Hepatitis C virus: five-year follow-up of patients with sustained virological response

Chronic hepatitis C virus infection is a health concern worldwide - 170 million people are believed to be infected. In our setting, the prevalence of hepatitis C is approximately 1.6-2.6% of the population, which means that 480,000 to 760,000 individuals may be infected (1). It is the most common cause of liver cirrhosis, hepatocarcinoma, and liver transplant (2).

The only therapy that is currently available is a combination of pegylated interferon (peg-IFN) and ribavirin (RBV) for 24-72 weeks. The goal of this therapy is the achievement of sustained viral response (SVR), defined as HCV-RNA negativity at six months after treatment completion; success rates oscillate from 54% to 56% in clinical trials (3), and the possibility of bringing this deadline forward to week 12 is currently under consideration given that most relapses occur within three months after therapy completion.

Patients achieving sustained virological response show decreased fibrosis progression, and a reduced incidence of cirrhosis and hepatocellular carcinoma (its risk, however, persists), and improved histology (4).

Available data on SVR in patients on long-term combined treatment are scarce, and values of 98-100% are reported (5-7). A recent paper in our country by Puig del Castillo et al. (8) reports on a descriptive study of 80 patients follow up for 5 years where SVR rates were 99%, which is consistent with the published literature.

According to a multicenter study by Swain et al. (9) in a cohort with over 1300 patients with SVR after a follow-up of 4 years, 99.1% of these subjects remained with undetectable plasma HCV-RNA levels. Patients were included in various groups depending on whether they had received combined therapy or monotherapy, on whether they were monoinfected or co-infected with HIV, on their genotype, on the type of peg-IFN received (alfa-2a or alfa-2b), on treatment duration, and on whether they had normal or abnormal transaminase levels at treatment onset. They saw that SVR results and permanence rates were similar among all groups of patients with no statistically significant differences.

In a multicenter study in Germany (10) that enrolled over 2300 patients SVR probability and predictive factors were assessed, and positive predictive factors for SVR were seen to include genotypes 2 and 3, and low viral load, whereas negative predictive factors included age over 40 years, increased GGT at baseline, and low platelet counts. In addition, this German study suggests that treatment with peg-IFN alfa-2a may also be a positive predictive factor versus peg-IFN alfa-2b.

All the above entails a controversy regarding whether SVR does eradicate the virus, and subsequent virological surveillance is therefore unnecessary. In this regard two aspects should be made clear:
On the one hand various concepts should be defined. The term relapse refers to HCV-RNA detection within 6 months after treatment completion. The term recurrence refers to HCV-RNA detection in the serum of a patient with SVR; therefore, while late relapse and recurrence could be used as one single concept, the difference is that recurrence does not imply a return of the original virus but might result from re-infection or a false negative result when SVR was established (11).

On the other hand the techniques and ways to measure HCV-RNA should be considered. Regarding the sensitivity of the various techniques, detection thresholds have changed over time, from a relatively high value of <600 IU/ml a few years ago to that currently achieved with a more sensitive real-time PCR technique (<15 IU/ml); thus, the finding of patients in one study who apparently exhibit viral recurrence may in fact result from false negative results at the time when SVR was established if detection thresholds differed then, which could be worked around should serotheques be available for all patients.

As regards RNA measurement, other methods have been described that exhibit higher sensitivity. Transcription-mediated amplification (TMA) is superior to PCR for the detection of minimal residual viremia (12). Other authors also suggest that a late virological relapse may be predicted if serum samples are re-examined with ultracentrifugation prior to PCR (13), which leads to think that, in the presence of an adequately sensitive technique, virological surveillance may be discontinued once SVR is established.

Concerning the way HCV-RNA is measured, tests are available that can detect its presence in mononuclear cells and liver tissue after SVR (14-16). A Spanish study (17) examined patients with SVR and found HCV-RNA in the liver tissue samples of most of them, and in a significant proportion of peripheral mononuclear cells; however, no such RNA was detected in the plasma. As a result, some authors suggest the subclinical infection concept, defined as the detection of hepatitis C virus in any tissues from patients considered in SVR by using any of the available HCV-RNA detection techniques, but this has not been translated into clinical practice.

We may conclude that, overall, that in patients receiving peg-IFN and RBV with SVR long-term relapse rates are very low, and that the SVR concept, empirically defined at 6 months from the start, is a sound one, since HCV-RNA negativity at month 6 represents cure.

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REFERENCES


