Hepatitis C

An Update on Next Generation Treatment and Clinical Cure

Erin DuHaime, PA-C

KEYWORDS

• Chronic hepatitis C • Hepatitis C treatment • Hepatitis C virus • Antiviral therapies • Direct-Acting antivirals • Sustained virologic response

KEY POINTS

- Hepatitis C is an important chronic infectious disease that has been historically difficult to treat with regimens that were difficult to tolerate and had poor efficacy.
- Now, with the introduction of new antiviral therapies for hepatitis C virus, there are regimens with markedly improved tolerability and dosing schedules and efficacy for all genotypes.
- It is important for providers to be familiar with the risk factors and screening guidelines/recommendations for hepatitis C.

INTRODUCTION

With regard to hepatitis C disease, it is an exciting time to practice medicine, particularly infectious disease, gastroenterology, hepatology and even primary care, as clinicians are finally able to offer patients who are chronically infected with hepatitis C virus (HCV) a clinical cure. For years, there were limited choices for hepatitis C therapy, with regimens that were ultimately difficult to tolerate and ineffective at achieving a sustained virologic response (SVR), or cure. Now, with the introduction of new antiviral therapies for hepatitis C, there are regimens with markedly improved tolerability and dosing schedules and efficacy approaching 100% for all genotypes.

ETIOLOGY

Hepatitis C is a disease caused by HCV, a spherical, enveloped, single-stranded RNA virus, approximately 9600 nucleotides in length, belonging to the family Flaviviridae, which is further divided into 3 genera: *Flavivirus, Pestivirus*, and *Hepacivirus*.

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North Texas Infectious Diseases Consultants, Baylor University Medical Center, 3409 Worth Street, Suite 710, Dallas, TX 75246, USA
E-mail address: erin.duhaime@ntidc.org

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Flaviviruses include yellow fever virus, dengue fever virus, Japanese encephalitis virus, and tick-borne encephalitis virus. *Pestiviruses* include bovine viral diarrhea virus, classical swine fever virus, and Border disease virus. HCV is a member of the *Hepacivirus* genus, which also includes tamarin virus and GB virus B and is closely related to human virus GB virus C.[1–3]

There are 6 major hepatitis C genotypes and more than 50 subtypes, which differ on a molecular level, including 1a, 1b, 2a, 2b, 3a, 3b, 4, 5, and 6. Although genotype 1 is the most common genotype found worldwide, HCV genotypes have a well-defined geographic distribution. Genotype 1 is most commonly found in the United States, Latin America, and Europe (2 and 3 are less commonly found, and 4, 5, and 6 are rare in these areas). Genotype 3 is most commonly found in India, Southeast Asia/Indonesia and Australia, and genotype 4 is most commonly found in Africa and the Middle East. Genotype 5 is the predominating HCV genotype in South Africa, whereas genotype 6 predominates in Southeast Asia (**Fig. 1**).[1,4,5]

Determining the HCV genotype is fundamental in treatment planning, as the response to antiviral therapy, dosing, and duration all depend on the genotype. Additionally, the genotype can indicate the rate of disease progression.[6] For example, genotype 1 is thought to have quicker disease progression to cirrhosis and hepatocellular carcinoma (HCC) and was traditionally more difficult to treat, whereas genotype 2 and 3 were typically most responsive to therapy. The emergence of new antiviral regimens, however, has leveled the playing ground, making treatment and clinical cure a possibility, despite the genotype.

PATHOPHYSIOLOGY

After transmission via blood-borne exposure, HCV enters the bloodstream and primarily infects the hepatocytes of the liver, replicating thru a complex series including viral attachment, entry, and fusion via endocytosis, translation of the HCV RNA genome, polyprotein processing, replication, viral assembly, and release. HCV replicates quickly within the cytoplasm of the cell, producing trillions of new viral particles daily, causing detectable viremia.[7,8] HCV replication is accomplished using HCV-specific proteins and enzymes (envelope proteins E1/2, nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A, NS5B, and polypeptide p7 of note), many of which are used as targets of new direct-acting antiviral agents (**Fig. 2**).[9]

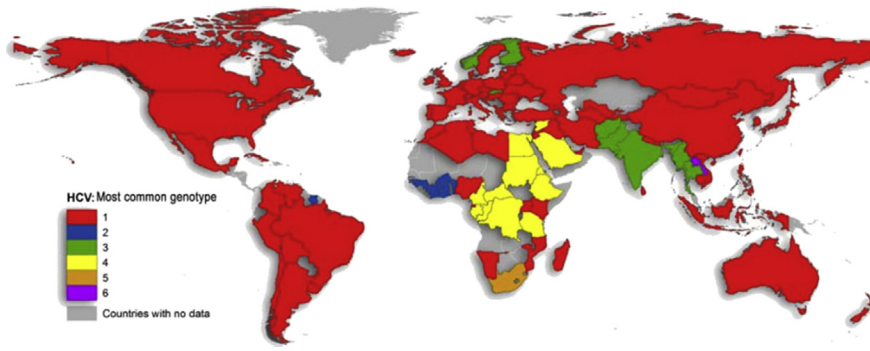

Fig. 1. World distribution of HCV genotypes. (*From* Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:82; with permission.)