blood advances

Doubling down on PK activation for sickle cell disease

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Comment on Saraf et al, page 4459

In this issue of *Blood Advances*, Saraf et al[1] report the results of the phase 1 multicenter, randomized, placebo-controlled study of etavopivat, a pyruvate kinase (PK) activator, under investigation to treat sickle cell disease (SCD). Results from this second-in-class oral PK activator confirm that targeting this mechanism reduces hemolysis in SCD, but the impact on SCD clinical outcomes is yet to be determined. Thirty-six participants living with SCD, most of whom had hemoglobin SS (n = 31), were enrolled in 4 treatment groups: single dose, 2 multiple ascending dose groups (MAD1 and MAD2), or open-label. Etavopivat doses administered were 700 mg (single dose), 300 mg (MAD1), 600 mg (MAD2), and 400 mg (open-label). There were placebo-treated participants in the single/MAD groups. Participants were treated for 14 days in the MAD groups and for 84 days in the open-label group.

Etavopivat increases PK activity, reducing 2,3-disphosphoglycerate (2,3-DPG) production and increasing adenosine triphosphate (ATP) production. Why might this be good for people with SCD? Under chronically anemic conditions, red cells increase 2,3-DPG production, which promotes oxygen release to tissue by lowering oxygen affinity for hemoglobin. In SCD, this physiological adaptation runs awry because deoxygenated hemoglobin S is prone to polymerization, leading to sickling, hemolysis, and the downstream pathobiology of SCD.[2] PK activation reduces 2,3-DPG, which may plausibly reduce hemolysis and improve red blood cell health via the increase in ATP concentration. Yet, as we have seen with voxelotor, reduced hemolysis may not translate to improvements in pain and other relevant SCD outcomes.[3,4]

As in the phase 1 study of mitapivat (a competing PK activator) in SCD,[5] etavopivat raised hemoglobin by >1g/dL on average (the mean maximal increase in hemoglobin was 1.6 g/dL), improved hemolytic markers, decreased 2,3-DPG, and increased intraerythrocytic ATP concentrations. Although these data do not address whether shifts in oxygen affinity affect tissue oxygen delivery, it is possible that changes in oxygen affinity may be less consequential for PK activators than for voxelotor.[6] Taken together, these data provide additional evidence of a physiologic effect of PK activation for individuals with SCD. With the Food and Drug Administration (FDA) approval of 2 gene therapies and 4 chronic SCD therapies, patients and clinicians are in a novel position to compare treatment choices. So how does etavopivat compare with mitapivat so far? Both drugs reduce hemolysis markers in SCD. Both drugs are being studied predominantly in people with hemoglobin SS disease and will include hydroxyurea-treated individuals. Etavopivat requires once daily dosing, whereas mitapivat requires twice daily dosing. Based on recent trends, the price of either therapy will likely be high. Finally, for both agents, there are concerns about rebound hemolysis with drug discontinuation. Adverse events in both PK activator trials have occurred at the end of treatment or during the taper period.[1,5] Information on this phenomenon is needed to address a salient treatment concern.

As studies move to phase 2 and 3 trials, clinical outcomes will help define use. Saraf et al report many adverse events, mostly with unclear attribution to the study drug. Treatment-emergent adverse events occurred in 87.5% of people in the MAD1 group, 75% of people in MAD2, and 100% of the open-label participants. The event rate was higher than in the placebo-treated group, in which a sole participant accounted for all adverse events. Most of the adverse events were low grade, and some painful crises occurred. In the open-label group, 5 serious adverse events occurred, including pain, acute chest, and deep vein thrombosis. These outcomes raise concerns about long-term tolerability and clinical efficacy.

Ongoing phase 2/3 studies of etavopivat (NCT04624659 and NCT04987489) will help clarify whether these events are treatment-related and whether PK activation also improves clinical SCD end points. There have been significant setbacks for new treatments for SCD, with the FDA approval for crizanlizumab thrown into question and voxelotor not yet demonstrating improvements in clinical outcomes alongside biomarker changes.[3,4,7] It is too soon to know how phase 2/3 studies of etavopivat will play out. We need firm clinical end points to inform the clinical use of all novel SCD therapies. There are enduring concerns about the side effects of therapy, using biomarker outcomes as a basis for drug approval, and the need for rigorous, long-term studies to gauge whether chronically reduced hemolysis meaningfully protects or improves end-organ function or quality of life. As ever, the need for focused pharmaceutical interventions for those with variant SCD genotypes and for rigorous understanding of the additive benefits of combination therapies, especially hydroxyurea, endures.

Still, we will save cynicism for better times. The therapeutic landscape for SCD is changing dramatically and more therapies are needed.[8] Enter etavopivat, a drug with potential to be a staple therapy in the expanding SCD-treatment toolbox.

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