# Recent Advances and Optimal Management of
# Erythropoietic Protoporphyria and X-linked Protoporphyria

**OVERVIEW**

Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are cutaneous porphyria responsible for a substantial burden on patients, their families, and the healthcare system. To address this burden, important treatment advances, including new classes of medications, continue to be made. In this educational activity, Karl Anderson, MD, discusses preventive and therapeutic options for patients with EPP and XLP, as well as the safety and efficacy of emerging treatments.

**CONTENT AREAS**

- Nonpharmacologic options
- Transplantation
- Afamelanotide
- Dersimelagon (MT-7117)
- Iron supplementation
- Cimetidine
- AON-V1

**TARGET AUDIENCE**

This activity is intended for a national audience of hematologists, hepatologists, gastroenterologists, medical geneticists, dermatologists, advanced care practitioners, primary care physicians, and other healthcare providers who may be involved in diagnosis and treatment of patients with EPP and XLP.

**LEARNING OBJECTIVES**

At the conclusion of this activity participants should be able to:

1. Employ preventive and therapeutic options for patients diagnosed with EPP and XLP that best fit the need of each patient
2. Describe the safety and efficacy of emerging treatments for patients with EPP and XLP

**FACULTY**

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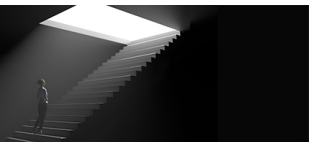

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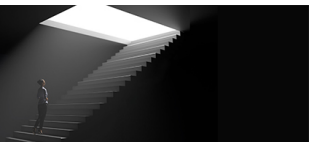

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## Introduction

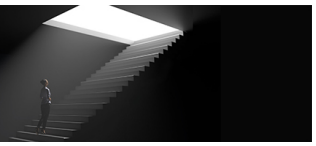
Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP), 2 of the 4 types of cutaneous porphyrias, result in skin symptoms such as pain, swelling, and redness after exposure to sunlight or artificial light, predominantly in the blue-violet region.[1,2] Unlike other cutaneous porphyrias, blistering and scarring are usually not prominent. Both are genetic disorders.[1] EPP results from mutations of the ferrochelatase (*FECH*) gene, while XLP results from mutations in the aminolevulinic acid synthase-2 (ALAS2) gene. The deficiency of *FECH* or gain-of-function mutations in ALAS2 both result in the accumulation of protoporphyrin IX (PPIX).[3] *FECH* is responsible for the insertion of iron into PPIX, which is the last step in heme synthesis. Gallstones containing large amounts of PPIX are common. Higher levels of total erythrocyte protoporphyrin are a major determinant of disease severity and risk of liver damage.[4]

## Nonpharmacological Strategies

Nonpharmacologic strategies play a primary role in the management of patients with EPP and XLP to mitigate the painful symptoms that occur. Of key importance is the avoidance of sunlight exposure by avoiding outdoor activities, covering the skin with long-sleeves, long-pants, gloves, shoes and wearing a hat when outdoors. These lifestyle changes can negatively impact patients' social activities and decrease their quality of life (QoL). Opaque sunscreens, such as 20% zinc oxide paste, may partially prevent protoporphyrin activation and provide some protection against visible light.[5] The addition of pigments to white paste sunscreens to some degree enhances protection against photosensitivity and cosmetic acceptability.[5]

### Afamelanotide for EPP

The US Food and Drug Administration approved afamelanotide (Scenesse) in 2019 as the first treatment to increase pain-free light exposure in adults with phototoxic



reactions from EPP. Afamelanotide is a potent analogue of human α-melanocyte-stimulating hormone (α-MSH) which binds to the melanocortin 1 receptor (MC1R) in melanocytes to boost the production of photoprotective eumelanin in the epidermis.[6] Afamelanotide was compared to placebo at a dose of 16 mg given as subcutaneous implants on days 0, 60, and 120 in 2 randomized, phase 3 studies, with 2 additional implants on days 180 and 240 in the second study.[6] In both studies, the duration of pain-free sun exposure after 6 months of treatment was significantly longer with afamelanotide than placebo. Of note, the first study, conducted in the European Union, showed the median number of hours in direct sunlight between 10 AM and 3 PM without pain after 9 months was 6 hours (range, 0-193 hours) in the afamelanotide group compared to 0.8 hours (range, 0-35 hours) in the placebo group (*P*=0.005). The second study, conducted in the United States, showed the median number of hours in direct sunlight between 10 AM and 6 PM without pain as 69.4 hours (range, 0-651 hours) in the afamelanotide group compared to 40.8 hours (range, 0-224 hours) in the placebo group (*P*=0.04). The differences observed in sunlight exposure without pain between the 2 studies are believed to be due to the higher latitudes of the European centers (range, 48° to 60°N) as compared with the US centers (range, 29° to 42°N). Both trials reported improved patient quality of life with afamelanotide. The number of phototoxic reactions was similar in the first study, but significantly less with afamelanotide vs placebo in the second study. The most common adverse events observed more frequently with afamelanotide were (placebo-adjusted): implant-site discoloration (11%-19%), nausea (1%), upper respiratory tract infection (2%-5%), cough (0%-7%), oropharyngeal pain (0%-10%), melanocytic nevus (0%-2%), pigmentation disorder (2%-8%), and pruritus (0%-2%).[6]

**Management of Hepatic Complications**

The management of patients with gallstones is the same as in patients without EPP, typically involving cholecystectomy if they become symptomatic. For patients who have developed protoporphyric hepatopathy, treatment is directed at reducing the amount of protoporphyrin delivered to the liver and its toxic effects, generally as a bridge to liver transplantation.[7] Limited evidence suggests benefit with the following interventions, guided by severity and progression of hepatopathy and observed effects on plasma and erythrocyte PPIX levels: red cell transfusions and intravenous hemin to reduce protoporphyrin production by the bone marrow, cholestyramine to reduce enterohepatic recirculation of protoporphyrin, ursodeoxycholic acid to enhance biliary excretion and removal of protoporphyrin from the liver; plasmapheresis to reduce exposure of the liver to protoporphyrin in plasma; erythrocyte exchange to reduce protoporphyrin contained in that compartment; and vitamin E to reduce oxidative damage to hepatocytes.[7] Although these medical interventions sometimes achieve remission, future recurrence of hepatopathy is likely.

**Liver and Bone Marrow Transplant**

Patients with progressively worsening protoporphyric hepatotoxicity often benefit from liver transplantation. Liver

transplantation can restore liver function and the ability to excrete protoporphyrin via the biliary system to normal. However, liver transplantation does not correct *FECH* deficiency in bone marrow erythroid cells, which continue to overproduce protoporphyrin.[8] Thus, transplanted patients can be expected to continue to have symptoms of EPP and are at risk of developing protoporphyric hepatopathy again in the transplanted liver. A hepatopathy recurrence rate of 65% has been reported in a cohort of 17 patients who survived more than 2 months following liver transplant.[9] The overall patient and graft survival rates were 85% at 1-year, 69% at 5-years, and 47% at 10-years.[8] Therefore, a second transplantation is sometimes required. Bone marrow transplantation after liver transplantation or even after remission of hepatopathy with medical treatment has been beneficial in some.[8]

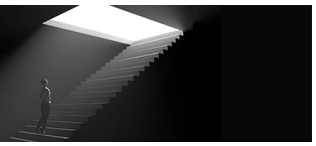
**Ongoing Management**

Annual monitoring is recommended for patients with EPP and XLP, to include complete blood count, serum ferritin, liver chemistries and erythrocyte and plasma porphyrin levels. Vitamin D supplementation is generally needed. The liver should be protected as much as possible because other types of liver disease can impair protoporphyrin excretion and might precipitate protoporphyric hepatopathy. Therefore, vaccination to prevent hepatitis A and B is important. Other infections that cause liver damage and excess use of alcohol should be avoided. Drugs with potential to cause liver damage or impair hepatic excretory function should be avoided or used with caution. Severe calorie restriction can exacerbate acute hepatic porphyrias, but effects in protoporphyrias are not known.

**Table. Safety and efficacy of emerging treatments for patients with EPP and XLP**

| Treatment/ Study | Study Design | Intervention | Primary Outcome | Secondary Outcomes | Conclusion |
|---|---|---|---|---|---|
| Dersimelagon (MT-7117)[10] ENDEAVOR Trial MT-7117-A01 (N=102) | Phase 2, multi-center, randomized, placebo-controlled study (16-week double blind treatment period) | Treatment groups:<br>1. Placebo once daily (n=35)<br>2. MT-7117 100 mg once daily (n=33)<br>3. MT-7117 300 mg once daily (n=34) | Increase in the average daily time (min) to first prodromal symptom during sunlight exposure<br>● Significant improvement in average daily time (> 50 min) to first prodromal symptom in subjects treated with MT-7117 100 mg (*P*=0.008) or 300 mg (*P*=0.003) at week 16 | 1. Average daily duration of sunlight exposure without prodromal symptoms<br>a. Significant increase in MT-7117 groups at week 16 (*P*<0.05) compared to placebo<br>2. Total number of sunlight exposure episodes with prodromal symptoms<br>a. 40% reduction 100 mg (*P*=0.019) and 300 mg (*P*=0.006) compared to placebo<br>3. Total number of pain events<br>a. 60% reduction in 100 mg (p=0.027) and 50% reduction in 300 mg (p=0.028) compared to placebo | The oral MC1R agonist dersimelagon was effective in increasing symptom-free light exposure in patients with EPP or XLP at doses of 100 mg or 300 mg once daily after 16 weeks of treatment compared to placebo. There was also an acceptable safety and tolerability profile. |

| Treatment/ Study | Study Design | Intervention | Primary Outcome | Secondary Outcomes | Conclusion |
|---|---|---|---|---|---|
| Dersimelagon (MT-7117)[11] NCT04402489 | Phase 3, multicenter, randomized, placebo-controlled, double-blind study | Treatment groups<br>1. Placebo once daily<br>2. MT-7117 low dose once daily<br>3. MT-7117 high dose once daily | Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at week 26. | 1. Patient Global Impression of Change (PGIC)<br>2. Total number of sunlight-induced pain events with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period. | *Pending results* |
| Cimetidine[12] NCT05020184 | Phase 2, prospective, blinded, randomized, 2x2 cross-over study | 1. Sequence 1: placebo twice daily (3 months)<br>2. Washout period: 3 months<br>3. Sequence 2: cimetidine 800 mg twice daily (3 months) | Erythrocyte total protoporphyrin level | 1. Time to prodrome<br>2. Patient-reported QOL<br>3. Phototoxic episodes<br>4. Light dose | *Pending results* |
| Oral Iron[13] NCT02979249 | Open-label | Ferrous sulfate 325 mg orally twice daily for 12 months | Relative difference in erythrocyte protoporphyrin levels between baseline and 12 months after treatment | 1. Erythrocyte protoporphyrin over time<br>2. EPP specific quality of life<br>3. Safety events | 1. Mean (± std. deviation) EPP levels were 2314.6 (±1820.3) µg/dL at baseline and 2240.4 (±2312.6) µg/dL at 12 months<br>2. Mean change in EPP QoL score of 3.3<br>3. 30% (3/10) of patients had serious adverse events |



**Other Therapeutic Options in Development**

Several treatment options are in development for patients with EPP and XLP. Dersimelagon is an oral melanocortin 1 receptor agonist that induces melanogenesis.[14] The phase 2 ENDEAVOR study randomized patients (N=102) with EPP or XLP to once-daily treatment with dersimelagon 100 mg or 300 mg or placebo (Table).[10] After 16 weeks, there was significant improvement in average daily time (>50 minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset in both dersimelagon groups compared to placebo. The increased average exposure time without prodromal symptoms was about 50 minutes greater in patients treated with dersimelagon at both doses compared to placebo. A post hoc analysis showed the increase in average daily time to first prodromal symptom was limited to the subgroup with a baseline total erythrocyte protoporphyrin IX level ≥1981 mcg/dL. Pain events were also significantly reduced in patients treated with dersimelagon at both doses compared to placebo.[10] The most common treatment-related adverse events were nausea (27.9%), freckles (23.5%), and skin hyperpigmentation (20.6%). Investigation of dersimelagon continues in an open-label, phase 3 extension study up to 24 months; trial completion is expected in September 2023 [NCT05005975].

The great majority of patients with EPP are heterozygous for a common *FECH* gene variant, $IVS_{3\text{-}4}8C > T$, which is a potential therapeutic target. This transition favors formation of an aberrantly spliced mRNA that is degraded prematurely, therefore, less *FECH* protein is produced. This low-expression (hypomorphic) variant does not by itself cause disease, even if homozygous, is found in ~10 % of normal Caucasian individuals, and is more common in east Asians but very rare in native Africans.[15] It contributes to causing EPP only if paired with a severe *FECH* variant that produces little or no enzyme activity. (In rare families, EPP results from 2 severe *FECH* variants in the absence of the low-expression allele.) A targeting antisense oligonucleotide (AON-V1) has been developed that redirects splicing to the physiological acceptor sites, resulting in increased production of functional *FECH* mRNA, and reduced accumulation of protoporphyrin. Transferrin receptor-1 (TRF1) has been used as a "Trojan horse" to deliver V1 to euthyroid progenitors. A bifunctional peptide (P1-9R) including TFR1-targeting peptide coupled with a 9-arginine cell-penetrating peptide increases the release of antisense oligonucleotide (AON).[15] Therefore, the P1-9R/V1 nanocomplex both increases *FECH* mRNA production and significantly decreases PPIX accumulation.[15]

Observational data with cimetidine in 3 children with EPP has suggested decreased photosensitivity.[16] Cimetidine is undergoing a double-blind, placebo-controlled, phase 2 study with an expected completion in September 2025 [NCT05020184]. The use of oral iron remains controversial because of its ability to upregulate ALAS2; its use should be limited to treat anemia and improve fatigue and subtle cognitive impairment due to iron deficiency.

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