

Hepatitis C

Natural STAT-C Resistance

Researchers are studying several specifically targeted antiviral therapies for hepatitis C ("STAT-C"), including HCV protease inhibitors and polymerase inhibitors. While some candidates have produced good results to date, the drawback of this approach is the emergence of drug resistance. As reported in the December 2008 *Hepatology* (and also at the 2008 AASLD meeting), T. Kuntzen and colleagues analyzed naturally occurring resistance mutations in more than 500 treatment-naïve genotype 1 hepatitis C patients in the U.S., Germany, and Switzerland.

Mutations associated with resistance to the HCV protease inhibitors telaprevir, ITMN-191,

boceprevir, SCH6, and BILN2061 (discontinued due to toxicity), the NS5B polymerase inhibitor AG-021541, and the NS4A antagonist ACH-806 were detected at frequencies ranging from 0.3% to 2.8% of the population. Two patients had possible multidrug resistance. Overall, people with genotype 1a were more likely than those with genotype 1b to have at least one dominant resistance mutation (8.6% vs. 1.4%). A majority of patients with such mutations had high HCV viral load, indicating that drug-resistant viral strains may replicate as well nonresistant virus. The impact of naturally existing resistance mutations requires further study, but may support the use of combination therapy.

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Liver Disease with Undetectable HCV RNA

People infected with HCV (as indicated by antibodies in the blood) who have an undetectable viral load are usually considered to have inactive disease, and undetectable HCV RNA six months after completion of treatment is regarded as a cure. But a study in the December 2008 *Hepatology* suggests hidden HCV may still cause liver disease progression. M. Hoare and colleagues studied 172 HCV antibody positive but HCV RNA negative individuals who underwent liver biopsies between 1992 and 2000. After 102 were excluded for having other possible causes of liver damage, the remaining 70 participants were analyzed after a median seven years of follow-up.

Within this group, 5.7% became HCV RNA positive during follow-up, but the rest had continued undetectable viral load. Only five participants had normal liver biopsies; 82% had some fibrosis, with 24% having moderate to advanced fibrosis (Ishak stage 2-3). HCV RNA negative individuals had fewer CD4 T-cells and more CD8 T-cells than uninfected con-

trol subjects, but the same number as patients with detectable viral load. These findings suggest that HCV antibody positive people with undetectable HCV RNA have an ongoing immune response in the liver, supporting the view that the virus may persist in the liver in a majority of these cases.

Effect of Diet in People with HCV

Chronic hepatitis C is associated with various metabolic complications such as insulin resistance, but the effects of diet on liver fibrosis progression and response to treatment are not well-understood. As reported in the December 2008 *American Journal of Gastroenterology, C*. Loguercio and colleagues studied 1084 chronic hepatitis C patients – 432 of whom were treated with interferon-based therapy – and 2326 uninfected control subjects. At baseline, there were no differences between the two groups with regard to dietary habits, metabolic status, or alcohol consumption; about half were classified as overweight and about 60% reported drinking alcohol. In a logistic regression analysis, intake of carbohydrates, lipids such as cholesterol,

polyunsaturated fatty acids, and alcohol were independent risk factors for liver damage. In addition to heavier alcohol consumption, intake of some dietary components (including unsaturated fatty acids, iron, zinc, vitamin A, and niacin) differed significantly between treatment responders and non-responders. "Our results show that dietary composition is related to the extent of liver damage," the study authors concluded. "This suggests that HCV patients may benefit from instructions regarding their diet."

Effects of Alcohol

It is well known that heavy alcohol consumption can lead to severe liver disease including cirrhosis and hepatocellular carcinoma, but the effects of alcohol on HCV and its treatment are less well studied. As described in the December 15, 2008 *Journal of Infectious Diseases*, E. McCartney and colleagues performed a laboratory study using cultured Huh-7 cells to examine the effects of alcohol metabolism on HCV replication and the antiviral activity of interferon. They found that exposing the cells to ethanol significantly increased HCV replication,

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which was dependent on oxidative stress; when the researchers added NAC to the cell cultures, ethanol no longer increased HCV replication. Furthermore, the anti-HCV activity of interferon was also reduced in the presence of ethanol. "These in vitro results mimic what is often noted clinically," the researchers concluded, supporting the recommendation that people with chronic hepatitis C should avoid alcohol or consume only small amounts.

Mother-to-Child HCV Transmission

Women with chronic hepatitis C may transmit HCV to their babies during pregnancy or delivery. This is uncommon overall – occurring at a rate of about 5% – but is more likely when the mother is HIV positive. As reported in the December 1, 2008 *Journal of Infectious Diseases*, K. Dowd and colleagues studied 63 HIV/HCV coinfecting pregnant women to assess whether lower levels of HCV-specific neutralizing antibodies are associated with an increased risk of mother-to-child HCV transmission. Sixteen women (25%) transmitted HCV to their infants. There was no significant difference be-

tween transmitting and non-transmitting mothers in terms of the ability of maternal plasma to neutralize HCV (median neutralizing antibody titers of 1:125 vs. 1:100, respectively). "In the setting of HIV/HCV coinfection, we found no evidence that HCV neutralizing antibodies are associated with the prevention of mother-to-child transmission of HCV," the researchers concluded.

Liver Transplant Allocation

Transplantation is the only treatment for end-stage liver failure, but suitable donor organs are in short supply. A new allocation scheme implemented in 2002 has improved racial disparities among transplant recipients, but women are still at a disadvantage, according to an analysis published in the November 26, 2008 *Journal of the American Medical Association*. C. Moylan and colleagues assessed the association between race, sex, and liver transplantation following introduction of the Model for End-Stage Liver Disease (MELD) system in February 2002. MELD estimates the risk of death within three months based on bilirubin and creatinine levels and prothrombin

time. The researchers looked at a retrospective cohort of 21,895 adult patients on the United Network for Organ Sharing (UNOS) liver transplant waiting list between January 1996 and December 2000 (pre-MELD) and 23,793 patients added to the list between February 2002 and March 2006 (post-MELD).

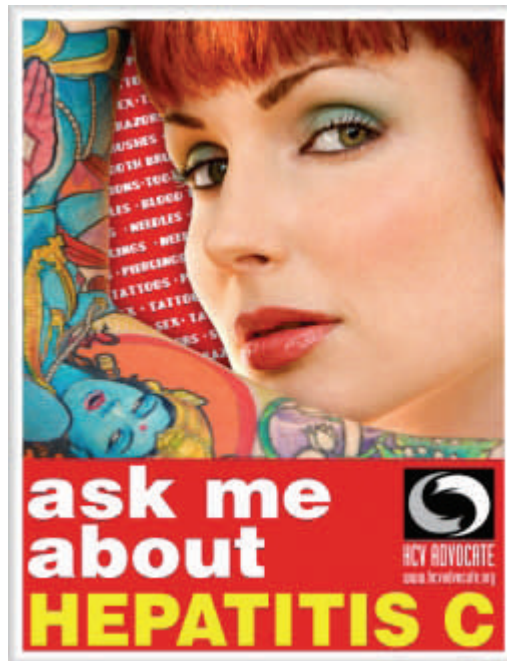
Overall, black patients were younger and sicker than white patients on the waiting list during both periods. In the pre-MELD cohort, black patients were significantly more likely than whites to die or become too sick for transplantation within three years of registering on the waiting list (27.0% vs. 21.7%; odds ratio [OR] 1.51); blacks were also less likely than whites to receive a liver transplant during this period (61.6% vs. 66.9%; OR 0.75). By contrast, in the post-MELD cohort, black race was no longer associated with increased likelihood of death or becoming too sick for transplantation (26.5% vs. 22.0%; OR 0.96), and blacks were no less likely than whites to receive a transplant (47.5% vs. 45.5%; OR 1.04).

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However, unlike the pre-MELD cohort, women were significantly more likely than men to die or become too sick for transplantation in the post-MELD period (23.7% vs. 21.4%; OR 1.30). Women were less likely than men to receive transplants within three years during both the pre-MELD (64.8% vs. 67.6%; OR 0.80) and post-MELD (39.9% vs. 48.7%; OR 0.70) periods. Following introduction of the MELD score, the researchers concluded, "race was no longer associated with receipt of a liver transplant or death on the waiting list, but disparities based on sex remain." They added that the elimination of the racial disparity likely reflects the fact that the MELD score accounts for the severity of disease when a patient is put on the waiting list. Women may receive fewer transplants due to their smaller size, since small donor livers may be used for large patients, but not vice versa.



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