Review

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Assessing long-term treatment efficacy in chronic hepatitis B and C: Between evidence and common sense

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Summary

Chronic infection with the hepatitis B and C virus represents a major health problem worldwide, as it is estimated that roughly 400 and 200 million people respectively, are infected by each virus. By definition, any antiviral therapy that claims to be effective should have as its ultimate efficacy end point an improvement in patients' survival, or at least a reduction in the development rates of liver-related complications. However, this is extremely complicated to prove as the natural course of both viral diseases is extremely slow, requiring decades to evolve in cirrhosis and even more years to lead to liver complications. For this reason, clinicians and health authorities have relied on so called surrogate end points to assess the efficacy of any therapeutic intervention for viral hepatitis. Obviously, this allows for standardization in study designs that ultimately translates into an accelerated time frame for therapeutic drugs as well as healthcare innovations to enter the viral hepatitis clinical practice. However, it also calls for demonstration that surrogate end points in the treatment of patients with chronic hepatitis B or C are good and reliable markers of long-term efficacy.

Introduction

Chronic infection with the hepatitis B (HBV) and C virus (HCV) represents a major health problem worldwide, as it is estimated that roughly 400 and 200 million people respectively, are infected by each virus [1]. These people are at increased risk of developing cirrhosis, hepatocellular carcinoma (HCC), liver decompensation, and esophageal variceal bleeding, that ultimately explains why HBV and HCV infection is the current leading cause of liver-related death and the main indication for liver transplantation in developed countries [2]. By definition, any anti-HBV or anti-HCV therapy that claims to be effective should have as its ultimate efficacy end point an improvement in patients' survival through the prevention, or at least reduction, of the development rates of liver-related complications. However, this is far from being convincingly demonstrated, especially since the dramatic and life threatening complications of HBV and HCV infection are likely to occur in most patients many decades after viral infection and many years after diagnosis of hepatitis. In theory, in patients with HBV or HCV chronic infection, a study designed to assess the impact of a specific therapeutic regimen, should therefore not only follow-up patients for impossibly long periods of time after treatment completion, but also exclude treatment failure patients from any form of retreatment whilst maintaining them on clinical observation, a feat that is obviously impossible and unethical. Clinicians, health authorities, and pharmaceutical companies have therefore relied on so called surrogate end points to assess the efficacy of any therapeutic intervention for viral hepatitis [3]. Obviously, this allows for an accelerated clinical/scientific progress in the hepatology field, as drugs as well as healthcare innovations can more rapidly be introduced in everyday clinical practice, however, it also calls for demonstration that surrogate end points in the treatment of patients with chronic hepatitis B or C are good and reliable markers of efficacy.

Defining antiviral treatment efficacy end points

HBV and HCV are characterized by peculiar biological and clinical characteristics, but probably the most important difference between these viruses is that HCV can be eradicated, while HBV remains detectable in the liver either integrated into the host DNA or as covalently closed circular DNA (cccDNA), the template for transcription of viral RNA [4,5]. For this reason, any anti-HCV regimen is aimed at persistent viral eradication, while anti-HBV regimens are aimed at sustained suppression of viral replication. Currently, in HCV patients, viral eradication is defined as a sustained virological response (SVR), which means serum HCV RNA undetectability 24 weeks after pegylated interferon (PegIFN) plus ribavirin (RBV) with or without a directly acting antiviral agent (DAA). This surrogate end point has been shown to reflect persistent serum viral eradication by a large study analyzing 1343 HCV patients followed for a mean time period of 3.9 years after an SVR to PegIFNα2a plus RBV, as 99.1% of the population remained persistently serum HCV RNA negative during the follow-up period [6]. The 0.9% rate of HCV-RNA positivity reported in this study is most likely to be caused by patients reacquiring

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HCV infection due to concomitant risk factors, more than by a late post-treatment relapse. Indeed, studies analyzing HCV RNA in the liver and in peripheral blood mononuclear cells have shown an SVR to be associated with HCV RNA elimination in these body districts, too [7]. Recently, both the Federal Drug Administration (FDA) and the European Medical Agency (EMA) have shortened the post-treatment follow-up period necessary to define an SVR by introducing the so called SVR12, defined as HCV RNA undetectability 12 weeks following PegIFN/RBV. This change is supported by the results of two studies in HCV patients, one in HIV/HCV co-infected patients and one in HCV post-transplant patients showing that 827 of 828 (99.9%) patients who had an SVR12 achieved an SVR24 [8–11].

In HBV patients, the therapeutic end points are a bit more complex, as chronic hepatitis B is characterized by a hepatitis B e antigen (HBeAg) positive phase and a HBeAg negative phase. The HBeAg positive phase usually precedes the HBeAg negative phase, and is further divided into an immune tolerant phase, where liver damage is generally mild and non-progressive, and an immune reactive phase, characterized by elevations of aminotransferases levels and more rapid progression of liver fibrosis. The HBeAg negative phase of chronic hepatitis B is associated with a high risk of progression to advanced fibrosis, cirrhosis and subsequent liver-related complications. Although in both HBeAg phases the ideal end point of therapy is sustained HBsAg loss with or without seroconversion to anti-HBs, as this is associated with a complete and definitive remission of the activity of chronic hepatitis B, this event is quite rare in clinical practice as only 1–7% of cases achieve it during a 1-year treatment period [4]. For this reason, in HBeAg-positive patients, durable HBe seroconversion is considered a satisfactory end point, while in the HBeAg-positive patients who do not achieve HBe seroconversion, and in all HBeAg-negative patients, a maintained undetectable HBV DNA level on treatment with nucleos(t)ide analogs (NUC) or a sustained undetectable HBV DNA level after IFN therapy, is the desired end point [4].

Do therapeutic end points modify the natural history of HBV infection?

Probably

Since serum HBV DNA undetectability is the prerequisite to define HBeAg and HBsAg seroconversion as an end point of anti-HBV therapy, suppression of HBV DNA is the most reliable response predictor of any HBV therapy. This notwithstanding, it is still debated whether persistent undetectability of serum HBV DNA, by highly sensitive and specific PCR based assays, really stands for a surrogate of a cure. In a minority of patients only, serum HBV DNA undetectability will definitively mirror HBV eradication, as clearly demonstrated by the almost universal recurrence of detectable viremia following withdrawal of antiviral regimens [4]. Working against the generalisability of a virological response in HBV patients as an index of treatment efficacy is also the observation that HBV DNA undetectability is restricted to long-term administration of third generation direct antivirals only, i.e., entecavir or tenofovir, since first (lamivudine) and second generation antivirals (adefovir, telbivudine) have time limited efficacy as a consequence of drug resistance developing in up to 80% of lamivudine-treated patients and in 29% of the adefovir treated patients [4]. Generalisability of a virological response in HBV patients is also limited by a different HBV DNA cut-off (<2000 IU/ml) for patients responding to PegIFN, which is a therapeutic option for a niche of patients only.

In weighing the long-term benefits of antiviral therapy in HBV, special consideration should be given to the evolution of serum HBV DNA assays, which have significantly improved in sensitivity over time, as well as the new therapeutic options that shifted from interferon as the only option with limited applicability, to NUC that have been successfully employed in patients with a variety of clinical conditions, including liver failure. Not to mention the evolution of oral analogs in terms of potency, from low genetic barrier and moderately potent drugs such as lamivudine, adefovir and telbivudine which kept physicians busy trying to put viral replication under control, to entecavir and tenofovir, which are more user friendly, providing full suppression of viral replication in >95% of the patients over 5 years of monotherapy [4] (Tables 1 and 2). Along the same line, treatment end points have evolved too, considering that in the interferon era, serological events, such as HBeAg and HBsAg seroconversion, were "the" end points of treatment, whereas nowadays undetectable HBV DNA by RT-PCR (<10–15 IU/ml) has become the standard of care to guide treatment with oral analogs. Further attenuating the importance of serological end points is not only their dependence on undetectable HBV DNA, but also the fact that end points, such as interferon-induced HBeAg seroconversion, are not durable in all patients and are not granting HBV suppression [12]. Even the clinical relevance of HBsAg seroconversion, the proxy to a cure, is now challenged by the new therapeutic algorithms in patients fully suppressed by NUC, in whom HBeAg and HBsAg seroconversion is now considered as a stopping rule rather than as "true" end point of therapy. Finally, last but not least, on-treatment quantification of serum HBsAg at week 12 has been shown to accurately predict non-response to Peg-IFN in both HBeAg positive and negative patients, with the aim to identify patients to be early withdrawn from interferon and to switch to long-term NUC therapy [4].

HBeAg seroconversion

Spontaneous HBeAg seroconversion occurs in 2–15% of chronic carriers depending on age, ALT levels, and HBV genotype [13], frequently heralding a decreased risk of cirrhosis and HCC, particularly when it occurs before the age of 30 [14]. For decades, HBeAg seroconversion has been the standard of care end point for interferon-treated HBeAg positive patients worldwide, due to its strict association not only with a decline of viral replication, but also with a clinical and histological remission of liver disease and increase in survival [15]. Approximately one third of all patients with active hepatitis will achieve HBeAg seroconversion following PegIFN therapy [4], with higher rates in those with a baseline HBV DNA below 7 log IU/ml, ALT levels >2–5 time ULN, genotype A and B of HBV, in the absence of basal core promoter and precore mutations (Table 1). In these patients, seroconversion is associated with a lower likelihood of progression to cirrhosis, development of HCC and liver-related mortality compared to non-responders or untreated patients [16], but the benefit of therapy are often challenged by limited durability of HBeAg seroconversion heralding the risk of evolving to HBeAg negative

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Table 1. Rates of virological and serological responses in patients with CHB treated with PegIFN, ETV or TDF. Responses were assessed at 6 months following 12 months of PegIFN and at 12 months NUC therapy [4].

	PegIFN (%)	ETV (%)	TDF (%)
HBeAg-positive CHB			
HBV-DNA <60-80 IU/ml	7-14	67	76
ALT normalization	32-41	68	68
HBeAg seroconversion	32-29	21	21
HBsAg loss	3-7	2	3
HBeAg negative CHB			
HBV-DNA <60-80 IU/ml	19	90	93
ALT normalization	59	78	76
HBsAg loss	4	0	0

Table 2. Rates of virological and serological responses in patients with CHB treated with ETV or TDF for 5 years [4].

	ETV (%)	TDF (%)
HBeAg-positive CHB		
HBV-DNA <60-80 IU/ml	94	96
ALT normalization	80	69
HBeAg seroconversion	54*	40
HBsAg loss	6.4*	11
Anti-HBs seroconversion	n.a.*	8
HBeAg negative CHB		
HBV-DNA <60-80 IU/ml	95**	99
ALT normalization	59**	85
HBsAg loss	n.a.**	<1
Anti-HBs seroconversion	n.a.**	<1

*For ETV, only selected patients continued therapy for 5 years.
**For ETV, 3-year data available.

chronic hepatitis B [12]. The latter risk is only exceptionally seen in serum-converters with HBV DNA levels persistently below 2000 IU/ml, creating the basis for a new definition of the HBeAg seroconversion end point, particularly for patients undergoing third generation NUC therapies that have been associated with high rates of compliance, adherence and HBeAg seroconversion (50%) (Table 2). Again, the durability and clinical significance of HBeAg seroconversion in these patients is doubtful since a number of patients following discontinuation of NUC seroreverted to HBeAg or developed serum HBeAg negative chronic hepatitis B, this worrisome finding, however, needs to be addressed by larger studies in different geographical areas [17–22].

Thus, HBeAg seroconversion coupled with serum HBV DNA levels <2000 IU/ml, is a reasonably trustable, but still imperfect, end point in both treated and untreated patients, whereas serum HBV DNA undetectability is a key therapeutic end point in the NUC scenario, where HBeAg seroconversion has been downgraded to the role of a potential, stopping rule. While HBeAg seropositive patients with mild to moderate chronic hepatitis B, and persistent HBV DNA undetectability showed attenuated progression to cirrhosis and related complications, including HCC, there are no data on overall patients survival.

HBsAg seroclearance and seroconversion

HBsAg seroclearance may spontaneously occur in carriers of inactive HBV infection as well as in patients with chronic active hepatitis following a successful virological response to therapy. Longitudinal studies in Asia clearly demonstrated that undetectable serum HBV DNA was the prerequisite to clear HBsAg in more than 95% of the patients [23]. Spontaneous HBsAg clearance occurs in less than 2% of the inactive carriers [24], whereas in responders to interferon-based regimens HBsAg sero-clearance is largely influenced by HBeAg status, patient age and underlying liver disease, ultimately ranging from 0.5% to 2.3% [25,26] (Table 1). The lower seroconversion rates are observed in HBeAg seronegative patients and those treated with direct antivirals that can only indirectly stimulate the immune mediated clearance of the infected hepatocytes, which is one of the key events in determining the serum levels of HBsAg (Table 2). Interferon-based regimens instead, exert a moderate antiviral activity together with a strong immunostimulatory activity, which accelerates the clearance of infected hepatocytes. Differences in the rates of HBsAg seroclearance following treatment with either interferon or direct antivirals is also underscored by differences in the on-treatment decline of serum levels of HBsAg, which are definitively quicker and more pronounced following interferon than direct antivirals [27]. Mitigating, however, against the assumption that HBsAg seroclearance and seroconversion in all cases stand for a cure of hepatitis B, are studies showing persistence of biologically active cccDNA of HBV in the livers of HBsAg seronegative individuals, even in subjects carrying the serum anti-HBs marker of protective immunity against HBV, a condition defined as occult HBV infection [4]. As a matter of fact, in a reanalysis of 298 patients in Hong Kong, HCC was found to develop in a significant number of patients from 1 year to more than 10 years following spontaneous clearance of serum HBsAg, with higher attack rates in patients over 50, a finding that led the authors to speculate on a potential pathogenic role of age-related factors like advanced liver fibrosis or long term exposure to the carcinogenic activity of occult HBV, or a combination of both [28]. Indeed, evidence has cumulated to indicate occult infection as an established risk factor of HCC in both patients with an originally pure HBV infection and those with co-morbidities like alcoholic liver disease and chronic hepatitis C [29]. The fact that spontaneous HBsAg seroconversion is a rare event, occurring in inactive carriers only, and that treatment-related HBsAg seroconversion occurs in association with HBV DNA undetectability, supports anti-HBV therapy and HBV DNA undetectability as disease modifying markers of chronic hepatitis B.

Certainly

Studies in cirrhotic patients who are more prone to develop clinical end points like decompensation or HCC, provided evidence for effective anti-HBV treatment to have a favorable impact on patients survival by the prevention of liver-related complications. Long-term suppressive therapy with NUC, in fact, was associated with histological regression of cirrhosis, prevention of clinical decompensation, reduction of the incidence rates of liver cancer, reversal of clinical decompensation, as well as increased listing to and survival following liver transplantation.

Histological regression of cirrhosis

In the face of remission or inactivation of cirrhosis spontaneously occurring in HBV carriers, there are recent reports of histological regression of HBV-related cirrhosis following successful anti-HBV treatment. With all the caveats related to the referral bias of a multicenter registration trial and the *post hoc* analysis of relatively sparse cases, Chang and co-workers first documented the histological reversal of cirrhosis in 4 out of 10 cases who met the criteria for efficacy analysis, while they were in a 3- to 7-year period of sustained virological response to entecavir [30] However, these results derive from a rather heterogeneous cohort composed of 354 HBeAg and 325 anti-HBe seropositive patients, with different HBV genotypes who were enrolled in two registration trials of a daily dose of 0.5 mg entecavir for 3 years (several HBeAg positive patients had also received lamivudine) and 1 mg in the rollover period of study. Interestingly, none of the patients enrolled in the study was able to clear serum HBsAg in the long term. More robust evidence of cirrhosis reversion was offered by the reanalysis of 96 patients with cirrhosis, mostly HBeAg negative, enrolled in the rollover study of the registration trial of tenofovir, who underwent a second liver biopsy after 5 years of undetectable serum HBV DNA by a PCR-based assay with a limit sensitivity of 69 IU/ml [31]. The findings that 70 (73%) patients had an Ishak staging decrease of at least 2 points as a consequence of successful antiviral therapy, and that 71 (74%) patients had cirrhosis histologically reversed, support persistent HBV suppression to translate into significant remodeling of the fibrotic matrix and septa, which accompanies chronic liver cell necro-inflammation elicited by HBV replication.

Prevention of liver disease progression

A landmark study in patients with advanced fibrosis (Ishak stage 4–6) from Hong Kong and the Pacific area, provided substantial evidence on the ability of lamivudine to delay progression of HBV-related liver disease, as it was cumulatively assessed in terms of increased Child Pugh score, liver failure or HCC development [32]. The study was prematurely interrupted at year 3 of treatment when the rates of liver disease progression were shown to differ between arms, subsequently resulting to be 24% in patients on placebo and 9% in those under active treatment ($p = 0.001$). While the clinical benefits were maintained in patients with a persistent virological response to lamivudine only, treatment-related benefits were in part lost in the lamivudine-treated patients who experienced a virological breakthrough, following the onset of lamivudine resistance. In these patients, the incidence rate of clinical end points, including HCC, was higher (11% *vs.* 5%) than in the placebo patients at month 32 ($p < 0.031$). Despite some caveats related to pooling clinical outcomes with a tumor end point that would require a separate assessment to guide anticipated interruption of a randomized study, when results had crossed the predefined boundary for showing efficacy, the study by Liaw and co-workers is universally taken as evidence of antiviral agents being able to prevent deterioration of chronic hepatitis B, a fact that for ethical reasons discouraged further controlled studies in the field. The most intriguing finding of the Hong Kong study was that patients, despite achieving a virological response to lamivudine, ultimately developed HCC, which was in fact the only complication arising in virological responders (Table 3). Other findings added to the debate of HCC arising in patients responding long term to NUCs. In a systematic review of studies of nucleos(t)ide analog treatment of patients with HBV, it was clearly defined that HCC was prevented in patients with chronic hepatitis but not in those with cirrhosis, and in general in patients that could not achieve complete virological suppression [33]. A recent cohort study from Greece confirmed that cirrhotic patients long-term responding to lamivudine remained at risk of liver cancer development [34]. However, all these studies enrolled patients treated with lamivudine or rescued with adefovir, i.e., regimens characterized by limited potency and low to moderate genetic barrier, which are not any more recommended by International guidelines, to treat patients with chronic hepatitis B in general, and especially in patients with compensated cirrhosis [35]. Moreover, the hope that more potent NUCs, like entecavir and tenofovir, might finally prevent liver cancer in responders with cirrhosis, rapidly faded away when a multicenter study in Italy, in patients with compensated cirrhosis who had persistently undetectable serum HBVDNA during 4 years of entecavir monotherapy, showed an annual rate of neoplastic transformation of the liver of approximately 2.5% [36], that mimics the HCC rates in untreated HBeAg negative patients in Europe (Table 3).

In an attempt to reconcile these findings with the optimistic reports of an histological regression of cirrhosis in the majority of long-term responders to HBV antivirals, it should be taken into account that development of HCC in successfully treated patients with cirrhosis is often the consequence of an extended survival provided by NUC, preventing clinical decompensation, as it was the case in the Italian multicenter study. On the other hand, HBV-related liver carcinogenesis is likely to be promoted by cellular events that are established early during chronic HBV infection, independently of the onset of cirrhosis. The Italian multicentre study clearly documented prevention of jaundice, ascites, encephalopathy during long-term suppressive therapy in cirrhotics. Small studies in Asia and Italy showed regression of esophageal varices in patients with HBV cirrhosis who were successfully treated with lamivudine associated or not with adefovir [37,38] that mimics the reduction of portal hypertension in treated patients measured through hepatic venous pressure gradient (HVPG) [39].

Reversal of clinical decompensation and increased survival following liver transplantation

Clinical decompensation is a major determinant of liver-related death in both HBeAg positive and negative patients with hepatitis B-related cirrhosis. This risk is predicted by persistently elevated levels of serum HBV DNA, independently of the HBeAg status [15,40,41]. The beneficial impact of antiviral therapy on patient survival is easy to demonstrate in patients with decompensated liver disease, where only 20% are alive after 5 years. In a phase 2, double-blind, randomized study in Asia, persistent HBV DNA suppression by entecavir or tenofovir led to reversal of clinical decompensation in most patients with decompensated HBV in terms of improved Child Pugh score (at least 2 points decrease on average) and MELD score (2 points decreased from baseline) [42]. A systemic review of the efficacy and safety of different antivirals in patients with decompensated HBV cirrhosis showed an approximately threefold higher rate of 1-year transplant-free survival of patients treated with lamivudine compared to untreated patients [43]. An additional proof of concept that HBV DNA suppression may translate into increased survival, is the observation that patients decompensated following antiviral

Table 3. HCC rates in NUC-naïve cirrhotic patients long-term treated with NUC.

Author, yr, [Ref.]	Study	Continent	Disease severity	NUC	Patients	HCC/yr (%)
Liaw *et al.*, 2004, [32]	RCT	Asia	Cirrhosis*	LAM	211 w/o resistance	1.5
Papatheodoridis *et al.*, 2010, [33]	Review	Asia/Europe	Cirrhotics	LAM	81 responders	2.4
Papatheodoridis *et al.*, 2011, [34]	R	Europe	Cirrhotics	LAM	62 responders	2.5
Kurokawa *et al.*, 2012, [35]	R	Japan	Cirrhotics	LAM	42 responders	2.8
Lampertico *et al.*, 2011, [36]	CP	Europe	Cirrhotics	ETV	164	2.5

RCT, randomized controlled trial; R, retrospective study; CP, cohort prospective study.
*Bridging fibrosis and cirrhosis.

resistance to first or second generation anti-HBV analogs, while being listed to liver transplant, and were successfully rescued with third generation analogs [44,45]. Tempering the growing optimism on the efficacy of these new analogs, was the report of approximately 20% of these severely ill patients with clinical decompensation who died within the first 6 months of therapy despite full suppression of viral replication or developed HCC during the first 2 years of therapy. This notwithstanding, NUC-related HBV DNA suppression and reversal of clinical decompensation accounted for the significant increase in listing patients with end-stage HBV for liver transplantation, worldwide. In Europe, between 1988 and 2007, 14,717 patients with viral cirrhosis received a liver graft, including 3627 patients with HBV alone (25%), 1109 with HBV/HDV (7%), 135 with HBV/HCV/HDV (1%), and 535 with HBV/HCV (4%), an overall 37% of patients requiring anti-HBV treatment and/or prophylaxis. While the highest rates of survival were observed in patients with end-stage HDV (90% at year 10), the aggregated survival of patients with HBV was greater than 70%, compared to HCV patients whose survival was around 60% [46]. Owing to the fact that the above cited pooled outcomes of liver transplantation in Europe cross two decades of clinical activity with anti-HBV therapy and prophylaxis of increasing efficacy and safety, the aggregate figures of survival of HBV recipients might underestimate the current success rates of liver transplantation in patients with end-stage HBV. In the reanalysis of 74 patients, with HCC and persistently suppressed serum HBV DNA by NUC, who consecutively received a liver graft in Milan, the 5-year survival was 89% with a 6% rate of tumor recurrence almost exclusively occurring in patients who were transplanted beyond the Milan criteria [47]. Though a chasm still exists in terms of disease severity between patients enrolled in trials and patient seen in field practice, it is really encouraging that the rates of HBV suppression, achieved in everyday clinical practice with third generation NUC, look very similar to those achieved in registration trials [48].

Do therapeutic end points modify the natural history of HCV infection?

Probably

Although the ultimate aim of anti-HCV therapy in patients without cirrhosis should be the prevention of liver-related mortality, this is a nearly impossible feat for various reasons. First of all, epidemiological studies in Europe and Australia have shown that mortality for non-liver-related reasons is the main death cause in HCV patients with a threefold higher rate compared to liver-related deaths [49,50]. Secondly, in HCV patients, the occurrence of liver-related complications leading to death requires the development of cirrhosis in the overwhelming majority of the cases. Cirrhosis determines a structural and vascular remodeling of the liver that leads to the development of portal hypertension and its clinical sequelae (ascites, variceal bleeding), and although experimental evidence supporting a direct oncogenic role of HCV exists, cirrhosis is also the main risk factor for HCC development [51]. This implies that to assess the benefit of an SVR on mortality rates treatment failure patients should be kept under observation until they develop cirrhosis, given that the time to progression to cirrhosis is extremely variable at the individual patient level but usually requires decades, it is clear why such a study cannot be designed.

However, we do have indirect evidence that HCV has a negative impact on survival in patients without cirrhosis and that viral clearance has clinical benefits also in terms of patients survival. In the above mentioned epidemiological studies from Europe and Australia, although liver-related mortality was not the main cause of death among HCV patients, still patients with HCV infection were more likely to die of liver-related death than those not HCV infected. Amin and colleagues in Australia found that among 75,834 patients with HCV infection the mortality rate for liver reasons was 16.9 times higher than that of the general population matched by age and sex [50]. Even more interestingly, Omland *et al.*, when analyzing 6292 patients with anti-HCV antibodies, 37% of whom had cleared the virus either spontaneously or following antiviral treatment, found that the 8-year liver-related death rate in chronic HCV patients was 5.5% compared to 2% in non-viremic patients, effectively proving that not only HCV infection increases liver-related mortality, but also that spontaneous or treatment-induced clearance can have a positive impact on these figures [49].

On the same page, a recent large study by the Veterans Affair health system in the US, analyzing 16,864 HCV patients treated with PegIFN and RBV, who were followed-up for a median period of 3.8 years, found SVR to be associated with a reduced risk of all-cause mortality (Odds Ratio: 0.7) [52]. Even if the cohort analyzed by Backus *et al.* had some peculiar features that might not reflect the typical European HCV population (20% had diabetes, 13% coronary artery disease, mean body mass index: 29) and unfortunately the study design could not provide data on the reasons for death, still it is the first prospective demonstration of a survival benefit associated with an SVR.

Studies analyzing post-SVR liver histology provide further support to the claim that HCV clearance in patients without cirrhosis has clinical benefits, indeed between 57% and 100% show improved inflammation when compared to pre-therapy histological findings and between 0% and 100% show a reduction in the

semi-quantitative score of liver fibrosis, providing evidence that an SVR prevents the progression to cirrhosis [53].

Key Points

- In HCV patients with cirrhosis the achievement of an SVR reduces the rates of liver related complications, may lead to cirrhosis regression and improves survival. In patients without cirrhosis an SVR prevents disease progression while protecting from the development of extra-hepatic manifestations of HCV
- Although maintained HBV DNA suppression is rarely associated with HBV clearance, it results in reduced rates of liver complications. Preliminary data show that some patients may also benefit from cirrhosis regression following long-term HBV DNA suppression
- Maintained HBV DNA suppression does not completely abrogate the risk of HCC in patients with pre-existing cirrhosis
- There is a gap between efficacy of anti-HCV and anti-HBV regimens as seen in clinical trials, and effectiveness of both regimens in real life clinical practice. This is attributable to under-diagnosis of the diseases, lack of referral to liver specialists, poor tolerability profile of current anti-HCV regimens and inadequate adherence to current HBV regimens

A secondary aim of anti-HCV treatment is to prevent the extra-hepatic manifestations of the virus [54]. HCV is known to lead to the production of cryoglobulins through B-lymphocyte cell activation in roughly 40% of the infected patients, with 20–30% of these patients developing the cryoglobulinemic syndrome characterized by purpura, arthralgias, and weakness. In some cases cryoglobulinemia may lead to a more serious systemic vasculitis characterized by neurological and/or renal involvement [55]. HCV has also been shown to interfere with lipid and glucose metabolism leading to liver steatosis, development of insulin resistance, increased incidence of diabetes and carotid atherosclerosis [56–60]. HCV can also impair kidney function by immune-mediated damage, determine cognitive dysfunction through central nervous system involvement, and activate B lymphocytes leading in some cases to the development of non-Hodgkin's lymphoma [61–63]. Several lines of evidence show that an SVR is associated with improvement or prevention of many of these conditions (Table 4) [64–67]. Most importantly, an SVR has been shown to be associated with reduced incidence of non-Hodgkin's lymphoma in a large study in Japan, where, during a 15-year follow-up period, none of the 1048 SVR patients developed lymphoma compared to 2.56% of the 2161 patients with persistent infection, hence further strengthening the positive impact of an SVR in HCV patients.

All in all, even if no randomized controlled trial will ever demonstrate that an SVR improves liver-related survival in HCV patients without cirrhosis, indirect evidence suggests this to be the case, supporting SVR as an excellent marker of efficacy in this subgroup of HCV patients.

Certainly

Patients with cirrhosis due to HCV are at risk of liver-related morbidity and mortality [68], with annual liver-related mortality ranging between 2% and 6%. For this reason, it is extremely simpler to assess the impact of an SVR on hard clinical end points in this population. Many studies have shown that an SVR can provide protection from development of liver-related complications, hence improving survival of HCV cirrhotics [69–71]. Among the first to demonstrate a beneficial impact of HCV eradication on the natural history of patients with HCV cirrhosis were Yoshida and colleagues, who retrospectively analyzed data from 2890 patients (337 cirrhotics) with any degree of liver fibrosis, and reported reduced annual incidence of HCC in patients with an SVR compared to patients without an SVR (0.38 *vs.* 1.41), while also demonstrating lower 5-year liver-related death rates in those with an SVR compared to those who failed to respond to IFN treatment (0.2% *vs.* 2%) [69,72]. Similarly, a prospective, non-randomized, controlled study from Japan reported a beneficial impact of SVR on 271 cirrhotic patients treated with IFN and followed-up for 7 years after treatment completion, since patients with an SVR showed reduced rates of both HCC (11/64 *vs.* 73/207, 17% *vs.* 35%, $p = 0.008$) and liver-related deaths (0/64 *vs.* 32/207, 0 *vs.* 15%, $p = 0.0002$) [73].

In Italy, when analyzing 920 patients with compensated cirrhosis who received IFN monotherapy and were followed-up for a median period of 96 months after treatment completion, Bruno *et al.* found that SVR patients had lower rates of liver-related complications (0 *vs.* 1.88 per 100 person-years), HCC (0.66 *vs.* 2.10 per 100 person-years) and liver-related death (0.19 *vs.* 1.44 per 100 person-year) [$p < 0.001$] compared to those with a treatment failure [74]. Finally, two studies analyzed the role of SVR on the clinical course of patients with advanced liver fibrosis, including not only patients with cirrhosis but those with lower stages of fibrosis, too [75,76]. Veldt and colleagues confirmed that an SVR was associated with a reduced risk of any liver-related events (4/142 *vs.* 87/337, 3% *vs.* 26%, $p < 0.0001$; adjusted HR 0.21; 95% CI 0.07–0.58, $p = 0.003$), including liver failure (0/142 *vs.* 42/337, 0 *vs.* 12%, $p < 0.0001$; HR 0.03; 95% CI 0.00–0.91) [75]. In the study conducted by Cardoso *et al.*, which included 307 patients with bridging fibrosis or cirrhosis followed-up for 3.5 years after the end of treatment, incidence rates per 100 person-years of liver-related complications, liver-related deaths, and HCC were significantly lower in SVR than in non-SVR patients (0.62 *vs.* 4.16, 0.61 *vs.* 3.76 and 1.24 *vs.* 5.85, respectively; $p < 0.001$ for all comparison) [76].

Two Italian studies have also prospectively validated the impact of an SVR on the clinical course of portal hypertension, by using repeated gastroscopies in cirrhotic patients who achieved an SVR [75,76]. Bruno and colleagues followed-up 218 patients for up to 18 years, and found SVR to be able to prevent the development of esophageal varices (EV) (0% for SVR *vs.* 39.1% for non-SVR, $p < 0.0001$) [77]. D'Ambrosio *et al.* found that in 127 patients followed-up for up to 108 months after the end of IFN-based regimens, EV development was seen in both SVR and non-SVR patients, although the incidence of *de novo* EV was reduced among patients with an SVR (3.5% *vs.* 15.1%, $p = 0.047$) [78].

Taken together, these data clearly demonstrate the ability of an SVR to prevent hard end points in HCV patients with advanced fibrosis/cirrhosis (Table 5), still the exact biological mechanisms

Table 4. The achievement of an SVR has an impact on extrahepatic manifestations of HCV.

Clinical event	Patients		Reference
	SVR (+)	SVR (-)	
Diabetes	26/1167 (2.2%)	117/1175 (9.9%)	Arase *et al.*, 2009 [64]
Malignant lymphoma	0/2161 (0%)	25/1048 (12.6%)	Kawamura *et al.*, 2007 [65]
Improved neurocognitive functions	8/8 (100%)	0/6 (0%)	Byrnes *et al.*, 2012 [66]

Table 5. Cumulative incidence of clinical events in HCV patients with cirrhosis or advanced fibrosis stratified by treatment response.

Endpoint	Reference	Patients	SVR (+)	SVR (-)
Hepatocellular carcinoma				
	Yoshida *et al.*, 1999 [72]	2890	1.9%	17.9%
	Shiratori *et al.*, 2005 [73]	271	17%	35%
	Bruno *et al.*, 2007 [74]	920	5.6%	16%
	Cardoso *et al.*, 2010 [76]	307	5.8%	19.6%
Decompensation				
	Veldt *et al.*, 2007 [75]	479	0%	12%
	Cardoso *et al.*, 2010 [76]	307	2.9%	13.7%
Development of esophageal varices				
	Bruno *et al.*, 2010 [77]	218	0%	39%
	D'Ambrosio *et al.*, 2011 [78]	127	3.5%	15.1%
Liver-related death				
	Yoshida *et al.*, 2002 [69]	2879	0.2%	2%
	Shiratori *et al.*, 2005 [73]	271	0%	15%
	Bruno *et al.*, 2007 [74]	920	1.7%	11.4%
	Cardoso *et al.*, 2010 [76]	307	2.9%	8.8%

through which this happens remain unclear. In theory, HCV eradication may prevent development of HCC by negating the carcinogenetic action of HCV, which has been extensively demonstrated *in vivo* and in mouse models. On the other hand, more recent studies attribute the protective effect of an SVR on the restoration of the pre-cirrhotic liver architecture. Recently, two European studies have investigated the histological benefits of an SVR, whilst also assessing the clinical impact of cirrhosis regression on the occurrence of liver-related complications [79,80]. In the Italian-French collaborative study conducted on 38 HCV cirrhotics treated with IFN-based regimens that underwent a post-SVR liver biopsy after a median follow-up of 61 months, an improvement in the liver architecture as assessed by the METAVIR score was demonstrated in more than half (61%) of the patients [80]. Interestingly, in this study a reduction in the amount of fibrosis as assessed by morphometry was demonstrated in the near totality of the patients, even in the absence of cirrhosis regression, once again confirming fibrosis to be a dynamic process that can be positively influenced by HCV clearance.

The study conducted by Mallet and colleagues has the added benefit of assessing the impact of cirrhosis regression, observed in 44% of the patients, with reduction in liver-related clinical events [79]. Indeed, while patients staged F4 after an SVR still developed clinical events (i.e., 3 liver-related deaths/OLT, 3 HCC and 1 variceal bleeding), none of the patients with cirrhosis regression showed any liver complication. These 2 studies highlight the histological benefits of an SVR, whilst also suggesting that occurrence of liver-related events post-SVR might actually rely more on the architectural improvement observed in the liver than on HCV clearance.

The clinical benefits of an SVR have also been convincingly shown in HCV patients undergoing liver transplantation for end-stage liver disease or HCC, as recurrent HCV infection is universal in patients who are viremic at transplantation, and also accounts for impaired post-OLT survival and increased graft loss [81]. Successful eradication of HCV prior to OLT has been shown to prevent recurrent infection of the graft and consequent graft damage, most interestingly, recent studies have also shown that if undetectable HCV RNA can be achieved by IFN-based regimens on the liver transplant waiting list, the risk of recurrence is reduced, with nearly 70% of patients being cured of HCV infection post-OLT [2]. Although this is incontrovertible evidence that SVR can positively modify survival, unfortunately, routine treatment of HCV cirrhotics on the OLT waiting list is associated with significant side effects, increased risk of systemic infections and increased mortality, especially if patients have decompensated cirrhosis, thus, in this particular setting, effectively questioning whether the theoretic efficacy of a regimen actually translates into effectiveness in clinical practice.

Conclusions

Even in the absence of randomized controlled trials, there is overwhelming evidence that surrogate end points, that are commonly used to assess efficacy of anti-HBV or anti-HCV regimens, are not surrogate but rather true markers of efficacy as clinical benefits are associated with their achievement. The enthusiasm for this finding is however mitigated by the fact that the efficacy of anti-HBV and anti-HCV therapies, as reported by controlled studies, does not always translate into effectiveness once these regimens are analyzed in the medical practice setting [82]. Although a detailed discussion of the reasons for this chasm is beyond the scope of this article, it is important to keep in mind that the main issues rely on under-diagnosis of chronic viral hepatitis, as well as unequal access to treatment. It is estimated that as few as 35% of patients with chronic HBV and only 25% of HCV patients are aware of their disease in developed countries, with this number obviously shrinking even more in developing countries [83]. Even more worrisome is the fact that in Europe and the USA, even if patients are diagnosed correctly, only 1–16% of HBV and HCV patients are estimated to receive treatment [84–86]. For HCV this can be partially explained by lack of health care resources that precludes access to treatment in some countries, and by the poor tolerability profile of the current therapeutic regimens, that unfortunately exclude from treatment a large proportion of eligible patients. This last point was recently magnified by a study conducted at the Veterans Affair health system in the US that showed 57% of the 82,785 HCV patients who did not receive PegIFN/RBV therapy to have contraindications to treatment [87]. Although there is hope that the development of an IFN-free regimen will help improve the rate of diagnosed patients who can actually be treated with anti-HCV regimens; up to that time, poor tolerability and acceptability of IFN based regimens will remain a major factor in maintaining the gap between efficacy and effectiveness in HCV patients [88,89].

For HBV infection, contraindications to treatment do not play a major role in limiting access to treatment, as NUC therapies are relatively adverse event free. Indeed, the major reasons for under-treatment in the US seem to be health care cost-related as well as patient reluctance to take long-term medication, especially in the absence of specific symptoms. The last point is supported by a study analyzing 1-year persistence to NUC treatment, defined as continuing acquisition of pharmacy claims, in 11,100 patients with chronic hepatitis B [90]. Overall, the persistence rate was 81%, and was significantly higher in those already on treatment (81.4%) than in those who NUC was prescribed for the first time (73.4%). Although the 81% persistence rate can be considered acceptable, as it is actually higher than the 1-year persistence rate to hypertensive medications and statins, it still shows that specific strategies to keep more HBV patients on medication are needed.

In conclusion, more than 30 years from the first introduction of effective anti-HBV and anti-HCV treatment options [91], we have solid treatment end points that allow us to determine the efficacy of an antiviral regimen and its ability to positively modify the natural course of the disease. Unfortunately, we still have quite some work ahead of us to improve diagnosis rates, ensure equal access to therapies and develop well tolerated therapies that will finally allow most, if not all, patients with viral hepatitis, to benefit from effective antiviral therapies.

Conflict of interest

Alessio Aghemo: Grant and research support: Roche, Gilead Sciences; speaking and teaching: Roche, Janssen; travel support: BMS, Glaxo Smith-Kline, Bayer, Janssen, Roche.

Pietro Lampertico: Advisory board: BMS, Roche, Gilead Sciences, GSK.

Massimo Colombo: Grant and research support: Merck, Roche, BMS, Gilead Science; advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Achillion; speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex.

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