New therapies for hepatitis infection

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'Estimates suggest that approximately 200 million individuals are infected with HBV or HCV without HIV co-infection, and that diagnosis rates are increasing.'

Infection with HIV is classically thought of as the most catastrophic example of genome emergence, propagation and transmission. This retroviral pandemic infects approximately 40 million individuals [1]. The prognosis of these individuals in established market economies has been revolutionized by the use of highly-active antiretroviral therapy, which has decreased morbidity and mortality in a number of randomized studies [2–4]. There are now over 20 approved antiretrovirals to treat HIV, and all target either the HIV protease or reverse transcriptase [5].

Owing to shared routes of transmission, many individuals with HIV are co-infected with either hepatitis B virus (HBV) [6], a highly contagious DNA virus, or hepatitis C virus (HCV) [7], a less contagious RNA virus. Estimates suggest that approximately 200 million individuals are infected with HBV or HCV without HIV co-infection, and that diagnosis rates are increasing. For HBV, a cure is not possible since it incorporates into the human genome (i.e., HIV) [8], whereas, for HCV, a cure is possible if the virus is eradicated (not incorporated into the host) [9]. Both hepatitis viruses cause cirrhosis and cancer, the latter occurring in the absence of cirrhosis for hepatitis B infection. End-stage liver disease accounts for one in 40 deaths worldwide; hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and the vast majority of cases are attributable to hepatitis (HBV being a greater contributor to HCC than HCV). However, a vaccine is available for HBV and current therapies, including lamivudine, tenofovir and adefovir [10], are significantly more advanced than for HCV therapy, which still relies on the poorly tolerated arduous cornerstones of interferon (IFN)- α and ribavirin.

For HCV, several new classes of molecules promise to enhance outcome by offering complete viral eradication with a reduced treatment duration from 1 year to 3 months (Table 1). While companies are competing for these new molecules,

there is the potential to combine therapies over the longer term. The most promising candidates are Vertex Pharmaceuticals Inc.'s VX-950, the most potent protease inhibitor, Idenix Pharmaceuticals's NM283, a polymerase inhibitor, and Human Genome Sciences Inc. and Novartis AG's AlbuferonTM, a more convenient IFN with a half-life 80% longer than the current market leader, Roche's Pegasys[®].

Since there is no latent reservoir, HCV eradication on a global scale is possible. Despite significant cardiac toxicity observed in animal models with previous HCV protease inhibitors (Boehringer Ingelheim GmbH's BILN-2061), Vertex's protease inhibitor is clearly in the lead in development, with a 4.4 log reduction in viral load following only 14 days, compared with Schering-Plough Corp.'s SCH 503034, which has a 2.1 log reduction. The HCV NS3-4A protease, which is essential for viral replication, is inhibited by these drugs. However, discovery of potent, selective and oral small-molecule inhibitors of the NS3-4A protease has been hampered by the shallow substrate-binding groove of the protease. Serine-trap warheads have been used with both these drugs to covalently anchor inhibitor scaffolds and to increase their affinity to the protease. While further data have demonstrated efficacy over 3 months and can be given in combination with IFN- α , questions remain regarding the emergence of resistant mutants, long-term tolerability and efficacy.

The HBV market is more mature and competitive than the HCV market, with less product differentiation in the pipeline. Bristol-Myers Squibb's entecavir has been launched, and Idenix/Novartis's telbivudine appears to be equally potent, with a clean safety profile. However, telbivudine has a resistance profile weakness. Since HBV can exist in a latent form within the host, maintenance therapy with such a highly selective nucleoside analog will become more commonplace, although, once again, long-term safety concerns are poorly understood.

Further improvement in hepatitis therapy will be sustained by understanding host-immune characteristics associated with disease remission. Even if the viruses cannot be eradicated, cirrhosis and cancer may be prevented.

Table 1. Drugs and vaccines in development to treat hepatitis C virus.

Description	Drug name	Drug sponsor	US FDA status (Phase)
Interferons			
IFN- β -1a	Rebif®	Ares Serono	III
Fusion protein	Albupherson®	Human Genome Sciences Inc.	II
IFN- α -albumin	Medusa® IFN	Flamel Technologies Inc.	II
Medusa IFN	Mutliferon®	Viragen, Inc.	II
Purified multi-subtype human IFN- α	Peg-alfacon	InterMune	II
Pegylated alfacon-1 IFN- ω	IFN- ω	Biomedicines	I
Oral IFN- α	Oral IFN- α	Amarillo Biosciences Inc.	I
Ribavirin alternatives			
Antiviral	Amantadine	Endo Labs, etc.	III
Amidine prodrug of ribavirin (nucleoside analog)	Viramidine	Valeant Pharmaceuticals	III
IMPDH inhibitors	Merimepodib (VX-497)	Vertex Pharmaceuticals Inc.	II
Mycophenolic acid	Mycophenolic acid	Roche Pharmaceuticals	I
Vaccines			
Therapeutic vaccine (viral E1 protein of HCV)	E1 vaccine	Innogenetics NV	II
Therapeutic vaccine	IC-41	Intercell	II
Vaccine	HCV-MF59	Chiron Corp.	I
Inhibitors of viral enzymes			
	(NM-283)	Idenix Pharmaceuticals	IIb
Polymerase inhibitor (non-nucleoside)	JTK-003	Japan Tobacco/Akros Pharmaceuticals	II
Serine protease inhibitor	Sch 503034	Schering-Plough Corp.	II
NS3–4A protease inhibitor	VX-950	Vertex Pharmaceuticals Inc.	Ib
Synthetic oligonucleotide and selective TLR9 agonist	Actillon™	Coley Pharmaceutical Group Inc.	I/II
Polymerase inhibitor (non-nucleoside)	HCV-796	Wyeth/ViroPharma Inc.	I
Nucleoside analog	R 1626	Roche Pharmaceuticals	I
Others			
Protease inhibitor	GS9132	Gilead Sciences Inc.	I
Glucosidase inhibitor	Celgosivir (MBI-3253)	Migenix Inc.	II
Caspase inhibitors	ID-6556	Idun Pharmaceuticals Inc.	II
Monoclonal antibody	XLT-6865	XTL	I/II
Prodrug of isatoribine and TLR7 agonist	ANA-975	Anadys Pharmaceuticals Inc.	I
Antiphospholipid	Tarvacin™	Peregrine	I

HCV: Hepatitis C virus; IFN: Interferon; IMPDH: Inosine monophosphate dehydrogenase; RdRp: RNA-dependent RNA polymerase; TLR: Toll-like receptor.

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