

# Outcome of direct-acting antiviral treatment for patients with chronic hepatitis C virus infection: clinical benefit proven?

## Raoel Maan, Adriaan J. van der Meer

Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands Correspondence to: Raoel Maan, MD, PhD. Department of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Room Na 6,

Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. Email: r.maan@erasmusmc.nl.

Provenance and Peer Review: This article was commissioned by the Editorial Office, Hepatobiliary Surgery and Nutrition. The article did not undergo external peer review.

*Comment on:* Carrat F, Fontaine H, Dorival C, *et al.* Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453-64.

Submitted Aug 29, 2019. Accepted for publication Sep 29, 2019. doi: 10.21037/hbsn.2019.10.04 View this article at: http://dx.doi.org/10.21037/hbsn.2019.10.04

The highly effective direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection were well-received by both patients and physicians as sustained virological response (SVR) was associated with an improved overall survival in patients with stable liver disease, even in case of cirrhosis (1). Yet, at that time these results were derived from retrospective cohort studies with long-term follow-up after interferon-based therapy. In patients with compensated liver disease there is confidence that SVR is a clinically relevant endpoint based on consistent positive results with smart use of statistics in numerous cohort studies. Currently, however, there remains a need for longterm follow-up data showing a clinical benefit of DAAinduced SVR, preferably with high-quality prospective data. The results from the French ANRS CO22 Hepather cohort, as published by Dr. Carrat and colleagues in the April issue of the Lancet, thus bring an important contribution to the field (2). It's the first prospective cohort study with reasonable follow-up time to assess all-cause mortality after DAA therapy.

Before the 1<sup>st</sup> of January 2016, 11,870 patients with chronic HCV monoinfection entered the cohort. Of these patients, 1,704 were excluded mainly due to a history of HCC or decompensated cirrhosis. In total, 9,895 untreated patients were included of which 7,344 patients (74%) received DAA therapy. The 2,551 untreated patients served as a comparison group. Patients who received DAAs were older, had more severe liver disease and had more comorbidities compared to untreated patients. This is as expected, as treatment was prioritized for patients with advanced liver disease during the first years after DAA approval. Of the patients who started DAA therapy, 76% achieved SVR and 5% did not achieve SVR. For the other patients there was insufficient follow-up or SVR status was unknown. Among the patients with a known virological response status, 94% were cured (92% in the subgroup with cirrhosis) leaving 6% with ongoing HCV infection. During a median follow-up time of 33.4 months (IQR, 24.0-40.7 months) in treated patients and 31.2 months (IQR, 21.5-41.0 months) in untreated patients, a total of 218 patients died. The crude incidence of allcause mortality was higher in patients exposed to antiviral therapy. However, adjusted multivariate Cox proportional hazards analyses showed that exposure to DAAs was significantly associated with a decreased all-cause mortality [hazard radio (HR) 0.48, 95% CI: 0.33-0.70, P<0.001]. Recently, Butt et al. reported a similar HR for DAA therapy with respect to all-cause mortality in a retrospective cohort of HCV Veterans (3). In this study, after a follow-up of 18 months, patients who received DAAs had a reduced risk of mortality as compared to a group of propensity score matched patients who remained untreated (HR 0.43, 95% CI: 0.33-0.57).

The first reports on an unexpectedly high rate of 'early' HCC recurrence or *de novo* HCC following DAA therapy caused major commotion and left physicians and patients in doubt about the clinical benefit of DAAs (4). Fortunately, shortly after, larger cohorts with more adequate methodology restored the confidence in the relation between successful antiviral therapy and a

reduced HCC occurrence, at least among patients with compensated cirrhosis (5). In the current study 258 patients were diagnosed with de novo HCC. As patients with a history of HCC were excluded, HCC recurrence was not assessed. Univariate analysis showed an increased risk for HCC among patients who underwent DAA therapy (HR 2.77, 95% CI: 2.07–3.71) as opposed to no antiviral therapy. This is not likely to be causative, however, but rather the result of selection bias as patients who received DAAs had, on average, more advanced liver disease. Indeed, when adjusting for multiple risk factors of HCC, DAA therapy was associated with a reduced risk of HCC (HR 0.66, 95% CI: 0.46–0.93). Also the results of this study suggest that this beneficial outcome is caused by HCV clearance, as only those with SVR had a lower risk of HCC. DAA-treated patients who did not achieve SVR were at higher risk of HCC (HR 2.23, 95% CI: 1.37-3.64), but again this is likely caused by selection as only 6% of patients failed antiviral therapy. The recent results of a nation-wide Scottish study, including 857 cirrhotic patients, are very much in line with the findings by Carrat et al. (6). Also in this study the increased risk of HCC with DAAs vs. IFN therapy (HR 2.48, P=0.021) in univariate analysis was confounded by an imbalance in relevant baseline characteristics. Multivariable analyses did not show such association at all (HR 1.15, P=0.744). So far it thus remains unlikely that DAA therapy is responsible for the development of HCC.

Another relevant result was that patients with a low bodymass index (<18.5) had a statistically significantly higher risk of all-cause mortality than patients with a normal bodymass index (HR 2.57, 95% CI: 1.36-4.85). Surely, as also highlighted in the recent EASL guideline, malnutrition in liver disease needs more attention as one of the most important risk factors for survival. Both malnutrition and sarcopenia (muscle mass loss) are associated with a higher rate of complications, such as infections, hepatic encephalopathy and ascites. The nutritional status in patients with liver disease should thus be intensively monitored, especially among those with decompensated cirrhosis or post liver transplantation. Considering the social context of the risk factor(s) of HCV infection, this population may be at higher risk of these nutritional disadvantages. Importantly, unlike other prognostic factors, nutritional status can be influenced.

Patients with decompensated cirrhosis represent a specific subgroup of interest, as our experiences with their post SVR outcome are limited. Interferon therapy was mostly unsuccessful if not contraindicated. Based on a favourable safety profile, DAAs are now increasingly used in our most advanced cirrhosis patients, with SVR rates around 80% (7). Currently, however, the clinical impact of DAA therapy remains uncertain in this population in which there is also a fear of inducing MELD purgatory with respect to donor liver allocation. At this time patients with a history of hepatic decompensation were excluded from the current study, but further results within this subgroup with most advanced liver disease are eagerly awaited.

This large prospective study by Carrat *et al.* again highlight the importance of successful antiviral treatment with DAAs among patients with chronic HCV infection and compensated cirrhosis, as the risk for all-cause mortality and HCC were significantly reduced among those with SVR. Moreover, in light of recent discussion, DAA therapy did not increase the risk for HCC. These results reassure HCVtreating physicians on the clinical relevance of DAAs and highlight that all patients with compensated liver disease should be treated. Although studies with longer follow-up are always relevant within this population, current efforts should address the short-term clinical outcome among patients with decompensated cirrhosis.

#### **Acknowledgments**

Funding: None.

#### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://hbsn. amegroups.com/article/view/10.21037/hbsn.2019.10.04/coif). RM received financial compensation for consultancy from AbbVie. AJ van der Meer received financial compensation for lecture activities for Zambon and research funding from Gilead, MSD, AbbVie and Zambon.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and

#### HepatoBiliary Surgery and Nutrition, Vol 9, No 2 April 2020

the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-ncnd/4.0/.

### References

- van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-93.
- Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453-64.
- Butt AA, Yan P, Simon TG, et al. Effect of Paritaprevir/ Ritonavir/Ombitasvir/Dasabuvir and Ledipasvir/ Sofosbuvir Regimens on Survival Compared With Untreated Hepatitis C Virus-Infected Persons: Results

**Cite this article as:** Maan R, van der Meer AJ. Outcome of direct-acting antiviral treatment for patients with chronic hepatitis C virus infection: clinical benefit proven? HepatoBiliary Surg Nutr 2020;9(2):257-259. doi: 10.21037/ hbsn.2019.10.04

From ERCHIVES. Clin Infect Dis 2017;65:1006-11.

- Reig M, Marino Z, Perello C, 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.
- Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. Gastroenterology 2018;155:411-21.e4.
- 6. Innes H, Barclay ST, Hayes PC, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: Role of the treatment regimen. J Hepatol 2018;68:646-54.
- Maan R, van Tilborg M, Deterding K, et al. Safety and Effectiveness of Direct-Acting Antiviral Agents for Treatment of Patients With Chronic Hepatitis C Virus Infection and Cirrhosis. Clin Gastroenterol Hepatol 2016;14:1821-30.e6.