Position Paper

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EASL position paper on clinical follow-up after HCV cure

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Summary

Following the advent of direct-acting antivirals (DAAs), hepatitis C virus (HCV) infection can be cured in almost all infected patients. This has led to a number of clinical questions regarding the optimal management of the millions of patients cured of HCV. This position statement provides specific guidance on the appropriate follow-up after a sustained virological response in patients without advanced fibrosis, those with compensated advanced chronic liver disease, and those with decompensated cirrhosis. Guidance on hepatocellular carcinoma risk assessment and the management of extrahepatic manifestations of HCV is also provided. Finally, guidance is provided on the monitoring and treatment of reinfection in at-risk patients. The recommendations are based on the best available evidence and are intended to help healthcare professionals involved in the management of patients after treatment for HCV.

Introduction

The introduction of all oral direct-acting antivirals (DAAs) has led to sustained virological response (SVR) in virtually all (>97%) hepatitis C virus (HCV)-infected patients regardless of HCV genotype or disease stage. Consequently, millions of patients have been treated and cured of HCV. This has led to nuanced clinical questions about how to manage different categories of patients cured of HCV, particularly in terms of the need for hepatocellular carcinoma (HCC) surveillance and follow-up in specialised care.

This position statement from the European Association for the Study of the Liver (EASL) seeks to summarise emerging data pertinent to the field of post-SVR care as well as to present clinical guidance to help healthcare professionals involved in the management of these patients.

Methods

As a first step, the experts identified the main areas in the field that required discussion. As a second step, the experts formulated relevant clinical questions within each area. Questions were assigned to the panel members based on their individual expertise and the answers were circulated among all the panel for review and discussion.

The recommendations are based on the best evidence available at the time of writing and interpreted by expert clinicians involved in the management of these patients. As this was not a formal clinical practice guideline, PICO questions and a Delphi panel were not used to generate this position paper.

Management of patients without advanced fibrosis after SVR

Which test should be used to assess liver fibrosis in patients with HCV?

Statements

- LSM by VCTE alone or in combination with blood-based scores are sufficient to rule out cACLD in patients with HCV prior to treatment. In the absence of VCTE-LSM, FIB-4 or APRI are useful methods to identify patients without advanced fibrosis or without cACLD.
- Early post-SVR decreases in VCTE-LSM and FIB-4 reflect decreased necroinflammation rather than true fibrosis regression. Long-term post-SVR decreases in VCTE-LSM and FIB-4 likely reflect “true” fibrosis regression, however, more evidence is needed.

Recommendation

- Non-invasive evaluation of liver fibrosis using LSM by VCTE or blood-based scores (FIB-4, APRI) before antiviral treatment can be used to determine which patients should and should not continue specialised follow-up after SVR.

In chronic hepatitis C, non-invasive tests (NITs) are generally recommended instead of liver biopsy to assess liver disease

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severity. NITs comprise blood-based scores, liver stiffness measurement (LSM) and imaging modalities (*e.g.* ultrasound).

LSM is well established to assess liver fibrosis (*e.g.* vibration-controlled transient elastography [VCTE], FibroScan®). Other liver elastography methods are less well validated but can also be used to assess liver fibrosis.[1] LSM by VCTE shows excellent performance for the diagnosis of cirrhosis in patients infected with HCV. On the other hand, the diagnostic performance of VCTE for significant fibrosis in large-scale prospective studies including patients with chronic hepatitis C[2,3] was good, with AUROCs ranging from 0.79 to 0.83, but LSM values still showed considerable overlap across lower fibrosis stages[4–7] Despite this, most patients without advanced liver fibrosis are well identified with this method.

Although VCTE-LSM is the most widely used method in Europe, not all centres have access to LSM and thus, well-established and readily available blood-based fibrosis scores can also be applied.[8] Among them, aspartate aminotransferase-to-platelet ratio index (APRI)[9] and fibrosis-4 (FIB-4)[10] are generally available, simple and inexpensive since they are based on routine parameters. Similar to LSM by VCTE, APRI and FIB-4 perform well in the identification of HCV-infected patients with compensated advanced chronic liver disease (cACLD), as originally defined in the Baveno V criteria (see Section cACLD).[11] This is relevant since patients with lower stages of fibrosis are at low risk of HCC and, in the absence of other cofactors for liver disease (see below), can be discharged from specialised care. Combining different blood-based biomarkers or using them together with LSM improves the accuracy of fibrosis staging.[12]

It is important to note that the accuracy of non-invasive testing before antiviral therapy cannot be translated to the post-SVR setting. Indeed, serum biomarkers may decline following SVR, but these changes may reflect an improvement of hepatic inflammatory activity[13–17] without amelioration of liver fibrosis. The latter is particularly true for early changes in NIT values, but once patients achieve SVR and are followed in the long term, improvements in NITs most likely reflect fibrosis regression.[18] Nevertheless, the cut-offs used for diagnosis of advanced fibrosis or cirrhosis before therapy should not be used after achieving SVR.[19,20] Larger prospective trials combining NITs, ultrasound and paired biopsies would be useful to establish VCTE-LSM cut-offs for histological fibrosis stages after SVR.[11]

How should discrepancies in the staging of fibrosis between different NITs be handled?

Recommendation

- A combination of two NITs improves the accuracy of identification of advanced fibrosis and cirrhosis. In case of discrepancies between non-invasive scores, an additional method should be used.

All non-invasive methods have their advantages and disadvantages and differ in their sensitivity and specificity to detect significant fibrosis and cirrhosis.[11,21] Thus, algorithms combining different fibrosis tests have been proposed to improve the accuracy of non-invasive methods for the correct staging of liver fibrosis and cirrhosis in patients with HCV infection. Some algorithms combine two serum-based models either simultaneously or sequentially.[22–25] Others combine a serum-based model with an imaging technique.[12,26] A systematic review including 151 studies using biochemical or imaging tests either alone or in combination confirmed that combinations of two modalities can reliably differentiate between minimal and significant fibrosis.[27,28]

An abdominal ultrasound examination before discharge is recommended in all patients who achieve SVR. Also, in case of a clear discrepancy between two NITs, an ultrasound performed by experienced operators could be useful to identify signs of cirrhosis (nodular surface) and portal hypertension (portosystemic collaterals, splenomegaly, enlarged portal vein diameter). Other evaluations such as upper endoscopy and hepatic venous pressure gradient (if available) may help rule out the presence of portal hypertension. Liver biopsy may be useful in certain cases of discrepancy or to rule out a concomitant liver disease.

Which patients can be discharged after SVR?

Recommendations

- Patients with mild fibrosis (VCTE-LSM <8 kPa or FIB-4 <1.45) can be discharged from specialised care after SVR and followed by a general practitioner. Education on a healthy lifestyle and avoidance of alcohol intake should be emphasised before discharge.
- If minimal fibrosis cannot be excluded after SVR (VCTE-LSM ≥8 kPa and <10 kPa and/or FIB-4 ≥1.45 and <3.25), specialised care is recommended in patients with MASLD and/or harmful alcohol intake, with yearly assessment of disease progression by NITs.

It is well known that in patients without advanced fibrosis achieving SVR, HCV infection can be considered as definitively cured and there is no risk of clinical decompensation and an extremely low risk of HCC.[18,29] The risk of HCC is significantly associated with cirrhosis, as approximately 90% of HCV-associated HCC cases are preceded by cirrhosis.[30] This has also been shown in studies in which risk assessment of HCC was evaluated by transient elastography.[27,28,31,32] Indeed, EASL HCV Clinical Practice Guidelines state that patients with absent to moderate fibrosis (Metavir score F0–F2) who achieve SVR and have no ongoing cofactors for liver disease can be discharged from specialised liver units.[11]

Nevertheless, before discharging a patient after SVR, cofactors and comorbidities that may impact liver disease outcomes should be assessed. In the post-SVR setting, patients with additional liver diseases requiring specialised treatment (hepatitis B, hemochromatosis, *etc.*) should continue their follow-up in liver clinics. The best setting for follow-up is less clear for concomitant metabolic dysfunction-associated steatotic liver disease (MASLD),[33] metabolic dysfunction and alcohol-related steatotic liver disease (MetALD),[34] and alcohol-related liver disease (ALD).

A number of studies have shown that the presence of certain comorbidities (such as diabetes mellitus, alcohol consumption) in patients with cACLD increases the risk of disease progression and HCC in patients who have achieved SVR after DAA treatment.[30,35–37] The impact of these cofactors in patients with mild HCV-related fibrosis is less known. Recent data have shown that in patients with current or past alcohol intake, the presence of steatosis increases the risk of disease progression (and clinical decompensation) independently of age, sex, and liver stiffness[38] (see section on extrahepatic manifestations). The latter may be relevant since weight gain is quite common after SVR and some patients may feel that resuming alcohol consumption is safe.[39–41] Thus, before patients are discharged after SVR, advice should be given on regular physical activity, maintaining a healthy diet, refraining from harmful alcohol intake, and avoiding weight gain. In those individuals in whom NITs cannot exclude that fibrosis is absent/minimal, follow-up by a liver specialist seems a reasonable choice if MASLD and harmful alcohol intake persist, even in the absence of cACLD. A comprehensive algorithm allocating patients to general practitioner or specialised care based on NIT findings and certain comorbidities is depicted in Fig. 1.

Patients with cACLD who achieve SVR

The risk of liver-related events in patients with cACLD, and particularly of the classical decompensation events such as variceal bleeding, ascites and hepatic encephalopathy, is linked to the presence of clinically significant portal hypertension (CSPH).[42] While HCC does not represent a classical decompensation event, HCC also occurs significantly more often in patients with CSPH.[43] Patients with HCV-associated cACLD should thus be screened for CSPH as this has important management implications.[44] HCV-associated cACLD is defined by any of the following criteria:

(i) Histological fibrosis stage F3 or F4 (METAVIR or Batts-Ludwig score)
(ii) LSM ≥10 kPa by VCTE
(iii) Gastroesophageal varices at esophagogastroduodenoscopy (EGD) (in the absence of presinusoidal/prehepatic causes of portal hypertension, such as portal vein thrombosis)
(iv) Hepatic venous pressure gradient (HVPG) ≥6 mmHg.

Importantly, SVR often leads to significant reductions in HVPG, potentially even to values below 10 mmHg (the threshold for CSPH)[45,46] thereby decreasing the risk of hepatic decompensation.[47] Varices may even disappear after HCV eradication, with one study reporting regression in 21.9% of patients after a median of 5.2 years.[48] Additionally, SVR also improves cACLD severity, in terms of histologic fibrosis regression[49,50] and decreases VCTE-LSM, sometimes to the extent that cACLD-defining criteria are no longer fulfilled. These patients should then be followed according to the recommendations given in the sections for patients without advanced fibrosis and for HCC screening.

Which NITs should be used for clinical follow-up of patients with cACLD prior to SVR?

Recommendation

- Annual VCTE-LSM combined with blood tests including platelet count, bilirubin and albumin should be performed post-SVR for patients with cACLD to enable a dynamic assessment of CSPH risk and liver function.

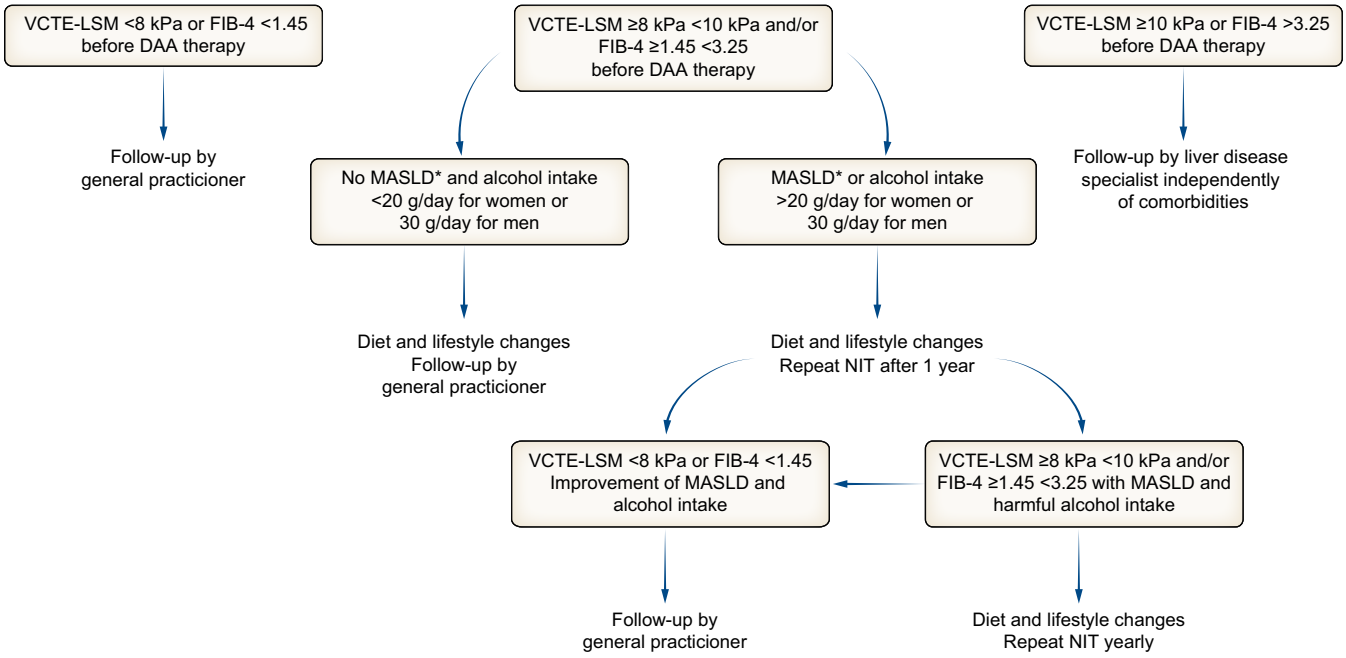

Fig. 1. Proposed algorithm to select patients who can be discharged from specialised care after SVR. *MASLD: hepatic steatosis and at least one cardiometabolic risk factor (overweight, pre/diabetes mellitus, arterial hypertension, dyslipidemia).[34] DAAs, direct-acting antivirals; FU, follow-up; MASLD, metabolic dysfunction-associated steatotic liver disease; NITs, non-invasive tests; VCTE-LSM, vibration-controlled transient elastography-liver stiffness measurement (Fibroscan (R)).

Post-SVR follow-up of patients with cACLD should include laboratory testing every 6-12 months including platelet count (PLT) as a surrogate for CSPH and bilirubin and albumin as well-established surrogates for hepatic function.[44,51] Table S1 summarises important features/characteristics that are linked to the risk of (CSPH-related) complications in patients after SVR. In the absence of an improvement in platelets, bilirubin or albumin, further workup for hepatic function, as well as screening for CSPH and the presence of varices, should be performed. As HVPG is not widely available and not commonly used in clinical practice for CSPH assessment, NITs and particularly VCTE-LSM are useful to identify patients at risk of CSPH[18] in patients with cACLD after SVR. Since imaging (ultrasound) is indicated in patients with cACLD at 6-month intervals for HCC screening, signs of CSPH (portosystemic collaterals, splenomegaly, enlarged portal vein diameter) and of decompensation (ascites) should be routinely assessed.

Which patients should be screened for varices?

Recommendations

- Patients with post-SVR VCTE-LSM <12 kPa and PLT ≥150 G/L do not need EGD because CSPH can be ruled out.
- In patients with post-SVR VCTE-LSM <20 kPa and PLT ≥150 G/L, high-risk varices can be ruled out and EGD is not necessary.
- Patients with post-SVR VCTE-LSM ≥20 kPa and/or PLT <150 G/L should undergo EGD if they are not already on non-selective beta-blocker (NSBB)/carvedilol therapy.
- In patients with pre-SVR cACLD who never had EGD, EGD may be performed at least once after SVR taking into account VCTE-LSM and PLT values.

Traditionally, a diagnosis of cirrhosis prompted screening for varices which was then periodically repeated. However, since the diagnostic modalities changed and cACLD is nowadays mostly non-invasively diagnosed by VCTE-LSM,[52] the readily available LSM results should also be used to stratify the individual patient's risk of CSPH[53] and of subsequent decompensation.[54] The Baveno VI consensus already introduced non-invasive criteria for avoiding unnecessary screening endoscopies,[55] and these criteria have subsequently been validated for patients after SVR.[56]

Given the significant decreases of LSM after SVR, the respective LSM cut-offs for non-invasive assessment of CSPH are different, and further evidence should be generated (Fig. 2). Generally, post-SVR VCTE-LSM <12 kPa and PLT ≥150 G/L identify patients without CSPH with high accuracy. Moreover, post-SVR VCTE-LSM <20 kPa and PLT ≥150 G/L rule out high-risk varices and thus, these patients do not need to undergo screening endoscopy. According to Baveno VII consensus VCTE-LSM ≥25 kPa rules-in CSPH in patients with viraemic HCV. However, insufficient evidence is available for the post-SVR setting in patients with obesity.[44]

Despite this, our recommendations for non-invasive CSPH monitoring are very conservative and may overestimate the low risk of decompensation, including of variceal bleeding after SVR. Future studies providing more data on the monitoring of portal hypertension post-SVR are awaited.

Which patients benefit from NSBB/carvedilol therapy and which patients may discontinue NSBB/carvedilol therapy?

Recommendations

- CSPH can be ruled out in patients with post-SVR VCTE-LSM <12 kPa and PLT ≥150 G/L; discontinuation of NSBB/carvedilol therapy can be considered.
- Patients with a history of variceal bleeding should continue secondary prophylaxis (endoscopic band ligation plus NSBB/carvedilol) unless post-SVR VCTE-LSM decreases to <12 kPa and PLT are ≥150 G/L.
- Patients with post-SVR VCTE-LSM 20-25 kPa or PLT <150 G/L may have CSPH; EGD should be performed in patients who are not already on NSBB/carvedilol.
- Patients with post-SVR VCTE-LSM >25 kPa have a high likelihood of CSPH; those already on NSBB/carvedilol should continue treatment. Those not on NSBB/carvedilol may be started on NSBB/carvedilol without endoscopic proof of varices. However, EGD may be performed if the decision to start NSBB/carvedilol depends on the presence of varices.

It has long been debated if patients with only small size varices should receive primary bleeding prophylaxis, but the PREDESCI study[57] has introduced the concept of treating all patients with CSPH with beta-blockers to prevent any decompensation (including non-bleeding events, such as ascites), and the Baveno VII consensus[44] has adapted this recommendation. Now, all patients with CSPH (including those with any size varices) should be treated with beta-blockers to prevent variceal bleeding and non-bleeding-related decompensation, and screening for CSPH rather than for varices has become a diagnostic priority. However, it is important to know that beta-blockers are only effective in decreasing portal pressure when there is hyperdynamic circulation, which usually develops in patients with HVPG ≥10 mmHg (*i.e.*, with CSPH).[58] Thus, discontinuation of beta-blockers can be considered if CSPH has been resolved after SVR (Fig. 2).

Patients with decompensated cirrhosis who achieve SVR

Several studies have evaluated the rate of clinical improvement in individuals with decompensated cirrhosis who achieve SVR. El-Sherif *et al.* performed a retrospective analysis of data from four clinical trials including hepatitis C-associated decompensated cirrhosis.[59] Overall, 502 patients with Child-Pugh class B and 120 with class C cirrhosis were included; 85% achieved SVR. The primary outcome was a reduction in disease severity to Child-Pugh class A compensated cirrhosis. Of the 528 patients who achieved SVR with follow-up data available to week 36, one-third of patients with Child-Pugh class B and 12% with Child-Pugh class C cirrhosis met the primary study endpoint. The presence of ascites or hepatic encephalopathy, serum levels of albumin <3.5 g/dl and BMI >25 were associated with a lack of improvement.

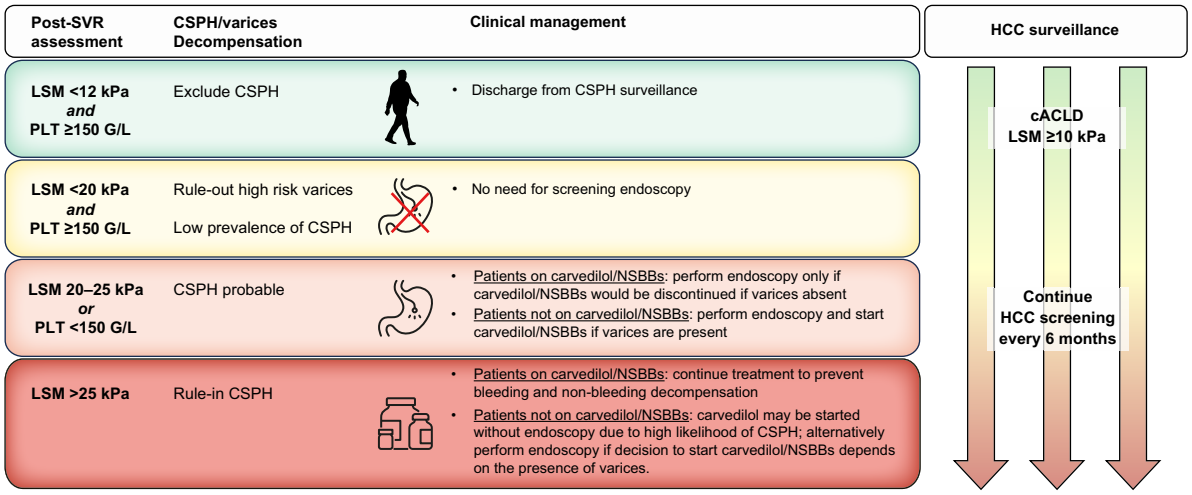

Fig. 2. CSPH risk stratification according to post-SVR VCTE-LSM (and PLT) categories and recommendation in terms of clinical management. CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement, NSBBs, non-selective beta-blockers; PLT, platelet count.

Despite the results mentioned above, not all studies have found a significant impact of SVR on liver function improvement in patients with decompensated cirrhosis. Krassenburg *et al.*[60] explored the impact of SVR in patients with compensated (n = 719) or decompensated (n = 120) cirrhosis. After a median follow-up of 27 months, the study did not demonstrate a lower rate of liver failure or death among those patients with decompensated cirrhosis who achieved SVR (80%). Similar results were obtained from the HCV-TARGET cohort study,[61] that explored long-term hepatic function after DAA treatment in a large real-world cohort. After a 4-year follow-up, improvements in the model for end-stage liver disease (MELD) score were only marginal among patients with decompensated cirrhosis. Reasons for these discrepancies are probably explained by the different characteristics of the analysed cohorts (including the different prevalence of cofactors of liver disease progression), the variability in the length of follow-up and the different definitions of liver function improvement and recompensation.

How to define clinical improvement in patients with HCV-related decompensated cirrhosis who achieve SVR?

Statement

- In HCV-related decompensated cirrhosis, post-SVR improvement in liver function can be defined by a significant and persistent (≥1 year) amelioration/disappearance of symptoms and complications (ascites, hepatic encephalopathy, variceal bleeding) and a consistent improvement in MELD (≥3 points) or reversion to Child-Pugh class A.

Recommendations

- The definition of cirrhosis recompensation requires resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and absence of variceal bleeding for ≥1 year in the absence of TIPS.
- In patients with decompensated cirrhosis who achieve SVR, the presence and grade of ascites and episodes of hepatic encephalopathy, as well as requirements for diuretics and lactulose/rifaximin should be assessed at each follow-up visit. Reduction or discontinuation of diuretics and/or lactulose/rifaximin is encouraged, particularly if clinical and laboratory improvements are documented.

Improvement in patients with decompensated cirrhosis may be defined based on liver function tests or on clinical variables. Despite MELD being a survival predictor and not a liver function score, a decrease of 3 points has been used in most studies and seems a reasonable target (except for patients with renal failure or those on anticoagulation). Child-Pugh score can also be used, particularly since it includes the albumin level. However, the subjective grading of the degree of ascites and hepatic encephalopathy represents a limitation of the Child-Pugh score.

Regarding clinical variables, most published articles consider recompensation as the following: 1) reduction or withdrawal of diuretic treatment in patients with ascites; 2) decrease in the frequency of hepatic encephalopathy episodes or a reduction of treatment requirements (*i.e.* discontinuation of rifaximin); 3) no new episodes of variceal bleeding. Since there is a certain degree of subjectivity when assessing changes in ascites and hepatic encephalopathy, particularly with regards to treatment requirement, the current definition of recompensation[44] requires resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin) and absence of variceal rebleeding for at least 12 months. Importantly, discontinuation of diuretics and medication for hepatic encephalopathy should be encouraged based on the extent of clinical/laboratory improvement. Regarding hepatic encephalopathy, the animal wording test may be a good tool for fine clinical evaluation.[62] For obvious reasons, these criteria cannot be applied in patients with TIPS (transjugular intrahepatic portosystemic shunt).

How long should one wait for an improvement in patients with HCV-related decompensated cirrhosis who achieve SVR?

Statement

- After SVR, improvement in portal hypertension (and thus, a decreased risk of further decompensation) may take long periods of time. Thus, it seems reasonable to wait at least 2 years to allow for clinical improvement and before assuming a patient will not recompensate.

As shown above, improvements in liver function and clinical decompensation can occur after HCV clearance, but the proportion of patients achieving amelioration is variable. A significant number of individuals will never experience an improvement. There is nowadays a consensus on the fact that there is a point of no return, beyond which recompensation is unlikely. With the data currently published it seems reasonable to wait for at least 2 years before excluding the possibility of improvement (see below).[46,63] Probably, the best marker to understand why some patients will not recompensate after HCV cure is the dynamic measurement of the HVPG. Lens *et al.*[46,63] prospectively explored the long-term outcome of HVPG in a large cohort of 226 patients with HCV-related cirrhosis who achieved SVR after DAA therapy and had an HVPG value >10 mmHg (CSPH). Patients underwent HVPG measurements 6 months and 2 years after HCV therapy. Two years after achieving SVR, CSPH (and thus the risk of clinical decompensation) persisted in 53% of patients. However, it is important to note that there was a significant proportion of patients (around 20%) who experienced a significant decrease in HVPG (below the 10 mmHg threshold) from 6 months to 2 years after DAA therapy.[63] The latter highlights the relevance of following these individuals during long periods of time before assuming a point of no return. In the aforementioned study, a history of ascites and baseline HVPG values ≥16 mmHg identified patients with a very low probability of reaching the 10 mmHg threshold (and thus, remaining at higher risk of *de novo* or further clinical decompensation).

What should be expected when treating HCV-infected patients awaiting liver transplantation who clear HCV?

Recommendation

- In patients awaiting liver transplantation due to HCV-related decompensated cirrhosis, SVR may be followed by significant laboratory and clinical improvement. Delisting is possible, particularly in patients without ascites and a low MELD score (<15). In case of delisting, clinical worsening is rare (<10%), but frequent clinical assessment is still recommended due to the lack of studies including large cohorts and long follow-up.

The impact of DAA therapy on the profile of patients awaiting transplantation has been the subject of great interest, and currently, most patients awaiting liver transplantation due to chronic HCV infection are listed due to HCC and only rarely due to clinical decompensation.[64,65] Several studies have focused on the impact of DAA treatment in HCV-infected patients awaiting liver transplantation. Despite the limitations of such studies in terms of the length of follow-up, there is a group of patients in whom HCV eradication is associated with clinical improvement leading to delisting. Rates of delisting (which only apply for those with decompensated cirrhosis) range from 7-30%. Criteria to delist patients may also vary from centre to centre, though in most studies they have been set as an improvement in the MELD score below 15 points and clinical recompensation. European studies report higher rates of delisting (around 20-30%) and variables associated with delisting are a lower baseline MELD (<20) and the absence of ascites.[66,67] Rates of delisting in US series are significantly lower. Indeed, a recent retrospective cohort study using US data found that delisting due to clinical improvement remained low (6.1%) in the DAA era (2013-2017), though when adjusting for clinical variables there was a 78% increase in delisting compared to the pre-DAA era (2005-2012).[68] The differences between European and US series are most likely due to the severity of patients awaiting LT. Indeed, the proportion of patients with MELD scores >20 was higher than 30% in the US (compared to 5-10% in the European series). Long-term follow-up of delisted patients indicates that liver-related complications are infrequent. Indeed, in a European series following 44 delisted patients, only four (10%) required re-listing and only one patient died.[69] Future studies are warranted to provided further evidence on sustained long-term improvements post-SVR in previously decompensated patients.

HCC risk assessment post-SVR

HCV eradication with interferon (IFN)-based therapies is associated with a significant reduction in HCC risk in comparison with patients who did not achieve sustained virological response (SVR).[70] The benefits of DAAs even in patients with previous contraindications to IFN have now been established beyond doubt.[71] However, patients with HCC or with more advanced liver disease were intentionally excluded from registration phase III randomised-controlled trials (RCTs); therefore, data about these patients come from post-marketing surveillance and from observational studies. Despite initial warnings, different meta-analyses that included a large number of studies[70,72] concluded that HCC occurrence following SVR was similar in the IFN and DAA groups (1.14/199 person-years [95% CI 0.86–1.52] and 2.96/100 person-years [95% CI 5–29.58]; respectively). Meta-regression adjusting for study follow-up and age showed that DAA therapy was not associated with a higher HCC occurrence (relative risk 0.68; 95% CI 0.18–255; $p = 0.55$). In addition, recent studies demonstrated the clinical benefit of DAA therapy, in terms of overall survival and reduced risk of hepatic decompensation, in patients with a history of HCC.[73–75] Despite SVR, the risk of developing HCC in DAA-treated patients with advanced liver disease remains high and may persist up to 10 years after successful treatment in patients with pre-SVR cirrhosis or high FIB-4 scores (≥3.25).[76] Therefore, refining HCC prediction in this growing population remains an unmet medical need.

How should HCC surveillance be performed in patients with cACLD after SVR?

Recommendation

- Based on the current literature, all patients with pre-SVR ACLD (F3 or F4 METAVIR) who achieve SVR with DAA therapy should undergo lifelong HCC surveillance with ultrasound screening every 6 months. The role of the combination of ultrasound and AFP in surveillance could soon be re-evaluated if the reduction of false positives in patients with SVR is confirmed.

The goal of HCC ultrasound surveillance programmes is the detection of liver tumours at the earliest stage possible, to allocate patients to curative procedures which have been shown to provide a survival benefit.[36] However, allocation of personalised screening procedures might be driven by HCC risk stratification according to some associated clinical (*e.g.* age, weight, alcohol intake, coinfection status) and molecular features that can change over time. Given this, it could be necessary to repeat measurements of HCC risk predictors to refine risk evaluation in a dynamic fashion. Several studies have aimed to identify predictors of higher or lower risk of HCC after SVR (Table 1).

Interestingly, the global annual HCC incidence in patients achieving SVR in the case of ACLD ranges from 0.2 to 2.5% and is similar to those observed in patients with cirrhosis due to controlled HBV infection or to non-viral causes, whether alcohol- or MASLD-related. In this sense, the use of a single scoring system (like the aMAP HCC model)[84] could be advocated regardless of the cause of the underlying liver disease. A recent study performed in the Veterans Affairs system reported the annual HCC incidence in DAA-treated patients with a known follow-up up to 7 years after SVR.[79] In patients with cirrhosis and/or pre-treatment FIB-4 score >3.25, yearly HCC incidence seemed to decline progressively each year but remained above the recommended threshold for surveillance.

The incremental benefit of adding AFP has been a matter of debate owing to the risk of low specificity. However, such information was mostly obtained in viraemic patients, in whom active hepatitis may act as a confounding factor at lower AFP thresholds (as low as 12–20 ng/ml) In fact, when virological cure is achieved, the diagnostic accuracy of AFP significantly increased.[85–89] More specifically, in HCV-cured patients, higher AFP levels have been shown to be associated with HCC occurrence, both at baseline[84,90] and during follow-up,[91] highlighting its potential value for both risk stratification and early diagnosis. Moreover, a recent cost-effective analysis comparing the strategies found ultrasound plus AFP was the most cost-effective approach.[92]

Well-conducted studies comprising a long follow-up of patients with SVR, taking into account the time-dependent variations in AFP values, will be able to address whether the dynamics of AFP provide useful information for HCC surveillance.

Is the long-term incidence of HCC after DAA therapy different than after IFN-based therapy in patients achieving SVR?

Statement

- A longer follow-up study of patients with advanced fibrosis or cirrhosis who achieved SVR to DAAs is required to assess long-term HCC incidence.

A larger number of cohort studies have reported HCC incidence following HCV eradication in patients with pre-SVR cirrhosis or advanced fibrosis in the IFN *vs.* the DAA era.[77,93] While there is no reason to think that risk reduction would differ between the two regimens, a longer follow-up of patients who achieved SVR with DAAs is required to accurately estimate long-term risk.[76,94,95] A recent meta-analysis of 44 cohort studies reported a global 2.1 per 100 person-years HCC incidence in patients with cirrhosis and 0.5 per 100 person-years in patients with F3 fibrosis.[72] A decrease in HCC incidence was observed for the longest follow-up after HCV eradication (adjusted relative risk per year increase in mean/median follow-up 0.87; 95% CI 0.79–0.96).

Is lifelong HCC surveillance following SVR cost-effective?

Statement

- HCC screening in patients with pre-SVR advanced liver disease (F4) is cost-effective. Patients with advanced fibrosis (F3) have a lower HCC risk and HCC surveillance is probably not cost-effective, but the evidence is still too limited (due to relatively short follow-up and low number of patients) to exclude them from screening programmes.

Table 1. Predictors of higher or lower risk of HCC post-SVR.

Study	Cohort	Factors	Risk of HCC
Calvaruso V, *et al.*[77]	N = 2,249	Albumin, platelets and no-SVR	Higher risk
Mariño Z *et al.*[78]	N = 1,123	Baseline liver function, alcohol intake, hepatic decompensation and non-characterised nodules	Higher risk
Kim NJ, *et al.*[79]	N = 29,003	Cirrhosis and FIB-4 >3.25	Higher risk
Semmler G, *et al.*[80]	N = 527 (derivation) N = 1,500 (validation)	Alcohol, albumin, AFP and LSM	Identifies a low-risk population <1%/year
Alonso-Lopez *et al.*[81]	N = 1,046	Albumin, LSM and dynamic changes (1-year Delta LSM and 1-year FIB-4 score)	Identifies a low-risk population <1%/year
Innes H, *et al.*[82]	N = 2,139	Age-male sex-ALBI-platelet count score (aMAP)	Higher risk
Audureau E, *et al.*[83]	N = 836	Elevated AST, low platelet count and shorter prothrombin time	Higher risk

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; SVR, sustained virological response.

The cost of surveillance per quality-adjusted life-year (QALY) decreases in parallel with the increase in HCC incidence.[96] The yearly HCC risk justifying surveillance in a cost-effective fashion is globally accepted to be above 1.5%, although this threshold remains a subject of debate.[36] In patients with pre-SVR cirrhosis, it is universally considered that HCC incidence is high enough to justify surveillance following HCV eradication.[71] In patients with advanced fibrosis (F3), international guidelines are inconsistent in their recommendations,[36,97] likely reflecting challenges in accurate fibrosis staging in the era of NITs and the unclear cost-effectiveness justification of HCC screening in this subgroup due to a lower HCC incidence.[71,98] In this context, while EASL (the European Association for the Study of the Liver) guidelines recommend patients with bridging fibrosis should be included in screening programmes, AASLD (the American Association for the Study of Liver Diseases) does not endorse it. The latter recommendation took into account the potential risk of cirrhosis misclassification by NITs leading to underestimation of HCC risk.[99,100] However, in a cohort of patients with F3/F4 and an absence of non-characterised nodules on ultrasound, no HCC was registered in patients with F3 after a median follow-up of 52.4 months.[101]

A Markov model approach was developed to assess the cost-effectiveness of HCC screening following HCV cure as a function of pre-SVR liver fibrosis status (advanced fibrosis or cirrhosis).[96] This study estimated that a yearly HCC incidence above 1.32% following SVR was the optimal threshold to achieve an incremental cost-effectiveness ratio (ICER) of <$50,000/QALY. Surveillance was considered cost-effective in patients with cirrhosis as highlighted by an ICER of $48,729/QALY, but not in F3 patients (ICER $188,157/QALY). These results were recently refined by a study using a decision-analytic model in patients who achieved SVR based on different age thresholds to start or stop surveillance.[102] The authors concluded that surveillance was cost-effective in patients with compensated cirrhosis ($79,500-$94,800/QALY) until the age of 70 and in patients with advanced fibrosis until the age of 60 ($124,600-$129,800/QALY).

What is the impact of aging on HCC incidence and HCC screening cost-effectiveness?

Recommendation

- Elderly patients with severe comorbidities (including frailty) that make them ineligible for treatment for HCC, regardless of liver function, should not undergo surveillance for HCC.

Aging is a risk factor for hepatic carcinogenesis. Furthermore, as patients age they may accumulate additional risk factors (*e.g.* diabetes, obesity, excessive alcohol consumption) following SVR. In addition, life expectancy of HCV-cured patients has been substantially improved, particularly in the case of cirrhosis.[47]

As stated earlier, a recent study identified (in patients with cirrhosis or bridging fibrosis) different age cut-offs at which surveillance may not be cost-effective anymore.[102] In these assumptions, HCC surveillance would not be considered cost-effective if the remaining life expectancy is less than 16 years in patients with cirrhosis and less than 28 years in patients with advanced fibrosis; which corresponded to cut-off ages of 70 in patients with cirrhosis and 60 in the case of advanced fibrosis. One of the main drivers of these findings is access to curative procedures for HCC – which can be impaired by older age, the presence of comorbidities, and liver dysfunction – and access to transplant. Nevertheless, as HCC management is strongly impacted by individual factors, it seems difficult to determine a definitive age threshold at which early HCC detection and subsequent allocation to curative treatment will not provide survival benefits. From a clinical point of view, rather than an age cut-off, we should consider the presence of comorbidities that would compromise the possibility of undergoing treatment in case of an early diagnosis of HCC. In fact, the severity of heart, lung or kidney disease, and the degree of frailty can compromise treatments regardless of the degree of residual liver function.[103] The ever-evolving landscape of better tolerated innovative immunotherapies for HCC should also be considered in this context.

Is there a dynamic change in the incidence of HCC following HCV eradication?

Statement

- A tailored approach to surveillance as a function of NIT trajectory following SVR requires additional research aimed at establishing a reliable correlation with changes in HCC incidence.

Individualised HCC screening using dynamic changes in liver disease parameters after SVR is an attractive option, considering the degree of liver regeneration and fibrosis resolution after HCV clearance, which would be expected to reduce HCC risk over time. The issue of whether surveillance can be safely discontinued in some patients is a matter of debate. Some studies suggest that HCC risk decreases with each additional year of follow-up after HCV cure in patients with cirrhosis.[72] While the evidence for this may still be insufficient for SVR after DAAs, such a decline has not been observed in IFN-treated patients, whose HCC incidence remained >2% per year even 10 years after SVR in patients with a high baseline FIB-4 >3.25 or histologic cirrhosis.[76] The extent to which such observations can be translated to DAA-treated patients is currently unknown given inherent selection biases in populations who achieved SVR on IFN-based regimens. Nevertheless, a recent study performed in the VA system reported annual HCC incidence in DAA-treated patients during follow-up up to 7 years after SVR.[79] In patients with cirrhosis and pre-treatment FIB-4 scores >3.25, yearly HCC incidence seemed to decline progressively each year but remained above the recommended threshold to trigger surveillance. These findings might suggest different surveillance strategies depending on how long it has been since SVR was achieved.

How can personalised HCC surveillance following SVR be implemented?

Statement

- HCC risk stratification models enable the identification of patients with a particularly high HCC incidence following SVR. Individualised HCC surveillance strategies could be proposed in these individuals using more sensitive and potentially also more expensive HCC screening procedures. The latter must first be proven to be superior to liver ultrasound in randomised trials that also consider cost-effectiveness.

Numerous HCC risk stratification models have been developed following HCV cure and might be used to define new surveillance strategies.[104] The goal of such personalised approaches is not to identify patients who have "zero risk" following viral eradication, but to reinforce surveillance in dedicated subgroups with a particularly high risk despite HCV cure. To date, these models developed and validated in large prospective cohorts[83,84,90] are based on simple clinical and biological routine parameters and may ultimately optimise the allocation of medical resources in a cost-effective fashion.[105] Because of the weak performance of ultrasound for the detection of early HCC,[106] numerous alternative tools are currently under investigation to overcome this pitfall; they include circulating biomarkers[107] or other imaging modalities such as abbreviated MRI.[108] However, because of their limited availability and higher costs, it is crucial to prioritise patients with the highest HCC incidence to implement these new procedures in the setting of risk stratification-based strategies.

For instance, HCC surveillance by means of semi-annual liver MRI, has been shown to be cost-effective in Asian HBV-infected patients with a yearly incidence of liver cancer >1.81%[109] and more recently in European patients with cirrhosis without active viral replication in whom the annual HCC incidence exceeded 3%.[90] The acceptability and cost-benefit ratio of new tools to enable earlier HCC detection are currently under study in various trials, the results of which will determine their potential deployment in clinical practice.

Management of the extrahepatic manifestations of HCV infection after SVR

In addition to liver-related morbidities, HCV is also associated with several extrahepatic manifestations (HCV-EHMs).[110–112] Suggested HCV-EHMs involve almost every organ system in the human body and increase the complexity of this disease, significantly contributing to economic burden, morbidity, reduced quality of life and mortality. For reasons of simplicity, we will focus on those extrahepatic manifestations that have shown a more solid association with HCV infection; namely cryoglobulinemia (including renal disease and neurological disorders), non-Hodgkin lymphomas and metabolic alterations. When compared with liver-related conditions caused by HCV infection, data on outcomes of HCV-EHMs after SVR are scarce, which makes it more difficult to establish solid recommendations.

Regarding mixed cryoglobulinemia (MC), clinical manifestations vary in patients, ranging from overt symptomatic conditions to only laboratory alterations (positive rheumatoid factor [RF] and low C3/C4 levels, in addition to serum cryoglobulins).[112] The MC syndrome or cryoglobulinemic vasculitis (CV) is characterised by the typical clinical *triad* of purpura, weakness, and arthralgias, and various visceral organ involvement, including renal and neurological disease. The clinical manifestations are extremely variable, ranging from mild/moderate diseases to severe/life threatening ones.

Do DAA-based antiviral treatments have clinical efficacy on CV and is this effect persistent?

Statement

- Patients with CV usually have a good and persistent clinical and immunological response after SVR. However, recurrence is possible but not frequent. The following conditions indicate a higher risk of CV recurrence after SVR: cirrhosis, high RF values post-SVR, respiratory infections, cancer, and (very rarely) vaccinations.

Most studies use the terms clinical and immunological responses. Clinical response (complete or partial) is used to assess the effects of SVR on the CV symptoms like purpura, arthralgias, and weakness, whereas immunological response is used to assess laboratory/serological data such as cryoglobulin, serum RF and C4 levels.[113–116] Overall, clinical response after antiviral therapy is described as the percentage of patients experiencing clinical CV improvement of most symptoms. However, the definition is not standardised and may vary across studies. In general, complete clinical response is described as improvement of all pre-SVR CV symptoms/signs whereas clinical partial response refers to improvement of more than half of CV symptoms. All remaining conditions (*e.g.* improvement of less than half of symptoms, maintenance or worsening of symptoms) are considered non-response.

Despite the different descriptions, the overall clinical response (complete + partial) was generally observed in most patients with CV after SVR (Table S2). Available data suggest that even neurological symptoms, when not irreversible, tend to improve significantly after SVR.[117] Interestingly, unlike IFN-based therapy, where symptoms usually increased during treatment, an improvement was usually noticed early during DAA-based therapy.[112] Recently, long-term post-treatment follow-up studies of patients with CV after DAAs confirmed the high frequency of CV response but also showed that CV may persist, relapse or even occur *de novo*, with some variables identifying patients at higher risk (Table 2). Importantly, as for persistent idiopathic CV manifestations, the occurrence of a CV flare after SVR does not always imply a clinically aggressive

Table 2. Relapses/flares of CV after treatment with DAAs with suggested triggering events or predisposing conditions.

First author, year, [ref]	Patients with CV flares (total patients, %)	Mean FU after EOT	Suggested triggering event or predisposing conditions	Pre-DAA clinical	Flare characteristics and evolution (transient/ persistent)
Sollima, 2016[119]	1 (7, 14%)	3 months	Triggering event: Influenza vaccine	Purpura, nephropathy	†CV
Visentini, 2018[120]	3 (ND)	22.8 months	Triggering events: Respiratory infection, lung carcinoma	Nephropathy 2/4, neuropathy 4/4, purpura 3/4, ulcers 1/4, arthralgia 1/4	Nephropathy 2/4, purpura 1/4, skin ulcers 1/4 (2 transient, 1 death, 1 ND)
Bonacci, 2018[121]	5 (46, 10.8%)	24 months	Predisposing condition: Cirrhosis	Purpura 3/5, neuropathy 2/5, nephropathy 1/5	Purpura (transient) 3/5, nephropathy 1/5, fatal acute mesenteric ischaemia 1/5
Sollima, 2018[122]	1 (ND)	18 months	Triggering event: Influenza vaccine	Purpura, nephropathy	Purpura, nephropathy, serum CGs (transient)
*Visentini, 2022[123]	9 (71, 12.7%)	ND	Triggering event: COVID-19 vaccine	8/71 +NHL	†CV
*Vacchi, 2023[124]	22 (416, 5.3%)	ND	Triggering event: COVID-19 vaccine	CV	Mainly neuropathy or purpura
Kondili 2022[125]	18 (137, 13%)	15 (13-27) months	Predisposing condition: High RF values	Purpura, weakness, SS, neuropathy	Purpura, neuropathy, other (transient in 66.7%)
Gragnani, 2023[126]	20 (374, 5%) post- vaccination 10 (51, 14%) post-COVID-19	137 (72–290) weeks	Triggering events: COVID-19 vaccine COVID-19	CV	†CV

*Studies also involving HCV-negative CV: 13 out of 71 patients, and 3 out of 6 relapsing ones in the study by Visentini *et al*.;[108] 127 out of 416 patients in the study by Vacchi *et al*.;[109]
†CV: disease relapses were mostly characterised by worsening of previous manifestations of CV. CGs, cryoglobulins; CV, cryoglobulinemic vasculitis; EOT, end of treatment; FU, follow-up; NHL, non-Hodgkin lymphoma; RF, rheumatoid factor; SS, sicca syndrome; ND, not done/specified.

course. In fact, most CV flares seem to be transient and respond well to treatment (*e.g.* steroids, immunosuppressants and rituximab).[118]

What is the recommended follow-up of patients with HCV-associated CV after SVR?

Recommendations

- In patients with CV, a complete response (clinical and immunological/laboratory response) should be evaluated 1 year after SVR and when confirmed, patients may be discharged from CV follow-up. However, physicians should be aware of potential clinical relapse – especially after certain triggering events (such as cancer, infections or vaccinations).
- Patients with clinical response after SVR, but persisting laboratory markers of CV, should be carefully assessed for potential triggering events, especially in case of post-SVR cirrhosis or high RF. The yearly follow-up programme should include the assessment of serum cryoglobulins, RF and complement levels.
- A long-term multidisciplinary follow-up is mandatory for patients with CV who do not achieve a clinical and immunological response.

Some demographic, clinical and laboratory parameters have been shown to represent adverse predictors of CV relapse after SVR and clinical response (Table 2 and Table S2). The evaluation of their presence and their combination in single cases could guide follow-up (Fig. 3).

Patients with CV after SVR may present variable aspects ranging from the complete disappearance of both clinical and laboratory data to the persistence of only laboratory data (*e.g.* cryoglobulinemia and/or RF and/or complement consumption) or the persistence of both clinical and laboratory data. Insufficient data are available to guide a rational follow-up strategy in the numerous patients showing only persistent laboratory activity (cryoglobulins and/or RF, and/or complement consumption). In patients with persisting cryocrit +/- high RF values after SVR, it would be reasonable to maintain a cautious attitude since the presence of cryoglobulins in serum implies the existence of clonal B-cell expansion (B-RF cells)[126]and potential flares following strong B lymphocyte stimulation or even possible evolution towards frank malignant B-cell lymphoma on long-term follow-up.

A rational follow-up approach should consider prognostic factors including laboratory, demographic and clinical markers[125,126] and possible triggers of CV flares, such as major infectious episodes (*e.g.* pneumonia and COVID-19) and some vaccinations[127] (see Table 2).

How should patients with renal disease be monitored after DAA-based SVR?

Recommendation

- In patients with a decreased estimated glomerular filtration rate after SVR, a workup including cryoglobulins, urinalysis and albumin/creatinine ratio should be performed. In those with abnormal results, risk factors for CKD (arterial hypertension, diabetes, *etc*.) should be evaluated. A multidisciplinary approach including evaluation by nephrologists is advised.

A strong association between HCV infection and the incidence of renal disease has been shown[128–130] and patients with HCV infection should be regarded as being at greater risk,

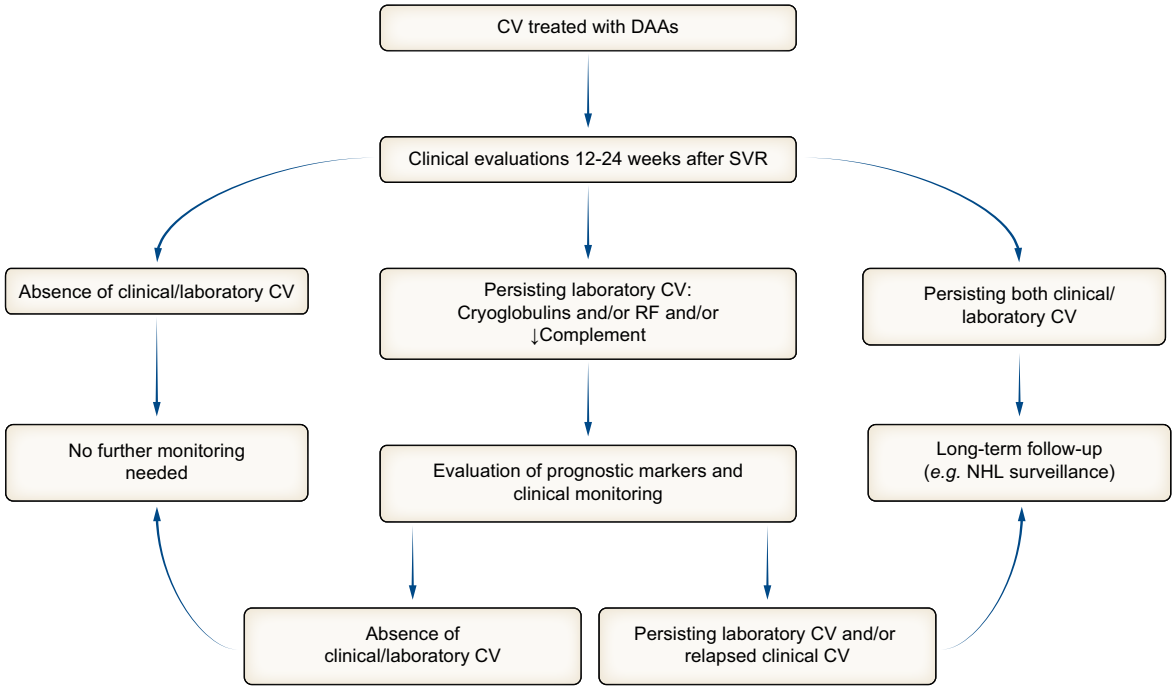

Fig. 3. Proposed follow-up of HCV MC patients after SVR. CV, cryoglobulinemic vasculitis; DAAs, direct-acting antivirals; MC, mixed cryoglobulinemia; NHL, non-Hodgkin lymphoma; RF, rheumatoid factor; SVR, sustained virological response.

regardless of the presence of conventional risk factors for kidney disease.[130] HCV infection is associated with a large spectrum of glomerular diseases. The most frequently observed is the cryoglobulinemic glomerulonephritis (cryoglobulinemic nephropathy) secondary to CV, and histologically characterised by type 1 MPGN (membranoproliferative glomerulonephritis). In patients with CV, renal involvement was reported at a prevalence ranging from 18% to 40%, with increasing percentages during follow-up and was associated with a significantly worse CV prognosis.[131]

Other nephropathies, including MPGN without cryoglobulinemia, membranous nephropathy and mesangioproliferative glomerulonephritis, focal segmental glomerulosclerosis, fibrillary or immunotactoid glomerulopathies or thrombotic microangiopathy, are rarely associated with HCV infection.[112,128–132]

The development of DAA therapy has changed and simplified the approach to HCV in all populations with chronic kidney disease (CKD), including most advanced stages (stages 4-5), patients undergoing dialysis and following kidney transplantation.[112] From a renal perspective, DAAs have a double advantage: they can improve prognosis of patients with established renal disease and can prevent the occurrence of *de novo* kidney disease. The preventive role of viral eradication is of primary importance. In terms of the effects of SVR on CKD, some studies report improvement or disappearance of the kidney involvement,[113,121] whereas other studies report a persistence of renal damage.[133] The stage of renal damage appears to play a key role in deciding the clinical response after SVR: early kidney involvement, with only urinalysis modifications and without evidence of persistent renal function impairment, may completely disappear after SVR (clinical response), whereas the probability of complete response is reduced in more advanced HCV-associated CKD. Negative prognostic factors of clinical response include the presence of CV (especially long-lasting), advanced age, severe CKD (stage 4–5 or on haemodialysis) and severe liver damage.

What is the recommended follow-up of patients with HCV-associated non-Hodgkin lymphoma after SVR?

Recommendations

- Treatment of HCV infection is recommended in all patients with non-Hodgkin lymphoma (NHL). If immunechemotherapy is indicated, DAA-based therapy may be performed either during or after chemotherapy. In some patients, SVR may induce long-lasting NHL remission.
- In patients with B-cell NHL, the post-SVR follow-up should be organised in cooperation with the haematologist. This is particularly relevant for patients with cACLD, who should undergo the usual HCC and portal hypertension screening.

HCV is involved in the development of both indolent and aggressive B-cell NHLs, in particular marginal zone lymphoma and diffuse large B-cell lymphoma (the most frequent aggressive lymphoma in Western countries).[134] In patients with HCV, a B-cell NHL can be found either as evolution of CV or independently from the presence of MC. The risk of NHL development was shown to be 35-fold higher in patients with MC than in the general population.[135]

In patients with B-cell indolent NHL, several retrospective studies (usually with short FU) and case reports identified consistent rates of lymphoma regression after DAA-based therapy.[136–141] More recently, the effects of DAAs on HCV-infected patients were studied in a prospective, multicentre trial including mostly marginal zone lymphomas (68%), but also lymphoplasmacytic, small lymphocytic, and follicular lymphoma. The study strongly suggested that, at least in subsets of NHL, the eradication of HCV with DAAs may result in lasting lymphoma regression.[141,142]

In patients with high-grade NHL, as well as in some cases of indolent NHL (*e.g.* systemic symptoms, bulky disease or symptomatic splenomegaly), it is necessary to treat with immune-chemotherapy. In such cases, which usually require rapid therapeutic intervention, DAA-based therapy may be performed either during or after chemotherapy, carefully considering possible drug interactions and liver damage.[143,144] After achieving SVR, patients should primarily be followed by haematologists and, in case of significant liver fibrosis, by liver disease specialists.

Regarding the risk of NHL development in HCV+ individuals, a study on a large population over a long follow-up period showed that the achievement of SVR significantly reduces the risk of NHL development. The reduction was statistically significant in younger patients[145]

What potential metabolic changes may occur after SVR and how should they be managed?

Recommendation

- Follow-up post-SVR should include the assessment of risk factors for cardiovascular disease, with associated counselling, and should ideally be performed by the general practitioner.

There is a well-established association between IFN-induced SVR and improved insulin resistance.[146] The latter has also been confirmed in patients who achieved SVR after DAA therapy, with some even reducing the dose of antidiabetics.[147,148] However, the effect of HCV clearance on other metabolic variables points in another direction, with increased LDL cholesterol levels, BMI and waist circumference.[149] The clinical relevance of these findings is not clear and several studies have shown beneficial effects in some surrogate markers of cardiovascular outcomes such as intima-media thickness.[150,151] What seems most relevant in this scenario is a thorough counselling on the benefits of a healthy lifestyle, avoiding weight gain and alcohol consumption, and exercising regularly. In the absence of MASLD and harmful alcohol drinking, follow-up should be carried out by the general practitioner.

HCV reinfection after achieving SVR

It is well known that achieving SVR does not protect individuals from subsequent reinfection with HCV if they are exposed to the virus again. Populations at risk of reinfection after SVR include people who continue to use/inject drugs (PWIDs), men who have sex with men (MSM), prisoners (especially in countries without access to needle and syringe provision [NSP] in correctional institutions) and those with ongoing nosocomial exposure to unsafe medical procedures (*e.g.* patients who undergo dialysis in resource-limited environments).

Who should be monitored for HCV reinfection after SVR?

Statement

- The main risk populations for reinfection are PWID and MSM with high-risk practices, including those residing in prisons. In addition, nosocomial acquisition may be another source of reinfection (*i.e.* in patients undergoing haemodialysis or with multiple hospital admissions).

The risk of reinfection in at-risk populations has been estimated to be in the range of 1%-10.5% per year. The precise risk almost certainly depends on the different populations, as well as the methodology used to estimate reinfection rates. A few recent studies have provided arguably more accurate estimates in well-characterised cohorts at high risk of reinfection. In a study from Tayside in Scotland, 100 reinfections were identified amongst 916 treatment episodes with confirmed SVR.[152] Reinfection rates amongst individuals attending the hospital-based clinic were low at 1.81 per 100 person-years, whereas the equivalent figure was 19.89 per 100 person-years in individuals attending an equipment provision site where a HCV treatment pathway was embedded. Similarly, a study from the North East of England investigated a cohort of 788 individuals who had achieved SVR between 2016 and 2021.[153] Importantly, only 443 individuals had HCV RNA testing post-SVR, highlighting some of the practical difficulties of ongoing testing in high-risk populations. Nevertheless, the reinfection rates in those re-tested were 10.5 per 100 person-years with the median time to reinfection being only 1.37 years. The only identified risk factor for reinfection in this study was a younger age. Finally, a study from Barcelona has recently demonstrated an even higher reinfection rate of 31 per 100 person-years among active PWID, with the main risk factors being HIV coinfection and daily injecting.[154]

Reinfection rates in prisoners have also been studied. In a study from two prisons in the Northeast of England, 21 individuals out of 111 who achieved a documented SVR were found to have become reinfected; a rate of 0.406 per person-year of follow-up.[155] The median time to reinfection was only 13 months. A study from Australia also analysed reinfection rates (confirmed by sequencing) amongst prisoners treated with DAAs who had confirmed SVR.[156] In this study the overall reinfection rate was 12.5 per 100 person-years but this increased to 28.7 per 100 person-years in those with injection drug use and needle/syringe sharing. This data underlines the importance of adequate NSP for high-risk PWID populations both within correctional institutions and in the community;

something which has recently been acknowledged by the WHO Global Health Sector Strategy, which has set minimal targets for NSP per active injector in member countries. It is also incumbent upon healthcare professionals to emphasise to their patients that natural immunity against HCV does not occur and being HCV antibody positive is not protective. Signposting to safe injecting practice and NSP provision is an important part of the HCV care continuum.

Another population at risk of HCV reinfection is the MSM population, especially those that engage in high-risk sexual practices or who use injectable drugs as part of chemsex parties. A study of the MOSAIC cohort demonstrated a reinfection rate of 11.5 per 100 person-years in HIV-positive MSM who had either spontaneously cleared or had successful treatment for HCV.[157] Risk factors for reinfection included condom-less receptive anal intercourse, use of sex toys, group sex and having 10 or more casual sexual partners in 6 months. Counselling individuals after curative treatment about safer sexual practices is, therefore, important and qualitative data from the French ANRS CO13 HEPAVIH cohort suggests that this can make a significant impact.[158]

The final at-risk population to consider are those that are at high risk of nosocomial acquisition of HCV through unsafe medical practices. Cases of 'holiday haemodialysis' involving patients with end-stage renal failure who dialyse in different settings during trips abroad have long been recognised.[159] Anecdotal cases of patients treated successfully for HCV but reinfected again are emerging although the overall risk may be low according to a study from Taiwan.[160] Nevertheless, many nephrology guidelines recommend using dedicated dialysis machines for a set period after return from holiday and many guidelines recommend testing for HCV antibodies once every 6 months in the general dialysis population.[161] Whether or not this should be extended to HCV PCR testing once every 6 months in those who have previously achieved SVR is a matter for debate. However, after any episode of dialysis in a different unit (especially one in a different country) it would probably be prudent for individuals to have HCV RNA testing once every 2-3 months for the first 6 months on return to their base dialysis unit.

How and how often should HCV reinfection be monitored after SVR?

Recommendation

- In individuals with ongoing risk behaviour and/or elevated alanine aminotransferase levels, HCV RNA or HCV antigen should be tested at least every 6 months. Point of care or dried blood spot testing are useful alternatives for monitoring HCV reinfection.

In individuals at risk of reinfection, testing for HCV should be solely based on either nucleic acid testing, usually by PCR-based methods, or antigen testing methods where available. Individuals at high risk of reinfection should be tested every 6 months as a minimum although in some populations (*e.g.* multiple documented new infections in a known injecting network) it may be preferable to perform testing every 3 months. Testing during each admission to a correctional institution is also recommended as these individuals are more likely to not be in contact with community drug services and have less access to NSP.

Acceptable forms of NAT/antigen testing include venous sampling, dry blood spot testing and point of care PCR testing using pin prick methods. The latter two modalities have gained increasing traction over the last few years due to the difficulty of formal venepuncture in many PWIDs and the wider availability and reduced training requirements required for pin prick testing. It is important for healthcare practitioners to be aware of the lower limit of detection of these alternative assays which are not as sensitive as PCR-based testing. A recent study has demonstrated that, in general, point of care testing using the GeneExpert system is more sensitive than dry blood spot testing, especially in patients with HCV RNA below 3,000 IU/ml.[162] That said, it is important to have knowledge of local lab performance of dried blood spot testing thresholds as protocols vary. Where practically possible, formal venous testing should be used to clarify discrepancies in results or in cases where there is a high clinical index of suspicion of reinfection/exposure to significant risk.

What is the appropriate treatment approach after a diagnosis of reinfection?

Recommendation

- When reinfection is documented, therapy with DAAs should be initiated to achieve SVR at the individual level and to prevent onward transmission of HCV.

All patients with documented reinfection, regardless of the route of transmission, should be offered retreatment with DAAs as soon as is practically possible as per individual country guidelines. Arbitrary limits on the number of DAA courses that an individual may receive are likely to hamper HCV elimination programmes as targeting these higher risk individuals will have the biggest public health impact in terms of preventing onward transmission of the virus.

Future perspectives

Despite the advances in knowledge regarding the impact of SVR in patients with HCV, the panel has identified several key areas of research that need to be addressed in the future (Box 1).

Box 1. Key future research areas.

Patients with mild fibrosis

- Accurate risk stratification based on comorbidities affecting liver disease progression is needed.

Patients with cACLD

- More evidence on non-invasive tests (including blood-based scores and spleen stiffness measurement) for CSPH risk assessment should be generated in the post-SVR setting.
- The value of non-VCTE elastography modalities for non-invasive CSPH risk assessment should be assessed in the post-SVR setting.
- Current non-invasive recommendations for the post-SVR setting should be validated by further studies assessing the liver-related event rates in the different risk strata.

Patients with decompensated cirrhosis

- Studies including patients with a long follow-up (>5 years) are still necessary to assess the long-term impact of HCV eradication and to better identify those individuals who will not improve (point of no return).

Risk of HCC post-SVR

- The age threshold to stop surveillance has not been established and should consider comorbidities. Defining an age threshold above which HCC surveillance could be considered futile requires dedicated studies.
- Patients with advanced fibrosis (F3) have a lower HCC risk and surveillance is probably not cost-effective in this population; however, dedicated prospective studies are needed before excluding them from screening programmes.
- A tailored approach to surveillance as a function of NIT trajectory following SVR requires additional research aimed at establishing a fair correlation with changes in HCC incidence.
- HCC risk stratification models enable the identification of patients with a particularly high HCC incidence following SVR. Tailored/Individualised HCC surveillance strategies could be proposed in these individuals using more sensitive and potentially also more expensive HCC screening procedures. The latter must first be proven to be superior to liver ultrasound in randomised trials that also investigate cost-effectiveness.

Management of HCV-related extrahepatic manifestations

- Post-SVR data for most extrahepatic manifestations are limited. Future studies based on in-depth analysis of the long-term evolution after HCV elimination will be of great interest.
- The long-term impact of SVR in patients with aggressive forms of lymphoma, where viral eradication is combined with immunochemotherapy, remains to be defined.

HCV reinfection after SVR

- Evidence-based interventions that reduce the likelihood of reinfection in at-risk populations are strongly needed (harm reduction strategies, peer support and navigation, educational strategies).
- Despite many years of research, efforts to successfully introduce an HCV vaccine have been fraught with difficulties. The development of such a vaccine is one clear area of unmet need in order to achieve HCV elimination.

cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NIT, non-invasive test; SVR, sustained virological response.

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Abbreviations

ALD, alcohol-related liver disease; APRI, aminotransferase-to-platelet ratio index; CKD, chronic kidney disease; CSPH, clinically significant portal hypertension; CV, cryoglobulinemic vasculitis; DAAs, direct-acting antivirals; EASL, European Association for the Study of the Liver; EGD, esophagogastroduodenoscopy; EHMs, extrahepatic manifestations; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; ICER, incremental cost-effectiveness ratio; ILCA, International Liver cancer Association; LSM, Liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MC, mixed cryoglobulinemia; MELD, model for end-stage liver disease; MSM, men who have sex with men; NHL, non-Hodgkin lymphoma; NIT, non-invasive test ; NSBB, non-selective beta-blocker; NSP, needle and syringe provision; QALY, quality-adjusted life-year; RF, rheumatoid factor; SVR, sustained virological response; TIPS, transjugular intrahepatic portosystemic shunt; VCTE, vibration-controlled transient elastography.

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Conflict of interest

TR received grant support from AbbVie, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Myr Pharmaceuticals, Philips Healthcare, Pliant, Siemens and W. L. Gore & Associates; speaking honoraria from Abbvie, Gilead, Intercept/Advanz Pharma, Roche, MSD, W. L. Gore & Associates; consulting/advisory board fee from Abbvie, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Resolution Therapeutics, Siemens; and travel support from Abbvie, Boehringer Ingelheim, Dr. Falk Pharma, Gilead and Roche. SL has received grants from Gilead and acted as advisor for Gilead, lecture fees and travel support from Gilead and Abbvie. GC participated in

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed to the design, writing and final review of the manuscript and approved its final format.

Supplementary data

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Author names in bold designate shared co-first authorship

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