Risk of Acute Liver Injury with Protease Inhibitor-Based Antiviral Therapy for Hepatitis C

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Background

- Acute liver injury has been reported among protease inhibitor (PI)-based direct acting antivirals (DAA) for the treatment of hepatitis C virus (HCV) infection
- Cytochrome P450 impairment in cirrhosis may result in toxic levels of PIs
- No comparative analyses have evaluated if PI-based DAAs have higher rates of acute liver injury than non-PI-based DAAs by cirrhosis status

Specific Aim

- Compare rates of acute liver injury with PI- versus non-PI-based DAA, accounting for baseline cirrhosis status

Methods

- **Study Design/Patients**:
  - Retrospective cohort study of 75,187 U.S. Veterans in the 1945-1965 Birth Cohort with treatment-naïve HCV initiating DAAs January 1, 2014 to June 30, 2019
  - Excluded patients with outcome of interest or coagulopathy within 2 years of DAA, or ever hepatitis B surface antigen+
- **Outcomes: Acute Liver Injury (ALI)** (≤30 days after DAA initiation):
  - Alanine aminotransferase (ALT) >200 U/L
  - Severe hepatic dysfunction: INR ≥1.5 & total bilirubin >2x upper limit of normal
  - Hepatic decompensation (defined by ICD-9 and ICD-10 diagnoses)
- **Data Collection**:
  - Baseline demographic, clinical, laboratory data ≤ 2 years of DAA
- **Statistical Analysis**:
  - Unadjusted incidence rates per 1,000 person-years
  - Logistic regression created propensity scores for PI-based versus non-PI-based DAA using all baseline characteristics and DAA date
  - Propensity score-adjusted hazard ratios for PI-based versus non-PI-based DAA were calculated
  - Results stratified by baseline cirrhosis status, as measured by Fibrosis-4 Index for Hepatic Fibrosis (FIB-4)

Table 1. Baseline Patient Characteristics

	PI-based DAA (n=20,872)	Non-PI-based DAA (n=54,315)
Median age, yr (IQR)	63.5 (60.2-66.8)	62.8 (59.5-66.1)
Male sex	97.1%	96.8%
Race/Ethnicity		
White	49.5%	48.2%
Black	40.5%	47.8%
Hispanic	5.5%	4.9%
Median BMI, kg/m² (IQR)	26.9 (23.7-30.5)	27.1 (24.0-30.8)
Diabetes	32.3%	28.6%
Alcohol dependence/abuse	52.6%	54.3%
Median HCV RNA, log IU/mL (IQR)	5.6 (1.2-6.7)	5.5 (1.2-6.7)
HCV genotype		
1	85.7%	81.6%
2	3.8%	6.1%
3	2.2%	4.5%
Other/Missing	8.3%	7.9%
HIV	1.9%	3.7%
FIB-4		
<1.45	37.7%	37.9%
1.45-3.25	48.7%	45.4%
>3.25	8.9%	10.7%
Hemoglobin <10 gm/dL	3.7%	1.7%
eGFR <30 mL/min	9.0%	0.8%
DAA regimen		
PrOD	29.8%	--
ELB/GRA	41.2%	--
GLE/PIB	28.9%	--
SOF/LED	--	85.8%
SOF/VEL	--	14.2%

Abbreviations: BMI: body mass index; DAA: direct acting antiviral; eGFR: estimated glomerular filtration rate; ELB/GRA: elbsavir/grazoprevir; GLE/PIB: glecaprevir/pibrentasvir; HCV: hepatitis C virus; IQR: interquartile range; PI: protease inhibitor; PrOD: paritaprevir/ritonavir/ombitasvir +/- dasabuvir; RNA: ribonucleic acid; SOF/LED: sofosbuvir/ledipasvir; SOF/VEL: sofosbuvir/velpatasvir

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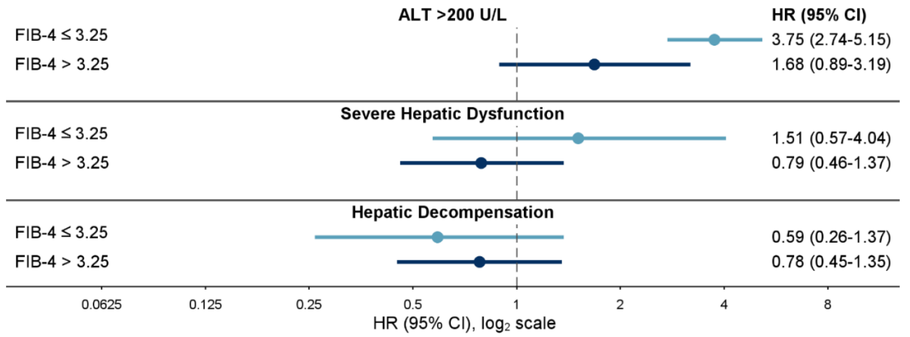
Table 2. Unadjusted Incidence Rates of Acute Liver Injury Outcomes, per 1,000 person-years (95% CI)

	ALT >200 U/L	Severe Hepatic Dysfunction	Hepatic Decompensation
FIB-4 ≤3.25			
PI-based DAA	18.5 (15.1-22.6)	2.0 (1.1-3.6)	2.2 (1.2-3.9)
Non-PI-based DAA	5.9 (4.7-7.3)	0.9 (0.5-1.6)	2.6 (1.9-3.6)
FIB-4 >3.25			
PI-based DAA	32.2 (20.0-51.7)	34.1 (21.5-54.1)	30.2 (18.5-49.4)
Non-PI-based DAA	18.4 (13.1-25.9)	46.0 (37.1-57.2)	46.0 (37.1-57.2)

Abbreviations: ALT: alanine aminotransferase; CI: confidence interval; DAA: direct acting antiviral; PI: protease inhibitor; SALI: severe acute liver injury

Figure 1. Forest Plot of Propensity Score Adjusted Hazard Ratios of PI-based versus Non-PI-based DAAs (95% CI)



Conclusion

- Risk of incident ALT elevations was increased among PI-based versus non-PI-based DAA initiators among people without cirrhosis, but no risk differences of severe hepatic dysfunction or hepatic decompensation were observed
- ALT elevation may be a due to: 1) immune-mediated inflammation with viral eradication or 2) drug-induced liver aminotransferase elevations that do not progress to hepatic dysfunction
- These findings demonstrate the comparable hepatic safety of PI-based and non-PI-based DAA therapies among chronic HCV-infected persons without decompensated cirrhosis