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Liver Disease Management & Transplant Program ■ Center for Complex Digestive Disease

# Liver & GI Review

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## Nonalcoholic Fatty Liver Disease

Cirrhosis Due to NAFLD Represents the Third Most Common Indication for Liver Transplantation

by Raphael Merriman, M.D. and Laura Miyashita

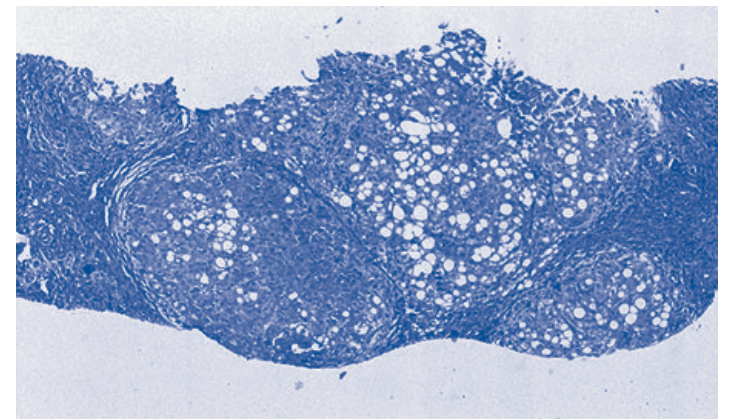
NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is characterized by the presence of excessive liver fat (steatosis) in persons who do not consume excessive alcohol. "The prevalence of NAFLD has increased rapidly in recent years, along with rising obesity," says Raphael Merriman, M.D., hepatologist and director of California Pacific's Fatty Liver Disease Clinic. According to Merriman, "Substantial progress has occurred within the last decade in understanding the pathogenesis of nonalcoholic fatty liver disease."

The term NAFLD encompasses three stages of increasing disease severity:

1. nonalcoholic steatosis (fatty liver, NAFL)—hepatocytes with excess fat only;
2. nonalcoholic steatohepatitis (NASH)—characterized by the added presence of necroinflammation and variable amounts of fibrosis; and
3. cirrhosis related to fatty liver disease.

### Prevalence

The true prevalence of NAFLD is unknown, in part



Cirrhosis due to non-alcoholic fatty liver disease (NAFLD) is now the third most common (non-tumor) indication for liver transplantation.

because accurate characterization depends upon obtaining liver histology. The estimated prevalence of NAFL is about 20% and NASH at least 2–3%.

In obese persons, especially if diabetic, prevalence rates of all forms of NAFLD are much higher. Features of Metabolic Syndrome—obesity, diabetes, hypertension and hyperlipidemia—comprise the main disease associations of and risk factors for NAFLD. Secondary causes of NAFLD are uncommon, often drug-related.

*Fatty Liver Disease, continued on page 4*

## Hepatitis B and C Clinical Studies Underway

by Todd Frederick, M.D. and Laura Miyashita

CALIFORNIA PACIFIC'S HEPATOLOGY Research Center continues to be at the forefront of research into new therapies for both chronic hepatitis B (HBV) and hepatitis C (HCV). We work with leading pharmaceutical companies to probe the capabilities of new therapies in eradicating these viral infections, halting disease progression and minimizing adverse effects. We welcome referral of patients with chronic hepatitis B or C infection, either through physician referral or direct contact to our Center.



### Hepatitis C Studies

Current and upcoming studies for HCV at California Pacific focus on the role of new medications combined with the current standard of care from Phase I through Phase III research. They include:

**Extending Interferon's Activity** A new interferon compound is being evaluated for its ability to remain active in the body for several weeks rather than five to nine days, as is the case with current pegylated interferon products. This compound, which uses an albumin molecule attached to interferon, has the potential to reduce the number of interferon injections required by 50–75%. Clinical studies to date suggest this compound may offer efficacy comparable or even superior to pegylated interferon. It also has the potential to improve in patients' quality of life by reducing side effects.

The Hepatology Research Center is currently enrolling patients who have not previously received HCV treatment in this Phase III trial.

*CLINICAL TRIALS, continued on page 2*

## CLINICAL TRIALS

continued from page 1

There are two studies underway: one for patients with genotype 1 and one for patients with genotypes 2 or 3.

### HCV Protease and Polymerase Inhibitors

New molecules being developed for HCV therapy focus on inhibiting of the molecular machinery of the virus. These protease and polymerase inhibitors—which inhibit HCV replication—are at the forefront of HCV research. Early results from small studies have confirmed initial expectations of enhanced efficacy in rapidly reducing viral load, however, sustained viral response (SVR) rates—the ultimate goal of therapy—remain to be determined. The Hepatology Research

Center is investigating the ability of these medications—usually given orally—to reduce HCV viral load or completely eradicate virus, either alone or in combination with interferon and ribavirin. The results of several of these studies are expected by late 2008.

### Continuous Delivery of Interferon

A new delivery system for interferon is under investigation for its potential to administer a consistent dose of medication over three months via an implantable device. While the current standard of care uses alpha interferon, this trial researches an alternative type 1 interferon molecule: omega interferon. According to Dr. Frederick, “Omega interferon has already shown efficacy in eradicating HCV and has actually shown increased potency

compared to alpha interferon in HCV replicon models.”

This study, which uses continuous delivery of omega interferon in combination with ribavirin, is open to patients who have had previous relapse of HCV after treatment with pegylated interferon and ribavirin.

### Hepatitis B Studies

Several new studies looking for ways to fine-tune and enhance HBV outcomes are underway or in the planning stages at the Hepatology Research Center. These studies are enrolling patients with either “e” antigen positivity or negativity without recent or ongoing HBV therapy.

### Combination Therapy vs. Monotherapy

The current standard of care for HBV includes monotherapy with nucleoside or nucleotide analogues, or interferon; however, resistance to some of these oral medications continues to be a problem. One study enrolling participants at California Pacific compares the efficacy of a combination of two oral medications for HBV in comparison to standard monotherapy. The study examines viral resistance as well as potency between the two methods of treatment.

Another study will delve into the efficacy and durability of combination therapy involving oral medication and pegylated interferon, compared to monotherapy alone.

### Optimal Dosage & Duration of Pegylated Interferon

The final HBV study focuses on fine-tuning the use of pegylated interferon for HBV to determine optimal dosage and duration of therapy (between 6–12 months).

### Targeted Molecular Therapy

A Phase I study underway at the Hepatology Research Center is investigating the use of a novel treatment for a chronic disease. This study employs targeted therapy at the molecular level with interfering RNA molecules. These molecules may have the potential to shut down the reproductive machinery of HBV within the liver cells. This study represents the first time this molecule has been used in humans, however similar technology has been employed for other diseases such as cystic fibrosis and macular degeneration.

### Clinical Trial Participation

Participation in clinical trials is critical for advancement of clinical medicine and the only way that new and successful treatments can be approved. If you would like additional information, a copy of a consent form, and/or to speak to a physician about any of the above studies, please contact the Hepatology Research Center at 415-600-1100.

## Liver Team Welcomes Hepatologist Raphael Merriman, M.D.

by Laura Miyashita



HEPATOLOGIST RAPHAEL B. MERRIMAN, M.D., RECENTLY joined California Pacific’s Liver Disease Management & Transplant Program. As part of our team, he will provide comprehensive evaluation and treatment for patients with hepatitis, liver cancer and other liver diseases, both in San Francisco and outreach sites in Northern California and Nevada.

Most recently, Dr. Merriman served as Assistant Professor of Medicine at the Division of Gastroenterology, University of California, San Francisco. His research interests include nonalcoholic fatty liver disease, an area in which he is an acknowledged expert and has received numerous research grants and awards. He has lectured nationally and internationally on the subject and has published extensively on

clinical and genetic aspects of this increasingly common liver disease. Dr. Merriman has served as a senior investigator for the National Institutes of Health, (NIDDK) Non-Alcoholic Steatohepatitis (NASH) Clinical Research Network.

At California Pacific Medical Center, Dr. Merriman will also direct the newly established Fatty Liver Disease Clinic, providing state-of-the-art diagnosis and management of this disorder and access to clinical research studies.

Dr. Merriman completed fellowships in Hepatology and Gastroenterology at the Divisions of Gastroenterology at UCSF and Washington University School of Medicine (St. Louis), respectively. He completed his residency in Internal Medicine and also served as a Chief Resident at Washington University. Dr. Merriman earned his medical degree at University College Dublin, Ireland and completed a residency in Internal Medicine at Trinity College, Dublin.

Dr. Merriman is board-certified in Internal Medicine in the British Isles and also with the American Board of Internal Medicine (ABIM). He is also board-certified in Gastroenterology and holds a Certificate of Added Qualification in Transplant Hepatology with the ABIM. He is a member of the Physician Foundation at California Pacific Medical Center.

# Customizing the Management of Chronic Hepatitis B Virus Infection

## Antiviral Therapy Should Offer Rapid Viral Suppression and Low Resistance

by Robert Gish, M.D. and Laura Miyashita

MANY OPTIONS ARE NOW AVAILABLE for treating chronic hepatitis B virus (HBV), a viral infection that can lead to cirrhosis and liver cancer in up to 30% of infected individuals. However, selecting the most appropriate treatment regimen has become more complex, both because of a greater choice of therapies and new information regarding resistance to some therapies.

“Six medications are now approved in the United States for managing chronic HBV and two more promising therapies are currently being tested,” says Robert Gish, M.D., medical director of California Pacific’s Liver Disease Management & Transplant Program. “Tailoring the medication regimen to each patient can be a challenge. Physicians have to consider when to start therapy, which agent to use when, and whether to combine therapies. Fortunately, we have several virological tests to help guide us in determining a plan of care.”

Tests that help physicians customize therapies include HBV genotyping, determining the presence of precore and core promoter mutations, as well as serum HBV DNA quantification before treatment. During treatment, determining viral suppression and a genomic analysis to detect virus mutations and its resistance to medication are key to providing the current standard of care.

### Current Trends in Therapy

In general, treatment of chronic hepatitis B seeks to reduce serum levels of HBV DNA, liver inflammation and fibrosis. According to Gish, “Current data has revealed that with proper treatment, we can decrease both the rate of liver cancer development and the number of patients with decompensated liver disease—thus reducing the death rate and need for liver transplantation.”

Depending on one’s test results and history, either interferon and/or nucleoside or nucleotide analogues are prescribed. While nucleos(t)ide analogues are generally better tolerated than interferon, they can be expensive due to indefinite treatment in most patients. Medication resistance can also occur in patients who have long-term treatment with nucleos(t)ide analogues.

“Initial therapy for HBV should offer rapid viral suppression and low resistance,” explains Gish. He continues, “Recent research indicates that early

### Comparison of Current Therapies for HBeAg-positive Chronic Hepatitis B

	Interferon	Peg-Interferon	Lamivudine	Adefovir	Entecavir	Telbivudine
Duration	4–6 months	12 months	>12 months	>12 months	>12 months	>12 months
HBeAg seroconversion	20–30%	30–35%	~20%/year 50%/5 years	12%/year 46%/3 years	21%/year 46%/3 years	22%/year 30%/2 years
HBsAg loss	8%	3%	0	0	5%	0
Durability HBsAg loss	80–90%	91%	50–80%	91%	67–82%	83%
Resistance	0	0	15–25%/year 75%/5 years	29%/5 years	<1%/4 years	4%/year 22%/2 years
Route	SC tiw	SC Qw	Oral qd	Oral qd	Oral qd	Oral qd
Side Effects	Many	Many	Negligible	Nephrotoxicity 1%/year	Negligible	Negligible

### Comparison of Current Therapies for HBeAg-negative Chronic Hepatitis B

	Interferon	Peg-Interferon	Lamivudine	Adefovir	Entecavir	Telbivudine
Duration	12–18 months	12–18 months	Indefinite	Indefinite	Indefinite	Indefinite
Serum HBV DNA loss on/off treatment	10–47%	19–60%	63%/10%	51%/33%*	97%/3%	88%/?
Serum HBV DNA log <sub>10</sub> reduction	NA	4.1	3.0–4.0	3.91	5.0	5.2
HBsAg loss	0	3%	0	0	0.3%	0
Relapse rate	>90%	~50%	~90%	66% 5 years	97% 1 year	NA
Resistance	0	0	14%/year 70%/4 years	29%/5 years	<1%/4 years	9%/2 years

\*Adefovir is the only medication for which five-year data is available.

treatment of HBV and maintaining a consistent treatment regimen (compliance) offer the best chance of suppressing the virus.” Gish explains that a patient’s response at 24-weeks with telbivudine may be a good predictor of his/her long-term response to that therapy. Some medications, such as lamivudine and telbivudine, can predict the risk of resistance by identifying patients who do not reach HBV DNA undetectable in three to six months. These patients are at the highest risk of resistance due to ongoing viral replication.

### Treatment Resistance and Viral Mutations

Because HBV has been shown to have a very high rate of resistant mutations following treatment with the nucleoside analogue lamivudine, this medication is no longer recommended as a first-line therapy for chronic HBV. According to Gish, “The incidence of resistance to lamivudine is 14–20% by the end of one

year of therapy and as high as 70% at the end of five years. This, coupled with the fact that resistance to lamivudine increases the likelihood of resistance to other nucleos(t)ide analogues, makes it a poor choice for first-line therapy.”

Treatment resistance is characterized by a high serum HBV DNA concentration, flares of liver disease, higher risk of progression to liver transplant and/or death. For patients who develop such resistance, combination therapy with multiple nucleos(t)ides is an option for further reducing the threat of disease. Combination therapy with lamivudine is the most widely researched, but tenofovir and other nucleotides are also being chosen for treatment of some patients. Preliminary findings show that telbivudine and entecavir suppress viral replication more rapidly than adefovir.

In the future, additional options may be available for chronic HBV infection. Phase III trials are currently underway to investigate the efficacy of two new nucleos(t)ide analogues—tenofovir and emtricitabine—in treating chronic HBV infection.

### Clinical Features

“Most patients with fatty liver are asymptomatic though some report right upper quadrant pain from liver capsule distention,” says Merriman. He explains, “The diagnosis is one of exclusion, usually suspected on the basis of elevated aminotransaminases (typically ALT > AST in earlier stages), in the presence of NAFLD disease associations.”

While imaging may indicate steatosis, only histology can confirm the diagnosis and precisely determine the presence and extent of necroinflammation and fibrosis—the important histologic prognostic markers. Exclusion of significant alcohol use is key. Many experts have suggested a limit of two drinks/day or less for men (half that for women) to confidently diagnose NAFLD.

Male gender, obesity, age > 45 years and diabetes predict more advanced fatty liver disease. Importantly, patients with any form of chronic liver disease should not drink alcohol.

### Pathogenesis

Hepatic insulin resistance, the metabolic hallmark of NASH, results from altered hepatocyte cell insulin signaling. Fatty acid flux to the liver is increased in NASH from adipose tissue and gut sources.

## Fatty Liver Disease Clinic

California Pacific Medical Center recently launched a dedicated Fatty Liver Disease Clinic under the expert direction of Dr. Raphael Merriman. This clinic offers prompt access to patients and facilitates the accurate assessment, diagnosis and coordinated management of all forms of fatty liver disease.

Patients with fatty liver disease can also participate in leading-edge research studies conducted at our clinic. These include:

**Clinical trials** offering emerging pharmacologic agents

**Magnetic resonance imaging** studies of fatty liver disease

**Genetic and metabolic studies** that address fundamental aspects of non-alcoholic fatty liver disease (NAFLD) pathogenesis

“Many investigators ascribe to the ‘two-hit’ theory of pathogenesis, the first hit characterized by triglyceride accumulation and the second consisting of oxidant/cytokine injury leading to lipid peroxidation, inflammation and fibrosis,” says Merriman. “Genetic factors are also important—we have a particular research focus in this field.”

### Fatty Liver Disease and Cirrhosis

Less than 1–2% of persons with NAFL progress to cirrhosis. However, about 15–20% of persons with NASH progress to cirrhosis, pointing to NASH as the target for therapeutic intervention. Prevalence rates of diabetes and obesity are similar in persons with NASH and cryptogenic cirrhosis (CC), suggesting that most persons with CC previously had NASH.

Patients with CC have a substantially increased risk of hepatocellular carcinoma and should be screened accordingly. Cirrhosis due to NAFLD is now the third most common (non-tumor) indication for liver transplantation.

### Medical Management

There is no proven pharmacological treatment for NASH. Treatment of associated conditions, such as diabetes, is suggested but, though prudent, remains unproven. Gradual weight reduction (< 1.6 kg/week) through diet and exercise is recommended though rarely sustained. If indicated, patients can use lipid-lowering drugs. Medications that improve insulin resistance in NASH would appear rational choices. To this end, large scale studies are now underway to evaluate insulin-sensitizing drugs and other agents in the treatment of NASH.



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