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LETTER TO THE EDITOR

Viral hepatitis: A global burden needs future directions for the management

Henu Kumar Verma, Kiran Prasad, Pramod Kumar, Bhaskar Lvks

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Abstract

Viral hepatitis is an acute or chronic liver disease due to the infection from Hepatitis A, B, C, D and E viruses. It can cause severe liver damage such as cirrhosis, liver failure and liver cancer. To avoid such fatal complications, hepatitis patients must be diagnosed, pathologized and treated as soon as possible. Furthermore, these hepatitis viruses infect through different routes, resulting in distinct disease pathologies, severity and even the need for specific treatment strategies to combat the infection.

Key Words: Viral hepatitis; Vaccination; Chronic; Acute; Viral therapy

Core Tip: Vaccination is the primary strategy for neutralizing several hepatitis viruses and it is highly effective against most hepatitis viruses. However, additional precautions must be taken for patients at a higher risk of infection such as those who take drugs, prisoners, the homeless or homosexuals. From interferon monotherapy and interferon combination therapy with direct-acting antiviral agents to interferon-free regimens which act by viral chain braking are among the measures to control hepatitis. These strategies can play a critical role in achieving World Health Organization's an ambitious but attainable goal of eliminating hepatitis infection by 2030.

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TO THE EDITOR

Viral hepatitis, particularly hepatitis B and C, are one of the biggest threats to human health contributing to nearly one-fourth of all deaths among overall infectious disease patients[1]. Despite the substantial evolvement in antiviral therapy and access to effective vaccines, the hepatitis virus elimination goal of the United Nations by the year 2030 is doubtful[2]. To this end, healthcare providers and physician assistants can reduce disease burden through infection prevention, early detection, medical management and collaborative care. At the same time, the development of interferon-based and interferon-free therapeutic approaches may help eradicate the hepatitis viral infection.

We recently read Dr. Persico's group paper entitled "Viral hepatitis: Milestones, unresolved issues and future goals" in your prestigious journal "*World Journal of Gastroenterology*[3]." We sincerely thank the author for providing details about the impact of various hepatitis viruses, current research, the gaps between effective management and currently applicable approaches, and finally, the plans that might effectively manage viral hepatitis.

Viral hepatitis is classified into several types: A, B, C, D, and E. Among these types, B and C are the most common types of viruses that can be transmitted through blood transfusions and are the most lethal due to the induction of chronic illness[4]. In the present review article, the authors mainly focused on the pathologies, clinical manifestations, and various advancements in therapeutic regimes of different hepatitis virus infections.

Furthermore, they elegantly demonstrated progression in hepatitis C virus (HCV) infection treatment regimens from interferon to direct-acting antiviral agents (DAAs) with a relative increase in sustained virological response (SVR) rate. Newer pan-genotypic antiviral therapies, such as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, have 98%-99% SVR in all genotypes of hepatitis C virus and low drug resistance. It was approved by the FDA in 2016. DAAs are now known to be effective in the treatment of HCV patients who do not have cirrhosis, have compensated cirrhosis or have extrahepatic manifestations and have a lower risk of hepatocellular carcinoma (HCC) recurrence[5]. Besides, various host targeting agents (HTAs) are under clinical studies that target molecules essential for hepatitis C virus entry and replication. Its main advantage is its low mutation rate. The primary targets of HTAs are microRNA-122, Cyclophilin A and HMG-CoA reductase[6].

Current hepatitis B virus (HBV) infection management protocols include the use of nucleoside/nucleotide analogues and interferons both of which reduce HBV replication but do not eradicate the virus. Current therapies' lack of direct impact on virus covalently closed circular DNA (cccDNA) is a major limiting factor for HBV virus elimination[7]. Thus, various gene-editing methods like transcription activator-like effector nucleases, CRISPR/Cas system and zinc finger nuclease are understudies to target cccDNA expression[8].

Several immunomodulatory agents that induce HBV-specific immune responses have recently been developed. Immunomodulatory therapies include agonists, immune checkpoint inhibitors, therapeutic vaccines and engineered HBV-specific T-cell transfer. Agonists activate Toll-like receptors, stimulator of IFN genes, and Retinoic Acid-Inducible Gene-1 to initiate the innate immune response. While immune checkpoint inhibitors such as programmed cell death-1 trigger an adaptive immune response. GS-4774 (vector-based vaccine) trials showed that the vaccine was safe but no significant reduction in HBsAg levels was observed. Other vaccines like INO-1800, TG-1050 and ABX-203 are under clinical investigation[9]. RNAi-based therapies are also evolving against HBV infection which exerts its antiviral activity by post-transcriptional silencing. ARC-520 and ARC-521 (RNAi-based drug) showed a reduction in HBsAg and HBV DNA levels but were discontinued due to rising safety concerns related to drug delivery. Both siRNA-based drug, JNJ-3989, earlier called ARO-HBV and VIR-218 has shown promising results against chronic HBV infection and are under ongoing clinical trials[10].

Hepatitis D virus infection occurs only in HBV-infected people. Pegylated interferon-alpha is the only effective therapy against HDV infection in clinical practice. However, HBV vaccination protects from both HBV and HDV infection. Other therapeutic drugs under clinical trials against HDV infection include Pegylated IFN-lambda, Myrcludex B that blocks hepatitis B and D virus entry in hepatocytes, Lonafarnib that inhibits farnesylation of L-HDAg and its subsequent interaction with HBsAg and REP 2139. Its mechanism is still unclear but it is known to be related to blocking HBsAg release[11].

For hepatitis A, no specific treatment is available. Both improving sanitary conditions and HAV vaccination is the most effective preventive strategy. Vaccination is recommended to high-risk people, patients having chronic liver disease, HIV-positive patients and pregnant women[4].

The authors describe various hepatitis E virus (HEV) genotypes and their transmission routes in detail. HEV1 and HEV2 are the only ones that infect humans and spread *via* the fecal-oral route. There is no effective HEV vaccine available to prevent infection. China developed the HEV-239 vaccine which is safe for pregnant women and provides longer protection. However, it is not permitted in other countries [12].

Other treatment strategies like liver transplantation and management of hepatitis in pregnant women can be included. Liver transplantation is the most effective therapy for HCC and cirrhosis due to HBV and HCV infections. Post-transplantation use of DAA reduces the risk of recurrence and increases the survival rate of patients[13].

Pregnant women are prone to acute and chronic hepatitis infection with a risk of developing fulminant hepatitis and vertical transmission, especially in hepatitis E. Seto *et al*[14] described various management strategies for different subtypes of hepatitis. Ribavirin is known to be teratogenic and thus should be avoided during pregnancy; however, supportive care is preferred. Breastfeeding is encouraged in hepatitis C, D, and A, while in hepatitis E, it is not recommended. HAV vaccination is opted to prevent fetal transmission. DAA treatment during pregnancy is still debatable[14]. Ledipasvir and sofosbuvir use during pregnancy in HCV infection has not been associated with safety concerns[15].

Even with advanced therapies like DAA, there are still challenges to cure and eradicate various subtypes of viral hepatitis. Thus, more investigations are required for multiple drugs under clinical trials to develop better preventive and management strategies. We genuinely appreciate Torre *et al*[3] and colleagues for providing relevant and detailed information on various subtypes of viral hepatitis along with their clinical manifestation and treatment methods.

FOOTNOTES

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