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LIVER DISEASE MANAGEMENT & TRANSPLANT SERVICES • CENTER FOR COMPLEX DIGESTIVE DISEASE

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Hepatology Research Update

by Laura Miyashita

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Welcome to the annual research issue for *Liver & GI Review*. This issue examines current research trials underway at California Pacific Medical Center for patients with hepatitis B and C virus (HBV and HCV). Because these viruses mutate easily, they have evaded researchers attempting to find cures. Instead, drug companies are feverishly working to find new therapies that may work better than currently approved medications

in clearing viral infections and halting disease progression.

California Pacific's Hepatology Research Center has a comprehensive clinical research program, offering concurrent trials for various liver diseases. Our clinical research is led by Natalie Bzowej, M.D., Ph.D., in conjunction with Robert Gish, M.D., Ed Wakil, M.D., Maurizio Bonacini, M.D., Todd Frederick, M.D., and Jamey Schmidt, R.D. We encourage referral of patients with hepatitis B or C viruses, either by a physician or through self-referrals. Participation in clinical trials is the only way that new and hopefully better treatments can be approved for these diseases. For patient referrals, call us at (415) 600-1182.

Exploring Clinical Trial Participation

Information on our clinical trials is included in this newsletter (*page 2*). Our trials are also listed on the Web at www.cpmc.org/research. If you would like additional information, a copy of the consent, and/or would like to speak to a physician about the study, please do not hesitate to contact the research coordinator for the study in which you are interested. Patients may also contact the research coordinator directly.

Overview of Current Hepatitis B Research

Drug Trials Seek to Better Suppress Virus Before and After Transplant

by Jamey Schmidt, R.D.

Presently, only three FDA-approved treatments exist for Hepatitis B Virus:

- alpha-interferon;
- lamivudine;
- adefovir.

While these treatments are good, they are not 100% effective for all patients. In fact, over time, patients may become resistant or show only a partial response to lamivudine and adefovir treatment, never reaching full viral suppression.

California Pacific's Hepatology Research Center has been on the forefront of HBV research. According to Director of Hepatology Research, Natalie Bzowej, M.D., Ph.D., "Our Research Center participated in the phase III clinical trials for lamivudine and adefovir, and we continue to follow some of the "original" study participants to examine long-term response to adefovir."

Entecavir and Telbivudine Research

Since the approval of lamivudine and adefovir, California Pacific's Hepatology Research Team has been investigating other promising drugs for HBV, such as entecavir and telbivudine. To date, patients who enrolled into the three different entecavir protocols (treatment naïve, lamivudine resistant and eAntigen negative) have completed one year of double-blind, randomized treatment. All subjects who participated in the phase II and III trials have been eligible for the long-term, open-label extension studies of entecavir. Additionally, we are currently enrolling subjects into a double-blind study for decompensated patients who are naïve to treatment or lamivudine resistant. These subjects are randomly assigned to entecavir or adefovir.

As the study sponsor, Bristol Myers-Squibb, prepares the data for FDA submission, physicians and

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Enrolling Studies

Disease/Drug/Sponsor	Trial Type	Inclusion	Exclusion	Procedure/Drug	Contact
HCV Exagen Diagnostics	<ul style="list-style-type: none"> ■ Diagnostic Study 	<ul style="list-style-type: none"> ■ Must be infected w/ HCV ■ Must be 18 yrs or older 	<ul style="list-style-type: none"> ■ Co-infected w/ HIV; had a liver transplant; have evidence of HCC 	<ul style="list-style-type: none"> ■ Co-infected w/ HIV; had a liver transplant; have evidence of HCC 	Milania dela Cruz (415) 600-1692 delacrmj@sutterhealth.org
HCV (naïve) Viramidine Ribapharm	<ul style="list-style-type: none"> ■ Phase III ■ Treatment Trial ■ Viramidine or Ribavirin + PEG IFN 	<ul style="list-style-type: none"> ■ HCV Treatment Naive with Compensated Chronic HCV ■ HCV RNA > 2000 copies/ml 	<ul style="list-style-type: none"> ■ Severe Neuropsychic disorder ■ History or clinical manifestations of metabolic, hematologic, pulmonary, heart, gastrointestinal, neurological, renal, urological, endocrine, ophthalmologic, or immune related disease. ■ Pregnant or breast feeding patients 	<ul style="list-style-type: none"> ■ Biopsy: Within 24 months of study ■ Dosing: 24 or 48 weeks ■ Follow-up: 24 weeks 	Nata DeVole (415) 600-1110 devolen@sutterhealth.org
HCV Caspase Inhibitor IDUN Pharmaceuticals	<ul style="list-style-type: none"> ■ Phase II ■ Safety and Efficacy ■ 12 Weeks Double-Blind ■ 12 Weeks Open-Label ■ Compassionate Use Option 	<ul style="list-style-type: none"> ■ Unsuccessful Prior HCV Treatment ■ Elevated Enzymes (1.5-10 x ULN x 2) 	<ul style="list-style-type: none"> ■ Cirrhosis ■ Bridging Fibrosis > 2 years 	<ul style="list-style-type: none"> ■ Dosing: Up to 24 weeks 	David Delman (415) 600-5892 delmandh@sutterhealth.org
Transplant-HCV XTL Pharmaceuticals HepX-C	<ul style="list-style-type: none"> ■ Phase II 	<ul style="list-style-type: none"> ■ Liver Transplant for HCV ■ HCV RNA + ■ Cadaver donor, negative for HBV, HCV, HIV 	<ul style="list-style-type: none"> ■ HIV ■ Pregnant ■ Chronic HBV 	<ul style="list-style-type: none"> ■ Drug: 13 weeks 	Nata DeVole (415) 600-1110 devolen@sutterhealth.org
HBV Entecavir Bristol-Meyer's Squibb (048)	<ul style="list-style-type: none"> ■ Phase III ■ Entecavir vs. Adefovir 	<ul style="list-style-type: none"> ■ Child-Pugh's Score ≥ 7 ■ DNA $\geq 1,000,000$ ■ HBsAg + 	<ul style="list-style-type: none"> ■ ALT > 15 Upper Limit Normal ■ Previous treatment with tenofovir, entecavir, adefovir or interferon within 12 weeks 	<ul style="list-style-type: none"> ■ Drug: 24-48 weeks (open label) 	Leslie Taylor (415) 600-1109 taylorLL@sutterhealth.org
Transplant-HBV XTL Pharmaceuticals HepX-B	<ul style="list-style-type: none"> ■ Phase II 	<ul style="list-style-type: none"> ■ 6 months post-liver transplant ■ Hepatitis B immune globulin (HBIG) regimen x 3 months ■ Undetectable HBsAg + HBV DNA x 2 tests 	<ul style="list-style-type: none"> ■ Received another organ transplant ■ HCV, HCV, HIV 	<ul style="list-style-type: none"> ■ Drug: 21 weeks ■ Follow-up: 2 weeks 	Nata DeVole (415) 600-1110 devolen@sutterhealth.org
Transplant-HBV National Institutes of Health	<ul style="list-style-type: none"> ■ Observation ■ High Replicator 	<ul style="list-style-type: none"> ■ HBV listed for transplant ■ Received liver or kidney transplant within last 12 months 	<ul style="list-style-type: none"> ■ Other Liver Diseases 	<ul style="list-style-type: none"> ■ Blood Draw: Every 6 months 	Nata DeVole (415) 600-1110 devolen@sutterhealth.org
Hepatology-Hyponatremia Tolvaptan Otsuka	<ul style="list-style-type: none"> ■ Phase III ■ Tolvaptan vs. Placebo 	<ul style="list-style-type: none"> ■ Hyponatremia—Serum Sodium <135 mEq/L 	<ul style="list-style-type: none"> ■ Acute/Reversible Hyponatremia ■ Criteria related to Cardiac, Neurologic, Renal, and Hepatic Safety 	<ul style="list-style-type: none"> ■ Drug: 30 days 	Nata DeVole (415) 600-1110 devolen@sutterhealth.org
HIV/Chronic Liver Disease Boehringer-Ingelheim Pharmaceuticals Inc.	<ul style="list-style-type: none"> ■ Phase IV 	<ul style="list-style-type: none"> ■ Biopsy: Within last 24 months ■ Taking Viramune® (Nevirapine) twice daily 	<ul style="list-style-type: none"> ■ Concurrent use of HIV antiviral therapy w/ other NNRTI's; use of antifungal agents, clarithromycin, rifampin, st. john's wort 	<ul style="list-style-type: none"> ■ Blood draw only 	Milania dela Cruz (415) 600-1692 delacrmj@sutterhealth.org

Clinical Studies Address Side Effects and Non-Responders to HCV Therapy

Viramidine, Thymosin and Merimepodib (MMPD) are the Subjects of Current Research

by Jamey Schmidt, R.D.

Research plays an important role in the treatment of Hepatitis C (HCV), a virus that has become a major health problem worldwide. In the United States alone, the Centers for Disease Control estimates between 2.4 to 4 million individuals are infected with HCV.

Currently, California Pacific Medical Center's Hepatology Research Center is focusing research efforts in four areas of HCV:

- Bringing new medications through phase II and III research to licensing;
- Reducing specific side effects;
- Testing investigational drugs on patients who did not respond to therapy;
- Testing approved treatments on patients post-transplant.

While research into new treatments for HCV continues, the current approved treatment is pegylated interferon combined with ribavirin—a drug therapy that is, on average, only 50% effective for the majority of Americans. Pegylated interferon is a drug that is injected weekly and ribavirin is a tablet that is taken twice a day for up to 48 weeks. The goal of treatment is to no longer be able to measure HCV in one's blood and to see less liver damage than before treatment.

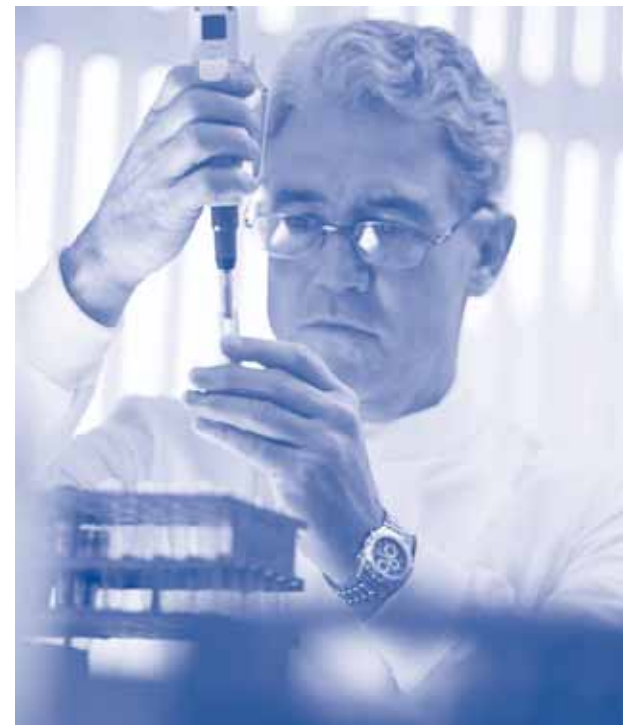
Reducing Side Effects of HCV Treatment

The treatment for HCV can be challenging, with patients experiencing side effects including flu-like symptoms, depression, anemia, nausea and fatigue. These side effects sometimes cause patients to either stop the drugs or reduce their dose, thereby affecting one's overall chances of responding to treatment.

Viramidine

One side effect that researchers are currently investigating is anemia—a condition that occurs in 20–30% of patients treated with combination therapy. Ribavirin is primarily responsible for causing anemia. Preliminary studies conducted by our Hepatology Research Center have shown that the investigational drug Viramidine™ has reduced anemia in patients who have been randomly assigned to viramidine when compared to ribavirin.

Presently, we are conducting another clinical trial investigating the effects of viramidine for patients who have never been treated for HCV infection. Patients are randomly assigned to pegylated interferon + viramidine or pegylated interferon + ribavirin for 48 weeks of treatment and six months of follow-up. A total of 435 patients will be enrolled in this study



nationwide to determine if viramidine reduces anemia when compared to ribavirin. If the investigational drug proves to significantly reduce anemia, the study sponsor, Valeant Pharmaceuticals, will submit information collected during the research study to the Food and Drug Administration (FDA) for approval.

To learn more about this study, contact Nata DeVole at (415) 600-1110 or devolen@sutterhealth.org.

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patients anxiously await the results. While entecavir has been shown to be as safe as lamivudine, data from the phase III clinical trials will determine if it is as effective as lamivudine.

The Hepatology Research Center is also testing the efficacy of telbivudine in comparison to lamivudine. Although this particular study closed enrollment in early 2004, we are working closely with the sponsor (Idenix) to implement other studies testing telbivudine's effectiveness.

The approved drugs and new drugs currently being tested provide the best chance for HBV patients to suppress their virus, minimize liver fibrosis and reduce the risk of hepatocellular carcinoma. Because the current treatments have not been effective for all patients, many have turned toward liver transplant as a life-saving option. Unfortunately, even with liver transplantation, HBV can recur post-transplant.

Uncovering the Course of HBV Post-Transplant

To try and understand the history of HBV, the Hepatology Research Center is participating in a National Institutes of Health study that observes patients with HBV while on the transplant list and post-transplant. This study follows a patient's course of HBV medications, laboratory values and medical history. We will work with each patient to collect a blood sample twice a year. This blood is sent to the University of Michigan where Principal Investigator Anna Lok, M.D., will analyze it for disease progression and mutation development.

After transplant, patients are instructed to inject with HBIg, a human serum-derived polyclonal preparation that, in combination with lamivudine or adefovir, can help prevent HBV re-infection. While the side effects of HBIg are considered minimal, its high cost is a limitation. In recognition of this, XTL Pharmaceuticals has created a combination of two monoclonal antibodies—called HepeX-B™—that can be consistently produced






without the infectious risks associated with plasma-derived products. Our Hepatology Research Center is currently recruiting subjects with HBV post-transplant to participate in a randomized study comparing HepeX-B to standard therapy of HBIg.

Our doctors and research coordinators are always eager to discuss investigational drugs available to fight the hepatitis B virus upon diagnosis, resistance and post-transplant. Please contact our Research Center at (415) 600-1182 or one of the hepatologists to learn more.

Non-Responder Treatment Options

About 50% of all patients who undergo treatment for HCV will be considered non-responders. Because there is currently no effective alternative therapy for non-responders, researchers hope that clinical studies may ultimately improve options for these patients.

 Responder	No detectable HCV in the blood 6 months after treatment
 Relapser	No HCV in the blood during treatment and perhaps at some point during follow-up, but HCV returns in the blood
 Non-Responder	HCV in the blood during treatment

Thymosin

Thymosin is a synthetic version of a key component of the normal immune system produced by the thymus gland. It acts to stimulate the immune system, which may help to fight HCV. Preliminary studies of thymosin in patients with HCV have proven the combination of thymosin + interferon to be more effective than treating patients with interferon alone. And, the side effects of thymosin to date have been minimal.

Our Hepatology Research Center is conducting two “non-responder” studies that are currently closed and in a follow-up phase. One is for patients with HCV without

cirrhosis and the other for patients with HCV with cirrhosis. All patients are randomly assigned to either pegylated interferon + thymosin or pegylated interferon + placebo (sugar pill) for a total of 48 weeks of study medication and six months of follow-up. A total of 500 subjects have been enrolled nationwide for each study. Once all subjects have completed their participation, the study sponsor, SciClone Pharmaceuticals, will submit all data to the FDA for approval. This study is closed to enrollment.

Caspase Inhibitors

Caspase Inhibitors are a new class of drugs being studied by the Hepatology Research Center. Caspases are groups of proteins found in cells. They promote cell death, including hepatocytes. In some diseases, there is thought to be too much of this type of cell death. The specific Caspase Inhibitor we are researching may protect liver cells from dying by blocking specific enzymes, thereby reducing liver damage.

Idun Pharmaceuticals is now conducting another phase II clinical trial with California Pacific Medical Center. The first study showed that the Caspase Inhibitor successfully reduced liver enzyme levels when compared to placebo. Our current study is enrolling patients with HCV who are non-responders or relapsers (without cirrhosis). To learn more about this study, contact David Delman at (415) 600-5892 or delmandh@sutterhealth.org.

Post-Transplant Studies

HCV is a challenging virus to eliminate from the liver and the blood. For patients who do not respond to the existing approved and/or investigational therapies, HCV can progress to cirrhosis and/or liver cancer, possibly requiring a liver transplant. While a liver transplant offers patients a healthy, functioning liver, the hepatitis C virus remains in one’s blood and, in all cases, returns post-transplant, ultimately affecting the transplanted liver.

Phoenix Study

Presently, there are no treatment guidelines for HCV recurrence post-transplant. The objective of the Phoenix study, headed by the Mayo Clinic and sponsored by Roche Pharmaceuticals, is to reduce the impact of post-transplant recurrence of HCV. This study will randomly assign patients to either 48 weeks of pegylated interferon + ribavirin or observation visits (no medication treatment for HCV) for 10-16 weeks after their liver transplant. If HCV becomes detectable in the blood among the patients assigned to observation only, they will be assigned to receive pegylated interferon + ribavirin for 48 weeks.

Because there is so much to learn about the hepatitis C virus, California Pacific’s Hepatology Research Center continuously adds new research studies. If you have a patient who may be a candidate for a HCV clinical trial, please contact the study coordinator for your particular study of interest.



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