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Current therapy for chronic hepatitis C: The role of direct-acting antivirals

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ABSTRACT

One of the most exciting developments in antiviral research has been the discovery of the direct-acting antivirals (DAAs) that effectively cure chronic hepatitis C virus (HCV) infections. Based on more than 100 clinical trials and real-world studies, we provide a comprehensive overview of FDA-approved therapies and newly discovered anti-HCV agents with a special focus on drug efficacy, mechanisms of action, and safety. We show that HCV drug development has advanced in multiple aspects: (i) interferon-based regimens were replaced by interferon-free regimens; (ii) genotype-specific drugs evolved to drugs for all HCV genotypes; (iii) therapies based upon multiple pills per day were simplified to a single pill per day; (iv) drug potency increased from moderate (~60%) to high (>90%) levels of sustained virologic responses; (v) treatment durations were shortened from 48 to 12 or 8 weeks; and (vi) therapies could be administered orally regardless of prior treatment history and cirrhotic status. However, despite these remarkable achievements made in HCV drug discovery, challenges remain in the management of difficult-to-treat patients.

Contents

Abbreviations: BID, twice a day; CDC, Centers for Disease Control and Prevention; DAA, direct-acting antiviral; EC_{50}, half maximal effective concentration; FDA, U S Food and Drug Administration; GT, genotype; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC_{50}, half maximal inhibitory concentration; PegIFNα, pegylated interferon alfa; QD, once a day; RBV, ribavirin; SVR12, sustained virologic response after the treatment for 12 weeks; SVR24, sustained virologic response after the treatment for 24 weeks; TID, three times a day; WHO, World Health Organization.

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1. Introduction

Over the past two decades, tremendous attempts have been made to discover antiviral drugs that effectively treat hepatitis C virus (HCV) infection (De Clercq, 2015; De Clercq, 2012; De Clercq, 2014; Welzel et al., 2014; De Clercq and Li, 2016). The first generation of FDA-approved HCV drugs includes: interferon alfacon-1 (approval year: 1997, discontinued in 2013 due to severe adverse events), ribavirin (1998), pegylated interferon alfa-2b (2001), and pegylated interferon alfa-2a (2002). These drugs had low cure rates and may cause severe adverse events (Manns et al., 2006); yet they have been the only standard-of-care treatments over a decade and are still popular in several countries. Subsequently, direct-acting antivirals (DAAs) represented a breakthrough in *in vitro* experiments and in clinical trials. In May 2011, telaprevir and boceprevir became the first FDA-approved drugs in the DAA class. The advent of DAAs marks a new era of anti-HCV drugs that directly target HCV proteins, offering promising cure rates and minimum adverse events. Similar to cocktail therapies against human immunodeficiency virus, combination therapies that target different stages of the HCV life cycle have been conceived to avoid cross-resistance. Importantly, their cure rates could attain more than 90% in clinical trials and real-world cohorts. Forthcoming therapies are endowed with higher cure rates, shorter treatment duration, lesser side effects, while being based upon all-oral regimens.

This review aims to summarize the latest trend of HCV drug development, focusing on FDA-approved therapies and newly discovered agents against HCV genotype 1 to 6 infections. We first provide a general overview of HCV infections. Subsequently, we summarize the approved HCV drugs and highlight their efficacy in clinical trials. Recent development of new agents is described. Challenges in HCV drug development are discussed at the end. To endorse this review, movies and teaching slides that highlight HCV drug actions are available from our online platform (http://www.virusface.com).

2. Literature selection

Here, our procedure for literature selection is described. We searched literature in PubMed using the keywords of HCV drugs within the publication period from 2013/01/01 to 2016/10/01. To search the most recent publications that are unavailable in PubMed, similar queries were also performed by visiting the websites of eleven journals (NEJM, JAMA, Lancet, Lancet infectious diseases, Gut, Clinical Infectious Diseases, Gastroenterology, Hepatology, Journal of hepatology, The American Journal of Gastroenterology, Annals of Internal Medicine). Only clinical trials in the phase 2, 3 and 4 stages were considered, while case reports were excluded from our literature review because of their small samples and rare subjects. We also extracted information about clinical trials from ClinicalTrials.gov (http://www.clinicaltrials.gov/) or the European Clinical Trials Database (EudraCT, https://eudract.ema.europa.eu/index.html). Clinical studies in the drug labeling of the FDA (https://www.accessdata.fda.gov) were also included in our literature search. Three exclusion criteria were undertaken. First, data from the meta-analysis or reports that summarized clinical trials in other publications were not considered so as to avoid duplicates. Second, publications (e.g. HCV-TARGET (Terrault et al., 2016), real-world study (Backus et al., 2016)) that reported the coinfections with HCV and other infectious diseases (e.g. HIV, HBV) were not collected because coinfections were beyond the focus of our review. Third, in order to highlight the SVR rates of antiviral drugs in each HCV genotype, only publications that clearly addressed SVR rates of HCV therapies in individual genotypes were summarized. Moreover, we communicated with every corresponding author if SVR rates in certain patient groups were not addressed in a publication. By doing so, we managed to obtain SVR data from most publications except for a phase 2 study (Osinusi et al., 2013), the ANRS C023 CUPILT study (Coilly et al., 2016), the A1444040 study (Sulkowski et al., 2014a), the C-EDGE Head-2-Head study (Sperl et al., 2016), and the C-EDGE treatment-experienced study (Kwo et al., 2017).

3. Overview of hepatitis C virus

3.1. HCV origin, epidemiology, and diversity

Hepatitis C virus is a *hepacivirus* in the *Flaviviridae* family, and it was first discovered from the serum of a person with non-A, non-B hepatitis in 1989 (Choo et al., 1989; Kuo et al., 1989). Now, HCV can be found in worldwide populations (Shepard et al., 2005), while the immediate sources of HCV associated with its pandemic spread have been traced to the circulation in Central and West sub-Saharan Africa and South and Southeast Asia over hundreds of years (Simmonds, 2013). Although its origin remains unclear, HCV might have originated from zoonotic sources such as non-human primates (e.g. monkeys, apes) and mammals (e.g. dogs, horses) (Simmonds, 2013). As of today, HCV has been recognized as one of the most lethal infectious diseases next to measles, influenza, respiratory syncytial virus, rotavirus, hepatitis B, and human immunodeficiency virus (Mortality, 2016; Disease et al., 2016). According to the WHO global health survey, 130 to 150 million people are currently living with HCV, causing approximately 700,000 deaths every year. Importantly, more than 95% of HCV-infected patients are unaware of their status in worldwide populations (Cox, 2015).

A single HCV particle is approximately 68 nm (range: 45–86 nm) in diameter (Catanese et al., 2013), and it contains a linear positive-sense single-stranded RNA genome encoding 10