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Emerging Therapeutic Targets for Hepatitis C Virus Infection

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Therapy for hepatitis C virus (HCV) is a rapidly evolving field wherein traditional treatment with the nonspecific antiviral agents pegylated interferon (IFN)-alfa and ribavirin has been and will continue to be supplanted by combinations of targeted therapies against HCV with and without concomitant pegylated IFN and/or ribavirin, resulting in markedly superior rates of viral clearance. Exhaustive study of HCV structure and replication through the development of in vitro systems has enabled the development of numerous novel direct acting antiviral agents that currently are undergoing clinical trials. As our understanding of the HCV virus and its antiviral targets increases, the future of HCV therapy holds the promise of high rates of viral eradication in all patient populations, many or all of whom will be treatable with IFN-free combinations of all-oral agents.

Keywords: Hepatitis C; Direct Acting Antivirals; Interferon-free Therapy; Telaprevir; Boceprevir.

Hepatitis C virus (HCV) is a member of the *Flaviviridae* family of positive-stranded RNA viruses that was identified as the cause of non-A, non-B hepatitis in 1989. It affects up to 200 million persons worldwide and approximately 4 million persons in the United States alone.[1,2] The viral genome encodes for a polyprotein that is cleaved into 3 structural and 7 nonstructural (NS) proteins by viral and host proteases. In 1999, the subgenomic replicon system was established, which is an in vitro system that allows for the replication of a partial genome in a human hepatoma cell line.[3] The replicon system has led to the screening of small molecules that can inhibit viral replication, facilitating the development of many drugs that directly inhibit viral proteins, so-called direct acting antivirals (DAAs). Inhibitors of the viral protease NS3/4A, the polymerase NS5B, and the multifunctional protein NS5A have shown great promise in clinical studies and are discussed in detail later. Inhibitors of other viral proteins, such as the NS2 and NS4B, or the helicase domain of NS3, are in preclinical or early phase clinical investigation and are discussed in detail elsewhere.[4] Hampered by the lack of model systems, drugs directed against other parts of the viral life cycle could not be studied until the discovery of an infectious clone in 2005.[5,6] This cell culture system has proven indispensable in our understanding of the viral life cycle, including viral entry and innate immunity against HCV in hepatocytes, and may in the future lead to clinically useful interventions.[7,8] Last, experiments with chimpanzees, the only natural host besides human beings, have been used for in vivo studies. These experiments have led to a better understanding of the adaptive immune response against HCV, and the chimpanzee model, although costly and increasingly controversial, remains the best model for vaccine development.[9–11] Targets that are the focus of currently available or investigational antiviral strategies are illustrated in Figure 1.

Current Standard of Care

Although the incidence of HCV infection is decreasing in the United States, the burden of liver disease resulting from chronic hepatitis C continues to increase.[12] The goal of HCV therapy has been to achieve sustained virologic response (SVR), defined as an undetectable serum HCV RNA level at 24 weeks after conclusion of treatment, which portends a more than 99% likelihood of remaining HCV RNA–negative long term.[13] Host factors influencing response include genetics, particularly interleukin (IL)-28B polymorphisms, race, obesity, insulin resistance, and severity of hepatic fibrosis, whereas viral characteristics include viral genotype and viral load at initiation of therapy.[14–18] Genotype 1 HCV, the most common in the United States, has been more difficult to treat with interferon-based therapy than other prevalent genotypes.[19–21] Until recently, the standard of care for patients with chronic HCV infection had been treatment with pegylated-interferon-alfa (Peg-IFN) in combination with ribavirin (RBV), given for 24 to 48 weeks, depending on viral genotype. SVR rates after treatment with Peg-IFN/RBV in genotype 1 HCV-infected patients have been 40% to 50%.[22]

A milestone in the evolution of HCV therapy occurred in 2011 with the approval of the first 2 DAAs: the NS3/4A serine protease inhibitors telaprevir (Incivek; Vertex, Cambridge, MA) and boceprevir (Victrelis; Merck, Whitehouse Station, NJ). The dramatic improvement in SVR rates when these agents are added to Peg-IFN and RBV has led to a new standard of care in patients with genotype 1 HCV infection.

Abbreviations used in this paper: **DAA, direct acting antiviral; HCV, hepatitis C virus; IL, interleukin; NS, nonstructural; Peg-IFN, pegylated interferon; quad, quadruple; RBV, ribavirin; RGT, response-guided therapy; SVR, sustained virologic response; SVR12, undetectable HCV RNA at 12 weeks after termination of therapy.**

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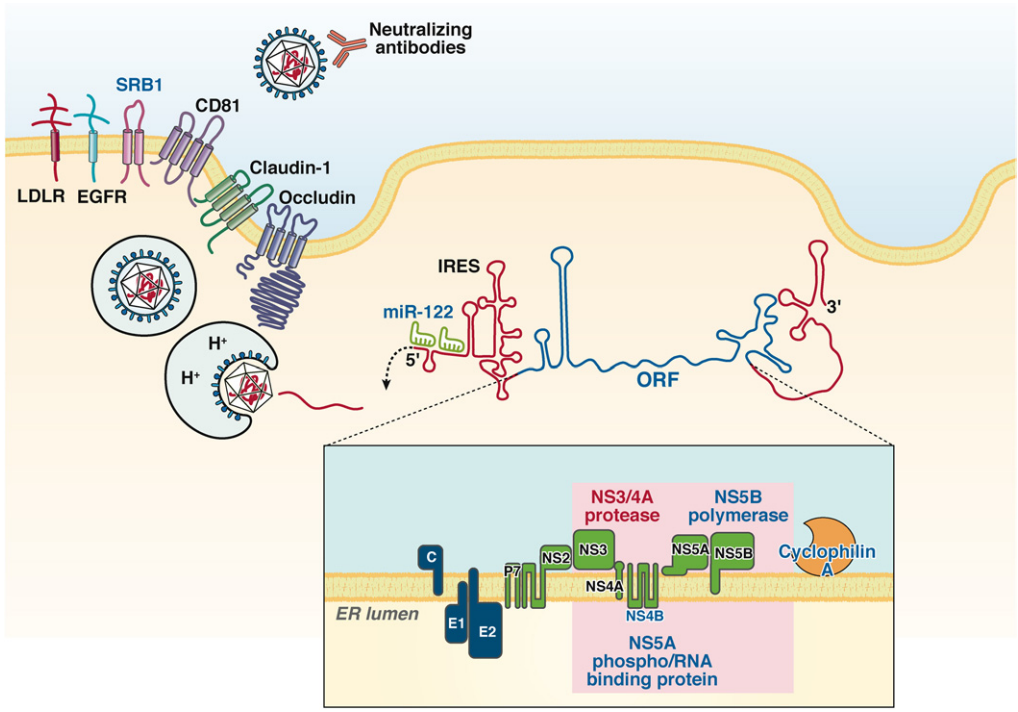

Figure 1. Current antiviral targets in the HCV life cycle. HCV requires several entry factors to infect hepatocytes. After the virus has entered the cell, its RNA genome, which contains the 5' untranslated region where the microRNA 122 (miR-122) binds, is released. Subsequent translation of one open reading frame (ORF) results in the expression of the polyprotein. This is cleaved into structural proteins core, E1, and E2, and the NS proteins p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. The proteins NS3 through NS5B form the replication complex (*shaded pink*), which also includes host factor cyclophilin A. Currently approved DAAs target the NS3/4A serine protease. Additional protease inhibitors, as well as NS5B polymerase and NS5A inhibitors, have completed or currently are being evaluated in phase 3 trials; other drugs in these classes are in earlier phases of development. Inhibitors of cyclophilin A, miR-122, NS4B, and SRB1, or other entry factors represent alternative strategies that have been studied to variable degrees and may become useful in the future. Adapted with permission from C.M. Rice. C, core protein; CD81, cluster of differentiation 81; E1/E2, envelope protein 1/2; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; IRES, internal ribosome entry site; LDLR, low density lipoprotein receptor; NS, nonstructural; SRB1, scavenger receptor B1.

Telaprevir

The ADVANCE (A New Direction in HCV Care: A Study of Treatment Naïve Hepatitis C patients with Telaprevir) study showed significantly higher SVR rates in treatment-naive patients who were given telaprevir-based regimens compared with those who received Peg-IFN/RBV alone.[23] The duration of therapy was determined by viral response to treatment, a concept known as response-guided therapy (RGT). The REALIZE (Retreatment of Patients with Telaprevir-based Regimen to Optimize Outcomes) trial showed that treatment-experienced patients achieved higher SVR rates when telaprevir was added to the re-treatment regimen compared with Peg-IFN and RBV alone, with prior relapsers having higher rates of SVR than responders.[24] The most significant side effects of telaprevir are anemia and rash.

Telparevir is now approved for use at a dose of 750 mg 3 times a day given in combination with Peg-IFN/RBV for 12 weeks followed by RGT (Peg-IFN/RBV for an additional 12 or 36 weeks, depending on viral response) in noncirrhotic treatment-naive patients and prior relapsers or followed by 36 weeks of Peg-IFN/RBV in prior partial or null responders, as well as patients with cirrhosis.[25] Recent results from the OPTIMIZE study in treatment-naive patients showed that twice-daily dosing of telaprevir 1125 mg had equivalent efficacy to 3 times per day dosing.[26]

Boceprevir

The benefit of adding boceprevir to Peg-IFN/RBV in treatment-naive patients was established in the SPRINT-2 (Serine Protease Inhibitor Therapy) trial, and in prior partial responders and relapsers in the RESPOND-2 trial (Retreatment with HCV Serine Protease Inhibtor Boceprevir and PegIntron/Rebetol).[27,28] These trials also established the foundation for RGT with boceprevir treatment. The most significant side effect of boceprevir is anemia.

Boceprevir is now approved for the treatment of genotype 1 HCV at a dose of 800 mg 3 times per day in combination with Peg-IFN/RBV.[29] All patients receive a 4-week lead-in period of Peg-IFN/RBV, and boceprevir in combination with Peg-IFN/RBV is added thereafter. Duration is determined by RGT based on the HCV RNA level at treatment weeks 8 through 24. Total treatment duration ranges from 28 weeks to 36 or 48 weeks based on prior treatment status and viral response.

Upcoming Direct Acting Antiviral Therapies

Telaprevir and boceprevir will be followed by other oral targeted therapies with various combinations of potency, barrier to resistance, side-effect profiles, and convenience of administration. These newer agents are being evaluated for use in