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Hepatology Is an Important New Frontier in Pharmaceutical Development

Liver diseases represent an important field of new drug development due to the unmet needs of patients with these illnesses. This article describes both these unmet needs and areas of opportunity to develop new compounds for common liver ailments.

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Hepatology—the study of liver diseases—represents a clinically important, dynamic, and lucrative arena of pharmaceutical development. The opportunity in this therapeutic sector stems from the growing population of patients worldwide afflicted by common liver ailments such as viral hepatitis (including hepatitis C and hepatitis B) and nonalcoholic fatty liver disease (NAFLD). Several unmet therapeutic needs within each of these liver injuries constitute major opportunities for drug development. This article focuses on hepatitis C, hepatitis B, and NAFLD, which are arguably of greatest commercial relevance to the pharmaceutical industry.

Hepatitis C

Epidemiology. Recent Centers for Disease Control and Prevention, Rockville, MD, (CDC) data indicate that approximately 4.1 million Americans (1.3% of the U.S. population) carry the hepatitis C virus (HCV), 3.2 million of whom are chronically infected. Between 10,000 and 12,000 deaths annually are attributed to HCV-associated liver disease; end-stage liver disease associated with chronic HCV provides the largest demand for liver transplantation. In the United States, the major routes of HCV transmission occur through intravenous drug usage, exposure to contaminated blood products, and solid organ transplantation. Although the U.S. incidence rate has fallen since the 1980s owing to such factors as advances in screening the blood supply, a growing demand for HCV therapy exists as more chronically infected patients present with advanced liver disease and thus become treatment candidates.

Current Treatment. The standard-of-care approach to treating chronic HCV involves a combination of pegylated interferon (PEG-INF) (available as Pegasys from Roche Laboratories, Nutley, NJ, or Peg-Intron from Schering-Plough, Kenilworth, NJ) plus ribavirin (RBV) (available as Copegus from Roche or Rebetol from Schering-Plough), administered based upon the genotype of the patient. Patients with genotype 1—the more frequently-occurring genotype—receive 48 weeks of PEG-INF plus RBV. Patients with genotypes 2 or 3, the less common genotypes, undergo treatment for 24 weeks.

Key Trends and Unmet Needs. The two major trends in the treatment of HCV include: (1) an expansion of treatment candidates as a function of more patients with chronic HCV presenting with advanced liver disease and (2) the potential retreatment of patients who have not responded to previous therapeutic options as a function of the availability of novel medications, noted below. The main unmet therapeutic needs in the treatment of HCV reside in the domains of both efficacy and tolerability. Treatment with PEG-INF plus RBV involves a considerable burden of adverse effects, most notably influenza-like symptoms, neuropsychiatric effects, and hematological abnormalities.

Medications in Development. Numerous medications are in development for HCV. Viramidine (taribavirin, Valeant Pharmaceuticals International, Alisa Viejo, CA), Telaprevir (VX-950, Vertex Pharmaceuticals, Inc., Cambridge, MA), Valopicitabine (NM 283, Idenix Pharmaceuticals, Inc., Cambridge, MA), SCH 503034 (Schering-Plough Corporation), GS-9132 (Gilead Sciences, Inc., Forest City, CA), and Albuferon (albumin-interferon alfa-2a, Human Genome Sciences, Rockville, MD, and Novartis International AG, Basel, Switzerland) may reach the marketplace earliest. Among the new medications, industry experts expect the protease and polymerase inhibitors to considerably improve rates of response and potentially truncate the length of treatment, especially in the more difficult-to-treat patients.

Researchers as also developing IDN-6556 (Idun Pharmaceuticals, Inc., recently acquired by New York City–based Pfizer Inc), a novel small-molecule caspase protease inhibitor that inhibits apoptosis (programmed cell death),

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TABLE: SELECT ANTI-HCV THERAPIES IN DEVELOPMENT

Drug Category	Drug Name and Sponsor	FDA Status
Interferons	Albuferon (Human Genome Sciences)	Phase 2
	Multiferon (Viragen, Inc.)	Phase 2
	Medusa interferon (Flamel Technologies S.A.)	Phase 2
	Rebif (Ares Serono)	Phase 3
Ribavirin Alternatives	Viramidine (Valeant Pharmaceuticals)	Phase 3
	Merimepodib (Vertex Pharmaceuticals, Inc.)	Phase 2
	Amantadine (Endo Laboratories, etc.)	Phase 3
Immunomodulators	Zadaxin (SciClone Pharmaceuticals, Inc.)	Phase 3
	Ceplene (Maxim Pharmaceuticals, Inc.)	Phase 2
	E1 vaccine (Innogenetics NV)	Phase 2
	IC-41 (Intercell)	Phase 2
	VX-950 (Vertex Pharmaceuticals, Inc.)	Phase 2
Antifibrotics	ISIS-14803 (Isis Pharmaceuticals, Inc.)	Phase 2
	IP-501 (Indevus Pharmaceuticals, Inc.)	Phase 3
Others	ID-6556 (Idun Pharmaceuticals, Inc.)	Phase 2

HCV = Hepatitis C virus.

implicated in the generation of fibrosis. The agent is also being evaluated in hepatitis B, primary biliary cirrhosis (PBC), and nonalcoholic steatohepatitis (NASH). Selected anti-HCV therapies in development are found in the Table.

Hepatitis B

Epidemiology. Worldwide, hepatitis B (HBV) is the most common viral illness. According to the CDC, 2 billion people have been infected with HBV, 360 million are chronically infected, and approximately 600,000 individuals die each year from HBV-related liver disease or hepatocellular carcinoma. An estimated 1.25 million Americans chronically carry HBV, and between 4,000 and 5,000 annual deaths attributed to chronic liver disease are caused by HBV.

From 1990 through 2002, the incidence of acute HBV fell 67%, from more than 21,000 per year to approximately 8,000 per year. Analysts attribute this drop to the availability of an HBV vaccine. The major routes of HBV transmission include exposure to contaminated blood (e.g., transfusion and intravenous drug use), vertical transmission (mother to child), sexual contact, and household and occupational exposure.

Treatment. The standard of care in the treatment of HBV involves one of two approaches. The original paradigm involved interferon (INF) therapy, Intron A from Schering-Plough Corporation. Most patients, however, currently receive therapy through small-molecule oral antiviral medications. Treatment options for HBV include oral nucleotide analogs or nucleoside analogs such as Gilead Sciences, Inc.'s Hepsera (adefovir), Bristol-Myers Squibb's Baraclude (entecavir) or GlaxoSmithKline (GSK's) Epivir-HBV (lamivudine). The FDA also approved Roche Laboratories' Pegasys and Schering-Plough Corporation's Intron A (interferon alfa-2b) for the treatment of HBV; in fourth quarter of 2006, Tyzeka (telbivudine/LdT), an oral nucleoside analog from Idenix Pharmaceuticals and Novartis Pharmaceuticals, was approved.

Key Trends. As a result of Epivir-HBV's high rates of resistance, a utilization shift has occurred in recent years from Epivir-HBV to Hepsera and Baraclude, both of which are associated with less development of resistance over time. In the future, treatment options may shift toward combination therapy as a strategy to perpetuate the activity of current drugs by preventing the onset of viral resistance.

Another important trend to consider in the management of HBV is the possible expansion of potential treatment candidates to encompass those with elevated HBV virus and normal liver enzyme levels (i.e., "immune-tolerant" patients). Currently, HBV treatment guidelines only recommend the treatment of patients with elevated liver enzymes. However, a recent study demonstrated that patients with a detectable HBV viral load are at higher risk for developing liver cancer.

Unmet Needs. Unmet therapeutic needs in the treatment of HBV relate to treatment efficacy, resistance, and duration of therapy. Rates of HBe antigen seroconversion, a key marker of therapeutic success in patients who have HBeAg-positive disease, remain relatively modest. In addition, curing a patient with hepatitis B is extremely rare.

Preventing antiviral resistance remains another unmet need in HBV treatment. As noted earlier, the growth in antiviral resistance drives physicians toward a combination-therapy approach.

Medications in Development. Several small-molecule antiviral agents are in development for the treatment of HBV. They include Gilead Sciences, Inc.'s Viread (tenofovir) and Truvada (a once-daily fixed dose combination of Viread and Emtriva [emtricitabine/FTC]); valtorcitabine from Idenix Pharmaceuticals, Inc.; clevudine from Pharmasset, Inc. (Princeton, NJ); and pradefovir, which was recently was acquired by Schering-Plough Corporation.

Nonalcoholic Fatty Liver Disease

Epidemiology. Nonalcoholic fatty liver disease is predicted to become the most common liver disease in the future. It describes an accumulation of excess fat in the liver to the extent that fat cells constitute 5% to 10% of the total weight of the organ. The disease is a direct result of the components of metabolic syndrome (i.e., obesity, type 2 diabetes

mellitus, dyslipidemia, and/or hypertension), or it may result from long-term usage of such medications as corticosteroids or antiretrovirals.

When patients become afflicted with nonalcoholic steatohepatitis (NASH), a condition caused when the liver becomes inflamed as a result of NAFLD, the inflammation resulting from the excess fat leads to the damage or destruction of liver cells. According to the American Liver Foundation, New York City, 10% to 20% of Americans have NAFLD and 2% to 5% have NASH.

Current Treatment. No approved or commonly accepted medications are available for the treatment of NAFLD/NASH. Practitioners generally urge patients to lose weight by adopting a low-carbohydrate, low-fat diet to attain better control of their diabetes, and/or to address their dyslipidemia and hypertension.

Liver disease represents a major new research and development frontier for the pharmaceutical industry.

Unmet Needs. Aside from a dearth of therapeutic options for the treatment of NAFLD/NASH, a key unmet need resides in the availability of noninvasive modes of assessing patients' liver status on an ongoing basis, and thus determining which patients are progressing from NAFLD to NASH. Liver biopsy prevails as the gold standard, but it is costly, painful, and subject to error. A second unmet need surfaces in the gastroenterology community's understanding of the natural course of NAFLD and NASH, especially an understanding of which patients with NASH will progress, and thus eventually may require treatment.

Medications in Development. As a function of the association between insulin resistance and NAFLD, most of the agents under investigation for treating NAFLD/NASH are insulin-sensitizing antidiabetic agents. These include metformin and the thiazolidinediones (TZDs), including both Avandia (rosiglitazone) from GSK and Actos (pioglitazone) from Eli Lilly and Company. The liver toxicity heritage of this class, however, does raise some concern; troglitazone was removed from the market because of acute idiopathic hepatitis. Aside from the TZDs, other agents that are being or have been considered for NASH include Merck & Co., Inc.'s Cozaar (losartan), Trental (pentoxifylline) from Sanofi-Aventis (Bridgewater, NJ), ursodeoxycholic acid, and sulfasalazine.

Conclusion

Liver disease represents a major new research and development frontier for the pharmaceutical industry as a function of the recognition and growth of viral hepatitis and NAFLD combined with the relative scarcity of effective and tolerable treatment options. Although numerous potential liver conditions exist—including viral hepatitis, metabolic liver injury, alcoholic liver disease, PBC, autoimmune hepatitis, hemochromatosis, primary sclerosing cholangitis, and Wilson's disease—HCV, HBV, and NAFLD/NASH presently represent the most commercially inviting targets for drug development. ■

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