HCV cure for everyone or which challenges remain?

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Abstract

Following the approval of the first HCV direct-acting antiviral (DAA) in 2011, an unforeseen revolution in the treatment of chronic hepatitis C has taken place. In 2015 several all-oral DAA regimens, combining agents from different families (NS5B nucleotide inhibitors, NS5B non-nucleoside inhibitors, NS5A replication complex inhibitors and NS3/4A protease inhibitors) are now commercially available. In clinical trials, these regimens result in an increase in sustained virological response (SVR) rates to above 90–95% and reduce the duration of treatment to 12 weeks or less. As these new all-oral therapies are easy to take, with some already available as simple fixed-dose combinations, and are associated with minimal adverse events, increasing numbers of HCV patients appear treatable with these modern regimens. Nevertheless, the questions remain on how far the spectacular treatment trial results can be reproduced in clinical practice and whether more challenging patient populations, including previous non-responders and patients with advanced cirrhosis, will continue to exist even in the era of all-oral DAA therapy.

Keywords: HCV, genotype, cirrhosis, liver transplantation, DAA

Introduction

The hepatitis C virus (HCV) was discovered in 1989 and was quickly established as the major cause of non-A, non-B hepatitis (NANB) [1,2]. HCV is an RNA virus that belongs to the family Flaviviridae. Overall, seven major genotypes and 67 subtypes have been described, with genotype 1 accounting for ~70% of infections in the US and Europe [3]. HCV genotypes have been particularly important in the past with regard to probability of achieving cure following an interferon (IFN)-based HCV therapy. Although this may become less relevant in the direct-acting antiviral (DAA) era, so far not all DAs are active against all genotypes. The prevalence of HCV is approximately 3% around the world [4]. This virus can cause chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Therefore, HCV treatment has always been a desirable goal in order to cure HCV and thereby prevent fibrosis progression and development of cirrhosis and other liver disease-related complications. Even before the discovery of the HCV virus, the first pilot studies had evaluated the efficacy and safety of IFN-α to treat patients with NANB hepatitis, following encouraging results from IFN treatment trials in hepatitis B [5]. Subsequently, IFN monotherapy administered thrice weekly for 24 weeks became the first HCV therapy, albeit with low sustained virological response (SVR) rates of only 6% [6]. Adding ribavirin, extending treatment duration and finally introducing pegylated interferon helped to substantially increase overall HCV cure rates to above 50% (Figure 1) [6,7]. Host factors that were associated with a good response were young age, female gender, non-African-American heritage and low fibrosis levels, and, more recently, presence of the IL-28B CC genotype [8]. More challenging patient groups were cirrhotics, previous IFN non-responders, patients with HCV recurrence after liver transplantation, and patients with HIV co-infection who, in controlled clinical trials, were much less likely to achieve SVR. Also, IFN-based therapy was strongly restricted in its widespread use because of its very significant adverse-event profile and high rate of treatment-related complications. Indeed, more than 50% of a given HCV cohort appeared to have contraindications against interferon, preventing its use accordingly. Therefore, the development of DAs that allowed all-oral IFN-free and, at best, also ribavirin-free HCV regimens, has introduced a whole new era of HCV therapy. Not only are these new therapies much better tolerated but they also achieve cure of HCV defined as SVR 12–24 weeks after stopping HCV therapy in more than 90–95% of patients, promising widespread cure for all [9–16]. Clearly, the most obvious limitation of these new therapies is their extremely high price, which has led to a considerable delay and hindrance in the uptake of these new treatment options. Indeed, there is still no access to these new therapies in many countries or their use is reserved only for patients with advanced F3–F4 fibrosis. In clinical practice the question remains, how will patients, particularly in the presence of liver cirrhosis and prior non-response or failure to a first DAA and IFN-containing HCV regimen, respond to these new drugs outside clinical trials? This review summarises the current successes and remaining challenges of modern all-oral HCV therapy.

HCV treatment data from real-life patient settings

One of the first large cohorts of HCV patients receiving DAA-based therapy was presented at AASLD in 2014 by the TRIOnetwork [17]. The objective of the study was to evaluate outcomes with sofosbuvir- and simeprevir-containing regimens in a real-world, heterogeneous population. Data were collected...
through the Trio Platform directly from electronic prescribing records. Overall, 1211 patients from 150 academic and community sites were included in this database. The main regimens examined were: sofosbuvir (SOF)/pegylated interferon (PEG)/ribavirin (RBV), SOF/RBV and SOF/sofosbuvir (SMV) ±RBV. Of 995 participants who could be analysed, 59% were male, 16% African-American, 30% had cirrhosis, 16% had platelet counts below 100,000/μL, 43% were treatment-experienced (35% null responders, 65% partial responders/relapsers) and 20% had already received an HCV protease inhibitor (PI) [17]. All baseline characteristics indicated that this was a more difficult-to-treat patient population than normally enrolled into clinical trials. The SVR12 rates for the different regimens (SOF/PEG/RBV and SOF/SMV ± RBV) for genotype 1 patients were 72% and 82%, respectively. Clearly, these results demonstrate that overall cure rates in clinical practice remain high and appear reproducible.

However, on average there is a 5–10% lower cure rate than in clinical trials. Indeed, there are a growing number of patients for whom treatment with DAA-based therapy has failed and who will require a more potent treatment option in the near future. This is particularly true for the more challenging patient populations such as the cirrhotic genotype 1 patient with a history of previous non-response to HCV treatment. Most impressively, treatment discontinuation rates were extremely low at only 5%, with 3% owing to non-adherence and 1.9% for adverse events only, underlining the good tolerability of modern all-oral HCV therapy. Similar data were presented at the same meeting from the TARGET database, which represents an ongoing longitudinal observational study at 43 academic and 13 community centres in North America (n=51) and Europe (n=5) [18]. Overall, 2330 HCV patients consented to be enrolled into this observational study: 52.2% of whom were treatment experienced, 48.4% had cirrhosis at baseline and 9.4% had already received a first HCV PI-based regimen that had failed. In addition, 19.2% of recorded patients were aged over 65 years, again highlighting that the patients within this study were much closer to real-world patient populations. Virological response rates were very encouraging. In HCV non-cirrhotic genotype 1 patients receiving SOF/SMV ±RBV, SVR4 was 92% (113/123) and 87% (1566/1800) in patients with cirrhosis. Patients with genotype 1a were only a little less likely to achieve SVR4 (89%; 47/53) than patients with genotype 1b (95%; 88/93).

HCV therapy in cirrhosis

Treatment of HCV in patients with cirrhosis and previous failure of HCV treatment seems to remain a challenge. Lower HCV cure rates have been reported particularly in patients with advanced cirrhosis and signs of portal hypertension (defined by low platelet count <75,000/μL) [19]. For patients with cirrhosis and previous non-response who were receiving ledipasvir (LDV)/SOF for 12 weeks, SVR12 was 90% and for the same group with platelet counts below 75,000/μL, only 82% [19]. The exact mechanisms for why patients with advanced liver disease seem to respond less well, or require longer treatment durations, remain unknown. The question is whether these response rates can be optimised with more potent combinations, but it still needs to be demonstrated in clinical trials. Unfortunately, these are exactly the type of patients who are precluded from being included in a clinical trial because more advanced cirrhosis is often an exclusion criterion.

Another important question in the treatment of HCV in more advanced cirrhosis stages has been whether there is a point of no return where HCV therapy, even if SVR is attained, might not be able to change the further course of liver disease. At AASLD 2014, a study was presented in 108 genotype 1 or 4 treatment-naïve or -experienced patients with decompensated cirrhosis (CPT class B (7–9) or C (score 10–12)) who were randomly allocated to 12 versus 24 weeks of LDV/SOF+RBV (escalating doses starting at 600 mg/day) [20]. Clearly, the overall cure rates with an SVR12 rate of 87% and 89% following 12 and 24 weeks of therapy, respectively, are very impressive in this particularly advanced patient population. The other very important observation from this trial was the quite drastic clinical improvement of the patients with successful HCV therapy, which was documented by an improvement in MELD score as well as an increase in serum albumin, all indicative of an improvement of liver synthesis function.

Use of ribavirin

Although dispensing with interferon clearly represents the most prominent breakthrough in HCV therapy, IFN/RBV-free regimens are the future for HCV therapy. Whereas no ribavirin appears necessary in treatment of genotype 1b patients, addition of ribavirin to the regimen of paritaprevir/ritonavir/ombitasvir and dasabuvir is recommended by clinical trial results when treating genotype 1a patients [8]. Also, addition of ribavirin to ledipasvir/sofosbuvir in compensated cirrhotics seems to achieve higher SVR rates after 12 weeks of therapy than without. Rates of anaemia, however, are higher in cirrhosis and underline why in the future there will still be a need for RBV-free regimens for the more difficult-to-treat patient populations. Indeed, in the meta-analyses of HCV trials in compensated cirrhotics with genotype 1 infection receiving ledipasvir/sofosbuvir ± ribavirin, the rate of haemoglobin below 100 g/L was 10% for the patients with additional ribavirin versus <1% in the group of patients receiving only ledipasvir/sofosbuvir [8]. In summary, tolerability of HCV regimens could still be substantially improved by eliminating ribavirin from future HCV regimens.

HCV treatment in genotype 3 patients

While sofosbuvir and ribavirin combination therapy has become the new gold standard for treatment in HCV genotype 2 infection, this particular combination seems to work less well in genotype 3 patients, particularly in those with cirrhosis and who have had a prior non-response to IFN-containing regimens and even when treatment was extended to 24 weeks [21–22]. Unfortunately, pangenotypic HCV DAAAs still remain the exception and clearly more pangenotypic drugs will be needed in the future especially when considering the worldwide distribution of the various genotypes.

Data on the combination of daclatasvir and sofosbuvir for treatment of HCV genotype 3 infections have been disappointing for patients with cirrhosis at baseline. Indeed, whereas overall SVR12 rate was 96% following 12 weeks of daclatasvir 60 mg + sofosbuvir 400 mg daily in the Ally-3 study, SVR12 rates decreased to 63% in patients with cirrhosis at baseline [23]. Cirrhosis in this study was determined in 141 patients by either liver biopsy (META VIR F4), FibroScan (>14.6 kPa), or FibroTest score ≥0.75 and APRI (aspartate aminotransferase to platelet ratio index) >2.

HCV-infected patients with severe renal insufficiency

In the past, rates of sustained virological response for HCV genotype 1 in patients with end-stage kidney disease have been lower than in patients with normal renal function. Use of ribavirin, which is mostly excreted renally, has been very challenging and adverse events under HCV therapy in end-stage renal disease have often precluded HCV treatment altogether. HCV infection is
also quite prevalent among dialysis patients owing to procedures leaving patients vulnerable to infection through blood contamination. In the DAA era, new treatment options may arise as most DAAAs are not excreted renally. Sofosbuvir, the current cornerstone of many DAA combinations, is an exception and is excreted 80% renally and so is currently contraindicated in patients with a glomerular filtration rate (GFR) below 30 mL/min. At AASLD 2014, first results from an open-label pilot trial including 10 patients with chronic HCV genotype 1 or 3 with a creatinine clearance (CrCl) less than 30 mL/min as calculated by the Cockcroft–Gault equation, but not on dialysis, who received SOF 200 mg + RBV 200 mg daily for 24 weeks were reported [25]. Overall SVR12 was 40%, 20% of patients discontinued, anaemia was frequent and 50% of patients received erythropoietin, clearly indicating that this for now remains a challenging patient population to treat. SOF levels were similar to those in patients without renal insufficiency receiving 400 mg, but levels of its major metabolite, GS-331007, were four times higher. 

Further trials are currently under way to evaluate efficacy and safety of various IFN-free DAA combinations. In another report from AASLD 2014, the experience of four patients with GFR <30 mL/min who urgently needed HCV treatment and were treated with a sofosbuvir-containing therapy was shared [26]. The four male patients with HCV genotype 1 (50% 1a) and mean age 58 years had severe renal insufficiency defined by GFR <30 mL/min or were on dialysis. Three of the four individuals achieved SVR after dose-adapted SOF-containing therapy. All received SOF 400 mg every other day, in combination with 150 mg SMV daily for 12 weeks or ribavirin for 24 weeks for three and one patient, respectively [26]. More data is required for renally impaired patients and preferably for ribavirin-free treatment approaches.

Treatment of recurrent HCV in orthotopic liver transplantation recipients

HCV recurrence has been one of the major limitations after liver transplantation, negatively affecting long-term outcome in this patient group. Fortunately, with the new DAA combinations, various options now exist, promising good cure rates, which should help to improve overall survival for these individuals. Drug–drug interactions between HCV agents and immunosuppressants do, however, need to be addressed prior to commencing HCV therapy. Recently, results from 34 liver-transplant recipients with no fibrosis or mild fibrosis, who received ombitasvir/ABT-450/ritonavir (at a once-daily dose of 25 mg ombitasvir, 150 mg ABT-450 and 100 mg ritonavir), dasabuvir (250 mg twice daily) and ribavirin for 24 weeks were reported [27]. Selection of the initial ribavirin dose and subsequent dose modifications for anaemia were at the investigator’s discretion. Of the 34 enrolled study participants, 33 had a sustained virological response at post-treatment weeks 12 and 24, for a rate of 97% [95% confidence interval (CI): 85–100]. The most common adverse events were fatigue, headache and cough. Five patients (15%) required erythropoietin; no patient required blood transfusion. One patient discontinued the study drugs owing to adverse events after week 18 but did have a sustained virological response. Blood levels of calcineurin inhibitors were monitored, and dosages were modified to maintain therapeutic levels; no episode of graft rejection was observed during the entire study period [27]. These first results clearly indicate that if blood levels of immunosuppressants are adapted as necessary, DAA-based HCV therapy can be delivered with high cure rates.

HCV therapy in HIV co-infection

In the era of IFN/RBV combination therapy, significantly lower HCV cure rates were reported from various trials in HIV/HCV dually infected individuals [28]. However, with the first DAA/PEG/RBV combinations, as well as the newer DAA IFN-free combination trials, comparable SVR rates have already been reported in HIV/HCV co-infection. This suggests that in the DAA era, differences in treatment outcome will no longer exist for this special patient population [22,28–32]. As a consequence, current EASL guidelines state that there should no longer be a difference with regard to indication or regimen selection in HIV co-infected versus HCV mono-infected subjects [33]. The only special consideration is the need to check for drug–drug interactions between HIV and HCV drugs (please see www.hep-druginteractions.org).

HCV resistance–associated mutations in HCV treatment failures or naturally occurring resistance–associated mutations: what role do they play?

Because of the high genetic heterogeneity of HCV and its rapid replication, monotherapy with DAA agents poses a high risk for selection of resistant variants. Whether this still plays a role in potent combination DAA therapy is controversial. Two potential scenarios are of obvious interest. First, are there any pre-existing polymorphisms or resistance–associated variants (RAVs) that may impact on the probability of achieving SVR under DAA combination therapy? Indeed, in the context of HCV protease inhibitors, the presence of a Q80K mutation has been described to confer a 10-fold reduction in SMV activity in vitro. Baseline Q80K has also been reported to have a minor effect on initial response to SMV/PEG/RBV but to result in lower SVR rates [34]. However, in DAA combinations such as simprevir and sofosbuvir, this no longer seems to have an impact. NSSA-associated mutations have also been shown to be prevalent at baseline in a minority of patients. In one recent study utilising a panel of genotypic-specific resistance assays, population sequencing was performed on plasma-derived viral RNA isolated from 138 patients infected with HCV genotypes 1–4 and not treated with DAA agents [35]. Amino acid substitutions associated with moderate– to high-level resistance to NSSA inhibitors were detected in two of 42 patients (4.76%) HCV genotype 1a-, three of 23 (13.04%) HCV genotype 1b-, four of 26 (15.38%) HCV genotype 2-, one of 24 (4.17%) HCV genotype 3- and one of 23 (4.35%) HCV genotype 4-infected patients who had not been treated with NSSA inhibitors. More recently resistance data were also reported from the C-WORTHY phase II trial. This was a study on efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for HCV genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis [35]. NSSA RAVs were noted at baseline in 14% of patients (34 of 243); the most common variants were at positions 31 and 93 reported in 7% (16/243) and 4% (9/243) of samples, respectively [36]. Among patients with NSSA RAVs, SVR12 was achieved in only 82% (28/34), whereas among the 209 patients with wild-type NSSA at baseline 97% (203/209) achieved SVR12, thereby suggesting that potentially there may be an impact on SVR rates depending on baseline RAVs.
The second major resistance question is obviously what impact development of resistance-conferring mutations will have on the efficacy of subsequent HCV salvage regimens. Again in the C-WORTHY trial, investigators reported that at the time of virological failure, RAVs for NS3 or NS5A were detected in most patients (8/10); the most commonly detected RAVs were NS3:Y56H, A156T/C/V and D168A/Y, and NS5A:M28T, Q30L/R, L31M, and Y93H/N [36]. Clearly more data is needed to clarify the open resistance questions and also to better define which salvage regimens can be recommended after DAA-based therapy has failed and with subsequent resistance development.

Conclusions

In summary, the revolution of DAA-based therapy has introduced highly promising HCV cure options for almost all patient types. Nevertheless, more potent combinations are still needed, particularly for patients with cirrhosis and previous HCV treatment failure as well as for patients with genotype 3 infection and cirrhosis. Overall, introduction of pangenotypic HCV agents that can be combined without ribavirin still represent an attractive goal in further HCV drug discovery and development.

Conflict of interest

JKR has received honoraria for speaking at educational events or consulting from Abbvie, Bionor, BMS, Boehringer, Gilead, Janssen, Merck, Tibotec and Viiv.

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