LICAVIR Study Synopsis and Table Shells

Background

Data from different studies on the risk of *de novo* hepatocellular carcinoma (HCC) in direct acting antiviral (DAA) treated patients are conflicting and inconsistent. While a potential mechanism may be immune modulation resulting from the rapid decrease of the hepatitis C virus (HCV) viral load [1], several studies from large cohorts found no evidence of an increased risk of de novo HCC in DAA-treated patients. [2-5]

Given the contemporaneous impact of liver inflammation and fibrosis, cirrhosis, duration of HCV infection, baseline patient demographics including patient age, HCV genotype, and prior treatment response associated with the development of HCC, the evaluation of the causal role of DAAs in the development of incident HCC in HCV infected patients is challenging.

The LICAVIR study was initiated by the ANRS (Agence Française de Recherches Sur Le VIH/Sida et Les Hépatites Virales)/INSERM (Institut National de la Santé et de la Recherche Médicale) and aims to study predisposing factors, clinical, biological, radiological and histological characteristics of HCC at the time of diagnosis from the data obtained from both CIRVIR and HEPATHER cohorts; HCC therapeutic procedures, prognosis and predictive factors of survival will also be analyzed.

AbbVie has engaged with the ANRS-INSERM group to obtain the results of the LICAVIR study and to present them to the Pharmacovigilance Risk Assessment Committee (PRAC) as the response to the following PRAC request: "The MAH should present the complete results of specific analyses from the HEPATHER and CIRVIR cohorts regarding the pattern of presentation of HCC cases (number, size, aggressiveness) in DAA treated and in untreated patients according to the indications presented in the PRAC Assessment Report and include them in the next PSURs."

Study objective

To characterize the *de novo* HCC cases that occurred with and without DAA treatment

Study methodology

A retrospective data collection from a cohort of patients with chronic HCV infection, who developed HCC up to the end of 2019.

A descriptive analysis of patients treated with any DAA who develop HCC after DAA initiation and patients who develop HCC without DAA treatment. No direct comparisons of treatment groups will be performed.

Table shells / data requests

Notes: for all tables, please provide summary statistics as appropriate. For categorical variables, please provide N (%); for continuous variables please provide N and mean (SD)

For variables that are only available in 1 cohort, please denote that in a footnote and add the N that contributed to that variable.

Patient characteristics should be measured over the period from data start through 1 day prior to HCC diagnosis. For characteristics with multiple measurements or assessments (i.e. labs, fibrosis stage, etc), report the value closest but prior to HCC diagnosis.

Table 1. Characteristics of treatments

	Frequency	Achieved SVR12, N (%)			Achieved SVR24, N (%)			Days since last treatment, Mean (SD)
	N, %	Yes	No	Missing	Yes	No	Missing	
DAA								
DAA only								
DAA + IFN								
DAA + ribavirin								
DAA + IFN + ribavirin								
No DAA treatment								
INF								
Ribavirin								
No treatment								

Table 2. Frequency of DAA therapy in the study population*

Treatment	N (%)
DAA	
sofosbuvir/ledipasvir	
sofosbuvir/daclatasvir	
sofosbuvir/simeprevir	
elbasvir/grazoprevir	
sofosbuvir/velpatasvir	
sofosbuvir/velpatasvir/voxilaprevir	
glecaprevir/pibrentasvir	
dasabuvir, ombitasvir, paritaprevir, and ritonavir	
Other DAA	

***These groups are not mutually exclusive and may include combination of therapy and/or multiple rounds of therapy**

Table 3. Patient characteristics at time of HCC diagnosis, with and without prior DAA treatment, in the LICAVIR study population

Baseline characteristics	DAA treated (N)	DAA untreated (N)
Gender		
Male, N (%)		
Female, N (%)		
Age, mean (SD) years		
Ethnicity/Race		
BMI, mean (SD) kg/m^2		
Diabetes, N (%)		
YES		
NO		
Missing		
Dyslipidemia, N (%)		
YES		
NO		
Missing		
Past history of cardiovascular events, N (%)		
YES		
NO		
Missing		
Arterial Hypertension, N (%)		
YES		
NO		
Missing		
HIV co-infection, N (%)		
YES		
NO		
Missing		
HBV co-infection, N (%)		
YES		
NO		
Missing		
Past excessive alcohol intake, N (%)		
YES		
NO		
Missing		

Ongoing alcohol consumption, N (%)		
YES		
NO		
Missing		
Injection drug use, N (%)		
Past		
Ongoing		
Never		
Missing		
Smoking, N (%)		
Past		
Ongoing		
Never		
Missing		
Past history of extrahepatic cancer, N (%)		
YES		
NO		
Missing		
Signs of Portal hypertension, N (%)		
Gastroesophageal varices,		
Thrombocytopenia		
LSE by TE ≥20-25kPa		
imaging showing collateral circulation		
missing		
Fibrosis stage, N (%)		
F0		
F1		
F2		
F3		
F4		
missing		
In F4/cirrhotic patients, Child-Pugh-Turcotte Classification and MELD score, N (%)		
Child-Pugh A		
Child-Pugh B		
Child-Pugh C		
MELD score (mean, SD)		
History of prior hepatic decompensation, N (%)		
YES		

NO		
Missing		
Laboratory testing		
HCV genotype, N (%)		
Genotype 1		
Genotype 2		
Genotype 3		
Genotype 4		
Genotype 5		
Genotype 6		
Serum albumin g/dL, mean (SD)		
Platelet count $10^3/mm^3$, mean (SD)		
Prothrombin time%, mean (SD)		
INR (no units) , mean (SD)		
Total bilirubin mg/dL, mean (SD)		
Alpha-fetoprotein ng/mL, mean (SD)		
AST U/L, mean (SD)		
ALT U/L, mean (SD)		
Anti-HBc antibodies (HBsAg), N (%)		
YES		
NO		
Missing		

Table 4: Characteristics of the HCC cases

Characteristics	**DAA treated**	**DAA untreated**
Number of patients with HCC		
Child-Pugh classification		
A		
B		
C		
Missing		
Diagnostic method used, %		
CT		
MRI		
contrast-enhanced ultrasound		
biopsy		
missing		
Number of nodules, %		
1		

2-3 nodules		
>3 nodules		
missing		
Diameter of largest nodule, mm, n (%)		
≤ 20		
21-30		
31-50		
missing		
Portal invasion, n (%)		
Yes		
No		
missing		
Within Milan criteria, n(%)		
1 nodule ≤ 50 mm		
2 or 3 nodules ≤ 30 mm		
Outside Milan criteria		
missing		
Days between last imaging examination and HCC diagnosis, mean (SD)		
Number of screening exams before HCC diagnosis, mean (SD)		
Extrahepatic spread, n (%)		
YES		
NO		
Missing		
Intervention for HCC treatment		
Curative treatment, N (%)		
Transplantation		
Resection**		
Ablation		
Pallative treatment, N (%)		
TACE		
Systemic therapy, 1st line		
Systemic therapy, 2nd line		
Best supportive care		
Missing		
AFP levels at HCC diagnosis, mean (SD)		
Imaging examinations performed during follow-up in HCC, N (%)		
Survival in days/months, mean (SD)		
Overall		
Progression-free		
Days until progression, Mean (SD)		

Death, N (%)		
YES		
NO		
Missing		
Hepatic decompensation, N (%)		
YES		
NO		
Missing		

References

1. Villani R, Vendemiale G, Serviddio G. Molecular Mechanisms Involved in HCC Recurrence after Direct-Acting Antiviral Therapy. *Int J Mol Sci.* 2019; 20: 49.

2. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol.* 2016;65:719-26.

3. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol.* 2018;68:25-32.

4. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology.* 2017;153:996-1005.e1.

5. Carrat F. First Prospective Evidence of Decreased Mortality after Direct Acting Antivirals in the French ANRS CO22 HEPATHER Cohort [Poster LB-28]. AASLD Meeting; 2017a; Washington, D.C.