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Peginterferon maintenance therapy in patients with advanced hepatitis C to prevent hepatocellular carcinoma: The plot thickens

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COMMENTARY ON:

Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, Everson GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Morgan TR; HALT-C Trial Group. Gastroenterology. 2011;140:840–9. Copyright (2011). Abstract reprinted with permission from the American Gastroenterological Association.

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Abstract: Background & Aims*: Interferon reportedly decreases the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial showed that 4 years of maintenance therapy with pegylated interferon (peginterferon) does not reduce liver disease progression. We investigated whether peginterferon decreases the incidence of HCC in the HALT-C cohort over a longer posttreatment follow-up period.*

Methods*: The study included 1048 patients with chronic hepatitis C (Ishak fibrosis scores ⩾3) who did not have a sustained virologic response (SVR) to therapy. They were randomly assigned to groups given a half-dose of peginterferon or no treatment (controls) for 3.5 years and followed up for a median of 6.1 (maximum, 8.7) years.*

Results*: Eighty-eight patients developed HCC (68 definite, 20 presumed): 37 of 515 who were given peginterferon (7.2%) and 51 of 533 controls (9.6%; p = 0.24). There was a significantly lower incidence of HCC among patients given peginterferon therapy who had cirrhosis, but not fibrosis, based on analysis of baseline biopsy samples. After 7 years, the cumulative incidences of HCC in treated and control patients with cirrhosis were 7.8% and 24.2%, respectively (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.24–0.83); in treated and control patients with fibrosis, incidences were 8.3% and 6.8%, respectively (HR, 1.44; 95% CI, 0.77–2.69). Treated patients with a ⩾2-point decrease in the histologic activity index, based on a follow-up biopsy, had a lower incidence of HCC than those with unchanged or increased scores (2.9% vs. 9.4%; p = 0.03).*

Conclusions*: Extended analysis of the HALT-C cohort showed that long-term peginterferon therapy does not reduce the incidence of HCC among patients with advanced hepatitis C who did not achieve SVRs. Patients with cirrhosis who received peginterferon treatment had a lower risk of HCC than controls.*

Although the achievement of a sustained virological response (SVR) is the endpoint of any Interferon-alpha (IFN) based anti viral treatment for patients with chronic hepatitis C virus (HCV) infection, its ultimate goal is to actually attenuate the progression rate to cirrhosis and the development of life threatening sequelae, namely hepatocellular carcinoma (HCC), liver decompensation, and variceal bleeding [1]. In the last years consistent evidence has emerged that these endpoints are indeed achievable once a SVR is obtained, both in non cirrhotic patients, as fibrosis progression is effectively halted following an SVR, as in those with cirrhosis, where a significant reduction in the rates of development of HCC, decompensation or variceal bleeding, that ultimately translates into increased survival, is seen following sustained viral clearance [2]. Unfortunately, in the last category of patients, the key benefits that follow an SVR clash with the low chances of reaching this endpoint, as cirrhosis is still a major reason for treatment failure to pegylated IFN (PegIFN) and ribavirin (Rbv) therapy [3]. For this matter, hope was kindled when one prospective trial demonstrated that in a subgroup of IFN non responsive patients, prolonged maintenance therapy with 24 months of IFN was associated with reduced serum transaminases values, improved histological grading and staging compared to patients on observation independently on the achievement of a SVR [4]. When this information was coupled with the results emerging from several retrospective studies in the late 1990's, that IFN therapy was associated with a reduction in the rates of HCC development as compared to clinical observation, the next logical step was to prospectively assess if indeed IFN maintenance therapy could provide clinical benefits to patients with advanced hepatitis C. Therefore, a large prospective randomized study of PegIFN maintenance therapy versus observation (HALT-C) was conducted in patients with bridging fibrosis or cirrhosis and a previous treatment failure to PegIFN and Rbv [5]. In the original publication, 3.5 years of low dose PegIFN maintenance therapy in 517 patients did not provide any benefit compared to observation in 533 patients, in terms of hard clinical endpoints such as death, decompensation or HCC development. However, in a recent extended analysis of the

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original HALT-C study, performed by Lok *et al.* and focused on the development of HCC, long-term PegIFN maintenance therapy was associated with reduced HCC rates in patients with pre-treatment cirrhosis [6]. Although in the overall population consisting of 1048 patients followed up for a mean period of 6.1 years (0–8.7 years), the incidence of HCC did not differ between the treated ones compared to the controls (7.2% *vs.* 9.6%, $p = 0.24$), when considering only patients with histological cirrhosis at randomization, a lower incidence of HCC was seen in the PegIFN maintenance therapy group (6.8% *vs.* 15.5%, $p = 0.01$). The cumulative incidence of HCC at 3, 5, and 7 years being 2.6%, 5.1%, and 7.8% in the PegIFN group and 4.0%, 11.1%, and 24.2% in the untreated group (log-rank test, $p = 0.009$). At this point to further dissect this surprising result, the authors conducted several sub analysis in the attempt to identify in which cirrhotic patients the added benefit of PegIFN maintenance therapy was more pronounced. By this approach they identified the importance of PegIFN therapy duration, as patients who received treatment for more than 2 years had lower incidence of HCC compared to those who had to discontinue PegIFN before the 2 year mark (HR, 0.36; 95% CI, 0.16–0.82, $p = 0.02$), and also describe a correlation between a decrease in the histological activity index (HAI) of at least 2 points in repeat liver biopsies and a lower risk of HCC development. When analyzing patients without cirrhosis at baseline, no protective effect of maintenance therapy was seen, as the incidence of HCC was 7.5% in the treated ones and 5.4% in the controls (HR 1.44; 95% CI 0.77–2.69, $p = 0.26$). Based on these results, the authors very cautiously conclude that in the extended follow-up of the HALT-C trial a modest benefit of long term maintenance therapy was seen in reducing the incidence of HCC in cirrhotic patients only, but still, as this effect was only marginal, PegIFN has an unfavorable side effect profile and no benefit was seen on mortality rates, the clinical implications of these results are unclear and the benefits of PegIFN maintenance therapy is doubtful.

Although we strongly agree with the authors conclusions, the study by Lok and colleagues unfortunately might add confusion to the debate on the potential benefits of PegIFN maintenance therapy. Indeed this was quite a hot topic in the past years, as the demonstration of a long term benefit of a low dose PegIFN regimen would have been quite a clinical, and commercial, breakthrough. For this reason the final results of 3 randomised controlled studies designed for this endpoint (Table 1) were eagerly awaited [5,7,8]. Although a direct comparison of the study results is partially precluded by differences in the patients characteristics and in the assigned treatment regimens, they unanimously failed to demonstrate any positive impact of PegIFN maintenance therapy on HCC incidence rates. The only beneficial effect seen in 2 studies was a reduced rate of development of gastro-esophageal varices or variceal bleeding in patients receiving PegIFN maintenance therapy compared to the control group, eventually suggesting a role of PegIFN in the prevention of the complications of portal hypertension more than in the development of HCC. Regarding HCC development, the question, therefore, is whether the extended follow-up of the HALT-C trial allowed us to finally see a protective role of PegIFN maintenance therapy, or if rather this result is just a consequence of chance. The causal role of PegIFN maintenance therapy is supported by the many statistical analysis conducted by the HALT-C investigators to corroborate their results. Moreover, the finding that patients who received treatment for more than 2 years or showed a decrease in HAI of more than 2 points in follow-up liver biopsies were the ones really benefitting from prolonged treatment provides a biological explanation to the study results. Casting some doubts over the clinical interpretation of these results, is the fact that the prolongation of an uncontrolled follow-up period by definition carries a risk of inherent biases, and probably most importantly, that the main finding derives from a subanalysis in which patients were stratified in being cirrhotic or non-cirrhotic by a baseline liver biopsy. Indeed, while liver biopsy is still the gold standard for fibrosis staging, it is universally acknowledged that a sampling error may lead to a misdiagnosis of cirrhosis in up to 30% of the specimens [9]. A misclassification of patients by liver biopsy may in part explain some of the HALT-C results, as not only PegIFN maintenance therapy resulted in similar HCC incidence rates compared to controls in non cirrhotic patients, but in the original paper it was actually associated with a significant higher mortality rate compared to controls (5% *vs.* 1.9%, $p = 0.04$) [5]. A result that would effectively suggest that PegIFN maintenance therapy has the obscure ability to protect cirrhotic patients from the risk of HCC while on the other hand, being potentially harmful in those with less advanced fibrosis. Quite frankly, this seems rather improbable and is likely the consequence of confounding factors we still have not quite yet understood. It seems, therefore, clear that we are still missing some key pieces in the maintenance therapy puzzle and that if such a therapy has a place in the treatment of patients with cirrhosis, at this moment we have not yet identified who these patients might be. In this context, the positive predictive power associated with the reduction in HAI score during treatment should not be overlooked, and efforts should be made to study if non invasive methods can be used to correctly identify this set of responders whilst also exploring if host genetic differences lie behind this different susceptibility to PegIFN maintenance therapy [10]. If these two points were to be demonstrated, and

Table 1. Study design and results of the 3 RCT on PegIFN maintenance therapy in HCV patients with advanced fibrosis and cirrhosis.

Trial	Patients No.	Disease stage	Treatment regimen	Follow-up period (months)	HCC cumulative incidence (Tx *vs.* Controls)
HALT-C [5]	1050	Bridging Fibrosis/Cirrhosis	Active: PegIFNα2a 90 μg/week Control: Observation	42 42	2.3% *vs.* 2.8%
EPIC[3] [7]	626	Cirrhosis	Active: PegIFNα2b 0.5 μg/kg/week Control: Observation	31.4 ± 16.1 30.2 ± 16.2	4% *vs.* 4%
COPILOT [8]	555	Bridging Fibrosis/Cirrhosis	Active: PegIFNα2b 0.5 μg/kg/week Control: Colchicine 0.6 mg/bid	48 48	9.1% *vs.* 4.4%

not forgetting the protective effect seen in patients with portal hypertension, PegIFN maintenance therapy could finally exit the limbo of mythology and enter the clinical practice for a niche of patients.

Conflict of interest

M.C. has received grants and research support from Merck, Roche, BMS, and Gilead Science; belongs to the advisory committees of Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, and Vertex; and has spoken and taught for Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, and Vertex. A.A. belongs to the advisory board of Roche and received travel support from Roche, Bayer, Glaxo Smith Kline, and Bristol Myers.

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