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Hepatitis C (HCV) Agents

Updated: June 21, 2018.

OVERVIEW

The hepatitis C virus (HCV) is a small RNA virus belonging to the family flavividirae and genus hepacivirus. The virion is approximately 50 nm in diameter and has an outer lipid associated envelop (E1 and E2) and inner nucleocapsid (Core). Within the nucleocapsid is a single molecule of single-stranded RNA of positive polarity approximately 9.5 kilobases in length. The RNA is transcribed into a large polyprotein that is subsequently cleaved into multiple polypeptides, labeled from the 5' to 3' end: core, envelope 1 and 2, and nonstructural proteins NS2, NS3, NS4 and NS5A and NS5B. The NS3 region encodes a viral helicase and protease. The NS5A region encodes a polypeptide that is essential for production and maintenance of the replicative complex. The NS5B region encodes a viral RNA dependent, RNA polymerase that is essential for replication. The NS3, NS5A and NS5B regions have been targeted with direct acting antiviral agents.

The initial agents used to treat chronic hepatitis C were interferon alfa, peginterferon and ribavirin. The antiviral activity of interferon and peginterferon is based upon their ability to stimulate interferon stimulated genes (ISGs) that have endogenous antiviral activities. Ribavirin is a nucleoside analogue that potentiates the effects of interferon against hepatitis C by as yet undefined mechanisms. Until 2010, the standard therapy of chronic hepatitis C was the combination of peginterferon and ribavirin given for 24 or 48 weeks. This combination led to sustained clearance of HCV and remission in disease in 40% to 50% of patients. Response rates were higher with certain HCV genotypes, so that response rates in patients with genotypes 2 and 3 were as high as 70% to 80%. Importantly, these remissions in disease have been shown to represent cure of the chronic viral infection, in that long term follow up demonstrated lack of HCV replication and resolution of disease activity in over 98% of patients. The shortcomings of peginterferon-ribavirin therapy were significant, most importantly the poor tolerance and side effects of this regimen. Thus, a high proportion of patients was intolerant or had contraindications to treatment. In 2010, three HCV-specific protease inhibitors were approved for use and introduced into practice: boceprevir, telaprevir and simeprevir. All three of these were specific to genotype 1 HCV and had little or no activity against genotypes 2 or 3 or the lesser common genotypes 4, 5 and 6. Triple therapy with peginterferon, ribavirin and a HCV-specific protease inhibitor (boceprevir, telaprevir or simeprevir) increased the response rate in patients with chronic hepatitis C, genotype 1 from 40%-45% to 65%-75%. A persistent difficulty, however, was the continued need to combine these agents with peginterferon and the considerable side effects which were worsened by these protease inhibitors.

An important advance in therapy of hepatitis C came in 2013 with the approval of an HCV specific RNA polymerase inhibitor, sofosbuvir. Sofosbuvir not only increased the response rate when combined with peginterferon and ribavirin, but also allowed for interferon-free treatment when combined with ribavirin, HCV protease inhibitors or a new class of agents that antagonized HCV NS5A activity. In 2014, all-oral HCV specific antiviral regimens were approved that yielded response rates in excess of 95% in patients with genotype 1. Furthermore, successful therapy required only 8 to 12 weeks of treatment in most patients. These all-oral

regimens revolutionized therapy of hepatitis C, allowing treatment of virtually all patients regardless of severity of illness or co-morbid conditions with few side effects and durations of therapy of 8, 12 or 24 weeks. Other all oral regimens, including treatments for the less common genotypes of hepatitis C began to become available in 2015, 2016 and 2017. The several classes of agents that are combined in either a two-, three- or four-drug regimens include HCV RNA polymerase inhibitors (nucleoside and nonnucleoside), HCV NS5A antagonists and the HCV protease inhibitors. In the future, other steps in the HCV replicative cycle may yield additional targets for small molecule therapy. Widespread application of these therapies to patients with chronic hepatitis C will likely decrease the morbidity and mortality of this disease and make significant inroads into decreasing the burden of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide.

The following drug records are discussed individually, or as a class or as a part of combination therapies:

- Interferon Based Therapies
  - Alpha Interferon and Peginterferon, Ribavirin
- HCV NS5A Inhibitors
  - Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, Pibrentasvir, Velpatasvir
- HCV NS5B (Polymerase) Inhibitors
  - Dasabuvir, Sofosbuvir
- HCV Protease Inhibitors
  - Asunaprevir, Boceprevir, Glecaprevir, Grazoprevir, Paritaprevir, Simeprevir, Telaprevir, Voxilaprevir
- Combination Therapies
  - Epclusa, Harvoni, Mavyret, Technive, Viekira Pak, Vosevi, Zepatier

ANNOTATED BIBLIOGRAPHY

References updated: 21 June 2018

Pawlotsky JM, Feld JJ, Zeuzem S, Hoofnagle JH. From non-A, non-B hepatitis to hepatitis C virus cure. J Hepatol 2015; 62 (1 Suppl): S87-99. PubMed PMID: 25920094.

(History of the development of therapy for chronic hepatitis C starting with the discovery of a third form of viral hepatitis, through early days of use of interferon alfa, the addition of ribavirin and development of peginterferon, concluding with the arrival of direct acting antiviral agents which in combination yielded response rates of more than 95% with well tolerated regimens of 8 and 12 weeks).

Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. Liver Int 2014; 34 Suppl 1: 69-78. PubMed PMID: 24373081.

(Summary of safety and efficacy of various all-oral regimens for therapy of hepatitis C; does not discuss hepatic decompensation, hepatotoxicity or ALT elevations during therapy).

European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63: 199-236. PubMed PMID: 25911336.

(Guidelines for the antiviral therapy of chronic hepatitis C from the European liver clinical, academic and research society).

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62: 932-54. PubMed PMID: 26111063.

(Guidelines for the antiviral therapy of chronic hepatitis C from the US liver and infectious diseases research and academic societies).

http://www.hcvguidelines.org/

(Web-based and regularly updated guidelines for the antiviral therapy of chronic hepatitis C from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America)