would predict a good long-term outcome. If it is indeed true that the vast majority (perhaps even all) of individuals achieving SVRs were destined not to develop long-term complications of liver disease, it would follow that SVRs would be associated with non-progressive disease but that antiviral therapy may not provide overall benefit to the treated group.

To validate the SVR as a surrogate outcome, RCTs in the future should compare patients treated with regimens that result in larger percentages of SVRs (e.g., 90%) to untreated patients and employ clinical events as the primary outcome. If patients in previous RCTs did not subsequently receive additional treatment, we would encourage the authors of those trials to assess the long-term clinical outcomes retrospectively. As of this time, treatment advocates are supporting treatment that has no level 1 (well designed and executed RCTs) evidence for improved clinical outcomes, but is costly and toxic (including occasional mortal).

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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Reply to: 'Evidence recommending antiviral therapy in hepatitis C'

To the Editor:

We thank Dr. Koretz and colleagues for responding to our appraisal of their Cochrane meta-analysis [1,2], The discussion on the clinical benefits of antiviral therapy for chronic hepatitis C virus (HCV) infection is important because physicians should be aware of the strengths of current evidence as well as of the remaining uncertainties.

Koretz *et al.* again highlight and explain that sustained virological response (SVR) is not a validated surrogate marker as substantial proof from randomized placebo-controlled trials that antiviral therapy improves clinical outcome is lacking. As was clearly discussed in our recent review, this is correct. We also mentioned that the repeatedly found association between SVR and reduced cirrhosis-related morbidity and mortality might potentially be subject to residual confounding. Indeed, this possibility cannot be excluded in the performed cohort studies. However, in light of the extensive multivariate analyses in which SVR remained the most important factor associated with beneficial clinical outcome, we agree with others that it is hard to think of a confounder which would completely annihilate this association [3–5].

While recognizing that the possibility of residual confounding remains a scientific limitation, we have indeed challenged the statement that no kind of antiviral therapy can currently be advocated. One of the key arguments by which Koretz *et al.* try to substantiate this statement is the increased mortality rate among interferon-treated patients as compared to controls, which was observed in their meta-analysis. However, it should be clearly mentioned that this was only found in the extended follow-up analyses of the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial, which almost solely drove their meta-analyses on SVR and mortality [6]. Unfortunately, in their response letter, Koretz *et al.* do not share their thoughts on the fact that all controls in the HALT-C study received a regular pegylated interferon (PegIFN) and ribavirin treatment course just prior to randomization. Consequently, this study compared long-term PegIFN therapy to short-term PegIFN therapy rather than to no treatment [7]. The design of the HALT-C trial thus prohibits extrapolation of the increased mortality rate as observed with long-term maintenance therapy to the regular PegIFN regimens. Therefore, this study should not have been included in the meta-analyses.

Our review did discuss that patients treated with interferon and ribavirin combination therapy had a beneficial clinical outcome as compared to patients treated with interferon mono therapy. In fact, as the improved clinical outcome is in line with the

improved SVR rate of combination therapy, we consider this to be another argument to strengthen our case. However, we acknowledge that the number needed to treat (NNT) to prevent cirrhosis-related events with these earlier interferon-based regimens was high. Awareness of this alternative measure of treatment efficacy is desired, especially when considering the cost-benefit ratio of new treatment regimens or the allocation of limited treatment resources. Based on our analyses among patients with HCV genotype 1 infection and cirrhosis, we have recently described the enormous decline in the NNT to prevent cirrhosis-related morbidity or mortality with the development of antiviral therapy over the last two decades [8].

Indeed, there is limited data available to assess the validity of SVR as surrogate endpoint, especially considering that trials assessing long-term low-dose PegIFN should be excluded. However, when validation of SVR is aimed, restriction to interferon mono therapy in treatment experienced patients is not needed. Still, randomized placebo-controlled trials on clinical endpoints are scarce and new trials, which might be able to settle this discussion, are unlikely to be executed. Recently, several phase 3 clinical studies showed SVR rates around 95% with 8–12 weeks of well-tolerated interferon-free regimens. These high response rates were independent of baseline characteristics, thereby excluding the unlikely possibility that we are only able to cure patients with a benign natural course of disease. First clinical data already suggest that viral suppression/eradication with these regimens is linked to an over proportionate treatment-related improvement in clinical outcome [9,10]. We are convinced that, in particular among patients with advanced liver disease, long-term follow-up assessment of these treated patient populations will further confirm the strong link between SVR and reduced mortality.

The data clearly show that treatment increases the rate of SVR. Although it is only now that data are emerging to validate the clinical importance of this longstanding and robust surrogate endpoint, we consider it to be unethical to generally withhold treatment and perform randomized studies, in which many patients are denied a good chance to eradicate their HCV infection, in order to confirm the well-supported and biologically plausible causal relation between SVR and improved clinical outcome.

Conflict of interest

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