World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i25.5623

World J Gastroenterol 2016 July 7; 22(25): 5623-5626
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Symbiotic chemo- and immuno-therapy for hepatitis B and C viruses

Babita Agrawal, Rakesh Kumar

Babita Agrawal, Department of Surgery, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G 2R3, Canada

Rakesh Kumar, Department of Laboratory Medicine and Pathology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G 2R3, Canada

Author contributions: Agrawal B and Kumar R wrote the manuscript.

Conflict-of-interest statement: Agrawal B and Kumar R have no conflict of interest to declare.

Manuscript source: Invited manuscript

Correspondence to: Dr. Rakesh Kumar, Professor, Department of Laboratory Medicine and Pathology, Faculty of Medicine and Dentistry, University of Alberta, 116 St and 85 Ave, Edmonton, AB T6G 2R3, Canada. rkumar@ualberta.ca
Telephone: +1-780-4927545

Received: May 4, 2016
Peer-review started: May 4, 2016
First decision: May 27, 2016
Revised: May 31, 2016
Accepted: June 13, 2016
Article in press: June 13, 2016
Published online: July 7, 2016

Abstract

Hepatitis B and C viruses (HBV and HCV), both cause serious chronic infections leading to fatal liver diseases. The prototype therapy for both HBV and HCV was based on IFN-α with or without ribavirin. The advent of direct-acting antivirals (DAA) for both HBV and HCV has remarkably improved the standard of treatment for both infections. While HCV can be eliminated following combination DAA therapy, HBV persists even after treatment, requiring life-long therapy with DAAs. Treatment with DAAs is also associated with high cost, the development of resistance and side effects. There is ample published evidence that both HBV and HCV can be eliminated from infected host cells through non-cytolytic immune mechanisms. We need to identify the mechanisms behind this successful elimination of replicating viruses and develop them into novel immunotherapeutic regimens. Moreover, a synergy of, chemo- and immuno-therapeutic strategies will be necessary to eradicate HBV or HCV from a host.

Key words: Hepatitis C virus; Hepatitis B virus; Direct-acting antiviral; Chemotherapy; Immunotherapy

Core tip: Immune related mechanisms have been shown to eliminate both Hepatitis B and C viruses (HBV and HCV) from chronically infected host cells *via* non-cytolytic mechanisms. Current direct-acting antivirals against replication of both HBV and HCV are effective and provide significant viral suppression in a relatively short period of time. This time window should be harnessed to target host-mediated immune mechanisms to clear the host of the infection. This strategy would lead to a significant reduction in cost, duration, side effects and development of resistance associated with direct-acting antivirals therapy. In summary, regimens combining chemo- and immuno-therapy must be used in a mutually beneficial manner to eradicate HBV and/or HCV from a host.

Agrawal B, Kumar R. Symbiotic chemo- and immuno-therapy for hepatitis B and C viruses. *World J Gastroenterol* 2016; 22(25): 5623-5626 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i25/5623.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i25.5623

INTRODUCTION

Hepatitis B and C viruses (HBV and HCV) cause serious chronic infections globally in about 350 million and about 170 million people, respectively, leading to fatal liver diseases such as fibrosis, cirrhosis and hepatocellular carcinoma (HCC). In addition, 7-10 million people are co-infected with both HBV and HCV, resulting in more severe liver disease and increased risks of hepatocellular carcinoma and higher mortality rates compared to mono-infected people[1].

HBV and HCV belong to different families of viruses and have entirely different genomes and modes of replication: HBV belongs to the family Hepadnaviridae, has a partially double stranded circular DNA and replicates through an RNA intermediate *via* reverse transcription, whereas HCV belongs to the family Flaviviridae, has a single stranded + sense RNA genome and undergoes RNA replication[2,3]. Apart from these major genetic differences, they have many similarities including routes of transmission, hepatotropism, ability to cause chronic infections, end-stage liver diseases and modulate host immunity. Importantly, both HBV and HCV can also trigger self-clearing acute infections by inducing protective and efficient immune responses in a fraction of infected individuals[2,3].

The very first successful therapy for HBV and HCV infections was immunotherapy with interferon-α (and peginterferon-α) and interferon-α plus ribavirin, respectively[4,5]. While these primitive immunotherapies have been used for decades, their exact mechanisms of action are still unclear and there are severe limitations associated with their use[4]. Nevertheless, they provide definitive proof of concept that both HBV and HCV are susceptible to immunotherapeutic regimens and their elimination can be associated with antiviral immune responses.

Great enthusiasm in HBV therapy was realized with the approval of direct acting antiviral (DAA) drug lamivudine, which was followed by the development of the next generation anti-HBV drugs entecavir, tenofovir, adefovir and telbivudine[6,7]. All of these are nucleoside analogs, which inhibit HBV DNA polymerase with varying potentials and have various resistance barriers[5-7]. These nucleosides efficiently suppress viral DNA replication in the majority of patients but seldom induce HBsAg seroconversion, a marker of a "functional cure" and eradication of intracellular virus[5,7]. Therefore, treatment of chronic HBV with these agents requires continued life-long therapy to achieve sustained inhibition of viral replication. However, this is expensive, and can result in drug toxicities and development of resistant viral strains[5,7]. Long-term suppression of viral DNA replication does indeed lead to the beneficial effects of preventing or reversing liver diseases such as fibrosis, cirrhosis and HCC, and partial restoration of immune responses[5-7]. But while viral DNA synthesis is efficiently inhibited by antiviral nucleosides, they have limited effects on the levels and activity of cccDNA, which can persist for decades in hepatocytes[7,8]. Although it was hypothesized initially that with continued suppression of HBV DNA replication, the pool of cccDNA will eventually diminish to negligible levels that would provide a cure, this expectation has not withstood the test of time[7]. Efforts are continuing to seek new drugs targeted at other steps of the viral replication cycle such as inhibitors of entry, cccDNA formation, secretion, nucleocapsid formation *etc*[5-8]. Whether or not these approaches will lead to "cure" from chronic HBV infection remains to be seen.

For about 20 years, the combination of interferon and ribavirin (RBV) was the standard of care (SOC) therapy for chronic HCV. This treatment had limited success rates (< 50%) and had severe side effects, which at times discouraged patients to even get treated[9]. The first DAAs approved for HCV therapy were protease inhibitors boceprevir and telaprevir, which were given with the SOC (IFN-α + RBV). Within the last few years, the treatment for HCV has exploded tremendously with the approval of several DAAs, acting directly on various enzymes/steps of HCV replication such as NS3, NS5A, NS5B and NS4. As a result, several interferon-free treatment regimens have been approved for chronic HCV, which include various 2-3 drug combinations comprising of sofosbuvir, ledipasvir, ritonavir, dasabuvir, simeprevir, daclatasavir, ombitasvir, velpatasvir *etc*[10,11]. These combinations of DAAs lead to sustained viral response (SVR) in about 95% of the treated patients harboring all HCV genotypes except genotype 3. SVR is a clinical surrogate of treatment success defined as an undetectable HCV RNA (< 15 IU/mL) 12 wk (SVR12) and 24 wk (SVR24) after the end of treatment. The patients who achieved SVR did not relapse to $HCVRNA^+$ status upon long-term follow-up (4-5 years), confirming SVR as an indication of cure[12,13]. Even with the 95% success rate, there are several limitations associated with the current all oral DAA regimens such as the very high cost of treatment, emergence of drug resistance, side effects, contraindications for patients with comorbidities, inefficacy in patients with genotype 3, the possibility of reinfection, *etc*[14]. Also, in real-life situations, patients may not comply with daily drug doses for 3 mo, especially if they are asymptomatic and are not feeling sick. Further, in a number of DAA combination regimens, ribavirin is still being recommended, suggesting that besides simultaneously targeting

several viral enzymes/processes by DAAs, an immunomodulatory component is required. At present, even in the United States, the DAA therapy is being used in < 20% of the diagnosed patients (in some cases, a triage system eliminates people with less-severe liver disease to reduce cost), and many more remain unaware of their infection status. Above all, the accessibility, affordability and questionable success of DAAs in resource-poor populations of the world, where the majority of the 170 million chronic HCV patients reside, remain major issues. Continued efforts are needed to search for more affordable, accessible, compliance-friendly approaches to cure HCV and eradicate it from the world.

Hepatocytes and hepatoma cell lines infected with HBV and/or HCV in cell culture and/or animal models have been investigated extensively to examine immune mediated viral clearance[15,16]. While there are ongoing debates and individual studies demonstrating the role of innate *vs* adaptive immunity and soluble vs. cellular immune components in viral clearance for both HBV and HCV, one aspect remains clear: non-cytolytic effector mechanisms induced by a number of cytokines and/or a combination of cytokines are most effective in clearing hepatocytes of HBV and/or HCV infections irrespective of whether they are produced by innate immune cells (*e.g.,* NK, NKT) or adaptive immune ($CD4^+$ and $CD8^+$ T) cells. Notably, clearance of long-lived HBV cccDNA from infected hepatocytes has only been demonstrated through immune effector mechanisms mediated by a number of cytokines[16-20]. Obviously, treatment with combinations of effector cytokines is not foreseeable even in the future due to associated toxicities and systemic side effects. Consequently, the research focus must shift towards investigating more natural and balanced ways of inducing physiological levels of these effector molecules at the target organ - liver.

After the discovery of innate receptors such as TLRs, NLRs, RIG1 etc., and the observations that in cell cultures the agonists of the innate receptors such as TLR receptors demonstrate very promising antiviral effects against both HBV and HCV, several synthetic TLR agonists were tested in clinical trials. However, due to the ubiquitous presence of TLRs throughout the body and induction of systemic, non-physiological amounts of cytokines, so far TLR agonists have not succeeded in providing a safe and successful immunotherapeutic approach, which can be used universally[21,22]. Immunotherapeutic vaccine approaches for treatment of chronic HBV and HCV have also not been very attractive because of limitations associated with targeting specific viral epitopes by T cells due to mechanisms including T cell exhaustion, tolerance *via* anergy and deletion of antigen-specific T cells, viral immune escape mutants *etc*[5]. There is a need to investigate and discover more natural and regulated means of stimulating physiological levels of immune effector molecules, which are induced and localized in the target organ, to obtain the viral eradication without associated immuno-toxicities and systemic inflammation.

Traditionally, research has been isolated in two camps with chemists and immunologists working in their own small silos. This approach has led to many groundbreaking discoveries, including the understanding of antiviral immune mechanisms and the direct acting antiviral treatments available to date. What has been remarkably demonstrated in animal models as well as in patients is that specific DAA regimens against both HBV and HCV are highly effective in suppressing viral replication in relatively short period of time. Importantly, this period of active suppression of extensive viral replication is associated with reduction in systemic viral antigens' levels and associated immune suppression or immune blockade, and restoration of some of the immune components[23]. This time window should be exploited with an immunotherapy administered on a weekly to monthly schedule that will help stimulate effector functions through innate and/or adaptive immune mechanisms and induce intrinsic non-cytolytic clearance of virus-infected hepatocytes. Such an approach should also allow substantial shortening of the DAA therapy in both HBV and HCV infections, leading to reduced costs, reduced emergence of drug-resistance, reduced side effects and improved compliance. This strategy, although attractive, is still far-sighted as there are not too many options available for immunotherapy. Consequently, there is an unprecedented need to identify a range of novel immunotherapies, which can be either combined or used sequentially with DAAs in a symbiotic relation to produce synergistic antiviral effects, if significant steps towards literal "cure" and "eradication" of HBV, HCV and HBV/HCV infections have to be realized.

REFERENCES

1 **Konstantinou D**, Deutsch M. The spectrum of HBV/HCV co-infection: epidemiology, clinical characteristics, viralinteractions and management. *Ann Gastroenterol* 2015; **28**: 221-228 [PMID: 25830779]

2 **Gish RG**, Given BD, Lai CL, Locarnini SA, Lau JY, Lewis DL, Schluep T. Chronic hepatitis B: Virology, natural history, current management and a glimpse at future opportunities. *Antiviral Res* 2015; **121**: 47-58 [PMID: 26092643 DOI: 10.1016/j.antiviral.2015.06.008]

3 **Alter MJ**. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436-2441 [PMID: 17552026 DOI: 10.3748/wjg.v13.i17.2436]

4 **Heim MH**. 25 years of interferon-based treatment of chronic hepatitis C: an epoch coming to an end. *Nat Rev Immunol* 2013; **13**: 535-542 [PMID: 23743475 DOI: 10.1038/nri3463]

5 **Liang TJ**, Block TM, McMahon BJ, Ghany MG, Urban S, Guo JT, Locarnini S, Zoulim F, Chang KM, Lok AS. Present and future therapies of hepatitis B: From discovery to cure. *Hepatology* 2015; **62**: 1893-1908 [PMID: 26239691 DOI: 10.1002/hep.28025]

6 **Jia H**, Rai D, Zhan P, Chen X, Jiang X, Liu X. Recent advance of the hepatitis B virus inhibitors: a medicinal chemistry overview. *Future Med Chem* 2015; **7**: 587-607 [PMID: 25921400 DOI:

10.4155/fmc.15.19]
7 **Nassal M**. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]
8 **Ohno M**, Otsuka M, Kishikawa T, Yoshikawa T, Takata A, Koike K. Novel therapeutic approaches for hepatitis B virus covalently closed circular DNA. *World J Gastroenterol* 2015; **21**: 7084-7088 [PMID: 26109795 DOI: 10.3748/wjg.v21.i23.7084]
9 **Enomoto H**, Nishiguchi S. Factors associated with the response to interferon-based antiviral therapies for chronic hepatitis C. *World J Hepatol* 2015; **7**: 2681-2687 [PMID: 26609345 DOI: 10.4254/wjh.v7.i26.2681]
10 **Zopf S**, Kremer AE, Neurath MF, Siebler J. Advances in hepatitis C therapy: What is the current state - what come's next? *World J Hepatol* 2016; **8**: 139-147 [PMID: 26839638 DOI: 10.4254/wjh.v8.i3.139]
11 **González-Grande R**, Jiménez-Pérez M, González Arjona C, Mostazo Torres J. New approaches in the treatment of hepatitis C. *World J Gastroenterol* 2016; **22**: 1421-1432 [PMID: 26819511 DOI: 10.3748/wjg.v22.i4.1421]
12 **Burgess SV**, Hussaini T, Yoshida EM. Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis c in the era of new oral direct-acting antivirals: A concise review. *Ann Hepatol* 2016; **15**: 154-159 [PMID: 26845592 DOI: 10.5604/16652681.1193693]
13 **Serfaty L**. Follow-up of patients with chronic hepatitis C and a sustained viral response. *Liver Int* 2016; **36** Suppl 1: 67-71 [PMID: 26725900 DOI: 10.1111/liv.13016]
14 **Banerjee D**, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Aliment Pharmacol Ther* 2016; **43**: 674-696 [PMID: 26787287 DOI: 10.1111/apt.13514]
15 **Guidotti LG**, Chisari FV. Immunobiology and pathogenesis of viral hepatitis. *Annu Rev Pathol* 2006; **1**: 23-61 [PMID: 18039107]
16 **Pasquetto V**, Wieland SF, Uprichard SL, Tripodi M, Chisari FV. Cytokine-sensitive replication of hepatitis B virus in immortalized mouse hepatocyte cultures. *J Virol* 2002; **76**: 5646-5653 [PMID: 11991993]
17 **Li HJ**, Zhai NC, Song HX, Yang Y, Cui A, Li TY, Tu ZK. The Role of Immune Cells in Chronic HBV Infection. *J Clin Transl Hepatol* 2015; **3**: 277-283 [PMID: 26807384 DOI: 10.14218/JCTH.2015.00026]
18 **Rehermann B**. Natural Killer Cells in Viral Hepatitis. *Cell Mol Gastroenterol Hepatol* 2015; **1**: 578-588 [PMID: 26682281]
19 **Li Y**, Zhang T, Ho C, Orange JS, Douglas SD, Ho WZ. Natural killer cells inhibit hepatitis C virus expression. *J Leukoc Biol* 2004; **76**: 1171-1179 [PMID: 15339939]
20 **Rehermann B**. Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. *J Clin Invest* 2009; **119**: 1745-1754 [PMID: 19587449 DOI: 10.1172/JCI39133]
21 **Baumert TF**, Verrier ER, Nassal M, Chung RT, Zeisel MB. Host-targeting agents for treatment of hepatitis B virus infection. *Curr Opin Virol* 2015; **14**: 41-46 [PMID: 26262886 DOI: 10.1016/j.coviro.2015.07.009]
22 **Chang J**, Guo JT. Treatment of chronic hepatitis B with pattern recognition receptor agonists: Current status and potential for a cure. *Antiviral Res* 2015; **121**: 152-159 [PMID: 26205674 DOI: 10.1016/j.antiviral.2015.07.006]
23 **Rehermann B**, Bertoletti A. Immunological aspects of antiviral therapy of chronic hepatitis B virus and hepatitis C virus infections. *Hepatology* 2015; **61**: 712-721 [PMID: 25048716 DOI: 10.1002/hep.27323]

P- Reviewer: Abdel-Fattah M, Farshadpour F, Purdy MA, Zeisel MB
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327