Hepatic Porphyrias

Addressing the Need for New Treatment Options

Hepatic porphyrias are a group of rare, inherited metabolic disorders that cause painful and potentially fatal neurovisceral attacks. They are caused by deficiencies in certain liver enzymes involved in the formation of heme, which serves as a cofactor for the activity of different proteins involved in processes like drug metabolism.\(^1,^2\)

Aminolevulinic acid synthase 1 (ALAS1) is a liver enzyme involved in the biosynthesis of heme.\(^3\) In patients with porphyria, hormonal changes, exposure to certain drugs and dieting can cause ALAS1 to be upregulated, leading to the overproduction of aminolevulinic acid (ALA) and porphobilinogen (PBG), which can trigger a porphyria attack.\(^2\) Porphyria attacks can cause severe abdominal pain, peripheral neuropathy, photosensitivity and, in severe cases, paralysis and respiratory failure.

Hepatic porphyrias are grouped according to their predominant manifestation—neurologic or cutaneous.\(^1\) The most prevalent, Acute Intermittent Porphyria (AIP), is characterized by a deficiency in the enzyme porphobilinogen deaminase (PBGD).\(^4\)

One in 75,000 people carry the genetic defect for hepatic porphyria.\(^4\) However, many never experience symptoms.\(^5\) In the United States and Europe, approximately 5,000 people suffer acute porphyria attacks annually, and approximately 1,000 experience recurrent debilitating attacks.\(^3\) Notably, the majority of individuals with hepatic porphyria are female.\(^4\)

Wide Array of Symptoms

Symptoms of hepatic porphyrias can vary by individual and usually first occur between ages 20 and 30. In some people, the disorder can present as a sudden life-threatening attack. Others may experience paralysis and respiratory failure. Most acute attacks last about one to two weeks.\(^1\)

The most commonly reported symptoms of acute attacks are:

- Severe abdominal pain
- Back or limb pain
- Nausea and vomiting
- Peripheral and autonomic neuropathy
- Urine that is reddish in color
- Neuropsychiatric symptoms
- Elevated heart rate

“I would suffer from psychotic episodes and hallucinations and loss of feeling in my limbs, and just blinding, terrible, unresolvable pain.”

Porphyria Patient
Accurate and Early Diagnosis is Critical
Porphyrias are often misdiagnosed because the symptoms are associated with other, more common diseases, such as irritable bowel syndrome. A potential delay in diagnosis can lead to increased burden of disease. A recent study of U.S. patients with genetically confirmed acute porphyria found the diagnosis was delayed by an average of 15 years from the onset of symptoms. A porphyria diagnosis is typically confirmed with blood and urine tests that screen for excess levels of PBG. In cases where porphyria patients do not experience symptoms, family screening is essential to preventing acute attacks.1

Current Treatment Options are Limited
Existing treatments may help manage the symptoms of an acute porphyria attack, and require intravenous (IV) infusions over several days.

Carbohydrate loading with IV glucose may be used to treat mild attacks. Infusion treatment with hemin (an iron-containing porphyrin) is also common and is recommended for those with moderate to severe attacks. In some porphyria patients who are not responsive to therapy, liver transplantation has been performed. Organ transplantation is a high-risk procedure, and this is typically used only for patients with severe recurrent attacks.6

Addressing an Unmet Need with RNAi Therapeutics
People living with acute intermittent porphyria (AIP) and other hepatic porphyria have unmet medical needs. Alnylam is developing givosiran (ALN-AS1), an investigational RNAi therapy that targets ALAS1 for the treatment of AIP. Inhibition of ALAS-1 is believed to reduce the accumulation of the toxic heme intermediates ALA and PBG, which cause the clinical manifestations of AIP. Givosiran is being evaluated as a monthly and quarterly subcutaneous regimen.

Givosiran is being studied to see if it can both prevent and treat acute prophyria attacks. Currently, there is no approved prophylaxis treatment for AIP recurrent attacks.

Phase 1 Givosiran Study Currently Underway
Alnylam is currently evaluating givosiran in a Phase 1 study (NCT02452372) in patients with AIP. This study is designed to evaluate the safety and tolerability of givosiran in patients with AIP, including asymptomatic high excreters (ASHE) patients, as well as in patients with recurrent attacks. ASHE patients have no porphyria symptoms; however, they have permanently elevated levels of ALA and PBG.

The study began in May 2015 and additional results are expected in 2017.


November 2016