



Specific Hepatitis C Virus Inhibitors

By Natalie Bzowej, M.D.

Currently, two principal targets of new antivirals are the hepatitis C virus (HCV) NS3 serine proteinase and the HCV RNA-dependent RNA polymerase. However, any functional HCV structure and any step of the life cycle can theoretically be inhibited, and new classes of inhibitors are likely to appear in the future.

NS3 serine protease inhibitors

BILN 2061 (Boehringer-Ingelheim) is an NS3 protease inhibitor targeted to HCV genotype 1 that profoundly and specifically inhibits HCV replication in vitro. However, this agent will not be developed because of myocardial toxicity in animal studies.

VX-950 (Vertex Pharmaceuticals) is another NS3 protease inhibitor that targets the catalytic site of the enzyme. The results of a 14-day trial were recently presented. VX-950 was administered at three dosages over 14 days in patients with HCV genotype 1 infection who had not responded to previous Interferon alfa therapy. All treatment groups achieved an average 3- to 4-log HCV RNA drop within the first hours or days of treatment. VX-950 was well tolerated, and no major side effects were reported.

The results of a 28-day, phase II study, which enrolled 12 treatment naïve patients with genotype 1 HCV, were reported in a February 2006 press release. Patients received VX-950 at a dose of 750 mg every eight hours for 28 days in combination with standard doses of pegylated interferon alfa-2a and ribavirin. At the end of 28 days patients completed dosing with VX-950 and were required to continue peg-IFN and ribavirin. HCV RNA was undetectable in all 12 patients at the end of dosing with VX-950. No patients showed viral breakthrough and no major side effects were reported. The trial is ongoing and, thus, sustained viral response remains unknown.

SCH 503034 (Schering-Plough) is another protease inhibitor that has been shown to have potent anti-HCV activity in preclinical studies. In a dose-ranging study of 61 patients who had previously failed peg-IFN therapy, patients treated with SCH 503034 1200 mg/day in three divided doses experienced a greater than two log₁₀ decrease in HCV RNA from baseline after 14 days. Adverse events were similar to those reported in patients receiving placebo. Phase II clinical trials of SCG 503034 are ongoing.

The protease inhibitors currently appear to be the most promising of the specific HCV inhibitors in clinical development. There has been the emergence of HCV resistance in observed relapses on therapy.



The impact of resistance, together with the mid- and long-term safety profiles, will determine the utility of these drugs in the treatment of chronic hepatitis C. Both VX-950 and SCH 503034 have received Fast Track designation from the U.S. Food and Drug Administration.

NS5B RNA-dependent RNA polymerase inhibitors

The HCV RNA-dependent RNA polymerase is a key viral enzyme responsible for HCV replication.

Valopicitabine (NM283, Idenix Pharmaceuticals) is a nucleoside analog that targets the NS5B polymerase active site. A double-blind, randomized, phase I dose escalation clinical trial evaluated the safety, pharmacokinetics, and antiviral activity of valopicitabine in patients with chronic HCV infection who were treated for 15 days and followed for two weeks. All patients were infected with HCV genotype 1 and had not responded to previous IFN-based therapy (87%) or were untreated (13%). Patients were randomly assigned to receive valopicitabine 50, 100, 200, 400, or 800 mg once daily, 200 mg twice daily, or placebo. Two additional groups were created to evaluate titrated dosages up to 800 mg/day with a goal of optimizing gastrointestinal tolerance of the higher doses. Each of the eight active treatment groups included 12 patients, ten receiving valopicitabine (nine in one group) and two receiving placebo. A dose-related, consistent but moderate viral load reduction was evident after 15 days of treatment. Patients receiving the highest overall dose exposure (800 mg/day) achieved a mean viral load reduction of 1.2 log₁₀. Although side effects were generally mild, an antiemetic (anti-vomiting medicine) was required for some patients during the first few days of dosing.

In a phase 2b trial, the antiviral efficacy of valopicitabine in combination with pegylated interferon is underway. Patients are receiving valopicitabine in

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Indicators of Hepatitis B Virus (HBV) Infection

Screening Panel Advocated for At-Risk Populations

By Robert Gish, M.D. and Laura Miyashita

Each year, the Centers for Disease Control (CDC) estimates that 73,000 to 80,000 new hepatitis B virus (HBV) infections occur, leading to about 21,000 to 23,000 acute clinically evident infections annually. While this number has declined from its peak in the mid-1980s, hepatitis B remains a critical disease, due in part to long-term consequences such as cirrhosis and hepatocellular carcinoma (HCC) that occur in up to 30% of people if one is not treated.

“For physicians who evaluate and treat at-risk populations, identification and prevention of hepatitis B needs to remain a priority,” explains Robert Gish, M.D., medical director of California Pacific Medical Center’s Liver Disease & Transplant Program. “Specifically, screening with an initial panel of HBsAg, anti-HBc and anti-HBs should be performed to distinguish infection, exposure and immunity.”

In the United States, hepatitis B is both a childhood (transmission from mother to child, or child to child) and an adult-acquired disease associated with high-risk behavior, including sexual contact and injection drug use. The childhood-associated disease is typical of immigrants to the U.S., many of whom arrive from areas of high endemicity. For example, although the prevalence of HBV infection is only 0.3% in the general U.S. population, it is as high as 15% among Asians and Pacific Islanders, who comprise 1.3 to 1.5 million known carriers of hepatitis B in the United States.

Candidates for Screening

Screening for hepatitis B is routinely performed in persons with elevated liver enzyme levels, jaundice or other evidence of acute liver disease. In addition, screening is warranted for anyone with risk factors for HBV infection. Individuals who are in an “at risk” group should receive HBV vaccination if infection is not evident after completion of screening.

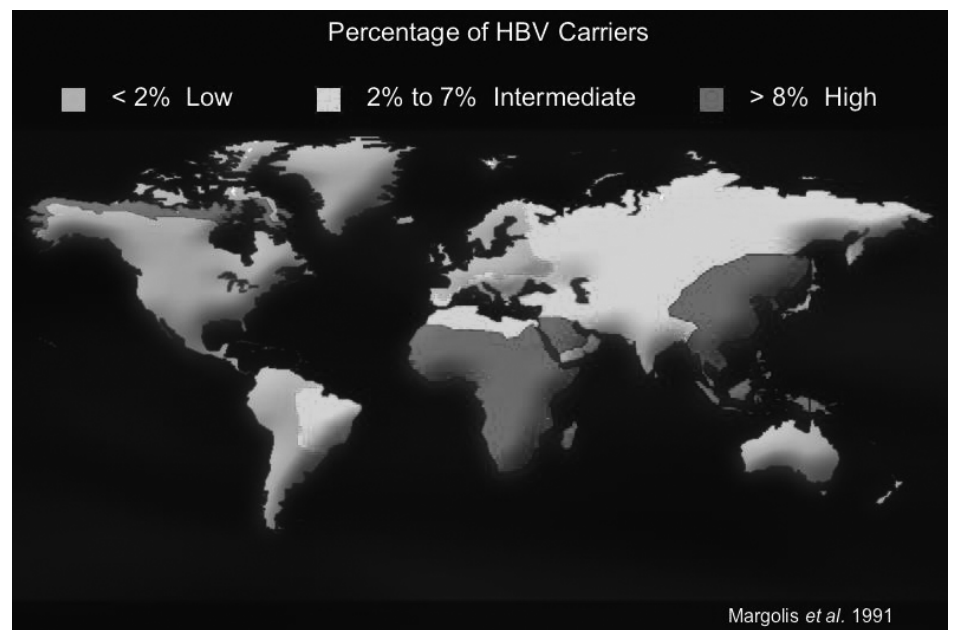
Individuals at risk for HBV include:

- Those who have engaged in high-risk sexual behaviors (men who have sex with men, anyone with multiple heterosexual sex partners, and persons recently diagnosed with a sexually transmitted disease)
- Injection drug users
- Immigrants, refugees or adoptees/orphans from areas of high endemicity
- Individuals who are immunosuppressed
- Dialysis patients
- Household members or sexual partners of known HBV carriers
- Those who have had occupational exposure to blood through needle sticks
- Recipients of certain blood products (e.g., clotting factors for hemophilia)
- Inmates in long-term correctional facilities
- residents in developmentally disabled institutions

Diagnostic Tests for Screening and Evaluation in Hepatitis B

An initial screen for hepatitis B should consist of hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs). A positive HBsAg is a general marker of acute or chronic infection. It is the first marker to appear and its persistence for >6 months indicates chronic infection. Anti-HBc is a marker of exposure that persists for life. Anti-HBs documents recovery and/or immunity to HBV and is detectable after immunity conferred by hepatitis B vaccination or previous infection.

“While there has been some controversy over the need for all three screening tests, we feel strongly that this full panel is the most effective means for screening an individual for the presence of HBV infection, exposure or immunity,” explains Gish.

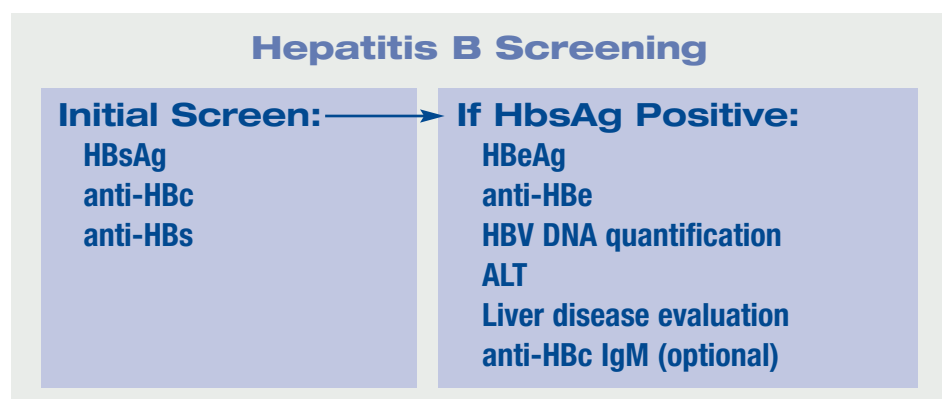


Further Evaluation for HBsAg+ Patients

“Individuals who are HBsAg positive should receive further serologic testing, including measurements of hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe), HBV DNA quantification by nucleic acid testing, alanine transaminase (ALT) and evaluation for signs of liver disease,” says Gish. He adds, “An optional test is the anti-HBc IgM, which is the best test to document an acute infection; if positive in a person known to have chronic infection, it imparts a worse prognosis.”

Gish recommends referral to a hepatologist for all patients with HBV and/or if a patient needs a liver biopsy or liver biopsy review. A liver transplant evaluation referral should be made if any signs of liver dysfunction are present, if there is suspicion of HCC, or if ascites or gastrointestinal bleed from varices occur.

To refer patients to California Pacific’s Liver Disease & Transplant Program, contact our Specialty Referral Line at 1-888-637-2762.



It's Time for New Drugs for Hepatic Encephalopathy

Research Studies Underway at California Pacific

By Todd Frederick, M.D. and Laura Miyashita

Two clinical studies at California Pacific Medical Center strive to uncover the effects of new medications for hepatic encephalopathy (HE). HE, a condition in which various toxins are not properly cleared by the liver, results in altered mental status, ranging from subtle concentration deficits to coma. Common in patients with cirrhosis, HE has historically been difficult to manage. Recently, the standard of care for HE—lactulose—has been challenged in terms of its efficacy. (“Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials” Bodil Als-Nielsen, Lise L Gluud, Christian Gluud. *BMJ*, 2004)

To provide better insight into potential treatments for encephalopathy, Hepatologist Todd Frederick, M.D. is the lead investigator for two studies based at California Pacific:

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Medications Identified as Causes of Drug-Induced Liver Injury

Research Studies Underway at California Pacific

By Maurizio Bonacini, M.D. and Laura Miyashita

Drug-induced liver injury (DILI) is an infrequent but potentially serious phenomenon that has become the most frequent cause of acute liver failure in the United States, according to the U.S. Food & Drug Administration (FDA). Because of the rising issue of new drug approvals and the potential for liver toxicity, major medical societies, including the National Institutes of Health (NIH) and American Association for the Study of Liver Disease (AASLD) gathered experts from different fields to discuss this topic at a single topic conference in Atlanta, GA in October 2005.

“Most recently, eight drugs and dietary supplements have been published as causing drug-induced liver injury,” says Maurizio Bonacini, M.D., a hepatologist with California Pacific Medical Center’s Liver Disease & Transplant Program.

Medications associated with DILI include:

- Beta-interferons
- Pantoprazole
- Bortezomid
- Dinitrophenol
- Camellia Sinensis (green tea)
- Psoralea Coryfolia
- Hydroxycut
- Anti-TNF agents (Enbrel)

“DILI is a diagnosis of exclusion, meaning that anytime we see elevated liver enzymes, either acutely or chronically, we need to remember drugs as a possible cause,” says Bonacini. While DILI can affect anyone, groups at higher risk include:

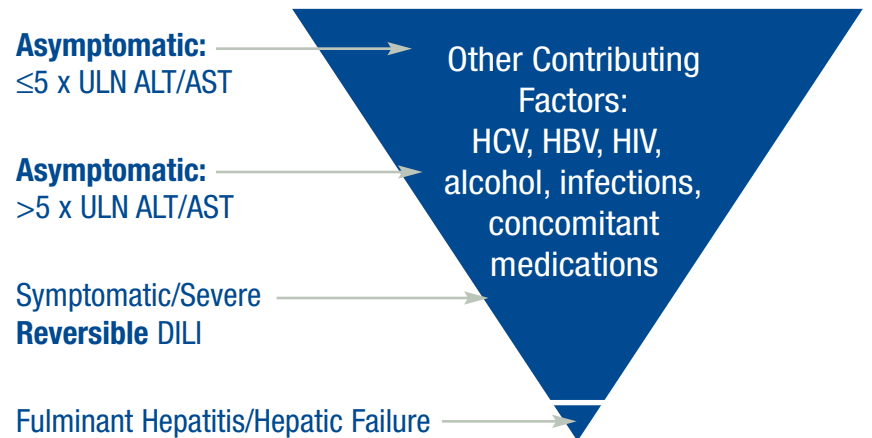
- Women
- Obese individuals
- People with pre-existing liver disease (alcoholism, HBV, HCV)
- Older patients (including those taking the drug INH)
- People living with HIV

Two rules put forth by physicians aim to shed light on the prognosis associated with DILI. The first rule, Hy’s rule, described by the late Hyman Zimmerman, M.D., of George Washington University, states that the combination of drug-induced hepatocellular injury and jaundice lead to a mortality rate of 10%. This rule was confirmed in 2005 by two prospective studies (Andrade et al. *Gastroenterology* 2005; Bjornsson and Olsson *Hepatology* 2005). The latter studies also show that hepatocellular injury has a worse prognosis than cholestatic injury. The “Rule of 3” explains that in order to confidently pick up an event, one needs three times the denominator for that event. According to Bonacini, “This means that most phase three studies that lead to FDA approval of drugs often lack the ability to pick up serious hepatic adverse events because only 3,000 to 5,000 patients are enrolled. Consequently, significant events (e.g. 1/5,000) are sometimes only uncovered in post-marketing studies, as was the case with troglitazone, an oral anti-diabetic medication.”

To further explore drug-induced liver toxicity, California Pacific Medical Center, along with seven other institutions, received funding in 2005 from the NIH for a two-year study. Part of this study focuses on developing a diagnostic scale that could help assess the likelihood that a drug is responsible for liver injury.

“Until we can further review causes of liver toxicity and study different genes that might be associated with drug metabolism, our Liver Team promotes the old dictum, ‘an ounce of prevention is worth a pound of cure,’” says Bonacini. To help prevent DILI, he encourages physicians to:

Clinical Spectrum of Hepatotoxicity



The figure depicts the fact that mild asymptomatic elevation of liver tests is common (e.g. users of NSAIDs) but more severe injury is much less common (see tip of the pyramid). Adapted from: Stern JO et al. XIV International AIDS Conference, July 7–12, 2002. Barcelona, Spain.

- Know side effects of all medication and inform patients of them.
- Monitor a patient’s liver levels for patients on Tacrine, NVP, INH, HAART or those with underlying liver disease.

If liver damage has already occurred as a possible result of DILI, anecdotal evidence suggests the following approaches:

- Discontinue suspected agent(s) (although this may not be easy to determine in some patients, such as those with HIV who are on multiple medications).
- Prednisone may help in patients with autoimmune-like disease.
- Use of ursodiol (dose of 15 mg/kg) in patients with cholestasis.
- For microvesicular steatosis seen in HIV patients with multiple nucleoside analogue therapy, the following may lead to clinical improvement: Vitamins B1, B6, C and E, N-Acetylcystein, Coenzyme Q and Carnitine.

If you have any cases of drug-induced liver injury that may be applicable for California Pacific’s DILI study, kindly contact Maurizio Bonacini, M.D. at (415) 600-1026 or by email at bonacim@sutterhealth.org.

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combination with pegylated interferon alfa-2a (Pegasys), 180 ug per week This on-going 48-week clinical trial includes five randomized treatment arms: (1) valopicitabine 800 mg daily; (2) valopicitabine 400 mg beginning on Day 1 plus pegylated interferon beginning on Day 8; (3) valopicitabine ramping up from 400 mg to 800 mg beginning on Day 1 plus pegylated interferon beginning on Day 8; (4) valopicitabine 800 mg beginning on Day 1 plus pegylated interferon beginning on Day 8; (5) pegylated interferon plus ribavirin with no valopicitabine. Interim 4-week data found that the four treatment arms that included valopicitabine in combination with pegylated interferon during the first four weeks all produced proportionally greater suppression of HCV RNA compared to the arm that included pegylated interferon plus ribavirin alone. Unfortunately, due to side effects, the FDA has requested that patients on the highest dose of valopicitabine (800 mg) be lowered for safety.

Numerous companies are also developing nucleosidic-nucleotidic and nonnucleosidic inhibitors of the HCV RNA-dependent RNA polymerase, some of which could enter clinical evaluation soon.

An Investigational Intravenous Medication for Treatment of Grade 3 or 4 Encephalopathy

This trial studies a medication that is currently approved for hyperammonemia in children with urea cycle defects. The drug uses “ammonia scavenger” compounds as alternative pathways for nitrogen disposal from the bloodstream. The goal of this Phase 2 randomized, active-controlled study is to compare the effects of this intravenous medication against the standard of care (lactulose) in adult patients with severe acute HE. The hope is the drug will help patients wake up faster, avoiding intubation and a prolonged ICU stay.

Study parameters include:

- Grade 3 or 4 encephalopathy (hospitalized with acute altered mental status or coma)
- Randomized to the IV infusion or current standard of care (Lactulose)
- Short-term study with 26-hour infusion period and total 48-hr observation period

“This is a novel concept in the treatment of hepatic encephalopathy, targeting one of the main purported toxins accumulating within our patients and delivering care intravenously rather than through the gut, which is often unreliable in its medication delivery and absorption. We are hoping to enroll 10 patients with new-onset or relapse of severe encephalopathy over the next 6–12 months,” says Todd Frederick, M.D., hepatologist and lead investigator at California Pacific Medical Center.

Rifaximin (Xifaxan®) for Maintenance of Encephalopathy Remission

To study the effects of rifaximin on maintaining remission of hepatic encephalopathy, California Pacific is participating in a Phase 3 multi-

center study. Currently rifaximin, manufactured by Salix Pharmaceutical, is approved for short-term use for traveler’s diarrhea. In Europe, the drug has been used for hepatic encephalopathy for nearly two decades. Recent studies show that it may be as effective as lactulose in preventing encephalopathy recurrence. Rifaximin is similar to Neomycin, another poorly absorbed antibiotic traditionally used for patients with HE refractory or intolerant to lactulose. These medications are believed to work by killing bacteria in the gut responsible for producing ammonia. However, rifaximin does not appear to have significant side effects such as oto- or nephrotoxicity, occasionally seen in this patient population with Neomycin use.

“We are desperate for effective and tolerable therapies for many of our patients with disabling encephalopathy,” says Frederick. “The current tools are crude and of questionable benefit, but remain in widespread use due to lack of alternatives and fear of relapse without them. This study will not only provide valuable information regarding the efficacy of rifaximin for preventing relapses of HE, it will also give us insight into the natural history of recurrent HE as many patients may discontinue lactulose during follow-up.”

Study parameters include:

- At least 2 episodes of Grade 2 or more encephalopathy in last six months
- 6-month double blind, randomized, placebo-controlled study
- Stable lactulose use allowed in either study arm. Lactulose will not be withdrawn from the patient’s regimen, but neither arm is required to continue lactulose.

For more information about either study, contact Todd Frederick, M.D. at (415) 600-1059 or fredertz@sutterhealth.org.



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