

New Antiviral Agents for Hepatitis C

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Abstract

Approximately 120-130 million individuals are chronically infected with hepatitis C virus (HCV) worldwide, although it is curable by therapy. Until recently, treatment of chronic hepatitis C was based on the combination of pegylated interferon- α and ribavirin. A number of models have been developed to study the HCV lifecycle and screen for potential HCV inhibitors. They led to the development of antiviral agents that specifically target a viral function (direct acting antivirals), and host-targeted agents that inhibit HCV replication. Direct acting antivirals in clinical development include NS3-4A protease inhibitors (two of which, telaprevir and boceprevir, have recently been approved for treatment of HCV genotype 1 infection in combination with pegylated interferon- α and ribavirin), nucleoside/nucleotide analogue and non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase, and NS5A inhibitors. Host-targeted agents include cyclophilin inhibitors. This article describes the direct acting antivirals and host-targeted agents that have recently been approved or have been tested in HCV-infected patients and discusses their two current paths of clinical development: with or without interferon- α .

Introduction

Hepatitis C virus (HCV) was discovered in 1989 [1]. It was found to be responsible for the vast majority of so-called chronic non-A, non-B hepatitis and cryptogenetic liver diseases [2-4]. In adults, acute HCV infection leads to chronic infection in approximately 80% of cases. Chronic HCV infection is responsible for chronic hepatitis, which is complicated by cirrhosis in approximately 20% of cases. Patients with cirrhosis are exposed to life-threatening complications, including end-stage liver disease, esophageal varices hemorrhage and the development of hepatocellular carcinoma, which occurs at an incidence of 4%-5% per year in these patients [5]. Approximately 120-130 million individuals are chronically infected with HCV worldwide [6]. Chronic HCV infection has become the leading cause of hepatocellular carcinoma (primary liver cancer) and the first indication of liver transplantation in industrialized countries [5]. Six genotypes (1 to 6) and a number of subtypes have been described. Genotype 1 (subtypes 1a and 1b) is by far the most frequent genotype worldwide [7].

Unlike other known chronic viral infections, HCV infection is curable by therapy. Cure of infection is characterized by the "sustained virological response", defined as undetectable HCV RNA in peripheral blood by means of sensitive molecular biology-based techniques. Until recently, treatment of chronic hepatitis C was based on the combination of a pegylated form of interferon (IFN)- α (pegylation improves the pharmacokinetic and pharmacodynamic properties and enhances the antiviral potency of IFN) and ribavirin [8-10]. This combination cures approximately 80% of infections in patients infected with HCV genotypes 2 or 3, but only 40%-50% in patients infected with genotypes 1 or 4. This emphasizes the need for more efficient antiviral strategies.

Over the past 10 years, a number of models have been developed to study the HCV lifecycle and screen for potential HCV inhibitors [11]. These models include cell-free enzyme assays for the HCV NS3-4A protease and RNA-dependent RNA polymerase, hepatoma cell lines harboring subgenomic and genomic replicons (nucleic

acids capable of autonomous replication), an infectious cell culture system (limited to genotype 2a), and humanized mouse models infectable by HCV. They led to the development of antiviral agents that specifically target a viral function, now collectively termed “direct acting antivirals”. In addition, “host-targeted agents” that inhibit HCV replication are also in development. This article describes the direct acting antivirals that have recently been approved and direct acting antivirals and host-targeted agents that have been tested in HCV-infected patients and discusses their current paths of clinical development: with or without IFN- α .

New HCV drugs in development

In principle, every step of the HCV lifecycle, including receptor binding, endocytosis, fusion, uncoating, translation, polyprotein processing, RNA replication, virion assembly, maturation, transport and release, can be a target for new anti-HCV drugs [12]. Thus far, drugs targeting two major steps of the HCV lifecycle have reached clinical development. They include inhibitors of the HCV NS3-4A protease that block polyprotein processing and

several drug families that block viral replication, including nucleoside/nucleotide inhibitors of the HCV RNA-dependent RNA polymerase, non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase, and inhibitors of the NS5A viral protein which plays a regulatory role in replication. Host-targeted agents that inhibit the host cell protein cyclophilin A, a protein required to interact with the replication complex for efficient viral genome production, are also in clinical development. Table 1 summarizes the drugs that have been tested in clinical trials and for which results have been published or presented at medical meetings as of November 2011.

Barrier to resistance of HCV drugs

Like antiretroviral drugs, HCV direct acting antivirals have been shown to select drug-resistant viral variants, the outgrowth of which is responsible for virological breakthrough and disease progression [13]. *In vivo*, the “barrier to resistance” of an HCV drug is influenced by three parameters: (a) the “genetic barrier to resistance” of the drug, defined as the number of amino acid substitutions needed for a viral variant to acquire full resistance to the

Table 1. New drugs that have reached clinical development for treating chronic hepatitis C (/*r* means boosted by ritonavir)

Drug	Manufacturer	Phase
<i>NS3-4A protease inhibitors</i>		
Telaprevir	Vertex & Janssen	Approved
Boceprevir	Merck	Approved
TMC435	Janssen	III
BI201335	Boehringer-Ingelheim	III
Danoprevir/ <i>r</i>	Roche/Genentech	II
Vaniprevir	Merck	II
Narlaprevir/ <i>r</i>	Merck	II
Asunaprevir	Bristol-Myers Squibb	II
GS-9256	Gilead	II
GS-9451	Gilead	II
ABT-450/ <i>r</i>	Abbott	II
ACH-1625	Achillion	II
ACH-2684	Achillion	Ib
MK-5172	Merck	II
<i>Nucleoside/nucleotide analogue inhibitors of HCV RNA-dependent RNA polymerase</i>		
PSI-7977	Pharmasset/Gilead	III
Mericitabine	Roche/Genentech	II
IDX184	Idenix	II
PSI-938	Pharmasset/Gilead	II
INX-189	Inhibitex	Ib
<i>Non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase</i>		
Tegobuvir	Gilead	II
Filibuvir	Pfizer	II
Setrobuvir	Roche/Genentech	II
BI207127	Boehringer-Ingelheim	II
ABT-333	Abbott	II
VX-222	Vertex	II
TMC-647055	Janssen	Ib
<i>NS5A inhibitors</i>		
Daclatasvir	Bristol-Myers Squibb	II
PPI-461	Presidio	Ib
GS-5885	Gilead	Ib
GSK2336805	GlaxoSmithKline	Ib
<i>Cyclophilin inhibitors</i>		
Alisporivir	Novartis	III
SCY-465	Scynexis	II

drug in question (if a single substitution is sufficient to confer high-level resistance, the drug is considered to have a low genetic barrier to resistance, while the need for three or more substitutions represents a high genetic barrier); (b) the “*in vivo* fitness” of the resistant viral variant population, defined as its ability to survive and grow in the replicative environment; and (c) drug exposure, defined as the drug concentration achieved *in vivo* relative to the 50% and 90% inhibitory concentrations (in enzyme assays) and efficient concentrations (in cellular assays) [13]. HCV drugs in development can be split into two groups according to their barrier to resistance, including drugs with a low barrier to resistance, and drugs with a high barrier to resistance.

HCV drugs with a low barrier to resistance

HCV drugs with a low barrier to resistance include the following direct acting antivirals: first-generation NS3-4A protease inhibitors, non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase and NS5A inhibitors.

A large number of NS3-4A protease inhibitors have reached clinical development, including two drugs, telaprevir and boceprevir (Table 1), that have recently been approved for use in combination with pegylated IFN- α and ribavirin in patients infected with genotype 1. NS3-4A protease inhibitors have closely related chemical structures. They inhibit viral replication by 3.5 to 4.5 Log international units (IU)/mL when administered alone for a few days (one log reduction means that the viral level has been divided by 10, 2 log by 100, etc). Telaprevir and boceprevir are active against genotypes 1 and 2 only, whereas other protease inhibitors have broader genotype coverage; however, none of the first-generation NS3-4A protease inhibitors are active against genotype 3. A large number of amino acid substitutions conferring resistance to protease inhibitors have been shown to pre-exist at generally low levels in infected patients and are selected within a few days to weeks on drug monotherapy [13]. Different resistance profiles have been reported for subtypes 1a and 1b. Second-generation NS3-4A protease inhibitors, such as MK-5172 or ACH-2684 (Table 1), are expected to have broader genotypic coverage and higher barriers to resistance.

In contrast to protease inhibitors, non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase are a heterogeneous group of drug families targeting one of four allosteric sites at the surface of the viral enzyme (Table 1). Their antiviral action is thus far restricted to HCV genotype 1. Different non-nucleoside inhibitors may have different antiviral potencies and select amino acid substitutions conferring resistance that is generally, but not always, located in close vicinity to their target site.

Extensive cross-resistance has been reported between drugs targeting the same site, and cross-resistance can also occur between drugs targeting different sites.

NS5A inhibitors are potent antiviral drugs that block the function of the NS5A protein through an, as yet, unclear mechanism (Table 1). They have broad genotypic coverage, but a low barrier to resistance, with the highest levels of resistance conferred by single amino acid substitutions in subtype 1a.

New HCV drugs with a high barrier to resistance

HCV drugs with a high barrier to resistance include nucleoside/nucleotide analogues and host-targeted agents, such as cyclophilin inhibitors. Nucleoside/nucleotide analogues target the catalytic site of the RNA-dependent RNA polymerase. Several nucleoside and nucleotide analogues have reached clinical development, including purine and pyrimidine analogues. They are effective on all known genotypes and subtypes. Although these drugs have a low “genetic barrier” to resistance (as one single amino acid substitution is sufficient to confer resistance to the drug), these amino acid substitutions alter the conformation of the enzyme catalytic site. Thus, resistant variants exhibit low fitness and are not clinically meaningful. In this respect, nucleoside/nucleotide analogues have a high “barrier” to resistance *in vivo*, as resistant viral populations on single drug administration grow very slowly with virological breakthrough eventually occurring after months of treatment.

Cyclophilin A plays an important role in the HCV replication cycle by binding to both NS5A and the RNA-dependent RNA polymerase within the viral replication complex. Blocking cyclophilin peptidyl-prolyl *cis-trans* isomerase enzyme activity results in a significant inhibition of HCV replication both *in vitro* and *in vivo*, through molecular mechanisms that remain unclear. Because their target is a host protein, cyclophilin inhibitors have broad genotypic coverage and a favorable resistance profile. Amino acid substitutions in the NS5A protein can be selected by these drugs, but they confer low-level resistance and the corresponding variants exhibit low fitness.

Newly approved NS3-4A protease inhibitors

The first available direct acting antivirals for clinical development in patients infected with HCV genotype 1 were the NS3-4A protease inhibitors telaprevir and boceprevir. Due to their low barrier to resistance, it soon appeared that they could not be used alone and should be combined with other compounds with potent antiviral properties and no cross-resistance with the protease inhibitors. Only pegylated IFN- α and ribavirin were

available for combination in Phase II and III clinical trials. It soon became apparent that ribavirin was also needed to improve the cure rates in combination with pegylated IFN- α and a protease inhibitor [14]. In 2011, the results of several Phase III trials have led to the approval of both telaprevir (Incivek, Vertex Pharmaceuticals, in the US; Incivo, Janssen, in Europe) and boceprevir (Victrelis, Merck) in combination with pegylated IFN- α and ribavirin [15-18]. Complex treatment algorithms have been issued in the US Food and Drug Administration and European Medicines Agency labels, which substantially differ between the two protease inhibitors (Tables 2 and 3). Treatment duration must be tailored to the severity of liver disease, prior virological response to pegylated IFN- α and ribavirin in previously treated patients, and the virological response during therapy (response-guided therapy). Sustained virological response rates in the range of 66% to 75% have been achieved in treatment-naïve patients in Phase III trials, significantly higher than with pegylated IFN- α and ribavirin alone [16,18]. In previously treated patients, the results strongly depended on the prior response to pegylated IFN- α and ribavirin, with sustained virological response rates of the order of 30% in prior null responders and up to approximately 85% in prior responder-relapsers [15,17].

In addition to the complexity of the approved treatment regimens, the new triple combination therapies raise a number of issues.

(a) They are restricted to HCV genotype 1.

(b) The addition of a third drug to pegylated IFN- α and ribavirin is associated with additional, and eventually severe, side effects. The principal adverse reactions associated with telaprevir are anemia, pruritus and rash [17,18]. Rash is observed in approximately half of cases. It is generally benign and responds well to topical

corticosteroids; however, severe cases have been reported in clinical trials, including occasional cases of Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. These complications can be life-threatening and impose rapid treatment interruption. Therefore, telaprevir therapy requires strict adherence to the rash management plan, in close collaboration with experienced dermatologists. Boceprevir administration is associated with anemia that aggravates hemolytic anemia due to ribavirin and dysgueusia [15,16].

(c) Selection of viral variants that are resistant to the protease inhibitor is an inevitable consequence of treatment failure, i.e. the failure to eradicate the virus on triple combination therapy. Such failure is due to an inadequate response to pegylated IFN- α and ribavirin, which does not prevent outgrowth of resistant variants selected by the protease inhibitor [13]. After treatment cessation, resistant viral populations progressively decrease in proportion and are no longer detectable with population sequencing after a period of a few months to two years [19-21]. Selection of resistant HCV variants does not appear to have a negative impact on the outcome of liver disease. Theoretically, it should not compromise the chance for a subsequent cure with another drug regimen.

(d) The addition of a protease inhibitor substantially increases the cost of therapy, raising issues regarding screening policies and access to care.

Two paths of clinical development of HCV direct acting antivirals

Issues raised by the recent approval of telaprevir and boceprevir in combination with pegylated IFN- α and ribavirin emphasize the need for alternative therapeutic strategies that ensure broader genotypic coverage, better efficacy, better tolerance and limited selection of resistant

Table 2. Telaprevir label (US and Europe)

Patients	HCV RNA		Treatment
	Week 4	Week 12	
Treatment-naïve and responder-relapsers	Undetectable	Undetectable	Treat with 3 drugs for 12 weeks Continue with pegylated IFN- α and ribavirin until week 24 Treat with 3 drugs for 12 weeks Continue with pegylated IFN- α and ribavirin until week 48
	Detectable (≤ 1000 IU/mL)	and/or Detectable (≤ 1000 IU/mL)	
Partial responders and null responders	All patients		Treat with 3 drugs for 12 weeks Continue with pegylated IFN- α and ribavirin until week 48

Telaprevir is administered at day 0 and for 12 weeks at the dose of 750 mg every 7-9 hours with fatty food, in combination with either pegylated IFN- α 2a (180 μ g/week subcutaneously) or pegylated IFN- α 2b (1.5 μ g/kg/week subcutaneously), and ribavirin (0.8 to 1.2 g/day according to body weight). Futility rule: stop therapy if HCV RNA >1000 IU/mL at week 4 or 12 or detectable at week 24. Abbreviations: IFN, interferon.

Table 3. Boceprevir labels (US and Europe)

Patients	HCV RNA		Treatment
	Week 4	Week 12	
Treatment-naïve without cirrhosis	Undetectable Detectable	Undetectable Undetectable	Treat with 3 drugs until week 28 Treat with 3 drugs until week 36 Continue with pegylated IFN- α and ribavirin until week 48
Responder-relapsers and partial responders without cirrhosis	Undetectable	Undetectable	US: Treat with 3 drugs until week 36 Europe: Treat with 3 drugs until week 36 Continue with pegylated IFN- α and ribavirin until week 48
	Detectable	Undetectable	Treat with 3 drugs until week 36 Continue with pegylated IFN- α and ribavirin until week 48
Null responders and all cirrhotics	All patients		Treat with 3 drugs until week 48

Boceprevir is administered after 4 weeks of "lead-in" with pegylated IFN- α and ribavirin alone at the dose of 800 mg every 7-9 hours with food, in combination with either pegylated IFN- α 2b (1.5 μ g/kg/week subcutaneously) or pegylated IFN- α 2a (180 μ g/week subcutaneously), and ribavirin (0.8 to 1.4 g/day according to body weight). Futility rule: stop therapy if HCV RNA >100 IU/mL at week 12 or detectable at week 24. Abbreviations: IFN, interferon.

HCV variants. The clinical development of new HCV drugs currently follows two paths, according to whether or not pegylated IFN- α is included in the drug combination.

IFN-based regimens

Most of the new direct acting antivirals and host-targeted agents in development are currently tested as part of triple combinations with pegylated IFN- α and ribavirin. The results of Phase II trials have been encouraging with other NS3-4A protease inhibitors, such as TMC435 or BI201335 (currently in Phase III evaluation), the NS5A inhibitor daclatasvir (BMS-790052), or the cyclophilin inhibitor alisporivir (DEBIO-025, currently in Phase III evaluation), with sustained virological response rates of the same order as those with telaprevir and boceprevir [22-25]. Results of trials with two non-nucleoside inhibitors, filibuvir and tegobuvir, have been disappointing. However, this result cannot be generalized to the wider group of non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase, as it seems to be essentially the result of the modest antiviral efficacy of the two individual compounds. Results are awaited with other drugs, tested in ongoing clinical trials. As with telaprevir and boceprevir, the response to IFN and ribavirin is a key determinant of the final outcome of therapy. It is too early to say whether the effect of IFN responsiveness will be attenuated when drugs with a high barrier to resistance are used in combination with pegylated IFN- α and ribavirin.

Interest was recently raised about quadruple combination treatment regimens that combine pegylated IFN- α , ribavirin, and two direct acting antivirals belonging to different drug classes without cross-resistance. In a study in patients who previously experienced a null response to

pegylated IFN- α and ribavirin, 10 out of 10 patients receiving a quadruple combination including both daclatasvir (an NS5A inhibitor) and asunaprevir (an NS3-4A protease inhibitor) showed a sustained virological response [26]. The number of patients in this study was too small to draw firm conclusions, and it also remains to be established whether two drugs with a low barrier to resistance do better in combination with pegylated IFN- α and ribavirin than one drug with a high barrier to resistance, or whether quadruple combinations may be further improved by including at least one drug with a high barrier to resistance.

All-oral, IFN-free regimens

Enthusiasm about IFN-free regimens has recently risen dramatically with reports of sustained virological response rates of the order of 100% in small groups of patients treated with one or two direct acting antivirals alone, with or without ribavirin. What is known about IFN-free regimens can be summarized as follows: (a) the combination of two oral drugs with a low barrier to resistance results in early virological breakthroughs due to the selection of viral populations that are resistant to both drugs [26-28]; (b) ribavirin accelerates HCV clearance in combination with direct acting antivirals in the absence of IFN and is useful for shortening treatment duration and preventing post-treatment relapses [27]; (c) the use of a nucleotide analogue (PSI-7977) with ribavirin in patients infected with HCV genotypes 2 and 3 [29], or of a combination of an NS3-4A protease inhibitor (asunaprevir) and an NS5A inhibitor (daclatasvir) in patients infected with genotype 1b [30], a population in which daclatasvir has a reasonably high barrier to resistance, yielded 100% sustained virological response rates in small groups of patients.

Overall, these results provide a proof-of-concept that HCV infection can be cured by an all-oral IFN-free treatment regimen within 12 to 24 weeks and that very high sustained virological response rates can be achieved with drugs or drug combinations that have a high barrier to resistance. They strongly suggest that the IFN era is coming to an end in hepatitis C therapy, although this end cannot yet be precisely dated. Further results are awaited that will allow the establishment of an ideal all-oral IFN treatment regimen for patients with chronic HCV infection.

Conclusion

A new standard-of-care is now available for patients infected with HCV genotype 1, based on the triple combination of pegylated IFN- α , ribavirin, and either telaprevir or boceprevir. However, these new therapies are associated with increased costs, additional side effects and more complex treatment strategies, whereas pegylated IFN- α and ribavirin remain the standard treatment for all other genotypes, as well as in resource-limited settings where the cost of these new therapies cannot be afforded. A universal, cost-effective, well-tolerated all-oral first-line treatment regimen is needed and will most likely be available within a few years, when more is known about the ideal combination of drugs and the optimal doses and duration. Nevertheless, antiviral therapy is not the solution to definitively eradicate HCV infection, most of the 120-130 million chronic carriers live in areas where screening, cost and access to care preclude the use of these novel therapies. An efficient prophylactic vaccine is still urgently needed. This will be the next, and probably last, challenge of the HCV story.

Abbreviations

HCV, hepatitis C virus; IFN, interferon.

Competing interests

The author has received research grants from Gilead and Roche/Genentech. He has served as an advisor for Abbott, Achillion, Anadys, Biotica, Boehringer-Ingelheim, Bristol-Myers Squibb, DebioPharm, Gen-Probe, Gilead, Glaxo-SmithKline, Idenix, Inhibitex, Janssen-Cilag, Madaus-Rottapharm, Sanofi-Aventis, Schering-Plough/Merck, Novartis, Pfizer, Roche/Genentech, Vertex and Virco.

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