

Advances in newly developing therapy for chronic hepatitis C virus infection

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Abstract Chronic hepatitis C virus (HCV) infection afflicts a reported 170 million people worldwide and is often complicated by cirrhosis and hepatocellular carcinoma. Morbidity and mortality are decreased with the successful treatment of chronic HCV infection. Increased understanding of the HCV has allowed further development of new direct-acting antiviral (DAA) agents against the HCV and has also allowed the development of IFN-free oral treatment regimens. In late 2013 the first nucleotide polymerase inhibitor regimen with RBV alone for genotypes 2/3 and in combination with a 12-week regimen of PEG-IFN + RBV for genotypes 1, 4 was approved for use in the US. A number of promising new DAA regimens which are IFN-free are in phase 3 development and the first will likely be approved for use in the US in 2014. The currently approved regimens are discussed in detail and currently available data on future regimens are reviewed herein.

Keywords direct-acting antiviral (DAA); nucleotide polymerase inhibitors; protease inhibitors

Introduction

A greater understanding of the hepatitis C virus (HCV) genome and proteins has enabled efforts to improve efficacy and tolerability of HCV treatment. Notably, multiple direct-acting antivirals (DAAs)—medications targeted at specific steps within the HCV life cycle—have been developed (Fig. 1). DAAs are molecules that target specific nonstructural proteins within the HCV, which results in disruption of viral replication and infection. There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. The four classes are NS3/4A protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors [1].

NS3/4A protease inhibitors

PIs are inhibitors of the NS3 protease, which is an enzyme involved in post-translational processing and replication of the HCV. The NS3 protease has a binding site, an NS2/NS3 proteinase substrate recognition site, a helicase RNA binding

site, and a zinc binding site. NS3 forms a heterodimeric complex with NS4A, a membrane protein that acts as a cofactor. PIs disrupt the HCV by blocking the NS3 catalytic site or the NS3/NS4A interaction [2].

In May 2011, the US Food and Drug Administration (FDA) approved the first DAAs, telaprevir and boceprevir, for the treatment of HCV [3,4]. Both compounds are first-generation PIs that were approved for use in conjunction with pegylated interferon (PEG-IFN) and ribavirin (RBV) in HCV genotype 1-infected (GT 1) individuals. This includes compensated cirrhotics who are treatment-naïve or had failed previous therapy. Telaprevir and boceprevir increase SVR rates to 75% and 67%, respectively. The difficulties encountered with first-generation PIs include cumbersome use: each requires multiple pills to be taken three times a day, and telaprevir needs to be administered with at least 20 g of fat. In clinical trials, 10%–12% of patients discontinued therapy due to adverse events (AEs), and 36%–45% developed significant anemia (< 10 g/dl) [5–8]. One of the significant AEs of telaprevir is a rash, occurring in up to 56% of cases. Most of these are mild; however, fatal and nonfatal serious skin reactions, including Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis, have been reported in patients treated with telaprevir combination therapy [9].

First-generation PIs have also been found to have a low barrier to resistance. The HCV has pre-existing amino acid

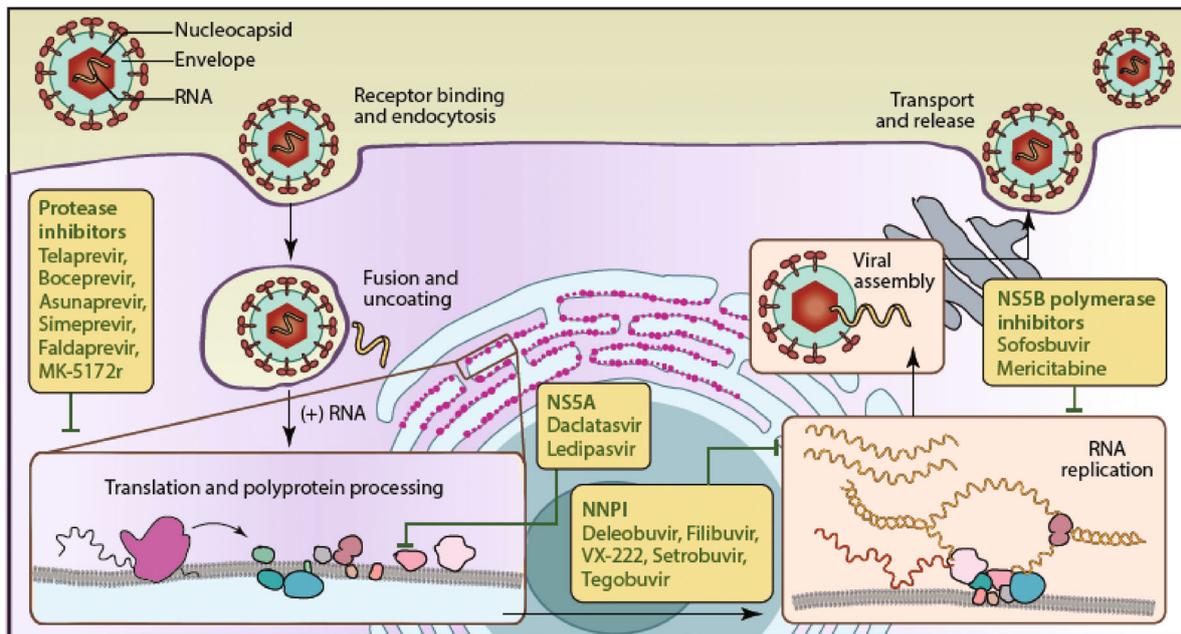


Fig. 1 Mechanism of action of antiviral therapies.

substitutions, which are usually found at low levels; however, these resistant strains may be selected within a short period of time once HCV treatment begins [10]. In addition to the problems with side effects and viral resistance, the use of first-generation PIs has also been significantly restricted due to a large number of drug-drug interactions with compounds that are commonly used for human immunodeficiency virus (HIV) infection, immunosuppression, hyperlipidemia, and pulmonary hypertension [3,4].

Second-generation PIs currently in development are generally thought to have fewer drug-drug interactions, improved dosing schedules, and less frequent and less severe side effects. Many of the second-generation PIs are macrocyclic molecules, which have been shown to be generally more potent and, depending on the location of the macrocycle, able to retain activity against resistant variants. Common wild-type and drug-resistant variants of the NS3 protein include Q80K, R155K, V36M/R155K, A156T, and D168A [11]. Second-generation PIs have also shown increased efficacy against genotype 1; however, they still have limited efficacy against other genotypes [12].

Simeprevir (SMV, Olysio™) is a second-generation PI that has now been approved for use in genotype 1-infected patients in the US as a single 150 mg capsule taken once daily with food [13]. Prescribing information does not recommend response-guided therapy (RGT), but rather a fixed duration of 12 weeks with PEG-IFN and weight-based RBV, followed by 12 weeks of PEG-IFN + RBV for treatment-naïve or relapse patients (including cirrhosis) or 36 weeks PEG-IFN + RBV

for partial or null responder patients (including cirrhosis). Simeprevir is ineffective in GT1a patients with a baseline Q80K polymorphism, so screening for this mutation prior to therapy has been recommended. Treatment futility rules at weeks 4, 12 and 24 are recommended, as well as sun protection measures due to photosensitivity. There are a number of drug-drug interactions that limit the use of this compound in HIV co-infected patients.

NS5A inhibitors

The NS5A enzyme plays a role in both viral replication and the assembly of the HCV [14,15]. NS5A inhibitors have been shown to significantly reduce HCV RNA and enhance SVR when given in conjunction with PEG-IFN + RBV [16]. As a class, these drugs are generally quite potent and are effective across all genotypes, but they have a low barrier to resistance and variable toxicity profiles. A number of NS5A inhibitors, such as ledipasvir (GS-5885) and daclatasvir (BMS-790052), have completed phase 3 trials and results are very promising (discussed below).

NS5B RNA-dependent RNA polymerase inhibitors

NS5B is an RNA-dependent RNA polymerase involved in post-translational processing that is necessary for replication

of the HCV. The enzyme has a catalytic site for nucleoside binding and at least four other sites at which a non-nucleoside compound can bind and cause allosteric alteration. The enzyme's structure is highly conserved across all HCV genotypes, giving NS5B inhibitors efficacy against all six genotypes [2].

There are two classes of polymerase inhibitors: nucleoside/nucleotide analogs (NPIs) and non-nucleoside analogs (NNPIs). The NPIs target the catalytic site of NS5B and result in chain termination while NNPIs act as allosteric inhibitors.

Nucleot(s)ide polymerase inhibitors (NPIs)

Nucleotide inhibitors are activated within the hepatocyte through phosphorylation to nucleoside triphosphate, which competes with nucleotides, resulting in chain termination during RNA replication of the viral genome. As a class, they have moderate to high efficacy across all six genotypes, have a very high barrier to resistance, are equally effective in genotypes 1a and 1b, and are taken once daily. However, the drug class as a whole has been plagued with toxicity problems limiting the number of drugs that have completed phase 3 development [2].

Sofosbuvir (SOF, Sovaldi™) is the first NS5B NPIs to be approved for use in the US. Sofosbuvir is a prodrug and undergoes intracellular metabolism to GS-461203, which is pharmacologically active and is incorporated into HCV RNA by NS5B polymerase where it acts as a chain terminator [17]. It is given as a single 400 mg tablet once daily with or without food [17]. Sofosbuvir efficacy has been established in GT 1, 2, 3 or 4 infection, including patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection. Mono-infected and HCV/HIV-1 patients with GT 1 or 4 infection are treated with 12 weeks in combination with PEG-IFN + RBV, whereas GT 2 and 3 patients are treated without PEG-IFN (GT 2 for 12 weeks and GT 3 for 24 weeks). Because no dose adjustment is needed for cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir, this drug regimen is a potential major breakthrough for HCV therapy in HIV co-infected, pre- and post-liver transplant and interferon (IFN)-ineligible patients.

Sofosbuvir has a very high resistance barrier [18,19]. Resistance testing in phase 2 trials (ATOMIC [20], PROTON [21] and ELECTRON [22]) and phase 3 trials (NEUTRINO [23], FISSION [23], POSITRON [24] and FUSION [24]) revealed that the S282T resistance mutation was not detected in any patient receiving sofosbuvir in combination with RBV with or without PEG-IFN. The S282T resistance mutation was detected in one patient with HCV genotype 2b infection who received sofosbuvir monotherapy in the phase 2 ELECTRON study [22].

The phase 3 non-placebo controlled, multicenter NEU-

TRINO trial examined the efficacy of 12 weeks' therapy with sofosbuvir plus PEG-IFN + RBV in treatment-naïve patients with chronic HCV GT 1, 4, 5 or 6 infection ($n = 327$) [23]. A sustained virological response was seen 12 weeks (SVR12) after the end of treatment (primary endpoint) in 90% of patients. When analyzed by HCV genotype, a sustained virological response was seen in 89% of the patients ($n = 291$) with HCV GT 1 infection, in 96% ($n = 28$) with HCV GT 4 infection, in the 1/1 patient with HCV GT 5 infection and in 6/6 patients with HCV GT 6 infection. The presence of cirrhosis or a non-CC IL28B genotype were associated with a reduced SVR12 [23].

The phase 3 randomized, open-label, multinational FISION trial examined the non-inferiority of 12 weeks' therapy with sofosbuvir plus RBV ($n = 256$) versus 24 weeks' therapy with PEG-IFN + RBV ($n = 243$) in treatment-naïve patients with chronic HCV GT 2 or 3 infection [23]. The SVR12 (primary endpoint) was 67% with sofosbuvir plus RBV and 67% with PEG-IFN + RBV. In patients with GTE2 there were very high (95%) while those with GT 3 were less impressive (56%) [23].

The phase 3 randomized, double-blind, multinational POSITRON trial compared the efficacy of 12 weeks' therapy with sofosbuvir plus RBV ($n = 207$) with that of placebo ($n = 71$) in patients with chronic HCV GT 2 or 3 infection who were IFN-intolerant, -ineligible or -unwilling [24]. The SVR12 was significantly higher with sofosbuvir plus RBV than with placebo (78% vs. 0%; $P < 0.001$). SVR12 rates were significantly lower among patients with HCV genotype 3 versus HCV genotype 2 infection [24].

The phase 3 randomized, double-blind, multinational FUSION trial examined the efficacy of sofosbuvir plus RBV for 12 weeks ($n = 103$) or 16 weeks ($n = 98$) in patients with chronic HCV GT 2 or 3 infection who had not responded to prior treatment with an interferon-containing regimen [24]. Among patients receiving 12 or 16 weeks' therapy with sofosbuvir plus ribavirin, SVR12 rates were 50% and 73%, respectively; these rates were significantly ($P < 0.001$) higher than the historical SVR of 25% seen in this patient population. Secondary analysis revealed that the SVR12 was significantly ($P < 0.001$) higher with 16 than with 12 weeks' treatment with sofosbuvir plus RBV, especially in the GT 3 patients. Sustained virological response rates were significantly lower among patients with HCV genotype 3 versus HCV genotype 2 infection [24].

The phase 3 randomized, double-blind, multinational VALENCE trial compared the efficacy of 12 weeks' therapy with sofosbuvir plus ribavirin ($n = 334$) with that of placebo ($n = 85$) in patients who were treatment naïve or had not achieved an SVR with previous interferon-based treatment and who had chronic HCV GT 2 or 3 infection [25]. In patients with HCV GT 2 infection who received 12 weeks' therapy with sofosbuvir plus RBV, the SVR12 rates were 93% overall, and 97% and 90% in treatment-naïve and treatment-experienced patients, respectively. In patients with

HCV GT 3 infection who received 24 weeks' therapy with sofosbuvir plus RBV, the SVR12 rates were 84% overall, and 93% and 77% in treatment-naïve and treatment-experienced patients, respectively [25].

The phase 3 non-comparative, multicenter PHOTON-1 trial examined the efficacy of sofosbuvir plus RBV in patients with chronic hepatitis C who were co-infected with HIV-1 [26]. Treatment-naïve patients had HCV GT 1, 2 or 3 infection, and treatment-experienced patients had HCV genotype 2 or 3 infection. Among patients with HCV GT 1 infection ($n = 114$) or HCV genotype 3 infection ($n = 13$) who received sofosbuvir plus RBV for 24 weeks, the SVR12 rates were 76% and 92%, respectively. Among patients with HCV GT 2 infection who received sofosbuvir plus RBV for 12 weeks ($n = 26$), the SVR12 was 88% [26].

In a phase 2 study patients with chronic hepatitis C (any genotype) and HCC who were awaiting liver transplantation ($n = 61$) received sofosbuvir plus ribavirin for up to 48 weeks [27]. All patients met the Milan criteria and had well compensated cirrhosis (MELD < 15). Among the 36 patients who were evaluable 12 weeks post-transplantation, the virological response rate (primary endpoint) was 64% [27]. However, the SVR12 was clearly associated with clearance of virus for 4 weeks or more prior to transplant that resulted in cure of all but 1 of 28 patients. In a non-comparative, phase 2 trial treatment-naïve or treatment-experienced patients with recurrent HCV infection (any genotype) following liver transplantation ($n = 40$) received sofosbuvir plus RBV for up to 24 weeks [28]. Interim results indicate that a sustained virological response was achieved 4 weeks post-treatment in 21 of 26 evaluable patients (81%) [28].

Non-nucleoside polymerase inhibitors (NNPIs)

The antiviral potency of NNPIs as monotherapy is less than that of NS3 PIs. The four allosteric sites that act as targets for NNPIs are thumb domains 1 and 2 and palm domains 1 and 2. As a class, NNPIs are less potent, tend to only be effective in genotype 1, have a low to moderate barrier to resistance, and have variable toxicity profiles [2]. Consequently, this class of drug has been used primarily as an adjunct to more potent compounds with higher barriers to resistance (See Table 1 for summary of advantages and disadvantages of the 4 classes of drugs).

Cyclophilin B inhibitors

Cyclophilin B is expressed in many types of human tissue and is critical for HCV replication by a number of incompletely understood mechanisms, such as the modulation of NS5B activity. Debio-025 (alisporivir) is an orally bioavailable cyclophilin B inhibitor exerting an antiviral impact on both

HCV and HIV replication. In clinical trials in HIV- and HCV-co-infected patients, treatment with 1200 mg alisporivir twice daily for 2 weeks led to a mean maximal \log_{10} reduction of HCV RNA of 3.6 and of HIV DNA of 1.0 [29].

Combination therapy using alisporivir 200, 600, or 1000 mg and PEG-IFN α -2a was evaluated in a phase 2 trial in treatment-naïve patients infected with HCV genotypes 1, 2, 3, or 4 and showed mean \log_{10} reductions in HCV RNA at day 29 of 4.75 (1000 mg), 4.61 (600 mg), and 1.8 (200 mg) across all 4 genotypes [30]. Alisporivir was generally tolerated but led to a reversible bilirubin increase. Development was put on hold in 2012 due to a death from pancreatitis in a patient who received the drug in combination with PEG-IFN-RBV [31]. The drug will now continue to be developed in interferon-free regimens.

Combination interferon-free regimens in development

Clearly IFN-free and RBV-free regimens are highly desirable due to the tolerability and safety issues associated with the two compounds. Many studies assessing the combination of 2 or more drugs without IFN or RBV have shown good efficacy in GT1b patients [32]. However, patients with GT1a infections, cirrhosis, prior treatment-failures, and HIV co-infection have proven to be more of a challenge. A number of recent studies not yet published have shown a significant breakthrough in these barriers with IFN-free and RBV-free regimens (for more information, see Table 1 "Phase 3 Trials of Interferon-free Regimens for the Treatment of HCV Infection" in Liang TJ, Ghany MG. Therapy of Hepatitis C — Back to the Future. *N Engl J Med*. Published on May 4, 2014, and updated on May 8, 2014, at NEJM.org. DOI: 10.1056/NEJMe11403619).

The combination of the NS5B NPI, SOF 400 mg, and the NS5A inhibitor, ledipasvir 90 mg (LDV), has been formulated in a fixed dose combination (FDC) tablet. This single tablet has proven extremely effective (SVR rates > 95%) in GT1 treatment-naïve patients and in difficult-to-treat populations in a 12-week regimen [33]. In a recently presented update from the ELECTRON studies, it was demonstrated that the addition of RBV to the FDC of SOF/LDV substantially enhances cure rates in patients with cirrhosis [34]. Alternatively, rather than administering RBV, the addition of a 3rd DAA (GS-9669) also enhances cure rates [31]. A 6-week regimen of the FDC of SOF/LDV is associated with increased relapse rates compared to 8 or 12 weeks, suggesting that this duration may be too short.

A combination of a ritonavir-boosted PI, an NNPI, and RBV has also been investigated as a possible IFN-free regimen [35]. ABT-450, a PI, along with low-dose ritonavir (ABT-450/r), ABT-333 (an NNPI), and RBV were given to non-cirrhotic GT 1 patients in a phase 2a, open-label, multicenter study and showed very high SVR rates.

Table 1 Comparison of DAAs in development for the treatment of chronic HCV

	Class	Study phase	Proposed therapy	Genotype studied	Previous treatment	Endpoint	Percent achieving endpoint	Adverse events
Asunaprevir	NS3 PI	II	TRIPLE: 600 mg BID×12 weeks + PEG-IFN/RBV for 24–48 weeks	1	Naïve	RVR at 4 and 12 weeks SVR	eRVR in 75% SVR in 83%	Hepatotoxicity
Simeprevir	NS3/4A PI	III	TRIPLE: 150 mg daily×12 weeks + PEG-IFN/RBV	1	Naïve	SVR12	81% overall 65% in cirrhotics	Fatigue, headache, pruritis, hyperbilirubinemia, rash
		III	TRIPLE: 150 mg daily×12 weeks + PEG-IFN/RBV	1	Relapse	SVR12	79% overall, 70% genotype 1a and 86% 1b	
Faldaprevir	NS3/4A PI	III	TRIPLE: 120 mg a day vs. 240 mg a day vs. placebo×12 weeks + PEG-IFN/RBV for 24 weeks	1	Naïve	SVR12	79% at 120 mg dose 80% at 240 mg dose	Rash, photosensitivity, unconjugated hyperbilirubinemia, anemia
MK-5172	NS3/4A PI	II	100 mg vs. 200 mg vs. 400 mg vs. 800 mg a day ×12 weeks + PEG-IFN/RBV ×24–48 weeks	1	Naïve	SVR24	86% at 100 mg 92% at 200 mg 91% at 400 mg 87% at 800 mg no effect of IL28B on SVR	Hyperbilirubinemia, elevated transaminases seen at higher doses. Rash, anemia
Daclatasvir	NS5A	III	3 mg vs. 10 mg vs. 60 mg a day + PEG-IFN/RBV ×48 weeks	1	Naïve	RVR at 4 and 12 weeks	42% at 3 mg 83% at 10 mg 75% at 60 mg	Diarrhea, headache
Sofosbuvir	NPI	III	400 mg daily + PEG-IFN/RBV	1, 4, 5, 6	Naïve	SVR12	89% genotype 1 96% genotype 4 100% genotypes 5 and 6	Fatigue, headache, nausea and insomnia
			400 mg daily + RBV×12 weeks vs. PEG-IFN/RBV ×24 weeks	2, 3	Naïve	SVR12	67% with sofosbuvir 67% with PEG-IFN/RBV	
Mericitabine*	NPI	II	1000 mg daily ×24 weeks + PEG-IFN/RBV×24–48 weeks	1, 4	Naïve	SVR12	56.8% vs. 36.5% placebo	Fatigue, headache, nausea
Deleobuvir*	NNPI	II	600 mg 3× a day + PEG-IFN/RBV ×28 days	1	Naïve	RVR	58%	GI events, rash, hyperbilirubinemia
VX-222*	NNPI	II	100 mg or 400 mg daily + DUAL: telaprevir vs. TRIPLE: tvr + RBV QUAD: tvr + RBV + IFN	1	Naïve	RVR at 12 weeks	85% on 100 mg QUAD therapy 90% on 400 mg QUAD therapy	Fatigue, GI upset
Setrobuvir*	NNPI	II	200 mg or 400 mg 2× a day + PEG-IFN/RBV	1	Naïve	SVR12	SVR equal between PEG-IFN/RBV and therapy with setrobuvir	Rash
Tegobuvir*	NNPI	II	40 mg 2× a day + DUAL: GS-9256 TRIPLE: GS-9256/RBV QUAD: GS-9256/PEG-IFN/RBV	1	Naïve	RVR at 28 days	7% DUAL 38% TRIPLE 100% QUAD	Transient elevations in bilirubin

*Development halted in the US in phase 2.

Subsequently, a larger study (AVIATOR) used a regimen with the addition of ABT-267, an NS5A inhibitor, and showed SVR rates of 93%–99% in treatment-naïve and null-responder patients [36]. No relapses were seen after treatment in any patients who received quadruple therapy for 12 or 24 weeks, and there was no clinically significant difference in response based on sex, HCV subtype, IL28B genotype, or fibrosis stage. A recent presentation has shown that RBV is not necessary if this regimen is used in a GT1b-infected treatment-naïve or null responder population [37].

The 12-week, IFN-free and ribavirin-free all-oral 3 DAA regimen with the NS5A inhibitor, daclatasvir (DCV), the second-generation PI, asunaprevir (ASV) and the NNPI, BMS-791325 achieved SVR12 in > 90% of patients even in GT1a or advanced fibrosis/cirrhosis [38]. This critical proof-of-concept study demonstrates that a combination of 3 DAAs without RBV can achieve SVR12 rates of 94% in a G1 treatment-naïve (TN) population. The data are a foundation for multiple large randomized phase 3 trials using this regimen in TNs, treatment-failure, cirrhotics, HIV co-infected and other genotypes, and thus it is important to the development of IFN- and RBV-free therapies for HCV.

The lack of efficacy seen in GT1a with the dual therapy published in 2012 [39] was successfully overcome simply by adding a NNPI. The implications may extend to other IFN-free DAA regimens in development, i.e., a NS5B NPI may not be required for the backbone of therapy, as it appears to be the case based on sofosbuvir studies [23,24]. Rather, a best-in-class drug, here daclatasvir for the NS5A class, may be added to 2 other relatively weak compounds and still have > 90% SVR rates as an IFN-free regimen.

A randomized, open-label trial examined the efficacy of various regimens comprising sofosbuvir and daclatasvir in non-cirrhotic, treatment-naïve patients with chronic HCV GT 1, 2 or 3 infection [40]. SVR12 was seen in 15 of 15 (100%) patients with HCV GT 1 infection and in 14 of 16 (88%) patients with HCV GT 2 or 3 infection who received sofosbuvir for 7 days followed by sofosbuvir plus daclatasvir for 23 weeks, in 14 of 14 (100%) patients with HCV GT1 infection and in 14 of 14 (100%) patients with HCV GT 2 or 3 infection who received sofosbuvir plus daclatasvir for 24 weeks, and in 15 of 15 (100%) patients with HCV GT 1 infection and in 12 of 14 (86%) patients with HCV GT 2 or 3 infection who received sofosbuvir plus daclatasvir and ribavirin for 24 weeks [40]. In non-cirrhotic patients with HCV genotype 1 infection who had previous breakthrough, relapse or nonresponse to PEG-IFN + RBV in combination with telaprevir or boceprevir ($n = 41$), 24 weeks' therapy with either sofosbuvir plus daclatasvir or sofosbuvir plus daclatasvir and ribavirin was associated with a sustained virological response rate at 4 weeks post-treatment of 100% [40].

Another once-daily PI in phase 3 development, faldaprevir, also allows for once daily dosing in comparison to telaprevir/boceprevir based HCV therapy with comparable high SVR

rates when used in a triple therapy in HCV treatment-naïve patients [41]. In an IFN-free combination with a NNPI, deleobuvir, faldaprevir has proved to be effective in GT1b, but not GT1a, patients and development of this regimen has been stopped [42].

Impressive SVR rates of > 95% were obtained in the first all oral combination of a pan-genotypic potent PI, MK-5172 and a NNPI, MK-8742 in GT1a and GT1b patients [43]. In addition, ribavirin is not needed for treatment of GT1b patients. We have not yet seen this combination in more challenging patient populations such as cirrhotics and null-responders, however, these studies are ongoing.

Prior trials have shown that many G1 HCV-infected patients are ineligible for or intolerant to PEG-IFN-based regimens due to prior severe side effects, worsening of cytopenias, exacerbation of underlying psychiatric disorders, or autoimmune disorders. These patients will not be candidates for treatment with the approvals of SMV and SOF due to the inclusion of with PEG-IFN in the GT1 treatment regimens [23,24]. The results of the COSMOS study, combining SOF + SMV, suggest that these patients are likely to have excellent responses to 12 weeks of therapy of SMV + SOF with or without RBV, and that 24 weeks are unnecessary [43]. These patients achieved an overall SVR among 171 patients of 89%. These data suggest that this combination regimen is compelling, even if the patient is Q80K-positive. Patients who fell into this group had an SVR of 86%–90%, compared to 100% for those who were Q80K-negative.

Thus, in many ways, the future of HCV therapy has now arrived: we have IFN-free treatments that are FDA-approved for GT 2 and 3 and potential IFN-free regimens that are not FDA-approved, but have been shown effective for GT 1 patients. We are rapidly approaching an era where IFN-free regimens that are safe, easy to take, well tolerated and short duration will be available, likely in late 2014. We can anticipate at least 4 different IFN-free regimens that will be available by 2015, which will allow the treatment market to be more competitive (Fig. 2). Despite their high cost, these treatments should be cost-effective and available for many Americans under health care reform, thus reducing the disease burden of HCV for the next decade [44].

Compliance with ethics guidelines

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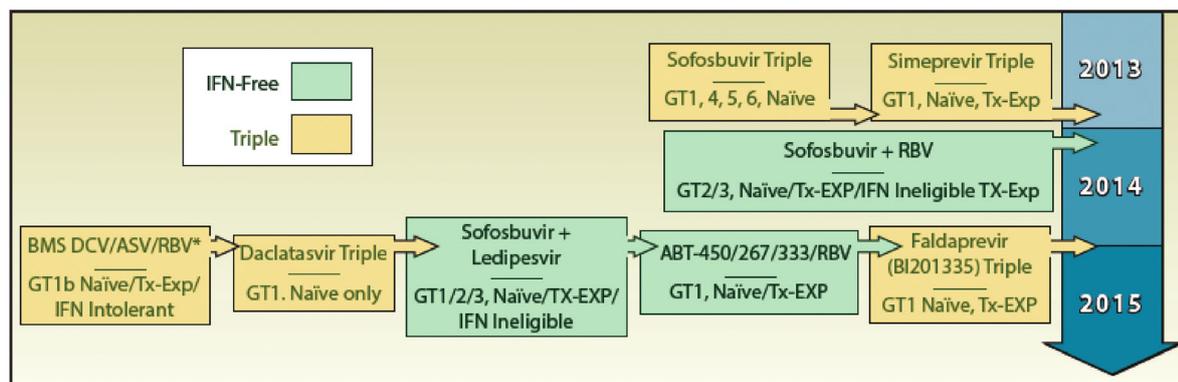


Fig. 2 Timing for new regimen launches.

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