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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).