A Syk inhibitor for sick platelets?

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In this issue of Blood, Podolanczuk and colleagues report that oral dosing with a selective inhibitor for the Syk kinase achieves sustained increases in platelet counts in mice with antibody-induced thrombocytopenia and a subset of human patients with ITP refractory to other treatment.

Chronic immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by low platelet counts and mucocutaneous bleeding. Patients with platelet counts below 30 × 10^9/L often develop petechiae or ecchymoses while those with counts below 10 × 10^9/L are at risk for internal bleeding. Low steady-state levels of circulating platelets may result from high rates of platelet clearance or reduced rates of platelet production. In the case of ITP, immune dysfunction affects both: auto-antibodies to platelet glycoproteins induce the immune-mediated destruction of platelets in the spleen, but also bind megakaryocytes in the bone marrow, reducing platelet production. To date, therapeutic approaches to ITP generally sought to reduce immune-mediated platelet clearance (prednisone, gamma globulin infusion, rituximab, and failing these, splenectomy). Unfortunately, 30% to 40% of patients remain refractory to splenectomy, prompting the search for new and better treatment modalities. Recently, agonists for the TPO receptor, c-mpl, have shown efficacy in ITP by enhancing platelet production.

Immune-mediated clearance of antibody-opsonized platelets in patients with ITP is mediated by macrophages activated by antibody binding to activating Fcγ receptors. The tyrosine kinase Syk induces phosphorylation of substrates controlling the phagocytic machinery of the antibody-activated macrophage. Inhibition of Syk activity reduces platelet depletion, most likely by inhibiting phagocytosis of antibody-opsonized platelets, but possibly also by reducing antibody production by activated B cells.
commonly noted in patients treated with other tyrosine kinase inhibitors.7 R788 was tested in a dose-escalation regimen: doses above 125 mg twice daily were associated with greater efficacy, but also with a higher rate of GI side effects. This suggests that the efficacy of R788 as a tyrosine kinase inhibitor is also associated with this toxicity. However, GI side effects were not universal and were the cause of withdrawal from the study for only 1 patient. Other toxicities observed were elevation in liver function tests, elevations in systolic blood pressure, and weight gain.

Patients diagnosed with ITP can be a heterogeneous group because the diagnosis is based largely on the presentation of thrombocytopenia in the absence of other recognized causes. Variability in patient responses to R788 may be partially explained by the inclusion of thrombocytopenias that are not solely immune-mediated in this group. There is evidence presented in the supplemental data that some patients who failed to maintain responses to R788 did not sustain adequate Syk inhibition: individual differences in drug metabolism may represent a challenge to optimal dosing. Particularly in patients with nonsustained responses to R788, it may be interesting to study responses to combination therapy in the future. The improvement in patient platelet counts is likely confined to reducing immune-mediated clearance, because mice with bone marrow reconstituted with Syk−/− cells have no increase in platelet counts.8 Thus, combination with a c-mpl agonist may be particularly attractive for patients with nonsustained responses to Syk inhibition. In general, this novel Syk inhibitor may provide a promising new addition to the arsenal of weapons used to treat ITP.

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REFERENCES

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The VWD2B saga continues to Montreal

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In this issue of Blood, Jackson and colleagues report that members of a large family with severe thrombocytopenia, spontaneous platelet aggregation, and giant platelets (which was previously published as MPS) possess the V1316M VWD2B mutation. This observation, which is important for patient care, highlights the link between VWF and platelet production.

Von Willebrand disease type 2B (VWD2B), a disease with an autosomal dominant inheritance, is characterized by an abnormal VWF structure resulting in enhanced affinity to platelet glycoprotein (GP)Ibα. The mutations that account for this modified function occur in exon 28 of the VWF gene and give rise to heterozygous amino acid substitutions in the VWF A1 domain. These result in gain-of-function binding to GP Ibα.1 Clinically, this inherited disease is responsible for a bleeding syndrome that can be severe. Biologically, it is characterized by positive ristocetin-induced platelet agglutination (RIPA), a defect in the largest multimers of VWF, and variable degrees of thrombocytopenia. Circulating platelet agglutinates have also been described in rare VWD2B families. All of these findings are present in the family described by Jackson et al.2 Classically, the thrombocytopenia in VWD2B has been attributed to enhanced elimination of platelets coated with VWF bound to platelet GP Ibα. This new report suggests that altered platelet production may contribute to the VWD2B phenotype in some families. In this regard, we have recently shown defective megakaryocytepoiesis in a VWD2B family with a R1308P mutation,3 confirmed recently in a second family with the same mutation.4 In VWD2B, severity of thrombocytopenia is variable, but always more pronounced during surgery, pregnancy, and stress periods, when VWF synthesis is increased. Using a nanobody, Federici et al showed that VWF circulates in increased amounts in a GP Ibα-binding conformation in VWD2B patients, at levels inversely correlated with the degree of thrombocytopenia.5