

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Pyruvate Kinase Deficiency: Clinical Expression and New Therapies



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H&O What is pyruvate kinase (PK) deficiency?

HA PK deficiency is a hereditary hemolytic anemia that is the most common cause of congenital, chronic non-spherocytic hemolytic anemia. Chronic hemolysis has multiple morbid manifestations, and chronic anemia usually results in a reduced quality of life and other limitations.

H&O What causes PK deficiency?

HA PK deficiency results from mutations in the *PKLR* gene, which codes for red cell PK, the final step in the glycolytic pathway. When PK is lacking, adenosine triphosphate (ATP) production is inadequate, and reduced ATP in red cells shortens their lifespan and causes hemolysis. PK deficiency is an autosomal recessive disease with no significant carrier state manifestations, so often, no sign of it is found in a family before someone in the family is born with it.

H&O How common is PK deficiency?

HA Although PK deficiency is the most common congenital, chronic non-spherocytic hemolytic anemia, it is a rare disease. We do not know the exact incidence and prevalence, but an estimated 1000 to 3000 people in the United States have PK deficiency, numbers corresponding to a prevalence of 1 in 100,000 to 1 in 300,000 people. Some evidence suggests that the prevalence is

higher in certain regions where malaria is endemic. In this respect, PK deficiency is similar to many of the other hemoglobinopathies.

H&O What are the signs and symptoms?

HA The spectrum of disease in patients with PK deficiency is broad. Some people are largely asymptomatic, with manifestations of note only when they are otherwise ill, whereas others have severe anemia and are transfusion-dependent from birth. In a typical childhood presentation, hemolytic anemia of unclear etiology is the initial diagnosis in a pediatric patient who has no family history of thalassemia, sickle cell disease, or any other hereditary hemolytic anemias; ultimately, PK deficiency is diagnosed. In a typical adult presentation, the patient has inaccurately been assigned a diagnosis of something else, like hereditary spherocytosis or Coombs-negative autoimmune hemolytic anemia.

Patients with PK deficiency have symptoms of anemia, such as reduced exercise tolerance, the inability to complete a full day at school or work, and a reduced ability to concentrate. They also have manifestations of hemolysis, which include jaundice. Yellow-tinted skin is especially noticeable in patients who are very pale from anemia. Psychosocial problems may develop as a result; children may be bullied by their peers, and adults may have problems with romantic relationships.

Another common manifestation of PK deficiency is

gallstones, which can be painful and necessitate cholecystectomy. Extramedullary hematopoiesis may also develop, manifesting as hepatosplenomegaly and/or extramedullary hematopoietic pseudotumors. These pseudotumors usually form along the spine, cause nerve pain, and can be mistaken for malignant tumors.

Reduced bone density and osteopenia or osteoporosis develop in most patients with PK deficiency, sometimes at a strikingly young age. Osteoporosis may develop even in patients in their teens or 20s who have this disease. Another major manifestation of PK deficiency is iron overload, which can lead to liver disease, liver cancer, heart failure, and other problems. The complications of iron overload may be fatal both in patients who do not regularly receive transfusions and in those who regularly receive transfusions but are not properly managed with iron chelation therapy. Endocrinopathies such as pituitary disease and hypothyroidism can also occur with PK deficiency, although these are less common than the other problems I mentioned.

H&O How is PK deficiency diagnosed?

HA The main screening test is a PK enzyme assay. This is a pretty good test, with a sensitivity rate of approximately 90% in patients who have not had a red cell transfusion in the preceding 90 days. We can improve the sensitivity of the PK enzyme assay in patients who have not recently had a transfusion by measuring another red cell enzyme, hexokinase, and calculating the PK-to-hexokinase enzyme activity ratio. The sensitivity of this ratio is as high as 98%, according to a study that we published in the *British Journal of Hematology* in 2021. Of course, transfusions are commonly administered to patients with chronic hemolytic anemias, and we cannot trust the PK enzyme assay when a patient has had a recent transfusion.

The confirmatory test for PK deficiency is genetic testing, although this is not perfect, either. False negatives occur in approximately 10% of patients who clearly have PK deficiency and undergo genetic testing. One reason is that typical genetic tests use only exon sequencing, and some of the patients have deep intronic mutations affecting splicing sites that are not identified on exon sequencing. PK deficiency is not like sickle cell disease, in which a single canonical mutation is present; it is more like thalassemia, in which many mutations occur—more than 350 mutations have been identified to date.

H&O What are the treatment options?

HA Until recently, the treatment of patients with PK deficiency was primarily supportive and included such things as blood transfusions, folic acid supplementation,

chelation to manage iron overload, and management of osteopenia or osteoporosis with the same medications used to treat those conditions in patients without PK deficiency. The threshold for transfusion in a patient with PK deficiency does not depend on a specific hemoglobin value; rather, it is based on how symptomatic the patient is and how the anemia is experienced. Some patients receive blood transfusions regularly, usually every 2 to 8 weeks. Others receive them only when they are sick, pregnant, or feeling particularly fatigued.

The more involved therapeutic options that traditionally have been used in PK deficiency include hematopoietic stem cell transplant and splenectomy. Few cases and case series of hematopoietic stem cell transplant have been published, and the largest case series reported suboptimal outcomes, with approximately one-third of patients dying of graft-versus-host disease. Because the procedure carries high risks, and we are essentially trading one chronic disease for another, we consider hematopoietic stem cell transplant only for pediatric patients who have the most severe disease.

Far more data are available for splenectomy, which has been shown to help approximately one-half of patients by improving their hemoglobin levels by 1 to 2 g/dL. In some cases, splenectomy can liberate a transfusion-dependent child from dependence. So, splenectomy is certainly worth considering in many cases. The procedure is irreversible, of course, and significantly increases thromboembolic risk over a patient's lifespan. Removal of the spleen also increases the risk for infection, including life-threatening sepsis, over the lifespan.

Because of the considerable limitations of those therapeutic options, it is especially encouraging that we now have mitapivat (Pyrukynd, Agios Pharmaceuticals), which is a US Food and Drug Administration (FDA)-approved therapeutic for PK deficiency. This small-molecule agent is a first-in-class oral allosteric activator of red cell PK. It has activity against a broad array of wild-type and mutant PK enzymes, revving up the enzyme and thereby increasing ATP production from PK. Because the agent works by upregulating the red cell PK enzyme, you need to have some enzyme around to be activated (which may not be the case in, for example, a patient with 2 nonsense mutations in *PKLR*). Mitapivat is taken twice daily in pill form.

H&O Could you discuss your study of mitapivat?

HA After a phase 1 study evaluated mitapivat in healthy people and the phase 2 DRIVE-PK study evaluated the agent in patients with PK deficiency, we undertook the phase 3 ACTIVATE study. We were encouraged because in DRIVE-PK, mitapivat increased the hemoglobin level in approximately half of patients and was safe and well

tolerated. DRIVE-PK also showed that patients without at least one non-R479H missense mutation did not respond to mitapivat, so we excluded these patients from the phase 3 study. The R479H mutation is a founder mutation that is very common in the Amish community in Pennsylvania. It is the only missense mutation we have identified that clearly negatively predicts for response to mitapivat. Most non-missense mutations (such as nonsense mutations) also appear to predict negatively for response to mitapivat; however, some non-missense mutations may have a relatively minor effect on the resulting red cell PK protein and therefore may not preclude a response to mitapivat.

ACTIVATE enrolled 80 patients with PK deficiency who did not receive transfusions regularly. The patients were randomly assigned in a 1:1 ratio to either mitapivat (5 mg twice daily, with potential escalation to 20 or 50 mg twice daily) or placebo for 24 weeks. We found that none of the patients in the placebo group had a hemoglobin response, as expected, whereas 40% of the patients in the mitapivat group had a response. The average improvement in the hemoglobin level in the mitapivat group in the study was approximately 1.8 g/dL. When we look at just the 16 patients who responded to mitapivat, the average improvement was nearly twice that amount, at approximately 3.5 g/dL. In the anemia world, this is a very substantial improvement.

The approval of mitapivat has been a major milestone for the PK deficiency community.

The take-home message of the genotype–response concept is that patients are much more likely to respond to mitapivat if they have at least one non-R479H missense mutation. PK deficiency involves more than 370 mutations, however, not all of which can be studied in an 80-person trial—there is no way to study every combination. In recognition of this problem, the FDA approval of mitapivat is for all patients with PK deficiency and does not depend upon genotype. Therefore, it is not necessary to know the patient's genotype before trying the drug. Mitapivat is not highly toxic or difficult to administer, so the approach that I and many of my colleagues are taking is simply to try the agent and see if the patient responds, because there are truly very few patients whose genotype is going to be absolutely predictive of treatment failure (essentially only R479H homozygotes). If a response

occurs, it becomes apparent within a few weeks after titration to the maximum dose. We usually spend several weeks titrating the dose from 5 mg twice daily to 20 mg twice daily and then 50 mg twice daily. If a patient does not respond after several weeks at the range of 20 to 50 mg twice daily, we simply discontinue the drug. Trying the drug is quite easy, and we know within a couple of months if the patient will respond.

H&O Does mitapivat have any other uses?

HA The partner study to ACTIVATE, which looked at mitapivat in patients who did not receive regular transfusions, was ACTIVATE-T, which looked at mitapivat in 27 patients who did receive regular transfusions. ACTIVATE-T was also a phase 3 study, but it was not randomized. It met its primary endpoint, showing a transfusion burden reduction of at least 33% in comparison with the historical transfusion burden in 37% of patients. ACTIVATE-T, currently published in abstract form, was presented by my co-investigator Dr Andreas Glenthøj at the 2021 European Hematology Association (EHA) Virtual Congress, the same meeting at which I initially presented the results from ACTIVATE. The message of both ACTIVATE and ACTIVATE-T is that mitapivat is efficacious in patients with PK deficiency regardless of their transfusion burden, and that is reflected in the FDA indication.

The potential use of mitapivat in other diseases is an exciting area, especially when those diseases are more common than PK deficiency. For example, at the 2021 American Society of Hematology (ASH) Annual Meeting and Exposition, Dr Julia Xu presented the results of a phase 1 study showing the efficacy and safety of mitapivat in patients with sickle cell disease. At the same meeting, my co-investigator Dr Kevin Kuo presented the results of a phase 2 study showing the efficacy and safety of mitapivat in patients with non-transfusion-dependent alpha and beta thalassemia. We do not have any disease-modifying drugs for patients with alpha thalassemia, and we do not have any oral disease-modifying options for patients with beta thalassemia, so we are definitely excited about these findings. In addition, the phase 3 ENERGIZE and ENERGIZE-T studies are evaluating mitapivat in transfusion-dependent and non-transfusion-dependent thalassemia, respectively. We are actively enrolling patients into these studies now.

Also at the 2021 ASH Annual Meeting, my colleague Dr Rachael Grace presented some data from the extension portion of the ACTIVATE and ACTIVATE-T studies on the longer-term use of mitapivat. The extension study showed that in addition to improving hemoglobin levels, this drug is likely to have long-term positive effects on other pathophysiological aspects of the disease, such as iron

overload. Many patients appeared to be put into a negative iron balance, which is excellent news for patients who are essentially all in a positive iron balance at baseline and in whom iron would otherwise be constantly accumulating in their organs. This finding raises additional hope that starting patients early on mitapivat can help prevent many of the complications that otherwise come with PK deficiency. In other cases, complications may possibly be arrested or even reversed.

H&O What concerns exist with mitapivat?

HA The side effect profile of mitapivat in the DRIVE-PK study was encouraging, and the ACTIVATE study results provided convincing data supporting the safety and tolerability of this agent. Dose reduction, interruption, or discontinuation owing to adverse events did not occur in any of the patients in the mitapivat arm, and no patients died. Conversely, dosing was interrupted in 2 patients in the placebo arm because of an adverse event. Most of the side effects observed with mitapivat were mild and transient, such as headache, nausea, and insomnia. An interesting finding was that headache and nausea—the most common side effects noted with mitapivat—were more common in the placebo arm of the study. We found that to be very encouraging, and our clinical experience shows us that patients tend to tolerate mitapivat quite well.

H&O What has been the effect of mitapivat approval?

HA The approval of mitapivat has been a major milestone for the PK deficiency community. My patients are thrilled to have a treatment option for their rare disease. Patients who did not qualify for the studies are now able to start therapy and are very happy about that. Although the agent does not work for everyone, it significantly improves health and quality of life when it does work because it is so well tolerated. Patients taking mitapivat can have hemoglobin levels in the normal range, which is remarkable.

H&O Are any other treatment options for PK deficiency being investigated?

HA A phase 1 study is currently looking at a lentiviral gene therapy product for PK deficiency. In a presentation at the 2021 ASH Annual Meeting, Dr Ami Shah described the findings from the first 2 patients treated. The results were quite promising, with hematologic parameters normalizing in both patients. A major downside to gene therapy is the requirement for myeloablative conditioning, which comes with concerns about acute

and late toxicity. For patients with severe disease that does not respond to mitapivat, however, gene therapy is a very promising potential option.

The ACTIVATE-Kids (NCT05175105) and ACTIVATE-KidsT (NCT05144256) studies will be looking at the use of mitapivat in the pediatric population. The Pyruvate Kinase Deficiency Global Longitudinal Registry (PEAK registry) is seeking to enroll up to 500 patients with PK deficiency (NCT03481738). The study is serving as a follow-up to the Pyruvate Kinase Deficiency Natural History Study, published in 2018, which was instrumental in improving our understanding of the disease.

H&O Is there anything that you would like to add?

HA In many people with PK deficiency, even adults, the disease remains undiagnosed. It is rare enough that physicians who do not have it on their radar will never diagnose it. That is why it is important to evaluate for rare conditions such as PK deficiency when we see a patient who has Coombs-negative chronic hemolytic anemia, but no diagnosis. I have diagnosed PK deficiency in patients who are in their 50s and 60s and have experienced significant manifestations of their disease, which is remarkable for a congenital hemolytic anemia. We all need to be on the alert for these rare conditions.

Disclosure

Dr Al-Samkari has done consulting for Agios Pharmaceuticals, argenx, Dova/Sobi, Novartis, Rigel Pharmaceuticals, Moderna, and Forma Therapeutics; and has received research funding from Agios, Dova/Sobi, and Amgen.

Suggested Readings

Al-Samkari H, Addonizio K, Glader B, et al. The pyruvate kinase (PK) to hexokinase enzyme activity ratio and erythrocyte PK protein level in the diagnosis and phenotype of PK deficiency. *Br J Haematol.* 2021;192(6):1092-1096.

Al-Samkari H, Galactéros F, Glenthøj A, et al; ACTIVATE Investigators. Mitapivat versus placebo for PK deficiency. *N Engl J Med.* 2022;386(15):1432-1442.

Grace RF, Bianchi P, van Beers EJ, et al. Clinical spectrum of pyruvate kinase deficiency: data from the Pyruvate Kinase Deficiency Natural History Study. *Blood.* 2018;131(20):2183-2192.

Grace RF, Glenthøj A, Barcellini W, et al. Durability of hemoglobin response and reduction in transfusion burden is maintained over time in patients with pyruvate kinase deficiency treated with mitapivat in a long-term extension study [ASH abstract 848]. *Blood.* 2021;138(1)(suppl).

Kuo KH, Layton DM, Lal A, et al. Long-term efficacy and safety of the oral pyruvate kinase activator mitapivat in adults with non-transfusion-dependent alpha- or beta-thalassemia [ASH abstract 576]. *Blood.* 2021;138(1)(suppl).

Shah AJ, Lorenzo JL, Navarro S, et al. Lentiviral mediated gene therapy for pyruvate kinase deficiency: interim results of a global phase 1 study for adult and pediatric patients [ASH abstract 563]. *Blood.* 2021;138(1)(suppl).

Xu JZ, Conrey A, Frey I, et al. Mitapivat (AG-348) demonstrates safety, tolerability, and improvements in anemia, hemolysis, oxygen affinity, and hemoglobin S polymerization kinetics in adults with sickle cell disease: a phase 1 dose escalation study [ASH abstract 10]. *Blood.* 2021;138(1)(suppl).