Syk Inhibition in Ischemic Stroke

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schematic stroke is a major global public health concern. Antiplatelet therapies are a mainstay of treatment. There remains a clinical need to prevent stroke when possible and to minimize neurological damage with minimal bleeding when stroke has occurred. That is why it is particularly exciting to see the work by van Eeuwijk et al1 from the group of Bernhard Nieswandt in this issue. Based on a compelling rationale of the role of nonreceptor protein tyrosine kinase Syk in platelet activation, van Eeuwijk et al report the use of a novel oral Syk inhibitor BI1002494 for prevention and treatment of ischemic stroke in a well-established mouse model.

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Platelet activation at the sites of ruptured atherosclerotic plaques results from adhesion that triggers generation or secretion of vasoactive and inflammatory mediators, aggregation, and formation of a procoagulant surface. If activation exceeds natural or pharmacological inhibition, then an occlusive thrombus results. Syk is a major signaling node for collagen receptor GPVI (glycoprotein VI), which couples to the FcγR chain and its immunoreceptor tyrosine activation motif to initiate platelet activation. Syk is also essential in platelets for signaling via FcγRIIB and CLEC-2 and for outside-in signaling through activated integrin αIIbβ3. In contrast, Syk has no, or perhaps a limited, role in response to G-protein coupled receptors, such as those for thrombin, thromboxane A2, and ADP (adenosine diphosphate). These are the targets of conventional antplatelet therapies, which have limitations in efficacy and safety. So the promise of Syk inhibitors is that thrombosis will be curtailed while hemostasis is preserved.

Proof of concept of the benefits of Syk inhibition in mouse models of thrombosis has been reported using other small molecules2–4 or a microRNA approach.5 However, ischemic stroke has not been reported previously. First-generation Syk inhibitors, such as R406/R788 (Rigel), PRT062607 (Portola), and GS-9973 (Gilead), have been used in humans safely; however, small-molecule inhibitors with greater potency and selectivity over other kinases have emerged more recently, including those from Merck,6 Almirall,7 and in the current report, Boehringer-Ingelheim.8

Van Eeuwijk, Nieswandt and colleagues report a comprehensive approach to their proof of concept for the actions of BI1002494 in ischemic stroke (Figure). They combined a genetic approach: mice selectively lacking Syk in platelets (Syk<sup>−/−</sup>Prf1<sup>−/−</sup>), with a pharmacological approach (BI1002494), in platelet function studies ex vivo and in the transient middle cerebral artery occlusion stroke model in vivo. In this model, a filament is threaded into one middle cerebral artery for 60 minutes, then removed, leaving an occlusive thrombus. Not only did pretreatment with BI1002494 reduce infarct size without bleeding, but also administration of the inhibitor after the stroke was generated had similar benefits.

Wild-type mice lack several receptors relevant to human platelet function in thrombosis, such as PAR1 and FcγRIIa. Syk has important functions in immune cells, a role that is being exploited when Syk inhibitors are used in allergic disorders, asthma, and autoimmune diseases.6–11 Syk inhibitors are in clinical trials for B cell malignancies.12,13 However, in contrast to the oncogenic role of Syk in B cells, Syk is a tumor suppressor in several important epithelial malignancies14; therefore, long-term use must be approached with caution. Despite these potential reservations, the results of this group provide a compelling case for continued investigation and translation to human patients.

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Disclosures
Dr McKenzie is inventor on a patent application (PCT/US15/64498) for use of anti-miRs that result in Syk inhibition in thrombosis.

References


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