ADVANCES IN HEPATITIS THERAPY

Rajender Reddy, MD

With the introduction of the direct acting antivirals, the treatment of the hepatitis C virus has entered a transformative era in which simpler, safer and more efficacious regimens for a broader range of hepatitis genotypes and patient populations may be possible.

Hepatitis C (HCV) provokes an immune-mediated inflammatory response in the liver that either clears the virus (~15% of cases) or leads to a chronic infection that is the precursor for cirrhosis, end-stage liver disease and hepatocellular carcinoma. In the United States today, HCV is the leading cause of liver transplantation, cirrhosis is the 8th leading cause of death and liver cancer has doubled in incidence in the last two decades. [US Burden of Disease Collaborators. JAMA 2010;310:591-608.]

Identified in 1989, the HCV genome consists of a linear single-stranded RNA molecule containing untranslated regions flanking a polyprotein processed into structural (C, E1, E2 and p7) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) subunits by host and viral protease. [Chisari FV. Nature 2005;436, 930-932.] The latter have become important targets for antiviral therapy. Of the six HCV genotypes now known, genotypes 1 and 2 account for the vast majority of chronic infections in the United States (~70% and 20%, respectively). The characteristic persistence of HCV infection can be attributed to the capacity of the virus to evade innate antiviral defenses and antagonize the host immune response. Soon after inoculation, a robust type 1 (IFN) reaction occurs in the liver. IFNs are the primary cytokines involved in the induction of the antiviral state in cells and the activation and regulation of innate immunity. In about 30% of infected persons, the initial IFN response is sufficient to clear the virus. In individuals in whom the IFN response is inadequate, however, the virus uses its NS3/4A and NS5A proteases, among others, to block molecular signaling within the IFN pathway, antagonizing the host response. Moreover, HCV can generate genetically distinct viral variants, each with its own capacity to evade and control the host response. The end result of these processes is a life-long, highly communicable infection.
SOFOSBUVIR CLINICAL TRIALS

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>GENOTYPE</th>
<th>PATIENTS</th>
<th>DURATION</th>
<th>REGIMEN</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUSION</td>
<td>2/3</td>
<td>EXPERIENCED</td>
<td>12 WKS/16 WKS</td>
<td>SOFOS+RBV</td>
<td>50%/73%</td>
</tr>
<tr>
<td>NEUTRINO</td>
<td>1/4/6/6</td>
<td>NAIVE</td>
<td>12 WKS</td>
<td>SOFOS+PEG IFN+RBV</td>
<td>90%</td>
</tr>
<tr>
<td>FISSION</td>
<td>2/3</td>
<td>NAIVE</td>
<td>12 WKS</td>
<td>SOFOS+RBV</td>
<td>67%</td>
</tr>
<tr>
<td>POSITRON</td>
<td>2/3</td>
<td>IFN INTOLERANT</td>
<td>12 WKS</td>
<td>SOFOS+RBV</td>
<td>78%</td>
</tr>
<tr>
<td>VALENCE</td>
<td>3</td>
<td>NAIVE</td>
<td>12/24 WKS</td>
<td>SOFOS+RBV</td>
<td>85% (12 WKS)</td>
</tr>
<tr>
<td>LONESTAR</td>
<td>1</td>
<td>NAIVE</td>
<td>8 WKS</td>
<td>SOFOS/LEDI</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 WKS</td>
<td>SOFOS/LEDI/RBV</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 WKS</td>
<td>SOFOS/LEDI</td>
<td>95%</td>
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</tbody>
</table>

It should be noted that cost is a significant issue with sofosbuvir ($15000/pill), and that the demographics and disease burden of the participants in the described clinical trials may not accurately reflect those of the HCV population as a whole.

Simeprevir is a second generation PI. In combination with pegIFN+RBV, simeprevir has established efficacy against HCV genotype 1 in patients with compensated liver disease, including cirrhosis. The drug has been studied in genotype 1 null responders, relapsed patients, partial responders, and treatment naïve patients. The treatment duration for treatment naïve and prior relapsers is 12 weeks of simeprevir/pegIFN+RBV with an additional 12 weeks of pegIFN+RBV. Partial and null responders receive simeprevir/pegIFN+RBV for 12 weeks. More data is needed before recommendations can be made for genotypes 5 and 6.

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PENN CENTER FOR VIRAL HEPATITIS

Established in 2010 under the direction of K. Rajender Reddy, MD, and associate director Kyong-Mi Chang, MD, the Penn Center for Viral Hepatitis is a regional nucleus for viral hepatitis care, research and education. Since its inception, the Center has played an essential role in bringing to market simpler, safer and more effective drug therapies for hepatitis C. Among other recent achievements, the Center participated in the Phase III studies to investigate the safety, tolerability and antiviral efficacy of a fixed-dose combination (FDC) of sofosbuvir and ledipasvir for the treatment of genotype 1 HCV infection in adults. The drug, the first of its kind to combine two DAAs in a single pill for use without IFN and possibly without ribavirin, is expected to be approved sometime in the next year. The Center has also participated in other cutting edge oral regimens in Phase II and III programs. Through these programs several of the patients benefited immensely through successful outcomes.

The education of medical students, residents, fellows, pharmacy students, and physician extenders occurs throughout the Center’s programs. Training involves the virology, immunology, epidemiology and clinical management of viral hepatitis and HIV viral hepatitis co-infection.

The center also seeks to enhance public awareness, patient education and patient advocacy of viral hepatitis infections and HIV viral hepatitis co-infection.
**LIVER CANCER TREATMENT AND RESEARCH AT PENN MEDICINE**

Edgar Ben-Josef, MD, Maarouf Hoteit, MD, David Kaplan, MD, Kim Olthoff, MD, Michael C Soulen, MD

Penn Medicine is a leading medical center in the nation in providing advanced clinical care and innovative investigational treatments to patients with liver cancer at every stage of the disease.

The liver cancer treatment program at Penn Medicine involves the integration of five national leading centers of treatment and research: The Abramson Cancer Center, the Penn Transplant Institute, the Roberts Proton Center, the Penn Center for Viral Hepatitis and the Division of Gastroenterology and Hepatology. Every patient with liver cancer at Penn benefits from the expertise of specialists in each section of the program. Cancer treatment is a collaborative process, as each decision is complicated by the need to consider different aspects of the disease. What the Penn liver cancer program does—and does well—is function as a team whose various medical and surgical disciplines are focused on state of the art care for patients with liver cancer.

The anchor of the Penn liver cancer treatment program is the weekly Liver Tumor Board, whose various medical and surgical disciplines are focused on state of the art care for patients with liver cancer. Each case is reviewed on the basis of the type and extent of cancer, health status, prior treatments and physical condition. Options are then considered and recommendations made.

**TREATMENT**

The standard curative therapies for HCC at Penn include surgical resection, radiofrequency ablation and liver transplantation. All curative treatments depend on confirmation that the cancer is contained within the liver, has not invaded the major liver vessels and that the number and size of the tumors are within the parameters for cure. Surgical resection is typically performed in patients with intact liver function. Patients with impaired liver function are candidates for transplantation. Patients with small tumors who are not healthy enough for surgery are candidates for radiofrequency ablation.

The treatments at Penn for advanced HCC include chemoembolization, radioembolization or external radiation for cancers contained to the liver in patients with good liver function. Patients also have access to systemic therapy in the form of sorafenib or a variety of investigational treatments in the setting of clinical trials, including biological therapies, targeted immunotherapies, and proton therapy.

**CLINICAL RESEARCH**

Penn Medicine prides itself in being a national leader in advancing the science of cancer medicine and in the development of innovative cancer treatments in the setting of clinical trials. There are a number of clinical trial options available to patients with Liver Cancer at Penn.

A Phase II study of proton beam irradiation of unresectable primary liver tumors [ClinicalTrials.gov Identifier: NCT00976898]Penn Medicine is part of a multi-center study to evaluate the efficacy and safety of proton therapy in patients with unresectable liver cancer. A recent addition to the armamentarium for HCC at Penn, proton therapy is available at the Roberts Proton Therapy Center - one of only five proton centers on the East coast.

Proton therapy is expected to have advantages in liver cancer because the liver is particularly sensitive to the effects of radiation. Proton dose distributions can be designed to conform closely to the tumor volume with a marked reduction in radiation exposure to the non-involved liver, allowing delivery of higher doses to tumors within the liver with minimal effects on the surrounding liver.

The objective of this trial is to demonstrate local control (an important endpoint in abdominal cancers) of >80% of patients at two years with proton beam irradiation for unresectable hepatocellular cancer. Secondary objectives include a determination of the safety and tolerance of the treatment program, an evaluation of tumor response, patterns of failure and five-year overall survival, among other goals.

Patients will receive proton beam irradiation in 15 fractions over 3 weeks. Acute toxicity evaluations will occur weekly during study treatment, and at 3 month follow up. Thereafter, evaluation for tumor response will be conducted using Response Evaluation Criteria In Solid Tumors (RECIST) criteria and for acute and late toxicity per Common Terminology Criteria for Adverse Events (CTCAE ) v.3.0.

**THIS TRIAL IS CURRENTLY RECRUITING**
The primary investigator at Penn is Edgar Ben-Josef, MD. Please contact Kristi Varilieo at 215.616.3273 for more information.

A Phase II randomized multicenter placebo-controlled blinded study of sorafenib adjuvant therapy in high risk orthotopic liver transplant (OLT) recipients with hepatocellular carcinoma (HCC)

Patients with evidence of a high risk liver cancer following liver transplantation form a group for whom limited options exist to reduce the risk of cancer recurrence. These patients are currently the subject of a randomized, blinded, placebo-controlled clinical trial at Penn Medicine to investigate the efficacy and safety of the protein kinase inhibitor sorafenib in the adjuvant setting after liver transplant. This trial is under the direction of Kim Olthoff, MD, of Penn Transplant Surgery; Maarouf Hoteit, MD, of Penn Gastroenterology and Nevena Damjanov, MD, of Penn Oncology.

The primary endpoint of the trial will be two-year recurrence-free survival. Other study endpoints include one-year recurrence-free survival; overall survival; safety; impact of drug-drug interactions (i.e. immunosuppression agents); impact of biomarkers (alpha-fetoprotein [AFP], protein-induced by vitamin K absence or antagonist II [PIVKA II]); the effects of therapy on wound healing; and the impact on hepatitis C viral recurrence.

The trial will include patients who had hepatocellular carcinoma (HCC) with one of the following at the time of the pathological analysis of the transplant: microvascular/macrovascular invasion, tumor outside of Milan criteria, or poor tumor differentiation. Patients with elevated surrogate markers (AFP≥500 or PIVKA≥400) pre transplant and with biopsy proven HCC prior to liver transplantation or at the time of transplant will also be included.

Patients will be randomized to one of two treatment arms: ARM I patients will receive sorafenib tosylate orally (PO) twice daily (BID). ARM II patients will receive placebo PO BID. Treatment will continue in both arms for 24 months in the absence of disease progression or unacceptable toxicity. After completion of study treatment, patients will be followed up every six months for two years.

**THIS STUDY IS CURRENTLY RECRUITING**
The contact for referrals and participants is Mary Shav, at 215.615.0528.
Ranjeeta Bahirwani, MD, is a transplant hepatologist with the Division of Gastroenterology at Penn Medicine. A graduate of the Feinberg School of Medicine at Northwestern University, Dr. Bahirwani completed her internship and residency in internal medicine at the Hospital of the University of Pennsylvania (HUP), where she subsequently completed fellowships in gastroenterology and transplant-hepatology. She is currently the associate fellowship program director in transplant-hepatology at the Perelman School of Medicine.

Dr. Bahirwani's research interests include post-transplant outcomes focusing on predictors of chronic kidney disease after liver transplantation; candidacy for simultaneous liver-kidney transplantation; ICU outcomes in patients with end-stage liver disease; ICU outcomes in patients with end-stage liver disease; and predictors of need for ICU care/ICU mortality.

Dr. Bahirwani is board certified in internal medicine, gastroenterology, and transplant-hepatology. She sees patients at the Perelman Center for Advanced Medicine.

Jesse A. Green, MD, has joined the Division of Gastroenterology at Penn Medicine. Dr. Green received his medical degree from the Mount Sinai School of Medicine (now the Icahn School of Medicine) in New York, NY, and completed his residency and internship in internal medicine at Mount Sinai Hospital. He then completed a fellowship in gastroenterology at the University of Miami Hospitals and Clinics in Miami, FL. Most recently, Dr. Green was a full Professor of Medicine at the Albany Medical College and Director of the Gastrointestinal Endoscopy Unit at Albany Medical Center Hospital, both in Albany, NY.

Dr. Green's clinical and research interests focus upon Crohn's disease and ulcerative colitis. As a co-author he has contributed to review articles, book chapters and presentations on these subjects, as well as on pancreatitis, infectious disease and general gastroenterology. He has also lectured widely on inflammatory bowel disease and its complications.

Dr. Green has had a long-standing interest in the quality assessment and improvement of gastrointestinal endoscopy in the hospital setting, and in the education and training of gastroenterology fellows, medical residents and medical students in general gastroenterology and gastrointestinal endoscopy, with an emphasis on IBD, where applicable.

Dr. Green is board-certified in internal medicine and gastroenterology. He will see patients at Penn Presbyterian Medical Center beginning in May 2014.

Dr. Vandana Khungar is a transplant hepatologist at the University of Pennsylvania. After completing an MSc in Epidemiology at Oxford University, where her thesis focused on inflammatory bowel disease, she received her medical degree at the University of Illinois College of Medicine at Chicago. Subsequently, Dr. Khungar completed an internship and residency in Internal Medicine at New York University, where she remained for one year after her training as a Clinical Instructor. In this position she served as the internist for the NYU World Trade Center clinic. She then went on to complete a fellowship in Gastroenterology at the University of California Los Angeles (UCLA) and a fellowship in Transplant Hepatology at Columbia University.

Dr. Khungar sees patients at the Perelman Center for Advanced Medicine and the Hospital of the University of Pennsylvania.

A Multicenter, Placebo-Controlled, Randomized Pilot Study of the Effect of Sorafenib on Portal Pressure in Patients with Cirrhosis, Portal Hypertension and Hepatocellular Carcinoma (HCC) Treated with Ablative Therapy and/or Transarterial Chemoembolization.

Contact Emily Panik 215.615.3756 / emily.panik@uphs.upenn.edu

A Phase 2b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination and Sofosbuvir + Ribavirin for Subjects with Chronic Hepatitis C Virus (HCV) and Inherited Bleeding Disorders.

Contact Grace Kim-Lee 215.898.3981 / graclekim.lee@uphs.upenn.edu

THC025HCPC009 (Galaxy) A Phase 2 Open-Label Study In Patients With Recurrent Genotype 1 Hepatitis C Post-Orthotopic Liver Transplant To Explore The Safety And Efficacy Of Simeprevir And Sofosbuvir With And Without Ribavirin.

Contact Aaron Blouin 215.349.8507 / aaron.blouin@uphs.upenn.edu

MERCK 5172-062 – A Phase 3 Randomized Clinical Trial To Study The Efficacy And Safety Of The Combination Regimen Of Mk-5172 And Mk-8742 In Subjects With Chronic Hepatitis C Virus Infection And Chronic Kidney Disease.

Contact Emily Panik 215.615.3756 / emily.panik@uphs.upenn.edu (Recruiting April 2, 2014)

MERCK 5172-060 – A Phase 3 Randomized Clinical Trial To Study The Efficacy And Safety Of The Combination Regimen Of Mk-5172/Mk-8742 In Treatment-Naive Subjects With Chronic HCV GT1, GT4, GT5, And GT6 Infection.

Contact Emily Panik 215.615.3756 / emily.panik@uphs.upenn.edu (Recruiting June 2014)

MERCK 5172-063 – A Phase 3 Open-Label Clinical Trial To Study The Efficacy And Safety Of The Combination Regimen Of Mk-5172/Mk-8742 + Ribavirin (RBV) In Treatment Naive And PR Treatment Experienced, Mono Or Co-Infected Subjects With Chronic HCV GT1, GT4, GT5, And GT6 Infection Who Are On Opiate Substitution Therapy.

Contact Emily Panik 215.615.3756 / emily.panik@uphs.upenn.edu (Recruiting June 2014)

MERCK 5172-068 – A Phase 3 Randomized Clinical Trial To Study The Efficacy And Safety Of The Combination Regimen Of Mk-5172/Mk-8742 In Subjects Who Have Failed Prior Treatment With Pegylated Interferon And Ribavirin (P/R) With Chronic HCV GT1, GT4, GT5, And GT6 Infection.

Contact Emily Panik 215.615.3756 / emily.panik@uphs.upenn.edu (Recruiting June 2014)
"I am delighted to update you on the following exciting developments at the Division of Gastroenterology at Penn Medicine."

**GARY W. FALK, MD, MSc,** has been recognized by the American Gastroenterological Association (AGA) for the AGA Distinguished Clinician Award and the AGA Imaging and Technology Distinguished Mentor Award.

**BEN STANGER, MD, PHD,** has received the Michael S. Brown New Investigator Research Award, a Penn Medicine Award of Excellence, and leads a team of researchers at Penn whose work contributed to the Basic Centers of Excellence (BCE) on cancer cell metabolism funded through the Abramson Cancer Center.

**REBECCA G. WELLS, MD,** has been appointed the associate editor of a new on-line journal, Cellular and Molecular Gastroenterology and Hepatology.

**GARY WU, MD,** is now the Ferdinand G. Weisbrod Professor in Gastroenterology.

For more information about research developments at Penn Gastroenterology, visit: [www.med.upenn.edu/gastro/news.shtml](http://www.med.upenn.edu/gastro/news.shtml)