HCV ADVOCATE

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Hepatitis C

Institute of Medicine Report

A new report from the U.S. Institute of Medicine (IOM) summarized in the March 2010 *Hepatology* recommends a comprehensive strategy for reducing cirrhosis, liver cancer, and other consequences of hepatitis B and C. Experts estimate that up to 3.9 million people in the U.S. are living with chronic HCV and up to 1.4 million with chronic HBV, both of which disproportionately affect people of color; these diseases are often asymptomatic at early stages, however, and many are not aware they are infected. The report, entitled *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*, calls for "a public awareness initiative along the lines of the effort that succeeded in increasing recognition, prevention, and treatment of HIV/AIDS." For further information, see "IOM Report" in the February 2010 *HCV Advocate*.

HCV Protease Inhibitor TMC435

As telaprevir and boceprevir near the end of the drug development pipeline, researchers continue to test new directly targeted anti-HCV agents. In the March 2010 *Gastroenterology*, H.W. Reesink and colleagues reported data from the first-in-humans Phase 1 clinical trial of TMC435, Tibotec's oral NS3/4A HCV protease inhibitor. In the first part of the study, 49 healthy HCV negative volunteers received TMC435 at single ascending doses (up to 600 mg) or multiple ascending doses over five days (100, 200, or 400 mg

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Executive Director
Editor-in-Chief,
HCSP Publications
Alan Franciscus

Contributor:
Liz Highleyman

Managing Editor, Webmaster
C.D. Mazoff, PhD

Design/Production
Alan Franciscus

Contact Information:
The Hepatitis C Support Project
PO Box 427037
San Francisco, CA 94142

www.hcvadvocate.org

once-daily or 200 mg twice-daily), or else placebo. In the open-label second part, six participants with hard-to-treat HCV genotype 1 received 200 mg once-daily TMC435 for five days.

The researchers observed no serious adverse events, grade 3 reactions, or treatment-related discontinuations, and the drug's pharmacokinetic profile was suitable for once-daily dosing. Among the patients with HCV, plasma viral load decreased rapidly in all cases, steeply at first (median reduction of 3.5 $\log_{10}$ IU/mL at day 3), followed by a more gradual decline. The median maximal reduction was 3.9 $\log_{10}$ IU/mL and occurred after a median of six days. No viral breakthroughs were seen during treatment or the first three days post-treatment, but HCV RNA returned to baseline levels by week 4 of follow-up. The researchers concluded that, "Once-daily TMC435 given orally was generally safe and well- tolerated, and demonstrated potent antiviral activity."

Resistance to Directly Targeted Drugs

One of the challenges facing specifically targeted antiviral therapies for hepatitis C, or STAT-C, is that the virus can develop mutations that confer drug resistance, especially when single agents are used alone. In the February 2010 *Journal of Antimicrobial Chemotherapy*, T.L. Kieffer from Vertex (developer of telaprevir) and coauthors presented an overview of viral resistance to these new types of drugs.

"[B]ecause of the remarkable sequence variation in HCV (resulting from the high viral replication rate and intrinsically error-prone nature of HCV polymerase), variants with reduced susceptibility to STAT-Cs can occur naturally before treatment, usually at low levels, and can be selected in patients not responding to potent STAT-C treatment," they wrote. The review described how resistance can develop and provided an overview of specific mutations that confer varying degrees of resistance. Most studies to date have combined single directly targeted agents with pegylated interferon and ribavirin, but trials of all-oral regimens of drugs that target different steps of the HCV lifecycle are currently underway. For more information, see "HCV Drug Resistance" in the February 2010 *HCV Advocate*.

Aging of People with HCV

While hepatitis C incidence, or new infections, has fallen during the two decades since the HCV virus was discovered, a growing number of people who were infected many years ago are now reaching the stage where they develop advanced liver disease. As reported in the February 2010 *Gastroenterology*, G.L. Davis and colleagues developed a mathematical model to project future prevalence of chronic hepatitis and its complications.

The model showed that chronic hepatitis C prevalence, or total infections, peaked at 3.6 million in 2001. Fibrosis progression was inversely related to age at the time of infection, so cirrhosis and its complications were most common after age 60, regardless of when infection occurred, the researchers noted. They projected that the *proportion* of people with chronic hepatitis C who will develop cirrhosis will reach 25% in 2010 and 45% in 2030, though the absolute *total* number with cirrhosis will peak at

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1 million (about 30% above the current level) in 2020. They also predicted that decompensated liver disease and liver cancer will continue to increase for about 10 more years. But if all HCV positive people were to be treated in 2010, the risk of cirrhosis, decompensation, liver cancer, and liver-related deaths would fall by 16%, 42%, 31%, and 36%, respectively, by 2020. "Incidence of hepatitis C cirrhosis and its complications will continue to increase through the next decade and will mostly affect those older than 60 years of age," the researchers concluded.

Pegylated Interferon/Ribavirin in Older Patients

While older people with hepatitis C have the greatest need for treatment, they may not respond as well to interferon-based therapy. In a study published in the March 1, 2010 *Journal of Infectious Diseases* C.F. Huang and colleagues from Taiwan compared the safety and efficacy of pegylated interferon alpha-2a (Pegasys) plus ribavirin in 70 chronic hepatitis C patients age 65 or older and 140 participants aged 50-64 years matched for sex and HCV genotype.

The older patients had significantly higher rates of treatment discontinuation (21% vs. 6%) and severe adverse events (34% vs. 20%) than the middle-aged participants. In an intent-to-treat analysis, the sustained virological response (SVR) rate was substantially lower in the older group compared with the middle-aged group (67% vs. 79%). Breaking this down by HCV genotype, the SVR rate remained significantly lower for older patients with genotype 1 (52% vs. 76%), but not for those with genotypes 2 or 3 (77% vs. 80%).

However, among older patients who experienced rapid virological response at week 4, SVR rates were similar for those with genotype 1 and those with genotypes 2 or 3 (88% vs. 80%, respectively). Among patients who received treatment for more than 80% of the expected duration, SVR rates were similar in the older and middle-aged groups regardless of genotype. "Older patients with HCV infection, especially those in the subgroup infected with HCV [genotype] 1, had a greater frequency of adverse events and poorer adherence to the standard-of-care regimen, which may be the major reason for treatment inferiority," the researchers concluded. Even the older group, however, had a very good genotype 1 SVR rate compared with other studies.

Treatment Response in Blacks and Hispanics

People of African descent are known to respond more poorly to interferon-based therapy for hepatitis C, but data have been less consistent for Hispanics/Latinos. In a study described in the February 2010 *Journal of Clinical Gastroenterology*, S.K. Satapathy and colleagues retrospectively evaluated rates of treatment completion and sustained response to pegylated interferon alpha-2a (Pegasysy) or alpha-2b (PegIntron) plus weight-adjusted ribavirin in 35 African-American patients (89% with genotype 1) and 68 Hispanic patients (75% with HCV genotype 1).

About half the participants dropped out before completion of treatment due to drug side effects, poor adherence, inadequate early response, or for other reasons, with statistically similar discon-

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tinuation rates for blacks (43%) and Hispanics (52%). Among the patients who completed treatment, overall end-of-treatment response rates were 20% for African-Americans and 34% Hispanics, and overall SVR rates were 20% and 25%, respectively (neither difference statistically significant). Looking only at people with HCV genotype 1, SVR rates again did not differ significantly according to racial/ethnic group (16% vs. 14%, respectively). Overall, the researchers concluded, "both groups had similar poor response rates, well below those reported for white patients."

Retreatment of HIV/HCV Coinfected Patients

People with HIV have a lower likelihood of responding to interferon-based therapy for hepatitis C than HIV negative individuals, but this is less clear with regard to retreatment. As reported in the March 1, 2010 *Journal of Acquired Immune Deficiency Syndromes*, P. Labarga and colleagues from Spain assessed the safety and efficacy of standard-of-care therapy using pegylated interferon alpha-2a plus 1000-1200 mg/day weight-adjusted ribavirin in 52 HIV/HCV coinfected patients (78% with genotype 1) who did not achieve sustained response with a previous suboptimal regimen: interferon monotherapy (20%), conventional interferon plus ribavirin (29%), or pegylated interferon plus 800 mg/day fixed-dose ribavirin (51%); about 60% were prior nonresponders and the rest were prior relapsers.

After 48 weeks, the SVR rates were 20% for genotypes 1 or 4 and 73% for genotypes 2 or 3. Having easier-to-treat HCV genotypes and a higher ribavirin trough concentration (lowest level between doses) were the only independent predictors of sustained response. The researchers concluded that retreatment with pegylated interferon plus weight-based ribavirin for 12 months results in HCV clearance in nearly one-third of HIV/HCV coinfected patients who failed a prior suboptimal course of treatment.