Chronic hepatitis C (CHC), one of the most common causes of chronic liver disease and cirrhosis, is a leading reason for liver transplantation in the United States. CHC most often is treated with a combination of pegylated alpha interferon (pegIFN) and ribavirin, but up to 45% of patients who receive 48 weeks of combination therapy nonetheless relapse after treatment is discontinued. About 70% of patients with hepatitis C have genotype 1 hepatitis C virus (HCV), which generally is less responsive to treatment and more likely to relapse.

The Center for the Study of Hepatitis C (CSHC) at NewYork-Presbyterian/Weill Cornell Medical Center is engaged in diverse HCV investigations. One of us (Dr. Talal) has undertaken research on viral kinetics, presenting the first evaluation of pegIFN pharmacokinetics in patients coinfected with HCV and HIV, finding that, although pharmacokinetic parameters do not differentiate sustained virological responders from nonresponders, certain pharmacodynamic measurements do and might therefore serve as useful predictors of treatment outcome. Another study elucidated early ribavirin pharmacokinetics in coinfected patients also receiving pegIFN. Having perfected a fine-needle aspiration technique that is less invasive than core needle biopsy and allows repeated sampling of the liver with less morbidity, the CSHC is now looking at HCV RNA and telaprevir levels to understand how the virus declines, both in the liver and in the blood, in response to treatment with a 3-drug antiviral combination of pegIFN, ribavirin, and telaprevir.

Another focus of CSHC research has been the role of chemotactic cytokines, known as chemokines, in hepatic inflammation by their recruitment of lymphocytes to the liver parenchyma. Intrahepatic inflammation is a major predictor of fibrosis progression in CHC and thus is an important element in assessing disease progression and, possibly, treatment options. One author (Dr. Talal) and others found that CXCR3-associated chemokines play an important role in hepatic necro-inflammation and fibrosis. A subsequent study suggested that these same chemokines might be used as noninvasive markers of liver fibrosis. The CSHC currently is studying whether this marker can be used in other patient populations in whom fibrosis is likely to progress.

The CSHC, working with NewYork-Presbyterian/Weill Cornell’s methadone maintenance treatment program, developed a model therapeutic approach in which the same physician who treats the substance abuse patient also treats that patient in the viral hepatitis clinic, thereby maintaining continuity of care. Although HCV infection affects up to 90% of substance abusers, evaluation and treatment following referral very frequently is not pursued. Of 125 patients from the Center’s methadone clinic who were eligible for referral to the CSHC’s hepatitis clinic, 76 (61%) adhered to the referral. Of these, 24 started therapy and 13 (54%) achieved sustained virological response (SVR). The success of this program, which was partially funded by the Clinton Global Initiative, offers hope that it could be expanded to other methadone clinics as well as other patient populations.

At the recent 2010 meeting of the American Association for the Study of Liver Diseases (AASLD), several studies involving NewYork-Presbyterian Hospital researchers elucidated potential new treatment pathways for CHC. For instance, NewYork-Presbyterian/Weill Cornell, under the direction of Ira Jacobson, MD, served as a study center for 2 important international trials. Both the ADVANCE (study drug: telaprevir) and SPRINT-2 (study drug: boceprevir) Phase III clinical trials demonstrated superiority over current standards of care; publications on both are planned in 2011. Dr. Jacobson presented the ADVANCE trial results at a plenary session and was a coauthor on the SPRINT-2 plenary presentation. Fred Poorad, MD, of Cedars-Sinai, Los Angeles, was lead author of the SPRINT-2 trial. Also at the AASLD, preliminary evidence of genetic influence on CHC progression and treatment response has emerged from the multicenter IDEAL (Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy) study of 3,070 patients with genotype 1 HCV, 1,604 of whom consented to genetic testing. This multi-site study, which included NewYork-Presbyterian/Weill Cornell, found that the interleukin (IL)28B polymorphism previously correlated with poor treatment response was significantly associated with lower serum low-density lipoprotein levels and higher rates of hepatic steatosis. Another linked an IL28B polymorphism to higher levels of baseline serum alanine aminotransferase (ALT) and Metavir A2-3 necro-inflammatory activity. However, researchers found no association between IL28B and either advanced hepatic fibrosis or IFN-related neutropenia.

Assessing Liver Transplant Prognosis

Post-transplant histologic recurrence is evident in up to 90% of CHC patients at 5 years, often leading to graft failure and death. However, patients who achieve SVR or who are transplanted with undetectable viral loads on therapy only have about a 1 in 5 likelihood of recurrence. However, by the time CHC-related liver disease has progressed to the point that transplantation is necessary, many patients experience concurrent exacerbations of encephalopathy, infections, and other serious adverse events (AES), with reduced likelihood of SVR and increased likelihood of treatment-related mortality.

A2ALL (the Adult-to-Adult Living Donor Liver Transplantation Cohort Study) is an NIH-sponsored 9-center study of adult living donor liver transplants (LDLT) in which...
NewYork-Presbyterian/Columbia University Medical Center (NYP/CU) has participated for more than 7 years; Jean C. Emond, MD, of NYP/CU, serves as chair of the executive committee. As part of A2ALL, one of us (Dr. Brown), with others from the multicenter trial, examined the use of a low, accelerating dosage regimen of pegIFN and ribavirin to prevent post-transplant recurrence of HCV infection.17 Seventy-nine patients were selected from 2 groups: candidates for LDLT whose potential donor was already identified, and candidates for deceased donor liver transplants who had been granted priority status due to stage T1 or T2 hepatocellular carcinoma. These patients had less severe liver disease than those awaiting transplant for complications of liver failure, and were thought more likely to tolerate an antiviral regimen.

The 58 patients in the treatment group received weekly doses of pegIFN-α2b, 0.75 mcg/kg of body weight, and 600 mg per day of ribavirin, with doses escalated as tolerated. Although 28% of treated patients achieved post-transplant viral response (pTVR), defined as negative HCV RNA for at least 6 months post-transplant, the treated patients experienced more AEs and serious AEs as well as infections than the 21 patients in the control group, although mortality rates were similar. Longer treatment duration and lower Model for End-stage Liver Disease (MELD) scores were associated with pTVR. Due to the incidence and severity of AEs, the study authors declared pegIFN and ribavirin to be “suboptimal” pretransplant treatments, and suggested that direct-acting antivirals may promote better outcomes. However, the study results do support the general concept of using pretransplant treatments for CHC to increase the likelihood of pTVR and decrease post-transplant AEs.

Improving Transplants for Patients With End-Stage HCV

The Center for Liver Disease and Transplantation (CLDT) at NewYork-Presbyterian Hospital has one of the nation’s largest LDLT programs and is the only center in the country to perform the donor opera- tion via laparoscopy in adult-to-child trans- plants. The CLDT will extend this technique to selected adult-to-adult LDLT procedures early in 2011. This procedure significantly reduces the donor’s recovery time, pain, scarring, and likelihood of complications. Faster, more comfortable liver donation could lead to an increase in the number of living donors, which in turn may improve the prognosis for recipients as wait times are reduced and patients are more likely to receive optimally healthy donated tissue.18 Very promising area of research is transplant immunology. Immunosup- pressive agents reduce the likelihood of transplant rejection but can be particularly detrimental to patients with CHC, especially when high doses are given in response to a rejection event. Megan Sykes, MD, director of the Columbia Center for Translational Immunology, Columbia University College of Physicians & Surgeons, has been experimenting, originally at Harvard Medical and Massachusetts General, with a new nonmyeloablative tolerance-inducing procedure, using the transplantation of any organ donor’s bone marrow to encourage the transplant recipient’s immune system to accept the donated organ. Following a trial of this procedure, 4 of 5 kidney recipients receiving bone marrow transplants from their kidney donors successfully discontinued the use of immunosuppressive drugs altogether and retained stable renal function so far for more than 3 to 6 years following transplantation.20 Animal studies are now underway at the CLDT to exam- ine the procedure’s utility in human liver transplantation.

Another means by which the supply of livers for transplantation can be increased is through hypothermic machine perfusion (HMP). HMP is an affirmed approach for the preservation of kidneys and is an improvement over cold storage (CS), but until recently, its use in liver transplantation only had been tested in animals. In the first clinical series of its kind, James V. Guarrera, MD, and co-authors from the CLDT (including Dr. Brown), report that, of 20 adults who received HMP-preserved livers centrifugally perfused with Vaso- sol, only 1 recipient experienced early allograft dysfunction compared with 5 in a matched control group that received CS-preserved livers.21 The HMP livers had no vascular complications, and only 2 bil- iary complications compared with 4 in the control group. Additionally, patients in the HMP group had significantly lower serum injury markers and significantly shorter mean hospital lengths of stay. The authors suggest that continuous centrifugal perfusion—which took place after the livers had been in CS for several hours during transportation from the donor hospital—brought nutrients and oxygen into the livers while flushing out cytokines, proteins, and tox- ins, helping to restore them to a healthy state and undo some of the damage that occurs during static CS. Future trials will determine whether patients with chronic diseases such as CHC show similar improvements to transplant outcomes following the substitution of HMP for CS during stages of liver storage prior to transplant.

NewYork-Presbyterian Hospital’s multi- disciplinary CLDT program is at the fore- front of the research and development of effective treatments for patients with CHC and other liver-related diseases.

References
