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A Syk inhibitor for sick platelets?

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CLINICAL TRIALS

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A Syk inhibitor for sick platelets?

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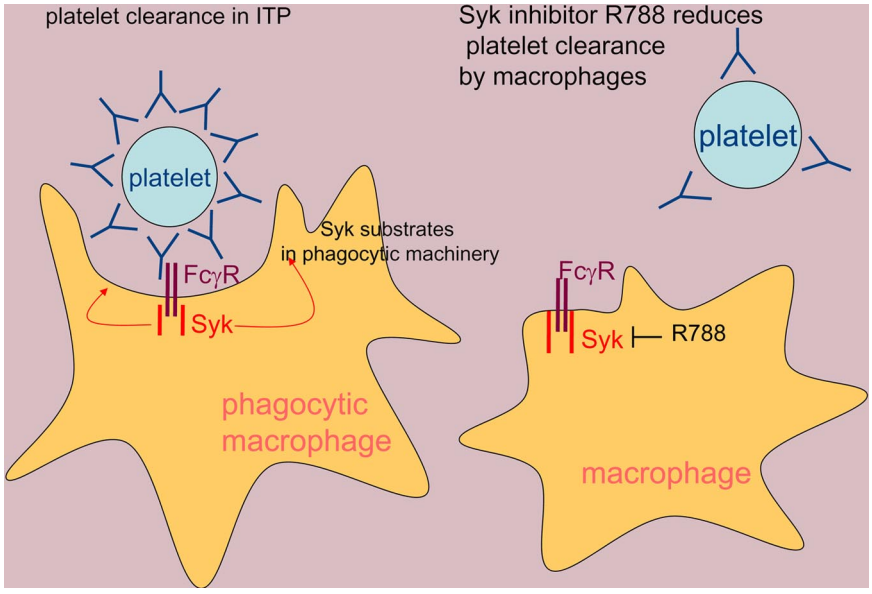
In this issue of *Blood*, Podolanczuk and colleagues report that oral dosing with a selective inhibitor for the Syk kinase achieves sustained increases in platelet counts in mice with antibody-induced thrombocytopenia and a subset of human patients with ITP refractory to other treatment.

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.[1] 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: autoantibodies to platelet glycoproteins induce the immune-mediated destruction of platelets in the spleen, but also bind megakarocytes in the bone marrow, reducing platelet production.[2,3] 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.[4,5] In this issue of *Blood*, Podolanczuk et al describe the use of a selective inhibitor of the tyrosine kinase Syk as a promising treatment for refractory ITP.[6] The pilot study is the first to demonstrate that reducing cellular signaling responses, presumably in the splenic macrophages deemed responsible for mediating platelet clearance, at least partially restores platelet counts in a mouse model of ITP as well as a subset of patients with refractory ITP.

Auto-antibodies generated to platelet glycoproteins induce signaling in macrophages through binding to activating macrophage Fcγ receptors, of which they express 3 (FcγRI, FcγRIIA, and FcγRIIIA). Activation of any of these receptors results in the recruitment of Syk to the intracellular immunoreceptor-activating motif (ITAM) of the receptor, which in turn induces tyrosine phosphorylation of a number of cytoskeletal substrates. This ultimately leads to the phagocytic engulfment of the antibody-opsonized platelet (see figure). By blocking Syk enzymatic activity, the authors hoped to reduce activation of the phagocytic macrophages, and possibly accessory activation of antibody-generating B lymphocytes that may contribute to platelet depletion. To test this idea, mice were dosed orally with Syk inhibitor R788 before injection with antibody to platelet α_{IIb}, a well-described model of mouse ITP. R788 protected mice from the antibody-induced thrombocytopenia.

Given the success of the compound in the murine model, the safety and efficacy of R788 was then tested in 16 human patients with ITP whose disease had remained refractory to at least 2 treatment regimens. Sustained response to treatment with oral R788 was achieved in 50% of patients, and 75% achieved at least a transient increase in platelet count. However, there were some toxicities or side effects associated with treatment. Chief among these were gastrointestinal (GI) complaints including nausea, vomiting, and diarrhea. These complaints are also



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.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● PLATELETS & THROMBOPOIESIS

Comment on Jackson et al, page 3348

The VWD2B saga continues to Montreal

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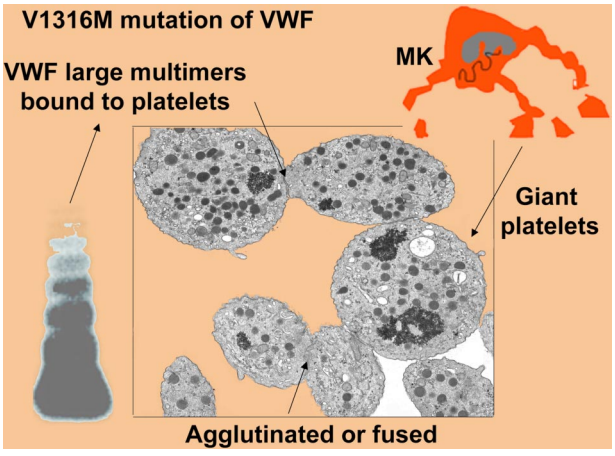
In this issue of *Blood*, Jackson and colleagues report that members of a large family with severe thrombocytopenia, spontaneous platelet aggregation, and giant platelets (which was previously published as MPS) possess the V1316M VWD2B mutation. This observation, which is important for patient care, 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 GPIbα.[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 GPIbα. 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 megakaryocytopoiesis 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 GPIbα-binding conformation in VWD2B patients, at levels inversely correlated with the degree of thrombocytopenia.[5]



Platelet agglutination and giant platelets, as shown by electron microscopy for a French patient with the V1316M mutation of VWF. These abnormally large platelets suggests that abnormal VWF may impact platelet production from megakaryocytes (MK).