Review

JOURNAL OF HEPATOLOGY

From non-A, non-B hepatitis to hepatitis C virus cure

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Summary

The hepatitis C virus (HCV) was discovered in the late 1980s. Interferon (IFN)-α was proposed as an antiviral treatment for chronic hepatitis C at about the same time. Successive improvements in IFN-α-based therapy (dose finding, pegylation, addition of ribavirin) increased the rates of sustained virologic response, i.e. the rates of curing HCV infection. These rates were further improved by adding the first available direct-acting antiviral (DAA) drugs to the combination of pegylated IFN-α and ribavirin. An IFN-free era finally started in 2014, yielding rates of sustained virologic response over 90% in patients treated for 8 to 24 weeks with all-oral regimens. Major challenges however remain in implementation of these new treatment strategies, not only in low- to middle-income countries, but also in high-income countries where the price of these therapies is still prohibitive. Elimination of HCV infection through treatment in certain areas is possible but raises major public health issues.

Introduction

Twenty-five years after the discovery of the hepatitis C virus (HCV), new orally administered antiviral drug combinations yielding infection cure rates over 90% were approved in 2014–2015 in Europe, the US and other regions of the world. Some called it a "revolution". A revolution is defined by "a sudden, complete or marked change in something". This definition does not apply to what happened to the field of HCV therapy. Instead, a slow, progressive, successful succession of discoveries in which academic scientists, clinicians and commercial entities were collaboratively involved, led to the current situation (Fig. 1). It is the story of this adventure, from discovery to cure, that we are telling here.

To begin at the beginning

The era of discovery

In the 1960s and early 1970s, viral hepatitis was considered to represent two clinically and epidemiologically distinct diseases: infectious and serum hepatitis [1]. Infectious hepatitis, or hepatitis A, was marked by a short incubation period (1–3 weeks), fecal-oral transmission, a high degree of contagiousness and an acute self-limited illness that could be protracted and severe (and even fatal) but did not result in chronic hepatitis or cirrhosis. Serum hepatitis, or hepatitis B, in contrast was marked by a longer incubation period (1–3 months), parenteral or sexual transmission, a low degree of contagiousness, and an acute illness, that was usually self-limited but could be severe or fatal and could also result in chronic infection, chronic hepatitis and even cirrhosis. This duality was supported by human transmission studies [1] and by the discovery that the Australia antigen was a part and parcel of the hepatitis B virus (HBV) [2–4], considered at the time to be the sole cause of serum hepatitis. Development of sensitive tests for Australia antigen, later named the hepatitis B surface antigen (HBsAg), provided means of diagnosis and screening that could be applied to blood donations and prevention of post-transfusion hepatitis [5]. Application of donor screening for HBsAg, however, led to a decrease in post-transfusion hepatitis of only 25–50% [6]. The residual cases were considered to be due to hepatitis A or to hepatitis B that was not detected by the then-available serologic assays.

The discovery of the hepatitis A virus (HAV) was another landmark advance in hepatitis research and paved the way for development of serological assays for diagnosis and epidemiologic studies and ultimately for an HAV vaccine [7]. This discovery also showed that hepatitis A was not a cause of post-transfusion hepatitis; indeed, virtually none of the non-B cases of hepatitis from blood products could be linked to HAV [8]. The third form of viral hepatitis was appropriately termed "non-A, non-B" (NANB) hepatitis.

Keywords: Hepatitis; Discovery; Direct-acting antivirals; Interferon; Ribavirin.
Received 26 January 2015; accepted 4 February 2015

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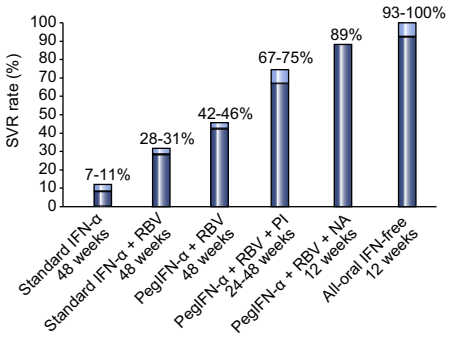

Fig. 1. Progress in therapy of chronic hepatitis C genotype 1 as shown by SVR rates with different antiviral regimens. PI, first-wave, first-generation protease inhibitor (telaprevir or boceprevir); NA, nucleotide analogue (sofosbuvir).

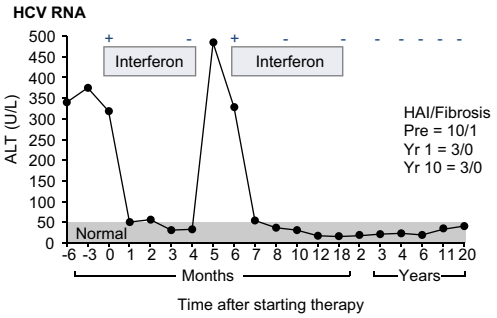

Fig. 2. Clinical, biochemical, histologic and virologic course of one of the patients of a pilot study of IFN-α2b for chronic non-A, non-B hepatitis [12]. Serum ALT levels were consistently higher than 8 times the upper limit of normal for a year before treatment and became normal within 1 month of starting IFN-α (5 MU daily), but rose to pretreatment values within a few weeks of stopping. Restarting IFN-α led to normalization of ALT levels again and they remained normal for the subsequent year of treatment (using gradually lower doses of IFN) and remained normal during long-term follow-up. A liver biopsy taken before treatment showed marked activity (histology activity index 10) and mild fibrosis (Ishak fibrosis score 1). At the end of treatment, the histology activity index score had decreased to 3 and fibrosis was no longer present. A repeat liver biopsy 10 years later showed similar minimal inflammation. Application of HCV RNA testing by polymerase chain reaction on stored samples showed that therapy was accompanied by loss of HCV RNA which remained undetectable in long-term follow-up and was not detectable in the liver tissue taken 10 years later.

The era of "non-A, non-B" hepatitis

Proof that there was another form of serum hepatitis was followed by major efforts to discover its agent. The search would continue for 15 years and employ all the methods that were successful in discovery and characterization of hepatitis A and B including immunodiffusion, complement fixation, fluorescence microscopy, radio- and enzyme linked-immunoassay, electron microscopy, transmission electron microscopy, immune electron microscopy, cell and tissue culture, molecular biology and animal transmission studies. Ultimately, the last two methods would provide the basis for the discovery of the HCV, but until that time, frustration ran high. Even without an identifiable agent, the clinical and epidemiological characteristics of NANB hepatitis were fairly well defined [9].

The disease was due to a transmissible agent, probably a virus, 40–60 nm in size, enveloped, sensitive to heat and chloroform inactivation. The disease was transmitted by blood and injection drug use but rarely by sexual or maternal-infant exposure. Acute infection tended to be mild and asymptomatic but could also cause jaundice and severe hepatitis. Importantly, acute NANB hepatitis frequently led to persistent infection and chronic hepatitis, and could lead to cirrhosis and hepatocellular carcinoma. Later studies would show that acute HCV infection led to persistent infection in at least 75% of cases and HCV was the most common cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma in much of the Western world.

At the same time that the clinical features and outcomes of NANB hepatitis were being described, advances were being made in the therapy of hepatitis B, using interferon (IFN)-α as well as antiviral agents that were effective in other viral infections. These successes led to pilot studies of therapy for NANB hepatitis. In small studies, corticosteroids were found to be ineffective, indeed probably harmful [10]. Acyclovir was similarly ineffective, even when given in high doses, intravenously [11]. IFN-α was an obvious agent to try. In cell culture, IFN-α had demonstrable antiviral activity against virtually all viral agents, both RNA and DNA. Furthermore, recombinant forms of IFN-α had recently been developed and the safety, tolerability, side effect profile and dosing requirements of the cytokine had been fairly well defined in studies of hepatitis B and D.

Accordingly, in early 1984, a pilot study of IFN-α was initiated in 10 patients with well defined chronic NANB hepatitis at the Clinical Center of the National Institutes of Health (NIH) [12]. All 10 patients had risk factors for NANB hepatitis (blood transfusion or injection drug use) and all had persistent and stable, moderate-to-severe elevations in serum aminotransferase levels and liver histology characteristic of chronic viral hepatitis. The protocol called for use of the regimen found effective in hepatitis B: 5 million units (MU) of IFN-α2b subcutaneously once daily for 16 weeks.

The results were immediate and dramatic. Serum aminotransferase levels fell rapidly on IFN therapy and were often normal within a month of starting treatment. This rapid change was all-the-more convincing of an effect because the 10 patients had previously been followed for 1–10 years and most had never had a normal serum alanine aminotransferase (ALT) value. The clinical, biochemical and ultimate virologic course of Patient 3 from that study is shown in Fig. 2. Within a month of starting therapy, serum ALT levels were normal and they remained normal for the 16 weeks of the initial course. Within a month of stopping treatment, ALT levels rose to baseline values. The improvement in ALT levels recurred when IFN-α was restarted and remained normal for a year of treatment despite a gradual decrease in dose to 1 MU daily. Importantly, on stopping therapy after a full year of treatment, serum ALT levels remained normal. This pattern of rapid response to treatment, normalization of ALT levels during a subsequent 12 months of therapy and lack of relapse when IFN-α was stopped was seen in 5 of the 10 patients. Three other patients developed normal or near-normal serum ALT levels on therapy, but relapsed upon stopping. Two others had only minimal decrease in ALT levels and little evidence of improvement during long-term follow-up. Another striking feature found in these 10 subjects was that IFN-α was poorly tolerated in hepatitis C, and most patients required dose reduction.

These findings were reported in 1986 [12], several years before the discovery of the HCV [13] and availability of sensitive assays for HCV RNA in serum. When those tests were developed, however, testing of stored serum samples showed that the improvements in ALT levels were associated with decrease in HCV RNA levels and that long-term remissions were

accompanied by long-term clearance of detectable HCV RNA [14]. Subject 3 shown in Fig. 2 was the first patient cured of hepatitis C by antiviral therapy. In long-term follow-up of more than a quarter of a century, he has remained free of evidence of HCV infection and liver injury with liver biopsy showing resolution of disease activity and no detectable HCV RNA. The other four subjects with a sustained biochemical response also had a sustained virologic response (SVR) and were alive and without evidence of liver injury 15–20 years later. In contrast, the five patients who did not respond continued to have evidence of chronic hepatitis and HCV RNA in serum; three developed hepatocellular carcinoma and all but one have died.

This pilot study of IFN-α in NANB hepatitis led to the initiation of two randomized controlled trials. Both trials used a 24-week course of treatment: a study from the NIH used 2 MU thrice weekly with a placebo control [15], whereas a multicenter US trial used either 1 or 3 MU thrice weekly with a non-treated control [16]. Both studies showed that IFN-α treatment led to improvements in serum ALT levels and liver histology, which was more frequent in the 2 MU (48%) and 3 MU (46%) than the 1 MU (28%) or control (0% and 8%) groups. Importantly, however, the endpoint for efficacy was measured at the end of treatment, while still on IFN. Based upon these studies and the demonstration that HCV RNA was eradicated in some patients, IFN-α2b was approved for use in chronic hepatitis C by the US Food and Drug Administration in 1991.

The early era of hepatitis C and its treatment with IFN-α

The initial enthusiasm for IFN-α therapy was soon dampened by experience in a broader spectrum of patients, by further follow-up of treated patients, and the application of sensitive virologic markers to treated patients. In 1997, an NIH Consensus Development Conference concluded that treatment of chronic hepatitis C with IFN-α was appropriate for patients with raised serum aminotransferase levels, HCV RNA in serum and liver histology showing fibrosis or marked disease activity [17]. The shortcomings of IFN therapy were the frequent side effects and the relatively low rate of sustained responses. Indeed, in subsequent large multicenter trials, the SVR rate to 24 weeks of IFN-α was only 6%, which increased to 13–19% with 48 weeks of treatment, largely due to a lower relapse rate [18,19]. Furthermore, genotyping of HCV showed that the SVR rate among patients with genotype 1 was even less: 2% with 24 and 7–11% with 48 weeks of treatment. Increasing the dose of IFN-α and extending therapy for more than a year was minimally more effective and considerably less well tolerated. Clearly what was needed was another antiviral agent, to either replace or add to IFN-α. The first such agent was the oral nucleoside analogue ribavirin.

The "good old time" of interferon and ribavirin

The era of standard IFN-α and ribavirin

Another major step forward was made in the early 1990s when Swedish authors had the idea to treat 10 patients with chronic hepatitis C with ribavirin, an orally administered guanosine analogue with a broad spectrum of antiviral action against both DNA and RNA viral agents. A dose of 1000–1200 mg per day (500 or 600 mg twice per day) for 12 weeks was used. Serum ALT levels significantly decreased in all patients on treatment, but increased back to baseline levels within 6 weeks post-therapy [20]. In another study from the NIH [21], 13 patients with chronic hepatitis C were treated for 6 months with a dose of ribavirin that was increased at 2-month intervals from 600 mg to 1000 mg to 1200 mg daily. Serum ALT levels decreased in all treated patients and normalized on treatment in 4 of them. Like in the Swedish study, ALT levels gradually rose to near pretreatment levels in all but one patient after cessation of ribavirin administration [21]. No reliable HCV RNA assay was available at the time these two studies were performed. It is only several years later that it was shown that ribavirin only has a modest (less than 0.5 log HCV RNA international units (IU)/ml on average) transient (a few days) direct antiviral effect on HCV when given as a monotherapy [22].

The dramatic effect of ribavirin monotherapy on ALT levels led Swedish and Italian groups to initiate two exploratory clinical trials combining IFN-α and ribavirin in patients with chronic hepatitis C [23,24]. In the first study, 20 non-responders to IFN-α monotherapy were randomized to receive IFN-α alone or the combination of IFN-α plus ribavirin for 24 weeks. None of the former, but 40% of the latter, achieved SVR [23]. In the other study, 9 of 10 patients who relapsed after and 3 of 10 patients who did not respond to IFN-α monotherapy definitively cleared HCV RNA after receiving 24 weeks of the combination of IFN-α and ribavirin [24].

Two large-scale multicenter, randomized, placebo-controlled Phase III clinical trials provided evidence that the combination of IFN-α2b (3 MU three times weekly) and ribavirin (1000 or 1200 mg daily according to body weight) is superior to IFN-α monotherapy in treatment-naïve patients with chronic hepatitis C. In the first trial performed outside the US [19], SVR 24 weeks after treatment (SVR24) was achieved in 43% of patients treated for 48 weeks with the combination of IFN-α and ribavirin, 35% of patients treated for 24 weeks with the combination of IFN-α and ribavirin ($p = 0.055$ with the previous group), and only 19% of patients treated for 48 weeks with IFN-α alone ($p < 0.001$ with both combination regimens). Logistic regression analysis identified five independent factors significantly associated with SVR: HCV genotype 2 or 3, HCV RNA level <2 million copies/ml, age 40 years or less, minimal fibrosis stage, and female sex [19].

In the second Phase III trial performed in the US [18], SVR was achieved in 38% of patients treated for 48 weeks with the combination of IFN-α and ribavirin, 31% of patients treated for 24 weeks with the combination of IFN-α and ribavirin, 13% of patients treated for 48 weeks with IFN-α alone and 6% of those treated for 24 weeks with IFN-α alone ($p < 0.001$ for the comparison of IFN-α alone with both 24 or 48 weeks of combination treatment). Among patients infected with HCV genotype 1, the highest rates of SVR occurred in those treated for 48 weeks with IFN-α and ribavirin, whereas in patients infected with HCV genotype 2 or 3, similar rates of SVR were achieved with 24 and 48 weeks of combination treatment [18].

The combination of standard IFN-α and ribavirin was approved in 1999 as the standard-of-care treatment of chronic hepatitis C. SVR was shown to be associated with favorable clinical outcomes and improved health-related quality of life; in contrast, patients failing to achieve SVR progressed to more severe liver disease [25].

Mathematical models of viral decay during IFN-α-based therapy were useful to understand the steady-state kinetics of HCV

infection. The estimated half-life of free HCV virions in peripheral blood was estimated to be about 2.7 h, with approximately 10^{12} virions produced and cleared each day [26]. After a short lag of a few hours following the first IFN-α injection, a biphasic decay of viral replication was observed in patients receiving daily IFN-α administration. The rapid first phase viral decline was dose-dependent and reflected blocking of HCV replication, as a result of the direct antiviral action of IFN-α. The slower second phase decline was hypothesized to result from the progressive clearance of infected cells in the context of efficient blocking of HCV production [26]. Further studies showed that ribavirin addition does not alter the first phase viral decline, but significantly accelerates the second phase decline through mechanisms that remain elusive, explaining the higher cure rates in patients taking both IFN-α and ribavirin [22,27]. Together, HCV kinetics studies were helpful to emphasize the importance of sustained IFN-α exposure and ribavirin in optimizing anti-HCV treatments [28,29].

The era of pegylation

Standard IFN-α administration three times weekly was associated with saw-toothed ups and downs of HCV RNA levels and a low likelihood of a steady second phase viral load decline [22]. Long-acting IFNs, that could be administered once weekly while maintaining a steady level of active drug, were generated by attaching the IFN-α molecule to a polyethylene glycol moiety. Two pegylated-IFNs (PegIFN) were developed: IFN-α2a was linked to a 40-kD branched polyethylene glycol molecule, while IFN-α2b was linked to a 12-kD linear polyethylene glycol molecule. Their elimination half-lives were approximately 75 and 30 h, respectively.

PegIFN-α2a was given as a single weekly injection of 180 μg per week, while PegIFN-α2b dosing was weight-based and, although various dosing strategies were evaluated, ultimately 1.5 μg/kg per week became the approved dose. PegIFN-α2a and PegIFN-α2b both proved superior to their unpegylated counterparts when given as monotherapy for 48 weeks [30,31]. As with standard IFN, the addition of ribavirin to PegIFN-α improved the rates of SVR. The Phase III trials demonstrated an important effect of the HCV genotype. Indeed, the SVR rates were 42 to 46% in patients with genotype 1 infection compared to 76 to 82% in those infected with genotypes 2 or 3 [32,33]. Ultimately a trial evaluating different durations and different ribavirin dosing strategies clarified that patients with genotype 1 infection needed 48 weeks of therapy and a high, weight-based dose of ribavirin, whereas those with genotypes 2 and 3 achieved high rates of SVR (in the order of 80%) with only 24 weeks of therapy and a fixed dose (800 mg) of ribavirin [34].

Multivariate analyses identified independent predictors of SVR with this regimen, including host factors (younger age, low body mass index, mild-to-moderate fibrosis, lack of steatosis and insulin resistance, non-black ethnicity) and viral parameters (HCV genotype other than 1 and 4, low baseline HCV RNA level). The combination of PegIFN-α and ribavirin became the new standard-of-care treatment of chronic hepatitis C and remained so for about 10 years.

The era of response-guided therapy

The next step was the discovery, through post-hoc analysis of the pivotal trials and performance of new studies, that treatment duration should be modulated according to the on treatment virologic responses. HCV RNA level measurement at baseline, weeks 4, 12, and 24, at the end of treatment, and 24 weeks after treatment withdrawal were used to characterize the virological response: the rapid virologic response (RVR) was defined as undetectable HCV RNA at week 4 of therapy; the early virologic response (EVR) as HCV RNA detectable at week 4 but undetectable at week 12; the slow or delayed virologic response (DVR) as HCV RNA detectable at week 12 but undetectable at week 24 [35]. Patients with an RVR and a low baseline HCV RNA level needed no more than 24 weeks of therapy [36]; patients who achieved an EVR required 48 weeks of therapy, whereas patients with a DVR appeared to benefit from extending treatment to 72 weeks (but tolerability was a limiting factor) [37–39]. Patients with less than a 2 log decline in HCV RNA level at week 12 were unlikely to experience an SVR and could be taken off therapy [35].

An important contribution to the field was the discovery, by means of genome-wide association studies (GWAS), of single nucleotide polymorphisms located upstream of the interleukin-28B (*IL28B*) gene strongly associated with the likelihood of an SVR after PegIFN-α and ribavirin therapy [40]. Single nucleotide polymorphism rs12979860 was the best baseline SVR predictor in patients infected with genotype 1 receiving this therapy [40]. The *IL28B* genotype is strongly associated with the ethnic origin and a genetic marker of the patient's IFN responsiveness [40]. More recently, another polymorphism in the same region was identified, which affects the coding of a novel protein, given the name IFN-λ4, and both spontaneous HCV clearance and the response to IFN-α-based therapy [41]. However, at the individual level, better prediction is achieved by the monitoring of viral kinetics on treatment.

The early era of direct-acting antiviral drugs

Major advances in the understanding of the molecular virology of HCV came with the development of genotype 1 subgenomic and genomic replicon systems and the identification of the genotype 2a JFH1 clone, that leads to productive infection in cell culture after transfection. With these new model systems and the resolution of the three-dimensional structure of key HCV enzymes, the multiple steps of the HCV lifecycle were unraveled, identifying multiple targets for drug discovery. Through a combination of compound screening and rational drug design, small molecules with potent activity against various HCV enzymes were discovered. The recognition that the NS3-4A protease inhibitor ciluprevir (BILN-2061) could rapidly suppress HCV replication by 4 logs in only 48 h validated this HCV enzyme as an optimal drug target. Although concerns about toxicity limited the development of this particular compound, it paved the way for the cascade of new direct-acting antivirals (DAAs) that would follow. The two first-wave, first-generation HCV NS3-4A protease inhibitors telaprevir and boceprevir were approved in combination with PegIFN-α and ribavirin for the treatment of chronic HCV genotype 1 infection in 2011 [42,43].

Telaprevir is an orally bioavailable NS3-4A protease inhibitor that belongs to the α-ketoamide group and binds the HCV protease covalently. Boceprevir is an orally bioavailable peptidomimetic α-ketoamide HCV NS3-4A protease inhibitor that forms a covalent but reversible complex with the enzyme. Both agents potently inhibit HCV replication, but they have a low

barrier to resistance leading to the rapid selection of resistance-associated variants when either used alone, or in combination in a patient with a poor response to PegIFN-α.

In an attempt to circumvent this issue, the concept of the "lead-in" phase was introduced, in which patients were treated with PegIFN-α and ribavirin for 4 weeks prior to introduction of the protease inhibitor, with the hope to lower HCV RNA levels prior to starting the DAA and thus reduce the incidence of treatment failures and resistance. Although the lead-in did not reduce rates of resistance or treatment failure in general, it was helpful in determining which patients were likely to benefit from protease inhibitor-based therapy. Indeed, patients with a less than 1 log IU/ml decline in HCV RNA during the 4-week lead-in had a low chance of response, particularly if they had previously failed therapy and had advanced fibrosis [44–46].

The lead-in was a measure of IFN responsiveness, the key determinant to the outcome of treatment with first-generation protease inhibitors. The importance of the IFN-response was particularly evident in patients who had failed prior PegIFN-α and ribavirin therapy. Those who had responded and relapsed, proving their intrinsic responsiveness to IFN, achieved high rates of SVR (>80%), even if they had cirrhosis. In contrast, patients with a prior null response to dual therapy had a low chance of responding to triple therapy (in the order of 30%) despite a full 48 weeks of treatment [44–46]. Other factors associated with the IFN-response (*IL28B* genotype, ethnicity, fibrosis stage, etc.) were also predictive of response to triple therapy with PegIFN-α, ribavirin and either protease inhibitor [44–50]. Patients with multiple negative predictors such as a prior null response and cirrhosis had a very low chance of SVR, in the order of 15%.

Due to different Phase III clinical trial designs, telaprevir and boceprevir were used differently in combination with PegIFN-α and ribavirin. Boceprevir was approved with a 4-week lead-in with PegIFN-α and ribavirin alone, continued for up to 44 weeks of dosing, whereas telaprevir was given to all patients for the initial 12 weeks of treatment with PegIFN-α and ribavirin, followed by 12 to 36 weeks of PegIFN-α and ribavirin alone. Differing regimens, response definitions, response-guided therapy approaches and futility rules between the two protease inhibitors significantly complicated treatment. The drugs were also both associated with additional side effects to those already present with PegIFN-α and RBV. Both telaprevir and boceprevir caused significant anemia, and telaprevir was also associated with cutaneous reactions, which on rare occasion were severe (Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms [DRESS] syndrome) or even fatal [44–48]. Despite the challenges with these new therapies, the improvements in SVR over PegIFN-α and ribavirin alone reported in the clinical trials led to rapid and enthusiastic treatment uptake with these new agents.

Treatment in the real world setting told a different story than the highly selected clinical trials. The CUPIC trial evaluated patients with cirrhosis who received treatment with either first-wave, first-generation protease inhibitors through the French Early Access Program [49,50]. Adverse events, including serious and even fatal events, were reported with much higher frequency than in the Phase III trials. Serious adverse events were particularly common in patients with cirrhosis who had early signs of portal hypertension (thrombocytopenia) and liver synthetic dysfunction (hypoalbuminemia). Patients with a platelet count below 100,000/μl and a serum albumin level less than 35 g/L had a 41% chance of experiencing a serious adverse event during therapy. In addition to the unexpected toxicity, SVR rates were lower than reported in controlled trials [49,50]. Although side effect management improved with experience, other real world registries also reported greater toxicity and lower efficacy for both agents. There was clearly room for improvement.

The DAA revolution

The development of HCV DAAs has occurred extremely rapidly, moving from approval of first-wave, first-generation protease inhibitors that were combined with PegIFN-α and ribavirin to all-oral single tablet DAA combinations, in less than 4 years. Despite the dramatic success of DAA development, there were challenges along the way. Initial treatment regimens were complicated and proved less effective and more toxic in the real world than in clinical trials. Multiple promising agents were abandoned for toxicity, including fatal complications in a small number of patients. Ultimately, combinations of agents targeting different stages of the lifecycle proved highly effective.

HCV DAAs approved and in development

The HCV lifecycle can be blocked at many steps [51,52]. HCV DAAs on the market or in clinical development include NS3-4A protease inhibitors, nucleotide analogue inhibitors of the HCV RNA-dependent RNA polymerase (RdRp), non-nucleoside inhibitors of the HCV RdRp and inhibitors of the non-structural 5A (NS5A) protein (Table 1). These drugs differ in their activity against the different HCV genotypes and their barrier to resistance.

NS3-4A protease inhibitors bind the catalytic site of the enzyme and block post-translational processing of the viral polyprotein. The first-wave, first-generation NS3-4A protease inhibitors, telaprevir and boceprevir, were active essentially against genotype 1, had low barriers to resistance and, as discussed above, were poorly tolerated. The second-wave, first-generation NS3-4A protease inhibitors are active against genotypes 1, 2, and 4, but not against genotype 3. They have a low barrier to resistance. Some of them can be boosted by ritonavir to extend dosing intervals while increasing patient exposure. Second-generation NS3-4A protease inhibitors have pangenotypic antiviral activity and a higher barrier to resistance than first-generation drugs.

Nucleotide analogues act as false substrates for the HCV RdRp, leading to chain termination after being incorporated into the newly synthesized viral RNA. They need two intracellular phosphorylations to become active at the target site. Nucleotide analogues are active against all HCV genotypes and have a high barrier to resistance.

Non-nucleoside inhibitors of HCV RdRp bind to one of 4 allosteric sites of the enzyme and alter the conformation of the RdRp, thereby blocking its catalytic function. Current non-nucleoside HCV RdRp inhibitors are generally active against HCV genotype 1 and have a low barrier to resistance.

NS5A inhibitors bind to domain 1 of the NS5A protein and block its ability to regulate HCV replication within the replication complex [53]. In addition, NS5A inhibitors inhibit assembly and release of viral particles [54,55]. Some first-generation NS5A

Table 1. Approved DAAs and DAAs in clinical development at the beginning of 2015.

Agent class	Generation	Compound	Phase of clinical development
NS3-4A protease inhibitors	First-wave, first-generation	Telaprevir Boceprevir	Approved
	Second-wave, first-generation	Simeprevir Paritaprevir/r	Approved
		Asunaprevir Vaniprevir Vedroprevir Sovaprevir	In clinical development
	Second-generation	Grazoprevir ACH-2684	In clinical development
Nucleoside/nucleotide analogues	Nucleotide analogues	Sofosbuvir	Approved
		MK-3682 ACH-3422 AL-335	In clinical development
Non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase	Palm domain I inhibitors	Dasabuvir	Approved
	Thumb domain I inhibitors	Beclabuvir	In clinical development
	Thumb domain II inhibitors	GS-9669	In clinical development
NS5A inhibitors	First-generation	Daclatasvir Ledipasvir Ombitasvir	Approved
	Second-generation	Elbasvir GS-5816 ACH-3102	In clinical development

/r, ritonavir-boosted.

inhibitors have pangenotypic activity whereas others are poorly active against genotype 3. They have a low barrier to resistance. Second-generation NS5A inhibitors are active against all HCV genotypes, but their barrier to resistance appears to be only modestly improved compared to first-generation compounds [56].

The end of the IFN era

In 2014, several strategies based on the use of a triple combination of PegIFN-α, ribavirin and one DAA were approved. Among them, the most attractive was the combination of PegIFN-α, ribavirin and the nucleotide analogue sofosbuvir (400 mg once daily), that yielded high SVR rates in patients infected with all genotypes after only 12 weeks of therapy. In the NEUTRINO Phase III trial [57], the SVR rates were 89% in genotype 1 (92% in subtype 1a, 82% in subtype 1b) and 96% in genotype 4 patients. One patient with genotype 5, and six patients with genotype 6 also achieved an SVR. The overall SVR rates were 92% in patients without cirrhosis *vs.* 80% in those with cirrhosis. Adverse events were similar to those reported with PegIFN-α and ribavirin alone. Importantly, treatment failures were not associated with the selection of resistant HCV variants [57]. Another Phase II study in treatment-experienced patients showed SVR rates of 96% and 83% with this regimen in patients with genotype 2 or 3 infection, respectively [58].

The triple combination of PegIFN-α, ribavirin and the second-wave, first-generation NS3-4A protease inhibitor simeprevir (150 mg once daily) has also been approved in 2014 for patients infected with HCV genotype 1 (and 4 in Europe), based on the results of the Phase III QUEST-1 and QUEST-2 studies in treatment-naïve HCV genotype 1 patients [59,60]. In these trials, the SVR rates were 80% and 81% *vs.* 50% and 50% in the control groups, respectively. They were 75% and 85% in patients infected with subtypes 1a and 1b, respectively. This difference was due to a 58% SVR rate in the subgroup of patients infected with subtype 1a who had a detectable Q80K substitution in the NS3 protease sequence at baseline *vs.* 84% in those without detectable Q80K [59,60]. Because this finding implied that patients should be tested prior to therapy for HCV subtype and, in those infected with subtype 1a, for the presence of the Q80K substitution [61], this combination has virtually not been used. Instead, the presence of both sofosbuvir and simeprevir on the market allowed practitioners to use them together, IFN-free, either off-label (US) or within the framework of early access programs (Europe). Simeprevir was well tolerated in all Phase III studies, although pruritus and rashes were slightly more frequent than in the control arms. Approximately 10% of patients developed mild, transient hyperbilirubinemia without changes in other liver parameters [61]. At the time of treatment failure, patients who did not respond to simeprevir-containing therapies harbored HCV protease inhibitor-resistant variants that disappeared as dominant species within 16 months post-treatment [62].

Phase II data were reported with the combination of PegIFN-α, ribavirin and the first-generation NS5A inhibitor daclatasvir (approved in the European Union only) [63,64], but this combination has not been used. Instead, the IFN-free combination of sofosbuvir and daclatasvir has been widely used in Europe, thus far essentially within the framework of early access programs in patients with advanced liver disease.

The dawn of the IFN-free era

Small Phase II studies with sofosbuvir and ribavirin in genotypes 2 and 3, and with a protease inhibitor (asunaprevir) and an NS5A inhibitor (daclatasvir) in genotype 1, proved that SVR was

possible without the need for PegIFN-α. In the FISSION Phase III trial in treatment-naïve patients [57], sofosbuvir and ribavirin given for 12 weeks yielded SVR rates of 95% in genotype 2 and 56% in genotype 3 patients *vs.* 78% and 63% with PegIFN-α and ribavirin for 24 weeks. In the Phase III FUSION trial in treatment-experienced patients treated with sofosbuvir plus ribavirin for 12 or 16 weeks [65], the SVR rates were 82% and 89% in genotype 2, and 30% and 62% in genotype 3 patients, respectively. In the VALENCE Phase III trial, in genotype 2-infected patients treated for 12 weeks, the SVR rates were 97% in naïve non-cirrhotic patients, 100% in naïve cirrhotic patients, 91% in experienced non-cirrhotic patients, and 88% in experienced cirrhotic patients. In genotype 3-infected patients treated for 24 weeks, they were 94%, 92%, 87%, and 60%, respectively [66]. The combination of sofosbuvir and ribavirin was well tolerated and relapses were not related to the selection of sofosbuvir-resistant HCV variants [57,65,66]. The standard-of-care treatment in patients infected with HCV genotype 2 is now the combination of sofosbuvir and ribavirin for 12 weeks. Treatment-experienced cirrhotic patients may need 16 to 20 weeks of therapy [61]. In patients infected with genotype 2, preliminary "real-life" data showed SVR rates in keeping with the results of Phase III trials [67]. Patients infected with genotype 3 must be treated for 24 weeks with the combination of sofosbuvir plus ribavirin or for 12 weeks with sofosbuvir, PegIFN-α and ribavirin.

The IFN-free combination of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily) was used based on the results of the small-size Phase II COSMOS study in patients infected with genotype 1 [68]. In the first cohort of prior null responders with F0–F2 METAVIR scores, the SVR rates were 96% and 93% after 12 weeks, and 79% and 93% after 24 weeks, with or without ribavirin, respectively. In the second cohort of treatment-naïve and –experienced patients with F3–F4 METAVIR scores, the SVR rates were 93% and 93% after 12 weeks, and 93% and 100% after 24 weeks, with or without ribavirin, respectively. When patients from both cohorts were pooled, the SVR rates in patients infected with subtype 1a with a detectable Q80K substitution at baseline were 88% and 89% after 12 weeks, and 83% and 100% after 24 weeks, with or without ribavirin, respectively. The combination was well tolerated [68]. Recent preliminary real-life data from the US showed SVR rates slightly below those in the COSMOS trial in patients with genotype 1 infection: 82% SVR12 in the TRIO study, 89% SVR4 in the TARGET study [67,69].

The combination of sofosbuvir (400 mg daily) and daclatasvir (60 mg daily) has been widely used in patients with advanced liver disease in Europe, based on the results of a Phase II study in patients infected with genotype 1 reporting SVR rates between 95% and 100% after 12 or 24 weeks with or without ribavirin in treatment-naïve patients and in patients who did not respond to the combination of PegIFN-α, ribavirin, and either telaprevir or boceprevir [70]. The combination was well tolerated over the course of therapy. Real-life data are awaited. This combination currently is the best IFN-free option for patients infected with genotype 3.

The triumph of IFN-free regimens

Two new IFN-free, DAA-based combinations have been approved in late 2014/early 2015 in the US and Europe. The combination of sofosbuvir (400 mg) plus ledipasvir (90 mg) in one single pill administered daily, with or without ribavirin according to the severity of liver disease, is approved for genotype 1 in the US, for genotypes 1, 3, and 4 in the European Union (indication in genotype 3 patients debatable based on available data). The triple combination of ritonavir-boosted paritaprevir and ombitasvir in one single pill (50 mg/75 mg/12.5 mg per pill, 2 pills per day) plus dasabuvir in another pill (250 mg per pill, 2 pills per day), with or without ribavirin according to the HCV subtype and the presence of cirrhosis, is approved for HCV genotype 1.

Three Phase III studies have been performed with the sofosbuvir-ledipasvir combination in patients infected with genotype 1. In ION-1 in treatment-naïve patients, the SVR rates were 99% and 97% after 12 weeks, 98% and 99% after 24 weeks, with or without ribavirin, respectively [71]. In ION-3, also in treatment-naïve non-cirrhotic patients, the SVR rates were 94% for 8 weeks without ribavirin, 93% for 8 weeks with ribavirin and 95% for 12 weeks without ribavirin [72]. Post-hoc analysis suggested that 8 weeks of treatment is sufficient in treatment-naïve patients with an HCV RNA level <6 million (6.7 log) IU/ml at baseline (to be confirmed in the real-life setting). In ION-2 in treatment-experienced patients, the SVR rates were 94% and 96% after 12 weeks, 99% and 99% after 24 weeks, with or without ribavirin, respectively [73]. No major safety signal was reported. Recent data suggest that the addition of ribavirin allows one to limit treatment duration to 12 weeks, even in patients with advanced liver disease, including patients with compensated cirrhosis (especially if they are treatment-experienced), patients with decompensated cirrhosis and subjects in the pre- and post-liver transplant setting [74–77]. High SVR rates can be achieved in these patients, in the order of 85 to 95% according to the severity of liver disease. High SVR rates have also been reported with the combination of sofosbuvir and ledipasvir in genotype 4 and 6 patients [78,79]. Patients who fail to eradicate HCV on sofosbuvir plus ledipasvir are likely to select viral populations that are resistant to the NS5A inhibitor but not to sofosbuvir. The NS5A resistant viruses may persist for many months to years as dominant viral populations, and their impact on subsequent retreatment is unknown.

The approval of the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir in patients infected with genotype 1 was supported by six Phase III clinical trials. In SAPPHIRE-I in treatment-naïve patients without cirrhosis treated for 12 weeks, the SVR rates with ribavirin were 95% in subtype 1a and 98% in subtype 1b [80]. In PEARL-IV, the SVR rates were 97% and 90% with and without ribavirin, respectively, in patients infected with subtype 1a, suggesting that ribavirin is needed with this subtype [81]. In PEARL-III, the SVR rates were 99% and 99% with and without ribavirin, respectively, in patients infected with subtype 1b, suggesting that ribavirin is not needed with this subtype [81]. In non-cirrhotic treatment-experienced patients treated for 12 weeks with ribavirin in SAPPHIRE-II, the SVR rates were 96% in subtype 1a and 97% in subtype 1b [82]. SVR was achieved in 97% with ribavirin and 100% without ribavirin in patients infected with subtype 1b in PEARL-II, confirming that ribavirin is not needed with this subtype [83]. In treatment-naïve and –experienced patients with HCV genotype 1 infection and compensated cirrhosis, the rates of SVR were 92% after 12 weeks and 96% after 24 weeks of the triple DAA combination plus ribavirin. The one group of patients who benefited from 24 weeks of treatment was the cohort of treatment-experienced cirrhotic patients with subtype 1a infection [82]. The triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir has

Table 2. Requirements for HCV elimination in high-income countries.

Diagnostics	Treatment regimens	Health infrastructure	Policy
• Inexpensive, point-of-care documentation of viremia • Widespread availability of non-invasive fibrosis staging	• One-size-fits-all regimens (all genotypes, all disease stages) • 95% SVR all sub-populations • Few adverse events • Few/no drug interactions • HCV vaccine*	• Treatment delivery in primary care facilities • Immediate link to treatment at time of diagnosis • High treatment in marginalized populations • Harm reduction strategies • Elimination of iatrogenic spread*	• National action plan for HCV elimination • Drug pricing reform

*Priority requirement in low/middle income countries.

been shown to be equally effective in HIV-coinfected patients and those after liver transplantation. However, drug-drug interactions are an important consideration, related in particular to ritonavir and paritaprevir [84,85]. High SVR rates were also reported in patients infected with genotype 4 with the combination of ritonavir-boosted paritaprevir and ombitasvir (without dasabuvir) [86]. This drug combination was well tolerated. Patients who fail to eradicate HCV on these combinations are likely to select viral populations that are resistant to one, two, or three of the DAAs administered.

Other treatment regimens are at the clinical developmental stage and could reach the market within the next couple of years. They include nucleotide analogue-based regimens; nucleotide-free triple combinations of three drugs, each with a low barrier to resistance, which collectively achieve a high barrier to resistance; and nucleotide-free double combinations of drugs that include at least one "second-generation" drug with a higher barrier to resistance [52].

What comes next?

The unprecedented progress in HCV therapeutics has created a situation in which it is likely that virtually all infected individuals will be able to be cured with well tolerated oral regimens if they are able to access therapy. Thus, the challenges in the HCV field are moving rapidly from drug discovery to treatment access and delivery. If these challenges can be addressed, the new HCV therapies present the rare possibility in medicine of local disease elimination and, potentially, even global disease eradication. To achieve these lofty goals, much more than effective, well tolerated therapies will be required. The issues will vary greatly depending on the local epidemiology, burden of disease, healthcare infrastructure and the local financial situation.

Is elimination possible?

The terms "elimination" and "eradication" are often used interchangeably despite having different meanings. Elimination refers to ridding a defined region or population, such as a state or country, of HCV [87]. Eradication means obliterating HCV from the earth, as has been done only with smallpox and rinderpest thus far [87]. Although the lack of an animal reservoir means that HCV could theoretically be eradicated globally [88], it is extremely unlikely that true eradication is feasible and almost certainly not without an efficient prophylactic vaccine. In contrast, elimination through treatment may be possible, although it will be challenging, at least in wealthy areas [89]. However, elimination will require much more than 100% SVR rates (Table 2): beyond issues remaining with the drug regimens themselves, major changes will be required in access to care, delivery of care and drug pricing policies. Without strong advocacy and political activism, these changes are unlikely to occur.

The regimens

The first challenge will be to refine the current regimens, to not only maximize rates of SVR but to simplify therapy. Indeed, elimination through treatment will require that all infected individuals receive therapy, which can only be accomplished if treatment is done in primary care settings. Compared to difficult, long-duration, IFN-based therapies, single tablet regimens are remarkably effective and relatively easy to use. However, treatment still requires specialty care, greatly limiting the prospect of widespread implementation. The subtleties of differing regimens with differing durations for specific sub-populations, whether defined by genotype, subtype, presence of cirrhosis or co-morbidities, will discourage new treaters from entering the field. Although some of the combinations in development hold promise for very simplified regimens that will be effective in almost all populations, some refinement is still required.

Currently, the priority is to maximize SVR while minimizing duration of therapy. Emerging data suggest that extending treatment duration overcomes reduced efficacy even in the hardest to cure sub-populations [71,73,82,90]. Although there are still some populations, such as treatment-experienced patients with genotype 3 infection and advanced cirrhosis for whom better therapies are still required, it is likely that there will be regimens that truly cure everyone provided they are treated "long enough". However, the long enough is a major issue. Given current drug pricing, there is a major incentive to minimize the duration of therapy and hence the cost of treatment. Nevertheless, with extremely safe and well tolerated regimens, there is little harm in overtreatment aside from cost.

A one-size-fits-all paradigm will be required if treatment is to move to primary care. The goal would be to test for viremia (or a simpler and cheaper measure of active infection such as HCV core antigen) and then institute treatment for a fixed duration, irrespective of genotype, subtype and, ideally, stage of liver disease. To ensure everyone achieves SVR with this approach, some (perhaps most) individuals will receive longer therapy than they might have required, which is what was done with IFN-based regimens. For this approach to gain acceptance, drug pricing reform is necessary. Although in the current model it may be more cost-effective to shorten duration and then retreat relapsers, it would be preferable if the cost of therapy did not differ by duration and everyone was cured with one fixed duration course.

Access to care: knowledge is key

The first and perhaps largest hurdle to accessing treatment currently is under-diagnosis. Although some countries, such as France, Scotland and Australia, have done a good job of identifying those infected, most countries have diagnosis rates well below 50% [91]. In many countries, the diagnosis rate is either completely unknown or estimates are based on poor quality data [92]. This is a critical issue: on the one hand undiagnosed individuals do not seek treatment, but more importantly, without a good handle on the prevalence and burden of HCV, governments cannot accurately budget for the resources required to scale up treatment. The World Health Organization found that only 47 countries had national strategies addressing viral hepatitis and, on further inspection, only 18 had viral hepatitis-specific action plans [93].

With the current alarm over drug pricing, governments may be reluctant to improve diagnosis rates for fear that they will then be responsible for treating those they identify. This shortsighted strategy will result in dealing with the consequences of end-stage liver disease in the future, but sadly may be rationalized by governments who recognize that it will not be their responsibility. Political activism has been extremely effective in other areas, particularly HIV, and will need to improve in the HCV community in order for governments to start taking action.

Once the local epidemiology has been clarified, the most appropriate strategies for case-finding can be developed. For example, in the US, birth cohort screening was shown to be cost-effective and has been adopted, while other strategies are likely more effective in Europe and other regions [94]. Even the specifics of a policy may differ by country. In Canada, the epidemiology supports extending birth cohort screening to include those born between 1945 and 1975 rather than 1945 and 1965 in the US [95]. In almost all regions, some type of population-based screening will be required to identify the majority of infected individuals.

Initial anti-HCV testing should be linked immediately to tests for viremia, whether HCV RNA or a cheaper/more accessible approach such as HCV core antigen. Drug development has outpaced improvement in diagnostics, which is an important issue particularly in resource-limited regions where HCV RNA testing might actually surpass the cost of HCV treatment [96]. Development of rapid, ideally point-of-care, diagnostics for HCV viremia is needed [96].

Diagnosis is only the first step. Data from the US on the cascade of care have shown that there is an immediate drop from initial diagnosis to any type of follow-up [97,98]. Individuals are indeed much more likely to follow-up in the clinic in which they were diagnosed, usually a primary care facility, than to attend a specialty clinic [99]. Ideally, individuals would find out the result of testing at the time it is performed and would be immediately linked to a discussion of treatment initiation. For this to occur, treatment must move out of specialty clinics.

Delivery of care

The complexity of therapy has required and arguably still requires specialty care for safe and effective delivery. The removal of IFN greatly simplifies treatment and makes many more patients eligible for therapy, but further refinements will be required for effective delivery in a primary care setting without additional support. Adoption of HIV treatment in primary care has shown that treatment can be delivered by non-specialists. However, in most cases, primary care providers who treat HIV have developed a sustained interest and expertise in this area [100]. The same model could be applied in HCV, ideally among primary care providers with a high prevalence of HCV in their patient populations, such as methadone and addiction clinics. To gain the initial expertise to start treating HCV, models of peer support such as Project ECHO, may be very useful. Project ECHO uses videoconferencing technology to connect specialists to primary care providers, allowing for co-management of patients as well as training. Initially pioneered in New Mexico with evidence showing equivalent outcomes in patients treated in a tertiary care facility or in primary care [101], Project ECHO has been replicated in many regions and is an ideal model for management of HCV and many chronic diseases [102].

Beyond treatment

To truly achieve elimination, more than treatment will be required. Widespread treatment may eventually eliminate prevalent cases. However, to eliminate HCV, incidence must also be addressed. Globally, iatrogenic spread remains the most common route of infection. However, in high- and many middle-income countries, injection drug use is the driver of transmission [91]. High uptake of antiretroviral therapy has been shown to reduce HIV transmission, making treatment as prevention a major strategy of global HIV control [103]. "Cure as prevention" has the potential to be even more effective for HCV. Even modest treatment uptake among people who inject drugs has the potential to significantly curb incident infections and to ultimately decrease population prevalence [104]. There are many challenges of delivering care in marginalized populations; however, numerous pilot projects have shown that it is feasible [105]. Treatment should be combined with harm reduction strategies such as opioid substitution therapy and needle syringe programs, which have benefits beyond HCV [105].

Addressing iatrogenic spread and contemplating elimination in low and middle-income countries is a more daunting task. Arguably iatrogenic transmission is largely a financial issue due to the lack of resources for reliable sterilized equipment. However, in many countries, injection therapy is seen as "preferable" by patients for many medical conditions, and delivery of care, including injections, is often given by relatively untrained practitioners [106]. Intra-familial spread has also been documented in high prevalence regions such as Egypt [107]. Even if treatment is made widely available, it is unlikely to curb incidence and reduce prevalence significantly without other strategies. Hopefully the progress in treatment will not deter government and industry from supporting research in effective prophylactic vaccine development.

Drug prices

The release of sofosbuvir at a price of $1000 USD per pill in the US led to uproar in the lay press. Although arguments have been made to justify the cost relative to other therapies in terms of cost-per-cure, cost-effectiveness or other measures, the fact remains that the price of therapies will be a major impediment to their widespread use. Even if these therapies are cost-effective, at their current prices, they are not cost-saving,

meaning that even when taking into account the downstream savings of reduced complications of HCV, treatment costs more than not treating [108]. Furthermore, the high prevalence of HCV means that the budget impact will be enormous for payers if everyone is treated immediately.

The most common strategy to address the cost is to limit access to therapy, usually based on the severity of liver disease. Although a rational approach, this will markedly delay progress towards elimination and is difficult for infected individuals to accept. The idea that "one is not sick enough" to warrant treatment is hard to rationalize. In addition, unless treatment is limited to those with cirrhosis, accurate fibrosis staging is required, which is often not available, particularly in primary care. The simplest answer to the price question is to simply lower the costs of the drugs.

Approaches such as pricing per treatment course rather than per pill would justify slightly longer courses of therapy to avoid relapse and to allow for one-size-fits-all treatment paradigms. In addition, novel payment approaches such as amortizing the cost of therapy over many years would make it more affordable for payers. Although the decision to cut prices in lower income regions is laudable, the reality is that in middle- and high-income countries, without major reform, drug pricing will be a major impediment to treatment and ultimately will be the downfall of elimination and eradication strategies.

Conclusions

Jay Hoofnagle

"The progress in therapy of hepatitis C since its humble beginnings 30 years ago has exceeded all expectations and is truly remarkable and welcomed; these feelings are soured only by the excessive prices being demanded for these life-saving therapies."

Stefan Zeuzem

"The treatment with IFN and ribavirin is history. However, it will remain a fine textbook example how intensive clinical research can enhance outcome (here: sustained virological response) with modification of dose and treatment duration of available drugs and likewise improve tolerability and safety of these drugs by adequate side effect management."

Jordan Feld

"I feel a bit like a surfer who after figuring out how to just stand up on the board suddenly catches a tsunami and takes the ride of a lifetime. I entered the HCV field at just the right time. As I finished my training, PegIFN-α was introduced. At the time, this was a major step forward as we finally started seeing a reasonable number of cures. But it was also a great research opportunity. Understanding why half the population did not respond to treatment became my primary goal. Although that was our focus, studying IFN responses (or the lack thereof) had the added benefit of improving our understanding of the innate antiviral immune response. It is because of HCV that many of the pathogen recognition and innate immune signaling pathways have been clarified. It has therefore been bittersweet to see the unprecedented progress in HCV therapy. That we would be curing near 100% of patients in the near future with easy to take tablets was beyond contemplation just a few years ago. This is an amazing advance and the scientists involved in the virology and drug discovery should be congratulated. I hope however that we remember that HCV has taught us a great deal and many of the questions that are no longer clinically important may still be very relevant to science.

Being part of the beginning of the end of HCV has been an exciting ride. The lightening speed with which the field has moved has been exhilarating and I feel lucky to have been in the right place at the right time. The good news is that I am young enough that I will hopefully see the real fruits of all of this labor. I look forward to the day when I tell residents in disbelief that HCV, that simple disease that we cure with a few weeks of pills, was the commonest indication for liver transplantation and the infectious disease that led to the greatest number of lives lost in Canada. I am not sure that I will see a world without HCV but I am optimistic that I will live in and visit many countries free of HCV. Making that a reality will be no small task; but it will be well worth the effort."

Jean-Michel Pawlotsky

"Three generations of scientists/hepatologists who witnessed the miracle of hepatitis C, from discovery to cure, joined their forces and memories to write this article. It has been an incredible luck and honor to be part of the HCV story, with them. This is not the end of the tunnel, but we see the light. Although I am not as young as Jordan Feld, I still hope I will also see the real fruits of all of this labor. . .."

Conflict of interest disclosure

Jean-Michel Pawlotsky has received research grants from Gilead Sciences. He has served as a scientific advisor for Abbvie, Achillion, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Idenix, Janssen, Merck, Novartis, and Roche.

Jordan J. Feld has received research grants from Abbvie, Boehringer-Ingelheim, Gilead Sciences, Janssen and Merck. He has served as a scientific advisor to Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and Theravance.

Stefan Zeuzem has served as a scientific advisor to Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck.

Jay H. Hoofnagle has no conflicts of interest or financial disclosures regarding diagnosis, management or therapy of hepatitis C. He is an employee of the United States National Institutes of Health and this manuscript was prepared as a part of his official responsibilities.

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