REVIEW ARTICLE

Remaining clinical issues in hepatitis C treatment

Alexander Wong MD[1], Cynthia Tsien MD[2], Sarah Mansour MD[2], Curtis Cooper MD, FRCPC[2,3]

ABSTRACT

Key advances in the evaluation and treatment of hepatitis C virus (HCV) infection have positively transformed the management and outcomes of those living with this chronic viral infection. Previously difficult-to-cure populations, including those coinfected with HIV infection, now enjoy similarly high success rates with interferon-free, orally administered direct-acting antiviral (DAA) therapies. Nonetheless, relevant unresolved clinical questions remain. The role and impact of viral resistance testing on treatment selection and outcome remain to be fully determined. The consequences of developing resistance while on DAA treatments that ultimately prove unsuccessful requires further evaluation. Optimal HCV management strategies in decompensated liver disease are unclear, and the role for ribavirin in DAA treatment-naïve and treatment-experienced patients is uncertain. A chief concern for those with cirrhosis relates to the risk for de novo and recurrent hepatocellular carcinoma among DAA recipients. In this article, we present and interpret current data and consider pragmatic, clinically useful options.

KEYWORDS: decompensation; direct-acting antivirals; HCV; hepatocellular carcinoma; resistance-associated substitutions

Author Affiliation

[1]*Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada;* [2]*Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada;* [3]*Department of Medicine, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*

Correspondence: Curtis Cooper, Department of Medicine, University of Ottawa, G12–501 Smyth Road, Ottawa, Ontario K1H 8L6 Canada. Telephone: 613-737-8924. Fax: 613-737-8164. E-mail: ccooper@toh.ca

INTRODUCTION

Key advances in the evaluation and treatment of hepatitis C virus (HCV) infection have transformed management of this chronic viral infection and dramatically improved outcomes for those living with it. Chief among these advances are noninvasive fibrosis assessment technologies, including transient elastography and other calculated measures of fibrosis (eg, the aspartate aminotransferase-to-platelet ratio index), that have eliminated the need for routine liver biopsy. The use of highly curative, well-tolerated, interferon-free, orally administered direct-acting antiviral (DAA) drugs has allowed many more HCV-infected individuals to receive treatment. Difficult-to-treat populations, including people who use drugs or alcohol, patients with concurrent mental health concerns, and people who live in isolated areas, can now engage in HCV care, begin treatment, and achieve cure rates that are similar to those obtained in clinical trials (1, 2). Previously difficult-to-cure populations, including those

Table 1: Key outstanding issues related to HCV treatment

	Comment
HCV resistance	
NS5B polymerase resistance to nucleotides	This class of RASs appears to have little impact on treatment outcomes with current nucleoside-based regimens (ie, sofosbuvir) and should not influence DAA regimen selection.
NS5A resistance	Key RASs may be clinically relevant for genotype 1a and 3 treatment outcomes, but not for genotype 1b or 2 outcomes.
NS3/4A protease resistance	NS3/4A RASs should have little impact on treatment selection because they typically do not influence treatment outcome with current first-line regimens.
Triple-class DAA combination regimens	The presence of RASs, including multiclass combinations in DAA treatment-experienced patients, can be overcome by triple-class combination regimens.
Ribavirin	Ribavirin continues to play a role in managing some scenarios involving RASs. The addition of ribavirin to elbasvir–grazoprevir maximizes SVR outcomes in treatment-naïve, genotype 1a infected patients with key NS5A RASs.The impact of ribavirin on SVR is more pronounced in patients receiving salvage treatment and in those with decompensated liver disease.
RAS management	All treatment-experienced patients, especially those with advanced fibrosis, may benefit from baseline resistance testing because the risk of virologic failure with a suboptimal regimen clearly has negative consequences for subsequent retreatment efforts. In these populations, baseline resistance testing provides an additional tool for selection of the most optimal DAA regimen and for informing the decision for or against ribavirin inclusion.
Decompensated cirrhosis	
General statements	Decompensated patients should be evaluated for treatment in an expert setting.If a regimen with a predicted high likelihood of safety and virologic success is available, then treatment should be pursued.Protease inhibitors are contraindicated.
Treatment naive	Although lower than in those with compensated cirrhosis, SVR rates are high, ranging from 80% to 90%.
Failed previous DAA therapy	Data are lacking to inform clear recommendations.
HCC risk after HCV cure	
All patients with cirrhosis	Screening in patients with cirrhosis is mandatory but often omitted.
De novo HCC	Little evidence supports concerns regarding increased HCC risk in DAA recipients without a previous HCC history.
Recurrent HCC	The risk for recurrent HCC remains unclear in the context of DAA exposure.

DAA = Direct-acting antiviral; HCC = Hepatocellular carcinoma; HCV = Hepatitis C virus; NS = nonstructural protein; RAS = Resistance-associated substitutions; SVR = sustained virologic response.

coinfected with HIV, now enjoy similarly high success rates, with sustained virologic response (SVR) rates approximating 95% (3). Race has been eliminated as a predictor of treatment success (4).

Despite these considerable advances, relevant clinical questions remain. The role and impact of viral resistance testing on treatment selection and outcome remain to be fully determined. The consequences of viral resistance development while on unsuccessful DAA treatments require further evaluation. Optimal management strategies for those with decompensated liver disease require exploration. The role of ribavirin in DAA treatment-naïve and treatment-experienced patients and in liver decompensation is unclear. A chief concern for those with cirrhosis relates to the risk of de novo and recurrent hepatocellular carcinoma (HCC) in DAA recipients. These key unresolved issues are considered, and management approaches are proposed (see Table 1).

HCV RESISTANCE

HCV viral replication occurs rapidly, without proofreading by the HCV RNA-dependent RNA polymerase, leading to amino acid substitutions and genetically diverse but closely related populations known as quasi-species (5, 6). Resistant-associated substitutions (RASs), mutations in the virus resulting from this lack of replicative fidelity, are less prevalent because of lower replicative fitness, but many remain present. Certain RASs may become enriched in the presence of DAAs as wild-type virus is suppressed (7). Replicative fitness determines the prevalence of specific virions with RAS as well as how long they remain detectable after DAA treatment has been completed. The likelihood of RAS detection depends on the assay used; the more sensitive the assay is, the more RASs will be detected. Population sequencing at the 15%–20% cut-off for detection is the currently accepted standard. Previous analyses suggest that DAA treatment responses are similar regardless of the specific cut-off used (8, 9).

The cut-off determining a mutation to confer diminished DAA susceptibility is another important parameter to consider when discussing RASs. Many laboratories and clinical trial publications use as a definition a specific substitution that confers a reduced class-specific susceptibility of more than 2.5-fold in the half maximal effective concentration (EC50) compared with a genotype-specific reference in a replicon model. The fold change in EC50 used often varies from one publication to another. In addition, the definition can also include any commonly emerging mutation in patients with virologic failure at the time of relapse. The impact of these RASs on DAA treatment outcome, the necessity of testing for them before treatment, and the influence that RASs should have on DAA regimen selection remain key points of uncertainty in the clinical management of HCV. The relevance of RASs varies according to DAA class.

Nonstructural protein (NS) 5B polymerase resistance to nucleotides

NS5B serves as the viral polymerase. In contrast to non-nucleotide inhibitors, which now have a diminished role in practice, the barrier to development of on-treatment RASs with a clinical impact on nucleotides is high (6). S282T, N142T, L159F, S282G, C316N, and L320F are NS5B RASs with a reported total pretreatment baseline prevalence of 2.5% (10). S282T confers a 10-fold (range 2.4- to 18.1-fold) resistance to sofosbuvir (11, 12). In early sofosbuvir phase 2–3 clinical trials, including monotherapy, 38 of 1,662 subjects had baseline NS5B RASs (none of which included S282T), and 92% achieved SVR (13). In ledipasvir–sofosbuvir phase 2–3 studies of more than 2,000 patients, 1 patient was identified with a S282T at virologic failure (12).

L159F, S282G, and L320S at baseline do not influence SVR (8, 13). NS5B RASs have low replicative fitness. To this point, the S282T RAS found at the time of virologic failure was not detected 12 weeks posttreatment (13). This class of RASs appears to have little impact on treatment outcomes with current nucleoside-based regimens (i.e., sofosbuvir) and should not influence DAA regimen selection.

NS5A resistance

Key clinically relevant NS5A RASs are located at the Q30H, L31M, and Y93H locations. Y93H leads to a more than 1,000-fold resistance to NS5A enzyme inhibitors in patients with genotype 1. Q30H and L31M RASs confer 100- to 1,000-fold resistance in patients with genotype 1 (8). Zeuzem et al. reported that among more than 5,000 NS5A inhibitor treatment-naïve patients, 13.0% and 17.6% of genotype 1a– and 1b–infected patients, respectively, possessed baseline NS5A RASs using a 15% cut-off assay (9). Y93H was detected in less than 1.5%, 3.8%–14.1%, 1.8%–8.3%, and 5.0%–13.0% of patients with genotypes 1a, 1b, 3, and 4, respectively.

SVR was reduced from 99% to 91% among treatment-naïve genotype 1a patients receiving ledipasvir–sofosbuvir who possessed ledipasvir-specific RASs (9). In contrast, the presence of baseline RASs did not influence SVR in treatment-naïve genotype 1b patients. SVR was 76%–80% among treatment-experienced genotype 1a patients with baseline NS5A RASs compared with 97%–98% among those without baseline NS5A RASs. A similar finding was reported among treatment-experienced genotype 1b patients, among whom those with baseline RASs had an SVR of 89%–91% compared with 98% among those without baseline RASs (9). Sarrazin et al. reported that 11 of 17 (65%) treatment-experienced, genotype 1 patients with high-level NS5A RASs achieved SVR for 12 or more weeks after the end of treatment (SVR12) with ledipasvir–sofosbuvir (8). Lawitz et al. reported that among those who failed previous ledipasvir–sofosbuvir treatment and possessed baseline NS5A RASs, only 18 of 30 (60%) achieved SVR after retreatment

with 24 weeks of ledipasvir–sofosbuvir. Those with Y93H at baseline had the lowest SVR (33%) (14). Issues related to NS5A RASs appear to have been diminished by the introduction of velpatasvir. There is little evidence that baseline RASs influence velpatasvir–sofosbuvir SVR rates in treatment-naïve populations, including those with compensated cirrhosis (4, 15). Even in treatment-naïve patients with decompensated cirrhosis, SVR rates in genotype 1–infected velpatasvir–sofosbuvir recipients were comparable between those with and without NS5A RASs (16).

The efficacy of elbasvir–grazoprevir in treatment-naïve patients with genotype 1a infection is influenced by NS5A RASs, but not it is not influenced in patients with genotype 1b infection (17). For this reason, many guideline documents recommend RAS testing before initiating treatment with this regimen. If present, treatment prolonged to 16 weeks with the addition of ribavirin is suggested to maximize the likelihood of SVR. Only 25% of cirrhotic genotype 3 patients with Y93H at baseline achieved SVR after treatment with daclatasvir–sofosbuvir (6). Most guidelines endorse baseline resistance testing for genotype 3 cirrhotic patients before treatment with daclatasvir–sofosbuvir and recommend adding ribavirin if Y93H is detected.

Virions with NS5A RASs are replicatively fit and were present at 96 weeks posttreatment in 86% of treatment relapsers (18). NS5A RASs are persistent and clearly influence SVR outcomes depending on specific patient characteristics, including genotype, fibrosis stage, and HCV treatment history. In more complex patients (eg, treatment-experienced patients with genotype 1a cirrhosis), RAS testing is advised with currently used NS5A–NS5B and NS5A–NS3/NS4a regimens.

NS3/4A resistance

NS3/4A serves as the viral protease. As many as half of patients with genotype 1a possess the Q80K NS3/4A RAS, which influences the efficacy of simeprevir, a protease inhibitor now rarely used in clinical practice (19). With the exception of Q80K, baseline NS3/4A RAS prevalence is 0.1%–3.1% in genotype 1 (10) Other therapeutically relevant NS3/4A RASs include H58, D82, S139, R155, and D168. Aside from Q80K on select protease inhibitors, the impact of baseline NS3/4A RASs is minimal. Baseline NS3/4A RASs did not affect SVR in genotype 1 patients treated with elbasvir–grazoprevir, a current first-line regimen (17). Sarrazin et al. reported findings of NS3/4A RASs at baseline in 164 of 467 patients, of whom 11% were treatment experienced and half were protease inhibitor treatment experienced. Despite this, the overall SVR was 95% in both subgroups (8).

NS3/4A RASs have low replicative fitness and become undetectable by population sequencing within a median of 9–13 months (20). Among treatment-experienced patients, NS3/4A RASs were detected at 24 weeks in 46% of patients and at 48 weeks in 9% (6). In summary, NS3/4A RASs should have little impact on treatment selection because they typically do not influence the outcome of treatment with current first-line regimens.

Newer DAA regimens, ribavirin, and RAS management

The three-DAA class regimen of sofosbuvir–velpatasvir–voxlipravir was evaluated in POLARIS-1. A treatment-experienced (including ledipasvir, daclatasvir and ombitasvir) patient population with NS5A was targeted. SVR12 was achieved in 96% (253 of 263) of study participants. All 9 participants with baseline single-class NS3/4A RASs achieved SVR, and 120 (96.8%) with only NS5A-class RASs achieved SVR. The 7 participants with virologic failure were cirrhotic, and 3 had Y93N/Y/H at baseline (21). These results suggest that the presence of RASs, including multiclass combinations in DAA treatment-experienced patients, can be overcome by triple-class combination regimens.

Glecaprevir–pibrentasvir in combination was recently approved by the US Food and Drug Administration and Health Canada (22). Glecaprevir maintains activity against NS3/4A RASs, including D168, which confers resistance to paritepravir and grazoprevir (6). In treatment-naïve populations evaluated in the ENDURANCE and EXPEDITION trials, baseline RASs did not appear to confer any negative impact on SVR (23, 24). In the MAGELLAN-1 study, 50 DAA treatment-experienced participants with genotype 1 were evaluated. Half had baseline NS5A RASs and 8 had Y93 RAS. SVR12 was achieved in 100%, 91%, and 93% of those with baseline NS3/4A, NS5A, and both NS3/NA and NS5A RASs, respectively (25). In part 2 of the MAGELLAN-1 study, additional patients with previous NS3/4A inhibitor or NS5A inhibitor experience received 12 weeks of glecaprevir–pibrentasvir. The overall SVR12 rate was 89% (39/44), but it was only 83% (20/24) in those with NS5A baseline RASs. Extension of

treatment to 16 weeks with glecaprevir–pibrentasvir achieved an overall SVR12 rate of 91% (43/47) and a rate of 96% (22/23) in those with baseline NS5A RASs (26). These results suggest that longer duration therapy may at least partially overcome the issue of baseline RASs in the treatment-experienced population.

Taken together, these data suggest that baseline RASs will have diminished, but not entirely eliminated, relevance in most treatment candidates, including DAA treatment-experienced individuals.

Ribavirin continues to play a role in managing some scenarios involving RASs. As described earlier, the addition of ribavirin to elbasvir–grazoprevir maximizes SVR outcomes in treatment-naïve, genotype 1a–infected patients with key NS5A RASs (17). The impact of ribavirin on SVR is more pronounced in patients receiving salvage treatment and in those with decompensated liver disease (see "HCV Treatment in Decompensated Cirrhosis" section). Of nine HIV–HCV coinfected study participants who relapsed with NS5A RASs after a 12-week course of ledipasvir–sofosbuvir, eight achieved SVR after retreatment with the same DAAs plus ribavirin for 24 weeks (27).

Using a similar approach, patients who failed 12 weeks of treatment with sofosbuvir–velpatasvir were retreated with the same regimen plus ribavirin for 24 weeks and achieved an overall 91% SVR rate (28). In both of these salvage studies, SVR rates were higher than what was achieved with 24 weeks of ledipasvir–sofosbuvir without ribavirin (14). Treatment-experienced genotype 3–infected patients with key NS5A RASs remain more refractory to cure despite the inclusion of ribavirin because this subgroup had a lower SVR rate (76%) (28).

RAS testing: practice recommendations

Baseline RAS testing is currently recommended before use of elbasvir–grazoprevir in genotype 1a patients, with daclatasvir–sofosbuvir and velpatasvir–sofosbuvir treatment in cirrhotic genotype 3 patients, and in salvage retreatment of treatment-experienced cirrhotic patients with NS5A (29). All treatment-experienced patients, especially those with advanced fibrosis, would benefit from baseline resistance testing because the risk of virologic failure with a suboptimal regimen clearly has negative consequences for subsequent retreatment efforts. In these populations, baseline resistance testing provides an additional tool for selection of the most optimal DAA regimen and for informing the decision for or against the inclusion of ribavirin.

Resistance testing has not been widely implemented in Canadian clinical practice. We speculate that this is a consequence of insufficient real-world data on outcomes to convince treaters of the value of RAS testing, confusing and conflicting representation of the RAS-related data in the literature, lack of expertise among low-volume treaters, perceived slow turnaround times, challenges in representation and interpretability of RAS reports, and logistical issues related to specimen transfer to the limited number of qualified laboratories with the competence and capacity to conduct RAS assessments.

HCV TREATMENT IN DECOMPENSATED CIRRHOSIS

Patients with HCV infection and decompensated cirrhosis represent a special challenge to clinicians. Concerns related to HCV treatment in this population include medication intolerance, drug–drug interactions, and precipitation of hepatic deterioration. Despite the risks of therapy, achieving SVR in this population is associated with a mortality benefit as well as a reduced risk of HCC and need for orthotopic liver transplant (30, 31) Historically, interferon-based therapies have generally been contraindicated and poorly tolerated if initiated, and they achieved very low rates of cure in this population. In dramatic contrast, DAA regimens demonstrate great promise in this population (16). Although SVR rates are lower than in those with compensated cirrhosis, they are still high, ranging from 80% to 90%. The reasons for this diminished success rate remain unclear. Contributing factors include portosystemic shunting with reduced hepatic medication exposure; the presence of poorly perfused regions within the cirrhotic liver, which may act as viral reservoirs leading to posttreatment relapse; and innate immune dysfunction associated with cirrhosis (32). To this final point, a robust immune response is important to clear virus, even with non–immune-modulating DAA treatment.

There is debate as to whether HCV should be treated in the pre- or posttransplant period. Although achieving SVR has been associated with improved MELD and Child-Turcotte-Pugh (CTP) scores, the long-term outcome for those with clinically significant portal hypertension remains unclear. Treating before transplant may improve

individuals' MELD score to a point at which they move further down the transplant waiting list or are removed altogether even though their overall health status remains poor (33). Conversely, electing to withhold HCV treatment pretransplant ensures that an individual's underlying liver condition will continue to deteriorate. Furthermore, not all candidates proceed to successful transplant, and many will die on the waiting list having never received HCV treatment.

Treatment recommendations for those with decompensated cirrhosis are influenced by HCV genotype, the severity of hepatic decompensation, past DAA treatment exposure, and whether the patient is eligible to receive ribavirin. Ribavirin-associated anemia is often challenging to manage in the context of cirrhosis. There is an increased risk of rapid-onset, severe anemia in those with renal dysfunction, which is often found concurrent with decompensated liver disease. No antiviral regimen containing an NS3/4A protease inhibitor has yet been approved for the treatment of HCV in patients with decompensated cirrhosis because drug levels of this class of medications are considerably increased. Also, safety and efficacy data are lacking. The initial product monograph for paritaprevir–ombitasvir–dasabuvir did not recommend its use in decompensated liver disease. The label was subsequently changed to contraindicate its use in decompensated cirrhosis after safety reports emerged that suggested higher rates of serious liver injury in patients with advanced liver disease (34).

Genotypes 1, 4, 5, and 6 HCV antiviral treatment

Currently recommended regimens for patients with decompensated cirrhosis with genotype 1, 4, 5, or 6 infection include ledipasvir–sofosbuvir and sofosbuvir–velpatasvir plus weight-based ribavirin for 12 weeks. If patients are deemed ineligible to receive ribavirin, then 24 weeks of sofosbuvir–velpatasvir is recommended as the preferred therapy. Low initial doses of ribavirin (600 mg daily) are recommended for patients with CTP class C. Daclatasvir–sofosbuvir plus weight-based ribavirin is recommended for genotype 1 or 4 infection.

In the SOLAR-1 study, 108 patients with HCV genotype 1 and 4 and decompensated cirrhosis were randomized to receive ledipasvir–sofosbuvir for 12 or 24 weeks with low-dose ribavirin (initial dose of 600 mg, increased as tolerated) (35). Excluding patients who underwent transplantation during the study, the SVR rate in CTP class B participants was 87% for those who received 12 weeks of treatment and 89% for those who received 24 weeks of treatment. For those with CTP class C, the SVR rate was 86% with 12 weeks of treatment and 87% with 24 weeks of treatment. The SOLAR-2 study achieved similar results: SVR rates were 87% in those who received 12 weeks of therapy and 89% in those who received 24 weeks of therapy. No deaths were attributable to antiviral therapy in either SOLAR study (36). Data on the use of ledipasvir–sofosbuvir in genotype 5 and 6 infection are very limited but suggest reasonable safety and efficacy.

In the ASTRAL-4 study, 267 participants with multiple HCV genotypes and decompensated cirrhosis were randomized in a 1:1:1 ratio to sofosbuvir–velpatasvir with or without weight-based ribavirin for 12 weeks or to sofosbuvir–velpatasvir for 24 weeks (16). Genotype 1 participants achieved SVR rates of 88% with sofosbuvir–velpatasvir for 12 weeks, 96% when treated with sofosbuvir–velpatasvir with ribavirin for 12 weeks, and 86% when treated with sofosbuvir–velpatasvir for 24 weeks. Similar benefits of ribavirin were noted in treatment recipients with genotype 3 infection.

ALLY-1 was an open-label study that targeted those with advanced cirrhosis (CTP classes B and C) and those with recurrent HCV infection after orthotopic liver transplant (37). All participants received 12 weeks of daclatasvir–sofosbuvir plus low-dose ribavirin (600 mg daily). The overall SVR12 rate was 76% in patients with genotype 1a infection and 100% in patients with genotype 1b.

Genotypes 2 and 3

Currently recommended regimens for patients with decompensated cirrhosis and genotype 2 or 3 infection include sofosbuvir–velpatasvir with weight-based ribavirin for 12 weeks or daclatasvir–sofosbuvir plus low initial-dose ribavirin (600 mg daily, increased as tolerated).

In ASTRAL-4, genotype 2 participants with CTP class B cirrhosis achieved 100% SVR with sofosbuvir–velpatasvir for 12 weeks with and without ribavirin and 75% SVR with sofosbuvir–velpatasvir for 24 weeks (16). In 39 genotype 3 participants with CTP class B cirrhosis, the SVR rate was only 50% with either 12 or 24 weeks of sofosbuvir–velpatasvir without ribavirin. This rate increased to 85% among those receiving 12 weeks of sofosbuvir–velpatasvir with ribavirin. In ALLY-1,

described previously, those with advanced cirrhosis and HCV genotype 3 achieved 83% SVR (37).

Patients with decompensated cirrhosis who have failed previous DAA therapy

Data are lacking to inform clear recommendations on how best to treat individuals with decompensated cirrhosis who have failed previous therapy with either sofosbuvir- or NS5A-containing regimens. Because protease inhibitors are contraindicated, salvage regimens will likely require prolonged treatment duration with an NS5B polymerase inhibitor plus a next-generation NS5A inhibitor, with or without ribavirin in those without contraindication. Further study is required in this specific area. Antiviral treatment of HCV patients with decompensated cirrhosis should be directed by experienced, expert clinicians to maximize SVR outcomes. This strategy will also minimize the proportion of patients who require subsequent salvage retreatment.

HCC RISK AFTER HCV CURE

Primary liver cancer is the fifth most common cancer worldwide (38), and it is one of the fastest growing causes of cancer-related deaths in the United States (39). Chronic HCV infection, through the development of established cirrhosis, is a major risk factor for the development of HCC (40). In patients with HCV cirrhosis, the annual incidence of HCC is 1%–8% (39), and HCC is more likely to occur in older men, individuals coinfected with HIV or hepatitis B, those with diabetes, those who are obese, and those who consume alcohol heavily (38, 41–44). Successful treatment of chronic HCV infection using interferon-based therapy has been shown to reduce liver-related complications and mortality (30, 45), including incidence of HCC, in observational, nonrandomized clinical trials (46). A prospective study of more than 1,300 patients with compensated HCV-related cirrhosis demonstrated a five-year cumulative incidence of HCC of 6.7% among subjects who achieved SVR, versus 18.5% in those who did not (hazard ratio [HR] 0.28; 95% CI 0.19 to 0.43; $P < .001$) (47).

Recently, several groups have reported preliminary results regarding HCC risk after treatment with interferon-free DAA HCV therapies. Among patients with compensated and decompensated cirrhosis who achieved SVR after DAA therapy, de novo HCC was detected in 5.0%–7.6% over a 24-week posttreatment follow-up period (48, 49). No significant difference was found in the incidence of de novo HCC between decompensated cirrhotic patients treated with DAAs and untreated patients (48, 50). A systematic review and meta-analysis compared rates of de novo HCC occurrence in cirrhotic patients who achieved SVR after treatment with DAAs versus interferon-based therapy. This analysis included 17 studies with 11,523 patients. DAA therapy was not associated with a higher occurrence of HCC than interferon-based therapy, after adjusting for study follow-up and age (relative risk [RR] 0.68; 95% CI 0.18 to 2.55; $P = .55$) (51). Although limited in terms of follow-up, the preliminary evidence indicates that DAA therapy in cirrhotic patients is not associated with a clinically significant difference in the incidence of de novo HCC, as compared with interferon-based therapy or no treatment at all. In fact, emerging cohort data suggest that the HCC risk is markedly diminished in DAA recipients who achieve SVR (0.90 vs 3.45 HCC/100 person-years; adjusted HR 0.28; 95% CI 0.22 to 0.36) (52).

In contrast, the emerging data on HCC RR post-DAA treatment has been contradictory and highly controversial. Two retrospective observational studies described higher rates of early, more aggressive HCC recurrence in treated patients with HCV cirrhosis and a previous history of early, localized, treated HCC. The reported incidence rates for these two studies were 28% and 29%, respectively, over the median follow-up periods of six months (49, 53). These studies were small ($N = 58$) with short-term follow-up and reported rates that were much higher than those in another large retrospective cohort study by the ANRS Collaborative Study Group on Hepatocellular Carcinoma (54). This group reported a six-month RR of 10.6% in 189 cirrhotic patients treated with DAAs, compared with an RR of 18.7% in 267 untreated patients (54). A subsequent prospective multicenter study in 143 patients with longer follow-up reported 6-, 12-, and 18-month HCC RRs of 12%, 27%, and 29%, respectively (55). A systematic review and meta-analysis by Waziry et al. (51) compared rates of HCC recurrence in cirrhotic patients who achieved SVR after treatment with DAAs (10 studies; $N = 867$) versus interferon-based therapy (7 studies; $N = 1,485$). This review demonstrated no increased rate of HCC recurrence with DAAs (RR 0.62; 95% CI 0.11 to 3.45; $P = .56$). Discrepancies in the results between these retrospective, uncontrolled studies may be attributed to

differences in inclusion criteria, methods and timing of imaging during follow-up, time lag between HCC cure and start of DAA therapy, and statistical analysis methods, as well as differences in baseline tumour size, HCC treatment, and tumour biology (53, 56, 57).

Several plausible mechanisms by which DAA therapy may be associated with an increased risk of HCC recurrence in cirrhotic patients have been proposed. Latency competent cancer cells may disseminate from a primary tumour and maintain tumour-initiating potential (58). The rapid virologic clearance achieved with DAA therapy is hypothesized to lead to disruption of immune system cancer surveillance, thus promoting metastatic cell survival and growth (59). Jühling et al. reported persistent epigenetic and transcriptional changes in chronic HCV infection that persist post-DAA treatment (60). These transcriptional changes were associated with a risk for developing HCC as compared with uninfected controls. These mechanisms are discussed in more details in the accompanying review by Mazouz et al. (cross reference to come).

Currently, there are no guidelines on the management of HCV in the context of HCC. It is generally held that until further data emerge, patients should continue to be offered DAA therapy given the proven benefits of HCV treatment for liver-specific events and overall mortality. Although whether DAA therapy is associated with earlier, more aggressive HCC recurrence remains controversial, it is clear that the risk of both de novo and recurrent HCC persists after SVR. As such, screening for HCC should continue in all cirrhotic patients after HCV treatment. Future research should focus on clinical, biochemical, and biologic factors that may identify the patients most at risk of HCC post-HCV cure as well as identify those cured patients who are at no risk and therefore do not require indefinite screening.

DISCUSSION

In HCV care, there is currently tension regarding striking the right balance between complexity and capacity. Viral resistance testing increases complexity of care but may improve outcomes for a small number of individuals. Requirements for universal resistance testing could potentially diminish capacity because fewer nonspecialists would be comfortable providing HCV treatment. However, ignoring the negative consequences of viral resistance on DAA outcomes could prove costly to some patient populations. We propose an approach that focuses RAS testing primarily on those with cirrhosis and those with prior DAA exposure. The evidence is most robust for genotypes 1a and 3. The need for testing with other genotypes is questionable. In our opinion, this strikes a reasonable balance between the complexity of HCV care and facilitating increased capacity to ensure that patients of all backgrounds have an opportunity to receive highly effective curative therapy. Continued postapproval evaluation of baseline RASs on treatment outcomes is important to confirm the findings of clinical trial analyses.

Irrespective of HCV antiviral treatment outcome, HCC screening in patients with cirrhosis is mandatory but often omitted. A primary focus of HCV care providers should be to ensure that serial monitoring according to guideline criteria occurs given the high risk of HCC in post-SVR patients with cirrhosis compared with patients without cirrhosis (1.82 vs 0.34/100 person-years; adjusted HR 4.73; 95% CI 3.34 to 6.68) (52). Little convincing evidence supports concerns regarding increased HCC risk in DAA recipients without prior HCC history. The risk for recurrent HCC remains unclear in the context of DAA exposure. Well-designed evaluations with careful posttreatment follow-up would help address this concern. It seems counterproductive to withhold potentially curative DAA therapy from this population given the likelihood of long-term benefits, including reduced risk for liver failure and need for transplantation.

Management of HCV patients with decompensated cirrhosis remains contentious given the uncertainty regarding the impact on key outcomes, including survival and the potential negative impact on transplant qualification. We suggest that all patients with decompensated cirrhosis be evaluated for treatment in an expert setting. If a protease inhibitor–free regimen with a predicted high likelihood of safety and virologic success is available, then treatment should be pursued. Successful cure will likely reduce HCC risk, arrest liver disease progression, and potentially reduce the need for liver transplantation.

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