

AGA Institute Clinical Practice Update: Care of Patients Who Have Achieved a Sustained Virologic Response (SVR) Following Antiviral Therapy for Chronic Hepatitis C Infection

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Table 1. Recommendations for the Care of Patients with Chronic HCV Infection Who Have Achieved a Sustained Virologic Response (SVR)

Description	The purpose of this clinical practice update is to define key principles in the care of patients with chronic HCV infection who have achieved a sustained virologic response (SVR) following completion of treatment with an all-oral regimen of direct-acting antiviral agents (DAAs)
Methods	The recommendations outlined in this expert review are based on available published evidence including randomized controlled trials, observational studies, and systematic reviews, and incorporates expert opinion where applicable
Best Practice Advice (BPA) Statements	<p>BPA 1: Sustained virologic response (SVR) should be confirmed by undetectable HCV RNA at 12 weeks following completion of an all-oral DAA treatment regimen.</p> <p>BPA 2: Routine confirmation of SVR at 48 weeks post end of treatment is recommended. Testing for HCV RNA at 24 weeks post treatment should be considered on an individual patient basis.</p> <p>BPA 3: Routine testing for HCV RNA beyond 48 weeks following end of treatment to evaluate for late virologic relapse is not supported by available evidence; periodic testing for HCV RNA is recommended for patients with ongoing risk factors for reinfection</p> <p>BPA 4: Surveillance for hepatocellular carcinoma with liver imaging +/- serum AFP should be pursued twice annually for an indefinite duration</p>

in all patients with stage 3 fibrosis or liver cirrhosis post-SVR.

BPA 5: Surveillance for hepatocellular carcinoma is not recommended for patients with stages 0-2 fibrosis post-SVR

BPA 6: Intensification of hepatocellular carcinoma (HCC) screening frequency in the immediate post-SVR context is not presently recommended

BPA 7: Initial endoscopic screening for esophagogastric varices is recommended for all patients with liver cirrhosis, independent of SVR

BPA 8: Repeat endoscopic screening should be pursued for cirrhotic patients post-SVR at 2-3 years if no varices or small varices were identified on initial screening exam.

BPA 9: If no varices are identified on endoscopy 2-3 years post-SVR, cessation of further endoscopic screening may be considered on an individual patient basis if there are no risk factors for progressive cirrhosis

BPA 10: Fibrosis assessment post-SVR with non-invasive tools such as liver elastography may be considered on an individual patient basis to assess for interval fibrosis progression or regression to guide clinical management, although improved fibrosis measurements should not alter the frequency of HCC surveillance at the present time

BPA 11: Patients who have achieved SVR should be counseled regarding sources of liver injury which may independently contribute

	to liver fibrosis progression, including alcohol, fatty liver, and other potential hepatotoxins, and should be evaluated for these and other sources of liver injury if serum levels of liver enzymes are elevated.
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Abstract

Chronic hepatitis C virus (HCV) infection is well-recognized as a common blood borne infection with global public health impact, affecting 3 to 5 million persons in the U.S. and over 170 million persons worldwide. Chronic HCV infection is associated with significant morbidity and mortality due to complications of liver cirrhosis and hepatocellular carcinoma (HCC). Current therapies with all-oral directly acting antiviral agents (DAAs) are associated with high rates of sustained virologic response (SVR), generally exceeding 90%. SVR is associated with a reduced risk of liver cirrhosis, hepatic decompensation, need for liver transplantation, and both liver-related and all-cause mortality. However, a subset of patients who achieve SVR will remain at long-term risk for progression to cirrhosis, liver failure, HCC, and liver-related mortality. Limited evidence is available to guide clinicians on which post-SVR patients should be monitored versus discharged, how to monitor and with which tests, how frequently should monitoring occur, and for how long. In this clinical practice update, available evidence and expert opinion are used to generate best practice recommendations on the care of patients with chronic HCV who have achieved SVR.

I. Introduction

The battle against hepatitis C virus (HCV) has culminated in remarkably high rates of sustained virologic response (SVR) conferred by six currently approved interferon-free direct-acting antiviral (DAA) regimens against genotypes 1-6 HCV (1-6). In the many countries where these regimens are available, the use of interferon has essentially ceased. Follow-up studies and cumulative experience have affirmed that, as with earlier interferon-based therapy, SVR is tantamount to virologic cure. Fewer than 1% of patients relapse after SVR, defined during the years of interferon therapy as HCV RNA undetectability 24 weeks (SVR24), and more recently as SVR12 (7-13).

With the increasingly frequent opportunity to celebrate virologic cure with patients comes the corresponding need to advise them about whether, when, and for how long ongoing care for liver disease is needed. Thus, it is critical to identify the ongoing risks for the individual patient and the measures needed to mitigate those risks. Numerous studies in patients cured of HCV by interferon-based therapy have demonstrated reductions in all-cause mortality, liver-related mortality, need for liver transplantation, variceal bleeding, and hepatocellular carcinoma (14-16) as well as a reduction in mortality from extrahepatic complications (17). Regression of fibrosis and even cirrhosis has been documented, as has been demonstrated in other liver diseases when the underlying cause has been controlled (18-21). Nevertheless, reduction in risk is still potentially relative rather than absolute, as ongoing surveillance and intervention may be required in some patients to reduce complications arising from liver damage that has already accrued by the time SVR has been attained. Of greatest concern is the ongoing risk of HCC in patients with pre-existing advanced fibrosis or cirrhosis. In this paper,

the considerations surrounding the care of patients who have achieved SVR will be discussed, and proposed recommendations will be presented.

II. Assessment of HCV RNA after SVR12 has been attained

With the initiation of trials of DAA regimens, initially in combination with interferon and later without it, the attainment of SVR 12 weeks after completion of treatment replaced SVR24 as the primary endpoint, defined as undetectable HCV RNA on a highly sensitive PCR assay (lower limit of detection <12 IU/mL). This transition was based upon the rarity of relapse after follow-up week 12, and it helped move the field ahead by shortening the intervals between successive trials in development programs (22). It has become apparent that late relapse beyond this time point is no more common, and perhaps less so, than it was after interferon-based therapy (<1%)(7-10, 12-13, 23-24) . For example, in a preliminary report of long term outcomes in patients treated with ledipasvir/sofosbuvir, none of 1850 patients relapsed between the 12th and 24th week of follow-up (24). As a result, the AASLD/IDSA Guidance document (25) has suggested that patients do not require another HCV RNA determination after SVR12, and can be dismissed from ongoing follow-up if they had Metavir F0-F2 fibrosis before treatment.

Recent data indicate, however, that late relapse can indeed occur in the absence of de novo reinfection. In a series of 1054 patients who achieved SVR12 after receiving a course of paritaprevir/ritonavir/ombitasvir and dasabuvir, representing 97% of patients treated in six pivotal trials, 5 (0.5%) had subsequent virologic failure, shown by phylogenetic analysis to be relapse in 4 patients (3 by post-treatment week 24, and 1 by post-treatment week 48), and reinfection in 1 patient. All virologic failures occurred in GT1a patients (13). In another study of

3004 patients receiving sofosbuvir-containing therapy, mostly without interferon, 3004 patients had SVR24, while 12 had reappearance of HCV RNA by follow-up week 24. Seven of the 12 were shown to have reinfection by phylogenetic analyses of either full-length or short fragment NS5B sequencing, while 5 patients (0.2%) demonstrated late relapse with the same virus (12). Although the risk of late relapse appears to be very low, some clinicians may feel it prudent to obtain another HCV RNA assay at follow-up week 24 and/or follow-up week 48 (the latter as recommended in the EASL Guidelines) (26), rather than stopping monitoring after SVR12 (25). There is no evidence at present that any particular viral genotype or patient type is more prone to this rare phenomenon. Registries pursuant to several of the pivotal trial programs are further evaluating this issue, and refinement of these recommendations may be appropriate at a future time. It should be noted that, using viral sequencing, relapse as late as 6-8 years of follow-up had historically been described after interferon therapy (27-28), but this has not been reported after DAA therapy and the extreme rarity of this occurrence, if it exists at all, does not presently justify late surveillance for viral reappearance years after DAA therapy.

III. Ongoing surveillance for hepatocellular carcinoma after SVR

HCC is strongly associated with established cirrhosis, occurring in 1-4% of patients with HCV-associated cirrhosis annually (29). Many studies, including meta-analyses, have convincingly demonstrated that the risk of de novo HCC decreases after SVR is attained with interferon-based regimens (30). In a pooled analysis of 12 studies, encompassing over 25,000 patients, SVR was associated with a relative risk of HCC of 0.24 (CI 0.18-0.31); 1.5% of SVR patients developed SVR compared with 6.2% of non-SVR patients. In a further meta-analysis of 6 studies

including 2649 patients with advanced hepatic fibrosis, the hazard ratio for development of SVR was 0.23 (CI 0.16-0.35)(31). In a large study of long-term outcomes in 530 patients after a median follow-up of 8.4 years in patients with advanced fibrosis, the 10 year cumulative HCC incidence rate was lower in patients who achieved SVR (5.1%) versus those without SVR (21.8%) (16). Over 10-fold reductions in liver-related mortality, liver transplant, and liver failure were observed in the SVR group. Notably, baseline factors significantly associated with all-cause mortality in this study included older age, genotype 3, higher Ishak fibrosis score, diabetes, and severe alcohol use. In another study of 307 patients, highly significant reductions in cumulative incidence of both liver cancer and liver-related complications were observed (15). Reduction in all-cause mortality in patients who achieve SVR has been observed even in the absence of baseline cirrhosis in a large U.S. Veterans Administration database (14).

The literature on this issue has not thus far revealed any finite point beyond which the risk of HCC in patients with a history of HCV-associated cirrhosis is reduced to the level of persons without a history of liver disease. Cases of HCC occurring beyond 5 years after attainment of SVR have been well documented. In a Japanese study of patients treated successfully with interferon-based therapy for HCV, the cumulative risk of HCC continued to rise through 15 years of follow-up. Among 562 patients with SVR after interferon-based therapy followed for a median observation period of 4.8 years (range 1 to 20.5 years), cumulative HCC rates were 3.1%, 10.1%, and 15.9% at 5, 10 and 15 years, respectively, compared with 15.8%, 35.5%, and 42.3% in 351 patients without SVR. Significant risk factors for HCC in this study included fibrosis stage F2-4, age at interferon start ≥ 50 years, ethanol consumption ≥ 30 grams/day and baseline serum AFP ≥ 8 ng/ml (32). In another Japanese study, the cumulative incidence of HCC

among 1094 patients with SVR after interferon therapy was 3% at a median follow-up of 37 months post-treatment. Cumulative incidence of HCC was 4% at 5 years, 6% at 10 years and 12% after 15 years, with multivariate analysis revealing significant predictors to be age \geq 60 years, male gender, Metavir F3/4, and AFP \geq 10 ng/ml at one year after SVR (33). The phenomenon of late HCC (>5 years) after SVR has been well documented in the Western literature as well, with no convincing evidence of geographic variability in incidence (16, 34). In a large U.S. Veterans Administration study of 10,817 patients who achieved SVR, with a cumulative rate of HCC after SVR in patients with cirrhosis of 1.39% per year, significant risk factors in multivariate analysis included cure after age 55 years, diabetes, genotype 3, alcohol use, and Hispanic ethnicity (34).

The ongoing risk of HCC in patients with pre-existing cirrhosis, although lower compared with untreated or unsuccessfully treated patients, has led to a widespread consensus that continued surveillance for HCC is warranted regardless of other risk factors. Although data from randomized trials are limited, the available evidence and clinical experience overwhelmingly suggest that surveillance is associated with decreased mortality from HCC (35), and should occur at six month intervals in all cirrhotic patients with or without SVR. Standard guidelines currently consider AFP determinations to be adjunctive to imaging or even optional (36); additional studies to determine the value of AFP in post-SVR surveillance would be of interest.

Ultrasound is the recommended imaging modality for hepatoma surveillance in both the AASLD Guidelines for hepatocellular carcinoma, and the AASLD/IDSA HCV guidance document (26,36). This recommendation is based upon considerations of cost-effectiveness and the historical use of ultrasound in studies that have shown an impact on outcome of early detection

of HCC. However, both CT and MRI compare favorably to ultrasound with regard to sensitivity for small HCCs, particularly in cirrhotic patients (37). Moreover, obesity and overlying bowel gas may impair the accuracy of ultrasound, and it is not uncommon to receive a radiologic report containing a recommendation to pursue an alternate imaging modality, leaving the clinician and patient in a potentially vulnerable position if the recommended imaging studies are not pursued. Patient-centered approaches are needed to balance the benefits and risks of contrast-enhanced cross-sectional imaging studies such as triphasic CT scan or MRI, which should be considered carefully, especially in patients with obesity, "indeterminate" lesions, or those in for whom liver ultrasound provides inadequate visualization of the liver parenchyma. Despite its greater cost than CT, MRI has the advantage of avoiding exposure to ionizing radiation. Strategies such as alternating MRI and liver ultrasound are commonly used in clinical practice, although require further evidence to be incorporated into formal guideline recommendations. Many radiologists recommend the routine use of gadoxeate (Eovist) rather than gadolinium contrast for HCC screening with MRI because of the superior enhancement of liver parenchyma with the former in patients with cirrhosis (38).

Although the risk of HCV-associated HCC is highest in patients with cirrhosis, HCC may also occur in patients with bridging fibrosis (39). In some cases, this may be attributable to under-sampling of the liver on biopsy or transition to cirrhosis after F3 fibrosis was present initially (40). Based on available evidence for the risk of HCC in this group, HCC surveillance recommendations for patients with cirrhosis (liver ultrasound \pm AFP twice per year) have been applied to patients with F3 fibrosis (25,26); the authors concur with this recommendation.

IV. Is HCC risk after SVR exclusive to patients with advanced fibrosis and cirrhosis?

In determining whether a patient needs post-SVR HCC screening, the distinction between “moderate” fibrosis (e.g. Metavir F2) and “advanced” fibrosis (F3/4) may not be easily defined. Moreover, it remains possible that even patients with mild or moderate fibrosis may on rare occasion develop HCC. This suggestion has emerged most strongly from a large series of patients with SVR after interferon therapy in Japan. In the study by Yamashita et al (32), 42% of patients who developed HCC among a cohort of 562 SVR patients followed for a median of 4.8 years post-SVR had F2 fibrosis on liver biopsy. Ikeda et al reported that 12 of 706 (1.7%) of patients with F1/2 developed HCC with an incidence of 0.27-0.47/100 person-years, and 10/267 (3.7%) patients with F3/4 with an incidence of 0.62-1.31 person-years (41). A third series similarly reported patients with F0-2 developing HCC, albeit at a much lower rate after 10-20 years than patients with F3/4 (33). It is unclear from these reports whether concomitant liver disease (e.g. nonalcoholic steatohepatitis, alcoholic liver disease) could have caused progressive liver fibrosis after SVR had been attained.

Far fewer patients with mild to moderate fibrosis and post-SVR HCC have been reported from the United States or Europe. In one study, 5 patients who were non-cirrhotic at SVR subsequently developed HCC (2 with F2 fibrosis, 1 with F2-3 fibrosis, 2 with F3 fibrosis) although one had evidence for cirrhosis at the time of HCC; HCC diagnoses occurred within 27 months post-SVR in all cases except one (68 months)(42). In another report of 5 patients who developed HCC at 3-7 years post-treatment, three did not have cirrhosis at baseline (1 with F0 fibrosis, 1 with F2 fibrosis, 1 with F3 fibrosis, 2 with cirrhosis); of note, the patient with F3 baseline at baseline had F2 fibrosis at the time of HCC diagnosis 5 years post-SVR (43). In the

large VA study by El-Serag et al (34), 42 of 100 cases of HCC post-SVR occurred in non-cirrhotic patients, 11 of whom were characterized as having low APRI scores, suggestive of F0-F2 fibrosis.

Based upon the available evidence, routine screening for HCC in patients with F0-2 fibrosis is not recommended after SVR, although some clinicians may choose to obtain a final ultrasound during the year after SVR following DAA therapy. Should additional data from “real-world” cohorts confirm the emergence of late HCC in F0-2 patients post-SVR, screening recommendations will require reconsideration.

V. *Can HCC surveillance ever be discontinued?*

Lifelong surveillance for HCC among patients with advanced fibrosis and cirrhosis entails substantial psychological and economic implications, as well as investments of time for both patients and clinicians. As evidence continues to accumulate that fibrosis regression may occur in many patients who achieve an SVR (18-21), it is conceivable that the risk of HCC could eventually decline to a point at which surveillance becomes unnecessary.

Unfortunately, there is relatively limited evidence supporting a correlation between measurable regression of cirrhosis as determined histologically and reduction of HCC risk. Mallet et al (44) studied 96 patients with Child-Pugh A cirrhosis, of whom 39 (41%) had SVR following interferon-based therapy. Follow-up liver biopsies were obtained a median of 17 months after treatment, and patients were followed for a median of 118 months. Eighteen (18%) experienced regression from F4 to F0-2, of whom 17 had had SVR and the remaining patient had persistently normal ALT. Ten year survival was 100% in those with cirrhosis regression and 74% in those without regression. Of the 57 patients without SVR, 14 (23%)

developed HCC compared with 3 (9%) of those with SVR. However, of the 18 patients with regression of cirrhosis on biopsy, including one who failed to have SVR, none developed HCC. In a more recent study in 97 SVR patients with paired liver biopsies, the stage of liver fibrosis regressed in 44 patients (45%) and progressed in only six patients (6%) at a mean 5.8 years after treatment. HCC was significantly more frequent in patients with progressive fibrosis than in those in whom fibrosis regressed or was stable (cumulative incidence 33% vs 4% at 5 years, $P < 0.05$) (19).

Suggestive as these studies are, post-SVR liver biopsies are not routinely performed and are not clinically practical, and it is unlikely that data derived from serial post-SVR liver biopsies will be sufficiently robust to establish whether discontinuation of HCC surveillance can be recommended in patients who demonstrate fibrosis regression. As such, future longitudinal studies utilizing non-invasive markers or imaging will likely be utilized to demonstrate long-term changes in liver fibrosis post-SVR and their potential association with HCC risk. Liver stiffness measurements, most commonly performed by transient elastography (TE) or other shear-wave based techniques, have assumed an increasingly prominent role in HCV management. Short term improvement in elastography scores during antiviral therapy appear to correlate with resolution of inflammation, declining transiently even in interferon nonresponders, rather than confirming true fibrosis regression (45). Beyond end of treatment, further improvement in liver fibrosis has been reported to occur through follow-up week 24 only in cirrhotic and non-cirrhotic patients who achieve SVR but not in nonresponders, in whom stiffness scores increase post-treatment (45-47). One of the few studies to evaluate changes in TE scores after interferon-free therapy showed similar changes to patients receiving interferon from baseline

to follow-up week 24, but only a statistically insignificant degree of additional improvement beyond follow-up week 24 (48). In another study including patients with advanced liver disease (mean liver stiffness measurement 32 kPa), improvement was observed only until end of treatment with a plateau during the follow-up period (49).

The degree of long-term improvement in liver stiffness beyond 6-12 months after end of treatment requires further clarification. Tachi et al (50) ¹ correlated acoustic radial force impulse (ARFI) elastography with liver biopsy findings after a mean of 5.9 years following treatment and demonstrated a high degree of accuracy for advanced fibrosis or cirrhosis. Patients with F0-3 fibrosis at baseline had more improvement in fibrosis after “long-term” than “short term” SVR, but patients with F4 did not.

A cautionary note regarding elastography was sounded by D’Ambrosio et al (51), who studied 33 cirrhotic patients with SVR after interferon based therapy. Of 20 patients with cirrhosis regression on biopsy, 19 (95%) had TE scores < 12 kPa; of 13 with persistent cirrhosis, TE scores were < 12 kPa in 5 (38%), conferring on elastography 61% sensitivity and 95% specificity for diagnosing F4 fibrosis after SVR. Reinforcing this cautionary theme, Sultanik et al (52) reported that in a cohort of 341 patients with confirmed HCV cirrhosis, 45 (13%) of whom achieved SVR, liver stiffness measurements by transient elastography were <12.5 kPa in three-fourths of those with SVR. Utilizing a threshold of 12.5 kPa, the AUROC curve was 0.66 for HCC in patients with SVR. Of 4 patients with HCC, 2 of 4 had elastography scores < 12 kPa post-SVR. Based on their cumulative data, the authors cautioned against performing liver stiffness measurements to follow regression of fibrosis or cirrhosis (52). A study from Taiwan of 278 patients with SVR with a median follow-up period of 7.6 years, comprised of both non-cirrhotic

and cirrhotic patients, showed a significantly greater risk of HCC with transient elastography score > 12 kPa. However, HCC also occurred with post-SVR scores < 12 kPa, including patients with pretreatment scores either above or below 12 kPa (53). At present, there is no reliable elastography score below which clinicians can confirm an absence of HCC risk with sufficient confidence to warrant discontinuation of surveillance.

The same conclusion can be derived from available studies on noninvasive blood or serum markers that assess fibrosis. Such markers often improve after SVR (54-55), and have correlated with risk of HCC in some studies (56), including a study in which the Forns index, but not FIB-4 or APRI, at follow-up week 24 correlated with long-term HCC risk. In a particularly long-term follow-up study spanning a 10-year period, FIB4 and APRI scores declined substantially in patients with SVR and were significantly lower than in untreated patients or those with treatment failure, but no correlations with HCC were drawn (57). Moreover, noninvasive blood markers have recently demonstrated poor correlation with post-SVR liver biopsy findings (58). Large databases will eventually address the question of whether there is an “inflection point” below which improved fibrosis as measured by elastography scores and/or other non-invasive methods are associated with negligible risks of HCC that obviate the need for ongoing screening. However, for the foreseeable future, twice yearly hepatic imaging for patients with advanced fibrosis and cirrhosis prior to treatment should be continued indefinitely after SVR.

VI. How should screening for, and management of, varices be affected by SVR?

Increasing evidence points to the capacity for SVR to result in resolution or reduction of portal hypertension (59), especially in patients with Child-Pugh A cirrhosis (59), laying a foundation for a favorable change in the natural history of esophageal varices after SVR. Clinical studies have indeed provided reassurance that the risk of variceal bleeding is low after attainment of SVR with interferon based therapy (29, 40, 61-63). Bruno et al. (64) studied 218 patients with cirrhosis who lacked varices at baseline. The patients underwent endoscopic surveillance every three years and had a median follow-up of 11 years. Of 34 patients with SVR, none (0%) developed de novo varices. In contrast, varices developed in 45 of 115 (39%) of nonresponders and 22 of 69 (32%) of untreated patients. Of four patients with measurement of hepatic venous pressure gradient (HPVG), all four experienced a decrease in HPVG to < 10 mm Hg. In another study of 127 patients with Child-Pugh A cirrhosis receiving interferon therapy, 62 attained SVR and 65 did not (65). Fifty-seven of 62 SVR patients followed for a median of 68 months had no varices at baseline, and only 2/57 (3%) developed de novo varices. Of five patients with small varices at baseline, progression of variceal size occurred in one (20%). In contrast, eight of 53 (15%) of patients had failing interferon therapy with no varices at baseline developed de novo varices after a median follow-up of 57 months, while 2 of 12 (16%) with small varices at baseline had progression. In the study by Mallet et al. (43) of 96 patients with Childs A cirrhosis treated with interferon, of whom 39 had SVR, and 18 of whom had regression of cirrhosis on follow-up liver biopsies, six of 57 (9.8%) without SVR experienced variceal bleeding versus one of 39 (2.9%) with SVR. Of the 78 patients without regression of cirrhosis, seven (9%) without regression of cirrhosis had variceal bleeding compared to none of 18 (0%) with such regression.

A somewhat different picture emerged from a study by Di Marco et al (54), which stratified a prospectively studied cohort of 444 patients with compensated HCV cirrhosis into 218 with “stage 1” disease and 226 with “stage 2” disease. The patients had received interferon and ribavirin with a median follow-up of 7.6 years (1-12.6 years). The distinction between the two stages was based upon the absence of varices (stage 1) or the presence of small varices (stage 2) at baseline. Patients with stage 1 disease and SVR were less likely to develop esophageal varices than stage 1 patients without an SVR (HR 0.23, CI 0.11-0.48, $p < 0.001$). In contrast, SVR was not associated with a lower frequency of development of further varices in the stage 2 patients (HR 1.58, CI 0.33-1.03). SVR reduced risk of decompensation, HCC and death regardless of whether the patients had esophageal varices.

Based on the available literature, a proposed practical approach to the issue of prophylaxis of variceal bleeding is as follows: (a) no varices on prior screening examination: follow-up endoscopy after 2-3 years and no further screening if varices are not found and there is no evidence of another progressive liver disease; (b) small varices on prior screening examination, no treatment considered necessary: follow-up endoscopy after 2-3 years, no further screening if varices unchanged or smaller, otherwise treat and follow-up as considered necessary; (c) varices on prior screening treated with primary prophylaxis with beta blockers and/or band ligation: repeat after 6-12 months, continue treatment if varices unchanged and repeat after 1-2 years, consider discontinuation of treatment if varices are reproducibly considered sufficiently small to be considered low-risk; (d) for decompensated patients or patients with a prior history of variceal bleeding: continue surveillance and/or treatment as already instituted. Although updated guidelines of the Baveno VI Consensus Workshop support risk stratification based on

transient elastography cut-off of <20 kPa and platelet count >150,000/uL to identify patients who are at low risk for clinically significant esophageal varices, and therefore may not require screening endoscopy, such data in patients post-SVR are not yet available and therefore application of these cut-offs in patients following SVR should be approached with caution and on an individual patient basis (66).

VII. ***Should patients be routinely monitored for regression of advanced fibrosis or cirrhosis?***

Patients who have attained SVR are frequently eager to know if pre-treatment liver fibrosis can be reversed, independent of HCC risk. In addition to the issue of whether HCC screening can eventually be discontinued based upon noninvasive parameters post-SVR, one can envision other potential roles for ongoing assessment of fibrosis in patients with advanced liver disease, including addressing patients' often expressed and understandable desire for information about improvement in their underlying liver condition, modulation of surveillance or management of gastroesophageal varices, the use or dosing of medications metabolized by the liver, guidance regarding alcohol consumption, and assessment of patient candidacy for major surgeries.

Although we anticipate that non-invasive post-SVR fibrosis assessment may be attractive for many patients post-treatment, the available evidence does not support a broad recommendation for routine post-SVR fibrosis testing. As is the case for HCC surveillance, this may change as new data emerge from large longitudinal observational database analyses addressing this issue. For the present, decisions about noninvasive assessment of fibrosis may

be individualized according to clinicians' judgement and/or patient preference, but the limitations inherent in the accuracy, predictive value and applicability of the information acquired should be discussed (67).

VIII. Recurrent HCC After SVR

- Two studies that have garnered significant attention in early 2016 suggested unexpectedly high rates of recurrent HCC in patients treated successfully with DAA regimens after their tumors had been treated by various methods other than transplant. In one study, 9 of 285 patients (3%) without a history of HCC were diagnosed with a de novo tumor within 24 weeks following all-oral DAA treatment, whereas 17 of 59 patients (29%) with prior HCC developed recurrent HCC post-DAA treatment (68); advanced cirrhosis represented a predictor of recurrent HCC on multivariate analysis. A second study demonstrated similar findings: 16 of 58 patients (28%) with previously treated HCC developed recurrent HCC shortly following completion of DAA therapy (69). It has been speculated that SVR results in downregulation of cytokines, including endogenous interferon, that have anti-tumor effects, thereby creating a more "permissive state" for re-emergence of latent malignant cells. In contrast, Pol et al. (70) studied three separate ANRS cohorts from large French multicenter studies of cirrhotic patients, and found no evidence of a significant increase in HCC incidence relative to comparator populations in any of the three groups, although the authors speculate that their patient populations had been subjected to prior therapies conferring a higher likelihood of complete tumor ablation. Similarly, an Italian study has suggested a reduction in recurrence of

HCC previously treated by ablation or curative resection of early stage liver cancer whether patients attained SVR after taking IFN-containing or IFN-free regimens (71).

Although the issue of recurrent HCC after SVR requires further study, at present there is insufficient evidence to warrant a change in surveillance strategy for such patients, nor is there sufficient evidence to suggest that DAA therapy should be withheld in patients who have undergone locoregional therapy for HCC previously. Some clinicians might choose to consider intensification of imaging frequency to every three months for a year after completion of HCV treatment, perhaps depending on the time elapsed since treatment of HCC and the level of confidence that the tumor had been ablated.

IX. Reinfection

The high prevalence of HCV infection in intravenous drug users has aroused intense interest in targeting this population for treatment with DAA therapy. Even in the interferon era, when many clinicians were reluctant to treat such patients, centers with expertise in the management of these patients had demonstrated good results with interferon therapy (72). A recent study confirmed that treatment of HCV with grazoprevir/elbasvir is feasible and associated with high SVR (97%) in patients treated within addiction treatment centers, many of whom were documented to have used illicit drugs actively during their HCV treatment (73). However, confirmed reinfection on population sequencing and phylogenetic analysis was identified in 6 of 301 patients at 24 weeks post-treatment for an incidence of 4.6 reinfections per 100 person-years (95% CI 1.7-10.0). A long-term follow-up study of 161 patients in a PWID population who achieved SVR revealed that HCV reinfection was confirmed in 10 of 94 (11%)

individuals with a history of injection drug use prior to treatment (incidence of 1.7 reinfections per 100 person-years, 95% CI 0.8-3.1), and in 10 of 37 (27%) individuals who relapsed to injection drug use after treatment (incidence of 4.9 reinfections per 100 person-years, 95% CI 2.3-8.9) (74). Although reinfection is an acknowledged risk in this population, the pendulum has swung toward a high level of advocacy for treatment of these patients (75-76), both to mitigate their own HCV-related risks and to reduce transmission in the community. Patients at risk of reinfection should be monitored by HCV RNA testing periodically for as long as their risks of exposure are believed to be ongoing, and referred to addiction management programs which promote clean needle exchange and relapse prevention.

X. Lifestyle Measures

Although many patients who achieve SVR have a favorable clinical course, which may include regression of liver fibrosis, some patients may experience fibrosis progression, hepatic decompensation, and/or hepatocellular carcinoma, with HCC the dominant persistent risk in SVR patients in the absence of concomitant liver disease. Long-term observational data addressing liver-related outcomes in patients post-SVR with oral DAA regimens are lacking. Available data in patients undergoing interferon-based therapy suggest that individuals who achieve SVR may continue to experience a higher mortality rate than the general population (77-78), even among non-cirrhotic patients who achieve SVR, with a significant contribution in the latter group from drug-related causes (79). As such, although most excess liver-related outcomes may be seen in patients with advanced liver fibrosis or cirrhosis due to persistent risk of liver cancer, all patients achieving SVR should undergo evaluation for modifiable risk factors

for liver injury such as alcohol, drug use, fatty liver, and diabetes mellitus. The impact of alcohol consumption on liver fibrosis progression and HCC risk in context of ongoing chronic hepatitis C infection is well documented, and even non-hazardous or low to moderate alcohol intake is associated with an increased risk of liver-related outcomes (80-81). Based on limited data in patients with eradication of HCV post-SVR, alcohol persists as a risk factor for all-cause mortality (77). No safe limit for alcohol consumption has been established post-SVR, and therefore avoidance of significant alcohol intake should be recommended for all patients, and complete abstinence is prudent in patients with advanced liver fibrosis or cirrhosis. Diabetes and fatty liver are commonly present in patients with chronic hepatitis C and may develop de novo or persist long-term as risk factors for liver fibrosis progression and HCC post-SVR. Diabetes has been confirmed to represent an important risk factor for HCC in patients with chronic HCV infection, and appears to remain a risk factor for cirrhosis-related complications including HCC post-SVR (34, 82-83) as well as HCC risk in non-cirrhotic patients (84). Fatty liver has independently demonstrated to represent a possible risk factor for liver fibrosis progression (85) and HCC (86) in patients who have achieved SVR following antiviral therapy. Until more data become available to provide evidence-based recommendations for addressing diabetes and fatty liver in patients post-SVR, patients at risk or with a known diagnosis should be advised of the risk of liver-related complications, and continue disease-specific management to optimize weight loss and glycemic control.

XI. Conclusions

With the marked increase in number of patients who achieve SVR with present direct-acting antiviral regimens for hepatitis C, there is a need to promote a broad-based understanding among clinicians regarding which patients can be discharged from further HCV-related care, the criteria that define a need for ongoing management, and the elements and duration of that management. We have herein proposed guidelines for management of the post-SVR patient representing a synthesis of the latest available evidence with expert opinion. Most of the published evidence and experience about long-term outcomes after SVR are derived from studies of interferon-based therapy. It is appropriate at present to formulate recommendations based upon that experience, but we expect and encourage large long-term studies of outcomes after interferon-free DAA therapy which will further refine our concepts of appropriate management and, like the guidelines governing antiviral treatment itself, should lead to dynamic reassessment of the best practices for management of patients post-SVR in the years ahead.

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