Hepatitis C antiviral therapy: the next generation

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Comment on: van der Ree MH, de Vree JM, Stelma F, *et al.* Safety, tolerability, and antiviral effect of RG-101 in patients with chronic hepatitis C: a phase 1B, double-blind, randomised controlled trial. Lancet 2017;389:709-17.

Received: 05 May 2017; Accepted: 16 May 2017; Published: 09 June 2017.

doi: 10.21037/amj.2017.05.10

View this article at: http://dx.doi.org/10.21037/amj.2017.05.10

In less than a decade, antiviral therapy for chronic hepatitis C (HCV) has undergone dramatic change. The sustained virologic response rate (SVR), defined as HCV RNA undetectability 12 weeks post-therapy, is recognized as being a virologic "cure" and has increased from 40–50%, with peginterferon and ribavirin, to 95–99% with the newest direct acting antiviral agents (DAA) (1). Unlike the non-specific antiviral and immunostimulatory effects of interferon, DAAs specifically target the HCV replicative machinery and include protease inhibitors, NS5a inhibitors and NS5b RNA dependent polymerase inhibitors. These DAAs, prescribed as a combination of antiviral drugs, usually co-formulated in a single pill, are well-tolerated and have made interferon-based therapy obsolete. To many, it would appear that "victory" on war against HCV is eminent and further antiviral drug development in this area is unnecessary. However, history has consistently demonstrated that pronouncements of victory can be premature, reflecting hubris and short-sightedness. Although one can hope that this is not the case with DAAs and HCV, there are a growing number of patients who have failed DAA therapy and are infected with HCV strains that are resistant to multiple DAAs. Even with a very high rate of SVR, selecting out resistant strains in a community that continues to spread infection via injection street drugs and other risky behaviours, may only create a future epidemic of HCV infections that are resistant to today's DAAs. Clearly, drug development must continue in this area, at least in the foreseeable future.

One of the potential targets of future antiviral therapies is the human host's intracellular machinery that HCV utilizes to replicate. Such antiviral therapy would have the benefit of a lower likelihood of viral resistance as it is the host's cellular components that are the targets, not the HCV itself. These indirectly acting antiviral agents would also be pan-genotypic as all HCV genotypes replicate similarly within the host. One such potential target is microRNA-122 (miR-122). miR-122 is a small non-replicating fragment of RNA found in mammalian cells that functions to repress gene expression (2). It is recognized that HCV utilizes miR-122 to replicate by binding to the 5' untranslated region (3) and to protect itself against degradation by endogenous RNA exonuclease (2). In a recent issue of *Lancet*, van der Ree *et al.* published a randomised, double-blind, placebo-controlled, multicentre, phase 1B trial, which examined the safety, tolerability, and antiviral effect of RG-101 (4). RG-101 is a hepatocyte targeted N-acetylgalactosamine conjugated oligonucleotide that antagonizes miR-122 and therefore has a novel antiviral effect. In this proof-of-concept study (1), RG-101 was given as a single subcutaneous injection of 2 or 4 mg/kg to patients with chronic HCV genotype 1, 3, or 4 who were either treatment-naive or relapsed after interferon-based therapy in the absence of decompensated liver disease. RG-101 did not result in any serious adverse events; however, treatment-related adverse events (fatigue, insomnia, emotional distress, local injection site reaction) were reported in 93% (26/28). The median viral load reduction at week 4 was 4.41 $\log_{10}$ IU/mL with 2 mg/kg and 5.07 $\log_{10}$ IU/mL with 4 mg/kg of RG-101. Virologic rebound at week 8 was absent in 22/28 and SVR at week 76 was achieved in 3/22.

Although these early results may appear to be modest, it should be kept in mind that RG-101 has been shown to exert a synergistic antiviral effects *in vitro* with direct-acting antivirals (4), such that combination therapy could potentially be an effective antiviral therapy. Such a combination with a novel "biologic" antiviral agent could be invaluable for patients who are intolerant/allergic to a given group of DAAs or as rescue therapy in patients with resistance-associated variants, such as have been reported for NS5a inhibitors including ledipasvir (5) and velpatasvir (6). It has to be kept in mind that targeting the host's own intracellular machinery could result in unforeseen pathophysiological effects. One potential concern is that miR-122 has been found to possess tumor suppressive effects and low levels induced by the administration of anti-miR-122 may result in the development of hepatocellular carcinoma (7). Furthermore, RG-101 appears to be associated with frequent short-term side effects and its long-term safety remains to be elucidated. Antiviral therapy with RG-101, or any other host-targeted antiviral agents, would most likely have to be of short duration. Clinical trials are underway to evaluate the safety and efficacy of RG-101 in combination with direct-acting antivirals but agents similar to RG-101 may constitute the next generation of anti-HCV therapies. Clearly, drug development in HCV will need to continue for the foreseeable future.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xingshun Qi (Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.05.10). Dr. Eric Yoshida has been an investigator of clinical trials sponsored by Gilead Sciences Inc, Merck Inc, Abbvie Inc, Janssen Inc, Intercept Inc, Springbank Inc, Genfit Inc. He has received Honoria for CME/Ad Board lectures sponsored by Gilead Sciences Canada Inc, Merck-Canada Inc , Abbvie Canada Inc, Celgene Canada Inc. Eric M. Yoshida serves as an unpaid board member of *AME Medical Journal* from Jun 2017 to Jun 2019. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2017.05.10
Cite this article as: Yau AH, Yoshida EM. Hepatitis C antiviral therapy: the next generation. AME Med J 2017;2:72.