



Is there sufficient evidence to recommend antiviral therapy in hepatitis C?

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Summary

While patients with chronic hepatitis C virus (HCV) infection are treated in order to prevent liver-related morbidity and mortality, we rely on sustained virological response (SVR) as a virological biomarker to evaluate treatment efficacy in both clinical practice as well as in drug development. However, conclusive evidence for the clinical benefit of antiviral therapy or validity of SVR as surrogate marker, as derived from trials randomizing patients to a treatment or control arm, is lacking. In fact, the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial recently showed an increased mortality rate among interferon-treated patients compared to untreated controls. Consequently, the recommendation to treat patients with chronic HCV infection was challenged.

Here, we argue that the possible harmful effect of long-term low-dose pegylated interferon mono therapy, as was observed in the HALT-C trial cohort, cannot be extrapolated to potentially curative short-term treatment regimens. Furthermore, we discuss SVR as a surrogate biomarker, based on numerous studies which indicated an association between SVR and improvements in health-related quality of life, hepatic inflammation and fibrosis, and portal pressure as well as a reduced risk for hepatocellular carcinoma (HCC), liver failure and mortality.

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 Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; HALT-C, Hepatitis C Antiviral Long-term Treatment Against Cirrhosis; HCC, hepatocellular carcinoma; RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval; MELD, Model for End-stage Liver Disease; HVPG, hepatic venous pressure gradient; HR, hazard ratio.

Introduction

For the treatment of HCV infection we currently rely on interferon-based antiviral regimens. These therapies are very effective to prevent chronification of the acute infection, and also have good potential to eradicate HCV in those chronically infected [1–4]. Sustained virological response (SVR) is defined as absence of viremia 24 weeks after cessation of antiviral therapy, which showed long-term durability [5]. Consequently, antiviral therapy is considered successful and patients are usually considered 'cured' upon achievement of SVR. Although SVR may be the most widely used endpoint to evaluate antiviral treatment efficacy, it remains an indirect outcome measure. Indeed, the main reason to treat patients with chronic HCV infection is to improve their prognosis, by preventing cirrhosis-related morbidity and mortality. Are we convinced that the currently available treatment regimens achieve this goal so that we are right to recommend antiviral therapy to our patients?

Findings of a recent Cochrane meta-analysis

Recently, this discussion flared up due to the Cochrane review of Dr. Koretz and colleagues which aimed to assess the efficacy of interferon-based re-treatment on solid clinical endpoints [6]. Their study included only randomized controlled trials (RCT), in which patients with chronic HCV infection and non-response or relapse to a prior interferon-based treatment course were randomized to interferon re-treatment or no treatment. Extensive literature searches resulted in seven eligible trials for meta-analyses. For each endpoint of interest a subset of these trials was used, depending on the described endpoints in the original study reports. Only three trials reported on clinical outcomes, with all-cause mortality as most definite endpoint [7–10]. These three studies solely included patients with significant hepatic fibrosis or cirrhosis, so that the meta-analyses on clinical outcomes focused on a difficult-to-treat subgroup of patients with advanced liver disease and prior treatment failure. Combining the results of these trials indicated a higher mortality rate among interferon re-treated patients as compared to patients who did



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not receive further antiviral therapy, although this difference was not statistically significant (Odds Ratio [OR] 1.30, 95% Confidence Interval [CI] 0.95–1.79). However, in a sensitivity analysis including only the two largest trials with a low risk of bias, the disadvantage for patients who received interferon did reach statistical significance (OR 1.41, 95% CI 1.02–1.95). With respect to the other clinical endpoints, the occurrence of liver-related mortality, encephalopathy, ascites, spontaneous bacterial peritonitis, and hepatocellular carcinoma (HCC) was not found to differ significantly between re-treated patients and controls. An exception was variceal bleeding, which occurred significantly less often among the patients who were randomized to interferon-based therapy (OR 0.26, 95% CI 0.09–0.71).

A secondary aim was to assess the validity of SVR as a surrogate endpoint of antiviral therapy. Although four studies reported on this virological efficacy measure, only two trials included patients that actually attained SVR [8,10]. However, because of the difficult-to-treat patient population and the assessment of suboptimal treatment regimens for HCV eradication, the number of patients with SVR was very low. Nevertheless, and as expected, SVR occurred more often among the patients treated with interferon (OR 14.73, 95% CI 2.78–77.97). The meta-analyses thus found a discrepancy between the effect of interferon therapy on the surrogate outcome measure SVR and the clinical outcome measure all-cause mortality, as both occurred more frequently among actively treated patients.

The harmful effect of interferon-based therapy on survival, which was found within clinical scenario of the included trials, led to the conclusion that (pegylated) interferon is not an effective treatment option for patients with chronic HCV infection who failed a previous antiviral treatment course. Since this negative effect of interferon-based therapy was not captured by suppression of HCV RNA, SVR failed the criteria to be considered as a valid surrogate endpoint [11–14]. Based on these findings, the authors subsequently stated that their results caution physicians to stop advocating antiviral interventions of any kind. Extrapolating their recommendation to anti-HCV therapy in general was thus not discouraged by the fact that their meta-analyses regarding all-cause mortality and SVR were almost exclusively based on the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial. However, this important limitation warrants more careful interpretation of the results of this review in order to prevent unbalanced statements with potentially major consequences for the HCV-infected population.

HALT-C trial

In brief, the HALT-C trial included 1050 patients with chronic HCV infection and advanced hepatic fibrosis, who were randomized to receive 3.5 years of 90 µg pegylated interferon alfa-2a weekly or no treatment. Interferon maintenance therapy was not found to slow down clinical and/or histological liver disease progression [8]. In fact, a *post hoc* analysis after prolonging the follow-up in this cohort indicated a poorer survival among patients in the interferon maintenance arm, as the cumulative 7-year mortality rate was 20% in treated and 15% in control patients ($p = 0.049$) [9]. This impaired overall survival was predominantly caused by deaths of non-liver-related origin among patients with advanced hepatic fibrosis (but not yet cirrhosis).

Based on this study, there is reasonable consensus that interferon maintenance therapy has no regular place in the treatment of chronic HCV infection. The findings of the recent Cochrane meta-analysis further underline this general perception.

There are, however, several reasons not to withhold short-term interferon-based therapy with the potential to eradicate the chronic HCV infection based on the HALT-C trial results. First, the patients in the control arm of the HALT-C trial were not treatment naive. All included patients showed an insufficient virological response to a full-dose pegylated interferon and ribavirin treatment course just prior to randomization. The survival among patients who received interferon maintenance therapy for 3.5 years was thus significantly reduced compared to that of patients who received short-term interferon-based treatment, indicating that the possible harmful effects of long-term pegylated interferon mono therapy cannot be projected onto standard 24–48 week regimens. Second, the increase in mortality only began to arise after 3 years of pegylated interferon therapy, suggesting that the possible off-target treatment effects require long-term continuous interferon stimulation. Third, patients in the control arm of the HALT-C more frequently underwent liver transplantation, which can substantially prolong the survival. Consequently, the survival also becomes dependent on non-patient-related factors such as the availability of donor livers. In fact, allocation of donor liver grafts based on the Model for End-stage Liver Disease (MELD score) favors those patients with poorest prognosis [15–17]. In the HALT-C trial, the 7-year cumulative rate of all-cause mortality or liver transplantation as a combined endpoint was similar among the patients who received maintenance therapy (25%) vs. those who did not (24%, $p = 0.45$) [9]. Last, as mentioned in the Cochrane review, the excess mortality in a subgroup of the treated patients in the HALT-C study could be a chance finding. A significant increase in mortality due to interferon-based therapy was neither confirmed in another large RCT evaluating 5 years of maintenance therapy (Evaluation of PegIntron in Control of Hepatitis C trial), nor in smaller RCTs with shorter durations of interferon treatment [7,10,18–24].

Furthermore, it can be questioned whether it is legitimate to assess the validity of SVR as a surrogate marker with a trial that did not aim to induce SVR and in fact assessed an interferon regimen almost unable to result in this virological endpoint. Indeed, the power was limited, as less than 4% of the treatment-experienced patients with advanced hepatic fibrosis attained SVR with the low-dose pegylated interferon maintenance regimen. Surely, these few patients with SVR could not significantly affect the clinical outcome of the entire treated study arm, whether or not a harmful effect would have been present.

SVR as surrogate endpoint

Currently, many clinical development trials aim to increase the SVR rate of anti-HCV therapy. In support, there are numerous arguments to consider SVR as a relevant endpoint. Treatment-induced viral clearance is important to prevent transmission of HCV and, even with the risk for re-infection among injecting drug users, antiviral therapy will decrease the prevalence of chronic HCV infection and the incidence of its sequelae [25,26]. Achieving SVR before liver transplantation in patients with advanced

cirrhosis showed to eliminate the risk for post-transplant HCV recurrence, which is known to limit graft and overall survival [27–29].

The majority of patients with chronic HCV infection are fortunate not to develop cirrhosis and the need for liver transplantation [30]. Although clinical outcome is often focused on solid cirrhosis-related endpoints such as hepatocellular carcinoma and mortality, it should be noted that the health-related quality of life is also impaired among patients with chronic HCV infection in absence of end stage liver disease [31]. Indeed, extrahepatic symptoms including fatigue, headaches, nausea, musculoskeletal and abdominal pain, and neuropsychiatric symptoms like depression and irritability can accompany the chronic infection [32]. Multiple studies indicated that the health-related quality of life, although further diminished for the duration of interferon-based treatment, improved compared to baseline in patients who attained SVR [31,33–37]. As the total burden of chronic HCV infection extends beyond the liver, the impact of SVR on patient-reported outcome measures covering physical, social as well as mental health should be appreciated.

Still, the predominant consequences of infection with HCV should be sought in the liver, where continuous inflammation can lead to fibrosis. Relevant are thus the many histological studies which showed regression of hepatic inflammation and fibrosis, as assessed by semi-quantitative grading and staging scores (Ishak and METAVIR), after interferon-induced eradication of HCV as the causative agent [38–45]. These histological improvements were frequently observed among patients who had already developed cirrhosis as well. In addition, the quantitatively measured total liver collagen content was also described to reduce upon achievement of SVR [38,46,47]. In fact, among patients with cirrhosis who did not show an improved METAVIR score in their post-SVR liver biopsy, the total amount of fibrosis was still significantly reduced [38]. Two prior Cochrane meta-analyses indicated that, compared to no treatment, interferon significantly improved liver histology, and that regression of hepatic fibrosis was more often achieved with interferon and ribavirin combination therapy compared to interferon therapy alone [48,49]. An important study by Mallet *et al.* linked the histological improvement following antiviral therapy to a favorable clinical outcome, as the ‘regression of cirrhosis’ was associated with reduced occurrence of cirrhosis-related morbidity and prolonged overall survival [40].

Improved histology could explain the reduction in portal pressure among patients with SVR, as measured by the hepatic venous pressure gradient (HVPG) [50–52]. Importantly, the HVPG is one of the best validated surrogate markers within the field of hepatology, as higher HVPG levels are associated with worse clinical outcome and RCTs have indicated that interventions to reduce the portal pressure resulted in both decreased HVPG levels as well as improved clinical outcome [12,53–55]. Indeed, cirrhotic patients with chronic HCV infection who attained SVR did not develop esophageal varices or variceal bleeding, the most direct clinical complication of portal hypertension which is associated with substantial mortality [50,56].

Several Western cohort studies assessed the relation between SVR and the occurrence of solid clinical endpoints such as liver failure, hepatocellular carcinoma, liver transplantation and death [56–61]. Our group was one of the first to show that patients with chronic HCV infection and advanced hepatic fibrosis had a

reduced risk for liver failure as well as liver-related mortality already shortly after SVR [62]. Studies with longer follow-up confirmed that these events remained rare among successfully treated patients, and also indicated a strong association between SVR and reduced occurrence of HCC (hazard ratios [HR] varying from 0.19 to 0.38) [56–60]. A partially prospective study with up to 7.5 years of follow-up found that all-cause mortality or liver transplantation, as a combined endpoint, occurred significantly less often among patients with SVR compared to those with virological non-response (HR 0.17, 95% CI 0.06–0.46, $p < 0.001$). In a multicenter study from Spain, which included 1599 patients with chronic HCV and human immunodeficiency virus co-infection who were followed for a median of approximately 5 years, SVR was independently associated with a reduced risk for non-liver-related, non-AIDS-related deaths (HR 0.35, 95% CI 0.13–0.93, $p = 0.036$) [63]. Population-based studies indicated a favorable overall survival among HCV-exposed patients without detectable HCV RNA. A study, expected to include over 90% of all Danish patients tested for HCV RNA, found a significantly lower 5-year survival among patients with chronic HCV infection compared to those who cleared HCV RNA (86% vs. 92%, respectively) [61]. Recent data from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (R.E.V.E.A.L.)-HCV study, a prospective natural history study from Taiwan including 19,636 HBsAg-seronegative patients, indicated that the cumulative 18-year all-cause mortality rate was similar among anti-HCV seropositive patients with undetectable HCV RNA (12.4%) and anti-HCV seronegative patients (12.8%) [64]. In contrast, the mortality rate was substantially higher among anti-HCV seropositive patients with detectable HCV RNA (30.1%; $p < 0.001$). Recently, important data have emerged regarding the association between SVR and reduced all-cause mortality as well. Multivariate analyses, stratified for HCV genotype, indicated SVR was independently associated with reduced risk for death of any cause (HR 0.51–0.70, $p < 0.01$ for HCV genotypes 1, 2, and 3) among almost 17,000 American veterans with chronic HCV infection and varying stages of liver disease [65]. An update of our cohort, including 530 patients with HCV-induced advanced hepatic fibrosis or cirrhosis, resulted in a median follow-up duration of 8.4 years, and showed a 10-year cumulative all-cause mortality rate of 9% among patients with SVR compared to 26% among patients without SVR ($p < 0.001$) [56]. Multivariate analyses indicated that SVR was the most important factor that was independently associated with improved survival, as patients with SVR had an approximately four-fold lower mortality risk compared to those without SVR (HR 0.26, 95% CI 0.14–0.49, $p < 0.001$). Together these large follow-up studies provide the most important data to endorse SVR as a relevant endpoint, as all showed similar and conclusive findings with strong adjusted hazard ratios for the association between SVR and improved clinical outcome.

Randomized controlled trials reporting on clinical outcome

It should, however, be recognized that cohort studies suggesting a clinical benefit of SVR share a similar limitation. Despite extensive multivariate analyses, the association between SVR and improved clinical outcome remains potentially influenced by unmeasured confounding factors [66]. In other words, observational studies cannot rule out the possibility that patients who

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have attained SVR are merely a selection of patients who would have a favorable natural history if left untreated as well. Indeed, several host and viral factors were related to a favorable long-term clinical outcome as well as to an adequate virological response to interferon-based therapy [56,58,59,67,68]. Thus, the frequently reported association between SVR and improved clinical outcome from cohort studies neither validates SVR as a surrogate endpoint nor confirms that antiviral therapy has clinical benefits. This requires RCTs to indicate that interferon therapy positively affects SVR as well as clinical outcome [11–14]. As discussed, this was not the case in the latest Cochrane meta-analysis [6].

Since RCTs on solid clinical endpoints usually require long and costly prospective follow-up, especially in a slowly progressive disease as chronic hepatitis C, it is not surprising that only few have been performed. The trials that have been performed all exclusively included patients with advanced liver disease, probably because these patients are at highest risk for clinical events. Due to the restriction to interferon re-treatment, not all RCTs reporting on clinical outcome events were included in the recent Cochrane review. Unfortunately, however, most of the additional trials are limited by a low number of included patients and the use of interferon-based regimens with relatively low antiviral efficacy [10,18–24]. Especially among patients with cirrhosis, SVR rates of the early interferon-based antiviral regimens have been poor [69]. Although several trials did report a clinical benefit of interferon-based antiviral therapy, the results varied and not all positive trials were without controversy [10,18,22,23]. Therefore, definite evidence for the clinical efficacy of interferon therapy was never established and SVR was never formally validated. The use of SVR as surrogate outcome measure thus remains with some uncertainty. Nevertheless, another recent Cochrane meta-analysis did indicate that the combination of interferon and ribavirin significantly reduced morbidity plus mortality, as a composite clinical endpoint, compared to interferon mono therapy [49]. This finding is in line with the increase in SVR rate due to the addition of ribavirin to interferon therapy [70,71].

Presently, new treatment regimens and the introduction of protease inhibitors have substantially increased the antiviral efficacy of interferon-based therapy. Also for patients with cirrhosis, pegylated interferon and ribavirin combination therapy (with the addition of a protease inhibitor for those with HCV genotype 1) is likely to increase SVR rates to above 50% [2–4,72–76]. None of the RCTs on clinical efficacy have assessed a full-dose pegylated interferon and ribavirin treatment course, however, while this has been the standard of care over the last decade. Future interferon-free regimens are even expected to further enhance antiviral efficacy, while simultaneously reducing treatment duration and improving side-effect profiles [77,78]. Thus, assuming the biologically plausible causal relation between HCV eradication and improved clinical outcome, RCTs with current antiviral regimens would have higher power to show a clinical benefit of antiviral therapy as well as to validate SVR as surrogate endpoint. However, the accumulated data suggesting patients benefit from SVR impedes justification of trials in which patients are denied a chance to eradicate their chronic HCV infection. Ethical concerns thus prevent us from performing the trials which could bring conclusive evidence regarding the clinical efficacy of antiviral therapy. Such trials should thus not be awaited for the decision to initiate antiviral therapy in the individual patient.

Key Points

- The recommendation to treat hepatitis C was recently challenged because patients receiving interferon maintenance therapy within the HALT-C trial had an increased mortality rate as compared to controls, despite attaining SVR more frequently
- The possible increase in mortality due to long-term interferon maintenance therapy cannot be extrapolated to the commonly applied short-term interferon-based regimens with the potential to eradicate the HCV infection
- Achievement of SVR has been repeatedly associated with regression of hepatic fibrosis, reduction of portal pressure, a lower risk for liver failure and hepatocellular carcinoma, as well as with an improved overall survival
- As viral eradication is likely to improve their prognosis, physicians should continue to treat their patients with chronic HCV infection

Conclusion

To conclude, we are aware that definite proof for the surrogacy of SVR and clinical benefit of interferon-based antiviral therapy is lacking. Nevertheless, SVR has been repeatedly associated with improvements in health-related quality of life, hepatic inflammation and fibrosis, and portal pressure as well as with a reduced occurrence of solid clinical endpoints such as hepatocellular carcinoma, liver failure and death. Collectively, this strongly argues that SVR is a patient-relevant endpoint and reasonably likely to predict clinical benefit [13]. Furthermore, there is no clear evidence to suggest a long-term harmful effect of 24–48 weeks of interferon-based therapy, by which we usually attempt to achieve this virological outcome measure in our patients. With future triple therapy, a treatment duration of 12 weeks might even be sufficient [79]. The increased mortality rate in a subgroup of patients who received long-term interferon maintenance therapy is not representative for short-term antiviral therapy with the potential to result in SVR. Nevertheless, we do acknowledge that interferon-based therapy is accompanied by substantial side-effects, which was also highlighted again by the recent meta-analysis [6]. Thus, careful patient selection remains a necessity at this time, and better tolerated interferon-free treatment regimens with combinations of direct-acting antiviral agents are urgently required. We oppose, however, that the results of the recent Cochrane meta-analysis, or more specifically the HALT-C study, should discourage physicians from treating their patients with chronic HCV infection in general.

Conflict of interest

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