INHIBITION OF GLYCINE TRANSPORTER 1 REDUCES EPP PHOTOTOXICITY IN A MOUSE MODEL OF ERYTHROPOIETIC PROTOPORPHYRIA

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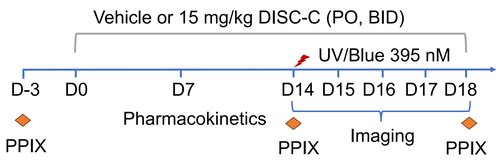
INTRODUCTION

Erythropoietic protoporphyria (EPP) is a genetic disorder typically caused by decreased activity of ferrochelatase (FECH), the enzyme that inserts ferrous iron into protoporphyrin IX (PPIX) in the final step of heme biosynthesis. EPP phototoxicity occurs when photosensitive metal-free PPIX in erythrocytes and skin is exposed to irradiation from sunlight. Patients with EPP suffer from acute and severe phototoxicity after sun exposure, significantly impacting their quality of life.

Glycine transporter 1 (GlyT1) mediates the import of glycine, a precursor for heme synthesis, to erythroid cells. The GlyT1 inhibitor bitopertin has been shown to decrease whole blood PPIX levels, improve measures of light tolerance, and reduce phototoxic reactions in patients with EPP.[1,2] In preclinical studies, bitopertin has been shown to reduce PPIX accumulation in the blood and alleviate liver fibrosis in the Fech^{m1Pas}/Fech^{m1Pas} EPP mouse model.[3] This study evaluated the effects of an orally bioavailable GlyT1 inhibitor, DISC-C, on PPIX levels and skin phototoxicity induced by ultraviolet (UV)/blue light in EPP mice.

METHODS

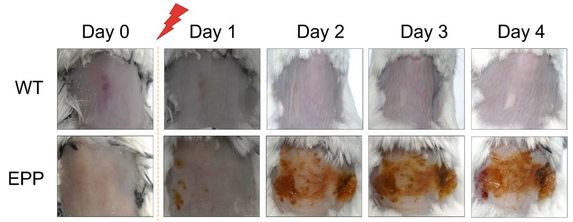


BID = twice a day

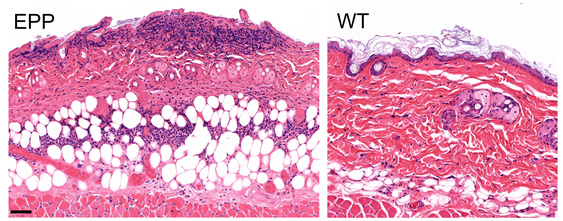
- EPP mice were orally (PO) administered Vehicle or DISC-C from Days 0 to 18
- Images were captured before light exposure on Day 14 and daily from Days 15 to 18
- Red blood cell (RBC) PPIX levels were measured by flow cytometry

RESULTS

EPP Mice Developed Progressively Worsening Skin Lesions after Exposure to Blue/UV Light



After exposure to blue/UV light, EPP mice, but not wild-type (WT) mice, developed progressively worsening skin lesions.



EPP mice, but not WT mice, developed skin lesions with histopathological characterization of sterile abscesses and dermal lymphocyte infiltration (scale bar = 50 µm).

DISC-C Is a Potent, Selective, GlyT1 Inhibitor

Assays	EC_{50}
PPIX inhibition in K562-EPP cells[1]	2.4 nM
In vitro glycine uptake inhibition (mouse blood)[2]	3.1 nM*
In vivo glycine uptake inhibition (mouse blood)[3]	1.8 nM*

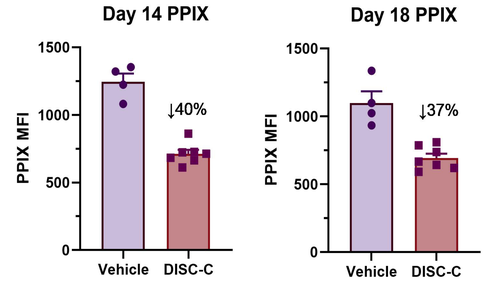
EC_{50} = half maximal effective concentration

1. *DISC-C decreased PPIX accumulation in K562-EPP cells, which have excessive PPIX accumulation due to decreased FECH activity.*
2. *DISC-C inhibited the uptake of ^{3}H-glycine in mouse peripheral RBCs in vitro.*
3. *DISC-C inhibited the uptake of ^{3}H-glycine in mouse peripheral RBCs in vivo.*

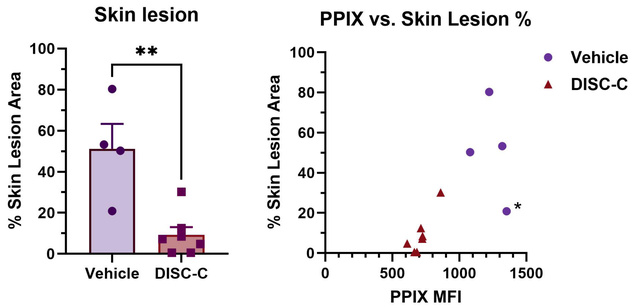
** Unbound plasma drug concentration*

RESULTS

GlyT1 Inhibition Decreased Protoporphyrin IX in Red Blood Cells of EPP Mice

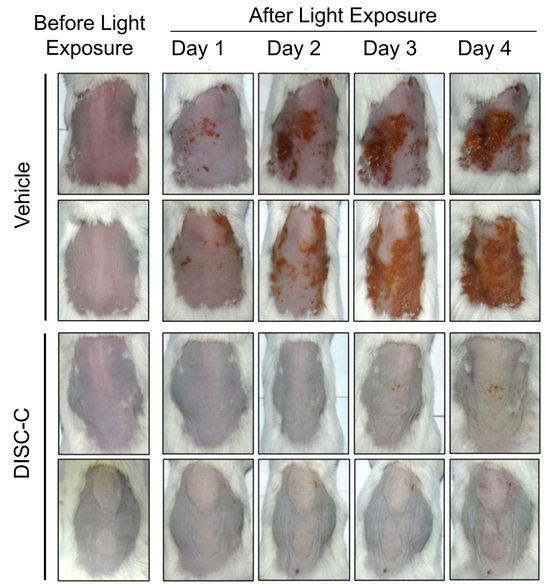


PPIX = protoporphyrin IX *MFI = mean fluorescence intensity*



** This animal had a region with thickened skin that prevented development of skin lesions within the region.*

GlyT1 Inhibition Ameliorated Skin Lesions after UV/Blue Light Exposure in EPP Mice



- GlyT1 inhibitor DISC-C decreased % skin lesion area
- The severity of phototoxicity correlated with RBC PPIX levels
- Results support PPIX as the pathological driver of phototoxicity

CONCLUSIONS

- EPP mice developed progressively worsening skin lesions after exposure to blue/UV light, with histopathological characterization of sterile abscesses, hyperkeratosis, and dermal lymphocyte infiltration.
- Repeated administration of the orally bioavailable GlyT1 inhibitor DISC-C decreased glycine uptake and PPIX levels in RBCs and mitigated phototoxicity in EPP mice. The extent of PPIX decreases in EPP mice administered DISC-C was comparable to that observed in patients with EPP treated with bitopertin in Phase 2 studies.
- Data supports the rationale for using a GlyT1 inhibitor to treat patients with EPP.

REFERENCES

[1] Dickey A, et al. EHA Library. 13Jun2024; 419662; P1575.
[2] Ross G, et al. EHA Library. 13Jun2024; 419656; P1569.
[3] Wu M, et al. Blood. 2022;140(Suppl1):8192-8193.

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