Editorial

Recent Advances in Antiviral Therapy for Chronic Hepatitis C

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Hepatitis C virus (HCV) infection is a major worldwide health problem. Chronic infection induces continuous inflammation in the liver progression of hepatic fibrosis, eventual cirrhosis, and possibly hepatocellular carcinoma. Eradication of the virus is one of the most important treatment aims. A number of promising new direct-acting antiviral 4Q2332s (DAAs) have been developed over the past 10 years. Due to their increased efficacy, safety and tolerability, interferon-free oral therapies with DAAs have been approved for patients with HCV including those with cirrhosis.[1,2]

Until recently, peg-interferon plus ribavirin combination therapy was the standard of care for treatment of HCV Genotype 1. Under this demanding treatment, weekly injections with peg-interferon and daily dosing of ribavirin continued for 48 weeks, with possible extension to 72 weeks in slow responders. However, older patients or patients with cirrhosis or other contra-indications were ineligible and even among eligible patients, expected SVR (sustained virologic response) rates remained below 50%. While some patients responded transiently to treatment, other patients failed to respond and showed no change in HCV RNA levels. Due to poor tolerability and low rates of SVR with interferon therapy, a novel approach was urgently needed.[3,4]

The addition of HCV protease and polymerase inhibitors with or without PEG IFN alfa and ribavirin has become the new standard of care for the treatment of chronic HCV infection.[1] Regimens that use these new agents significantly improve sustained virologic response rates in patients with genotype 1 HCV infection and, often, they also allow shorter treatment durations. Sofosbuvir is an oral NS5B polymerase inhibitor that was FDA-approved for HCV genotypes 1, 2, 3, and 4. The combination of ledipasvir/sofosbuvir is the first oral regimen without INF and ribavirin approved by the FDA for HCV. Sofosbuvir treatment regimens and duration are dependent on both viral genotype and patient population. Patients with genotype 1 or 4 are treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. Those with genotype 2 or 3 are part of an all oral drug regimen consisting of sofosbuvir plus ribavirin for 12 or 24 weeks respectively.[5]

Harvoni is a combination oral product containing ledipasvir, an NS5A protein inhibitor, and sofosbuvir that was approved by the FDA in October 2014 for HCV genotype 1. Since its original approval in the United States, the indication has been expanded to include genotypes 1, 4, 5, and 6. It is administered once daily and does not need to be administered with interferon. Some regimens may require ribavirin. In November 2014, the FDA approved an all-oral regimen of simeprevir plus sofosbuvir for treatment-naïve or treatment-experienced patients; the duration of treatment is 12 weeks for patients without cirrhosis and 24 weeks for those with cirrhosis.[5]

Daclatasvir (Daklinza), an NS5A inhibitor, was FDA approved in July 2015 for use with sofosbuvir for chronic HCV genotype 3 infection in treatment-naive or treatment-experienced patients.[6,7]

Ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) is another IFN-free combination regimen that has been FDA approved. It is indicated for the treatment of chronic HCV genotype 1 infection, including patients with compensated cirrhosis. This combination regimen also may be used for patients with HCV/HIV-1 coinfection.

Ombitasvir/paritaprevir/ritonavir and dasabuvir is used in combination with ribavirin in certain patient populations (ie, those with genotype 1a, with or without cirrhosis; those with genotype 1b, with cirrhosis).[7,8]

The combination product ombitasvir/paritaprevir/ritonavir (Technivie) was FDA approved in July 2015. It is indicated for the treatment of genotype 4 chronic HCV infections without cirrhosis in patients who were either treatment naive or did not achieve a virologic response with prior treatment with pegylated interferon/ribavirin (pegIFN/RBV). It is recommended to be used in combination with ribavirin, although it may be considered for treatment-naïve patients who cannot take or tolerate ribavirin.[9,10]

Recently, on August 3, 2017, U.S.FDA approved hepatitis C treatment Mavyret, for all genotypes, for patients without cirrhosis and those with compensated

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cirrhosis. It can be used in patients with genotype 1 who have been previously treated with an HCV NS5A inhibitor or NS3/4A protease inhibitor but not both and for patients with severe kidney disease, including those on dialysis. It is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, is taken without ribavirin. The recommended oral dosage of Mavyret is three tablets taken once daily with food. It is recommended for all genotypes: 1, 2, 3, 4, 5, 6 patients without any treatment experience and no cirrhosis, treatment is for 8 weeks. Patients without any treatment experience with compensated cirrhosis, treatment is for 12 weeks.[5]

Patients with HCV infection should be monitored closely for adverse effects as well as response to therapy. Tests to help monitor drug toxicity include the following: complete blood count with differential, renal function testing, liver function tests (including alanine aminotransferase [ALT] level), thyrotropin level. While measurement of ALT levels is useful for monitoring the effectiveness of therapy for HCV infection, ALT levels can fluctuate. The sustained virologic response (SVR) has become the best indication of successful therapy for HCV infection; SVR is defined as an absence of detectable HCV RNA in the serum with use of an assay with a sensitivity of at least 50 IU/mL 6 months after therapy is complete. Although there is some support for the identification of SVR as early as 12 weeks after treatment, the 24-week post therapy determination of SVR remains the gold standard for treatment success.[2,5]

The HCV RNA level should be rechecked 6 months after the completion of treatment; if HCV RNA is detectable, the patient has had a relapse of disease and an alternative treatment should therefore be considered. If HCV RNA is undetectable and test results remain negative, the patient has developed an SVR. With the current standard of care, pegylated interferon and ribavirin, patients with chronic HCV infection can achieve SVR 54%–56% of the time. However, SVR with new antivirals agents is now as high as 97 %. Combination of 2 direct antiviral agents like in latest available drug mavyret (glecaprevir/pibrentasvir) has resulted in SVR reaching up to 99 % in clinical trials. To summarize, this is new era of anti viral agents and hepatitis C is no more an incurable disease with treatment success rates reaching up to more than 90%.

REFERENCES

1. Mohd HK, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013 Apr;57(4):1333-42.
2. Lavanchy D. The global burden of hepatitis C. Liver Int. 2009 Jan;29 Suppl 1:74-81. doi: 10.1111/j.1478-3231.2008.01934.x.
3. Chayama K, Hayes CN, Yoshioka K, Moriwaki H, Okanoue T, Sakisaka S, et al. Accumulation of refractory factors for pegylated interferon plus ribavirintherapy in older female patients with chronic hepatitis C. Hepatol Res. 2010 Dec;40(12):1155-67. doi: 10.1111/j.1872-034X.2010.00726.x. Epub 2010 Oct 7.
4. Yoshimi S, Imamura M, Murakami E, Hiraga N, Tsuge M, Kawakami Y, et al. Long term persistence of NS5A inhibitor resistant hepatitis C virus in patientswho failed daclatasvir and asunaprevir therapy. J Med Virol. 2015 Nov;87(11):1913-20. doi: 10.1002/jmv.24255. Epub 2015 Jun 16.
5. Aghemo A, De Francesco R. New horizons in hepatitis C antiviral therapy with direct-acting antivirals. Hepatology. 2013 Jul;58(1):428-38.
6. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011 Jun 23;364(25):2405-16.
7. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.
8. Hayashi N, Izumi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, et al. Simeprevir with peginterferon/ribavirin for treatment-naïve hepatitis C genotype1 patients in Japan: CONCERTO-1, a phase III trial. J Hepatol. 2014 Aug;61(2):219-27.
9. Hayashi N, Mobashery N, Izumi N. Vaniprevir plus peginterferon alfa-2a and ribavirin in treatment-experiencedJapanese patients with hepatitis C virus genotype 1 infection: a randomizedphase II study. J Gastroenterol. 2015 Feb;50(2):238-48.
10. Kumada H, Mochida S, Suzuki F, Chayama K, Karino Y, Nakamura K, et al. Vaniprevir plus peginterferon alfa-2b and ribavirin in treatment-experienced Japanese patients with hepatitis C virus genotype 1 (GT1b) infection: Phase 3 studies. J Gastroenterol Hepatol. 2016 Oct;31(10):1674-83.