Current Treatment for Hepatitis C Patients: A Review

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ABSTRACT

Hepatitis C is an RNA virus that affects millions in the United States and globally, but with recent pharmacological achievements, the cure rate of hepatitis C has increased greatly. Hepatitis C is transmitted by blood, with the main infections in the US being cause by IV drug use and blood transfusions prior to 1992. Hepatitis C has six genotypes, but the overwhelming majority of cases in America are genotypes 1, 2, and 3. Diagnosis of hepatitis C is difficult due to the lack of symptoms on presentation. Screening in high risk populations has shown to be efficacious in diagnosing the disease. Previous treatment norms consisted of interferon, but cure rates were very low. In 2011, direct-acting antivirals were introduced and revolutionized the treatment of hepatitis C. Response rates have increased exponentially to over 95%, and the medications are much more tolerable.

INTRODUCTION

Hepatitis C (HCV) is an inflammatory ribonucleic acid, or RNA, virus affecting liver cells and is the most common blood-borne disease in the United States. Of those who develop acute HCV, 75 percent develop a chronic infection, and 10 to 20 percent develop cirrhosis, a serious complication that can lead to hepatocellular carcinoma or liver failure.[3] Americans born between 1945 to 1965, current or former injection drug users, and recipients of blood transfusions prior to 1992 are at the highest risk for hepatitis C.[4] There are six genotypes of hepatitis C based on nucleotide variations, with genotype one being the most predominant.[1] The treatment of hepatitis C is very complex and is aimed at achieving sustained virologic response (SVR), meaning an undetectable RNA level.[1] Interferon-based therapy was previously the treatment norm, but had low SVR rates.[5] Direct-acting antiviral agents were recently introduced and have proven to be efficacious in reducing toxicity and increasing SVR.[6]

PATHOPHYSIOLOGY

HCV virus targets hepatocytes, with studies showing that in an infected individual, over 50 percent of hepatocytes are infected with HCV.[7] HCV is transmitted through percutaneous blood exposure. Six genotypes of HCV have been found based on nucleotide variations, numbered 1 through 6. As previously stated, genotype 1 is the most predominant worldwide and in the United States.[7] Genotype 2 occurs in around 10-15 percent of HCV individuals in the United States, and genotypes 3 though 6 are relatively uncommon, with less than 5 percent prevalence.[1] Each direct-acting antiviral acts on different genotypes of hepatitis C.

Direct-acting antivirals target HCV-encoded proteins that are responsible for the replication of the virus. Viral RNA is translated into a polyprotein which is then cleaved by viral proteases into 10 viral proteins.[7] Direct-acting antivirals inhibit NS3/4A protease, the NS5A protein, and the NS5B polymerase.[6]

DIAGNOSIS

- Initial screening options test for HCV antibodies, which do not differentiate between acute, chronic, and recovered disease states.[2,9]
- Follow-up virologic assays to help detect current HCV infection: HCV RNA test and the HCV core antigen test.[9]
- Further testing done once diagnosis is established: CBC, CMP, and creatinine.[8]
- Serology is also suggested to identify any possible coinfections such as hepatitis B or HIV.[8]
- Staging of liver fibrosis is done via METAVIR scoring, serum tests, or imaging via ultrasound, CT, or MRI.[2]

CLINICAL PRESENTATION

The acute phase of HCV lasts from 1 to 3 weeks, with most patients showing few symptoms.[7] Those who do not mount an immune response during the acute phase then go on to have chronic hepatitis C.[2]

During chronic infection, hepatic cells are inflamed leading to liver fibrosis. The combination of liver fibrosis and cell death results in cirrhosis in around 20 percent of individuals. Cirrhosis can manifest in a myriad of ways including esophageal varices, hepatomegaly, ascites, gynecomastia, infertility, spider angiomas, and palmar erythema.[2,8] The rapid death and regeneration of hepatocytes that is seen in hepatitis C increases the risk of cell becoming malignant. Thus, hepatocellular carcinoma can then develop in approximately 3 percent of individuals.[2]

Both acute and chronic hepatitis C can have extra-hepatic manifestations. HCV is strongly associated with cryoglobulinemia and B-cell non-Hodgkin lymphoma.[8] Other manifestations include renal insufficiency, type 2 diabetes, insulin resistance, sicca syndrome, rheumatoid-like arthritis, porphyria cutanea tarda, lichen planus, and depression.[2,8]

MANAGEMENT

Prior to the development of direct-acting antivirals in 2011, interferon-based therapies were the treatment norm.[5] Patients were treated for up to 48 weeks; however, there were low rates of SVR, along with a host of side effects.[8] Ribavirin was added to interferon therapy to increase efficacy, and SVR rates increased.[8]

The first generation of direct-acting antivirals were developed in 2011. Direct-acting antivirals have now increased SVR rates to 95 to 100 percent.[2] Treatment regimens no longer include the combination of interferon due to the major adverse effects and poor efficacy; however, Ribavirin is still a critical addition to treatment regimens in patients with cirrhosis.[2] As previously stated, there are four main drug classes of direct-acting antivirals that are used alone or in combination depending on the HCV genotype.[8,10] Direct-acting antivirals are much better tolerated than previous HCV treatments. HCV RNA level should be checked at week 6 and week 12 to assess SVR. If viral load has shown to have increased at week 6, treatment should be discontinued.[2] Once treatment has been completed and SVR has been attained, patients with fibrosis and cirrhosis should undergo a liver ultrasound and endoscopy every 6 months to assess the risk of hepatocellular carcinoma and esophageal varices.[9,11] Candidates for liver transplantation include patients whose HCV has progressed to decompensated cirrhosis or hepatocellular carcinoma. Model for End-Stage Liver Disease (MELD) scoring helps assess degree of cirrhosis.[3]

Medication Brand (Generic)	Genotypes Covered	Duration of Therapy (Weeks)	SVR Rates (%)	Comments
Epclusa (sofosbuvir/ velpatasvir)	1, 2, 3, 4, 5, 6	12	97–100	Pangenotypic; can use in decompensated cirrhosis
Zepatier (elbasvir/ grazoprevir)	1, 4	12-16	95-100	Can use in severe renal impairment
Mavyret (glecaprevir/pibrentasvir)	1, 2, 5, 6	8-12	98-100	Can use in renal impairment and HIV coinfection
Vosevi (sofosbuvir/velpatasvir/ voxilaprevir)	1, 2, 3, 4, 5, 6	8	96-100	Pangenotypic
Sovaldi (sofosbuvir)	1, 2, 3, 4	24	80-94	Can use in advanced liver disease
Harvoni (ledipasvir/ sofosbuvir)	1, 4, 5, 6	12-24	93-98	Can use in decompensated cirrhosis

CONCLUSIONS

Hepatitis C is a very complex disease, and management options have come a long way in an incredibly short period of time. Just a decade ago, interferon and ribavirin were the mainstay of treatment; however, this led to low rates of SVR and high rates of adverse effects. In 2020, we have six main direct-acting antiviral drugs that provide SVR rates of up to 100 percent. While identifying the disease still remains difficult due to the few symptoms early on, a diagnosis of hepatitis C is no longer one that inevitably leads to liver failure. The advancements in hepatitis C management since 2011 have been groundbreaking.

REFERENCES

1. Murfin M. New medications for treatment of chronic hepatitis C. *J Am Acad PAs*. 2015;28(7):57–59. doi:10.1097/01.JAA.0000466592.48713.85
2. Bragg DA, Crowl A, Manlove E. Hepatitis C. *Prim Care Clin Off Pract*. 2017;44(4):631-642. doi:10.1016/j.pop.2017.07.006
3. Loader M, Moravek R, Witowski SE, Driscoll LM. A clinical review of viral hepatitis. *J Am Acad PAs*. 2019;32(11):15–20. doi:10.1097/01.JAA.0000586300.88300.84
4. Hepatitis C: Practice Essentials, Background, Pathophysiology. https://emedicine.medscape.com/article/177792-overview. Published March 22, 2020. Accessed April 6, 2020.
5. Kwo PY, Puenpatom A, Zhang Z, Hui SL, Kelley AA, Muschi D. Initial uptake, time to treatment, and real-world effectiveness of all-oral direct-acting antivirals for hepatitis C virus infection in the United States: A retrospective cohort analysis. *PLOS ONE*. 2019;14(8):e0218759. doi:10.1371/journal.pone.0218759
6. Hong C-M, Liu C-H, Su T-H, et al. Real-world effectiveness of direct-acting antiviral agents for chronic hepatitis C in Taiwan: Real-world data. *J Microbiol Immunol Infect*. September 2018. doi:10.1016/j.jmii.2018.09.005
7. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. *The Lancet*. 2015;385(9973):1124-1135. doi:10.1016/S0140-6736(14)62401-6
8. Dahiya M, Hussaini T, Yoshida EM. The revolutionary changes in hepatitis c treatment: A concise review. *Br Columbia Med J*. 2019;61:72-77.
9. Boucher CM, Walsh A, Forest CP. Healing livers, saving lives: Hepatitis C screening in an era of cure. *J Am Acad PAs*. 2016;29(5):20–28. doi:10.1097/01.JAA.0000482295.08412.4a
10. Grennan D. Treating Hepatitis C. *JAMA*. 2018;320(21):2280-2280. doi:10.1001/jama.2018.15997
11. Hudson B, Walker AJ, Irving WL. Comorbidities and medications of patients with chronic hepatitis C under specialist care in the UK. *J Med Virol*. 2017;89(12):2158-2164. doi:10.1002/jmv.24848