Wyoming Drug Utilization Review

Treatment of Hepatitis C in Treatment-Experienced Patients

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The hepatitis C virus (HCV) is a single stranded, 9600-nucleotide RNA virus that easily evades the immune system.[1] There are 6 major genotypes of HCV, and over 50 subtypes within each genotype due to high viral mutation rates.[1] Genotype 1 is the most common HCV and accounts for 70% of infections in the United States.[1] Genotypes 2 and 3 account for the remaining 30% and types 4, 5 and 6 are predominately found in Egypt, South Africa and Hong Kong, respectively.[1] Despite differences in the viral nucleotide sequencing, each genotype does not differ in pathogenicity or clinical progression (except genotype 3, in which hepatic steatosis and clinical progression are more likely).[1] However, each genotype differs in viral responsiveness to antiviral therapy.[1]

In the United States, it is estimated that 2.7-3.9 million people have chronic hepatitis C, which accounts for approximately 40% of all chronic liver diseases.[1,3] Approximately 15-25% of people infected with HCV will spontaneously clear the infection on their own, and while the mechanism is not well understood, genetic differences between persons infected may account for this effect.[1,3] If not promptly treated after exposure, the infection develops into chronic hepatitis C for the majority of patients, characterized by detectable infection for at least 6 months.[2] Chronic liver disease develops in 60-70% of those infected with HCV; 5-20% will develop cirrhosis in a 20 to 30 year period, and 1%-5% will eventually die from hepatitis C complications (cirrhosis or liver cancer).[3] In an effort to prevent these complications, it is important to treat patients infected with HCV.

The current HCV treatments of choice are direct-acting antiviral (DAA) medications.[2,4] This class of medications include NS3/4 protease inhibitors, NS5B nucleoside and non-nucleoside polymerase inhibitors, and NS5A inhibitors. NS3/4 protease inhibitors, like glecaprevir and grazoprevir, prevent the proteolytic cleavage of the viral polyprotein into its constituent proteins, thus rendering the proteins useless for further replication or assembly.[2] NS5B polymerase inhibitors, like sofosbuvir, interfere with the viral RNA-dependent RNA polymerase, which effectively prevents replication of the HCV RNA. NS5A is an endoplasmic reticulum membrane associated viral phosphoprotein, and inhibitors (elbasvir, pibrentasvir, ledipasvir, velpatasvir) interfere with this protein which is essential to the RNA replication complex. There are several different combinations of DAAs that are recommended for a duration of 8 to 12 weeks which have high rates of SVR (>95%).[2] Those who fail treatment make up a small percentage, however an estimated 3.9 million people in the U.S. have chronic hepatitis C, which translates to hundreds of thousands of patients potentially failing therapy. There are options for treatment-experienced patients, which include retreatment with a different DAA combination with or without the addition of ribavirin, for a longer duration (24 weeks in decompensated cirrhosis).

The regimen chosen for treatment-experienced patients depends on the regimen that was received initially.[2,4] Interferon therapy with ribavirin was the only option for patients between 1991 and 2011, and had a SVR of 40-80% depending on the genotype.[2] Due to a high failure rate with this regimen there are several recommendations to treat patients who are peginterferon/ribavirin treatment-experienced.

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For patients who have previously failed a peginterferon/ribavirin regimen, many of the treatments are very similar to the current recommendations for first-line therapy for treatment-naïve patients,[4] and many studies have demonstrated the effectiveness of these regimens in this population. The choice of regimen in this patient population is dependent upon drug interactions, comorbidities, renal and hepatic function and cost. These treatment options are straight-forward as peginterferon/ribavirin regimens work differently than the DAA containing regimens.[2] Special treatment considerations must be made when a patient is infected with genotype 1a. Approximately 10-15% of patients infected with genotype 1a have NS5A resistance-associated substitutions (RASs) that cause a 5 fold reduction in the activity of NS5A inhibitors which can result in treatment failure.[2,4] Testing for the presence of RASs in genotype 1a-infected patients, before deciding on a regimen, will help predict whether elbasvir/grazoprevir, for example, can be used in either treatment-naïve or treatment-experienced patients.[4] For patients who test positive for RASs, elbasvir/grazoprevir can be used if treatment is extended to 16 weeks and weight-based ribavirin is added to the regimen.[2,4] Several different RASs mutations can appear in patients with genotype 1a, and sequencing of the viral genome may be beneficial to understand and tailor treatment for patients who continue to fail treatment.

When a patient has failed treatment with DAAs, retreatment becomes more complicated because we must consider treatment emergent RASs/resistance or perhaps extending the duration of viral contact time with DAAs. Genotype 1-infected DAA treatment-experienced patients have several treatment choices, but criteria guiding regimen choice is slightly complex.

For genotypes 3-6 who have failed DAA therapy, a new DAA combination sofosbuvir/velpatasvir/voxilaprevir (Vosevi) is an effective 12 week treatment choice.[4] This is true even for those who have failed prior NS5A inhibitors, despite containing the NS5A inhibitor velpatasvir (except genotype 3 with cirrhosis, which necessitates the addition of weight-based ribavirin).[4] This drug attacks HCV through several mechanisms: NS5B RNA-dependent RNA polymerase inhibition, NS5A phosphoprotein inhibition and NS3/4A protease inhibition.

Sofosbuvir/velpatasvir/voxilaprevir appears to be an effective antiviral combination for almost all genotypes, and this has been proven through clinical trials. A placebo-controlled, phase 3 trial called POLARIS-1, examined the effectiveness of 12 weeks of the combination in 150 genotype 1-infected patients, and demonstrated that the rate of SVR is 96% and 100% in subtypes 1a and 1b, respectively.[5] The addition of voxilaprevir appears to provide added effectiveness to the combination of NS5B and NS5A inhibitors.[5] This is especially true for genotype 3, which was examined in POLARIS-4.[5] Genotype 3-infected patients (n=106) were randomized to receive sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir for 12 weeks, and the SVRs were 85% and 96%, respectively.[5] When patients with genotype 4 were examined, SVR was only 91% in those who had previously failed treatment containing an NS5A inhibitor; however those who did not receive NS5A inhibitors achieved SVR of 100%.[5] There is little data for patients with genotype 5 and 6, but there were 7 patients with either of these genotypes in POLARIS-1, and all 7 achieved SVR.[5] For patients infected with genotype 2, POLARIS-4 compared 12 weeks of sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir, which resulted in an SVR of 97% (32/33) with sofosbuvir/velpatasvir and 100% for those who used sofosbuvir/velpatasvir/voxilaprevir.[5] Despite sofosbuvir/velpatasvir/voxilaprevir appearing more effective in this trial, the one genotype 2 SVR failure in the sofosbuvir/velpatasvir arm had virologic breakthrough due to development of NS5B RAS mutation.[5] In an effort to conserve treatment options, sofosbuvir/velpatasvir is recommended for treatment of genotype 2-infected patients.[4,5]

Glecaprevir/pibrentasvir (Mavyret) is the newest DAA combination for HCV treatment, approved by the FDA August, 2017.[6] This combination is effective for treatment-experienced patients who have genotypes 1, 2, 4, 5 and 6 HCV infections.[7] The EXPEDITION-1 trial examined the effectiveness of 12 weeks of daily glecaprevir/pibrentasvir in 146 treatment-experienced patients with genotypes 1, 2, 4, 5 and 6, and 145 patients achieved SVR. Only one genotype 1a patient relapsed 8 weeks after treatment due to development of NS5A RASs.[7] This combination is not recommended for genotype 3-infected treatment-experienced patients because 12 weeks of treatment resulted in an SVR rate of 92%.[8]

Sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir are the newest drug combinations to treat

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P&T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on February 8, 2018.

Highlights of this meeting include:

Trelegy, Symproic and Ozempic were all referred to the Department of Health for cost analysis and determination of PDL placement as there was no evidence of a difference in safety or efficacy compared to agents in their respective classes.

Xenazine will be limited to a maximum dose of 50 mg per day.

The Adult ADHD criteria will be implemented effective March 14, 2018. Adult patients will be required to meet DSM-V diagnosis criteria, including demonstrable symptoms in two locations, one of which is school or work.

The proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to April 1, 2018.

The next P&T Committee meeting will be held May 3, 2018 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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patients with hepatitis C. The most common adverse effects for both of these drugs are headache, fatigue, nausea and diarrhea.[6] These drugs also contain black box warnings regarding hepatitis B virus reactivation, therefore patients with a history of hepatitis B should be monitored for laboratory and clinical signs of reactivation.[6] As with any hepatitis C treatment, quantitative hepatitis C viral load testing is recommended before the start of therapy, after 4 weeks of therapy and 12 weeks after completion of therapy.[4,6] The use of sofosbuvir/velpatasvir/voxilaprevir is not recommended in Child-Pugh class B or C, and glecaprevir/pibrentasvir is not recommended in class B and contraindicated in class C, therefore liver function should be assessed before the start of therapy.[6]

If a patient infected with any genotype fails their first-line treatment, then there are options for them due to advancements in direct-acting antiviral drugs in the last six years. The second treatment of choice is dependent upon the first treatment. There are also many considerations in choosing a regimen, which include level of cirrhosis, renal function, comorbidities, drug interactions and cost. Hepatitis C drugs are being developed very rapidly, and new options should give patients new hope for becoming infection free.

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