Postsustained Virological Response Management in Hepatitis C Patients

Chiara Masetti, MD[1] Ana Lleo, MD, PhD[1,2] Matteo Colombo, MD[1,2] Massimo Colombo, MD, PhD[1] Alessio Aghemo, MD, PhD[1,2]

[1] Division of Internal Medicine and Hepatology, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy
[2] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

Address for correspondence Alessio Aghemo, MD, PhD, Department of Biomedical Sciences, Humanitas University, Division of Internal Medicine and Hepatology, Department of Gastroenterology, Humanitas Clinical and Research Center IRCCS, Via A. Manzoni 56, 20089 Rozzano, Milan, Italy (e-mail: alessio.aghemo@hunimed.eu).

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Abstract

The introduction of direct-acting antiviral agents (DAA) has revolutionized management and care of patients with chronic hepatitis C virus (HCV) infection, leading to cure rates higher than 90% in patients with advanced liver disease as well. Viral eradication has been associated with longer survival, reduced mortality from both hepatic and extrahepatic causes, improvement in liver function, and reduced incidence of HCV-related extrahepatic diseases. While patients with mild fibrosis can safely be discharged after achievement of a sustained virological response, patients with advanced fibrosis and cirrhosis remain at risk of developing complications of liver disease, thus requiring regular and life-long surveillance. Major complications of cirrhosis that need to be monitored are hepatocellular carcinoma onset and development or progression of clinically significant portal hypertension.

Keywords
- HCV
- SVR
- complications

Hepatitis C virus (HCV) infection represents a global health problem, affecting all regions in the world, with nearly 71 million people living with chronic HCV infection. Chronic HCV exposes patients to the development of advanced liver disease, clinically significant portal hypertension (CSPH), and hepatocellular carcinoma (HCC).[1] Chronic HCV infection also determines an increased mortality risk also for extrahepatic causes, such as non-Hodgkin's lymphoma (NHL), cardiovascular diseases, and chronic kidney disease. In a study published in 2012 on a large cohort of more than 20,000 patients, anti-HCV positivity was associated with a higher risk of death both from hepatic and extrahepatic diseases (odds ratio 12.5 and 1.3, respectively).[2] The introduction of direct-acting antiviral agents (DAA) had an impressive impact on the management of HCV infection, allowing effective and safe treatment also in patients who were previously excluded from interferon (IFN)-based regimens, such as those with decompensated liver cirrhosis, autoimmune or psychiatric diseases. As a result, according to both European and American guidelines,[3,4] all patients with documented chronic HCV infection should be considered for treatment, providing they have no contraindications to therapy, such as limited life expectancy due to severe comorbidities. The goal of treatment is to achieve a sustained virological response (SVR), which means absence of HCV-ribonucleic acid (RNA) detectability 12 weeks after end-of-treatment (EOT).[3] While IFN-based treatments were effective in less than 50% of the patients, DAAs carry an extremely high rate of cure (> 95%), regardless of viral genotype, age, treatment schedule, and comorbidities.[5]

In this article we will analyze the clinical benefits of an SVR while providing evidence-based recommendations for the management of patients post-SVR.

Clinical Benefits of an SVR in HCV-Infected Patients

While SVR is the virological end point of any antiviral treatment for HCV infection, the ultimate clinical end point is to

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improve survival and quality of life of HCV patients, and also to reduce the risk of HCV transmission. The analysis of these end points requires long-term follow-up studies, and for this reason most of the data derive from IFN-based regimens rather than DAA regimens. A direct comparison between IFN-based and DAA-based cohort studies is impossible due to the fact that the indications for treatment and the treatment efficacy of the two regimens are dramatically different. Not only were IFN-based regimens less effective, but also IFN was contraindicated or poorly tolerated in patients with older age, concomitant severe comorbidities, or decompensated cirrhosis. For this reason cohort studies with DAAs are enriched in factors associated with the development of complications making direct comparisons between studies and databases faulty. Still, after correction for these factors, there is no biological reason to differentiate an SVR to IFN-containing regimens from one obtained with IFN-free regimens.

Viral Eradication

SVR is a durable end point. In a study including more than 1,300 patients who achieved an SVR following IFN-based regimens, HCV-RNA negativity was maintained in 99.1% of the cases after a 4-year follow-up.[6] Similarly, in two recent cohorts of DAA-treated patients including more than 7,000 patients, during a 2 to 3-year follow-up period, more than 99.6% of the patients remained HCV-RNA negative.[7,8] Overall, less than 0.5% of the patients who achieve an SVR will revert to HCV-RNA positivity when followed for more than 3 years, with the majority of those patients being HCV-reinfected through high-risk procedures such as substance abuse.[9] Incidence of HCV reinfection is estimated to be 2 to 6/100 PY in people who inject drugs and 10 to 15/100 PY among men who have sex with men, especially if coinfected with HIV.[10,11] Recently, high rates of reinfection were documented also in prison inmates, with a median time from SVR to reinfection of only 13 months.[12] In these groups at high risk of reinfection, counselling is warranted and HCV-RNA testing is recommended every year or if an increase in ALT occurs.[13] On the other hand, in SVR patients without any at risk behaviors, repeated HCV-RNA testing in the follow-up is not needed.

Extrahepatic Diseases

It is widely accepted that HCV infection can be considered as a systemic infection, affecting many organs other than the liver. There is growing evidence that an SVR can provide measurable benefits also on extrahepatic complications of HCV, such as glycemic control,[14] vascular disease,[15] and crioglobulinemia.[16] In a recent prospective study from Carrat et al,[17] the achievement of an SVR following treatment with DAA has been associated with a significant decrease in all-cause mortality, including nonliver-related mortality (►**Table 1**). SVR has been associated with a significant reduction in the number of vascular events in two large French cohorts of HCV cirrhotic patients.[18,19]

In a large retrospective cohort study of more than 45,000 patients treated for HCV and followed up for a mean period of time of 2 years, successful DAA treatment was associated with a reduced incidence in mixed cryoglobulinemia, glomerulonephritis, and lichen planus while risk of NHL and diabetes was not significantly reduced.[20] However, several other studies including a meta-analysis support a strong benefit of HCV cure in patients with concomitant NHL. Indeed, when analyzing 20 studies that evaluated antiviral treatment in HCV-NHL, the rate of lymphoma response was higher in those who achieved an SVR (83% response rate, 95% > confidence interval [CI], 76–88%) compared with patients who failed in achieving an SVR (53% response rate, 95% > CI, 39–67%, $p = 0.0002$).[21] Further data on the benefit of DAA-based treatment in patients with lymphoproliferative disorders also come from a small study conducted on 46 patients who received DAA-based treatment in Italy[22]; 67% had a lymphoproliferative disease response while 12 (26%) achieved a complete response. After 8 months of median follow-up, 1-year progression-free rate was 75% and survival rate was 98%.

In patients with hepatitis C virus-associated cryoglobulinemic vasculitis (HCV-CV), high rates of remission after treatment with DAA have been reported. In a large multicenter cohort study on 148 patients with symptomatic HCV-CV, a complete clinical response, defined as improvement of all organs involved at baseline and absence of clinical relapse, was observed in 106 patients (72%).[16] Even in the prospective study by Bonacci et al,[23] among 46 patients with HCV-CV, 66% had an immunologic response and almost 91% had a clinical response after a median time of 24 months after treatment. Nevertheless, five patients (four with cirrhosis) had a severe relapse of the vasculitis within the first 2 years; therefore, continuous follow up is still warranted.

Hepatitis C infection has been also associated with a higher risk of developing extrahepatic cancers, such as biliary duct, pancreas, and various types of skin cancers.[24,25] Two recent cohort studies from France analyzing HCV patients who received treatment with both IFN-free and IFN-containing regimens, failed to demonstrate a reduction in the rate of extrahepatic cancer following an SVR. Nahon et al[26] when analyzing more than 1,600 patients with HCV cirrhosis who received antiviral treatment found that the 5-year incidence of extrahepatic cancers was not different in SVR (7.5%) versus non-SVR patients (5.4%). Interestingly, Allaire et al[27] found that in HCV patients with an SVR, the age-adjusted risk of incident extrahepatic cancers compared with the general French population was 1.57; 95% CI, 1.08 to 2.22. These studies not only suggest no benefit of an SVR on the incidence of extrahepatic cancers, but also raise doubts on the need for reinforced screening and surveillance policies in SVR patients. Further data are needed to assess this issue and guide recommendations.

Hepatic Complications: HCC

The achievement of an SVR has been shown to be associated with improved survival and reduced rate of liver-related complications. This finding has been confirmed both in patients with advanced fibrosis/cirrhosis as in those with moderate or mild fibrosis. Indeed, pretreatment fibrosis is the major determinant of post-SVR complications as it is the main determinant of survival in the absence of antiviral

Table 1 Impact of SVR on hepatic and extrahepatic complications

Impact of SVR on hepatic complications			
Outcomes	**Author (y)**	**Number of patients—study design**	**Results**
Hepatic decompensation	Nahon et al (2017)[18]	1,323—Prospective	Hepatic decompensation after SVR (HR 0.26, 0.17–0.39; $p < 0.001$);
	Carrat et al (2019)[17]	9,895—Prospective	Hepatic decompensation after SVR (HR 1.14, 0.57–2.27; $p = 0.72$)
	Di Marco et al (2016)[40]	444—Prospective	Hepatic decompensation after SVR (HR 0.22, 0.09 − 0.50; $p < 0.001$)
Portal hypertension—esophageal varices	Lens et al (2017)[38]	226—Prospective	HVPG decrease after SVR (2.1 ± 3.2 mm Hg; $p < 0.01$); CSPH persisted in 78% of the patients after SVR
	Di Marco et al (2016)[40]	444—Prospective	Varices development after SVR (HR 0.2, 0.11–0.48; $p < 0.001$); Further varices development after SVR (HR 1.58, 0.33–1.03; $p = 0.07$)
	Afdhal et al (2017)[39]	50—Prospective	20% reduction in HVPG after SVR48 in 89% (8/9) of patients[3]
De novo HCC—HCC recurrence	Nahon et al (2017)[18]	1,323—Prospective	HCC after SVR (HR 0.28, 0.19–0.43; $p < 0.001$)
	Carrat et al (2019)[17]	9,895—Prospective	HCC after SVR (HR 0.66, 0.46–0.93; $p = 0.018$)
	Di Marco et al (2016)[40]	444—Prospective	HCC after SVR (HR 0.25, 0.12–0.55; $p < 0.001$)
Impact of SVR on extrahepatic complications			
Outcomes	**Author (y)**	**Number of patients—study design**	**Results**
Cryoglobulinemic vasculitis	El-Serag et al (2019)[20]	45,260—Retrospective	Mixed cryoglobulinemia after SVR (HR 0.23, 0.10–0.56)
	Cacoub et al (2019)[16]	148—Prospective	Full or partial response of symptoms after SVR in > 95% of the patients
Non-Hodgkin's lymphoma	El-Serag et al (2019)[20]	45,260—Retrospective	Non-Hodgkin's lymphoma after SVR (HR 0.86, 0.52–1.43)
	Peveling-Oberhag et al (2016)[21]	254—Meta-analysis	Lymphoma response rate after SVR (83%, 76–88% vs. 53%, 39–67%; $p = 0.0002$)
Other extrahepatic disease	Nahon et al (2017)[18]	1,323—Prospective	Vascular events after SVR (HR 0.42, 0.25–0.69; $p = 0.001$); Bacterial infection after SVR (HR 0.44, 0.29–0.68; $p < 0.001$)
	El-Serag et al (2019)[20]	45,260—Retrospective	Glomerulonephritis after SVR (HR 0.61, 0.41–0.90); Porphyria cutanea tarda after SVR (HR 0.33, 0.11–1.03); Lichen planus after SVR (HR 0.46, 0.30–0.70)
	Petta et al (2018)[15]	182—Prospective	IMT decreased after SVR (0.94 ± 0.29 mm vs. 0.81 ± 0.27, $p < 0.001$)
Extrahepatic malignancy	Nahon et al (2017)[18]	1,323—Prospective	Extrahepatic cancers after SVR (HR 1.52, 0.96–2.39; $p = 0.07$)
	Allaire et al (2018)[27]	1,323—Prospective	Age-adjusted incidence of after SVR (1.57, 1.08–2.22, $p = 0.013$)

Abbreviations: CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HR, hazard ratio; HVPG, hepatic venous pressure gradient; IMT, intima-media thickness; SVR, sustained virological response.

treatment. In a recent study enrolling more than 103,000 patients without advanced fibrosis, an SVR was associated with a 65 to 70% reduction in mortality compared with untreated patients.[28] Carrat et al[17] reported an extremely low incidence of liver-related mortality (0.08 per 100 persons/y) and liver-related complications (0.29 per 100 persons/y) in patients with mild–moderate fibrosis who received antiviral treatment. When looking at patients with advanced fibrosis/cirrhosis the benefits of an SVR are even clearer. In a long-term follow-up study from Italy,[29] the

survival of patients with pretreatment cirrhosis who achieved an SVR was comparable to that of the age- and sex-matched general population. When analyzing mortality rates in more than 15,000 patients with advanced fibrosis, the achievement of an SVR was associated with 78.9% reduction in mortality. While the achievement of an SVR provides patients with advanced fibrosis with improved survival, they still remain at risk of developing liver-related complications such as HCC, variceal bleeding, and liver decompensation, however, at a lower incidence.

Carrat et al[17] found that the incidence of HCC was much lower when an SVR was obtained (HR 0.57; 0.40–0.81), a finding consistently reported by studies from many geographical regions. Identification of factors associated with HCC development post SVR has been the core of liver research in the last years. In a multicenter Italian study conducted by Lleo et al,[30] patients with SVR and absence of portal hypertension showed a lower risk of HCC development in a 1 year follow-up period. Calvaruso et al[31] on the other hand found that low albumin and reduced baseline platelet levels were associated with increased HCC incidence. Lastly Degasperi et al,[32] found male sex and diabetes to be independent predictors of HCC incidence in 565 cirrhotic patients treated with DAAs and followed up for a median time of 25 months after starting antiviral therapy. Host genetic factors may also be involved in HCC development. In a recent systematic review, Walker et al found 17 and 37 genes with evidence of respectively "good" and "significant" association with HCC; most evidence has been documented with PNPLA3, IFNL3/4, and TNFα genes.[33] While helpful in identifying clinical variables associated with the development of HCC, these studies have limited clinical value as they do not allow for a tailored surveillance protocol nor evaluate clinical variables in a dynamic fashion. Alpha-fetoprotein (AFP) is widely used in clinical practice as a serological marker for the diagnosis of HCC, even if both sensibility and specificity are low in patients with HCV infection. It has been observed that AFP rapidly decreases during treatment with DAA, mostly as a result of the concomitant attenuation of liver inflammation.[34] Recently, Masetti et al[35] found that an absence of reduction in AFP levels during treatment with DAA predicts subsequent development of HCC during the follow-up, suggesting that dynamic variations in this marker may be useful in identifying patients at higher risk of HCC.

Since the publication in 2016 of two papers raising concerns about a possible increase in HCC recurrence after treatment with DAAs,[36,37] an incredible amount of literature has been published on the argument, which is still open. Until further data are generated, guidelines still suggest antiviral treatment in these patients, even if the optimal timing between treatment of HCC and start of DAA therapy has not been yet defined.

Hepatic Complications: Portal Hypertension

Due to the relatively short post-SVR follow-up period in studies evaluating HCV patients who received DAAs, long-term hemodynamic changes in cirrhotic patients following an SVR have not been widely investigated yet; however, this remains a central issue, as patients with CSPH not only achieve suboptimal SVR rates, but also remain at risk of liver decompensation. In a prospective study from Spain conducted on 226 patients, Lens et al found that hepatic venous pressure gradient (HVPG) significantly decreased in most patients after treatment with DAA; nevertheless 78% of the patients still presented CSPH, defined as an HVPG of 10 mm Hg or more.[38] Afdhal et al[39] observed the impact of treatment on HVPG at the end and 1 year after treatment in a cohort of patients with compensated and decompensated cirrhosis. Changes in HVPG were minimal at EOT but became more consistent 1 year after treatment. Indeed at EOT only 24% of the patients had a significant ($>$ 20% from baseline) reduction in HVPG, while at 48-weeks posttreatment, 89% of the patients reached this target. Interestingly, among patients with pretreatment CSPH, only one-third achieved an HVPG $<$ 12 mm Hg. Similarly in a large study from the RESIST cohort in Italy,[40] SVR was associated with a reduction both in development and progression of esophageal varices, still among patients with CSPH at baseline, 34% had a progression in esophageal varices, suggesting that eradication of HCV is not always associated with a regression of portal hypertension. The identification of patients who will develop CSPH post-SVR, defined by varices which require medical or endoscopic treatment, is crucial as it will allow to contain health care costs by sparing unnecessary endoscopies. During the Baveno VI consensus the central role of platelet count and Fibroscan values to identify patients with CSPH emerged, as the cutoff of Fibroscan $<$ 20 kPa and platelets count $>$ 150,000 were chosen to select patients who could spare endoscopy examination.[41] These cutoffs have recently been validated also in patients who achieved an SVR. Thabut et al reported that among 64 patients with positive Baveno cutoff values (Fibroscan $<$ 20 kPa and platelet values $>$ 150,000), before and after antiviral treatment, the rate of development of CSPH was 0% at 5 years compared with 8.1% in those who showed a worsening of the Baveno status.[42] Patients with favorable Baveno status who achieved viral suppression showed also the lowest mortality rate (1.7% at 5-years, compared with 7.3% and 18.4 in patients with unfavorable Baveno status with or without viral suppression).[43]

Hepatic Complications: Decompensated Cirrhosis

Few data are now available in literature regarding the long-term effects of IFN-free therapies in patients with already decompensated disease before treatment. Treating patients with Child Pugh B-C cirrhosis with DAAs can lead to an improvement both in CPT and MELD scores, whether this benefit is durable is still unclear.[44] In a small study on 64 patients with decompensated cirrhosis, Romano et al found that 1 year after-SVR, between 30 and 50% showed ascites and hepatic encephalopathy resolution, respectively.[45] Even Gentile et al found that after treatment with DAAs of 89 cirrhotic Child B patients, 61.8% of them improved to class A, 33.7% remained class B, and only 4.5% worsened to class C.[46] This issue is particularly important in the liver transplantation setting, as it could translate in delisting of a significant number of recipients due to improvement of liver function.[47]

Table 2 Management of post-SVR patients according to Fibroscan values at baseline

Pre treatment Fibroscan	HCV RNA retesting	Follow-up	Ultrasound	EGDS	Counseling
< 10 kPa	Annual only if risk of reinfection	Only if > ALT, obesity, diabetes, alcohol use	12 mo[a]	No	Alcohol use, reinfection extrahepatic cancer
> 10 kPa	Annual only if risk of reinfection	Lifelong	6 mo ± AFP	2 y if small varices 1 y if large varices No if TE[b,c] < 20 kPA and PLT > 150.000	Alcohol use, reinfection extrahepatic cancer

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; CPT, Child-Turcotte Pugh; EGDS, esophagogastroduodenoscopy; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; PLT, platelets; RNA, ribonucleic acid.
[a]If patient needs follow-up.
[b]TE, transient elastography.
[c]Annual evaluation.

Recommendations and Expert Opinion

In terms of liver-related complications, management of patients with an SVR appears to be strictly correlated with the stage of fibrosis assessed before treatment, which is usually determined with noninvasive tests such as transient elastography, Fib-4, or APRI score. When using transient elastography a cutoff of 10 kPa is usually used to rule out F3 fibrosis with a positive predictive value of 62% and a negative predictive value of 89%.[5] Both serologic and elastographic tests cannot be used to assess fibrosis stage once an SVR is achieved as they are influenced by concomitant resolution of inflammatory activity and changes in collagen content. D'Ambrosio et al evaluated transient elastography accuracy in a group of patients with pretreatment cirrhosis who underwent a second liver biopsy 5-years post-SVR. Authors found that the traditional cut-off of 12 kPa showed low sensitivity (61%) for cirrhosis leading to misclassification of cirrhosis in 21% of the patients.[48] Even serological tests resulted inadequate in predicting residual fibrosis, with 5 to 40% of the patients with residual cirrhosis being classified as regressors.[49]

According to current guidelines, patients with low degrees of fibrosis pretreatment (stage F0–F2 = transient elastography < 10 kPa) do not need further follow-up and may safely be discharged as the risk development of cirrhosis or hepatic complications is extremely low. The EASL recommendations state that this rule should be applied only in the absence of factors associated with persistent liver damage which include viral coinfections with HBV or HIV, diabetes, or alcohol abuse.[50] Whether the presence of post-SVR nonalcoholic fatty liver disease (NAFLD) should warrant lifelong follow-up is unclear. Noureddin et al[51] found that 47.5% of the patients who achieved an SVR had NAFLD, with some patients, having clinically significant fibrosis despite presenting with normal liver enzymes. In a recent study from Mauss et al,[52] male sex, advanced liver disease, and obesity were associated with persistence of ALT elevations in patients with SVR, suggesting fatty liver disease could be a potential cofactor of fibrosis progression. These authors therefore recommend to search for steatosis after SVR and continue lifelong surveillance in patients with documented fatty liver disease. In conclusion, while the concomitant presence of the above mentioned cofactors triggers lifelong surveillance, the optimal management and follow-up schedule has not been specified. It is our opinion that annual liver ultrasound (US) and routine blood tests should be prescribed with the aim to identify progression to advanced fibrosis/cirrhosis.

Patients with F3-F4 fibrosis (transient elastography > 10 kPa) need to continue regular follow-up (►**Table 2**), as their risk for future complications is reduced but still present. Surveillance with US examination with or without AFP assay every 6 months[3,4] is currently recommended for screening of HCC. AFP should not supplant US surveillance as the risk of false negative results is high, but increasing values of AFP with normal US could be useful in triggering second level imaging tests or shortening the surveillance interval.[53] After achievement of SVR, Baveno VI guidelines[41] suggest to perform surveillance endoscopy every 2 years in patients presenting with small varices at screening. In patients who had a positive Baveno status before starting treatment (liver stiffness < 20 kPa and platelet count > 150,000) the risk of developing clinically significant varices in a 5-year follow-up period is null provided they remain in a positive Baveno Status. In these patients annual evaluation of transient elastography is warranted.

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All authors equally contributed to this paper with the conception and design of the study, literature review, and analysis, drafting, critical revision and editing, and approval of the final version.

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