Meet the Classes of Directly Acting Antiviral Agents: Strengths and Weaknesses

Kristina R. Chacko, MD, Paul J. Gaglio, MD*

KEYWORDS

• Direct-acting antiviral agents • Protease inhibitors • Polymerase inhibitors
• NS5A inhibitors

KEY POINTS

- Understanding the life cycle of hepatitis C virus (HCV) provides the opportunity to directly target and inhibit key components required for viral replication.
- Combining direct-acting antiviral therapies can successfully eradicate HCV by inhibiting viral replication.
- Different classes of direct-acting antiviral agents have different potency, barriers to resistance, and toxicities.

INTRODUCTION

Infection with hepatitis C virus (HCV) contributes to substantial worldwide morbidity and mortality. Chronic liver injury induced by the virus may produce hepatocellular injury and fibrosis with progression to cirrhosis, leading to significant consequences including portal hypertension, liver cancer, and death. Cirrhosis caused by HCV represents the most common indication for liver transplantation in the United States, and one of the most common causes of liver cancer worldwide. Over the last few years, efficacy and tolerability of HCV therapy have improved dramatically, and all-oral direct-acting antiviral (DAA) therapies that effectively inhibit viral replication are now available. This article discusses the various classes of DAAs, outlines their strengths and weaknesses, and discusses strategies to combine these agents to achieve optimal results.

Dr P.J. Gaglio has received research support from Abbvie, BMS, BI, Gilead, Merck, Janssen, and has served on advisory boards for Abbvie, BMS, BI, Gilead, Merck and Janssen. Dr K.R. Chacko has nothing to disclose.
Division of Hepatology, Department of Medicine, Montefiore Einstein Liver Center, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210 Street Rosenthal 2 Red Zone, Bronx, NY 10467, USA
* Corresponding author.
E-mail address: pgaglio@montefiore.org

Clin Liver Dis 19 (2015) 605–617
http://dx.doi.org/10.1016/j.cld.2015.06.002 **liver.theclinics.com**
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THE HEPATITIS C VIRUS LIFE CYCLE

Understanding the HCV life cycle has facilitated the development of novel, targeted DAAs that effectively inhibit viral replication. HCV was originally identified in 1989 as a single-stranded, positive sense RNA virus. It consists of the RNA genome, core protein, and envelope glycoproteins E1 and E2. The HCV particle has a viral envelope consisting of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) that anchors the envelope glycoproteins.[1] Therefore, it is has been observed that hepatocellular lipid metabolism and lipid receptors play an important role in the HCV life cycle. Apolipoproteins, especially apolipoprotein E (ApoE), are highly associated with HCV particles and are involved both in viral entry into the hepatocyte and viral replication.[2]

VIRAL ENTRY

HCV attaches to the hepatocyte cell surface through interactions with scavenger receptor B1 (SRB1) and heparan sulfate proteoglycan syndecan-1.[3] The viral particle gains entry into hepatocytes through a complex process involving viral envelope glycoproteins and host cellular molecules. Cell surface protein CD81 is a tetraspanin protein located on hepatocytes and other cell types whose extracellular loop binds HCV E2 and mediates internalization of the virus into the hepatocyte, with claudin-1 (CLDN-1) serving as a vital co-factor.[4] SRB1 also plays a significant role in viral entry, both through interactions with the lipid-rich viral particle and direct binding of E2.[5] Additional host cell surface molecules, including glycosaminoglycans, members of the claudin family (CLDN1, 6 and 9), occludin, epidermal growth factor receptor, and mannose-binding lectins DC-SIGN and L-SIGN serve as receptors or coreceptors and are involved in HCV binding and entry.[6] The association of HCV with lipoproteins suggests an important role for the LDL receptor in the HCV life cycle. Although originally thought to be involved in viral entry, it appears that the LDL receptor is linked to postentry viral replication[7] (**Fig. 1**).[8]

VIRAL REPLICATION

After undergoing fusion and uncoating, the RNA virus is translated into a unique polyprotein mediated by the internal ribosome entry site (IRES).[8] During post-translational processing, the HCV polyprotein subsequently undergoes cleavage by host and viral peptidases into structural proteins (core protein C, envelope glycoproteins E1 and E2, p7) and nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B). NS2, a zinc-dependent metalloproteinase, is a viral peptidase that cleaves NS2 from NS3. NS3 assembles with its cofactor, NS4A, creating NS3/4A protease, which cleaves the downstream NS proteins, NS4A-NS4B, NS4B-NS5A, and NS5A-NS5B (**Fig. 2**[8] and **Fig. 3**[9]).

Together, the various NS proteins are responsible for HCV replication. NS4B functions as a scaffold, inducing rearrangements of intracytoplasmic membranes into a membranous web that serves as the HCV replication complex.[3] All NS proteins, as well as a number of host factors, play important roles in the creation of the membranous web, leading to HCV replication. NS5A is a zinc–metalloprotein involved in assembly and regulation of the replication complex, and it interacts with host enzymes cyclophilin A and phosphatidylinositol 4-kinase IIIa (PI4KIIIa) to serve as a modulator of the life cycle of the virus.[10] Cyclophilin A, a vital HCV replication factor, aids in protein folding and regulates polyprotein processing. PI4KIIIa is a lipid kinase residing in the endoplasmic reticulum (ER) membrane responsible for the phosphorylation of NS5A.[11] NS5B, an RNA-dependent RNA polymerase (RdRp), is the key enzyme controlling RNA synthesis.

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