Treatments for Acute Intermittent Porphyria

Subjects: Gastroenterology & Hepatology

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Rare diseases, especially monogenic diseases, which usually affect a single target protein, have attracted growing interest in drug research by encouraging pharmaceutical companies to design and develop therapeutic products to be tested in the clinical arena. Acute intermittent porphyria (AIP) is one of these rare diseases. AIP is characterized by haploinsufficiency in the third enzyme of the heme biosynthesis pathway. Identification of the liver as the target organ and a detailed molecular characterization have enabled the development and approval of several therapies to manage this disease.

Keywords: rare metabolic diseases ; hemoproteins ; liver function ; mitochondrial cytochromes

1. Introduction

Heme is a porphyric ring composed of ferrous iron (Fe^{2+}) and protoporphyrin IX. Although it is produced in all nucleated cells, the bone marrow and liver are the main organs for heme synthesis, producing 80% and 15% of total heme, respectively [1]. In the liver, heme is an essential component of hemoproteins which participates in the removal of waste products and poisonous substances from the blood, regulating glucose homeostasis, and facilitating the antioxidant response, cell proliferation, and energy supply of cells through the cytochromes of the mitochondrial respiratory chain.

Maintaining an appropriate intracellular heme level is crucial, since excess heme is toxic, and its deficiency is detrimental to cell metabolism. The first enzyme of the pathway, δ-aminolevulinic acid synthase (ALAS, EC 2.3.1.37), tightly regulates heme biosynthesis (**Figure 1**). However, loss-of-function mutations in any of the following seven enzymes cause specific metabolic disturbances, which contribute to a heterogeneous group of orphan diseases called porphyrias (**Table 1**)[2]. The management of porphyrias is challenging as their pathogenesis is not sufficiently understood and their treatment is still an unmet medical need because current drugs do not fully restore the disease in either biochemical or clinical terms. The knowledge generated in reference centers is of great value to better describe the natural history of rare diseases and to leverage the efforts of pharmaceutical companies in the design and development of innovative orphan drugs to be tested in the clinical arena.

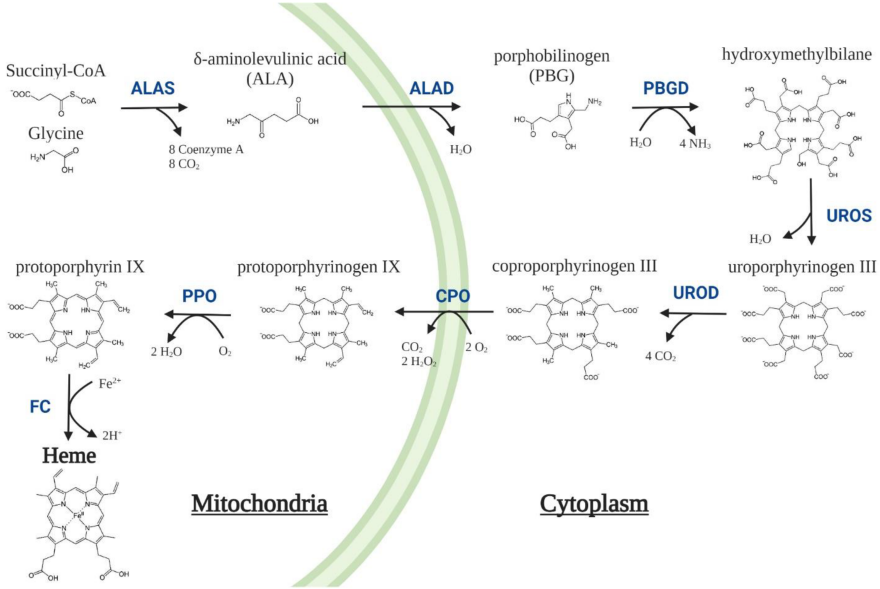

Figure 1. Heme biosynthesis pathway in mammalian cells. The pathway involves eight enzymes, four located in the cytoplasm and the other four in the mitochondria. The first and limiting step is the decarboxylative condensation of the non-essential amino acid glycine with succinyl-CoA coming from the tricarboxylic acid (TCA) cycle, which is catalysed to

form δ-aminolevulinic acid (ALA) by ALA-synthase (ALAS). Eight ALA molecules are required to synthesize four porphobilinogen (PBG) molecules that, subsequently, are used for the synthesis of a single hydroxymethylbilane molecule that is promptly converted to cyclic tetrapyrroles known as porphyrinogens, and finally to a heme prosthetic group. ALAD = δ-aminolevulinic acid dehydratase; PBGD = porphobilinogen deaminase; UROS = Uroporphyrinogen III synthase; UROD = Uroporphyrinogen III decarboxylase; CPO = coproporphyrinogen oxidase; PPO = protoporphyrinogen oxidase; FC = ferrochelatase.

Table 1. Type of porphyria associated with the abnormalities in each specific enzyme in the heme synthesis pathway. Porphyrias are characterized by loss-of-function mutations in any of the last seven enzymes, except X-linked Protoporphyria, which is associated with gain-of-function mutations in erythroid ALAS2. In contrast, ALAS2 deficient activity is associated with X-linked sideroblastic anemia (OMIM 300751)[3]. Pathogenic mutations in the housekeeping ALAS1 gene have not been reported. Hepatoerythropoietic porphyria refers to a homozygous form of PCT, which has a childhood onset. GoF = gain-of-function mutation. LoF = loss-of-function mutation.

Enzyme	Mutation	Disease	OMIM
δ-Aminolevulinic acid synthase 2 (ALAS2, EC 2.3.1.37)	GoF	X-linked Protoporphyria (XLP)	300752
δ-Aminolevulinic acid dehydratase (ALAD, EC 4.2.1.24)	LoF	ALAD Deficiency Porphyria (ADP)	612740
Porphobilinogen deaminase (PBGD, EC 2.5.1.61)	LoF	Acute Intermittent Porphyria (AIP)	176000
Uroporphyrinogen III synthase (UROS, EC 4.2.1.75)	LoF	Congenital Erythropoietic Porphyria (CEP)	263700
Uroporphyrinogen III decarboxylase (UROD, EC 4.1.1.37)	LoF	Porphyria Cutanea Tarda (PCT) Hepatoerythropoietic porphyria (HEP)	176100
Coproporphyrinogen oxidase(CPO, EC 1.3.3.3)	LoF	Hereditary Coproporphyria (HCP)	121300
Protoporphyrinogen oxidase(PPO, EC 1.3.3.4)	LoF	Variegate Porphyria (VP)	176200
Ferrochelatase(FC, EC 4.99.1.1)	LoF	Erythropoietic Protoporphyria (EPP)	177000

2. Acute Intermittent Porphyria

Acute intermittent porphyria (AIP) is caused by haploinsufficiency of porphobilinogen deaminase (PBGD) and is characterized by disabling neurovisceral attacks and chronic disease symptoms. The prevalence of AIP is estimated to be 5–10 per million in the US, UK, and western Europe. In Sweden (100 per million), and in two valleys in the Murcia region in Spain (53.8 per million), it appears with a very high prevalence due to founder mutations. However, the prevalence of genetic defects in the general population is much higher (1 in 1780 Caucasian individuals in USA, or 1 in 1675 in a study of the French population), implying low penetrance of the disease[4].

In classical AIP, both the non-erythroid and erythroid-specific enzymes have reduced activity (50%), whereas in the so-called variant AIP, the enzymatic defect is present only in non-erythroid cells and is caused by defects in exon 1. Treatment of patients with the classical or erythroid AIP variant is based on the restoration of the liver heme synthesis pathway, since this organ is the main source of the toxic porphyrin precursors associated with the pathogenesis of acute attacks: δ-aminolevulinic acid (ALA) and porphobilinogen (PBG). This therapeutically relevant notion is supported by experimental and clinical evidence that is explained below.

Bone marrow transplantation restored erythrocyte PBGD activity in AIP mice, emulating the AIP variant[5]. However, phenobarbital administration in these mice reproduced key features of acute attacks, such as a massive increase in urinary porphyrin precursors excretion and impaired motor coordination. In humans, complete biochemical and symptomatic resolution of AIP was observed in all patients after orthotopic liver transplantation (OLT)[6]. In contrast, domino liver transplantation of AIP livers was sufficient to cause acute attacks in nonporphyric recipients with normal heme synthesis in the other organs[7]. Therefore, these data point to the liver as the major etiologic site of this disorder.

Acute Neurovisceral Attacks

A secondary up-regulation of the first and rate-limiting enzyme in hepatic heme synthesis ALAS1 results in an overproduction of the potentially neurotoxic heme precursors ALA and PBG, closely associated with neurovisceral attacks. Indeed, the first acute attack emerges in most patients after exposure to precipitating factors such as drugs or other chemicals (Drugs database: http://www.drugs-porphyria.org, accessed on 11 November 2022), alcohol intake, acute illness, infection, stress, physical exhaustion, calorie deprivation, and steroid hormones, mainly oestrogens and

progesterone, that regulate the reproductive cycle in women. All these triggering factors have in common the induction of liver ALAS1 mRNA expression either directly through the peroxisome proliferator-activated receptor-gamma coactivator (PGC1α, e.g., fasting)[8] by positive feedback caused by excessive heme consumption to form hemoproteins (for example, CYP450), or by increasing its degradation through the induction of heme oxygenase-1 (HO-1), the key enzyme of heme catabolism[9]. HO-1 is up-regulated in the event of the hypoxia, inflammation, or oxidative stress associated with acute illness, infection, stress, or physical exhaustion, among other factors[10].

The two main hypotheses proposed for the physiological origin of acute attacks are the potential neurotoxicity of ALA/PBG accumulation, or heme deficiency leading to decreased hemoprotein function[11] and energy production in the mitochondria. The first is the most widely accepted hypothesis, as the onset of acute attacks has always been associated with the accumulation of porphyrin precursors. Specifically, symptomatology has been attributed to ALA because (i) patients with other diseases, such as hereditary type I (OMIM 276700), lead poisoning, or the ultrarare hepatic ALAD deficiency porphyria (**Table 1**), are associated with neurological diseases similar to acute attacks but only accumulated ALA; (ii) in vitro assays confirm the association of ALA with oxidative stress; (iii) ALA selectively competes for the binding of γ-aminobutyric acid (GABA) to synaptic GABA receptors in the postsynaptic membrane of neurons. Furthermore, some authors suggest that polymorphisms in peptide transporter 2 (PEPT2), particularly PEPT2 * 1 * 1, greatly increase serum ALA affinity, which could be related to the passage of toxic ALA to the brain through the choroid plexus, and an increased susceptibility to developing neuropsychiatric symptoms[12].

Despite all of this, the relationship between porphyrin precursor levels and prodrome symptoms is still unclear. Different authors have also pointed out that in porphyria, elevation of ALA may be necessary but not sufficient for the development of an acute attack[13], since ALA administration in a male volunteer and in mice did not produce acute symptoms. In fact, a large urinary loss of liver succinyl-CoA and glycine (used for the production of ALA and PBG) during the acute porphyria attack supports the hypothesis of a profound, although reversible, impact of acute attack on mitochondrial energy metabolism[14]. More recently, preventive treatment with experimental liver-targeted insulin (the fusion protein of insulin and apolipoprotein A-I, Ins-ApoAI) in AIP mice improved pain and motor coordination although excretion of ALA and PBG remained high[15]. This insulin-ApoAI showed an increased serum half-life and high hepatic tropism compared to unconjugated insulins, which improved the mobilization of adipose tissue energy stores and increased hepatocyte glucose uptake[16]. In addition to increasing the energy supply to the liver of porphyria mice, the ApoAI component induced mitochondrial biogenesis[17], which secondarily protected against the porphyrinogenic effects of phenobarbital administration[15]. These data support that low energy production, caused by cataplerosis of the TCA cycle and the reduced availability of energy metabolites during acute attacks, could play a role in modulating the severity of porphyria attacks.

3. Current Treatments

Current treatments are based on down-regulation of hepatic *ALAS1* expression using carbohydrate loading, intravenous (iv) hemin therapy, or the subcutaneous (sc) administration of a small interfering RNA (siRNA) targeting *ALAS1* mRNA. The frequency and severity of acute attacks determine the classification of patients into different groups, which can condition their treatment.

1. Latent porphyria. After a first attack, the precipitating agent is identified and, if possible, removed. Although most patients may not experience an acute attack again, they may maintain high urinary excretion of ALA and PBG for years and are called Asymptomatic High Excretors (ASHE). These patients do not receive treatment, although a recent study shows that 46.4% report chronic symptoms associated with porphyria, such as abdominal pain, fatigue, muscle pain, and insomnia[18].

2. Patients suffering sporadic acute attacks (1 to 3 per year). Symptoms are very heterogeneous and include autonomous (intense pain typically in the abdomen that can also affect the back, legs, arms, or chest; nausea; vomiting; diarrhea/constipation; hypertension; and/or tachycardia), central (seizures, anxiety, depression, reduced consciousness, psychosis, insomnia, hallucinations or posterior reversible encephalopathy syndrome (PRES) on MRI scan, among others) and peripheral (muscle weakness, paralysis, reduced tendon reflexes) nervous system involvement. Severe neurological complications may cause death due to respiratory and bulbar paralysis[19].

   Carbohydrate overload (300 to 500 g/day, based on oral or iv glucose infusions) is recommended for the treatment of patients mild pain and no paresis. A mild attack can quickly become a severe attack, characterized by severe neuropathic abdominal and muscle pain, significant hyponatremia, urinary retention or incontinence, peripheral neuropathy (85% of sporadic AIP), or central nervous system (CNS) involvement. The treatment recommended for

severe porphyria attacks consists of daily intravenous administration of hemin (hemin arginate, Normosang® in Europe and lyophilized hematin, Panhematin® in the US, both from Recordati, Milan, Italy) for a period of 4 days (3–4 mg/kg of hemin/day). It is more effective than glucose in reducing the formation of porphyrin precursors but is more expensive and is not available in all countries. Hemin therapy acts through retroinhibition of the ALAS1, which reduces production and accumulation of PBG and ALA (**Figure 2**). Hemin treatment lasted from one to four days, and biochemical remission of ALA and PBG is typically not produced until two or three days after the beginning of treatment. The reduction in abdominal pain is typically observed on the third day of treatment[20].

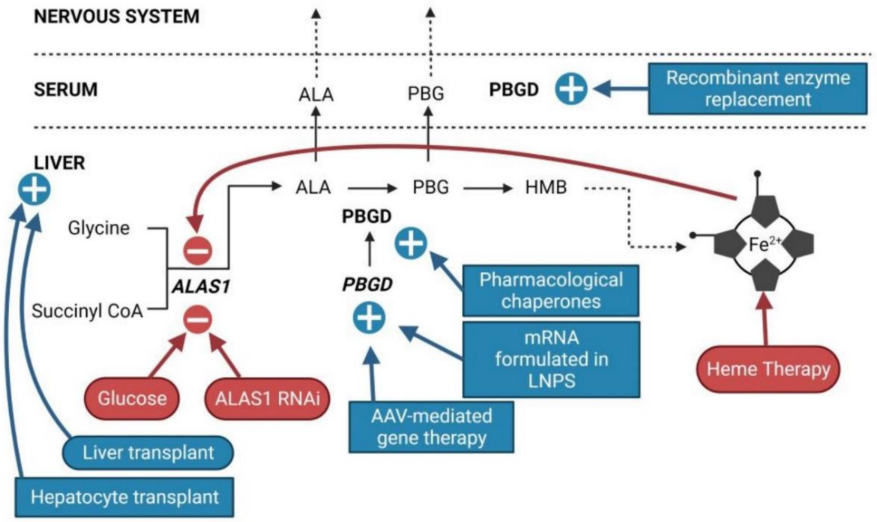

Figure 2. Sites of action of current and innovative therapeutic options for AIP. Current approved therapies are represented in round outlines. Emerging innovative therapies are represented in square outlines. Therapies that inhibit *ALAS1* are in red. Therapies that increase PBGD activity are in blue.

3. Patients suffering frequent acute attacks (≥3 attacks per year). This group of AIP patients represents approximately 5% of symptomatic patients, mainly women (80%). This group of patients usually requires hospitalization and experiences chronic symptoms that adversely influence daily functioning and undermine their quality of life[21]. Chronic opiate therapy is often needed to control pain. Furthermore, these patients are chronically exposed to the potential toxicity of heme precursors when passing through the kidney, especially ALA, which has been identified as being responsible for progressive renal failure[22], or to an increased risk of developing hepatocellular carcinoma[23][24], the long-term complications associated with acute hepatic porphyrias.

Although there are no reports confirming the efficacy of hemin administration in preventing acute attacks, off-label administration of prophylactic iv heme infusions is commonly used. An audit report by the National Acute Porphyria Service in England concluded that prophylactic hemin arginate appears to be beneficial in patients with recurrent acute porphyria symptoms, but more studies are required to support its use[25]. However, repeated administration of hemin therapy can cause unwanted effects and complications, such as thrombophlebitis at the peripheral vein infusion site (requiring administration through a central vein), iron overload (each 250 mg dose of hemo contains 22.7 mg of iron), or induction of the HO-1 enzyme, causing the reduction of the regulatory free heme level in hepatocytes. This situation re-induces the regulatory feedback mechanism of heme in cells through the activation of *ALAS1* expression, reducing the therapeutic efficacy of hemin administration over time.

Recently, sc administration of an ALAS1 siRNA (givosiran, givlaari®, Alnylam Therapeutics, Cambridge, MA, USA) has been approved for the treatment of severely affected patients who experience recurrent porphyria acute attacks (**Figure 2**). Givosiran therapy is based on the fact that the accumulation of ALA and PBG precursors is the sole cause of the pathophysiology of the disease. The Phase III clinical trial (NCT03338816) and a 24 month interim analysis of efficacy and safety have shown good results in preventing ALA/PBG accumulation and reduced the frequency of acute attacks by 87%. Although givosiran had an acceptable safety profile and was generally well tolerated in patients with acute hepatic porphyrias in clinical studies[26], adverse events (AE) (90% vs. 80%), severe AEs (17% vs. 11%), and serious AEs (21% vs. 9%) were more common with givosiran than with placebo in the ENVISION trial[26]. Among AEs, injection site reactions (25% vs. 0%), nausea (27% vs. 11%), chronic kidney disease (10% vs. 0%), decreased estimated Glomerular Filtration Rate (eGFR) (6% vs. 0%), rash (6% vs. 0%), increased levels of alanine transaminase (8% vs. 2%), and fatigue (10% vs. 4%) were more frequent among the patients receiving givosiran than in the placebo group. Interpreting the safety data is complicated by the fact that chronic kidney disease and liver damage are common coexisting illnesses and long-term complications of acute hepatic porphyria[27]. Reduced availability of heme in the liver could be associated with the

reported AEs associated with ALAS-1 iRNA, such as bile acid disorders, reduced drug metabolization rates, or dysregulation of one-carbon metabolism[28]. Concomitant hypermethioninemia and hyperhomocysteinemia resembling classic homocystinuria have been associated with givosiran treatment. These are likely to be attributable to an impairment in the trans-sulfuration pathway catalyzed by cystathionine β-synthase. This enzyme uses vitamin B6 as a cofactor and S-adenosylmethionine as an allosteric activator of enzyme activity[29].

Hepatic targeting of givosiran is mediated by interaction of *N-acetylgalactosamine* linked to siRNA with the asialoglycoprotein receptor (ASGPR). However, ASGPR is also expressed in renal tubular cells, and its ligation could be related to changes in serum creatinine and kidney function complications, assessed by decreased eGFR[26]. A recent report of patients followed for two years concluded that givosiran is associated with a moderate transient increase in serum creatinine without signs of kidney injury. However, the long-term deleterious impact of *ALAS1* inhibition on renal function cannot be ruled out[30].

Available evidence indicates that givosiran is an efficient therapeutic option to prevent acute attacks with recurrent porphyria in severely affected patients. However, there is still room for improvement in AIP therapy to cover the full spectrum of the disease, from sporadic to recurrent attacks, regardless of their severity; and to prevent the appearance of the AEs and severe AEs associated with recurrent administrations of givosiran.

4. Innovative Therapies

The current prevalent R&D trends related to AIP therapy focus on increasing hepatic PBGD activity and restoring the physiological regulation of the heme synthesis pathway (**Figure 2**). Based on the PoC obtained in animal models, increasing PBGD levels appears to be a promising strategy for the etiological treatment of AIP, regardless of whether it is achieved by the administration of a recombinant rApoAI-PBGD protein[31], an rAAV-mediated GT[32], or mRNA encapsulated in LNPs[33]. Indeed, a single administration of the PBGD-mRNA induced a rapid and efficient overexpression of a functional PBGD protein in the liver of mice and large animals. The messenger RNA technology is being successfully tested in several clinical trials for five metabolic diseases (NCT 05095727: Glycogen storage disease Type 1A; NTC 04574830: Glycogen storage disease Type 3; NCT05130437: Propionic Acidemia; NCT 04899310: Methylmalonic Acidemia; NTC 04442347: Ornithine transcarbamilase deficiency) so that experience could quickly be transferred to patients with porphyria. Furthermore, this product could be applied to all patients regardless of clinical course, both chronic and sporadic presentations, as well as ASHE until normalization of the urinary excretion of porphyrin precursors.

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