

Hepatitis C

Validity of 12-Week SVR

Sustained virological response (SVR) to hepatitis C treatment is usually defined as continued undetectable HCV viral load 24 weeks after completion of therapy. But maintaining undetectable HCV RNA for 12 weeks after stopping treatment may be an equally good predictor of a cure, according to a study described in the April 2010 *Hepatology*.

M. Martinot-Peignoux and colleagues from France analyzed sustained outcomes among 573 chronic hepatitis C patients treated with pegylated interferon (Pegasys or PegIntron) plus ribavirin. All participants had undetectable HCV RNA at the end of treatment; the researchers used a sensitive TMA assay (limit of detection 5-10 IU/mL) to determine if any of these patients experienced viral relapse between the 12th and

24th week post-treatment.

At 24 week post-treatment, 71% of participants achieved SVR. Looking back at week 12 results, all but one of the patients who were undetectable at week 12 remained so at week 24, for a positive predictive value of 99.7%. The researchers concluded that assessment of serum HCV RNA 12 weeks after the end of treatment using a highly sensitive test "is as relevant as after 24 weeks" for predicting sustained response and making decisions about patient management, leading them to suggest a new definition for SVR.

Interferon Prevents Liver Cancer Recurrence

Over years or decades, chronic hepatitis C can lead to advanced liver disease including cirrhosis and hepatocellular carcinoma

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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

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(HCC). Studies have shown that interferon-based therapy can reduce the risk of developing liver cancer; now, a meta-analysis published in the April 2010 *Journal of Viral Hepatitis* indicates that treatment can also prevent HCC recurrence.

Y. Miyake and colleagues from Japan performed a meta-analysis of five previous trials including a total of 355 participants, 167 of whom received interferon alfa after curative treatment of primary liver tumors (within the Milan criteria of three or fewer nodules of 3 cm or less or a single nodule of 5 cm or less in diameter).

Receiving interferon after curative therapy for primary HCC tumors significantly reduced the likelihood of liver cancer recurrence (relative risk 0.33, or a decrease of about two-thirds). Subgroup analyses revealed that interferon reduced HCC recurrence in two studies with SVR rates greater than 30% (relative risk 0.20) and three studies with rates of 30% or lower (relative risk 0.44). This finding suggests that even treatment that does not cure hepatitis C still helps reduce liver cancer recurrence, although higher SVR rates "may be associated with better preventive effect," the investigators concluded.

Benefits of Vitamin D

A low vitamin D level is associated with more severe liver fibrosis and poor treatment response, according to a study published in the April 2010 *Hepatology* and supporting research presented at the April meeting of the European Association for the Study of the Liver (EASL). Prior research indicates that vitamin D is an immune modulator that influences inflammatory responses and fibrogenesis (fibrosis formation); it may also improve insulin sensitivity and even inhibit HCV replication.

S. Petta and colleagues from Italy looked at the link between vitamin D and response to interferon-based therapy among 197 genotype 1 chronic hepatitis C patients (85% of whom were treated with pegylated interferon plus ribavirin) and 49 healthy HCV negative control subjects. They measured serum levels of 25-hydroxyvitamin D and tissue expression of two liver enzymes (CYP27A1 and CYP2R1) that process vitamin D.

Average serum vitamin D levels were significantly lower in hepatitis C patients compared with control subjects (25.07 vs. 43.06 mcg/L). Women on average had lower vitamin D levels than men, and people with hepatic ne-

croinflammation had lower levels than those with healthy livers. Levels of CYP27A1 (but not CYP2R1) were directly correlated with vitamin D levels. After adjusting for other factors, low vitamin D was an independent predictor of severe liver fibrosis or cirrhosis (stage F3-F4). Overall, 41% of patients achieved SVR; a low vitamin D level was likewise an independent predictor of poor treatment response.

In the study presented at EASL, S. Abu Mouch and colleagues from Israel evaluated whether vitamin D supplements would improve the likelihood of sustained response to hepatitis C therapy. In an initial analysis of 157 genotype 1 chronic hepatitis C patients treated at their clinic, fully 84% had low vitamin D levels and one-third had severe deficiency. Then, in a randomized study, 67 patients were treated with pegylated interferon alfa-2b (PegIntron) plus ribavirin for 48 weeks, with or without 1000-4000 IU/day vitamin D3.

At 4 weeks, 44% of participants receiving vitamin D supplements achieved rapid virological response, compared with just 18% in the unsupplemented group. SVR rates were likewise significantly higher in the vitamin D group, 85% vs. 43%, respectively. People with dark skin

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produce less vitamin D when exposed to the sun and are more likely to be deficient, leading the researchers to suggest that vitamin D deficiency might contribute to the well-known strong racial/ethnic disparities in interferon response rates.

Treatment of Urban Minorities

People of color treated in a "real world" urban setting may not respond as well to hepatitis C treatment as participants in controlled clinical trials, according to a report in the April 2010 *Hepatology*. P. Feuerstadt and colleagues evaluated the effectiveness of pegylated interferon plus ribavirin among 255 HIV negative, treatment-naive chronic hepatitis C patients treated at Albert Einstein College of Medicine or Montefiore Medical Center in the Bronx, New York City, between 2001-2006. About 60% were men, 58% were Hispanic, 20% were African American, and 9% were white; most (68%) had hard-to-treat HCV genotype 1.

About half the participants completed treatment. In an intent-to-treat analysis (including patients who discontinued therapy early), SVR rates were just 14% for genotype 1 patients and 37% for genotype 2 or 3 patients, compared with rates of around 50% and 60%-70%, respec-

tively, typically observed in controlled clinical trials. Looking at all 1,656 treatment-naive HIV negative hepatitis C patients seen at the clinics (including those who did not start treatment), only 3.3% were cured. "Current hepatitis C therapies may sometimes be unavailable to, inappropriate for, and ineffective in United States urban patients," the researchers concluded. "New strategies are needed to care for such patients." For more details about this study, see "Minorities and Real World Treatment Results" in the May 2010 *HCV Advocate*.

Side Effects Linked to Treatment Response

HIV/HCV coinfecting individuals who experience side effects during interferon-based treatment for hepatitis C are more likely to achieve a cure, according to a report in the April 1, 2010 *Journal of Acquired Immune Deficiency Syndromes*. A. Osinusi from the National Institutes of Health and colleagues conducted two prospective, open-label trials in which about 50 HIV/HCV coinfecting participants were treated with pegylated interferon plus ribavirin for 48 weeks. They monitored participants for side effects through week 72 using laboratory data, assessment of psychiatric side effects such as depression and anxiety, and

ophthalmologic (eye) evaluations.

Half the participants experienced psychiatric side effects, and all but one of this group (26 out of 27) were virological responders (defined as HCV RNA decline of at least 2 log). In contrast, only a single nonresponder (one out of 14) experienced psychiatric side effects. Other adverse events, including anemia and eye problems, were also more common in responders than in nonresponders. Finally, a decline in CD4 T-cell count (a marker of immune system damage and HIV disease progression) was also strongly correlated with HCV viral load decline.

Occurrence of side effects may be an indicator that the drugs are reaching adequate levels in the body and may show that treatment is stimulating a strong immune response against HCV; management of side effects also requires more intensive care, which may lead to better outcomes. "Our study demonstrates coupling of antiviral effect and occurrence of adverse events in HIV/HCV coinfecting patients," the researcher concluded. "These patients with interferon-related adverse effects need a multidisciplinary treatment approach, hence, they are more likely to achieve sustained virologic response."