The Porphyrias

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Hematology Education Online
May 26, 2022

Mount Sinai

Disclosures

- Advisory board participation: Alnylam therapeutics, Recordati Rare Diseases, Mitsubishi Tanabe, Disc Medicine
- Clinical trial support: Alnylam therapeutics, Mitsubishi-Tanabe

Institutional disclosure:

- The Icahn School of Medicine at Mount Sinai (“ISMMS”) holds issued and pending patents related to the study drug Givosiran and has licensed these patents to Alnylam. As part of the license to Alnylam, ISMMS will receive payments from Alnylam, including a payment when Givosiran enters Phase 3 clinical studies, as well as future payments if Givosiran becomes a marketed treatment for Acute Hepatic Porphyria. ISMMS, as well as the ISMMS faculty that are named inventors on the licensed patents will benefit financially

Disease Overview

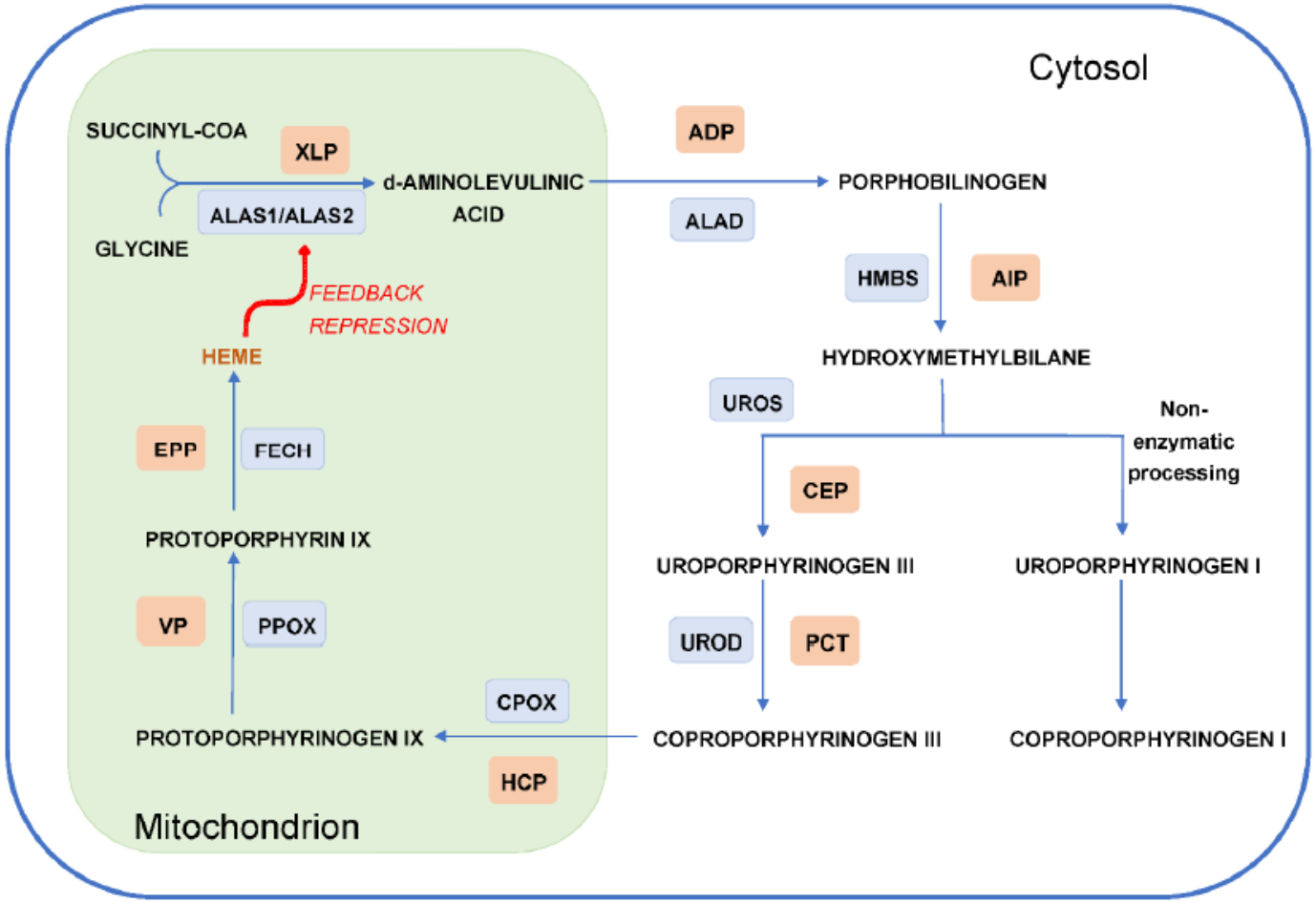
The Porphyrias

- Rare metabolic disorders of the heme-biosynthetic pathway
- Classified either based on the primary site of the enzymatic defect or clinical presentation

Acute
Acute Intermittent Porphyria
Hereditary Coproporphyria*
Variegate Porphyria*
ALAD Porphyria
Cutaneous
Erythropoietic Protoporphyria
X-linked Protoporphyria
Congenital Erythropoietic Protoporphyria
Porphyria Cutanea Tarda

Hepatic
Acute Intermittent Porphyria
Hereditary Coproporphyria*
Variegate Porphyria*
ALAD Porphyria
Porphyria Cutanea Tarda
Erythropoietic
Erythropoietic Protoporphyria
X-linked Protoporphyria
Congenital Erythropoietic Protoporphyria

Heme biosynthetic pathway



- Eight enzymatic steps to the end product heme
- Heme exerts a negative feedback on the first enzyme of the heme biosynthetic pathway, ALAS1
- While ALAS1 is ubiquitously expressed, its isoform, ALAS2, is erythroid specific and is regulated by erythroid-specific transcription factors
- Dysfunction of each enzyme results in a different type of porphyria due to accumulation of the different heme precursors and porphyrins in various tissues

Erwin et al, Diagnostics 2021

Acute Hepatic Porphyrias

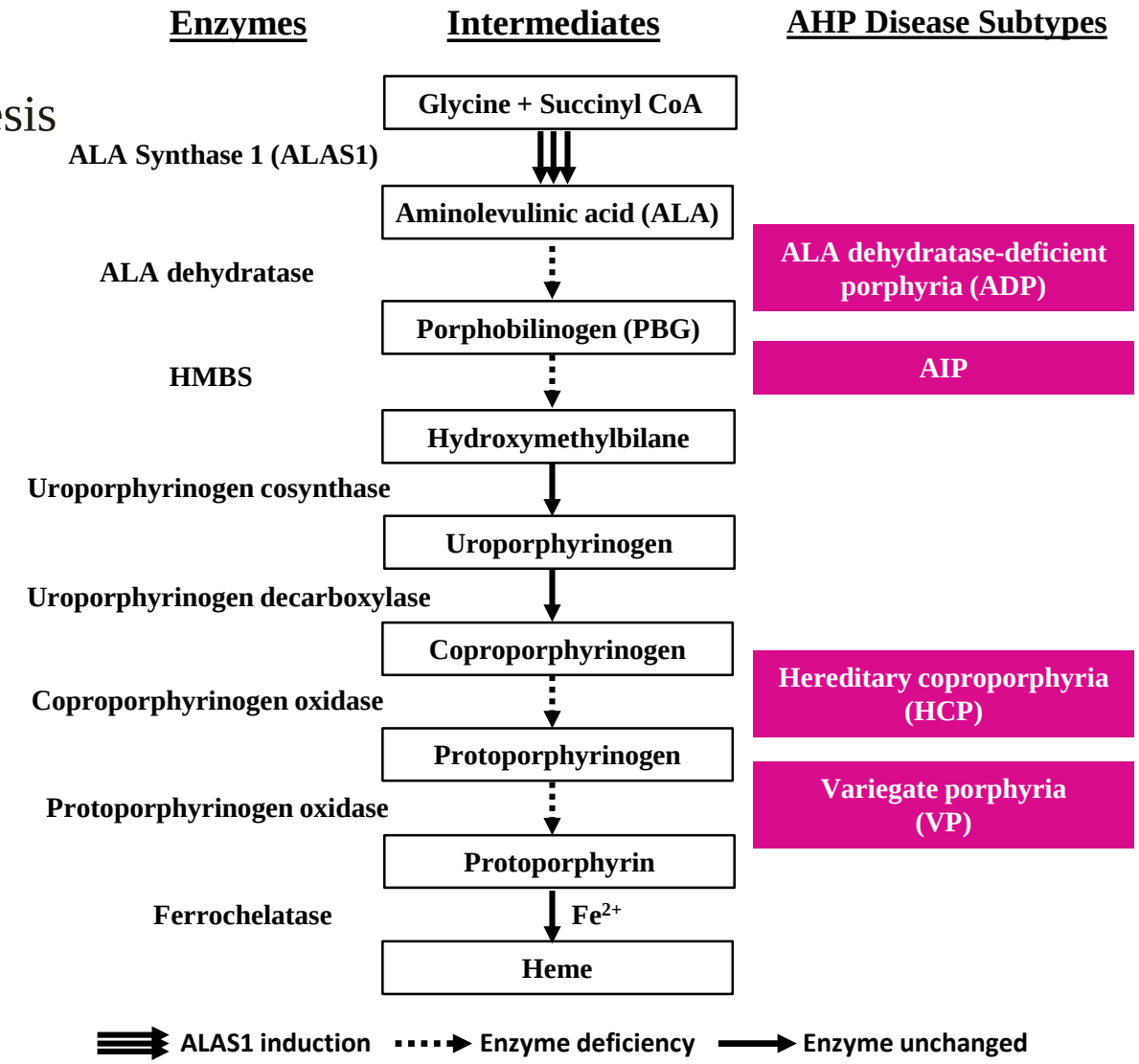
Acute Hepatic Porphyria (AHP)

Disease Overview

- Deficiency in one of the enzymes in heme biosynthesis in liver
- Autosomal Dominant (except for ADP)
- Acute intermittent porphyria (AIP) most common, caused by pathogenic variants in the *HMBS* gene

Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG)
- ALA and PBG are factors associated with attacks or other disease manifestations of AHP



- 1. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 2. Elder et al. *J Inherit Metab Dis* 2013;36:849–57; 3. Balwani et al. *Hepatology* 2017;66:1314–22; 4. Bonkovsky et al. *Mol Genet Metabo* 2019. doi: 10.1016/j.ymgme.2019.03.002. [Epub ahead of print]

AHP Patient Population

Female patients of childbearing age

HMBS Pathogenic Variant Prevalence

~1 in 1600–1700

Disease penetrance

~1%

(~20% in families of symptomatic AHP)

Majority of patients are **age 18-45** at onset

Predominantly **female**

- 1. Elder et al., 2013; 2 Nordmann et al. *J Intern Med* 1997;242:213–7; 3. Chen et al. *Hum Mutat* 2016;37:1215–222 4. Bissell DM et al. N Engl J Med. 2017;377:862-872 3. Lenglet H et al. Hum Mol Genet. 2018 Apr 1;27(7):1164-1173

Acute Hepatic Porphyria Types

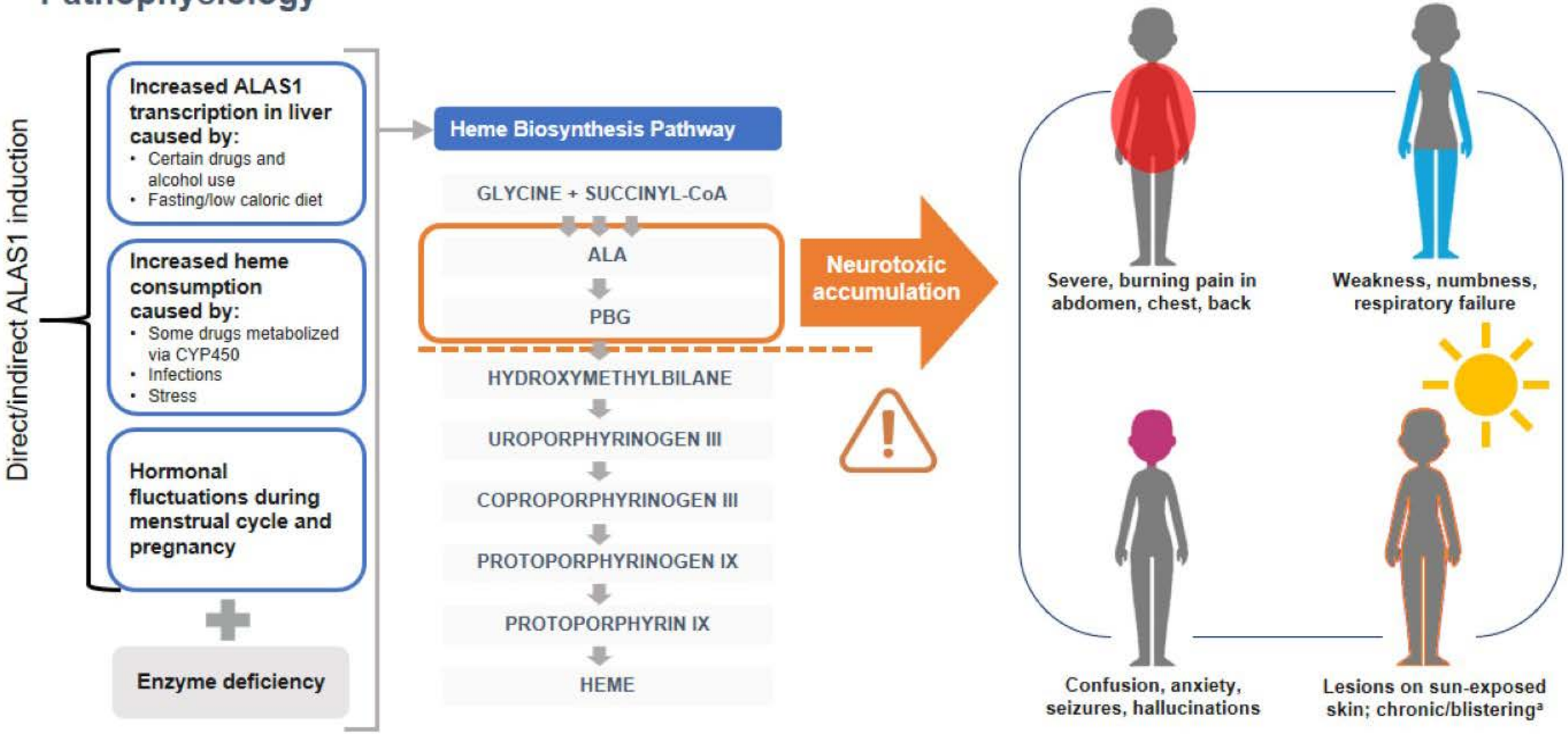
AHP Type	Sex	Age of Onset	Typical Presenting Symptoms		Estimated % of AHP
			Acute attacks	Cutaneous	
AIP	Symptomatic patients are predominantly female	18–45 years	✓		Most Prevalent AHP Type (~80%)
VP			✓	✓	Less Prevalent
HCP			✓	✓	Less Prevalent
ADP	All recorded symptomatic patients have been male	Variable	✓		Least Prevalent <10 cases ever reported worldwide

More prevalent

- 1. Ramanujam & Anderson. *Curr Protoc Hum Genet* 2015;86:1–263; 2. Elder et al. *J Inherit Metab Dis* 2013;36:849–57

Acute Hepatic Porphyria (AHP)

Pathophysiology



[a]Only occurs in VP and HCP

1. Anderson et al. *Ann Intern Med*. 2005;142:439–50; 2. Ventura et al. *Eur J Intern Med*. 2014;25:497–505; 3. Bonkovsky et al. Presented at American Association for the Study of Liver Disease, November 2018; 4. Besur et al. *Metabolites*. 2014;4:977–1006; 5. Pischik & Kauppinen. *Appl Clin Genet*. 2015;8:201–14

Acute Hepatic Porphyria (AHP)

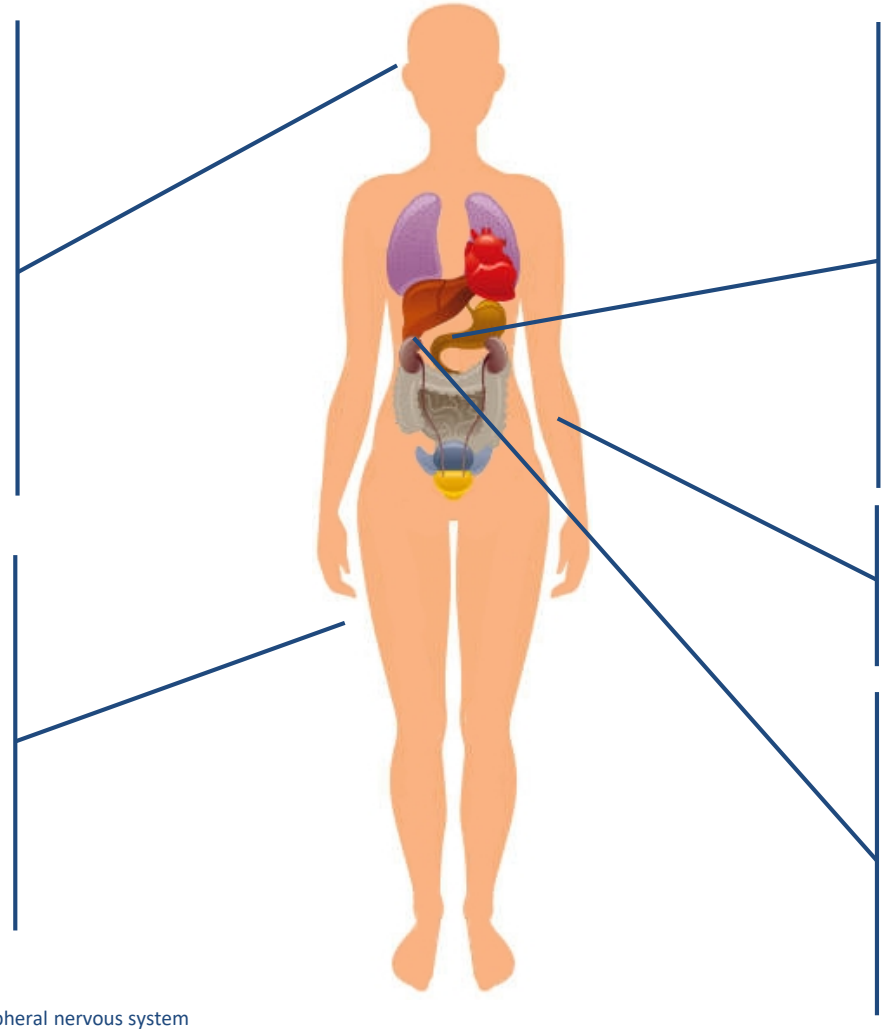
Clinical Characteristics

CNS Manifestations

- Confusion
- Anxiety
- Memory loss
- Depression
- Tiredness
- Hallucinations[a]
- Seizures[a]

PNS Manifestations

- Neuropathic pain
- Sensory loss
- Muscle weakness
- Paralysis[a]
- Respiratory failure[a]



ANS Manifestations

- Severe pain in the abdomen, chest, or back
- Hypertension
- Tachycardia
- Nausea and vomiting
- Constipation
- Hyponatremia

Cutaneous Manifestations[b]

- Lesions on sun-exposed skin

Long-Term Complications

- Hepatocellular carcinoma
- Chronic kidney disease (CKD)
- Neuronal damage
- Hypertension

- [a]Only occurs in severe cases. [b]Only occurs in VP and HCP
- ANS, autonomic nervous system; CNS, central nervous system; PNS, peripheral nervous system
- Anderson et al. *Ann Intern Med* 2005;142:439–50; Gouya et al. Presented at the International Liver Congress, April 2018; Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; Simon et al. *Patient* 2018;11:527–37

Acute Porphyrias in the USA: Features of 108 Subjects from Porphyrias Consortium

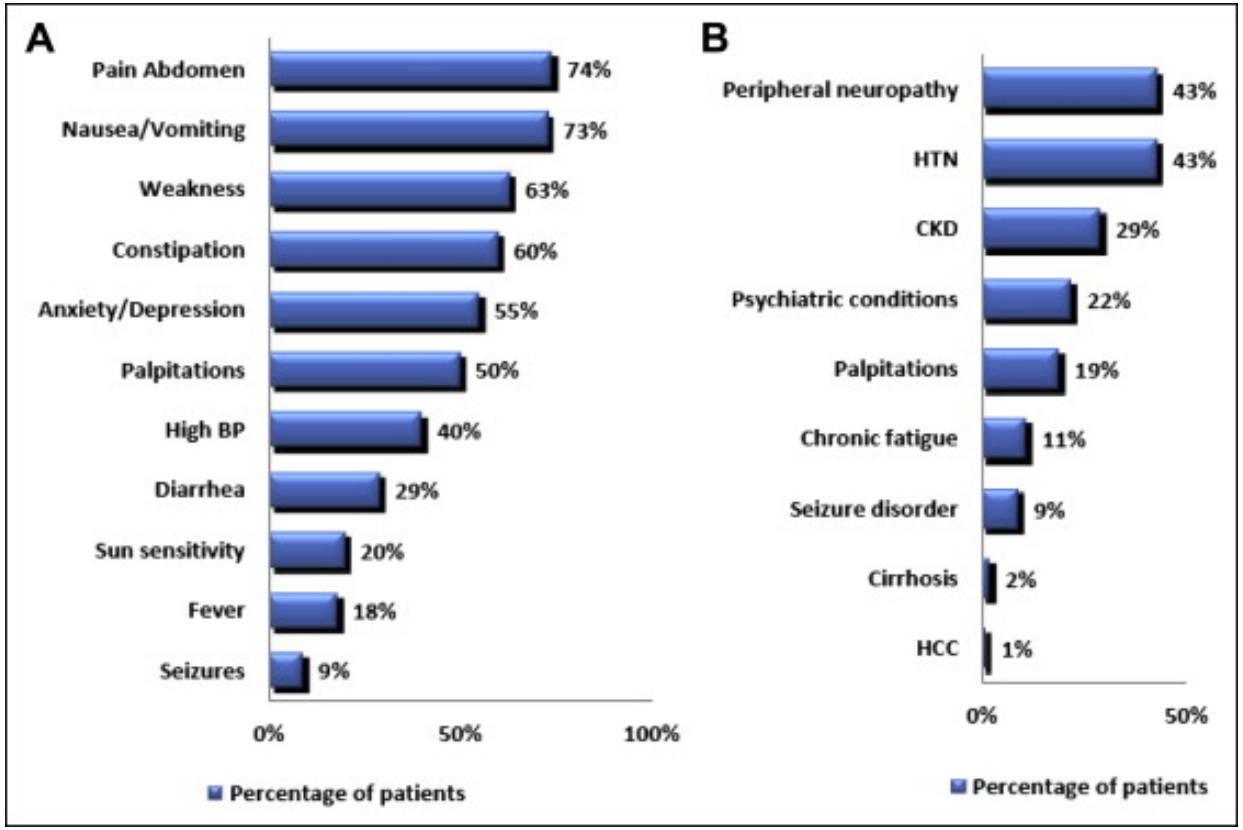


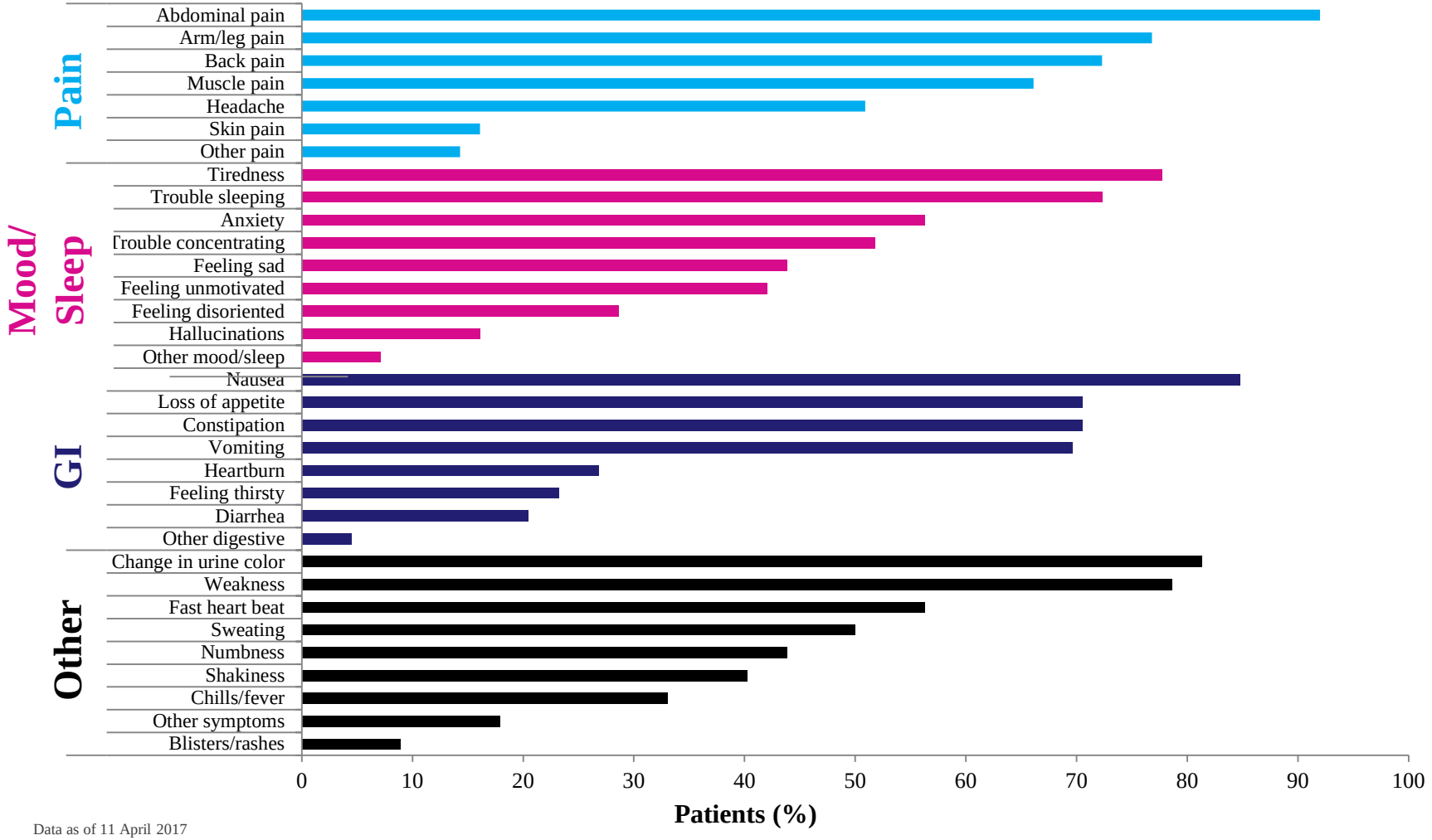
Figure 1. (A) Symptoms and signs during acute attacks in acute intermittent porphyria. (B) Medical conditions associated with acute intermittent porphyria. BP = blood pressure; CKD = chronic kidney disease; HCC = hepatocellular carcinoma; HTN = hypertension.

Bonkovsky HL et al, The Am Journal of Medicine, 2014

EXPLORE Natural History Study

Baseline Patient-Reported Attack Symptoms

- Symptoms reported by > 80% of patients: abdominal pain, nausea, change in urine color

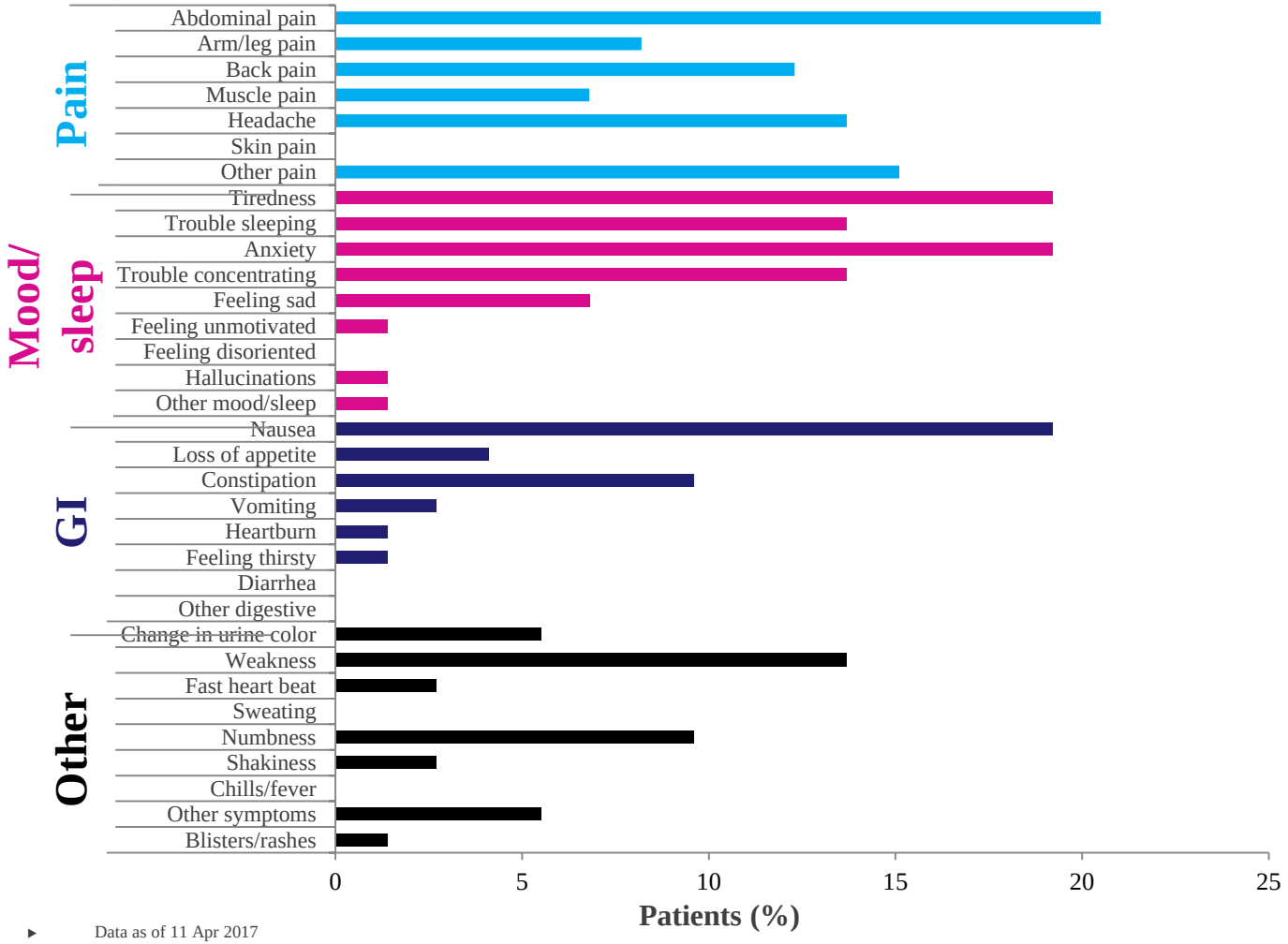


- Data as of 11 April 2017

EXPLORE Natural History Study

Baseline Patient-Reported Chronic Symptoms

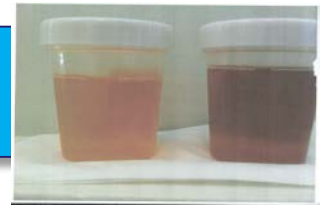
- 65% patients with chronic symptoms, most commonly pain, tiredness, anxiety and nausea, with 46% reporting daily symptoms



▸ Data as of 11 Apr 2017

Diagnosis

Diagnostic Testing Methods



- Average duration from presentation to accurate diagnosis can be up to 15 years
- Accuracy and speed are vital in diagnosing patients as delaying treatment of an AHP attack can lead to complications

Biochemical Testing

- **AHP is diagnosed with random (spot) urine tests for ALA, Porphobilinogen (PBG)**
- Urine porphyrins is a non-specific test and should not be used in isolation for diagnosing AHP
- Ideal time to test is during or shortly after an attack; however, testing can be performed anytime if there is suspicion of AHP*
- Additional biochemical tests including plasma or fecal porphyrins can be performed to confirm diagnosis and AHP type but are not specific for AHP when tested alone

Genetic Testing

- Genetic testing can be performed to confirm AHP type
  - Can rule out AHP if patient does not have mutation
  - Important for carrier/family testing
  - Can provide important information for patients being evaluated outside of an attack where ALA/PBG may be normal

➢ *results should be normalized to urine creatine

➢ 1. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 2. Anderson et al. *Ann Intern Med* 2005;142:439–50; 3. Whatley & Badminton. Acute Intermittent Porphyria. In: GeneReviews. Seattle, WA: University of Washington, Seattle; Updated 2013

AIP

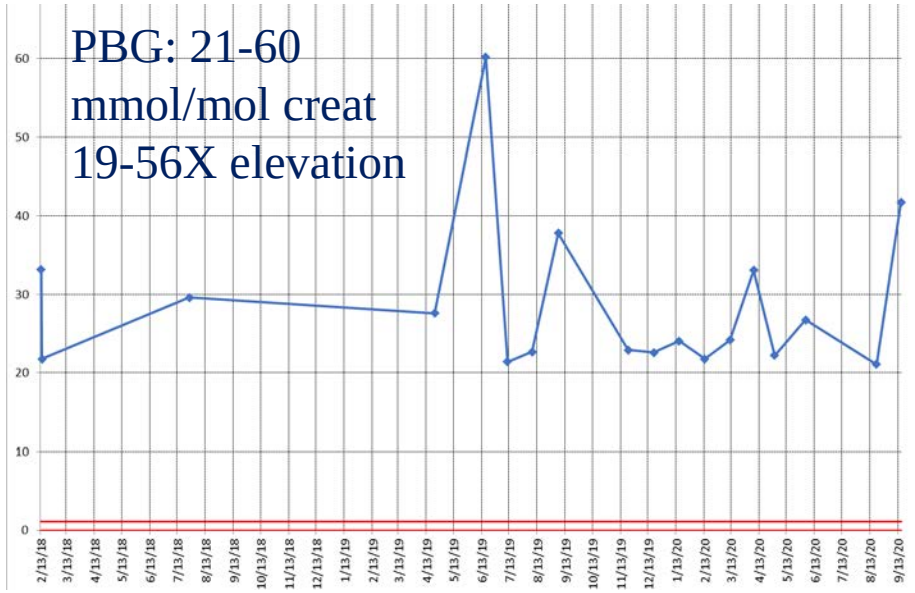
RESULT SUMMARY

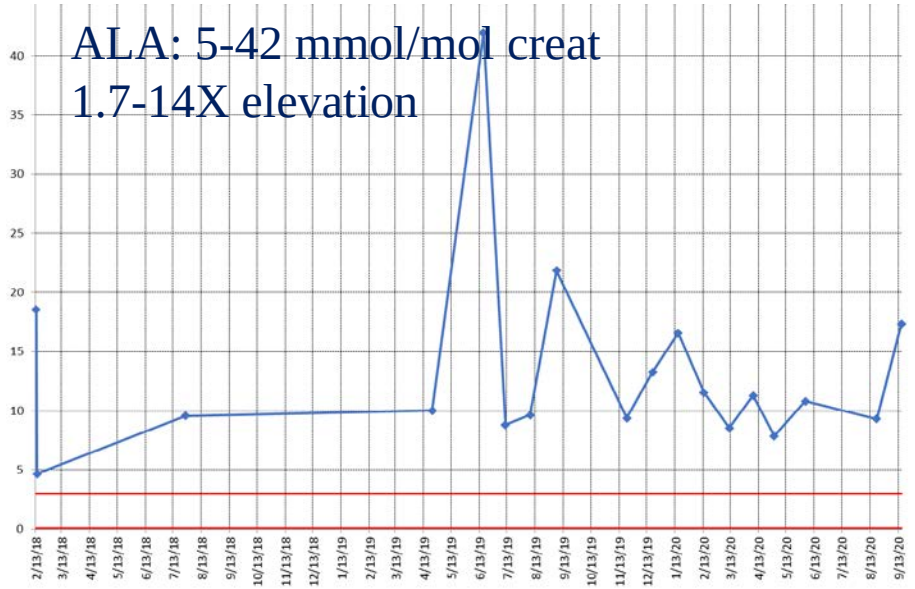
	mmol/mol creat	Normal	Note
Aminolevulinic Acid	41.97	0.09 - 2.97	HH
Porphobilinogen	60.17	0 - 1.08	HH

HH –very high, H –high, L-low, ND-not detected

Interpretation
Follow up study of a known AIP patient. Urinary 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels are highly elevated and higher than previous. Recommend clinical correlation.

Test Method and Comments
5-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels are measured by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The test is clinically utilized for screening patients suspected of acute porphyria, as well as long term monitoring of confirmed porphyria patients for management.





Management and Treatment

Clinical Vignette

- 20 year old female with severe abdominal pain x 2 weeks
- ED work up: CT abd/pelvis and transvaginal US were unremarkable
- Started on nitrofurantoin for presumed UTI due to dark colored urine and urinary difficulty
- Symptoms progressively worsened, accompanied by protracted nausea and vomiting
- Evaluated at urgent care and discharged home with different antibiotic (Trimethoprim/Sulfamethoxazole)

Clinical Vignette

- Returned to ED and treated with IV fluids and IV antibiotics and discharged home
- She continued to have intractable abdominal pain that progressed to generalized body pain, dark colored urine, difficulty voiding, nausea, vomiting, constipation, and inability to tolerate po.
- Returned to the ED and was admitted for 4 days for bowel obstruction
- Treated with enemas, IV hydration, and stool softeners and discharged home

Clinical Vignette

- Returned to ED for persistent abdominal pain and was admitted
- Hospital course: nausea, vomiting, tachycardia, hypertension, hypokalemia, hyponatremia, muscle weakness and seizure
- CT, EEG, MRI of head/neck/spine were all normal
- **Urine porphobilinogen (PBG) 76.6mg/24hr; ref range <2.4**
- Treated with hemin therapy x 4 doses
- Prolonged hospitalization
- Referred for consultation for AIP

Most Common Misdiagnoses

Urinary tract infection

Appendicitis

Acute pancreatitis

Cholecystitis

Irritable bowel syndrome

Ovarian cyst

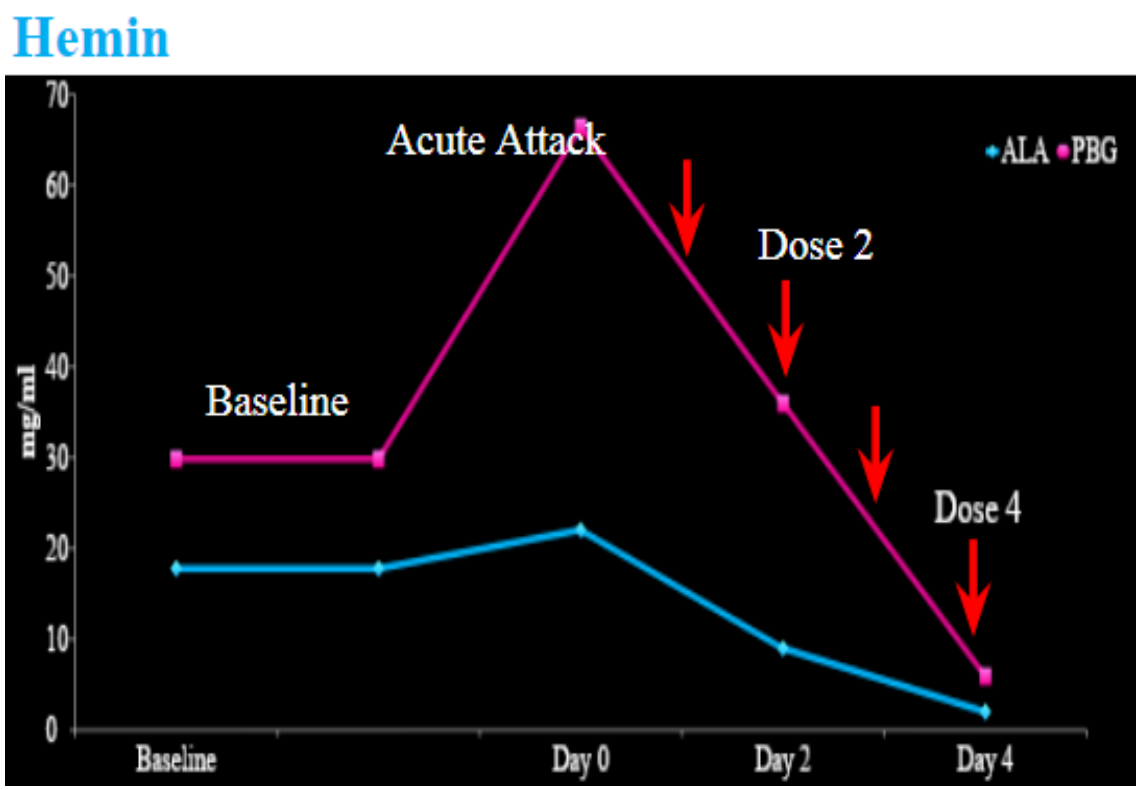
Gastrointestinal illness

Inpatient Management

- Identify and remove known triggers
- Check online drug database prior to administering new medication
- Send urine porphobilinogen and blood work
- Supportive care including pain medications
- **Start hemin:** First-line treatment for acute attacks
- **Hemin (Panhematin®) dose:** 3-4mg/kg daily x 4 days or based on clinical response
- **Start IV dextrose:** D5W or D10 ½ NS (300 gm/24 hr) while waiting for hemin

Hemin

- Hemin therapy:
  - Heme in the form of lyophilized hematin
  - Heme-albumin is more stable
  - Depending on severity: 3-4 mg/kg infused daily for 4 days
  - Downregulates stressed hepatic heme biosynthesis



Discharge and Rehabilitation

- Physical therapy
- Occupational therapy
- Taper pain medications
- Referral to a specialist

General Recommendations for AHP

- Avoid known precipitating factors
- Check drug database prior to starting new medications
- Eat a well-balanced diet, avoid crash diet or rapid weight loss
- Medical alert bracelet and Medical ID on smart phone
- Stay up to date with immunizations (e.g. Hepatitis A&B, yearly flu vaccine) to minimize risk of infections
- Testing of first degree family members
- Ongoing follow-up

Frequency of Acute Neurovisceral Attacks

- **Recurrent attacks**: >4 attacks/year
  - Can have monthly attacks (women during the luteal phase of menstrual cycle)
- **Sporadic Attacks:** < 4 attacks/year
- **Asymptomatic High Excretors (ASHE)/Chronic High Excretors (CHE):**
  - Clinically asymptomatic with high levels of ALA and PBG (may have a history of previous attack)

Latent and Asymptomatic High Excretors

- Individuals with latent disease should be counseled about potential triggers and means to avoid them
- Asymptomatic High Excretors:
  - -Monitor kidney and liver function
  - -Urine ALA/PBG
  - -CBC

Management Approaches for AHP

Symptomatic and supportive management

Treatment of AHP symptoms

Patients with AHP often receive medications for symptoms including but not limited to, nausea, hypertensive crises, neuropathy, seizures, metabolic changes, anxiety, and depression

Glucose and carbohydrate loading

May downregulate the heme biosynthesis pathway and may be most effective in patients who are malnourished or where dietary restrictions have contributed to an attack

Pain medications

Patients with AHP are commonly prescribed opioid and non-opioid pain medications

Hormone therapy

GnRH agonists may be used chronically for women experiencing an acute attack related to their menstrual cycles

- GnRH, gonadotropin-releasing hormone
- 1. Balwani M, et al. *Hepatology.* 2017;66(4):1314-1322. 2. Wang. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatol Commun. 2018 Dec 20;3(2):193-206. 3. PANHEMATIN [Package Insert]. Lebanon, NJ: Recordati Rare Diseases, Inc; 2017. 4. Anderson, KE. *Mol Genet and Metab,* https://doi.org/10.1016/j.ymgme.2019.07.002.

Management Approaches for AHP

Disease targeted treatment

Hemin

Approved for the treatment of AHP attacks and is also used on-demand or prophylactically

Givosiran

Small interfering RNA indicated for the treatment of adults with AHP

Liver transplantation

Liver transplantation is reserved for patients with intractable acute attacks which are not responsive to other therapies

Outpatient vs. Inpatient Hemin Therapy

OUTPATIENT

- Patients who can identify prodromal symptoms
- Abdominal pain
- Nausea without vomiting

INPATIENT

- Severe abdominal pain
- Requiring opioid analgesic
- Vomiting
- Hypertension
- Tachycardia
- Seizure
- Psychiatric manifestations

Treatment

Hemin therapy

Challenges

Need large bore peripheral IV, PICC line or implanted port for infusion

Risk of thrombophlebitis

Difficult to set up infusion locally

Not available at all ED/hospitals

Long-term complications: iron overload and hepatic fibrosis

Monitoring

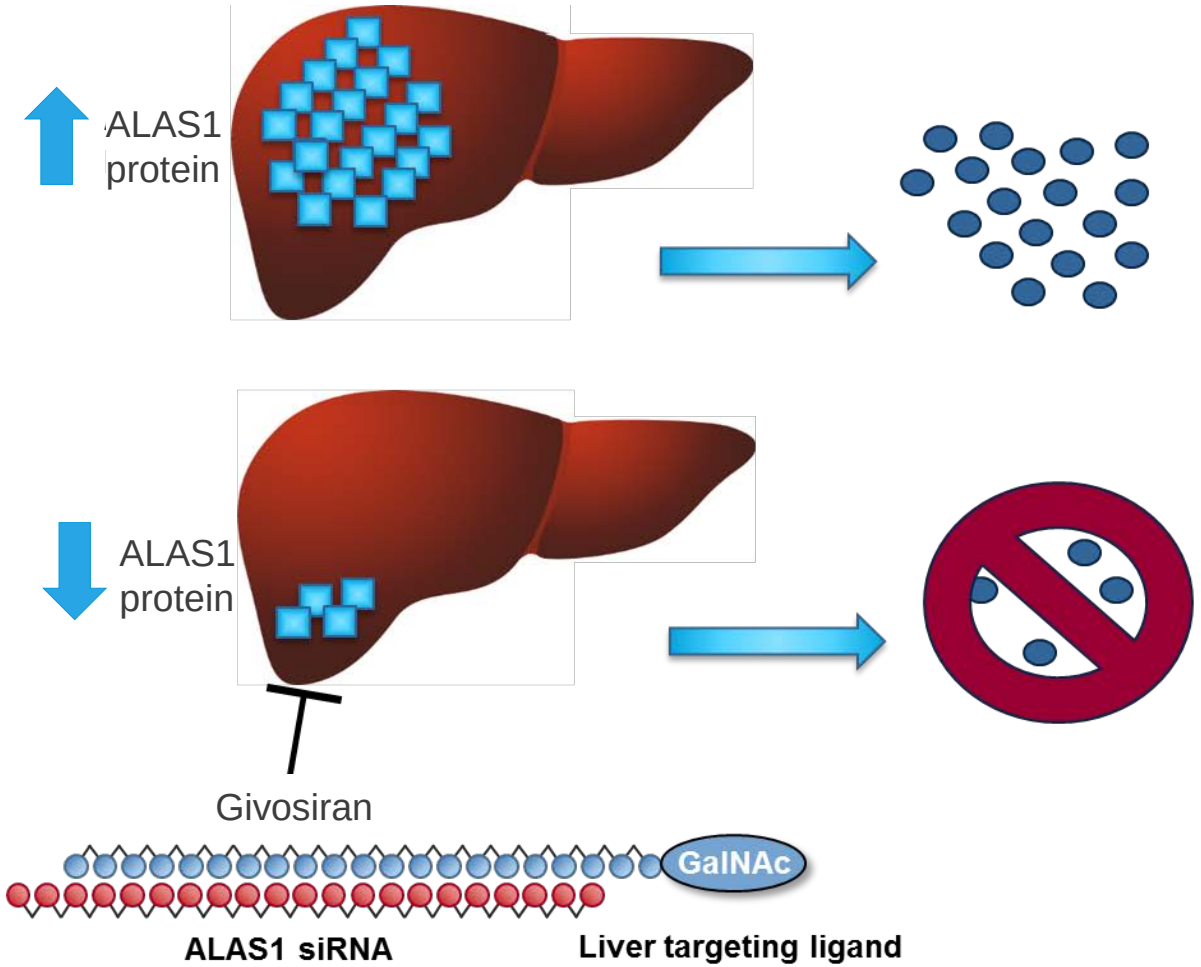
Ferritin

Liver enzymes

Givosiran

Mechanism of Action

Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference



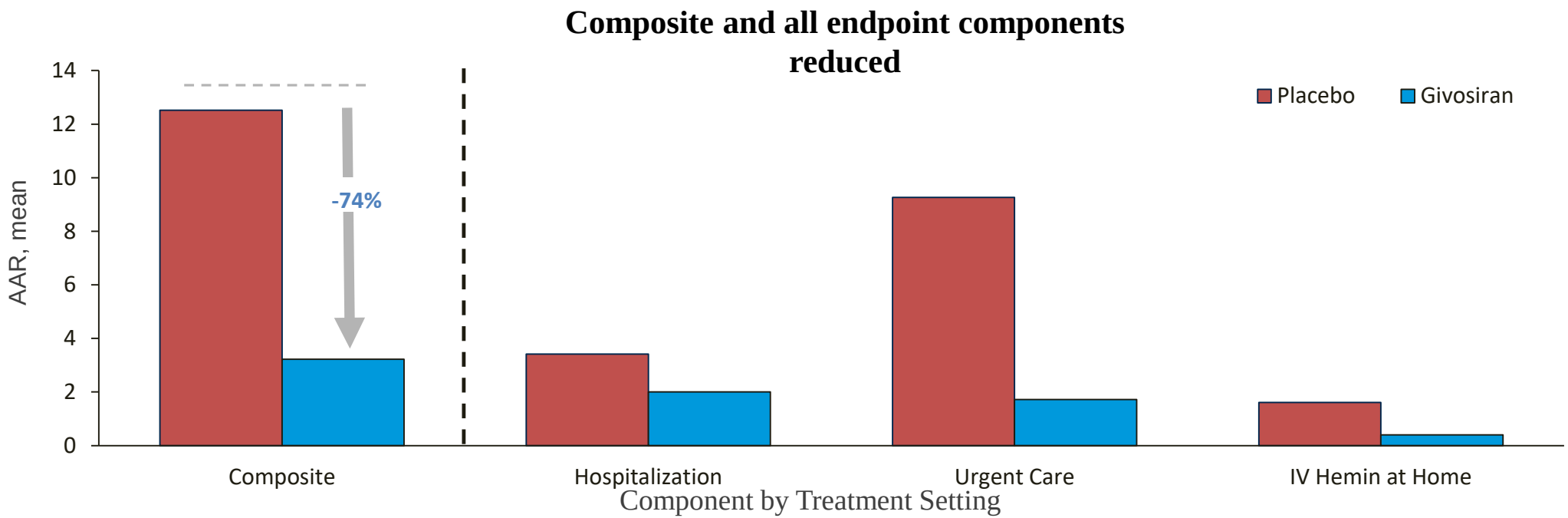
ALA and PBG are neurotoxic intermediates associated with attacks or other disease manifestations

Givosiran reduces the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of ALA and PBG

- GIVLAARI [Package Insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; 2019.

Phase 3 clinical trial: Primary Efficacy Endpoint: Annualized Attack Rate (AAR) in Patients with AIP

Primary Endpoint	Givosiran (N=46)	Placebo (N=43)	Rate Ratio (95% CI) (givosiran vs placebo)	P-Value
Composite AAR, mean (95% CI)	3.2 (2.25, 4.59)	12.5 (9.35, 16.76)	0.26 (0.16, 0.41)	6.04×10^{-9}



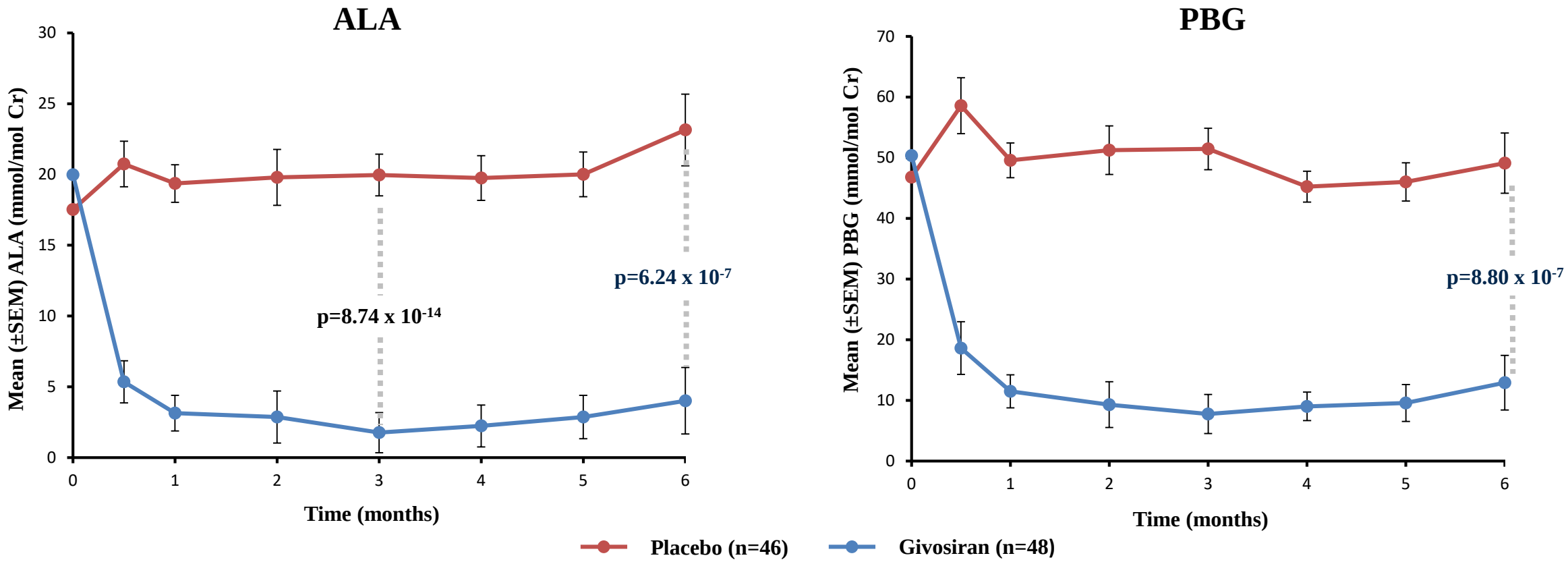
The efficacy data described above, based on data from the ENVISION study as reported in September 2019, may differ from the efficacy data contained in the U.S. Prescribing Information for GIVLAARI

Mean AAR was derived using the negative binomial regression model; mean AAR for components was duration-weighted AAR; median AAR was calculated from the individual's patient's AAR

Gouya et al. Presented at the International Congress on Porphyrins and Porphyrias, September 2019

ALA and PBG Levels in AIP Patients

- Givosiran showed robust and sustained reductions in urinary ALA and PBG over six months
- Mean ALA and PBG were reduced by 77% and 76%, respectively, compared with baseline at 6 months
- Median ALA and PBG were reduced by 86% and 91%, respectively, compared with baseline at 6 months



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Gouya et al. Presented at the International Congress on Porphyrins and Porphyrias, September 2019

Common Adverse Events (≥5% difference in treatment groups)

Category, n (%) / number events	Placebo (N=46)	Givosiran (N=48)
AEs with Higher Frequency in the Givosiran Group		
Injection site reaction	0	8 (16.7)/15
Nausea	5 (10.9)/6	13 (27.1)/15
Chronic kidney disease	0	5 (10.4)/5
Glomerular filtration rate decreased	0	3 (6.3)/3
Rash	0	3 (6.3)/3
Alanine aminotransferase increased	1 (2.2)/1	4 (8.3)/6
Fatigue	2 (4.3)/2	5 (10.4)/6

- Majority of ALT elevations were mild to moderate, occurred ~3 to 5 months after givosiran started, and resolved or stabilized by Month 6

  ALT > 3x ULN in 7 (14.6%) givosiran patients and 1 (2.2%) placebo patient.
- 7 (15%) givosiran patients and 2 (4.3%) placebo patients had renal AEs of increased creatinine and/or decreased eGFR, including 5 AEs of CKD in givosiran patients
- Generally small increases in serum creatinine (median change 0.07 mg/dL at Month 3) and decreases in eGFR with givosiran that resolved or stabilized by Month 6

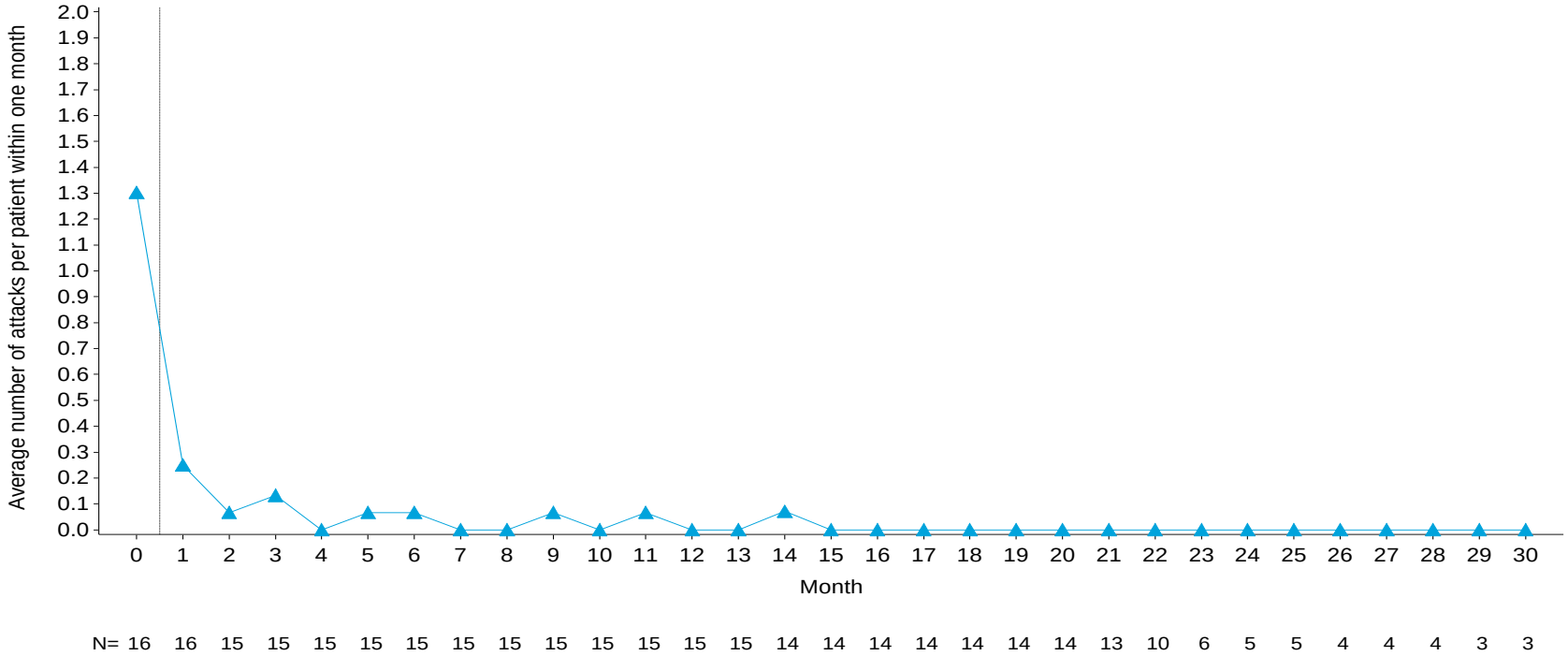
AE, Adverse Event

Balwani Met al. N Engl J Med. 2020 Jun 11;382(24):2289-2301

Phase 1/2 Open Label Extension (OLE) Results

Sustained Reduction of Attack Rate in Recurrent Attack Patients Over Time

- **Ongoing monthly dosing at 2.5 mg/kg maintained the reduction in mean attack rate out to Month 30, with median patient-level AAR of 0.22**



- Data as of 19 Apr 201[illegible]
- * Previously reported Sardh et al. EASL Meeting, Apr 2018; Anderson et al. AASLD Meeting, Nov 2018; Bissell et al. EAN Meeting, June 2019. OLE: Open-label extension. AAR: Annualized attack rate
- †Attacks requiring hospitalization, urgent health care visit, or IV hemin at home
- Month 0: Run-In Period in Phase 1 Part C, and the estimate is calculated as total number of attacks/total duration in months.
- Month 1 and beyond are categorized relative to the first dose of givosiran 2.5mg/kg QM in Phase 1/2 OLE, and the estimate is calculated as total number of attacks/total number of patients reached that month.
- The dashed line indicates the gap in time between Phase 1 Part C baseline and the first visit in Study Phase 1/2 OLE.
- One month = 28 days is used in categorization.

Bonkovsky et al. Presented at the International Congress on Porphyrins and Porphyrias, September 2019

Summary

- Reductions in annualized rate of composite porphyria attacks in patients with AHP were sustained or enhanced during the OLE
- Givosiran treatment led to sustained lowering of ALA and PBG levels
- Reductions in the annualized days of hemin use in patients with AHP were sustained
- Givosiran treatment led to reductions in daily worst pain and analgesic use, and improvements in quality of life compared to placebo according to PCS of the SF-12 and PPEQ measurements
- Safety profile of givosiran remained acceptable

Monitoring on Givosiran

- Liver enzymes
- Creatinine and eGFR
- Amylase and Lipase
- Homocysteine
- Vitamin B12/Folate/B6

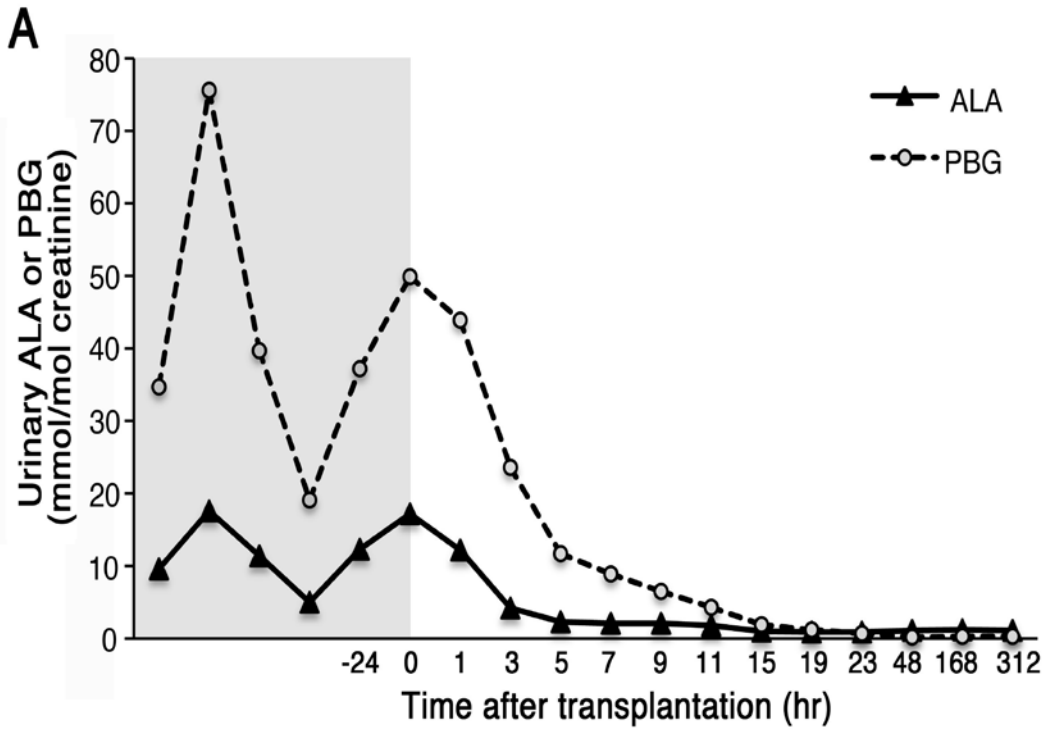
Balwani Met al. N Engl J Med. 2020 Jun 11;382(24):2289-2301, To-Figueras J, et al, J Inherit Metab Dis. 2021 Jul;44(4):961-971Vassiliou D et al, J Intern Med. 2021 Oct;290(4):928-930

Liver Transplantation

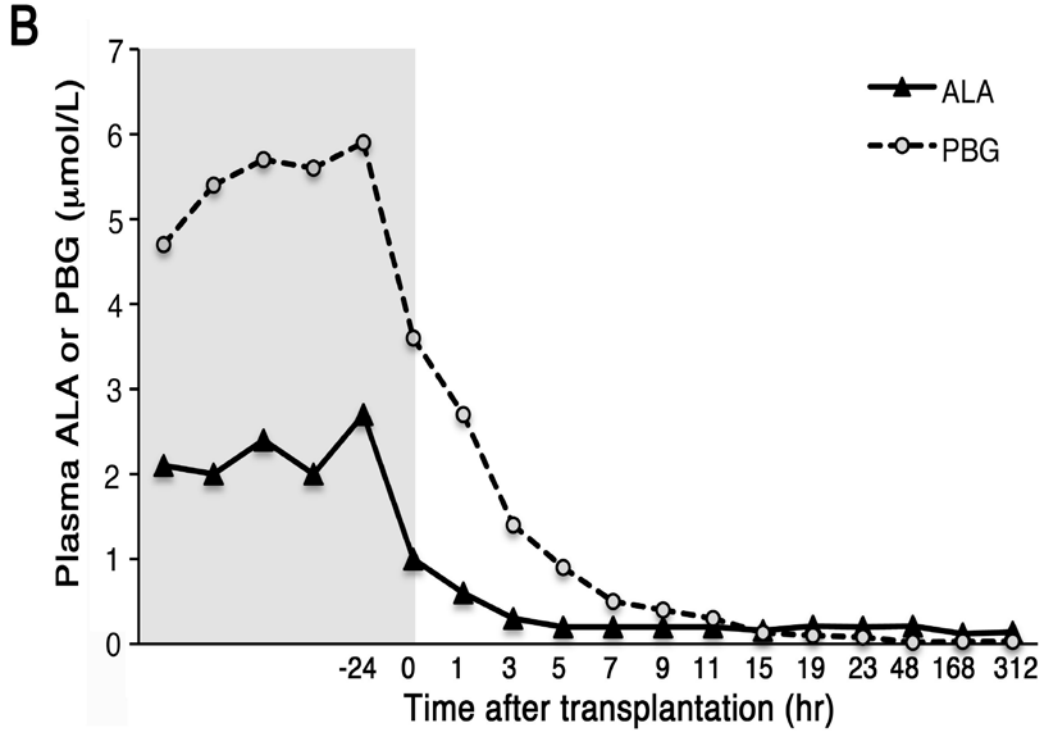
- Orthotopic liver transplantation (OLT) has been successful and curative in patients with severe, disabling, intractable attacks that are refractory to hemin therapy.
  - Considered a treatment of last resort
  - Patients who already have advanced neuropathy with quadriplegia and respiratory paralysis are considered poor candidates for transplantation
- Domino liver transplant from patients with AIP resulted in acute attacks in recipients (Dowman J et al 2011)
- Living donor transplant from sibling resulted in recurrence of AIP after transplantation (Al-Samkari H et 2019)

Liver Transplantation Rapidly Normalized Plasma and Urinary ALA & PBG

Liver Transplant

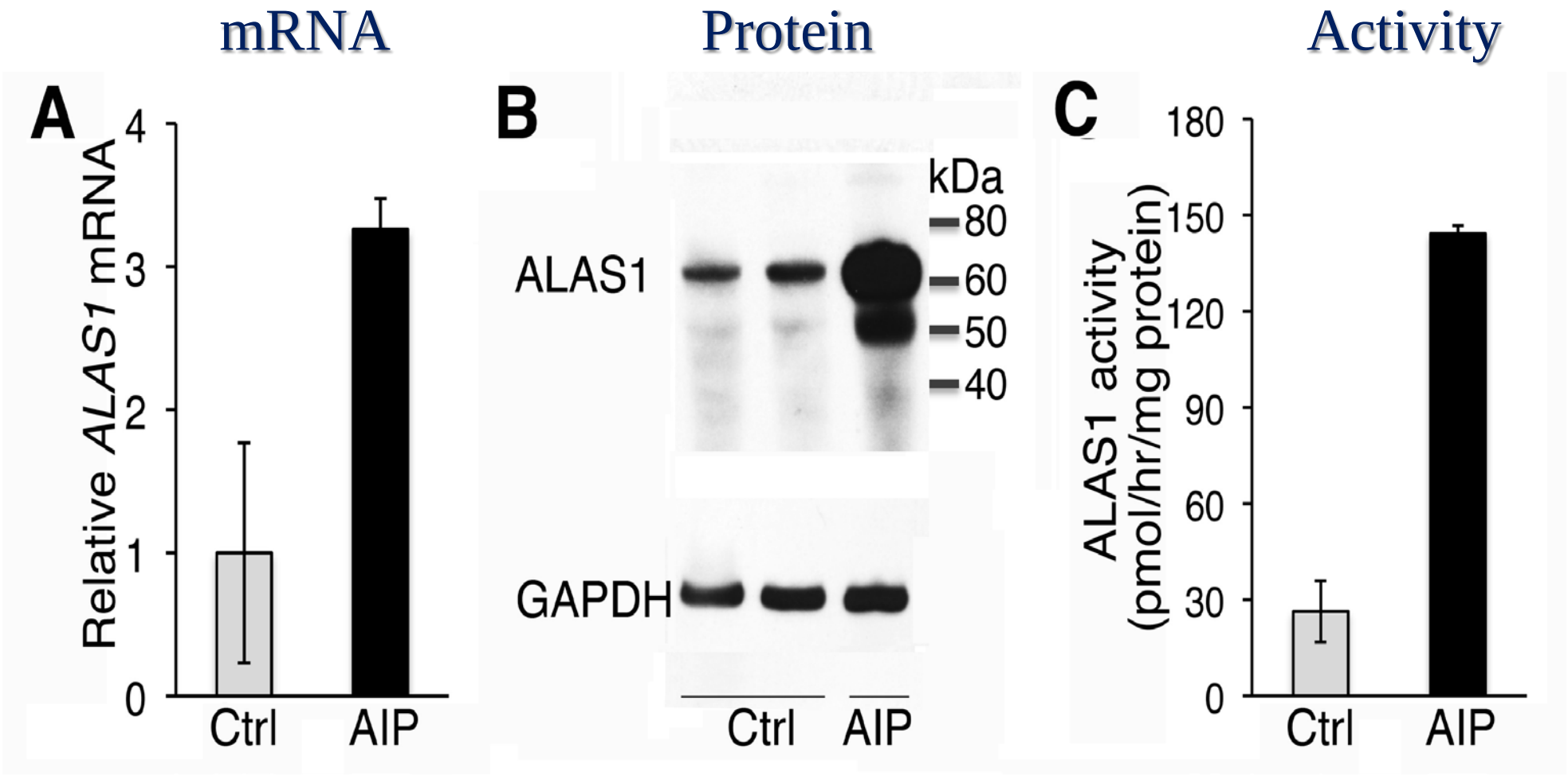


Liver Transplant



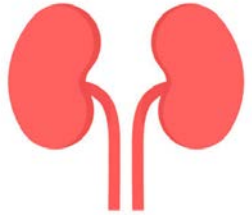
Yasuda M, Erwin AL, Liu LU, et al. Liver Transplantation for Acute Intermittent Porphyria: Biochemical and Pathologic Studies of the Explanted Liver. Mol Med. 2015;21(1):487-495. Published 2015 Jun 5. doi:10.2119/molmed.2015.00099

Hepatic ALAS1 Expression is Markedly Increased in AIP Patient



Yasuda M, Erwin AL, Liu LU, et al. Liver Transplantation for Acute Intermittent Porphyria: Biochemical and Pathologic Studies of the Explanted Liver. Mol Med. 2015;21(1):487-495. Published 2015 Jun 5. doi:10.2119/molmed.2015.00099

Long Term Complications: Kidney disease



- Porphyria associated kidney disease (PAKD) occurs in >50% of pts with symptomatic AIP
  - 60% of pts with PAKD have HTN
- PEPT2 is involved in reabsorption of ALA
  - PEPT2 variants may alter tubular reabsorption
  - Independent variable for severity of PAKD
- Pathology: chronic tubulo-interstitial changes
- Kidney transplant in ESRD patients
  - immunosuppression well tolerated
- Kidney transplant can improve acute attack symptoms

1. Pallet N, Karras A, Thervet E, Gouya L, Karim Z, Puy H. Porphyria and kidney diseases. Clinical kidney journal. 2018;11(2):191-197. doi:10.1093/ckj/sfx146
2. Tchernitchko D, Tavernier Q, Lamoril J, et al. A Variant of Peptide Transporter 2 Predicts the Severity of Porphyria-Associated Kidney Disease. Journal of the American Society of Nephrology. 2017;28(6):1924-1932. doi:10.1681/asn.2016080918
3. Lazareth H, Talbi N, Kamar N, Levi C, Moulin B, Caillard S, Frimat L, Chemouny J, Chatelet V, Vachey C, Snanoudj R, Lefebvre T, Karras A, Gouya L, Schmitt C, Puy H, Pallet N. Kidney transplantation improves the clinical outcomes of Acute Intermittent Porphyria. Mol Genet Metab. 2020 Sep-Oct;131(1-2):259-266

Long Term Complications: Liver Disease

Liver disease

- Increased risk of developing Primary Liver Cancer
- Chronic increased ALA levels could lead to free radical generation → hepatic carcinogenesis
- Increased risk of HCC (1.5%) in a US study
  - Occurred in the absence of cirrhosis or fibrosis
- Surveillance recommended at age 50 with AFP and USG[2]
- Risk of fibrosis and chronic inflammatory hepatic disease with frequent hemin use

1. Andant C, Puy H, Bogard C, et al. Hepatocellular carcinoma in patients with acute hepatic porphyria: frequency of occurrence and related factors. Journal of hepatology. 2000;32(6):933-939. doi:10.1016/S0168-8278(00)80097-5
2. Saberi B, Naik H, Overbey JR, et al. Hepatocellular Carcinoma in Acute Hepatic Porphyrias: Results from the Longitudinal Study of the U.S. Porphyrias Consortium. Hepatology (Baltimore, Md). Published online July 18, 2020. doi:10.1002/hep.31460
3. Schmitt C, Lenglet H, Yu A, et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. Journal of internal medicine. 2018;284(1):78-91. doi:10.1111/joim.12750
4. Katell Peoc'h, Hana Manceau, Zoubida Karim, Staffan Wahlin, Laurent Gouya, Hervé Puy, Jean-Charles Deybach,Hepatocellular carcinoma in acute hepatic porphyrias: A Damocles Sword, Molecular Genetics and Metabolism, Volume 128, Issue 3, 2019,

Recommendations for Follow Up

TABLE 2. Follow-Up Assessments

			Sporadic and Recurrent Attacks		
	Latent	ASHE Every 12 Months	Every 3 Months	Every 6 Months	Every 12 Months
Medical history	As clinically indicated	X			X
Physical examination		X			X
Medication review		X			X
Quality of life		X			X
Biochemical tests					
Urine ALA and PBG		X			X
Additional laboratory tests					
CBC		X			X
CMP with eGFR		X			X
Hepatic function panel		X			X
Monitoring for HCC (>50 years)					
Liver US		X		X	
AFP		X		X	

Balwani et al Hepatology 2017

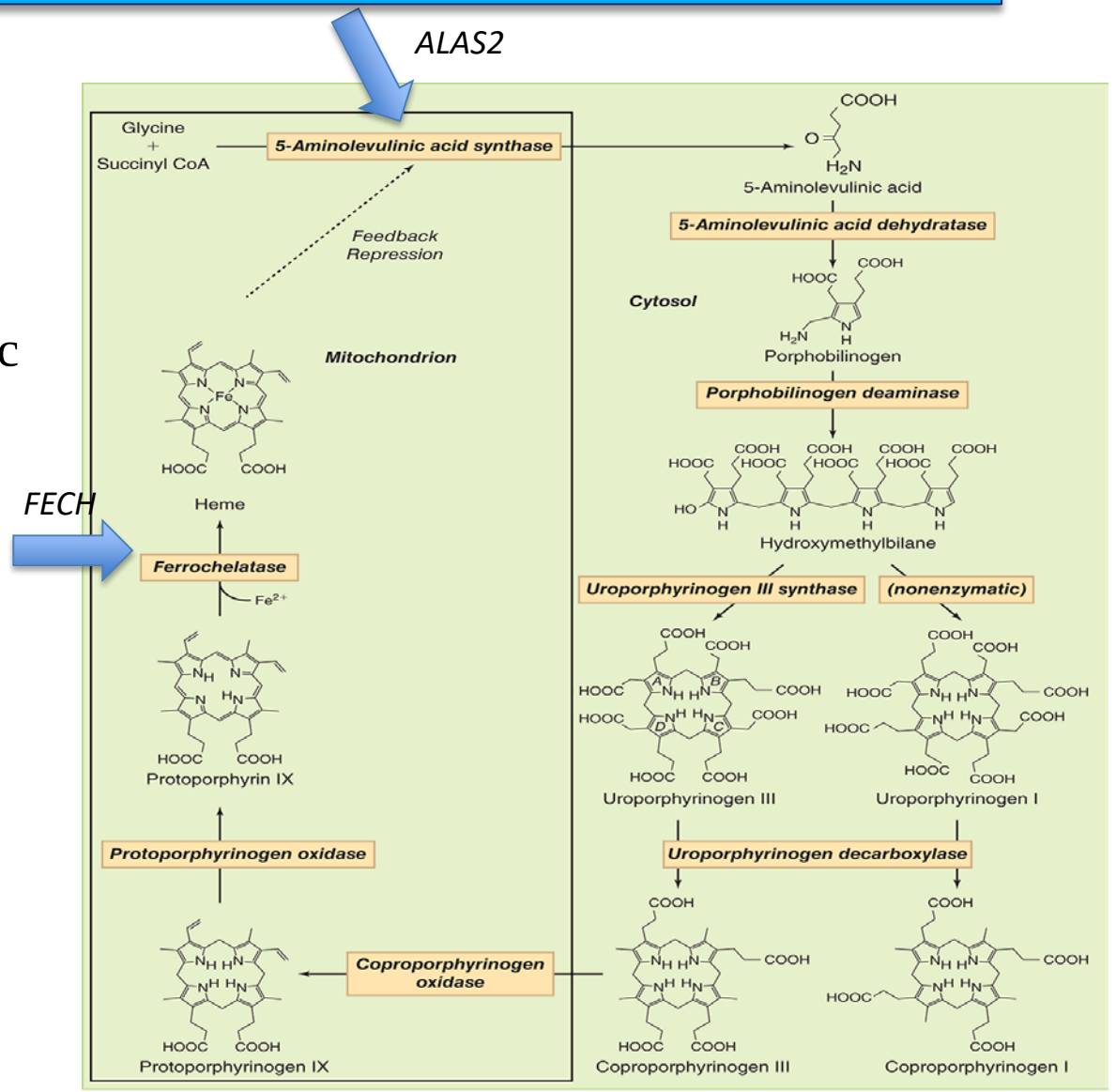
Summary

- The AHPs are a group of rare disorders, each occurring due to a deficiency in one of the enzymes of the heme-biosynthesis pathway
- Clinical manifestations are diverse including effects on the autonomic, central and peripheral systems
- Long term complications include neuropathy, chronic kidney disease and increase risk of HCC
- Diagnosis is made by biochemical testing on a spot sample of urine for PBG
- Genetic testing is useful for confirmation, identifying type of AHP and testing of family members
- Patients with recurrent attacks will need active medical management and monitoring

Cutaneous Porphyrias

Erythropoietic Protoporphyria (EPP)

- Most common cutaneous porphyria in children
- Results from a deficiency of ferrochelatase (FECH) the last enzyme in the heme biosynthetic pathway
- Accumulation of protoporphyrin (PROTO) in bone marrow reticulocytes, plasma, and liver.
- Diagnosed biochemically by demonstration of significantly elevated levels of protoporphyrins in erythrocytes, with predominantly metal-PROTO (97%) rather than z-PROTO (3%).



X-Linked Protoporphyria (XLP)

- Gain of function mutations and over expression of *ALAS2*
- Accounts for about 10% of cases in North America
- XLP males are more severely affected and significant clinical variability in XLP females
- Higher protoporphyrin levels and risk of liver disease

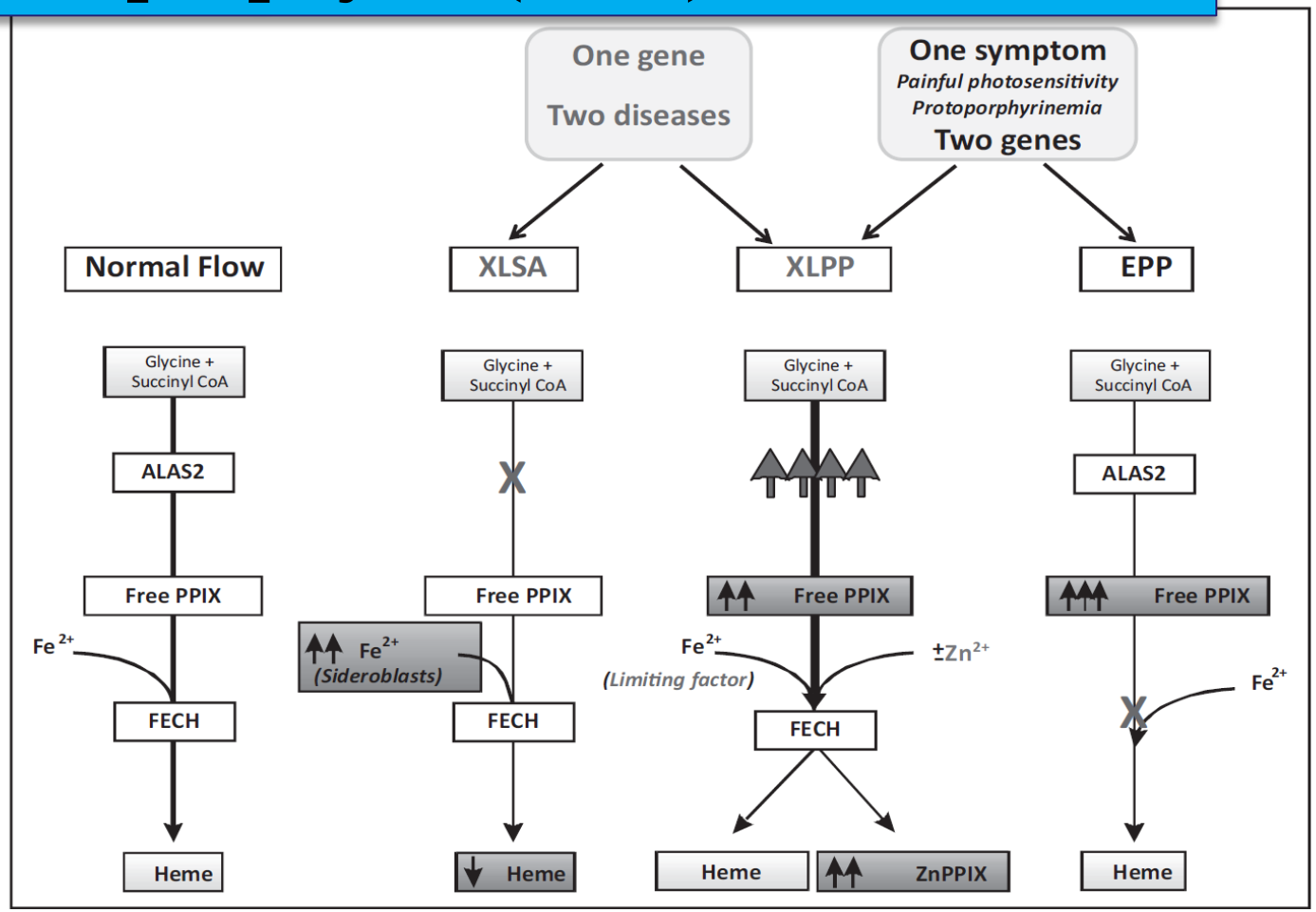


FIGURE 6. Physiopathology of erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLPP) and X-linked sideroblastic anemia (XLSA). Erythropoietic protoporphyria is caused by partial deficiency in ferrochelatase. X-linked protoporphyria results from increased activity of *ALAS2*. Loss of function *ALAS2* mutations causes recessive X-linked sideroblastic anemia. ALAS2, ALA synthase 2; PPIX, protopophyrin IX; ZnPPIX, zinc protoporphyrin IX; FECH, ferrochelatase.

Manceau et al 2017

EPP Prevalence

- Prevalence estimates range from 1:75,000 in the Netherlands to 1: 180,000 in Sweden
- Prevalence in the US is unknown
- Recent study from the UK Biobank showed that EPP was 1.7 to 3 times more common than previously estimated
- Average diagnostic delay is over a decade

Average age of symptom onset is **3-4 years**

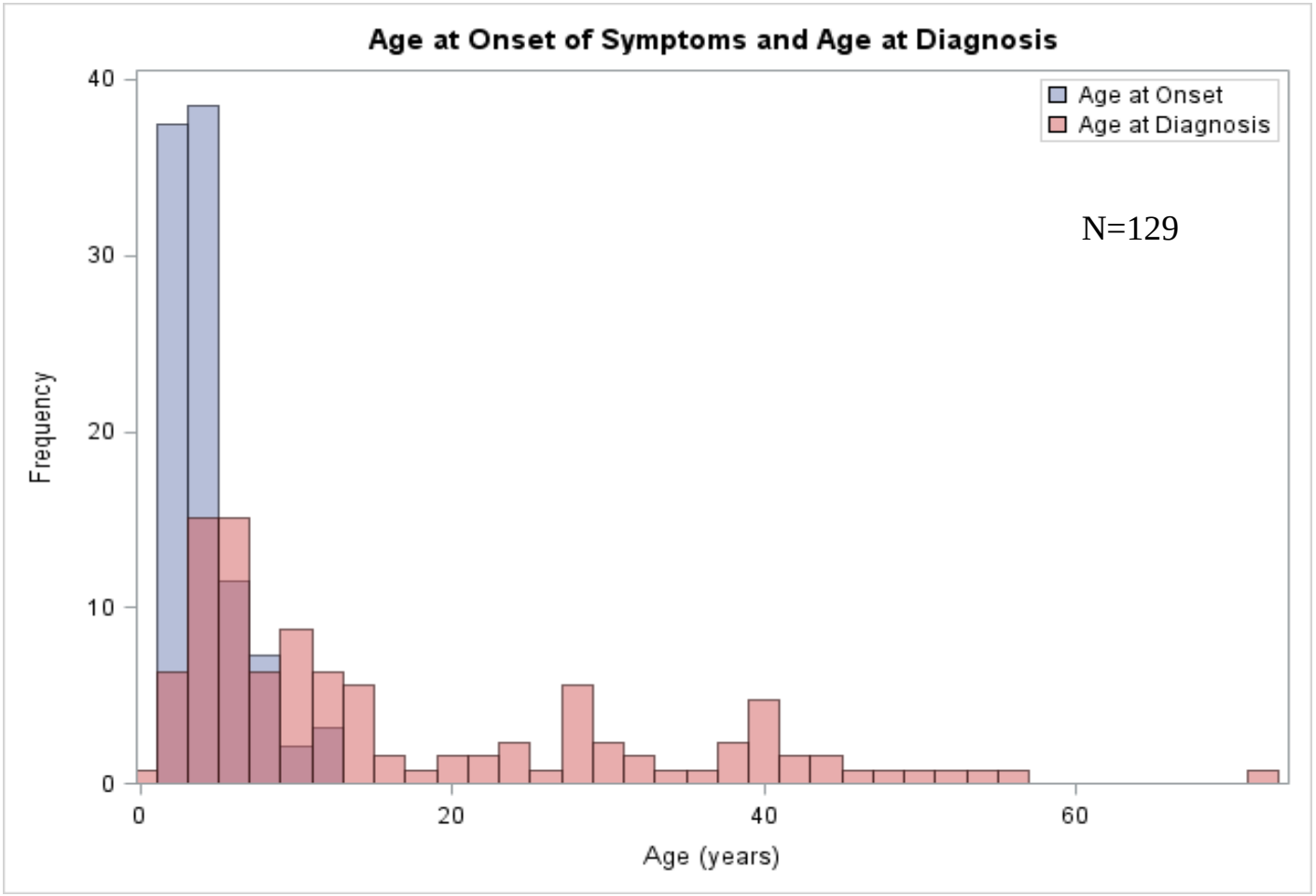
EPP is fully penetrant

Males and Females equally affected in EPP

Males more severely affected than females in XLP

Lala S, J. Pediatr 2018,
Balwani, M, JAMA Derm 2017

Diagnostic Delay



Mean numbers of years between symptoms and diagnosis=13 years

Genetics

Gene	Inheritance	Variant	Mechanism	Phenotype	% of cases
FECH	Autosomal Recessive	Pathogenic variant/IVS3-48 C	Loss-of-function	EPP	~90%
FECH	Autosomal Recessive	Pathogenic variant/Pathogenic variant	Loss-of-function	EPP	?*
FECH	Autosomal Recessive	IVS3-48C/IVS3-48 C	Loss-of-function	?	-
ALAS2	X-linked	Deletion of terminal exon of the ALAS2 gene	Gain-of-function	XLP M>F	2-10%
CLPX	Autosomal Dominant	Pathogenic variant	Dominant negative	CLPX associated EPP	Single family
?	?	Unknown	Unknown	EPP	~4%

*~4% of cases in the UK

Acquired EPP and XLP

- Typically later onset > 40 years
- Associated with myelodysplastic or myeloproliferative syndromes
- Results from a somatic mutation or deletion in the ferrochelatase gene in hematopoietic cells
- Acquired XLP has been reported in one case with somatic mosaicism in the bone marrow for a known pathogenic variant in *ALAS2* (p.Q548X)

D. Blagojevic et a; Ann. Hematol., 89 (2010), pp. 743-744, C. Aplin et al J Invest Dermatol, 117 (2001), pp. 1647-1649C.B. Livideanu et al J Invest Dermatol, 133 (2013), pp. 1688-1690

Pathophysiology

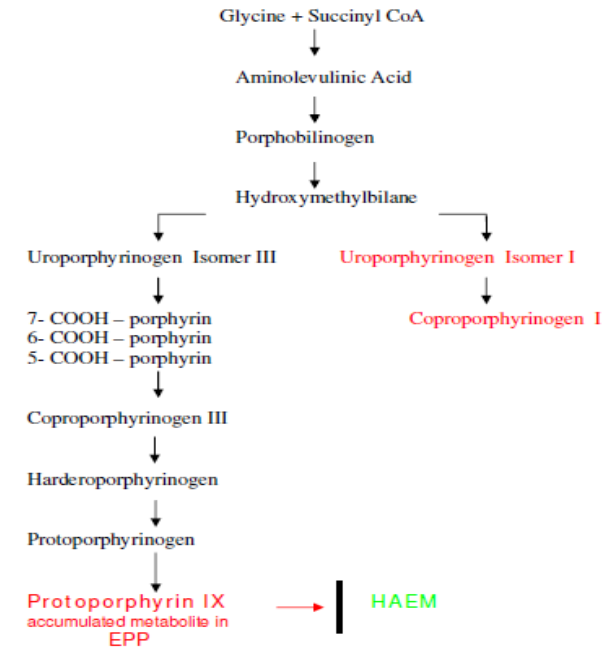
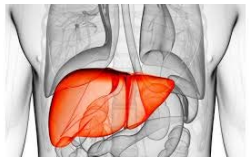


Figure I
The haem biosynthesis pathway.

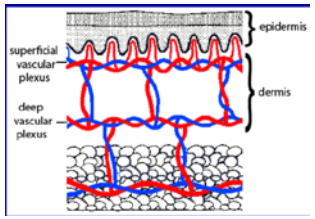
Bone marrow

Circulating RBCs Plasma

Liver



Vascular endothelium

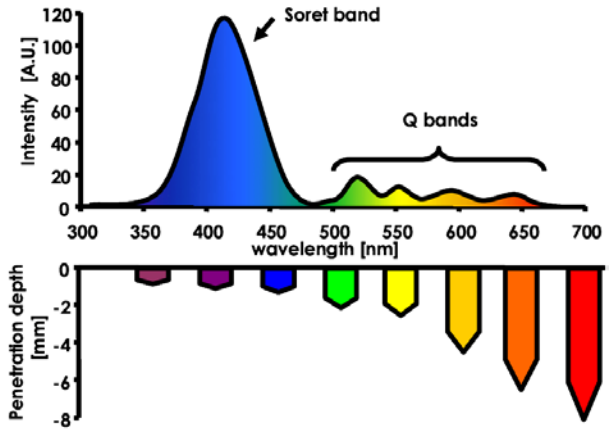


RBCs in skin blood vessels

Fig: Lecha M, Orphanet 2009

Pathophysiology

visible light spectrum (320-595 nm)

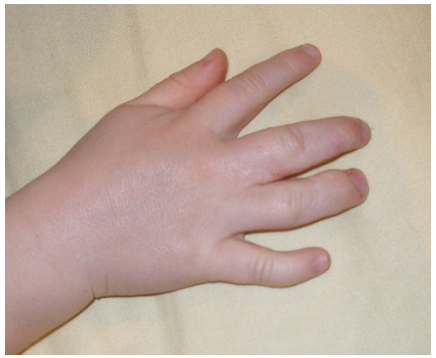


400-410nm

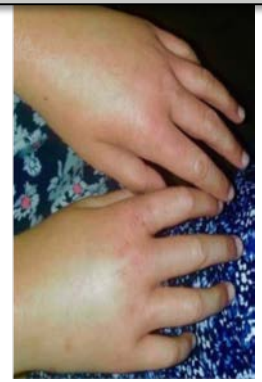
Variables

- Weather conditions
- Protoporphyrin levels
- Priming
- Fitzpatrick score

Photoactivation of PPIX
Formation of highly reactive singlet oxygen species



Photoactivation of accumulated vascular PPIX
Irreversible cellular damage/Necrosis
Complement activation/Mast cell degranulation
Inflammation/Erythema/Edema



<10 min to >2 hrs

Time to prodrome

Reversible

Prodrome

Tingling
Itching
Burning

Progression

Phototoxicity

Pain
Redness
Swelling

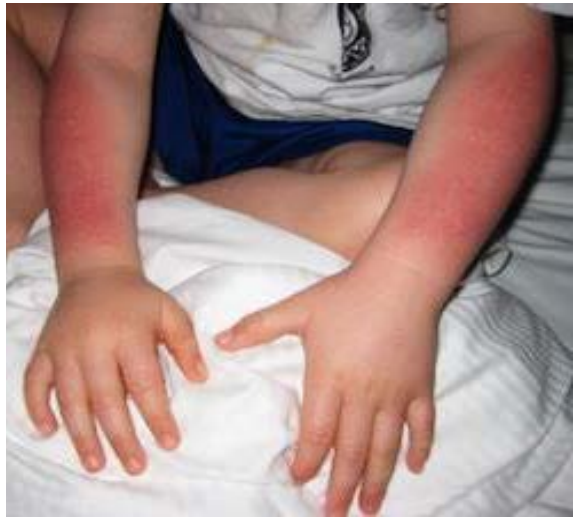
Recovery

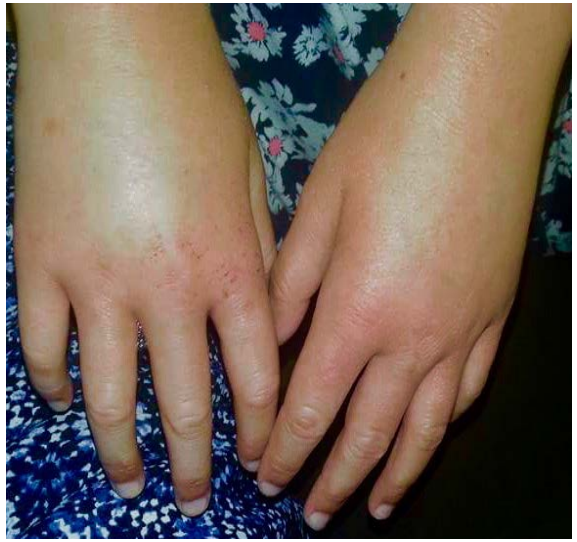
2-7 days

Sun avoidance
Decreased QoL

Adapted from Wensink et al 2021

Clinical manifestations

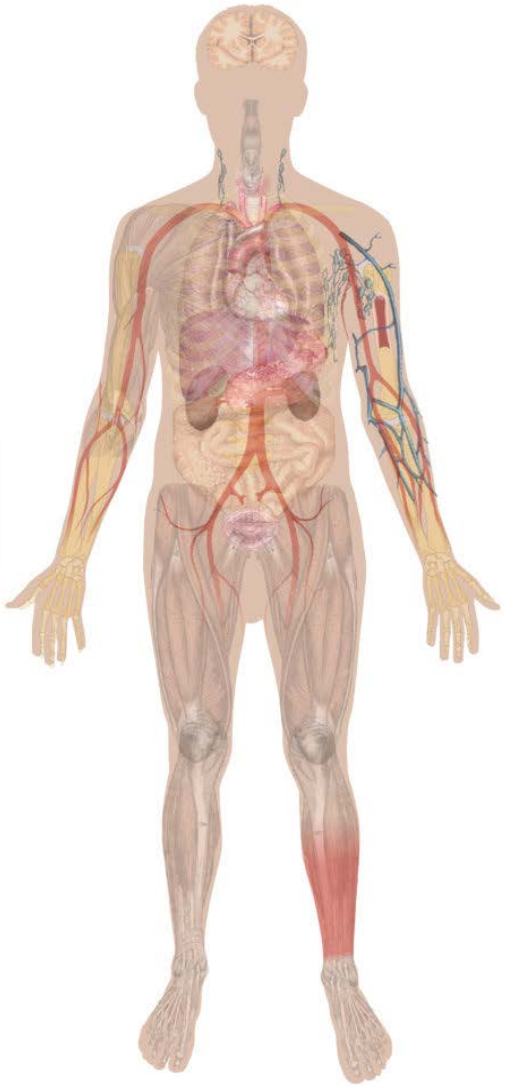




- **Acute, painful phototoxicity within minutes of sun-exposure**
- **Prodromal symptoms-tingling, burning, itching**
- **Erythema and Edema**
- **Recovery takes several days**
- **No blistering**

Multi-Systemic Involvement

Organ system	Signs and Symptoms
Liver	Elevated liver enzymes Cholestasis Gallstones Liver failure
Spleen	Anemia Thrombocytopenia Iron deficiency
Bone marrow	Phototoxicity Lichenification Palmar Keratoderma
Skin	Vitamin D deficiency Osteopenia
Skeletal	



Liver Disease in EPP

Liver Disease in EPP/XLP

Longitudinal study of the PC

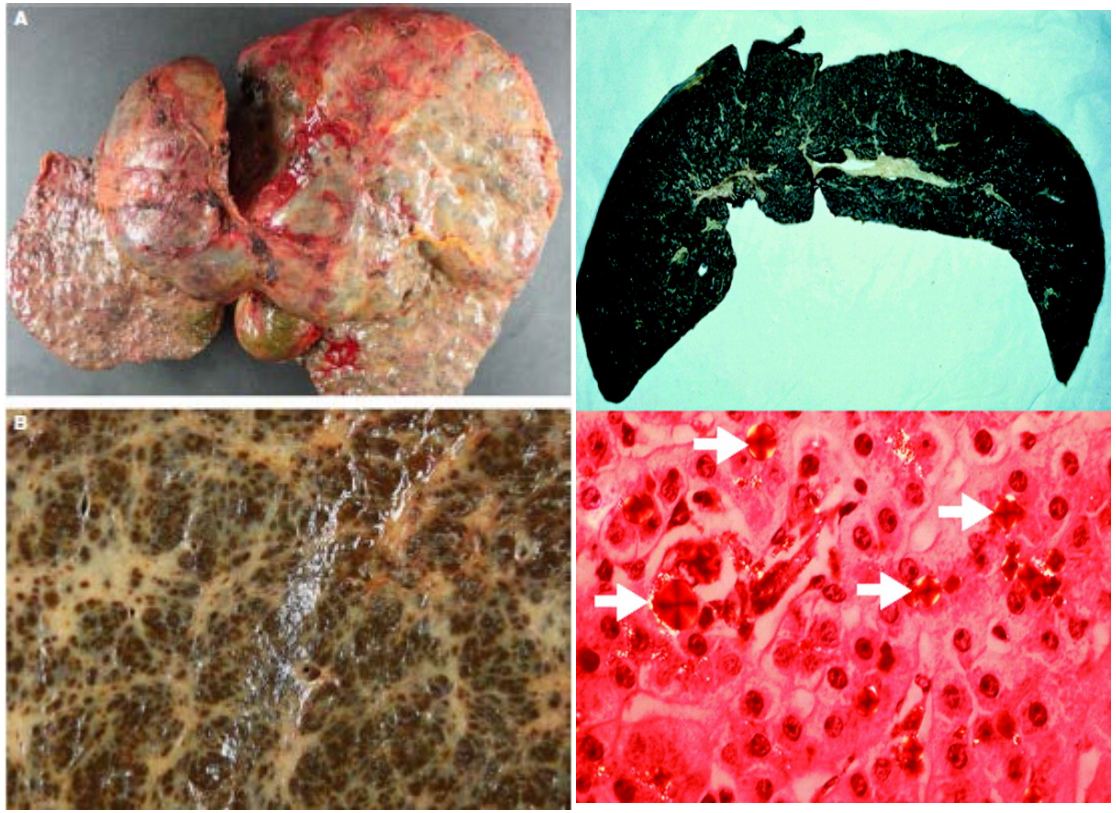
- 27% of patients with h/o abnormal liver enzymes
- 23.5% of patients with Gallstones

Single site data from Netherlands

- 29% of patients with hepatic steatosis
- 9.6% with fibrosis

Determinants of Risk

- Higher protoporphyrin levels
- Biallelic pathogenic variants in FECH
- Male patients with XLP
- Comorbid conditions?



Pic: Windon et al 2017

Balwani et al 2017, Wensink et al 2021

Management Approaches for EPP/XLP

Focused primarily on symptom avoidance and symptomatic management

Avoidance of phototoxic reactions
Sun protective clothing including long sleeves, gloves, and wide-brimmed hats
Sunscreens containing physical reflecting agents, window tints

Non-pharmacologic management of symptoms
Cold compresses, aloe, cold lotions, Ice packs, cold air, CBD

Use of supplements and medications
Vitamin C, Beta-carotene,
N-acetyl cysteine, Cimetidine

Management of progressive liver disease
Hemin, Plasmapheresis, Cholestyramine,
Ursodeoxycholic acid (UCDA)

Liver transplantation
End-stage liver disease
Not curative
High risk of morbidity and mortality

Bone marrow transplantation
Curative
+/- with Liver transplantation
High risk of morbidity and mortality

Pharmacologic management
Scenesse, subcutaneously administered α-MSH analogue

Afamelanotide (Scenesse)

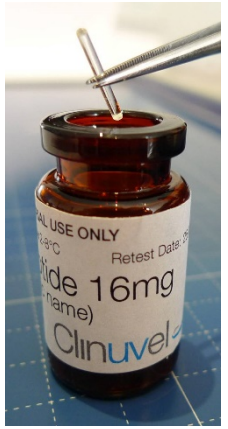
ORIGINAL ARTICLE

Afamelanotide for Erythropoietic Protoporphyria

J.G. Langendonk, M. Balwani, K.E. Anderson, H.L. Bonkovsky, A.V. Anstey, D.M. Bissell, J. Bloomer, C. Edwards, N.J. Neumann, C. Parker, J.D. Phillips, H.W. Lim, I. Hamzavi, J.-C. Deybach, R. Kauppinen, L.E. Rhodes, J. Frank, G.M. Murphy, F.P.J. Karstens, E.J.G. Sijbrands, F.W.M. de Rooij, M. Lebwohl, H. Naik, C.R. Goding, J.H.P. Wilson, and R.J. Desnick

- US trial (6 months) :
  Increased pain free sun exposure in afamelanotide group vs placebo (median, 69.4 hours vs 40.8 hours, p=0.04)
- European Union study (9 months)
  Increased pain free sun exposure in afamelanotide group vs placebo (median 6.0 hours vs 0.8 hours; p=0.005)
  Decreased number of phototoxic reactions (77 vs 146, p=0.04)

Improved quality of life in both studies

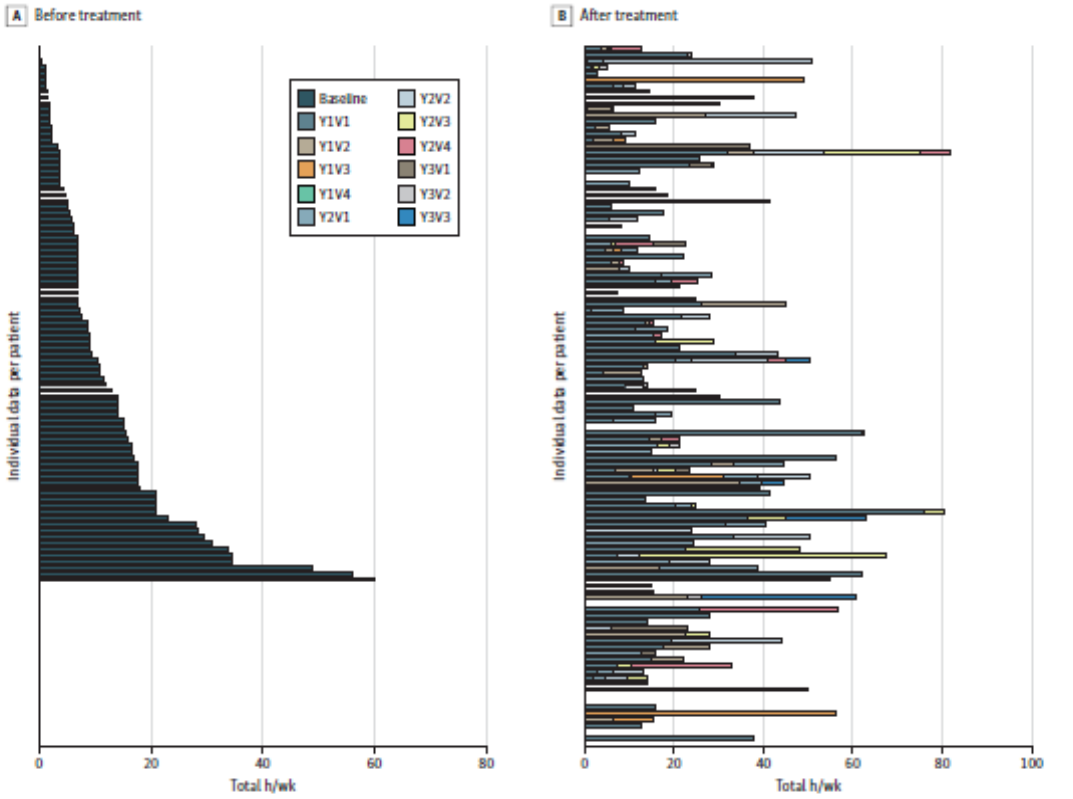


Afamelanotide (α-MSH stimulating analogue)

Approved by the EMA in 2014 and FDA in 2019

Afamelanotide in clinical practice: single site data

Figure. Individual Patient-Reported Time Outside



Before (A) and after (B) treatment with afamelanotide, displayed as total hours spent outside during a week for their best treated period. In panel B, the total length of the bar represents the total hours in the week in which time spent outside was the longest (maximum). The colors provide information on how time spent outside increases over the subsequent visits, until it reaches its maximum. For patients with missing data, before or after treatment, the value 0 was filled in. Each line of data represents the same patient in panel A and panel B. Y indicates year; V, visit.

- Improved clinical outcomes
- Less painful phototoxic reactions
- Improved quality of life
- Minor self limiting adverse events
- Improved outcomes with longer treatment duration
- 98% continuation rate
- Treatment response varied between individuals
- Mean time spent outside during treatment increased significantly by an added 6.1 hours per week compared to baseline

Wensink D et al, JAMA Dermatol. 2020 May 1;156(5):570-575

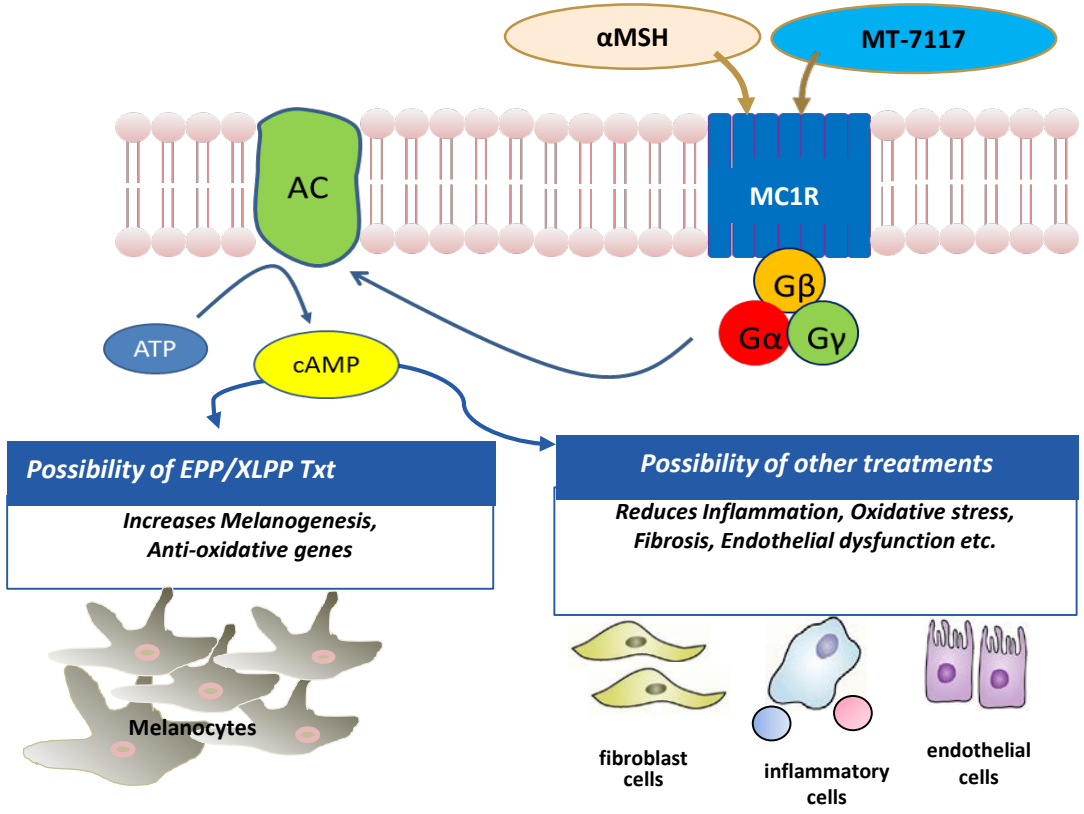
Investigational Therapies

MT-7117 (Dersimelagon) Proposed Mechanism of Action

MT-7117 is a synthetic, orally-administered, small molecule agonist of the melanocortin-1 receptor (MC1R)

Proposed Mechanisms of MC1R Agonism in EPP/XLP

1. Activation of MC1R, coupled to the cAMP signaling pathway, leads to stimulation of melanogenesis and a switch from the pheomelanin synthesis to the production of eumelanin pigments (protective)
2. Increased melanin reduces penetration of the damaging UV and visible light
3. MC1R agonists may also:
   - Enhance DNA repair
   - Upregulate antioxidant enzymes
   - Reduce production of pro-inflammatory cytokines (minimizing the PPIX-mediated damage and resulting pain)

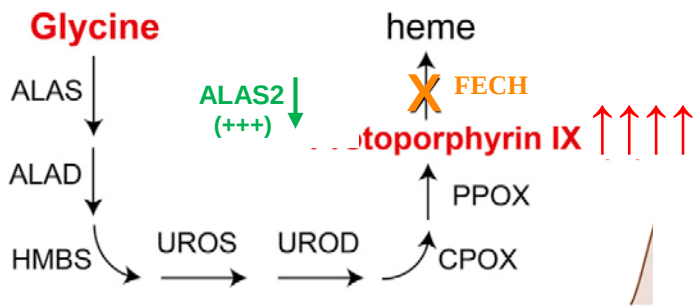


Ahmed TJ, et al. *Intl J Inflamm.* 2013;Article ID 985815:1-10; Brzoska T, et al. *Endocrine Reviews.* 2008;29(5):581-602.

Bitopertin: Highly selective glycine reuptake inhibitor (GlyT-1)

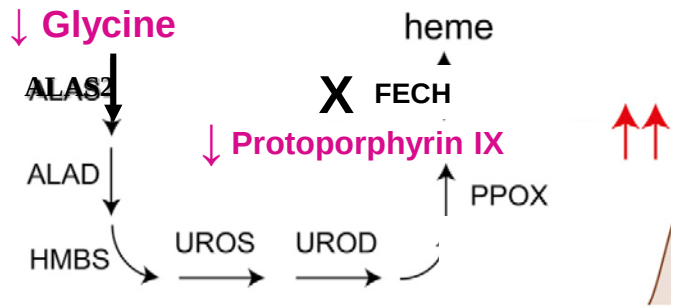
Reduce disease-causing PPIX by limiting uptake of glycine in developing erythrocytes

EPP and XLPP Patients
High PPIX Levels



Mutations result in reservoir of supra-physiologic levels of PPIX

Bitopertin Treatment
Reduce and Normalize PPIX Levels



Potential Functional Cure for EPP and XLPP Patients

Acknowledgements:

Patients and their families

Study investigators and coordinators

Alnylam, Mitsubishi and Disc for sharing slides