Advances in the Treatment of Hepatitis C

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According to Raymond T. Chung, MD, Massachusetts General Hospital, Boston, Massachusetts, USA, hepatitis C virus (HCV) was first discovered 25 years ago. Approximately 185 million people worldwide are infected with HCV [Hanafiah M et al. *Hepatology.* 2013], including >3 million people in the United States [http://www.cdc.gov/hepatitis/hcv/]. HCV genotype 1 predominates and is responsible for about 75% of HCV infections, with genotypes 2 and 3 causing the remaining 25% of HCV infections. It is one of the most common reasons for liver transplantation globally and is the leading cause of hepatocellular carcinoma (HCC) in the United States [http://www.cdc.gov/hepatitis/]. The scope of the problem due to hepatitis C was particularly highlighted recently, when, in 2006, HCV surpassed HIV as a cause of death [Ly KN et al. *Ann Intern Med.* 2012].

NATURAL HISTORY OF HCV INFECTION

Dr Chung explained that hepatitis C is largely an indolent disease, and about 80% of patients who acquire the virus progress to develop chronic HCV infection [Chen SL, Morgan TR. *Int J Med Sci.* 2006]. The infection can persist for decades before complications are recognized. Approximately 20% of chronically infected patients develop irreversible hepatic fibrosis and cirrhosis, and about 25% will progress to liver failure, the need for liver transplantation, and death from liver failure and will also be at increased risk of developing HCC. The time frame for these events is approximately 20 to 25 years.

MOLECULAR VIROLOGY

The HCV lifecycle broadly involves viral entry to the cell, followed by fusion and uncoating, polyprotein processing, RNA replication, viral assembly, and eventual release of mature virions. Improved knowledge of the molecular virology of HCV has led to the design of specific therapeutic agents to exploit different steps of this lifecycle, namely key proteases encoded in the viral genome that coordinate steps of the lifecycle.

ANTIVIRAL REGIMENS

Genotype 1 Infection

The recent standard of care (SOC) in HCV treatment primarily focused on the use of pegylated (PEG) interferon alfa (IFN-α) and ribavirin (RBV) combination therapy (PEG-RBV), with the addition of first-generation protease inhibitors in 2011. Addition of a protease inhibitor to PEG-RBV combination therapy succeeded in increasing sustained virologic response from about 40% to about 70% in patients with HCV genotype 1 infection [Jacobson IM et al. *N Engl J Med.* 2011; Poordad F et al. *N Engl J Med.* 2011]. The effectiveness of these triple-therapy regimens, however, was limited by their adverse effects.

Triple therapy subsequently became more refined with the addition of newer direct-acting antiviral agents (DAAs) such as sofosbuvir (SOF) and simeprevir (SIM), and most recently there has been a progression to the use of IFN-free DAA treatment regimens in this patient population.

According to Dr Chung, the NS5B polymerase inhibitor SOF was licensed in late 2013. Phase 3 data from the NEUTRINO study [Lawitz E et al. *N Engl J Med.* 2013] demonstrated that SOF in triple combination with PEG-RBV resulted in an overall sustained virologic response (SVR) of 90% at 12 weeks in patients with HCV genotypes 1, 4, 5, and 6. The SVR was 89% for patients with genotype 1 and 80% for those with cirrhosis.

The recent phase 2 COSMOS study demonstrated the first meaningful SVRs without the use of IFN [Lawitz E et al. *Lancet.* 2014]. It evaluated the efficacy of the polymerase inhibitor SIM in combination with SOF, with or without RBV, in patients with genotype 1 who were treatment naïve or prior

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null responders. Data demonstrated excellent responses after 12 or 24 weeks of treatment, with SVRs > 90% in null responder patients and in those with advanced fibrosis.

The phase 3 ION-1 and ION-2 trials [Afdhal N et al. *N Engl J Med*. April 12, 2014; April 17, 2014] demonstrated similar SVRs > 97% in treatment-naïve and treatment-resistant patients with genotype 1, using the NS5A inhibitor ledipasvir in combination with SOF, with or without RBV, for 12 to 24 weeks. In ION-2, a subgroup of patients with cirrhosis performed less well overall, with SVRs of approximately 80% at 12 weeks. However, extending the treatment duration to 24 weeks resulted in 100% SVRs [Afdhal N et al. *N Engl J Med*. April 17, 2014]. Data from ION-3 showed comparable SVRs in excess of 90% using the same drug combination for 8 and 12 weeks in treatment-naïve patients with genotype 1 without cirrhosis [Kowdley KV et al. *N Engl J Med*. 2014].

The IFN-free, DAA combination regimen of a protease inhibitor ABT-450 with ritonavir (ABT-450/r), ombitasvir (NS5A inhibitor), and dasabuvir (polymerase inhibitor), plus RBV, will soon be approved. In SAPPHIRE-1 [Feld JJ et al. *N Engl J Med*. 2014], this all-oral therapy resulted in an overall SVR of 96% at 12 weeks in patients with genotype 1 without cirrhosis who were treatment naïve or treatment experienced. TURQUOISE-2 [Poordad F et al. *N Engl J Med*. 2014] investigated this regimen in patients with cirrhosis, also showing SVRs > 90%. However, treatment-experienced (null responder) patients again comprised a subgroup that performed slightly less well overall.

Combination therapy using daclatasvir (NS5A inhibitor) plus SOF, with or without RBV, has shown efficacy in a recent phase 2b trial in patients with genotype 1 without cirrhosis who had failed to respond to treatment with telaprevir (TPR) or boceprevir (BOC) plus PEG-RBV. Data showed that this group of patients was successfully treated using this regimen for 24 weeks [Sulkowski MS et al. *N Engl J Med*. 2014].

Genotypes 2 and 3

The phase 3 FISSION study [Lawitz E et al. *N Engl J Med*. 2013] compared the old SOC regimen using PEG-RBV for 24 weeks, with SOF plus RBV for 12 weeks. In patients with genotype 2 at 12 weeks, the SVR was 97% with SOF-RBV, compared with 78% with PEG-RBV. However, the SVR for genotype 3 was only 56%.

In an attempt to improve the care of patients with genotype 3 infection, the phase 3 VALENCE trial [Zeuzem S et al. *N Engl J Med*. 2014] investigated the use of SOF-RBV in individuals who were treatment naïve and treatment experienced. Those with genotype 2 were treated for 12 weeks, and those with genotype 3 were treated for 24 weeks. SVRs > 90% were again shown in patients with genotype 2, with and without cirrhosis, as well as in those with genotype 3 without cirrhosis. However, individuals with genotype 3 infection and cirrhosis again performed slightly less well, with an SVR of 68%.

EXTRAHEPATIC MANIFESTATIONS OF HCV

According to Dr Chung, chronic infection with HCV is also further complicated by extrahepatic manifestations, one of the most important of which is cryoglobulinemia. HCV is most commonly associated with mixed cryoglobulinemia (MC) which is classified as type 2, comprising polyclonal immunoglobulin (Ig)G and monoclonal IgM or IgA and rheumatoid factor (RF) activity, or type 3, comprising polyclonal IgG and polyclonal IgM or IgA, and RF activity. HCV infection accounts for > 80% of cases of type 2 cryoglobulinemia, overt symptoms of which develop in about 5% to 10% of chronically infected patients.

Treatment for HCV-associated MC has traditionally been IFN based, but although PEG-RBV therapy has been shown to be safe and useful for patients with HCV and MC, it is associated with relapse in > 40% of cases [Mazzarro C et al. *J Hepatol*. 2005]. Other treatment strategies have therefore been used for the management of this patient population, said Dr Chung. Maintenance IFN therapy has proven effective in some of the most severely affected patients, and corticosteroids, cytotoxic agents, and plasmapheresis have been useful for those with severe, acute disease. The anti-CD20 monoclonal antibody, rituximab, has also emerged as a mainstay treatment, with reports demonstrating > 80% efficacy in patients with type 2 MC, most of whom were steroid or IFN intolerant [Pekow J, Chung RT. *J Clin Gastro*. 2006; Sansonno D et al. *Blood*. 2003; Zaja F et al. *Blood*. 2003]. However, it is important to evaluate hepatitis B virus (HBV) serology in these individuals, because rituximab can reactivate the virus in those who have previously had natural HBV infection.

Another recent report showed complete cryoglobulinemia response using triple therapy comprising PEG-RBV and DAAs (TPR or BOC) in patients with genotype 1 HCV and MC who were prior PEG-RBV relapsers or nonresponders. Nevertheless, despite the efficacy of this combination, patients did find it difficult to tolerate [Saadoun D et al. *Hepatology*. 2012 (Abstract 790)]. Dr Chung also shared data from treatment of patients with HCV-associated MC with direct HCV antiviral agents at Massachusetts General Hospital, demonstrating encouraging results using SOF-RBV or SOF-SIM.

Treatment advances provide high cure rates in patients with chronic HCV infection. However, only about 50% of persons with HCV have been identified and benefit from treatment.