

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Extrahepatic Benefits Achieved With Sustained Virologic Response in Patients With Hepatitis C Virus Infection



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**G&H** What are the hepatic benefits achieved with sustained virologic response in patients infected with hepatitis C virus?

**MK** In patients with chronic hepatitis C virus (HCV) infection, there are 2 clear hepatic benefits associated with achieving sustained virologic response (SVR). One is to arrest inflammation, and the other is to stop fibrosis, which is usually the consequence of chronic inflammatory processes. Thus, the liver itself improves, the liver markers of inflammation improve, and liver fibrosis regresses in up to 50% of patients who achieve SVR. A 2002 paper by Poynard and colleagues looked at liver biopsies of HCV patients after 48 weeks of interferon-based treatment and found a 49% reversal of liver cirrhosis. However, there have not been longer-term studies, which would likely show reversal of fibrosis in more than 50% of patients.

**G&H** With the current therapies, how often are these benefits achieved?

**MK** The current HCV therapies cure approximately 98% of patients, so inflammation is improved or stopped in approximately 98% of patients and fibrosis is improved in approximately half of them. However, if the treatment population has more advanced liver disease (ie, if there is overrepresentation of patients with cirrhosis, particularly decompensated cirrhosis), then fewer patients may achieve fibrosis regression.

**G&H** Do any patient subgroups still have difficulty achieving SVR and the associated hepatic benefits?

**MK** As far as achieving SVR or cure, which is defined as an undetectable virus 12 weeks after stopping treatment, the most difficult to treat group likely consists of patients with genotype 3, in particular those who have failed direct-acting antiviral agents and have liver cirrhosis. However, recently approved treatments are achieving higher SVR rates in this setting, ranging from 90% to 95%.

Patients with cirrhosis, in particular those with Child-Turcotte-Pugh class C decompensated cirrhosis, are less likely to derive these hepatic benefits. These patients may not be able to improve their liver function, and they may not be able to reverse the decompensation of their liver disease. If they improve only a little and stay in a decompensated state, it is controversial whether that is actually beneficial to the patients.

**G&H** Should some of these patient subgroups receive higher priority for treatment?

**MK** All patients who are chronically infected with HCV should be treated. Clearly, patients with advanced fibrosis (stage 3) and cirrhosis (stage 4) and those with extrahepatic manifestations are the ones who should receive the highest priority for HCV treatment. However, all doctors should make an effort to identify and treat all HCV patients. There are easy ways of screening and diagnosing HCV infection, and, as mentioned above, treatments are available that are effective for the vast majority of patients. HCV infection is often mistakenly thought of as just a liver disease. A shift should occur so that health care practitioners consider HCV to be a systemic viral infection that has multiple manifestations, consequences, and

risks that should be treated to achieve systemic benefits, both liver- and nonliver-related. Although the liver is the organ that is most affected, it is certainly not the only one. Enough literature has been published involving benefits of SVR both related and not related to the liver, such as improvements in quality of life, diabetes and insulin resistance, cryoglobulinemia, renal disease, lymphoma risk, cardiovascular disease, and cerebrovascular disease.

#### **G&H** What is the current understanding of the relationship between diabetes and HCV infection?

**MK** The relationship between type 2 diabetes and chronic HCV infection is multifaceted. Patients with chronic HCV infection are not necessarily at higher risk of developing type 2 diabetes, but they are at risk of developing type 2 diabetes at an earlier age. Patients who have liver cirrhosis, however, do have a higher risk of developing type 2 diabetes. Another aspect of this relationship is that patients with type 2 diabetes who are chronically infected with HCV are more likely to develop worse liver disease, in particular hepatocellular carcinoma and/or hepatic decompensation when they have liver cirrhosis. The majority of cirrhotic patients have insulin resistance, and some develop overt type 2 diabetes. Insulin resistance is a precursor of type 2 diabetes. Type 2 diabetes and insulin resistance can be worsened by chronic inflammatory conditions, such as chronic HCV infection.

In addition, there are several interplays between diabetes and cirrhosis, whereby cirrhosis makes the control of diabetes more difficult (as well as the lifestyle for those patients), and diabetes increases the risk of progression from cirrhosis to decompensated cirrhosis as well as the progression of cirrhosis to liver cancer. In other words, HCV infection makes diabetes worse, and diabetes makes HCV infection and liver disease worse.

#### **G&H** Is SVR more difficult to achieve in HCV patients with diabetes?

**MK** At this time, the answer is no. In the era of interferon-based therapies, interferon response was affected by the presence of diabetes. However, in the era of direct-acting antiviral therapies, the presence of diabetes is not a risk factor for lack of response.

#### **G&H** Does insulin resistance have the same relationship with SVR that diabetes has?

**MK** By and large, the relationship is likely the same, although it may be worse for overt diabetes. However, there was a study in the era of interferon therapy that a baseline glucose level over 100 mg/dL was a negative

predictive factor for cure; therefore, just insulin resistance was a poor prognostic factor.

#### **G&H** Why, specifically, does SVR affect insulin resistance?

**MK** Reducing inflammation and the cascade of cytokines and byproducts of inflammation may affect insulin resistance. In addition, freeing the machinery of the hepatocyte by stopping HCV replication may allow for better insulin metabolism in the liver itself.

#### **G&H** Does this occur in all HCV patients?

**MK** In HCV patients with glucose metabolism derangement that is purely related to the virus, insulin resistance will likely improve, but many of the patients have other factors, including increasing age and metabolic syndrome. As patients become older, they develop other issues, such as high blood pressure and dyslipidemia, all of which work into the diabetes equation. Thus, not all HCV patients with insulin resistance will get better when their HCV is cured.

#### **G&H** How common is cryoglobulinemia in HCV patients?

**MK** Studies from the 1990s show that cryoglobulinemia can be detected in approximately 40% of patients. The challenge is that although many patients have this condition, very few are symptomatic. Probably the most common manifestation is arthralgias, but this symptom usually goes undiagnosed or is mistreated as a rheumatologic condition, as opposed to being related to the HCV infection.

#### **G&H** According to studies thus far, what is the relationship between cryoglobulinemia and HCV clinical course/treatment response?

**MK** Cryoglobulinemia can cause renal disease as well as other manifestations, and renal disease impacts the use of both interferon and ribavirin therapies. In the era where those therapies were common, usually patients who could tolerate treatment would get better, although there was a high risk of relapse after completing the treatment course.

In the current treatment era, there is no suggestion that cryoglobulinemia is more difficult to treat or is a negative predictive factor for HCV cure. Patients who have renal insufficiency have to be treated like any other patients. Those with advanced chronic kidney disease, stage 4 or 5, are eligible for some available treatments but not others. Also, at this time, cryoglobulinemia does not affect SVR.

### G&H How common is renal disease in patients with HCV infection?

**MK** The average HCV patient is in the late 50s and has other conditions that may affect renal function, such as hypertension and diabetes. Thus, renal disease is becoming more common in patients with chronic HCV infection. The virus affects the kidneys directly through a condition called membranoproliferative glomerulonephritis, which is an antigen/antibody-mediated inflammation of the kidney glomeruli that leads to chronic kidney disease and that can improve and/or be cured by treating the patient's HCV.

### G&H How should HCV treatment be adjusted for renal disease?

**MK** Currently, there is no need to adjust treatment for mild disease. Patients with a creatinine clearance of less than 30 cc/min or chronic kidney disease, stage 4 or 5, cannot use sofosbuvir (Sovaldi, Gilead)-based therapies. At the current time, these patients have to use regimens that are not sofosbuvir-based, such as glecaprevir/pibrentasvir (Mavyret, AbbVie), elbasvir/grazoprevir (Zepatier, Merck), and ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak, AbbVie). Sofosbuvir is metabolized to a metabolite that accumulates in patients with chronic kidney insufficiency, stage 4 or 5, and can be toxic.

### G&H What is the risk of lymphoma in HCV patients?

**MK** The risk is likely 1% or less in this setting, but there is a known association between chronic HCV infection and an increased risk of lymphoma, probably driven by chronic inflammation and chronic stimulation of the immune system. These lymphomas may start in extranodal sites, including the liver and gastrointestinal tract.

### G&H How does SVR affect this risk?

**MK** SVR likely decreases the risk, although it is unclear by how much, by reducing the chronic inflammatory stimulus to the immune system. I think that every patient benefits from this, although it is not a problem that affects the majority of HCV patients.

### G&H What is the relationship between HCV infection and cardiovascular and cerebrovascular diseases?

**MK** Chronic inflammatory conditions and showering of the cardiovascular and cerebrovascular systems with inflammatory mediators cause an increased risk for vascular disease and atherosclerotic vascular disease. In addition, cirrhosis affects cardiac function.

### G&H How does SVR affect these diseases?

**MK** The effect of SVR is that it removes one of the drivers of these conditions, and, therefore, the risk of these diseases decreases. However, cardiovascular and cerebrovascular diseases have many other risk factors in these patients, starting with age.

### G&H Are there any other extrahepatic benefits that may be achieved with SVR?

**MK** Yes, SVR can result in dermatologic and musculoskeletal benefits (eg, arthralgias and myalgias). Importantly, approximately 50% of all patients who achieve SVR experience a sensation of improved well-being/quality of life and a sensation of having more energy. The improvement in quality of life has been documented by Younossi and colleagues. In my clinical experience, approximately 50% of HCV patients, after they have achieved a viral cure, will come back and tell me that they did not remember that they could feel this well and have so much energy. This is probably the most important benefit that patients with chronic HCV infection can achieve with SVR.

*Dr Kugelmas is a consultant to, gives commercial talks for, and receives research grants from AbbVie, Gilead, and Merck.*

## Suggested Reading

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