoantibodies, bleeding complications have been reported, although bleeding in these patients were mainly attributed to concomitant GPVI deficiency.4 However, in patients with anti-GPVI autoantibodies, bleeding complications have been reported, although bleeding in these patients were mainly attributed to concomitant GPVI deficiency and thrombocytopenia.5 In light of this, it is encouraging that in this clinical trial, ACT017 treatment did not affect platelet count or GPVI expression at any of the doses or timepoints tested.

The observations from mice and patients with a GPVI deficiency have put forward targeting GPVI as an attractive antithrombotic strategy without the apparent risk of bleeding complications. The latter is highly relevant in the setting of stroke, where even small intracranial hemorrhages can have detrimental clinical consequences. Emerging and established data demonstrate that platelets have a dual role in the setting of ischemic stroke. Undeniably, platelets are key players in pathological thrombus formation, causing cerebral vessel occlusion and ischemia/reperfusion injury.6 Nevertheless, however, platelets are also essential to maintain vascular integrity after thrombus resolution and subsequent reperfusion of the ischemic brain. This duality of platelet functions in stroke was elegantly shown by 2 independent research groups who depleted platelets in a mouse model ischemic stroke. In both studies, platelet depletion prevented ischemic stroke brain injury; however, this was accompanied by hemorrhagic transformations in the brain.7,8

Preclinical studies on the involvement of platelet receptor-ligand interactions in acute stroke have revealed that interfering with early steps of platelet adhesion (via anti-GPIb antibodies) and activation (via anti-GPVI antibodies) limits infarct progression, without increasing the risk of intracranial bleeding.9 In contrast, inhibiting platelet aggregation (via anti-GPIIb/IIIa antibodies) not only failed to protect mice from an ischemic stroke but also increased mortality rates and induced significant intracranial hemorrhages.9 Notably, Kraft et al10 subsequently confirmed these findings in aged and comorbid mice. In this study, GPVI inhibition conferred protection from stroke in aged mice, mice with diabetes mellitus, and hypertensive mice. In addition, in all these models, GPVI inhibition resulted in smaller cerebral infarcts, better functional outcomes, and reduced intracerebral hemorrhage rates compared with mice treated with inhibitors of GPIIb/IIIa. It is noteworthy that the harm of GPIIb/IIIa inhibition in these experimental murine models recapitulates adverse outcomes clinical studies of stroke. In patients with stroke, GPIIb/IIIa inhibitors (which effectively prevent thrombosis) are associated with a significantly increased risk of intracranial hemorrhage.10 Whether strategies targeting GPVI will be safer in the clinical setting of stroke remains to be seen, although the preclinical stroke data are promising.

In parallel to direct targeting of GPVI by ACT017, an indirect GPVI-targeting strategy has also advanced into clinical trials (Figure). Revacept is a soluble dimeric GPVI-Fc fusion protein which acts as a competitive inhibitor of GPVI by irreversibly binding to exposed vascular collagen.12 Similar to ACT017, Revacept induced specific, dose-related inhibition of collagen-induced platelet aggregation while preserving general hemostasis in healthy individuals.12 As Revacept technically only works at sites of vascular injury, it was initially expected to have a smaller risk of bleeding complications. However, in an ex vivo model of human, atherosclerotic plaque–induced platelet aggregation, Revacept was found to be less effective than antibodies directly targeting GPVI.13 This was attributed to platelets adhering at Revacept-free segments of collagen fibers, subsequently recruiting and activating additional platelets.
How both strategies targeting GPVI will compare in a real-life thrombotic settings remains to be seen and warrants additional clinical investigation. Yet, the safe profile of both compounds in healthy volunteers and the absence of bleeding complications in patients with a genetic deficiency of GPVI is encouraging for further development of GPVI-targeted anti-thrombotic strategies.

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Disclosures

None.

References


3. Reininger A, Ruggeri ZM, Ware J. The contribution of glycoprotein VI to platelet αIIbβ3 function can be achieved either by antibodies directly targeting the GPVI receptor (ACT017) or, indirectly, by preventing GPVI from binding to collagen that may be exposed on areas of damaged endothelium (Revacept).

Figure. Anti-thrombotic therapies are targeting platelet GP (glycoprotein) receptors. Clinically approved inhibitors targeting integrin αIIbβ3 (eg, GPIIb/IIIa) are listed in the top left. While these drugs are effective at preventing thrombosis, they are also associated with an increased bleeding risk in many patients. These bleeding complications may limit their use in the setting of ischemic stroke. In contrast, targeting GPVI may offer effective protection from thrombosis, without increasing bleeding risk. Blocking GPVI function can be achieved either by antibodies directly targeting the GPVI receptor (ACT017) or, indirectly, by preventing GPVI from binding to collagen that may be exposed on areas of damaged endothelium (Revacept).