Direct-Acting Antiviral Agents and the Path to Interferon Independence

Warren N. Schmidt,[*,‡] David R. Nelson,[§] Jean–Michel Pawlotsky,[||,¶] Kenneth E. Sherman,[#] David L. Thomas,[**] and Raymond T. Chung[‡‡]

[*]Department of Internal Medicine and Research Service, Veterans Affairs Medical Center, Iowa City, Iowa; [‡]Roy G. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa; [§]University of Florida, Section of Hepatobiliary Disease, Gainesville, Florida; [||]National Reference Center for Viral Hepatitis B, C and Delta, Department of Virology, Henri Mondor Hospital, University of Paris-Est, Créteil, France; [¶]INSERM U955, Créteil, France; [#]University of Cincinnati, College of Medicine, Division of Digestive Diseases, Hepatology Section, Cincinnati, Ohio; [**]Johns Hopkins Medical Institution, Baltimore, Maryland; and [‡‡]GI Division and Liver Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Chronic infection with hepatitis C virus (HCV) is a major global health problem; there are approximately 120 to 130 million chronic infections worldwide. Since the discovery of HCV 24 years ago, there has been a relentless effort to develop successful antiviral therapies. Studies of interferon-α–based therapies have helped define treatment parameters, and these treatment strategies have cured a substantial percentage of patients. However, interferon-α must be injected; there are problems with tolerability, adherence, and incomplete response in a large percentage of patients. New drug candidates designed to target the virus or the host have recently been introduced at an unprecedented pace. In phase I–III studies, these agents have exceeded expectations and achieved rates of response previously not thought possible. We are, therefore, entering a new era of therapy for HCV infection and interferon independence.

Keywords: DAA; NS3/4A Protease Inhibitor; Nucleoside/Nucleotide; Non-nucleoside.

Hepatitis C virus (HCV) has a positive-stranded RNA genome with a single, long, open-reading frame that is translated into a large polyprotein and processed by host and viral proteases into structural and nonstructural (NS) proteins.[1] All steps in the HCV life cycle can be considered vulnerable to pharmacologic intervention, including entry, translation, RNA replication, assembly, and export of progeny viruses (Figure 1). Viral enzymes and proteins involved in essential functions of the HCV life cycle are the most common targets for new drugs, which are now called direct-acting antiviral agents (DAAs). Host cellular proteins that are essential for the viral life cycle may also be responsive to antiviral intervention, and these compounds are termed host-targeted antiviral agents (HTAs). This review focuses on those DAAs in advanced clinical development that are moving HCV treatment paradigms to interferon (IFN)-free regimens. These include NS3/4A protease inhibitors (PIs), nucleoside/nucleotide and non-nucleoside inhibitors (NIs and NNIs, respectively) of the RNA-dependent RNA polymerase (RdRp), and NS5A inhibitors (Figure 1).

Interferon and Ribavirin

Type I IFN-α is the prototypical HTA and was the first effective antiviral agent used against chronic HCV infection even before the viral species was identified.[2] IFN monotherapy achieved only low rates of sustained virologic responses (SVRs); however, later combination regimens of pegylated IFN and ribavirin (RBV) led to SVR rates of nearly 50% in patients entered into large clinical trials.[3] Numerous trials during the IFN era established working guidelines for optimal treatment outcomes, and the concept of response-guided management for patients with different host and viral variables emerged. Although these principles are solid and continue to guide new DAA drug development, new IFN-free regimens have redefined treatment intervals and some response parameters.

Type I IFN exerts primary antiviral activities against both RNA and DNA viruses through numerous IFN-stimulated gene (ISG) products, which antagonize HCV replication and within hours decrease the serum viral load. Different ISGs target both host and viral processes resulting in a broad antiviral attack.[4] In response, HCV evolved highly efficient mechanisms to evade host IFN signaling at key pathogen recognition points that limit the antiviral effectiveness of IFN-based therapies and impair the host's ability to resolve acute infection.[5]

Abbreviations used in this paper: **DAA, direct-acting antiviral agent; DCV, daclatasvir; HCV, hepatitis C virus; HTA, host-targeted antiviral agent; IFN, interferon; ISG, interferon-stimulated gene; NI, nucleoside inhibitor; NNI, non-nucleoside inhibitor; NR, null responder; PI, protease inhibitor; PR, partial responder; RBV, ribavirin; RdRp, RNA-dependent RNA polymerase; RR, responder/relapser; SOF, sofosbuvir; SVR, sustained virologic response; SVR, SVR at week 12.**

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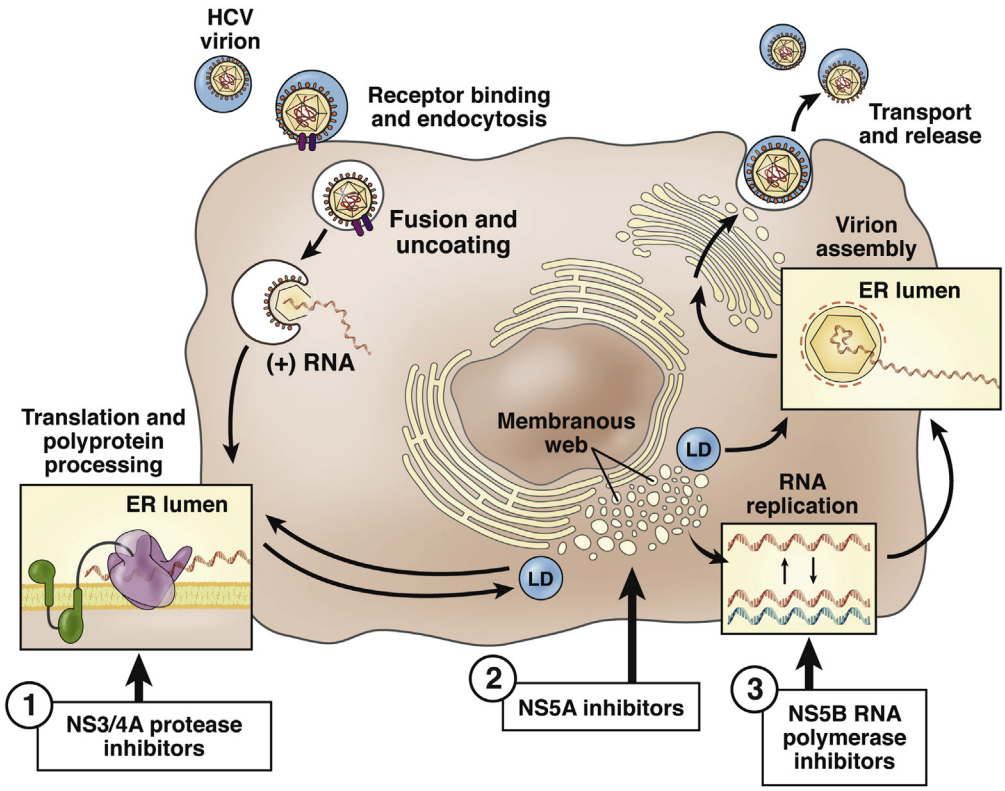

Figure 1. Therapeutic targets of the HCV replication cycle. DAA viral target sites in advanced clinical development are numbered 1–3. ER, endoplasmic reticulum; LD, luminal domain.

IFN gene expression is variable at the cellular level; in some patients, ISG expression is diminished.[4] Those patients with reduced ISG expression appear more sensitive to exogenous IFN therapy. IFN sensitivity is significantly associated with single nucleotide polymorphisms located in the interleukin 28B (IL28B) gene promoter region. The genotype for the most commonly used single nucleotide polymorphisms, rs12979860 (CC, CT, or TT), is strongly associated with the treatment outcome, with CC patients showing the highest rates of SVR as compared with patients with a T allele.[6] In chronically infected people, the responsive CC genotype is inversely correlated with ISG expression.[7]

RBV has limited direct antiviral effects when given alone, yet in combination with IFN promotes a major increase in SVR by accelerating the long-term decline of HCV RNA.[8] However, the primary mechanism whereby RBV enhances SVR in patients is not clear. Pharmacologically, RBV is a synthetic guanosine analogue; but the drug shows multiple other intracellular drug actions, such as promotion of viral mutagenesis, enhancement of ISG expression, and immunomodulatory behavior.[9]

Antiviral Treatment Response

IFN therapy initially defined patient response parameters. SVR was defined as HCV becoming undetectable in blood during treatment and remaining so 24 weeks after the end of treatment, as assessed using a sensitive viral detection method, (limit of detection: $\leq$10–15 IU/mL). Responder/relapsers (RRs) achieve undetectable HCV RNA during therapy, yet the virus reappears after treatment. Partial responders (PRs) show more than a 2-log drop by week 12 without a loss of detectable virus; and null responders (NRs) do not achieve a 2-log drop in viral load by week 12. While this terminology has persisted into the DAA era, more prognostic, shorter-term response intervals are now emerging that reflect the more rapid kinetic decline of the virus seen with DAAs. Recent data indicate that undetectable HCV RNA at 12 weeks after treatment is highly reliable to predict SVR.[10]

SVR is considered curative with presumed clearance of all HCV-infected cells in the patient's body. Viral kinetic modeling studies performed on patient blood samples established 2 viral disappearance rates during IFN treatment that are necessary to achieve an SVR[11]: (1) a rapid phase I decline in circulating HCV RNA indicating inhibition of viral production and (2) a significant second phase decline in circulating HCV RNA that is steep enough to ensure complete eradication of the virus from liver cells during the treatment time. Otherwise infected cells remain and rapidly restore infection after treatment is completed. PR and NR have decreased phase I slopes, resulting from suboptimal drug dosing, and/or an insufficient host response. Early modeling data with DAAs suggest that the more effective the drug, the earlier HCV RNA can be eliminated from infected cells, resulting in an overall shorter treatment duration.[12] Understanding of DAA viral clearance kinetics will be important for drug selection for IFN-free regimens.