Gardos pathway to sickle cell therapies?

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In this issue of Blood, Ataga and colleagues report that treatment of sickle cell disease patients with senicapoc, a Gardos channel inhibitor, reduces the number of dehydrated cells, increases hemoglobin levels, and diminishes hemolysis.

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The journey from laboratory bench to this clinical study began half a century ago with 2 independent observations. In 1958, the Hungarian physiologist Gyorgy Gárdos described calcium-dependent potassium loss from red cells. 1 The “Gardos pathway” is now known to be mediated by a calcium-activated K channel. D. C. Tosteson’s seminal studies of abnormal cation content and permeability in sickle cells led to the characterization of dehydrated cells with high hemoglobin concentration. The importance of these dehydrated cells was reinforced by subsequent discoveries that polymerization is exquisitely sensitive to HbS concentration, and that dehydrated sickle cells are very short-lived, selectively trapped in the microcirculation, and removed during vaso-occlusive episodes.

Sickle cell dehydration is thought to result from a complex interplay of HbS polymerization and several cation transport systems in sickle cells. A transport pathway that normally regulates volume in reticulocytes, the potassium-chloride cotransporter (KCC) appears to function pathologically in sickle cells, overshooting its target hemoglobin concentration and priming the reticulocyte to sickle. HbS polymerization activates a nonselective cation leak pathway in a fraction of sickle cells upon deoxygenation. Calcium entry via this sickling-induced pathway triggers activation of the Gardos channel, which mediates rapid KCl and water loss. Abnormal KCC activity in the sickle reticulocyte may thus facilitate a vicious spiral in which sickling and Gardos channel activation reinforce each other to dehydrate the cell. In vitro and animal studies have been insufficient, however, to elucidate how these pathways interact in vivo. Brugnara’s pioneering clinical investigation of another Gardos channel blocker, clotrimazole, laid the foundation for the development of senicapoc. The demonstration in the current study that senicapoc reduces the number of dense sickle cells establishes conclusively that the Gardos pathway is active in vivo and contributes to sickle cell dehydration.

Ataga and colleagues show that senicapoc treatment was well-tolerated, resulted in increased hemoglobin, and reduced markers of hemolysis—reticulocyte count, bilirubin, LDH levels—strongly suggesting that sickle cell survival was improved. Thus, the study demonstrates that prevention of dehydration in a clinical setting is feasible and decreases in vivo hemolysis in sickle disease.

Recently, a phase 3 trial of senicapoc was terminated early because of low probability of achieving a reduction in crisis rate, the primary
Clinical observations

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VWD type 1: a calculated diagnosis

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Tosetto and colleagues have developed a mathematical method to quantify the odds of having type 1 von Willebrand Disease based on a person’s family history, bleeding score, and VWF level.

Accurate diagnosis of type 1 von Willebrand disease (VWD) remains a clinical challenge. In many instances, there is great overlap between VWD patients and normal individuals in both clinical and laboratory outcomes. To address these difficulties, provisional diagnostic criteria established by experts focus on 3 components of disease: (1) presence of bleeding symptoms, (2) reduced von Willebrand factor (VWF) levels, and (3) autosomal inheritance of the phenotype. In this issue of Blood, Tosetto and colleagues have developed a novel method that allows for a more rigorous, quantitative analysis of the relative contribution of these 3 components to the odds of having VWD.

In the general population, prevalence estimates of VWD range from 0.1% to 1%, meaning that a random person would have a 0.1% to 1% chance of having VWD.3,4 Intuitively, gathering more information about the person (such as bleeding score) changes one’s estimation of his or her probability of having VWD. In their study, Tosetto and colleagues have translated this intuitive concept into a mathematical model. Based on the Bayes theorem, their algorithm utilizes clinical and laboratory phenotypes to update individual odds of having VWD. Statistically speaking, population prevalence serves as the prior estimate of disease that is multiplied by likelihood ratios (LRs) for specific outcomes to obtain a person’s final odds of having the disease.

Corresponding to the clinical definition of disease and to the 3 components of the provisional diagnostic criteria, Tosetto and colleagues have defined 3 informative LRs for assessing disease odds: an LR based on bleeding score, an LR based on VWF level, and an LR based on family history of disease. Although their methods are theoretically sound, the strength of their results hinges on the appropriateness of the populations used to derive these likelihood ratios. To retain multiplicative properties of the method, the 3 populations must be independent from each other (for example, platelet function analyzer [PFA-100TM; Dade Behring, Deerfield, IL] values cannot determine an independent LR because they are directly correlated with VWF levels).

Results reported by Tosetto and colleagues offer important insights into VWD diagnostic
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