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New Hepatitis C Therapies: The Toolbox, Strategies, and Challenges

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Therapy for hepatitis C is undergoing a revolution. Several new drugs against the hepatitis C virus (HCV) have reached the market and many others, including direct-acting antivirals and host-targeted agents, are in phase II or III clinical development. All-oral, interferon-free combinations of drugs are expected to cure more than 90% of infections. A vast amount of data from clinical trials are presented regularly at international conferences or released to the press before peer-review, creating confusion in the viral hepatitis field. The goal of this review is to clarify the current stage of HCV therapy and drug development. This review describes the different classes of drugs and their mechanisms and properties, as well as treatment strategies in development, including those that are interferon-based and interferon-free. HCV treatment options that will be available in 2014–2015 are presented for each genotype. A number of unanswered questions and challenges remain, such as how to treat special populations, the role of ribavirin in interferon-free regimens, the role of HCV resistance in treatment failures, and how to best re-treat patients who failed on treatment. Strategic choices, cost issues, HCV screening, and improving access to care in resource-constrained areas also are discussed.

Keywords: Direct-Acting Antivirals; Interferon-Free Regimens; Sofosbuvir; Simeprevir; Daclatasvir.

Hepatitis C therapy is undergoing a revolution. After nearly 25 years of incremental improvements of interferon (IFN)α-based therapies, enormous research and development efforts have produced a large number of new antiviral drugs, including direct-acting antiviral (DAA) and host-targeted agents (HTAs). More than 90% of infections were reported to be cured in phase II and III trials, with or without pegylated IFNα and/or ribavirin. As we begin 2014, the toolbox (the number and diversity of available hepatitis C virus [HCV] drugs) is impressive. The strategies are clear and moving forward. However, a number of unresolved issues remain.

The Toolbox

Pegylated IFNα and Ribavirin

Pegylated IFNα will remain the backbone of some HCV treatment strategies in 2014 and 2015, before slowly but definitively disappearing from HCV treatment regimens—at least in areas of the world that will be able to afford the high cost of IFN-free combinations. Ribavirin can be used to increase rates of sustained virologic response (SVR) (ie, rates of infection cure) or to shorten treatment duration without altering the rates of SVR with both pegylated IFNα and IFN-free regimens, because it prevents relapses through unknown mechanisms. It therefore could remain a useful adjunct in some IFN-free treatment strategies.

DAAs and HTAs

The HCV life cycle is now well understood.[1–4] In theory, every step of the viral life cycle can be the target of specific inhibitory approaches through various mechanisms.[5] However, antiviral drugs already on the market or in clinical development include only inhibitors of HCV polyprotein maturation (NS3-4A protease inhibitors) and inhibitors of HCV RNA synthesis (ie, viral replication; all the other DAAs or HTAs in development). Both antiviral approaches efficiently shutdown virus production in infected cells. Inhibition of viral protein maturation also inhibits replication because functional nonstructural viral proteins are no longer generated and thus cannot be used for the formation of replication complexes. Conversely, blocking HCV replication also blocks viral protein synthesis because the amount of HCV-RNA genomes that can be used as messenger RNAs dramatically decreases in the cells. Although a number of alternative mechanisms of antiviral inhibition have been explored, it is likely that no other classes of drugs will be needed in the future and that only improved generations of the current drug classes will be developed.

Table 1 shows the DAAs and HTAs in clinical development at the beginning of 2014. Their antiviral effectiveness is high and can be optimized by combining several drugs with additive or synergistic effects. These drugs differ in their activity against the different HCV genotypes[6] and their barrier to resistance. Given as monotherapies, drugs with a low barrier to resistance rapidly select fit pre-existing viral

Abbreviations used in this paper: **DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTA, host-targeted agent; IFN, interferon; RdRp, RNA–dependent RNA polymerase; SVR, sustained virologic response.**

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Table 1. DAAs and HTAs in Clinical Development at the Beginning of 2014

Agent class	Generation	Compound	Manufacturer	Phase of clinical development
NS3-4A protease inhibitors	First-wave, first-generation	Telaprevir	Vertex, Janssen, Mitsubishi	Approved
		Boceprevir	Merck	Approved
	Second-wave, first-generation	Simeprevir	Janssen	Approved
		Faldaprevir	Boehringer-Ingelheim	III
		Asunaprevir	Bristol-Myers Squibb	III
		ABT-450/r	Abbvie	III
		Danoprevir/r	Roche	II
		Sovaprevir	Achillion	II[a]
		Vedroprevir	Gilead	II
		IDX320	Idenix	II
		Vaniprevir	Merck	III (Japan)
	Second-generation	MK-5172	Merck	III
		ACH-2684	Achillion	II
Nucleoside/nucleotide analogues	Nucleotide analogues	Sofosbuvir	Gilead	Approved
		VX-135	Vertex	II[b]
	Nucleoside analogue	Mericitabine	Roche	II
Non-nucleoside inhibitors of the HCV RdRp	Thumb domain I inhibitors	BMS-791325	Bristol-Myers Squibb	III
		TMC647055	Janssen	II
	Thumb domain II inhibitors	Lomibuvir	Vertex	II
		GS-9669	Gilead	II
	Palm domain I inhibitors	Dasabuvir	Abbvie	III
		ABT-072	Abbvie	II
		Setrobuvir	Roche	II
NS5A inhibitors	First-generation	Daclatasvir	Bristol-Myers Squibb	III
		Ledipasvir	Gilead	III
		Ombitasvir	Abbvie	III
		PPI-668	Presidio	II
		PPI-461	Presidio	II
		ACH-2928	Achillion	II
		GSK2336805	GlaxoSmithKline	II
		BMS824393	Bristol-Myers Squibb	II
		Samatasvir	Idenix	II
	Second-generation	MK-8742	Merck	II
		ACH-3102	Achillion	II
		GS-5816	Gilead	II
Cyclophilin inhibitors	First-generation	Alisporivir	Novartis	II[c]
		SCY-635	Scynexis	II
Antagonist of miRNA-122	First-generation	Miravirsen	Santaris	II

NOTE. All data presented are based on those presented at international conferences or published.
/r, ritonavir-boosted.
[a]On clinical hold owing to alanine aminotransferase increases and high atazanavir concentrations in HIV-coinfected patients receiving this antiretroviral drug.
[b]On partial clinical hold at high doses owing to reversible alanine aminotransferase increases.
[c]On clinical hold in combination with IFNα, in development with DAAs.

variants bearing amino acid substitutions that confer resistance to their antiviral action.[7] In contrast, drugs with a high barrier to resistance do not select such variants, either because they are unlikely to pre-exist naturally in infected patients (a high genetic barrier) or because they are not fit enough to replicate at clinically meaningful levels if selected.[7] Drugs from the same class share cross-resistance, meaning that the same amino acid substitution(s) confer(s) reduced susceptibility to all drugs from the class, with minor qualitative and quantitative differences. As a result, combining drugs from different classes is mandatory to increase the barrier to resistance of the combination regimen.

NS3-4A protease inhibitors. NS3-4A protease inhibitors are peptidomimetic compounds. They bind into the catalytic site of the enzyme and block post-translational processing of the viral polyprotein at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A, and NS5A/NS5B cleavage sites, preventing the release of functional nonstructural proteins. Two first-wave, first-generation NS3-4A protease inhibitors, telaprevir (Vertex, Cambridge, MA; Janssen, Raritan, NJ; and Mitsubishi, Osaka, Japan) and boceprevir (Merck, Whitehouse Station, NJ) (Table 1), are approved for use in combination with pegylated IFNα and ribavirin in patients infected with HCV genotype 1.[8–11] These drugs are active against genotype 1 (telaprevir also is active against genotype 2) and have low barriers to resistance. They are given every 8 hours (telaprevir can be given every 12 hours).

A number of second-wave, first-generation NS3-4A protease inhibitors have reached phase II or III clinical development, including simeprevir (Janssen),[12] approved in November 2013 in the United States and in May 2014 in the European Union, faldaprevir (Boehringer-Ingelheim, Ingelheim, Germany),[13,14] asunaprevir (Bristol-Myers Squibb, Princeton, NJ),[15] ABT-450 (Abbvie, North Chicago, IL), danoprevir (Roche, Basel, Switzerland),[16] sovaprevir (Achillion, New Haven, CT), vaniprevir (Merck),[17] vedroprevir (Gilead, Foster City, CA),[18,19] and IDX320 (Idenix, Cambridge, MA) (Table 1). These drugs are dosed once or twice per day. They are active against at least genotypes 1, 2, and 4, but none of them has effectiveness against genotype 3. They have a low barrier to resistance and share extensive cross-resistance among them and with telaprevir and boceprevir. ABT-450 and danoprevir are boosted by ritonavir (100 mg/day) to extend dosing intervals while increasing patient exposure and reducing side effects.

Second-generation NS3-4A protease inhibitors, such as MK-5172 (Merck)[20] or ACH-2684 (Achillion), are purported to have pangenotypic antiviral activity, including on genotype 3. However, their antiviral effectiveness against this genotype is less than against others. They have a higher barrier to resistance than first-generation drugs.[21,22] Nevertheless, second-generation NS3-4A protease inhibitors select resistant variants that also are selected by first-generation compounds, including variants with substitutions at position A156, which are unlikely to replicate at high levels in vivo, and variants with substitutions at position D168, which have been associated with virologic breakthroughs with these drugs.[21,22] We therefore await third-generation NS3-4A protease inhibitors with equal antiviral effectiveness against all HCV genotypes and a high barrier to resistance.

Nucleoside/nucleotide analogue inhibitors. Nucleoside/nucleotide analogues act as false substrates for the HCV-RNA–dependent RNA polymerase (RdRp). They lead to chain termination after being incorporated into the newly synthesized viral RNA. Nucleoside analogues, such as mericitabine (Roche),[23] need 3 phosphorylations to be activated. In contrast, nucleotide analogues, such as sofosbuvir (Gilead)[24] and VX-135 (Vertex), need only 2 phosphorylations, making them more rapidly active at the target site (Table 1). Because of their mechanism of action, nucleoside/nucleotide analogues are active against all HCV genotypes. They have a high barrier to resistance because the viral variants they select are not fit enough to replicate at high levels in vitro or in vivo.

Non-nucleoside inhibitors of the HCV-RNA–dependent RNA polymerase. Non-nucleoside inhibitors of HCV RdRp bind to 1 of 4 allosteric sites at the surface of the enzyme.[25] By altering the conformation of the RdRp, they block its catalytic function, thereby indirectly blocking RNA replication. The HCV RdRp is known to have a right hand shape, with a thumb, a palm, and finger domains. Non-nucleoside HCV RdRp inhibitors are split into 4 groups: inhibitors of thumb domain I (BMS-791325 [Bristol-Myers Squibb][26] and TMC647055 [Janssen][27]), thumb domain II (lomibuvir [Vertex][28] and GS-9669 [Gilead][29]), palm domain I (setrobuvir [Roche], dasabuvir, formerly known as ABT-333, and ABT-072 [Abbvie]), and palm domain II (no drug still in clinical development) (Table 1).[25] First-generation non-nucleoside HCV RdRp inhibitors are generally active against essentially HCV genotype 1 and have a low barrier to resistance. Cross-resistance exists between drugs targeting the same allosteric domain and, to some extent, between drugs targeting different sites. Second-generation non-nucleoside inhibitors of HCV RdRp with broader genotypic activity and a higher barrier to resistance are in preclinical development.

NS5A inhibitors. NS5A inhibitors bind to domain 1 of the NS5A protein and block its ability to regulate HCV replication within the replication complex, through unclear mechanisms.[30] In addition, NS5A inhibitors inhibit assembly and release of viral particles.[31,32] This dual mechanism allows for potent and rapid shutdown of virus production during the first days of their administration. First-generation NS5A inhibitors are active against genotypes 1 and 4; not all are active against genotypes 2 and/or 3. They have a low barrier to resistance.[30] First-generation NS5A inhibitors include daclatasvir (Bristol-Myers Squibb),[33] ledipasvir (Gilead),[34] ombitasvir, formerly known as ABT-267 (Abbvie),[35] PPI-668 and PPI-461 (Presidio, San Francisco, CA),[36] ACH-2928 (Achillion),[37] BMS824393 (Bristol-Myers Squibb), GSK2336805 (GlaxoSmithKline, London, United Kingdom),[38] and samatasvir (Idenix) (Table 1).

Second-generation NS5A inhibitors include MK-8742 (Merck),[39] ACH-3102 (Achillion),[40] and GS-5816 (Gilead).[41] They are active against all HCV genotypes, but some of them are less active against genotypes 2 and 3 than other genotypes. Their barrier to resistance is improved compared with first-generation NS5A inhibitors.[21] However, they can select resistant viruses in vivo—especially those with substitutions at NS5A positions Q30, L31, and Y93, which also are selected by first-generation compounds. We await third-generation NS5A inhibitors with pangenotypic activity and a high barrier to resistance.

HTAs. HCV replication can be blocked by targeting cell components that contribute to the HCV life cycle. Because their target is a host protein, these agents have pangenotypic antiviral activity and a high barrier to resistance. Cyclophilin inhibitors inhibit HCV replication by blocking the peptidyl-prolyl *cis-trans* isomerase activity of cyclophilin A, which is required for efficient HCV replication.[42] Drugs in clinical development include alisporivir (Novartis, Basel, Switzerland)[42] and SCY-635 (Scynexis, Research Triangle Park, NC)[43] (Table 1).

An antagonist of microRNA 122, miravirsen (Santaris, Horsholm, Denmark), has shown antiviral activity in vitro and in vivo; it inhibits binding of microRNA 122 to the 5' untranslated region of the HCV genome, which is required for efficient RNA replication.[44,45] This compound is injected and thus unlikely to be used in the era of all-oral therapies. Depletion of microRNA 122 has been associated with the development of hepatocellular carcinomas in mice, raising issues about its safety in human beings.[46]

Future Developments

Researchers aim to improve the currently available classes of HCV drugs. Second- and third-generation NS3-4A protease inhibitors, nucleoside/nucleotide analogues, non-nucleoside inhibitors of HCV RdRp, and NS5A inhibitors that have increased potency, pangenotypic antiviral activity, and high barriers to resistance likely will enter clinical development within the next 2–5 years. It is unlikely that further investment will be made beyond this point because there will be a sufficient number and range of drugs to fulfill clinical needs.

Strategies

In 2014 and 2015, new IFN-containing and IFN-free regimens will become available. Starting in 2015 and onward, IFN-containing regimens will be replaced by all-oral, IFN-free therapies, at least in areas of the world where these regimens are approved and their cost is covered.

Available Strategies

Available strategies include IFN-containing and all-oral, IFN-free regimens.

IFN-containing regimens. The use of IFN is contraindicated in a substantial proportion of patients. It is associated with side effects that can be serious. The results of IFN-based therapies depend mainly on the patients' responsiveness to IFN, which is determined genetically, the absence or presence of cirrhosis, and the HCV genotype. However, IFN-free regimens are not yet available or efficacious enough in some subsets of patients. In addition, IFN-based regimens are generally cheaper than combinations of DAAs without IFN. They thus could be imposed as first-line therapies in some settings. Therefore, IFN-containing regimens still will be used in 2014 and possibly 2015. They probably will be replaced definitively by well-tolerated, highly efficacious, IFN-free regimens in the following years, at least in settings where their costs can be covered.

Triple IFN-containing regimens with a DAA with a low barrier to resistance. Several new triple combinations, including a DAA agent with a low barrier to resistance, will become available in 2014 and afterward. Data from phase III trials of simeprevir and faldaprevir have been presented, along with data from phase II trials of asunaprevir, danoprevir, vaniprevir, and daclatasvir. These trials generally included response-guided therapy, with the total treatment durations varying from 24 to 48 weeks according to the on-treatment virologic response, vs 48 weeks of pegylated IFNα and ribavirin in the control arms (genotype 1).

Simeprevir. In the phase III QUEST-1 and QUEST-2 trials of simeprevir (150 mg once daily), the rates of SVR in treatment-naive HCV genotype 1 patients were 80% (210 of 264) and 81% (209 of 257) vs 50% (65 of 130) and 50% (67 of 134) in the control groups, respectively.[47,48] The rates were 75% and 85% in patients infected with HCV subtypes 1a and 1b, respectively. This difference was owing to a 58% rate of SVR in the subgroup of patients infected with subtype 1a who had a detectable Q80K substitution in the NS3 protease sequence at baseline (approximately one third of cases) vs 84% in those without detectable Q80K. The stage of fibrosis was an important determinant of the response, with rates of SVR in QUEST-1 and QUEST-2 of 83% (152 of 183) and 85% (165 of 195) in patients with mild disease (F0–F2), 78% (36 of 46) and 67% (24 of 36) in patients with extensive fibrosis (F3), and 58% (18 of 31) and 65% (11 of 17) in patients with cirrhosis (F4), respectively.[47,48]

In the PROMISE phase III trial, among prior relapsers infected with genotype 1,[49] 70% (78 of 111) had an SVR for subtype 1a (47% vs 78% in patients with and without detectable Q80K at baseline, respectively), and 86% (128 of 149) had an SVR for subtype 1b, vs 28% (15 of 54) and 43% (34 of 79) in the control groups, respectively.[49]

Results from the phase III C212 study of patients co-infected with human immunodeficiency virus (HIV) showed that 79% of treatment-naive patients achieved an SVR (42 of 53), as did 87% of prior relapsers (13 of 15), receiving 12 weeks of the combination of pegylated IFNα, ribavirin, and simeprevir, followed by response-guided pegylated IFNα and ribavirin therapy (total duration, 24 or 48 weeks). With a fixed duration of 48 weeks (including 12 weeks of the triple combination), the rates of SVR were 70% (7 of 10) in partial responders and 57% (16 of 28) in null responders (Dieterich et al, unpublished data).

Simeprevir was well tolerated in all phase III studies. Pruritus and rashes were slightly more frequent in groups given simeprevir than in the control groups. Approximately 10% of cases developed mild, transient hyperbilirubinemia not accompanied by changes in other liver parameters. At the time of treatment failure, most patients who did not respond to simeprevir therapy harbored variants of HCV with substitutions in the NS3 protease sequence that confer resistance to this class of drugs, including substitutions at positions Q80, R155, and D168.[47–49] Preliminary data also indicate efficacy in patients infected with HCV genotype 4 (Moreno et al, unpublished data).

Faldaprevir. In the phase III trials of STARTVerso1 and STARTVerso2 in treatment-naive patients with genotype 1 infection (pooled analysis),[50] rates of SVR were 73% (382 of 521) and 72% (378 of 524) among patients receiving 120 mg faldaprevir once daily (12 or 24 weeks, response-guided) or 240 mg faldaprevir once daily (12 weeks), respectively, vs 50% (131 of 264) in the control group. In the phase III STARTVerso3 trial in treatment-experienced patients with HCV genotype 1 infection receiving 12 or 24 weeks of faldaprevir, 240 mg daily, the rates of SVR were 70% (69 of 99) and 70% (71 of 102) in prior relapsers (vs 14% in the control group), 58% (33 of 57) and 47% (26 of 55) in prior partial responders (vs 3% in the control group), and 33% (48 of 145) and 33% (46 of 141) in prior null responders (there was no control group), respectively.[51] Results of the STARTVerso4 phase III trial of patients with HIV co-infection receiving response-guided pegylated IFNα, ribavirin, and faldaprevir (for a total of 24 or 48 weeks)

reported SVR rates of 71% (87 of 123) in patients receiving 120 mg faldaprevir daily for 24 weeks, and 72% (134 of 185) in those receiving 240 mg daily for 12 or 24 weeks (pooled rate of SVR).[52]

No baseline polymorphism was associated with a reduced rate of SVR to faldaprevir. Treatment failures were associated with the presence of substitutions in the NS3 protease sequence that confer resistance to protease inhibitors. Faldaprevir was well tolerated. Rashes were reported and protection against sun exposure was included in the study protocols, owing to a relatively high incidence of photosensitivity in phase Ib and II trials. Nauseas and hyperbilirubinemia were more frequent in patients receiving 240 rather than 120 mg of faldaprevir each day.

Other NS3-4A protease inhibitors. In a phase II trial of asunaprevir (200 mg twice daily) for treatment-naive patients infected with genotypes 1 or 4, SVR was achieved in 64% of patients (59% [55 of 94] in subtype 1a, 71% [45 of 63] in subtype 1b) vs 44% (24 of 54) in the control group.[53] Rates of SVR were 68% (49 of 72), 85% (61 of 72), and 76% (38 of 50) in treatment-naive patients with genotype 1 HCV infection and F1–F2 fibrosis who received danoprevir 300 mg every 8 hours, 600 mg every 12 hours, or 900 mg every 12 hours, respectively, compared with 42% (13 of 31) in the placebo group (ATLAS study).[54] In the MATTERHORN and MAD studies, rates of SVR were 30% (8 of 27) in patients without cirrhosis with HCV subtype 1a infection and 82% (18 of 22) in those with HCV subtype 1b infection who were prior partial responders and received ritonavir-boosted danoprevir (100 mg twice daily) for 24 weeks. In null responders receiving the same combination for 12 weeks, 25% (2 of 8) of those with subtype 1a and 88% (14 of 16) of those with subtype 1b HCV infections achieved SVR.[55] With vaniprevir (a drug that will be commercialized only in Japan) the rates of SVR in treatment-experienced patients without cirrhosis, infected with HCV genotype 1, were 67% (26 of 39) and 78% (91 of 117) with 300 or 600 mg twice daily, respectively, vs 19% (8 of 42) in the control group.[56] Among patients with cirrhosis, rates of SVR were 53% (8 of 15) and 68% (28 of 41), respectively, vs 14% in the control group (2 of 14).[57]

Daclatasvir. In treatment-naive patients, 24 or 48 weeks of response-guided triple therapy with 20 or 60 mg/day of the NS5A inhibitor daclatasvir yielded rates of SVR of 59% (63 of 106) and 58% (66 of 113) in subtype 1a subjects (vs 36% [21 of 56] in the control group), 78% (32 of 41) and 87% (27 of 31) in subtype 1b subjects (vs 31% [5 of 16] in the control group), and 67% (8 of 12) and 100% (12 of 12) in genotype 4 subjects (vs 50% [3 of 6] in the control group), respectively.[58] Response-guided triple therapy with daclatasvir (60 mg/day for 12–24 weeks) for treatment-naive patients produced SVR rates of 83% (39 of 47) in those with genotype 2 infection (vs 63% in the control group) and 68% (36 of 53) for those with genotype 3 infection (vs 59% in the control group).[59]

IFN-containing regimens with a DAA or HTA with a high barrier to resistance. A DAA or HTA with a high barrier to resistance maintains low levels of HCV replication during treatment. This restores IFN responsiveness to a substantial proportion of patients who would have virologic breakthroughs if a drug with a low barrier to resistance had been used.

Sofosbuvir. In the NEUTRINO phase III trial of treatment-naive patients,[60] 12 weeks of triple-combination therapy with sofosbuvir, 400 mg once daily, resulted in SVR rates of 89% (259 of 291) in HCV genotype 1 patients (92% [207 of 225] for subtype 1a, 82% [54 of 66] for subtype 1b), and 96% (27 of 28) in genotype 4 patients. The single patient with genotype 5 and all 6 patients with genotype 6 achieved an SVR. In this trial, the overall rates of SVR were 92% (251 of 273) in patients without cirrhosis vs 80% (43 of 54) in those with cirrhosis. Adverse events were similar to those reported with pegylated IFNα and ribavirin alone, and treatment failures were not associated with the selection of resistant HCV variants.[60] In the phase II LONESTAR-2 study of pegylated IFNα, ribavirin, and sofosbuvir (400 mg/day for 12 weeks) in treatment-experienced patients, rates of SVR were 96% (22 of 23) in patients with genotype 2 infection and 83% (20 of 24) in those with genotype 3 infection.[61] There are limited data on the effects of this combination in treatment-experienced patients infected with HCV genotypes 1 or 4–6, particularly for those who did not respond to pegylated IFNα or ribavirin alone.

MK-5172. Administration of pegylated IFNα, ribavirin, and different doses of the second-generation NS3-4A protease inhibitor MK-5172 for 12 weeks, followed by response-guided pegylated IFNα and ribavirin for an additional 12 or 36 weeks, produced SVRs in more than 90% of patients in a small phase II study (vs 54% in the control group, which received boceprevir-containing triple therapy).[62]

Alisporivir. Phase II studies have been conducted of the combination of pegylated IFNα, ribavirin, and the cyclophilin inhibitor alisporivir. However, these trials were stopped because some patients developed severe cases (1 fatal) of acute pancreatitis.

Quadruple IFN-containing regimens with 2 DAAs. Combining 2 DAAs with a low barrier to resistance substantially increases the barrier to resistance. Results have been presented from small studies of the combination of pegylated IFNα, ribavirin, the NS5A inhibitor daclatasvir, and the NS3-4A protease inhibitor asunaprevir in treatment-naive patients and prior nonresponders infected with HCV genotype 1; rates of SVR were about 95%.[63] In the MATTERHORN study of danoprevir and mericitabine in treatment-experienced patients infected with HCV genotype 1, rates of SVR were 75% (18 of 24) and 73% (32 of 44) in prior partial and null responders, respectively, with subtype 1a infection, and 96% (25 of 26) and 100% (30 of 30) in those with subtype 1b infection.[64]

All-oral, IFN-free regimens. Three all-oral, IFN-free strategies are being investigated in phase II and III trials. These include nucleoside/nucleotide analogue-based regimens, nucleoside/nucleotide-free triple combinations of drugs with low barriers to resistance, and nucleoside/

Table 2. All-Oral, IFN-Free HCV Therapeutic Agents in Clinical Development, 2014–2015

Strategy	Company	Nucleoside/ nucleotide analogue	NS3-4A protease inhibitor	NS5A inhibitor	Non-nucleoside inhibitor of HCV RdRp	Cyclophilin inhibitor	Ribavirin
Nucleoside/nucleotide analogue-based strategy	Gilead	Sofosbuvir		Ledipasvir			±
	Gilead	Sofosbuvir		GS-5816			±
	Gilead	Sofosbuvir		Ledipasvir	GS-9669		-
	Gilead	Sofosbuvir	Vedroprevir	Ledipasvir			-
	Gilead/Janssen	Sofosbuvir	Simeprevir				±
	Gilead/Bristol-Myers Squibb	Sofosbuvir		Daclatasvir			±
	Vertex	VX-135			Lomibuvir		
	Vertex/Janssen	VX-135	Simeprevir				±
	Vertex/Bristol-Myers Squibb	VX-135		Daclatasvir			±
	Roche (emerging markets)	Mericitabine	Danoprevir/r		Setrobuvir		±
Nucleoside-free triple combo strategy	Abbvie		ABT-450/r	Ombitasvir	Dasabuvir		±
	Bristol-Myers Squibb		Asunaprevir	Daclatasvir	BMS791325		±
	Boehringer-Ingelheim/Presidio		Faldaprevir	PPI-668	?[a]		±
	Janssen/GlaxoSmithKline		Simeprevir	GSK2336805	TMC647055		±
	Janssen/Idenix		Simeprevir	Samatasvir	TMC647055		±
Nucleoside-free double combo strategy with a high-barrier-to-resistance drug	Merck		MK-5172	MK-8742			±
	Achillion		ACH-2684	ACH-3102			±
	Novartis					Alisporivir	±

/r, ritonavir-boosted.
[a]Deleobuvir development was halted in January 2014 owing to digestive toxicity.

nucleotide-free double combinations that include at least one drug with a high barrier to resistance. Table 2 shows these regimens.

Nucleoside/nucleotide analogue-based strategies. Because of its high barrier to resistance, a nucleoside/nucleotide analogue can be used as a backbone of therapy, in combination with ribavirin, or with 1 or 2 DAAs, with or without ribavirin.

Sofosbuvir plus ribavirin. Phase II studies have indicated that the combination of sofosbuvir and ribavirin is suboptimal in patients infected with HCV genotype 1, with or without HIV infection,[65–68] except for those who will undergo liver transplantation and therefore do not need their liver to be virus-free. In a recent study of patients infected with HCV genotypes 1–4, 93% (41 of 44) of those who received sofosbuvir (400 mg/day) and weight-based ribavirin before liver transplantation (for hepatocellular carcinoma) were HCV-RNA negative at the time of transplantation; HCV RNA was undetectable 12 weeks after transplantation in 64% (25 of 39) of patients.[69] The duration of undetectable HCV RNA before transplantation was the main determinant of prevention of HCV recurrence—the graft became infected in only 1 patient with undetectable HCV RNA for more than 30 days before transplantation.[69]

Results from 4 phase III trials of sofosbuvir, 400 mg/day, and weight-based ribavirin led to the approval of this combination in the United States and Europe for patients infected with HCV genotypes 2 or 3. Figure 1 summarizes results from the phase III sofosbuvir and ribavirin trials based on genotype, prior therapy, and the presence of cirrhosis. In FISSION,[60] sofosbuvir and ribavirin were given to treatment-naive patients for 12 weeks, in comparison with 24 weeks of pegylated IFNα and ribavirin: 95% (69 of 73) of genotype 2 and 56% (102 of 183) of genotype 3 patients achieved an SVR, vs 78% (52 of 67) and 63% (111 of 176) in the pegylated IFNα and ribavirin arms, respectively. Patients without cirrhosis responded better than those with compensated cirrhosis (97% vs 83% in genotype 2 patients, 61% vs 34% in genotype 3 patients) (Figure 1*A–C*).[60]

In the POSITRON trial, 93% of patients with genotype 2 infection (101 of 109) and 61% of those with genotype 3 infection (60 of 98) who were ineligible or intolerant to IFN-based therapy achieved SVRs to the same drug regimen.[70] FUSION compared 12 and 16 weeks of sofosbuvir plus ribavirin in treatment-experienced patients infected with genotypes 2 and 3.[70] Rates of SVR were 82% (32 of 39) and 89% (31 of 35) in genotype 2 (not significant), and 30% (19 of 64) and 62% (39 of 63) in genotype 3, respectively. In patients with cirrhosis, they were 60% (6 of 10) and 78% (7 of 9) for genotype 2, and 19% (5 of 26) and 61% (14 of 23) for genotype 3, respectively (Figure 1*A*, *B*, and *D*).[70] Finally, 12 and 24 weeks of sofosbuvir plus ribavirin were tested in treatment-naive and treatment-experienced patients infected with genotypes 2 and 3 in the VALENCE trial.[71] In genotype 2–infected patients treated for 12 weeks, the SVR

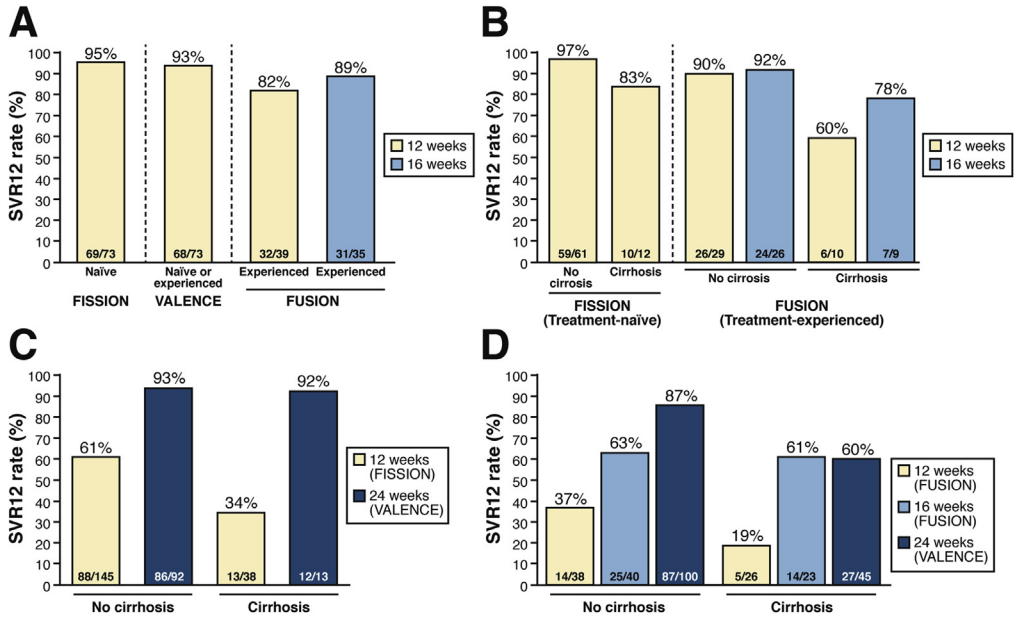

Figure 1. Rates of SVR12 in the FISSION, FUSION, and VALENCE phase III trials. Patients infected with HCV genotypes 2 or 3 received sofosbuvir (400 mg, once daily) plus weight-based ribavirin.[60,70,71] These results were generated in different studies; although the inclusion and exclusion criteria were similar across the 3 studies, the different groups cannot be compared as if patients had been assigned randomly to groups in a single study. (*A*) Rates of SVR12 among treatment-naive and treatment-experienced patients infected with HCV genotype 2, treated for 12 or 16 weeks in the FISSION, VALENCE, and FUSION trials. (*B*) Rates of SVR12 among treatment-naive and treatment-experienced patients infected with HCV genotype 2 according to fibrosis stage (cirrhosis vs no cirrhosis) and treatment duration (12 or 16 weeks) in the FISSION and FUSION trials. (*C*) Rates of SVR12 in treatment-naive patients infected with HCV genotype 3 according to fibrosis stage (cirrhosis vs no cirrhosis) and treatment duration (12 or 24 weeks) in the FISSION and VALENCE trials. (*D*) Rates of SVR12 in treatment-experienced patients infected with HCV genotype 3 according to the fibrosis stage (cirrhosis vs no cirrhosis) and treatment duration (12, 16, or 24 weeks) in the FUSION and VALENCE trials.

rates were 97% (29 of 30) in naive noncirrhotics, 100% (2 of 2) in naive cirrhotics, 91% (30 of 33) in experienced noncirrhotics, and 88% (7 of 8) in experienced cirrhotics. In genotype 3–infected patients treated for 24 weeks, the SVR rates were 93% (86 of 92), 92% (12 of 13), 87% (87 of 100), and 60% (27 of 45) in the same groups, respectively (Figure 1*A*, *C*, and *D*).[71] The combination of sofosbuvir and ribavirin was well tolerated. No virologic breakthroughs were observed among patients who adhered to the regimen, and relapses were not related to the selection of sofosbuvir-resistant HCV variants.[60,70,71]

Sofosbuvir plus another DAA, with or without ribavirin. In patients infected with HCV genotypes other than 2 or 3, the combination of a nucleotide analogue with a second drug with a lower barrier to resistance is a valuable option, providing antiviral potency and a high barrier to resistance. A press release reported preliminary results from 3 phase III trials of treatment-naive and treatment-experienced patients infected with HCV genotype 1 who received the combination of sofosbuvir (400 mg/day) and the NS5A inhibitor ledipasvir (90 mg/day), in a fixed-dose combination (ie, a single pill containing both drugs), for 8–24 weeks (ION trials).[72]

In the ION-1 trial of treatment-naive patients given sofosbuvir/ledipasvir fixed-dose combination (16% with cirrhosis), rates of SVR were 98% (209 of 214) and 97% (211 of 217) after 12 weeks of treatment with or without ribavirin, respectively (Figure 2*A*); results from 24 weeks are pending.[72] In the ION-3 trial in treatment-naive patients with mild to moderate liver disease (F0–F2), the rates of SVR were 94% (202 of 215) without ribavirin for 8 weeks, 93% (201 of 216) with ribavirin for 8 weeks, and 95% (205 of 216) without ribavirin for 12 weeks (Figure 2*A*).[72] Recent data from the National Institutes of Health SYNERGY phase II trial suggest that similar rates of SVR can be achieved after only 6 weeks of therapy when a third DAA (the NS3-4A protease inhibitor vedroprevir or the non-nucleoside inhibitor of HCV RdRp GS-9669) is added to the fixed-dose combination of sofosbuvir and ledipasvir in treatment-naive patients infected with HCV genotype 1 without cirrhosis (100% [20 of 20] and 95% [19 of 20], respectively) (Kohli et al, unpublished data). Finally, in the ION-2 trial in treatment-experienced patients (including 20% with cirrhosis), the rates of SVR after 12 weeks of therapy were 94% (102 of 109) and 96% (107 of 111) with or without ribavirin, respectively. After 24 weeks of therapy, they were 99% (108 of 109) and 99% (110 of 111) with or without ribavirin, respectively (Figure 2*B*).[72] No major safety signal was reported.

Other combinations of sofosbuvir and a DAA with a low barrier to resistance yielded high rates of SVR in smaller phase II trials. In the COSMOS trial, sofosbuvir (400 mg/day) was combined with simeprevir (150 mg/day) for 12 or 24 weeks, with or without ribavirin.[73] In the first cohort of prior null responders with F0–F2 METAVIR scores, rates of SVR were 79% (19 of 24) and 93% (14 of 15) after 24 weeks and 96% (26 of 27) and 93% (13 of 14) after 12 weeks, with or without ribavirin, respectively. Preliminary data from a second cohort of patients with F3–F4 Metavir scores indicated that rates of SVR at week 4 were 100% (7 of 7 and 12 of 12 with and without ribavirin, respectively) in treatment-naive patients, and 100% (7 of 7) and 93% (14 of 15) with and without ribavirin, respectively, in prior null responders.[73] Interestingly, all of the patients with virologic failure were infected with HCV genotype 1a and had a detectable Q80K substitution in the NS3 protease sequence at baseline. This combination was well tolerated.[73]

The combination of sofosbuvir (400 mg/day) and the NS5A inhibitor daclatasvir (60 mg/day) for 24 weeks yielded SVR rates of 100% (14 of 14 and 15 of 15, with and without ribavirin, respectively) in treatment-naive patients infected with genotype 1, 100% (14 of 14) and 93% (13 of 14), respectively, in treatment-naive patients infected with genotypes 2 or 3, and 100% (21 of 21) and 95% (19 of 21), respectively, in patients who did not respond to the combination of pegylated IFNα, ribavirin, and either telaprevir or boceprevir.[74] Forty of 41 treatment-naive patients infected with genotype 1 treated with sofosbuvir and daclatasvir without ribavirin for 12 weeks achieved an SVR (the remaining patient was lost to

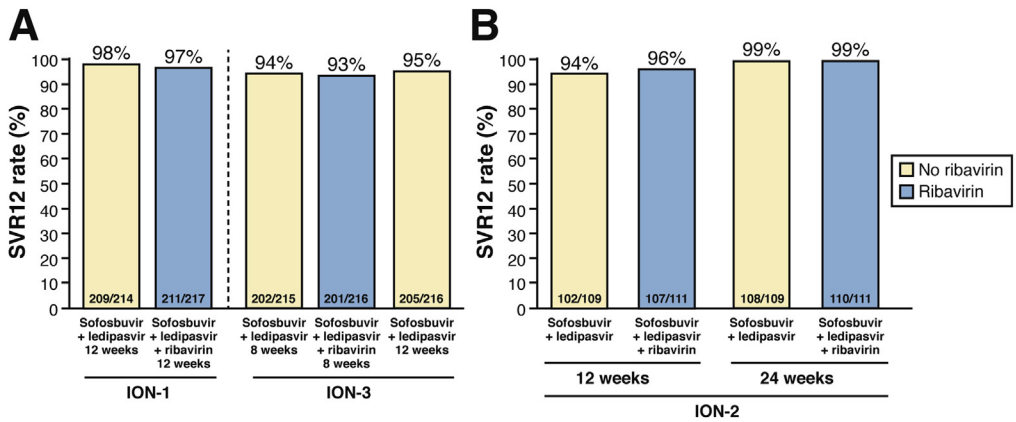

Figure 2. Rates of SVR12 in the ION-1, ION-2, and ION-3 phase III trials. Patients infected with HCV genotype 1 were treated for 8–12 weeks with a combination of sofosbuvir (400 mg, once daily) and ledipasvir (90 mg, once daily) in a fixed-dose combination, with or without ribavirin.[72] (*A*) ION-1 (including 16% [136 of 865] of patients with cirrhosis) and ION-3 trials in treatment-naive patients. (*B*) ION-2 trial (including 20% [88 of 440] of patients with cirrhosis) in treatment-experienced patients.

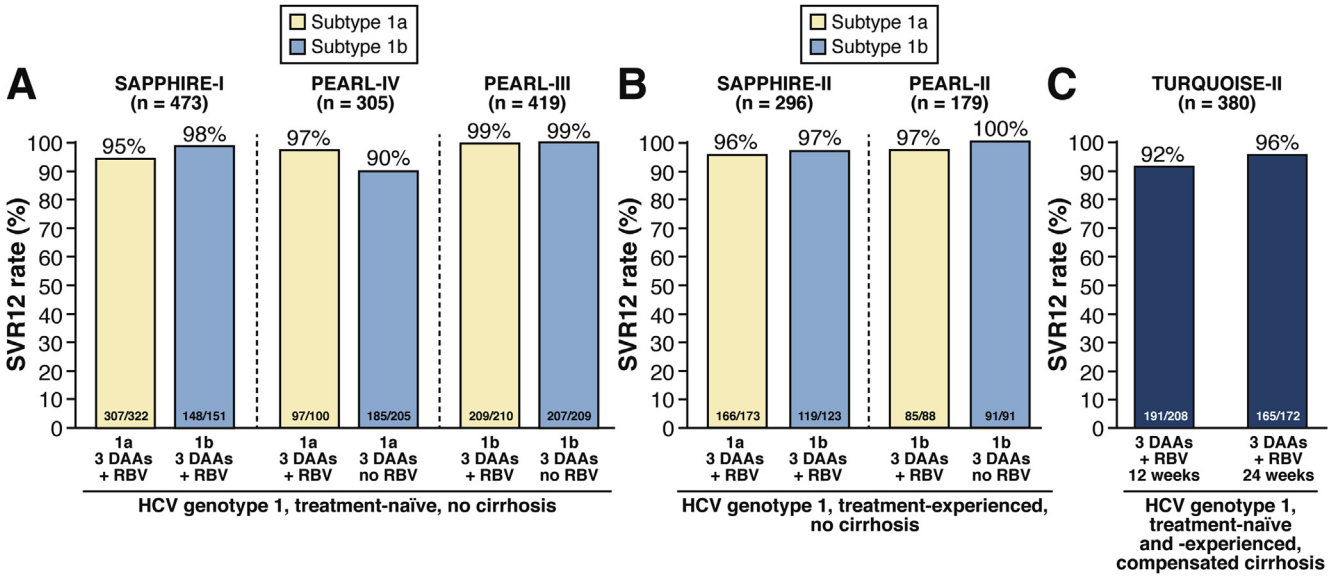

Figure 3. Rates of SVR12 in the SAPPHIRE-I, SAPPHIRE-II, PEARL-II, PEARL-III, PEARL-IV, and TURQUOISE-II phase III trials. Treatment-naive and treatment-experienced patients infected with HCV genotype 1 received 12 or 24 weeks of a combination of ritonavir-boosted ABT-450 (150 mg/100 mg), co-formulated with ombitasvir (25 mg once daily), and dasabuvir (250 mg twice daily), with or without weight-based ribavirin.[80,81] (*A*) Treatment-naive patients without cirrhosis treated for 12 weeks in SAPPHIRE-I (3 DAAs plus ribavirin in patients infected with subtype 1a or 1b), PEARL-IV (3 DAAs with or without ribavirin in patients infected with subtype 1a), and PEARL-III (3 DAAs with or without ribavirin in patients infected with subtype 1b). (*B*) Treatment-experienced patients without cirrhosis treated for 12 weeks in SAPPHIRE-II (3 DAAs plus ribavirin in patients infected with subtype 1a or 1b) and PEARL-II (3 DAAs with or without ribavirin in patients infected with subtype 1b). (*C*) Treatment-naive and treatment-experienced patients with compensated cirrhosis treated for 12 or 24 weeks with 3 DAAs plus ribavirin in TURQUOISE-II.

follow-up evaluation).[74] The combination of sofosbuvir and daclatasvir also has been reported to produce SVRs in patients who have experienced HCV recurrence after liver transplantation.[75]

The nucleotide analogue VX-135 (on partial clinical hold) currently is being tested in combination with simeprevir, daclatasvir, or the non-nucleoside RdRp inhibitor lomibuvir (Table 2).

Nucleoside/nucleotide analogue-free triple-combination strategies. There is no backbone drug with a high barrier to resistance, so it is necessary to combine several drugs with a low barrier to resistance. The overall barrier to resistance for the combination must be high.

Combinations of 2 DAAs with low barriers to resistance. The combination of 2 DAAs with low barriers to resistance did not yield high enough rates of SVR owing to the early selection of multidrug-resistant viruses, except in easy-to-cure subpopulations of patients, such as those infected with HCV subtype 1b and/or with a CC *interleukin 28B* genotype. In a phase III study of Japanese patients infected with HCV genotype 1b, 24 weeks of treatment with a combination of the NS3-4A protease inhibitor asunaprevir (100 mg twice daily) and the NS5A inhibitor daclatasvir (60 mg/day) yielded SVR rates of 87% (118 of 135) in IFN-ineligible or IFN-intolerant patients, and 80% (70 of 87) in patients who did not respond previously to IFN-based regimens.[76] In the SOUND-C2 study, the combination of faldaprevir and the thumb I non-nucleoside RdRp inhibitor deleobuvir (halted in January 2014) with ribavirin was associated with an 85% rate of SVR (41 of 48) after 28 weeks of therapy in treatment-naive genotype 1b–infected patients.[77] The SVR rate with the same regimen for 16 weeks in the same population was 95% in the SOUND-C3 trial.[78] Finally, in the PEARL-I study, the combination of the NS3-4A protease inhibitor ABT-450 (150 mg/day), boosted by 100 mg of ritonavir, and the NS5A inhibitor ombitasvir (25 mg/day), for 12 weeks, yielded SVR rates of 95% (40 of 42) and 90% (36 of 40) in treatment-naive and null-responder patients infected with HCV subtype 1b without cirrhosis, respectively.[79]

Combinations of 3 drugs with low barriers to resistance. In patients infected with HCV genotype 1, a combination of 3 drugs with a low barrier to resistance (an NS3-4A protease inhibitor, an NS5A inhibitor, and a non-nucleoside RdRp inhibitor) has potent antiviral effects and a high barrier to resistance. This ensures high rates of SVR.

Press releases have reported preliminary results from 6 phase III clinical trials of patients with HCV genotype 1 infection, with and without cirrhosis, given the combination of ritonavir-boosted ABT-450 (150 mg/100 mg) co-formulated with ombitasvir (25 mg/day), and the non-nucleoside RdRp inhibitor dasabuvir (250 mg twice daily), with or without weight-based ribavirin for 12 or 24 weeks (Figure 3).[80–82] In treatment-naive patients without cirrhosis treated for 12 weeks (Figure 3*A*), rates of SVR with ribavirin in SAPPHIRE-I were 95% (307 of 322) in subtype 1a, and 98% (148 of 151) in subtype 1b. Rates of SVR were 97% (97 of 100) and 90% (185 of 205) with and without ribavirin, respectively, in patients infected with subtype 1a in PEARL-IV, and 99% (209 of 210) and 99% (207 of 209)

with and without ribavirin, respectively, in patients infected with subtype 1b in PEARL-III.[80,82] In noncirrhotic treatment-experienced patients treated for 12 weeks (Figure 3*B*), the rates of SVR were 96% (166 of 173) in subtype 1a and 97% (119 of 123) in subtype 1b in SAPPHIRE-II, which included 49% of prior null responders; the rates of SVR were 97% (85 of 88) and 100% (91 of 91) with and without ribavirin, respectively, in patients infected with subtype 1b in PEARL-II.[81,82] In treatment-naive and treatment-experienced patients with HCV genotype 1 infection and compensated cirrhosis (Figure 3*C*), the rates of SVR were 92% (191 of 208) after 12 weeks and 96% (165 of 172) after 24 weeks of the triple DAA combination plus ribavirin in TURQUOISE-II.[82] The drug combination was well tolerated in the different studies.

A phase II trial assessing an equivalent combination of the NS3-4A protease inhibitor asunaprevir (200 mg, twice daily), the NS5A inhibitor daclatasvir (30 mg, twice daily), and the non-nucleoside RdRp inhibitor BMS-791325 (75 or 150 mg, twice daily), produced SVR rates of 94% (15 of 16) and 94% (15 of 16) after 12 weeks of therapy, and 94% (15 of 16) and 89% (16 of 18) after 24 weeks of therapy, respectively.[83] A number of similar triple-combination regimens currently are being assessed (Table 2). Efficacy against genotypes other than 1 cannot be expected owing to the lack of antiviral effectiveness of the non-nucleoside RdRp inhibitors they contain and, for some genotypes, of the NS3-4A protease inhibitor and/or the NS5A inhibitor.

Nucleoside/nucleotide analogue-free double-combination strategies with at least one drug with a higher barrier to resistance. Nucleoside/nucleotide analogue-free regimens have been studied. These 2-drug combinations include at least 1 drug with a higher barrier to resistance, such as a second-generation NS3-4A or NS5A inhibitor or a cyclophilin inhibitor. In the phase II C-WORTHY study,[84] treatment-naive patients with HCV genotype 1 infection without cirrhosis were given a fixed dose of the second-generation NS3-4A protease inhibitor MK-5172 and different doses of the second-generation NS5A inhibitor MK-8742. Rates of SVR were 100% (22 of 22) for MK-5172 (100 mg/day) and MK-8742 (20 mg/day) plus ribavirin, 96% (23 of 24) for 100 mg and 50 mg daily plus ribavirin, and 100% (12 of 12) for 100 mg and 50 mg daily without ribavirin, respectively.[84] Other trials are underway (Table 2).

Practical Choices in 2014–2015

Simeprevir and sofosbuvir were approved for the treatment of HCV infection in 2013 in the United States and in early 2014 in Europe. Other drugs are likely to be approved later in 2014 or 2015; these include daclatasvir, faldaprevir, the triple combination of co-formulated ritonavir-boosted ABT-450 and ombitasvir plus dasabuvir, and the fixed-dose combination of sofosbuvir and ledipasvir. Table 3 summarizes the HCV treatment options that likely will be available in 2014–2015, based on HCV genotype.

HCV genotype 1. In 2014, patients infected with HCV genotype 1 will have the choice to combine pegylated IFNα and ribavirin with either simeprevir or sofosbuvir. Simeprevir should be administered at a dose of 150 mg (1 capsule) daily for 12 weeks with pegylated IFNα and ribavirin.[85] Treatment-naive patients and prior relapsers should receive an additional 12 weeks of pegylated IFNα and ribavirin (total duration, 24 weeks), prior partial and null responders should receive an additional 36 weeks of

Table 3. HCV Therapeutic Options Likely to Be Available in 2014–2015

HCV genotype 1	Simeprevir + pegylated IFNα + ribavirin	24–48 weeks
	Sofosbuvir + pegylated IFNα + ribavirin	12 weeks
	Faldaprevir + pegylated IFNα + ribavirin	24–48 weeks
	Daclatasvir + pegylated IFNα + ribavirin	24 weeks
	Asunaprevir + daclatasvir + pegylated IFNα + ribavirin	24 weeks
	Sofosbuvir + ribavirin (IFN-intolerant/ineligible, pretransplant)	24 weeks, up to transplantation
	ABT-450/r + ombitasvir + dasabuvir ± ribavirin	12 weeks
	Sofosbuvir + simeprevir ± ribavirin (off label?)	12 weeks
	Sofosbuvir + faldaprevir ± ribavirin (off label?)	12 weeks
	Sofosbuvir + daclatasvir ± ribavirin (off label?)	12–24 weeks
	Sofosbuvir + ledipasvir fixed dose combination ± ribavirin	8–12 weeks
HCV genotype 2	Sofosbuvir + ribavirin	12–16 weeks
HCV genotype 3	Sofosbuvir + pegylated IFNα + ribavirin (off-label in the United States)	12 weeks
	Sofosbuvir + ribavirin	24 weeks
	Sofosbuvir + daclatasvir ± ribavirin (off label?)	12 weeks
HCV genotype 4	Sofosbuvir + pegylated IFNα + ribavirin	12 weeks
	Sofosbuvir + ribavirin (IFN-intolerant/ineligible, pretransplant)	24 weeks, up to transplantation
	Simeprevir + pegylated IFNα + ribavirin (off-label?)	24–48 weeks
	Sofosbuvir + simeprevir ± ribavirin (off label?)	12 weeks
	Sofosbuvir + daclatasvir ± ribavirin (off label?)	12–24 weeks
	Sofosbuvir + ledipasvir fixed dose combination ± ribavirin	8–12 weeks
HCV genotypes 5 and 6	Sofosbuvir + pegylated IFNα + ribavirin (off-label in the United States)	12 weeks
	Sofosbuvir + ribavirin (IFN-intolerant/ineligible, pretransplant)	24 weeks, up to transplantation

NOTE. Off-label use was dependent on local interpretation of the label.
/r, ritonavir-boosted.

pegylated IFNα and ribavirin (total duration, 48 weeks). Simeprevir-based triple-combination therapy is indicated for patients with genotype 1 infection with compensated liver disease, including cirrhosis. This triple combination should not be used in patients infected with HCV subtype 1a with a detectable Q80K substitution in the protease sequence at baseline. Therapy should be discontinued if HCV-RNA levels are greater than 25 IU/mL at weeks 4, 12, or 24.[85]

Sofosbuvir should be administered at a dose of 400 mg (1 tablet/day) for 12 weeks in combination with pegylated IFNα and ribavirin.[86,87] Sofosbuvir-based triple-combination therapy is indicated for patients with chronic HCV genotype 1 infection, with or without HIV infection. No dose recommendation can be made for patients with severe renal impairment or end-stage renal disease owing to higher exposures (>20-fold) of the predominant sofosbuvir metabolite.[86,87]

Twenty-four weeks of treatment with sofosbuvir is indicated, in combination with ribavirin and without IFN, for IFN-intolerant or IFN-ineligible patients with genotype 1 infections, and for patients with hepatocellular carcinoma awaiting liver transplantation, until the time of transplantation (as long as 48 weeks).[86,87] Preliminary data indicate that at least 30 days of undetectable HCV RNA are needed to efficiently prevent post-transplant HCV recurrence.[69]

Given the high rates of SVR among patients with or without cirrhosis who received 12 weeks of treatment with a combination of sofosbuvir and simeprevir, with or without ribavirin (COSMOS trial),[73] this IFN-free combination appears to be an attractive option. Whether it will be prescribed on- or off-label depends on the interpretation of the recommendations of regulatory agencies. The US sofosbuvir label indicates that it can be used "as a component of a combination antiviral treatment regimen,"[86] leaving the payers to decide whether this option is acceptable.[86] The European Commission has granted sofosbuvir marketing authorization "in combination with other medicinal products for the treatment of chronic hepatitis C in adults."[87] The combination of sofosbuvir and simeprevir will be expensive and, although both drugs are well tolerated individually, cautious monitoring will be needed in the absence of large-scale safety data for this combination.

New triple combinations with pegylated IFNα and ribavirin (faldaprevir, daclatasvir, asunaprevir) could be approved in late 2014 or 2015. These drugs could be prescribed on- or off-label in combination with sofosbuvir, depending on local reimbursement policies. However, mid-scale safety data in combination with sofosbuvir are available for daclatasvir only.

The excellent results from phase III trials of ritonavir-boosted ABT-450, ombitasvir, and dasabuvir with ribavirin (Figure 3),[80,81] and of the fixed-dose combination of sofosbuvir and ledipasvir, with or without ribavirin (Figure 2),[72] in treatment-naive and treatment-experienced patients, indicate that both combinations will be approved in late 2014 or early 2015. They could become the standard-of-care for HCV genotype 1 infection (pending additional phase III data to be presented in 2014).

HCV genotype 2. In patients infected with HCV genotype 2, the standard-of-care is the IFN-free combination of sofosbuvir and ribavirin for 12 weeks,[86,87] which produces high rates of SVR. However, patients with cirrhosis, especially if they are treatment-experienced, may need longer treatment, although the number of patients included in this study was small (Figure 1*B*). Prolonged therapy, for more than 12 weeks (possibly up to 16 or 20 weeks), therefore should be considered (off-label) for these patients.

HCV genotype 3. With the current anti-HCV drugs, HCV genotype 3 has become the most difficult-to-cure genotype. Two options will be available in 2014. Only the combination of sofosbuvir and ribavirin for 24 weeks has been approved in the United States,[86] whereas this option and 12 weeks of the triple combination of pegylated IFNα, ribavirin, and sofosbuvir have been approved in Europe.[87] The combination of sofosbuvir and ribavirin produces SVR rates greater than 90% in treatment-naive patients, but it is suboptimal in treatment-experienced patients—especially those with cirrhosis (Figure 1*C* and *D*).[60,70]

For other genotypes, the combination of pegylated IFNα, ribavirin, and sofosbuvir for 12 weeks yields SVR rates greater than 90%[60]; preliminary data from the LONESTAR-2 trial showed that this regimen produced an 83% rate of SVR among treatment-experienced patients with genotype 3 infection.[61] Overall, the ideal treatment for patients infected with HCV genotype 3 is not known. More studies are needed to identify the best combination and the ideal duration for different subgroups of patients, particularly for the most difficult-to-cure patients (those with cirrhosis and/or treatment-experienced individuals). Neither ledipasvir nor ABT-450 and dasabuvir have antiviral effectiveness against genotype 3. Daclatasvir inhibits genotype 3 replication, but to a lesser extent than that of other genotypes. However, 89% of 18 patients with genotype 3 infection given the combination of sofosbuvir and daclatasvir achieved SVRs.[74] Whether this combination, with or without ribavirin, will be a valuable option for genotype 3 patients remains to be determined in larger trials. If not, more years will be needed before a highly active drug combination is available for this genotype.

HCV genotype 4. The combination of pegylated IFNα, ribavirin, and sofosbuvir for 12 weeks is approved for HCV genotype 4 in the United States and Europe, with the same indication as for genotype 1.[86,87] It will become the standard-of-care for this genotype in 2014. Sofosbuvir also can be given with ribavirin, for 24 weeks, to IFN-intolerant or IFN-ineligible patients.[86,87] However, other options are possible because simeprevir, faldaprevir, ledipasvir, daclatasvir, ABT-450, and ombitasvir have antiviral effectiveness against genotype 4. More studies will be needed to identify the best regimen for this genotype.

HCV genotypes 5 and 6. Despite the small number of patients studied (1 patient with genotype 5 and 6 patients with genotype 6), the best treatment option for HCV genotypes 5 and 6 appears to be the combination of pegylated IFNα, ribavirin, and sofosbuvir for 12 weeks. Sofosbuvir also can be given with ribavirin, for 24 weeks, to IFN-intolerant or IFN-ineligible patients. These combinations have been approved in Europe but not in the United States.[86,87] Future

studies will identify the best treatment regimen for these genotypes, which are prevalent in different areas of the world.

Challenges

Unsolved Scientific Questions

A number of unsolved scientific questions remain. They will need to be explored within the next months to years.

Special populations. With the introduction of DAAs, rates of SVR and side-effect profiles do not differ substantially between patients with HCV infection with or without HIV infection. It therefore is possible to extrapolate results from large-scale studies of patients infected with only HCV to those also infected with HIV. Interactions with antiretroviral drugs could be a problem, especially in combinations that include multiple DAAs or HTAs. Antiretroviral therapy might have to be adapted before treatment for HCV infection.

Patients with cirrhosis are a particular challenge. Although data are available from phase II and III trials of these patients, those enrolled in phase III trials had compensated liver disease with little or no evidence of portal hypertension and platelet counts greater than 90.10^9/L. Recent findings from real-life studies of patients with cirrhosis have indicated that rates of SVR can be substantially lower and side-effect profiles substantially worse in patients with advanced liver disease.[88] Although patients with and without cirrhosis respond equally to the antiviral effects of anti-HCV drugs, patients with cirrhosis have a reduced ability to clear or cure infected cells, because of unknown factors. These patients might need higher doses or longer durations of treatment. Little is known about the safety of many DAA combinations in patients with severe portal hypertension and low platelet counts, or in patients with decompensated liver disease. These factors need to be explored in real-life settings with the new combinations, in particular in patients who did not respond to prior therapies or in those with decompensated cirrhosis, who could greatly benefit from IFN-free regimens and eventually be removed from liver transplantation waitlists. More trials are needed in the pretransplant and post-transplant setting to identify regimens that efficiently prevent HCV recurrence and strategies that produce high rates of SVR in patients who have received liver transplants.

DAA-based regimens also could be problematic for patients with impaired renal function, such as those with an estimated glomerular filtration rate of less than 50 mL/min, who often require a dose reduction of ribavirin. Little guidance has been provided on how DAA doses should be adjusted and whether dose reductions affect rates of SVR. More studies are needed in this subpopulation of HCV-infected patients.

Treatment and monitoring strategies for other special populations will need to be established in appropriate clinical trials. These populations include patients with acute hepatitis C, elderly patients, hemodialysis patients, patients with mixed cryoglobulinemias and associated vasculitis, pregnant women, and children, which thus far have been excluded from HCV drug trials.

The role of ribavirin. Although high rates of SVR have been reported with some treatment regimens without ribavirin, ribavirin remains a key component of others strategies because it efficiently reduces the time needed for IFN-containing and IFN-free regimens to cure HCV infection. Ribavirin can be used to increase the rate of SVR from a specific regimen, or to reduce the duration of a regimen without reducing the SVR.

Ribavirin is a cheap drug that is reasonably well tolerated in patients not receiving IFN. It should be used to optimize therapy—especially for difficult-to-treat, real-life patients. Ribavirin-containing and ribavirin-free strategies will need to be tested post-approval, ideally in independent investigator-initiated studies.

The role of HCV resistance in treatment failure. The role of HCV resistance in treatment failures in phase II and III trials of the new drugs has been reported superficially. We carefully should assess the effects of exposure to telaprevir or boceprevir, and eventual resistance selection, on the results and indications of new IFN-free treatment regimens that include a protease inhibitor. Baseline infection of patients with HCV genotype 1a that contains the Q80K substitution has been associated with lower rates of SVR after treatment with simeprevir. Patients with subtype 1a infection therefore should be tested for resistance before therapy begins. This raises questions about access to tests and the unreliability of their results in certain settings, which could affect the prescription and outcomes of simeprevir-based therapies.

Viral resistance will become an issue for patients who do not respond to all-oral, IFN-free regimens. Because the strategies described in Table 2 have high barriers to resistance, virologic failures as a result of breakthrough or relapse with resistant viruses were rare in phase II or III trials. When the drugs are approved, erroneous prescriptions, treatment of more difficult-to-cure, real-life patients, and/or suboptimal adherence to therapy will generate more frequent treatment failures, owing to selection of viruses that are resistant to the different classes of drugs. Viral populations that are resistant to NS3-4A protease inhibitors progressively decline and are replaced by wild-type viruses within a few months after treatment withdrawal (generally more rapidly in patients infected with subtype 1b than in those infected with subtype 1a HCV). In contrast, viral populations resistant to NS5A protease inhibitors persist, possibly for years, after the end of drug administration.[89–92] The actual incidence and post-treatment dynamics of viral resistance will need to be monitored carefully after approval. It will be particularly important to understand their effects on re-treatment strategies with alternative regimens.

Re-treatment strategies. There were many patients who did not respond to combination regimens of pegylated IFNα, ribavirin, and telaprevir or boceprevir and selected for viruses resistant to first-generation NS3-4A

protease inhibitors. With the arrival of new anti-HCV drug combinations, there will be an increasing number of patients harboring HCV variants resistant to NS3-4A protease inhibitors, NS5A inhibitors, non-nucleoside inhibitors of HCV RdRp, or 2 or 3 of these drug classes. Little is known about the dynamics of resistant viral populations in patients with multidrug resistance and their effects on the different possible re-treatment strategies. Clinical trials are needed urgently to define re-treatment options that produce high rates of SVR in these patients.

Strategic Choices

Table 3 shows the HCV treatment regimens that will be available in 2014–2015. The manufacturers of these therapies will compete for a market that, although big in principle, strongly depends on local screening and diagnostic and reimbursement strategies. In theory, individual treatment choices should be based on the expected rates of SVR, treatment duration, and side-effect profile. This means that the shortest and best-tolerated regimen should be chosen to obtain the best possible rate of SVR. However, this may be more complicated in real life.

First, besides labeled regimens, off-label combinations will be tempting when the drugs are on the market, for instance, in the case of IFN-free combinations of sofosbuvir with simeprevir and/or daclatasvir for treatment of different HCV genotypes, which were shown to produce high rates of SVR in phase II trials. However, there are few data on the safety of these combinations, and they will raise reimbursement issues because the prices of the individual drugs will be added.

More generally, the cost of the new HCV therapies will be very high. No one knows how payers will control treatment decisions in different areas of the world. However, it is unlikely that prescriptions will be entirely free in many places. Strategies using first-, second-, and third-line treatment regimens may have to be implemented, as in other therapeutic areas. Whether all HCV-infected patients now should be treated also is debatable. Except for those with advanced liver disease (F3–F4), most patients can wait until an affordable regimen that produces rates of SVR greater than 90% is available for their subgroup and location. Some practitioners may choose to monitor these patients until such regimens are available, most likely within the next 2–3 years.

The HCV drug market therefore is likely to be highly segmented, with different approaches being preferred in different areas of the world. It will be important that these experiences are reported carefully because they may be useful when new markets gain access to specific therapies. In this respect, networks are starting to collect data and experiences in real-life practice in the United States and several European countries.

The Global Perspective

The new HCV therapeutic options described will reach a limited number of markets initially, including North America, Europe, Japan, and Australia. These markets are heterogeneous. Furthermore, most HCV-infected patients live elsewhere.

Through its National Plan against viral hepatitis, launched in 1999, France has now identified more than 70% of its estimated infected population. These patients have been given access to fully reimbursed therapy, either through the national social insurance system or in numerous trials of new drugs, performed at reference centers. As a result, most of the easy-to-cure patients have been cured and France now has to deal with the most advanced and difficult-to-cure population, using the new drugs. In contrast, the US Centers for Disease Control and Prevention recommend HCV screening for anyone born between 1945 and 1965 (it is estimated that 75% of adults with hepatitis C were born during these years). This will bring to treatment a large number of treatment-naive patients with more or less advanced disease at the time the new drugs become available, raising important issues about cost, coverage, and indications for therapy. At the opposite side of the spectrum, some countries that will soon have access to the new drugs have not yet implemented any organized screening policy, and may hesitate to do so given the potential costs if diagnosed patients must be treated.

Unfortunately, most HCV-infected patients live in areas where neither diagnostic and monitoring tools, nor new therapies, will be available for many years. Low-cost and generic drugs have been made available for HIV therapy in these areas, with success. It recently was announced that generic sofosbuvir will be manufactured in India at prices estimated to be less than 5% of those in the United States; other drug manufacturers may follow this example. Nevertheless, this approach may not be suited to HCV infection because hepatitis C is a silent disease that remains undiagnosed until serious, and potentially lethal, complications occur. In addition to adequate health systems and organizations, access to HCV therapy requires active screening of exposed populations. This cannot be envisaged in many areas in the world, despite the high morbidity and mortality associated with HCV infection—especially as a comorbid condition with other infectious diseases such as HIV infection, malaria, tuberculosis, or hepatitis B.

Conclusions

The treatment of HCV infection will change dramatically in 2014–2015 and onward. Many unresolved scientific questions will never be answered because new therapeutic approaches will replace existing ones within a short timeframe until the field stabilizes, probably with the next generation of HCV drugs still at the preclinical or early clinical developmental stages. Pragmatic approaches based on careful interpretation of existing data and the generation of small-scale postapproval studies addressing specific questions of interest in clinical practice will be needed. The development of an efficient vaccine to prevent HCV infection has been hampered by the difficulty in raising protective immune responses in human beings using classic approaches, and also

by the uncertain definition of the target populations. These factors have caused many companies to withdraw from this field of investigation. The antiviral approach therefore probably will be the only option to control the HCV epidemic. This will be possible only by combining highly efficient and well-tolerated, affordable drug combinations, active screening strategies, and easy access to care.

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