Assessment of the effect of hepatic impairment on iptacopan pharmacokinetics

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Introduction

Iptacopan (LNP023) is an oral, first-in-class, low molecular weight inhibitor of Factor B in clinical development for the treatment of diseases associated with activation of the alternative complement pathway. Phase 3 studies of iptacopan are ongoing in paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis, IgA nephropathy, and atypical hemolytic uremic syndrome. Previous studies indicated the liver as the primary organ of iptacopan elimination, necessitating this study.

Methods

Participants with mild (n=8; Child-Pugh [CP] score 5–6), moderate (n=8; CP score 7–9) or severe (n=6; CP score 10–15) hepatic impairment (HI) or normal liver function (n=16; control group) were enrolled. Each participant with HI was demographically matched with a control participant. All participants received a single oral dose of iptacopan 200 mg, followed by serial pharmacokinetic sampling of total and unbound iptacopan.

Results

Treatment with iptacopan was well tolerated. The G_{mean} ratio (90% CI) for iptacopan C_{max} and AUC are shown below for each group relative to the control group. HI had no clinically relevant effect on peak (C_{max}) or total (AUC) iptacopan plasma exposure. Unbound iptacopan exposure increased by 2–4 fold in participants with severe HI.

	Geometric mean ratio (90% CI)		
	Mild HI vs Control	Moderate HI vs Control	Severe HI vs Control
Cmax	1.04 (0.89-1.22)	0.95 (0.82-1.11)	0.92 (0.77-1.10)
AUCinf	1.03 (0.88-1.22)	1.01 (0.86-1.19)	1.03 (0.85-1.25)
AUClast	1.03 (0.88-1.21)	1.01 (0.86-1.19)	1.03 (0.85-1.25)

AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; G_{mean}, geometric mean.

Conclusion

The lack of effect of HI on total iptacopan exposure indicates that no dose adjustment is required. The increase in unbound iptacopan exposure with increasing severity of HI is an expected consequence of reduced hepatic protein synthesis. These results support the clinical dose of oral iptacopan 200 mg twice daily to provide durable inhibition of the alternative pathway in patients with hepatic impairment.

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Theme

The Kidney Losing Function: Dialysis, CKD-MBD, Anemia and Interventional Nephrology

Topic

CKD, experimental models, biomarkers, precision medicine

Key words (5 maximum)

complement, iptacopan, C3G, IgAN, hepatic impairment

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