Editorial

Newer therapeutics for hepatitis C

Bhawna Poonia[1,2], Shyam Kottilil[1,2]

[1]Division of Basic Sciences, [2]Division of Clinical Care and Research, Institute of Human Virology, University of Maryland, Baltimore, MD, USA
Correspondence to: Shyam Kottilil, MD, PhD. Professor of Medicine, Institute of Human Virology, University of Maryland, 725 W Lombard St, Baltimore, MD 21201, USA. Email: skottilil@ihv.umaryland.edu.

Submitted Oct 07, 2015. Accepted for publication Oct 09, 2015.
doi: 10.3978/j.issn.2305-5839.2015.10.06
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.10.06

Chronic hepatitis C affects over 180 million people and is responsible for 3–4 million new infections each year worldwide (1). Most newly infected patients go on to develop persistent liver disease characterize by viremia and progressive liver fibrosis (2). Over time, many chronically infected patients develop liver cirrhosis, hepatocellular carcinoma and liver failure. Chronic hepatitis C remains the premier cause for liver transplantation in the Western World (3). Chronic hepatitis C is a curable disease with people achieving sustained virologic response (SVR: absence of plasma HCV RNA 12 weeks after stopping treatment). Until recently, treatment for hepatitis C included use of pegylated interferon-α (IFN-α) and ribavirin, which resulted in modest cure rates, despite having significant dose limiting adverse reactions (4). Recently, new class of antiviral agents termed directly acting antiviral agents (DAA) have been shown to achieve high rates of cure for HCV without the use of IFN-α (5). However, wide use of such DAA only regimens is restricted by cost and availability of new providers with expertise in management of hepatitis C (6). Hence, it is ideal if we can develop more affordable agents with antiviral efficacy for the treatment of hepatitis C infection.

In a recent study, He *et al*. (7) has accomplished exactly that. Using a high throughput screening for antiviral efficacy against HCV using the well described JFH-1 continuous culture system, they identified chlorcyclizine (CCZ) as an effective agent against HCV. CCZ is an FDA approved, over the counter anti-histamine drug widely used for alleviation of allergy symptoms, not previously known for its antiviral effects. Furthermore, the investigators evaluated the antiviral efficacy of CCZ using two separate *in vitro* systems of HCV replication. Initially they used human hepatoma cells, Huh7.5.1 cells infected with HCV JFH-1 strain (genotype 2a). In the presence of enantiomer (S) CCZ, the intracellular and extracellular HCV RNA levels diminished in a dose dependent fashion, confirming the antiviral properties of CCZ. In addition, they used primary human hepatocyte culture system to evaluate the spectrum of antiviral efficacy of CCZ against all HCV genotypes. CCZ exhibited a pangenotypic activity against all strains of HCV tested as demonstrated by decrease in extracellular HCV RNA levels and infectivity in the presence of CCZ.

Even though the *in vitro* assay unequivocally established the antiviral efficacy of CCZ, the mode of action of CCZ was not completely understood at this point. To date, most DAAs that are approved by the US Food and Drug Administration include compounds that block HCV replication by interfering with HCV serine protease (NS3/4A inhibitors: telaprevir, boceprevir, paritaprevir, asunaprevir, grazoprevir), or RNA dependent RNA polymerase (NS5B inhibitors: sofosbuvir, dasabuvir) or replication complex formation (NS5A inhibitors: daclatasvir, ledipsavir, ombitasvir, elbasvir). In order to understand the exact mode of action of CCZ, the authors performed three distinct *in vitro* assays. First, they used HCV single cycle infection assay, which utilizes a core defective HCV single round infection that does not assemble into new virions allowing to test effects of antiviral on HCV replication prior to virion assembly. Second, they used a sub-genomic replicon system to investigate whether CCZ would target HCV replication without an effect on viral entry. Finally, they also used HCV pseudoparticle (HCVpp) assay system to test the efficacy of blocking HCV entry into cells. Results showed CCZ had a significant effect on HCV single-cycle infection assay while had no effect on sub-genomic replicon assay and HCVpp assay. These results suggest a novel mode of action for CCZ in blocking HCV entry and early stages

of HCV replication and could complement the effects of other widely used DAAs that block HCV replication instead. To delineate the exact step in which CCZ inhibits HCV replication, they used two controls, bafilomycin, an HCV entry inhibitor and sofosbuvir, an NS5B RNA dependent RNA polymerase inhibitor. Strikingly, CCZ showed the most potent suppression of HCV replication when added during viral attachment, suggesting an effect on late viral entry into hepatocytes. Since CCZ did not have any effect on HCV co-receptors, CD81, claudin, occludin and BRB-1 and Niemann-Pick C1 like-1 (NPC1L1) receptors, the antiviral effect of CCZ does not involve modulation of HCV co-receptors on cells.

Since HCV therapy involves combination therapy using synergistic drugs, the authors examined *in vitro* synergy between CCZ and various antiviral agents currently being used for treatment of HCV infection, including ribavirin, IFN-α, telaprevir, boceprevir, sofosbuvir, and daclatasvir. Co-administration of CCZ resulted in synergistic suppression of HCV replication with each one of these antiviral agents without cell cytotoxicity.

Given the potent anti-HCV effect of CCZ, a wider screen for the spectrum of antiviral therapy was performed, which showed no significant effect on Dengue (a Flavi virus, similar to HCV), hepatitis B, HIV, Herpes simplex virus, human CMV, RSV, vaccinia, influenza A, SARS coronavirus, polio virus, Rift Valley fever virus, Tacarive and Venzuelan equine encephailitis virus.

In order to address the *in vivo* efficacy and pharmacokinetics of CCZ, the investigators used an albumin-urokinase plasminogen activator/severe combined immunodeficient chimeric mouse model (engrafted with human hepatocytes) infected with HCV 1b or 2a. CCZ treatment resulted in a similar antiviral effect on both genotypes without rebound suggesting lack of emergence of primary resistance to CCZ.

In summary, the authors characterize the antiviral efficacy of CCZ, a popular antihistamine possibly inhibiting HCV replication by interfering with late entry events. This is in addition to several similar compounds, which have been found to have activity against HCV such as ezetimibe (lipid lowering agent) ferroquine (antimalarial), nitazoxanide (antiprotozoal), and dasatinib (anticancer) in recent times. The authors anticipate CCZ to have a better pharmacokinetic profile, cheaper cost, and favorable safety profile over the other agents. Hence they suggest CCZ will have to be further investigated for antiviral efficacy *in vivo* among patients with chronic hepatitis C infection.

Summary and conclusions

In summary, demonstration of CCZ as a potent antiviral agent against HCV is indeed a promising first step in the process of adding to the ever-widening list of DAA agents. It is definitely an advantage to have agents that are already approved by the FDA and have demonstrated a good safety profile to be used as part of HCV therapy. To date, there has not been an effective antiviral agent that has been developed against HCV that blocks HCV entry.

As shown in *Figure 1*, an HCV entry blocker could be very effective in the management of hepatitis C infection. However, there have not been any completed clinical trials that have demonstrated efficacy of CCZ in hepatitis C infected patients. Hence, this agent could add to the HCV therapeutics quite easily. Chlorcyclizine is a first-generation antihistamine of the phenylpiperazine class marketed in the United States and certain other countries. It is approved to be used to alleviate allergy symptoms such as rhinitis, urticaria, and pruritus. It may also be used as an antiemetic since chlorcyclizine also has some anticholinergic, antiserotonergic, and local anesthetic properties, in addition to the antihistaminic properties. The medication has several disadvantages. First, it has to be taken multiple times during the day due to the short half-life, which complicates HCV management. Recent studies have demonstrated that adherence to medications drop significantly with medications that require frequent administration. Second, the major side effect of CCZ administration is drowsiness, which restricts the use of this agent for longer period of time as it interferes with normal activities such as driving. Finally, many antiviral agents, including nitazoxanide, demonstrated great antiviral efficacy, but failed to find a role in the clinical management of HCV. A major argument put forward by the investigators is that CCZ is cheap. This obviously is true, however, we still have to use CCZ along with other antiviral agents to achieve SVR. This includes agents that could be expensive. The current SVR rates for chronic hepatitis C patients with FDA approved therapy are between 90-95% (8). It is nearly impossible to demonstrate clinically that addition of a newer agent can result in improved efficacy or SVR. Conceptually, this approach has been done to perfection in the recent NIAID SYNERGY trial, where addition of a third agent to two DAA based therapy allowed to reduce total duration of treatment from 12 to 6 weeks (9). Hence, a similar trial should use CCZ in addition to approved DAA regimens to reduce duration of HCV therapy. If proven this approach will change the landscape of HCV therapy world-wide.

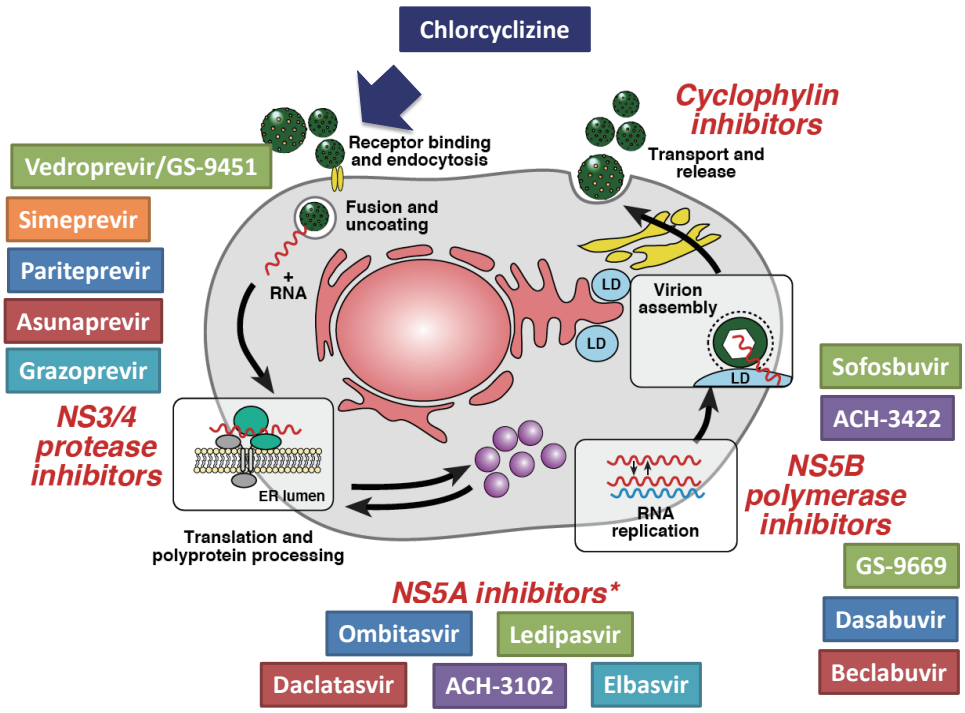

Figure 1 The major sites of action of existing and newer antiviral agents being developed for the management of hepatitis C. Chlorcyclizine allows us a novel mode of action and could complement existing DAA therapy.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Junhong Wang, MD, PhD (Department of Geriatric Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clin Infect Dis 2012;55 Suppl 1:S10-5.
2. Ferenci P, Kozbial K, Mandorfer M, et al. HCV targeting of patients with cirrhosis. J Hepatol 2015;63:1015-22.
3. Mitchell O, Gurakar A. Management of Hepatitis C Post-liver Transplantation: a Comprehensive Review. J Clin Transl Hepatol 2015;3:140-8.
4. Sulkowski MS, Cooper C, Hunyady B, et al. Management of adverse effects of Peg-IFN and ribavirin therapy for hepatitis C. Nat Rev Gastroenterol Hepatol 2011;8:212-23.
5. Cortez KJ, Kottilil S. Beyond interferon: rationale and prospects for newer treatment paradigms for chronic hepatitis C. Ther Adv Chronic Dis 2015;6:4-14.
6. Petta S, Craxì A. Current and future HCV therapy: do we still need other anti-HCV drugs? Liver Int 2015;35 Suppl 1:4-10.
7. He S, Lin B, Chu V, et al. Repurposing of the antihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection. Sci Transl Med 2015;7:282ra49.
8. Kohli A, Shaffer A, Sherman A, et al. Treatment of hepatitis C: a systematic review. JAMA 2014;312:631-40.
9. Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. Lancet 2015;385:1107-13.

Cite this article as: Poonia B, Kottilil S. Newer therapeutics for hepatitis C. Ann Transl Med 2016;4(2):31. doi: 10.3978/j.issn.2305-5839.2015.10.06

