controlled fashion over 30 days. The intervention group experienced a significant decrease in portal hypertension that was additive to the effects of propranolol. Moreover, liver tests increased more often with placebo than simvastatin [5].

The correspondents generalize, without support, that non-USA physicians have no trouble giving statins to patients with liver disease. In the editorial, I cite an international HCV treatment study where the majority of authors are not from the USA [6]. Only 3% of the 403 patients were on statins; whereas, given the customary age range for participants in HCV studies, one would expect 30% or more of these latter study patients to need a statin. These data would seem to indicate a bias by hepatologists worldwide not to give statins to patients who have at least hepatitis C disease.

The problem the correspondents fail to apprehend with RUCAM methodology is its extremely low positive predictive value (PPV). With RUCAM, the probability of a statin being correctly identified as the "true" cause of idiopathic test abnormalities is less than 1% [4]. That is, if the RUCAM determines the statin is the culprit, 99 out of a 100 times it is wrong. Not the type of certainty one would want in a court of law, for example. While this level of uncertainty may be sufficient to withdraw a drug from a patient, it is not compelling enough to conclude scientifically that statins cause idiosyncratic reactions. Thus, there remains legitimate doubt as to whether statins are responsible for rare instances of idiosyncrasy. All of the cases presented by Bjornsson et al. could easily be counted as background noise [7]. Nevertheless, until we become more scientific and settle the issue with proteomics and microarray testing, we are stuck with clinical opinion; the variations of RUCAM represent only attempts to score clinical judgment with numbers.

The terminology for the subject is critical otherwise the reader will confuse what the message of statin mythology has been all about. The letter writers use the term "hepatotoxicity" both as a general term, and for predictable dose-dependent reactions. I believe universal practice is to now use "DILI" or "drug-induced liver injury" as a general term, and restrict hepatotoxicity to the predictable, dose-dependent setting [8].

The remaining concerns of the correspondents have become moot since the revisions of 28 February 2012 by the FDA.

### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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# Which is the real efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in HCV infected patients with advanced fibrosis?

To the Editor:
We have read with great interest the article of Prati et al. [1]. The authors concluded that patients infected with HCV genotypes 1–4 that received PegIFNα-2A plus ribavirin with advanced fibrosis (staging ⩾3 according to Ishak classification) had an end treatment response (ETR) and sustained virological response (SVR) rates that were not influenced by fibrosis stage. In contrast, PegIFNα-2B plus ribavirin was less effective than PegIFNα-2A and led to a lower rate of both ETR and SVR in patients with staging ⩾3. We are concerned about part of the content of the paper. The article analyzed a heterogeneous population of patients infected with HCV that included "difficult to treat patients" infected with genotypes 1–4 and "easy to treat patients" infected

with genotypes 2 and 3. Those infected with HCV genotypes 1-4 were analyzed together and stratified according to the Ishak classification staging score. However, several questions remain unanswered: What was the distribution of patients with genotype 4 in the different staging groups? What was the percentage of Egyptian patients in the genotype 4 group included in the study? In Northern Italy, HCV genotype 4 was reported in about 2% of all patients infected with HCV [2]. In addition, different studies have reported that patients infected with genotype 4 presented a better SVR compared to those infected with genotype 1, particularly in patients that achieved a rapid virological response (RVR) [3,4]. Furthermore, Egyptian patients infected with genotype 4 with advanced fibrosis had a better SVR compared to European and

African patients with genotype 4 that presented with a similar stage of liver fibrosis [5]. Therefore, we believe that the inclusion of patients with genotype 4 could have influenced the SVR achieved in the genotype 1–4 group of patients with staging ⩾3.

According to the Ishak classification staging score, the stage 3 classification is defined as a fibrous expansion over most of the portal area with occasional fibrous bridging from portal to portal regions. In contrast, central-to-portal bridging fibrosis, classified as stage 4 in the Ishak score, is an important component of severe chronic active hepatitis [6]. It is an important factor for rapid progression to cirrhosis, because contraction of collagen-rich bridges may produce rapid, severe distortion of the normal hepatic microstructure. In our opinion, stage 3 should not be considered as a surrogate of advanced liver fibrosis. The inclusion of stage 3 patients in a group with so called "advanced fibrosis" might have caused an underestimation of the impact of liver fibrosis in patients treated with PegIFNα-2A that achieved SVR.

We have studied 388 patients infected with genotype 1a/1b in different stages, according to the Ishak classification. Part of that data was derived from our previous study [7]. We stratified the patients according to S0–S3 and S4–S6 groups. We defined advanced fibrosis as stages S4–S6. The patients were treated with PegIFNα-2A at 180 µg/week plus ribavirin or with PegIFNα-2B at 1.5 µg/kg/week plus ribavirin. The two treatment groups, stratified by fibrosis stage (S0–S3 and S4–S6), showed similar clinical and demographic features, except that the S0–S3 group treated with PegIFNα-2B had a lower HCV RNA value (HCV RNA $\log_{10}$, IU/ml) than the group treated with PegIFNα-2A ($5.79 \pm 0.4$ $vs.$ $5.93 \pm 0.5$ IU/ml; $p <0.001$). In the S0–S3 group, patients treated with PegIFNα-2B had an ETR of 66.3% compared to 71.7% for those treated with PegIFNα-2A; the SVRs were 58% $vs.$ 53%, respectively. In the S4-S6 group, patients treated with PegIFNα-2B had an ETR of 44.8% compared to 62.5% for those treated with PegIFNα-2A ($p <0.06$); the SVRs were 34.4% $vs.$ 40.2%, respectively (not statistically significant). By step-logistic regression analysis, significant predictor of treatment failure was a staging ⩾4, in both the PegIFNα-2B and PegIFNα-2A treatment groups. Moreover, significant predictors of SVR were an RVR in both antiviral treatment groups and male sex in the PegIFNα-2B treatment group (Table 1). In conclusion, in Italian patients with genotype 1 HCV infection treated with PegIFNα-2B or PegIFNα-2A plus ribavirin, a staging ⩾4 influenced the achievement of SVR with both treatments. The Chariot study demonstrated that, despite adequate therapeutic dosing with PegIFNα-2A plus ribavirin, there was a low virological response and a high relapse rate in patients infected with genotype 1 that had advanced fibrosis [8]. In fact, a marked step-wise decline in SVR was associated with fibrosis stage, evaluated by the METAVIR score. Advanced liver fibrosis remained the strongest negative predictive factor of SVR in patients infected with genotype 1 and treated with antiviral therapy, despite the use of different types of pegylated interferon.

## Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Table 1. Odds ratio and corresponding 95% confidence intervals (95% CI) from the multivariate logistic regression analysis including independent predictors of treatment achievement or failure.

| | OR | 95% CI | $p$ value |
|---|---|---|---|
| PegIFNα-2B | | | |
| Male | 3.1 | 1.0-9.0 | 0.035 |
| RVR+ | 22.1 | 6.8-31.1 | 0.001 |
| S ⩾4 | 0.78 | 0.5-0.9 | 0.04 |
| PegIFNα-2A | | | |
| RVR+ | 11.4 | 4.7-27.6 | 0.001 |
| S ⩾4 | 0.46 | 0.2-0.8 | 0.017 |