POSITION PAPER

HCV Council – critical appraisal of data: recommendations for clinical practice in a rapidly evolving therapeutic landscape

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Abstract

Background & Aims: HCV Council 2014, like its predecessor HCV Council 2011, assembled leading clinicians and researchers in the field of hepatitis C to critically evaluate current data regarding best practices for managing patients with chronic hepatitis C virus (HCV). *Methods:* Clinical practice statements were developed that reflect the areas of potential controversy with high clinical impact. Faculty members were responsible for reviewing the literature to support or reject these statements. After a review and comprehensive discussion of the data, the HCV Council faculty voted on the nature of the evidence and the level of support for each statement. *Results:* The results of the detailed analysis with expert opinion are summarized in this article. *Conclusion:* Numerous questions regarding optimal management of certain populations and clinical scenarios remain unanswered. The discussion in the article provides a summary of evidenced-based expert opinion that may help guide clinicians as additional information is developed.

The therapeutic landscape for the treatment of chronic hepatitis C virus (HCV) infection has been rapidly evolving since the approval of the first direct-acting antiviral agents (DAAs), telaprevir and boceprevir, in 2011. In 2013, sofosbuvir (SOF) became the first nucleoside NS5B polymerase inhibitor to be approved and offered a potent DAA with a

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Key points

• HCV Council assembled leading clinicians and researchers in the field of hepatitis C to critically evaluate current data regarding best practices for managing patients with chronic hepatitis C virus.
• Clinical practice statements were developed in the field of hepatitis C that reflect areas of potential controversy with high clinical impact.
• After a review and comprehensive discussion of the data, the HCV Council faculty voted on the nature of the evidence and the level of support for each statement.
• The discussion in the article provides a summary of evidenced-based expert opinion that may help guide clinicians as additional information is developed.

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high genetic-barrier that led the transformation of HCV treatment to all-oral regimens. Over the last 2 years, the US Food and Drug Administration (FDA) approved four all-oral regimens: (i) SOF plus ribavirin (RBV); (ii) SOF plus simeprevir (SMV), an NS3 protease inhibitor (PI); (iii) the fixed-dose combination of SOF with the NS5A inhibitor ledipasvir (LDV/SOF) (1); and (iv) a 3 DAA (3D) ± RBV regimen [paritaprevir (NS3/4A PI) boosted with ritonavir, ombitasvir (NS5A inhibitor) and dasabuvir (non-nucleoside NS5B polymerase inhibitor)]. The Phase 3 clinical trials provided guidance for the FDA labelling and informed clinicians about optimizing therapy with these drugs. However, not all patient scenarios can be anticipated, and often a more nuanced interpretation of Phase 3 trial results, coupled with rapidly evolving data from ongoing Phase 2 clinical trials, will also provide important information to guide practice. In 2013, the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA)/International Antiviral Society USA (IAS–USA) formed a task force to provide ongoing treatment recommendations incorporating the most up-to-date clinical data and to serve as an additional resource for clinicians who manage patients with HCV (2).

Complementing this effort, the HCV Council 2014, like its predecessor HCV Council 2011 (3), assembled leading clinicians and researchers in the field of hepatitis C in July 2014, to critically evaluate current data regarding best practices for managing patients with chronic HCV. The methodology of the HCV Council has been described previously (3). Clinical practice statements (Table 1) were developed that reflect areas of potential controversy with high clinical impact. Faculty members were responsible for reviewing the literature to support or reject these statements. After a review and comprehensive discussion of the data, the HCV Council faculty voted on the nature of the evidence and the level of support for each statement (Table 2). Voting results were based on data available in July 2014. Additional data available from July 2014 to August 2015 have been added to supplement the findings. The results of the detailed analysis with expert opinion are summarized below.

Statement 1: patients with cirrhosis have lower rates of sustained virological response compared to non-cirrhotic patients and, thus, treatment efficacy remains suboptimal for this population

Rationale and definition of statement

Patients with advanced fibrosis and cirrhosis are most in need of HCV therapy, as successful therapy has been shown to decrease liver-related mortality (4). Interferon (IFN)-based antiviral treatment in these patients had been challenging because of patient tolerance, the risk of serious adverse events, and hyporesponsiveness to therapy. Bridging fibrosis and cirrhosis have traditionally been negative predictors of HCV treatment outcome.

Summary of evidence

The disparity in sustained virological response (SVR) between cirrhotic and non-cirrhotic patients was evident during treatment with peginterferon (PEG-IFN) and RBV and was not mitigated by the addition of first generation PIs (5, 6). The advent of all-oral DAA regimens considerably altered the treatment landscape by achieving superior tolerability as well as increased SVR rates despite truncated treatment durations (Table 3). The combination of LDV/SOF with or without RBV given for 12 or 24 weeks, has been evaluated in subsets of genotype 1 patients with cirrhosis in both treatment-naïve and treatment-experienced patients (7, 8). The SVR in treatment-naïve patients ranged from 94 to 100% (7). In cirrhotic patients who had failed therapy, including a PI, this regimen achieved an SVR of 82 to 100% with higher SVR rates noted with the 24-week regimen, regardless of the use of RBV (8). Further studies that were enriched with cirrhotic patients who had failed prior PIs show that 12 weeks of LDV/SOF with RBV has equivalent efficacy to 24 weeks of LDV/SOF (9, 10).

In a trial exclusively for patients with cirrhosis who were treatment-naïve or prior PEG-IFN/RBV failures, the 3D regimen [paritaprevir/r (ritonavir boosted PI), ombitasvir (an NS5A inhibitor) and dasabuvir (a non-nucleoside inhibitor)], with RBV for 12 or 24 weeks achieved high SVR rates of 92–96% respectively. Prior null responders and those with genotype 1a had a slightly lower numerical response of 87 and 89%, respectively, with a 12-week regimen, while the 24-week regimen achieved an SVR of 95 and 94% respectively (11). The presence of cirrhosis also lowers efficacy in non-genotype 1 patients, as highlighted below.

Discussion

The panel agreed that all-oral therapy for patients with HCV and cirrhosis has been a major advancement. Although many of the traditional treatment obstacles

Table 1. HCV Council statements for evaluation

Workshop I: clinical management and treatment strategies: utilizing the new SOC in HCV
Patients with cirrhosis have lower rates of SVR compared to non-cirrhotic patients and, thus, treatment efficacy remains suboptimal for this population
Patients with easier-to-treat characteristics can be defined and treated for shorter duration
Genotype 1a and 1b will be treated with different regimens
The preferred approach to treatment for all subgroups of patients with genotype 3 is sofosbuvir and ribavirin for 24 weeks
The preferred approach to treatment for all subgroups of patients with genotype 2 is sofosbuvir and ribavirin for 12 weeks. *See the supplemental section for review of this statement*
Workshop II: a patient-oriented approach: addressing treatment challenges
Due to the high costs of medications, only patients with advanced fibrosis should be offered treatment with all-oral regimens for HCV
Given the high-efficacy and low-viral breakthrough rates, on-treatment viral load monitoring is no longer required
Patients with decompensated cirrhosis should be treated with an all-oral regimen for HCV to improve survival
Patients co-infected with HIV-HCV should no longer be considered a 'special population'. *See the supplemental section for review of this statement*
Treatment of hepatitis C should remain within the domain of hepatologists, gastroenterologists and ID physicians. *See the supplemental section for review of this statement*

Table 2. Council voting schemes

Category	Nature of evidence
I	Evidence obtained from at least 1 well-designed, randomized, controlled trial
II	Evidence obtained from well-designed cohort or case-controlled studies
III	Evidence obtained from case series, case reports, or flawed clinical trials
IV	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
V	Insufficient evidence to form an opinion
	Level of support for each statement
1	Accept statement completely
2	Accept statement with some reservations
3	Accept statement with major reservations
4	Reject statement with reservations
5	Reject statement completely

have been overcome and patients with cirrhosis can expect high SVR rates, challenges remain. Subsets of patients with cirrhosis, particularly those with prior treatment failure, will require a longer duration of therapy or other modifications, such as the addition of RBV, to maximize treatment response. Benefit in patients with decompensated cirrhosis is under active investigation.

Statement 2: patients with easier-to-treat characteristics can be defined and treated for shorter duration

Rationale and definition of statement

From the outset of HCV antiviral therapy, host and viral factors predicted an ability to shorten therapy without a compromise in efficacy. Low baseline viral levels, the presence of *IL28B* CC, and rapid on-treatment virological decay represented parameters that allowed for SVR with shorter durations of IFN-based regimens (12–14). Early-stage liver disease, likewise, reflected a cohort that was 'easier-to-treat'. Entering into the all-oral DAA era where cost and compliance will drive therapy, there have been attempts made to shorten treatment durations further.

Summary of evidence

In the ION-3 program, two 8-week regimens of LDV/SOF were compared with one 12-week regimen among non-cirrhotic genotype 1 patients, and the SVR rates were similar in the shorter duration arms (15). These results support the notion that 'easier-to-treat' non-cirrhotic patients could shorten therapy.

Nevertheless, there were numerically more relapsers in the 8-week arms, leading to concern that using a shorter duration for all non-cirrhotic genotype 1 patients may come with unacceptable relapse rates and without a defined salvage regimen (15). Post-hoc analyses suggested that treatment naïve, non-cirrhotic patients with HCV RNA levels <6 million IU did well with 8 weeks of LDV/SOF and that relapse rates were comparable to 12-week regimens, leading to the FDA recommendation that 8 weeks of treatment can be considered in this subset. Additional post-hoc analysis also found that gender and *IL28B* genotype were associated with favourable response. There was a numeric but not statistically significant difference in race, age and subgenotype (16). The phase 2b study, AVIATOR, also demonstrated a higher relapse rate in treatment-naïve non-cirrhotic patients treated with 8 weeks of 3D (88% SVR24 compared to 96% with 12 weeks) (17). In addition, in the 3D development program, to optimize prior null responders to PEG-IFN/RBV who had cirrhosis and genotype 1a, a longer, 24-week course offered

Table 3. Sustained virological response between cirrhotic and non-cirrhotic genotype 1 patients

Treatment-naïve	Non-cirrhotics	Cirrhotics	
Ledipasvir and sofosbuvir	12 Weeks 99% (176/177)	12 Weeks 94% (32/34)	
Paritaprevir/r-ombitasvir + dasabuvir + RBV	12 Weeks 96.2% (455/473)	12 Weeks 94.2% (81/86)	24 Weeks 94.6% (70/74)

	Non-cirrhotics		Cirrhotics	
Treatment experienced	12 Weeks	24 Weeks	12 Weeks	24 Weeks
Ledipasvir and sofosbuvir	95% (83/87)	99% (85/86)	86% (19/22)	100% (22/22)
Paritaprevir/r-ombitasvir + dasabuvir + RBV	96.3% (286/297)	–	Relapse 96.6% (28/29)	100% (23/23)
			Partial response 94.4% (17/18)	100% (13/13)
			Null response 86.7% (65/75)	95.2% (59/62)

Treatment-naïve or prior null responders	Non-cirrhotics (F0–3)		Cirrhotics (F4)	
Simeprevir + sofosbuvir	12 weeks 95% (20/21)	24 weeks 95% (20/21)	12 weeks 86% (6/7)	24 weeks 100% (10/10)

Ledipasvir and sofosbuvir (LDV/SOF) (1), Afdhal *et al.* (7), Afdhal *et al.* (8), Poordad *et al.* (11), Feld *et al.* (50), Zeuzem *et al.* (53).
Simeprevir Prescribing Information. Janssen Therapeutics, Division of Janssen Products, Revised: November 2014.

higher cure rates, as compared to the 12-week group (11).

Discussion

Most Phase 3 trials of all-oral DAA therapy have focused on lengthening therapy for more 'difficult-to-treat' populations vs shortening therapy for those considered 'easy-to-treat'. While evidence shows that certain patients with mild disease can achieve high rates of SVR with shorter duration of therapy, others, such as those with cirrhosis, benefit from a longer duration of treatment. Definitively excluding cirrhosis may be challenging in the real world. Misclassifying patients with advanced fibrosis as 'non-cirrhotic' and mandating only 8 weeks of therapy could lead to higher than expected relapse rates. Thus, although the majority of the Council members agreed that the statement was supported by a well-designed randomized controlled trial, considerable controversy existed regarding whether such a blanket statement could translate into clinical practice in 2015.

Statement 3: genotype 1a and 1b will be treated with different regimens

Rationale and definition of statement

Higher rates of SVR with HCV genotype 1b compared to genotype 1a were first recognized with PEG-IFN/RBV (18). This trend was attenuated with the first DAAs, telaprevir and boceprevir (19, 20). However, the Phase 3 registration trial of simeprevir-based triple therapy (SMV/PEG-IFN/RBV) demonstrated substantially higher rates of SVR in genotype 1b compared to genotype 1a as a result of a pre-existing resistance mutation Q80K, which occurs almost exclusively in HCV genotype 1a (21). The impact of subtype was less apparent with SOF-based triple therapy. Pooled data from the Phase 3 NEUTRINO (22) and Phase 2 ATOMIC trials (23) suggested an SVR advantage in genotype 1a (92%) over genotype 1b (82%), although the latter group also had disproportionately higher frequency of negative response characteristics.

Summary of evidence

The combination of drugs or duration of therapy may vary depending on HCV subtype. The PEARL-III and -IV studies nicely demonstrated that the addition of RBV to the 12-week 3D regimen does not enhance the efficacy in genotype 1b (SVR 99.5% with RBV and 99.0% without) (24). However, SVR rates were significantly lower in the genotype 1a subjects that did not receive RBV (97% with compared to 90.2% without) (Fig. 1) (24). TURQUOISE-II found that a 24-week regimen was optimal for genotype 1a patients with cirrhosis with prior null response: SVR rates of 88.6% with 12 weeks of treatment compared to 94.2% when extended to 24 weeks (11). This improvement in efficacy was not seen in any other subgroup including those genotype 1b patients with cirrhosis and prior null response (SVR rates of 98.5% with 12 weeks compared to 100% with 24 weeks) (11). Lastly, the need to tailor a regimen by subtype will depend on the agents utilized. The Phase 3 ION-1, ION-2 and ION-3 studies showed no difference in efficacy between genotype 1 subtypes with or without RBV for durations of 12 or 24 weeks, even when shortening therapy to 8 weeks in a non-cirrhotic
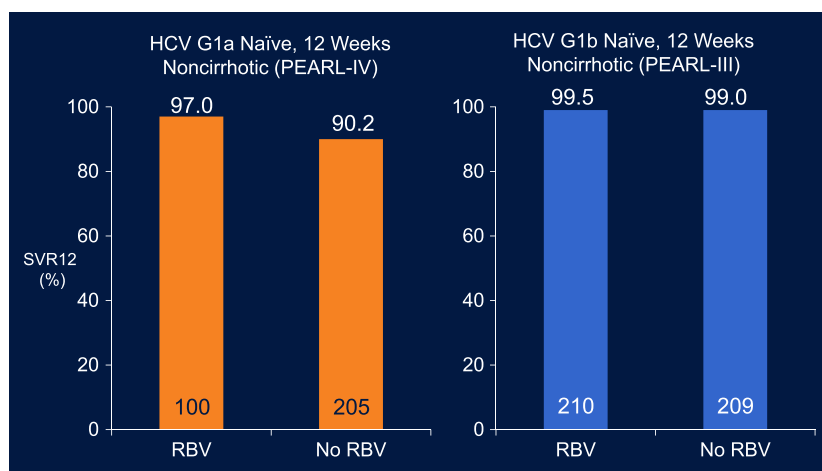
Fig. 1. 3D (paritaprevir/r-ombitasvir + dasabuvir) ± ribavirin (RBV). Ferenci *et al.* (24).

treatment-naïve cohort (7, 8, 15). However, baseline testing NS5A resistance-associated variants (RAVs) may be necessary in a subset of genotype 1a patients being considered for therapy with grazoprevir-elbasvir, as the presence of a baseline RAV lowered efficacy in the 1a subgenotype but did not appear to affect outcomes in genotype 1b patients (25).

Discussion

Although relatively simple treatment algorithms will apply for most populations, the agents and length of therapy will be directed by HCV subtype and disease severity. This is reflected in the recently released AASLD-IDSA guidance document (2). As supported by the data above, subtype did not impact treatment recommendations when using combination LDV/SOF; however, the addition of RBV to 3D was advised in all individuals with G1a and, as well as treatment extension to 24 weeks for G1a patients with cirrhosis irrespective of prior treatment response (2). Other modifications such as baseline RAV testing also may be needed to optimize therapy based on subgenotype.

Statement 4: the preferred approach to treatment for all subgroups of patients with genotype 2 is SOF and RBV for 12 weeks

Rationale and definition of statement

Although genotype 2 is traditionally seen as the most treatment-responsive type of HCV to cure, efficacy is not 100% for all populations and alternative regimens may be considered in special circumstances. The AASLD-IDSA guidance recommends daily SOF (400 mg) and weight-based RBV [1000 mg (<75 kg) to 1200 mg (≥75 kg)] for 12 weeks for treatment-naive or treatment-experienced patients with HCV genotype 2 infection, with the additional caveat that 16 weeks of therapy may be more beneficial for patients with cirrhosis based on the results of the FUSION trial (2). The guidelines further suggested that an alternative regimen for PEG-IFN/RBV non-responder patients with HCV genotype 2 infection who are eligible to receive IFN is retreatment with daily SOF (400 mg) and weight-based RBV [1000 mg (<75 kg) to 1200 mg (≥75 kg)] plus weekly PEG-IFN for 12 weeks, based on the results of a small Phase 2 trial called LONESTAR (2, 26).

Summary of evidence

Studies have demonstrated that genotype 2 patients have high SVR rates with SOF + RBV for 12 weeks but that cirrhosis and prior treatment response still affect efficacy (27). There are additional meta-analysis data to indicate that one needs at least five of six negative predictors in genotype 2 to see a significant decrease in the efficacy of a SOF/RBV regimen (prior treatment, gender, weight, *IL28B*, cirrhosis and HCV RNA levels), so most patients will likely qualify for the 12 weeks of SOF + RBV treatment (28). Treatment with daclatasvir (DCV) + SOF for 24 weeks showed a 92% SVR in genotype 2 patients, although the regimen was not tested in patients with cirrhosis and was given for 24 rather than 12 weeks (29). DCV + SOF did show high efficacy in G2 HCV-HIV co-infected patients treated for 12 weeks, making this a viable alternative for individuals who cannot tolerate RBV (30). The recently presented BOSON study also demonstrated high SVR12 rates in genotype 2 treatment-experienced cirrhotics with 16 weeks of SOF/RBV (87%), SOF/RBV for 24 weeks (100%) and PEG-IFN/RBV + SOF for 12 weeks (94%) (31).

Discussion

The opinion of the panel was split regarding the statement with fair-to-poor evidence of support vs rejecting the statement, mostly based on concerns about the efficacy in prior treatment-experienced patients with cirrhosis. All Council members agreed that there was insufficient evidence to support the statement fully, likely because of doubts about cirrhotic non-responder efficacy and the limited data that supports other therapies available to this population. Nevertheless, in the current therapeutic landscape, a 12-week regimen with SOF/RBV remains the most efficacious for the majority of patients with genotype 2.

Statement 5: the preferred approach to treatment for all subgroups of patients with genotype 3 is SOF and RBV for 24 weeks

Rationale and definition of statement

Hepatitis C virus G3 is associated with an increased risk of cirrhosis and liver cancer. As a result, it has been identified as a population prioritized for therapy. Unfortunately, available treatment alternatives may not offer high rates of viral eradication. Recommended IFN-free regimens for patients with HCV genotype 3 infection include SOF/RBV administered for 24 weeks and SOF/DCV (2).

Summary of evidence

The first reported Phase 3 trials (FISSION, POSITRON and FUSION) predominantly evaluated 12-week treatment durations and showed substantially lower SVR rates in genotype 3 compared with genotype 2 patients (22, 27). Treatment-experienced patients with genotype 3 and cirrhosis were at the greatest disadvantage. The FUSION study, demonstrating a marked increment in SVR rates in genotype 3 patients when treatment was given for 16 weeks rather than 12 weeks (37 vs 63% in non-cirrhotics and 19 vs 61% in cirrhotics) (27), suggested that a longer duration for genotype 3 patients would be more effective. This hypothesis was validated by the VALENCE trial, which evaluated 24-weeks of SOF/RBV in 250 genotype 3 patients, and showed SVR rates in 92–93% of treatment-naïve patients and 87% of treatment-experienced non-cirrhotic patients (32). However, the SVR rate of 62% in treatment-experienced patients with cirrhosis was similar to the 61% SVR rate in a comparable population that received 16 weeks of treatment in FUSION (27).

Several observations suggest that a 12-week course of PEG-IFN/RBV and SOF may offer comparable or even superior efficacy to that attained with 24 weeks of SOF/RBV in some genotype 3 patients. Thirty-nine genotype 3 treatment-naïve non-cirrhotic patients were treated for 12 weeks with SOF/RBV combined with 4–12 weeks of PEG-IFN, with 38 (97%) achieving SVR (33). Another

modest-sized study presented at the European Association for the Study of the Liver (EASL) 2014 lent credence to the potential role of a 12-week triple regimen by showing that both non-cirrhotic and cirrhotic genotype 3 patients who had failed a 12- to 16-week course of SOF and RBV had higher SVR rates with 12 weeks of PEG-IFN, RBV and SOF than with 24 weeks of SOF and RBV (34). More recently, the BOSON trial showed superior efficacy with 12 weeks of triple therapy ($n = 168/181$ with SVR12 93%) compared to 24 weeks of SOF/RBV ($n = 153/182$ with SVR 84%) (31). Importantly, PEG/RBV/SOF demonstrated higher SVR 12 rates in all arms, regardless of cirrhosis status or treatment history.

Furthermore, it is possible that combinations of DAAs will improve SVR rates. The ALLY-3 study demonstrated overall SVR rates of 90 and 86% among treatment-naïve and treatment-experienced patients, respectively, who were treated with a 12-week regimen of SOF and DCV (35). However, the SVR rate fell to 63% among genotype 3 cirrhotic patients treated with this regimen. Two 'real world' studies presented at EASL 2015 clearly indicate that extension of this regimen, with or without RBV, to 24 weeks confers superior results in this population (36–38). As predicted by the relative *in vitro* activities, real-world data from Foster *et al.* (38) showed a significant benefit of DCV over ledipasvir for genotype 3 patients when each agent was combined with SOF.

Discussion

Studies have demonstrated a propensity for HCV genotype 3 infection to cause progressive fibrosis, cirrhosis and hepatocellular carcinoma (HCC) more frequently than is seen in other HCV genotypes (39). In the light of this, some clinicians perceive that a course of therapy that leaves no resistance in the event of virological failure, as is the case with SOF/RBV, should be offered to all patients with genotype 3. Other clinicians may elect to use PEG-IFN/RBV and SOF in selected patients. However, as reflected in the updated HCV guidance documents, regimens incorporating a second DAA, such as a potent, pangenotypic NS5A inhibitor, with SOF is the preferred first-line treatment for genotype 3 (40). As of August 7, 2015, SOF in combination with RBV for 24 weeks is considered only an alternative regimen. DCV/SOF for 12–24 weeks and PEG-RBV/SOF for 12 weeks are the recommended treatment options for genotype 3 patients.

Statement 6: due to the high costs of medications, only patients with advanced fibrosis should be offered treatment with all-oral regimens for HCV

Rationale and definition of statement

This statement is based on the premise that patients with advanced fibrosis have the most risk and thus the most to gain with therapy, while those with mild disease can wait. Based on wholesale acquisition cost to treat the entire US

HCV population would cost in excess of $300 billion, thus the desire to prioritize and restrict access to therapy (41).

Summary of evidence

Hepatitis C virus has a significant effect on morbidity and mortality that is highest in patients with cirrhosis, but also impacts patients that are non-cirrhotic. In the USA, chronic HCV is the most common cause of liver disease. HCV is responsible for at least 15 000 deaths annually, with increasing mortality expected over the next decades (2, 42). Despite slow progression to cirrhosis, HCV-related mortality because of liver failure and HCC has increased substantially since 1995, especially in persons 45 years and older, with the greatest increases seen in males and non-Hispanic blacks (43). HCV is an important cause of premature mortality (43). In addition, chronic HCV affects well-being in all patients, regardless of fibrosis (44), although the burden is greatest in those with cirrhosis. In a recent cohort analysis of 528 cirrhotic HCV patients, baseline health-related quality of life was significantly impaired, with the most profound impairments seen in physical activity, energy, vitality and fatigue (45). Eradication of HCV improves health-related quality of life and work productivity (46).

The main goal of HCV treatment is to eradicate HCV, thereby preventing progressive liver disease. SVR is associated with reduced risk of HCC, histological reversal of liver fibrosis and reduced risk of liver-related death (4). Cure of HCV infection has also been associated with a decrease in all-cause mortality, decreased incidence of diabetes and improved insulin resistance (4, 47). A decrease in all-cause mortality was confirmed in a study of 21 000 US Veterans (48). Survival advantage was seen even in those without evidence of cirrhosis, suggesting an effect on non-liver related comorbidities (cardiovascular disease, diabetes, non-liver related cancers). These results were also supported by a meta-analysis of more than 34 000 patients treated with IFN-based therapy (Fig. 2) (49). This favours the

treatment of all patients infected with HCV, regardless of degree of liver fibrosis. Another group prioritized for treatment includes individuals at high risk for transmission, such as healthcare workers, haemodialysis patients, incarcerated individuals, those of childbearing age, and those who engage in high-risk behaviours (2).

Data from Phase 3 all-oral regimens suggest that cirrhosis remains a pretreatment factor that negatively affects SVR. Longer durations of therapy are required to maximize response in some cirrhotic patients, irrespective of genotype (8, 11, 27, 50). Thus, restricting care to the cirrhotic population will impose higher costs per treatment regimen. A recent cost-effectiveness model examined the treatment of all patients infected with HCV vs using a fibrosis-restricted decision model (e.g. only treating F3–F4). The 'treat all' strategy was the most cost-effective [incremental cost-effectiveness ratio (ICER) of $15 709/quality-adjusted life year (QALY)] and was also associated with the lowest risk of developing advanced liver disease (51).

Discussion

The HCV Council faculty felt strongly that this statement should be rejected based on the proven benefit in morbidity and mortality for eradicating HCV in patients who are non-cirrhotic; along with the overall cost-effectiveness advantage. Although prioritization of treatment will likely continue to focus on those with advanced disease, the group thought that there is strong evidence to encourage therapy in all patients infected with HCV.

Statement 7: given the high-efficacy and low-viral breakthrough rates, on-treatment viral load monitoring is no longer required

Rationale and definition of statement

Direct-acting antiviral agent studies have reported viral clearance rates of nearly 100% on therapy, eliminating
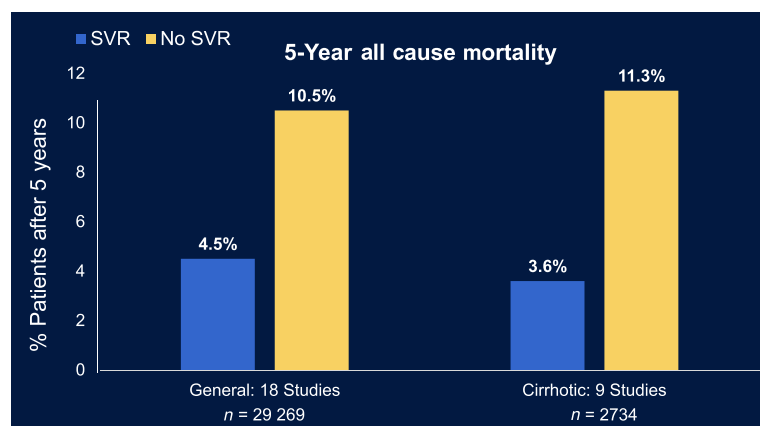

Fig. 2. Effects of sustained virological response (SVR) on risk of death. Meta-analysis of 129 studies; RR substantially reduced for all groups with SVR. Adapted from Saleem *et al.* (49).

the prognostic significance of early viral response and response-guided therapy. The meaning of low-level positive viral load on therapy, though uncommon, is unknown. Given the lack of prognostic significance, the absence of futility rules and the inability to shorten duration in rapid responders, the role of viral load monitoring while on therapy is unclear. This statement investigates the rationale for monitoring HCV viral load while on therapy.

Summary of evidence

Several large multicenter trials show rapid achievement of viral negativity in virtually all subjects, low rates of viral breakthrough (<2%), lack of stopping rules for futility, lack of prognostic significance based on the rate of achieving viral clearance, or rules for response-guided therapy (36, 52). SVR rates are over 90% with current first-line therapy and virtually all fail through relapse. As not even the rate of viral clearance predicts relapse, the prognostic or clinical significance of measuring viral load on-treatment is unclear.

Ledipasvir/SOF registration trials (ION-1, 2 and 3) enrolled 1950 patients. Only two patients had viral breakthrough (<1%). SVR rates were over 95% in all groups, with 36 (1.8%) failures from relapse (7, 8, 15). These findings are not unique to SOF-based therapy. SAPPHIRE-I, II and TURQUOISE II evaluated 3D in cirrhotic and non-cirrhotic genotype 1 patients (11, 50, 53). In more than 1100 patients, 1.5% experienced breakthrough, and 2.2% relapsed. This is not likely to change in the future as other investigational therapies report similar results (54).

The lack of prognostic significance of a positive or negative viral load at week 4 questions the utility of monitoring on-treatment viral response. Several potential reasons for assessing on-treatment viral load remain. Firstly, it is believed that a negative HCV RNA is a powerful motivator that reinforces patient adherence. Secondly, a detectable HCV RNA may be a marker for non-compliance or a drug–drug interaction (DDI) and, thus, drug failure. Assessment can easily be incorporated at a time when other labs are drawn. However, one would have to be certain to exclude false-positive results and prevent treatment disruption, as discontinuing treatment could disadvantage many patients who could still achieve SVR (36, 52).

Discussion

Achieving clearance of HCV RNA by week 4 with highly potent DAA agents is expected in over 95% of patients. The rate of viral breakthrough is <2%, and virtually all failures to achieve SVR will be due to non-compliance or relapse. There are no on-treatment viral predictors of who will relapse, and it is not possible to use on-treatment viral load monitoring to develop either response-guided algorithms or futility rules. Thus, the prognostic significance of HCV-RNA on treatment is low.

Nevertheless, the panel felt that it was highly likely that HCV RNA would be measured during treatment in most patients, more as reinforcement of adherence than as a true need to alter the therapeutic regimen. They cautioned against discontinuing treatment in patients with detectable viraemia unless non-adherence could be established. They were strongly against incorporating viral load measurements into algorithms for continuing authorization of treatment by payers, a requirement that has the potential to lead to treatment interruption.

Statement 8: patients with decompensated cirrhosis should be treated with an all-oral regimen for HCV to improve survival

Rationale and definition of statement

The term decompensated cirrhosis implies that the patient has experienced variceal haemorrhage, ascites, spontaneous bacterial peritonitis, encephalopathy or coagulopathy. IFN treatment is compromised by poor tolerability, adverse events and low rates of virological response (55). IFN-free regimens are the only options available for patients with decompensated cirrhosis. Until data support the use of PIs (NS3/4) in decompensated cirrhosis (Child B/C), this class should also be avoided.

Summary of evidence

Preliminary reports indicate that high rates of SVR can be achieved in patients with decompensated cirrhosis. LDV/SOF/RBV was administered to approximately 100 patients with Child–Turcotte–Pugh (CTP)-B or CTP-C cirrhosis for 12 or 24 weeks (56). SVR rates were 87 and 89% overall, respectively, and did not vary by CTP class (Fig. 3). The regimen was well tolerated with few patients discontinuing due to adverse events. Importantly, model for end-stage liver disease (MELD) score decreased in most patients, and serum albumin increased, indicating that improvement in clinical status was also associated with SVR. This same regimen was used to treat patients with post-transplant recurrent hepatitis C and also demonstrated high rates of SVR (96% in CTP-A and 83–85% among CTP-B patients) that was well tolerated. Similar improvement in MELD and albumin were noted. The combination of DCV, SOF and RBV for 12 weeks also demonstrated high efficacy in 60 decompensated cirrhotics in the ALLY-1 trial (57). Reported SVR12 rates were 92% in Childs A, 94% in Childs B and 56% in Childs C.

Benefit from therapy in this fragile population may require more than simply an improvement in biochemical parameters. The English EAP (Early Access Program)
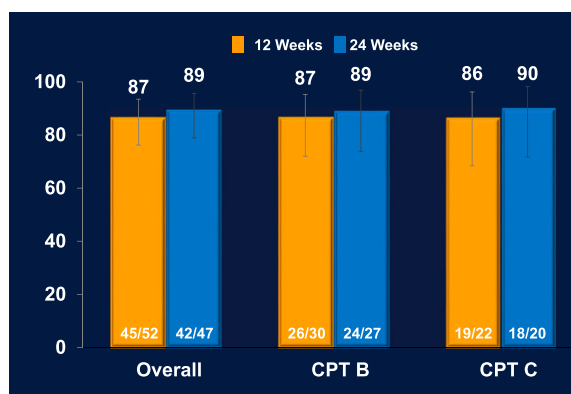
Fig. 3. Ledipasvir/sofosbuvir + ribavirin (RBV) in patients with decompensated cirrhosis: preliminary result of a prospective, multicenter study. Randomized to sofosbuvir (SOF) + ledipasvir (LDV) (600 mg w/escalation) for 12 or 24 weeks. Patients with G1 or G4 and decompensated cirrhosis. Most patients with MELD > 10 (MELD = 16–20 in 10–46%). Median albumin = 2.6–3.0 g/l; Median platelets = 71–88 K. Flamm *et al.* (56).

showed similar results in 467 patients with decompensated cirrhosis treated with 12 weeks of all-oral therapy (SOF/LDV/RBV, SOF/LDV, SOF/DCV/RBV or SOF/DCV) (38). Overall SVR 12 rates were between 71 and 80%. Hepatic function (reflected by MELD score) improved in 40%; however, the investigators felt that the benefit was primarily gained in subjects younger than 65 with a baseline albumin above 3.5 g/dl.

Several additional challenges exist in managing decompensated cirrhosis, even with all-oral regimens. Many patients with decompensated disease have impaired renal function. SOF and RBV are cleared by the kidney, and there are no dose recommendations for patients with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 or in patients on dialysis (58, 59). The clearance of other DAA agents may be impaired by altered hepatic metabolism or portal-systemic shunting; for example, simeprevir is not recommended in CTP C cirrhosis due to substantially higher simeprevir exposures (60). DDIs may alter therapeutic efficacy and increase toxicity (61).

Discussion

The panel concurred that all-oral regimens were the treatment of choice for patients with decompensated liver disease, although PIs should be avoided in CTP C cirrhosis. Clearly, SVR can be safely achieved in the majority of patients. However, the major unanswered question is whether SVR in a decompensated patient will obviate the need for liver transplantation with continued improvement in hepatic function or whether it will just provide a temporary respite from progressive liver disease without affecting overall survival. It is expected that long-term follow-up of these patients will help answer this important question and inform whether a pre-transplant or post-transplant antiviral treatment strategy is most effective.

Statement 9: patients co-infected with HIV/HCV should no longer be considered a 'special population'

Rationale and definition of statement

In the USA, up to 25% of those infected with the human immunodeficiency virus (HIV) harbour co-infection with HCV (62). The burden is thought to range from 250 000 to 300 000 patients with dual infection. Viewed from the opposite direction, approximately 10% of those with chronic HCV infection are also infected with HIV. From a global perspective, these numbers are much larger, with estimates of 4–8 million patients co-infected with HIV/HCV. Historically, unique features of HIV/HCV co-infection led to the designation of this group as a 'special population'.

Summary of evidence

To determine the validity of the proposed statement, the definition of what constitutes a 'special population' and the effect of such a designation requires further scrutiny. Both the FDA and *European Medicines Agency* (EMA) (USA and European drug regulatory bodies) regard HIV/HCV as a 'special population' group. The designation is designed to ensure that an appropriate number of subjects are entered and treated in clinical trials leading to drug approval so that both patients and healthcare providers have sufficient data on efficacy, safety and unique management considerations. In the FDA *Guidance for Industry* published in October 2013, the agency specifically notes the need for appropriate DDI studies with commonly used HIV medications and safety data regarding loss of HIV efficacy. They suggest that 300 co-infected patients are needed to complete these assessments.

Several unique and relevant biological issues can affect outcomes in HIV/HCV co-infected patients. These include (i) faster rates of fibrotic progression (63, 64); (ii) increased risk for hepatic decompensation (65, 66); c) higher viral loads (67) and (iii) risk of DDIs, particularly between HCV DAA agents and antiretroviral agents (61, 68).

Phase 2 and Phase 3 trial data oppose the need for a 'special population' designation in HIV/HCV co-infected populations, as treatment response rates in coinfected patients are similar to mono-infected subjects with HCV. In the PHOTON-1 trial, treatment-naïve patients with HCV/HIV co-infection were treated with SOF/RBV for 24 weeks if genotype 1 and 12 weeks if genotype 2 or 3. Among those with HCV genotype 1, the SVR12 was 75%. It was 88% in genotype 2 and 67% in genotype 3 (69). SVR12 data among co-infected patients treated with LDV/SOF for 12 weeks yielded 96% response rates among a cohort of 335 patients, with 95% seen in naïve, 97% in experienced, 96% without cirrhosis and 94% with cirrhosis (70). Other regimens continue to show efficacy comparable to mono-infected subjects. Overall SVR12 rates of 97% were achieved with 12 weeks of DCV/SOF in HIV/HCV co-infected subjects in ALLY-2. SVR rates were highly independent of race, baseline HCV RNA, advanced fibrosis, and prior treatment exposure (71). This study also included an 8-week duration for treatment-naïve subjects, 10% of whom had cirrhosis. However, relapse rates were higher with an SVR12 of 76%. At this time, shortened treatment duration (8 week) cannot be recommended with this or any other regimen.

Of note, antiretroviral regimens were quite limited in some trials. In other DAA studies, alternative dosing regimens were required to adjust for DDIs. In the simeprevir Phase 3 C212 trial, patients were not permitted to use any HIV PIs or efavirenz (72). These restrictions do not reflect real-world use of antiretroviral regimens. Future regimens, such as DCV/SOF, will be compatible with a wide range of antiretrovirals.

Discussion

The panel agreed that co-infected patients should remain as a 'special population' based on the importance of DDI and monitoring the effects of treatment on HIV disease. However, from an efficacy standpoint, HIV/HCV co-infected patients do as well with potent DAA regimens when treated for 12 weeks as do mono-infected patients.

Statement 10: treatment of hepatitis C should remain within the domain of hepatologists, gastroenterologists and ID physicians

Rationale and definition of statement

HCV therapy is now characterized by short courses of safe and well-tolerated, all-oral regimens with SVR rates exceeding 90% (7, 8, 11, 15, 24, 50). However, the effect of therapy will be blunted by ongoing deficits in the diagnosis, linkage to care and treatment of chronic HCV infection. Expansion of HCV treatment to non-specialty providers such as primary care physicians (PCPs) may help address the substantial burden of HCV infection in the USA.

Summary of evidence

Sparse data exist to support or oppose the role of PCPs in the management of HCV. Traditionally, HCV treatment has remained within the realm of specialists. However, with the transition from highly complex regimens to simplified regimens, an opportunity exists to expand the treater pool to non-specialty providers.

The need to expand treatment capacity is underscored by profound deficits at each successive step within the HCV care cascade: screening, diagnosis, linkage to care, treatment initiation, treatment completion and achievement of SVR (73–75). Among 99 166 veterans with HCV, 60.0% underwent genotype confirmation, 35.9% had no contraindications to HCV treatment, 11.6% received standard HCV treatment (PEG-IFN/RBV), 6.4% completed treatment and a sobering 3.5% achieved SVR (76). A systematic review and meta-analysis of 10 studies addressing the USA, HCV care cascade revealed that only 50% of patients were diagnosed and aware of their infection, 43% had access to outpatient care, 27% had HCV RNA confirmation, 16% were prescribed treatment and 9% achieved SVR (77).

Although no controversy exists regarding the important role of PCPs in the care cascade, questions remain regarding the level of motivation, knowledge base and capacity of PCPs in treating HCV. Literature suggests significant deficits in both knowledge and current practices of PCPs and trainees regarding the diagnosis and management of HCV. Despite the ability to identify risk factors, few PCPs screen patients for risk factors, test for HCV in patients with risk factors, provide hepatitis A and B vaccinations, or refer infected patients to providers who have experience in antiviral therapy (78–85). Only a small minority of PCPs is familiar with existing therapies (85), and a recent survey revealed that 56% of PCPs did not believe HCV can be cured (78). Furthermore, approximately three-quarters of surveyed PCPs were unaware that the FDA had approved oral HCV therapy, and approximately one-third expect to always refer HCV patients to a specialist for management (79).

Many reports describe the ability to integrate antiviral therapy within primary care. Unfortunately, most are case reports and demonstration models within specific clinical contexts, such as methadone clinics, community health centers or prison clinics (86–88). The most robust support comes from PROJECT ECHO, a prospective observational cohort study in which outcomes of 261 patients managed by PCPs at 21 rural

satellite clinics were compared to 146 patients managed by the primary university, which supervised HCV case management via telemedicine for the satellite clinics. The SVR outcomes between patients managed by specialty and PCPs were equivalent (89). Importantly, the ECHO model relies upon formal, structured partnership between the specialty providers with HCV expertise and PCPs (90).

Literature suggests that adherence to general Medicare Physician Quality Reporting System (PQRS) HCV quality measures (HCV RNA confirmation, HAV and HBV vaccination) is higher for patients receiving care by both a specialist and PCP than by either a specialist or PCP alone, whereas adherence to treatment-related quality measures (antivirals prescribed, HCV genotype before treatment, HCV RNA at baseline and treatment week 12) was higher for specialists with or without PCP care than was seen in PCP care alone (91). Individuals with optimum pretreatment care were more likely to receive antiviral therapy (OR 3.2, 95% CI 2.9–3.5), complete treatment (OR 1.26, 95% CI 1.13–1.43) and achieve SVR (OR 1.3, 95% CI 1.01–1.65) (92). Patients seen by a specialist are more likely to be prescribed antiviral therapy (OR 9.34, 95% CI 8.03–10.87) (93), although site experience (defined as ≥200 patients treated with antiviral agents), not provider type, was associated with treatment completion (OR 1.87, 95% CI 1.56–2.24) (94). In a large retrospect cohort study of US veterans, only low site experience (defined as <25 treated patients) was associated with SVR (OR 0.71, 95% CI 0.56–0.90); no differences were observed by management (gastroenterology or hepatology, infectious diseases or internal medicine) (95). Simple and effective regimens may amplify treatment experience and success rates across all treater groups.

Discussion

The HCV Council panel recognizes that the evidence to support or oppose this statement is poor. However, based on expert consensus, the majority argues that HCV treatment should remain within the realm of specialists who have the requisite knowledge, clinical judgment and treatment experience required to provide the best patient care. The current antiviral paradigm remains complex, with the need for an expert clinician to carefully consider multiple factors in guiding patients in treatment decisions, such as HCV genotype and/or subtype, stage of liver fibrosis, prior treatment experience, HIV co-infection and liver disease status (e.g. decompensation, liver cancer, post-transplant). The Council fully anticipates that as treatment transitions to increasingly simple, short and effective regimens which form the basis for 'one size fits all' across genotypes and patient characteristics, the growing role of PCPs in HCV treatment will be welcomed and considered an inevitable and necessary step in our goal of HCV eradication in the USA.

Conclusion

All-oral regimens have become the new standard of care for chronic HCV and have already demonstrated remarkable rates of SVR with well-tolerated, convenient dosing across a broad population of patients who previously could not tolerate nor benefit from IFN-based regimens. Despite the rapid accumulation of data and the prompt revisions of treatment recommendations, numerous questions regarding optimal management of certain populations and clinical scenarios remain unanswered. The discussion above provides a summary of evidenced-based expert opinion that may help guide clinicians as additional information is developed.

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