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The Burden of Chronic Hepatitis D in Mongolia

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Hepatitis D is a liver disease in both acute and chronic forms caused by the hepatitis D virus (HDV) that requires hepatitis B virus (HBV) for its replication. In other words, HDV infection occurs only simultaneously or as a superinfection with HBV [1]. The estimated worldwide prevalence of HDV infection was 5% among hepatitis B virus patients. Unfortunately, Mongolia is one of the high-prevalence hotspots for HDV infection worldwide [2]. Our study showed that the HDV co-infection rate in Mongolia was 80.1% among patients with chronic hepatitis B [3]. According to the WHO, the Republic of Moldova and countries in Western and Middle Africa are other geographic hotspots [2].

Since parenteral transmission is the primary route of spreading the virus, intravenous drug users, patients on hemodialysis [4], men who have sex with men, and commercial sex workers [5] are considered high-risk groups. Also, familial clustering indicates that HDV is transmitted by personal contacts, presumably through permucosal or percutaneous passage during close or intimate contact [6].

The high rates of HBV and HDV infection in Mongolia now result from the epidemic of acute hepatitis B in 1950-1980, caused by the widespread use of boiled syringes in medical practice and vaccination programs [7]. Approximately 400,000 acute hepatitis cases and 7,000 deaths were registered from 1952 to 1986 [8]. Davaalkham et al. reported that past medical history of acute hepatitis, surgery, blood transfusion and being a family member of patients with chronic viral hepatitis were the main risk factors for HDV infection in Mongolia [9].

Chronic hepatitis Delta is considered the most aggressive form of chronic viral hepatitis due to a much higher risk of developing liver cirrhosis, more rapid progression towards liver-related death, and hepatocellular carcinoma. About 70% of HDV infected patients were diagnosed with liver cirrhosis within ten years [10] and liver cancer risk was 3-fold higher than in HBV-infected patients [11]. Our study demonstrated similar findings. Patients with chronic hepatitis D had more aggressive disease, including higher transaminase and lower platelet levels than patients with HBV [12]. We previously found that the number of cirrhotic patients was significantly higher in the HDV group vs. HBV group (44.8% vs. 10.8%, $p < 0.001$) [3]. Oyunsuren et al. reported that HDV infection is strongly associated with liver cancer development in younger patients [13]. These facts imply that Mongolia's large burden of chronic HBV and HDV infection, with its subsequent liver cirrhosis and hepatocellular carcinoma, are priority issues requiring the attention of public health and healthcare providers in general.

In 2017, the Mongolian Government initially launched the nationwide program Viral Hepatitis Prevention, Control, and Elimination. Since then, we have successfully implemented broad programs, such as performing mass screening tests among the populations at risk for

early viral hepatitis. This program provides good treatment options and supplies government-supported antiviral drugs at a low cost to gradually eliminate viral hepatitis caused by HBV and HCV using newly-updated international guidelines. However, our hepatologists are still concerned that the treatment of chronic hepatitis D remains an unresolved issue.

Lack of effective treatment is causing a serious barrier to eliminate HDV infection. Although 48-weeks of pegylated interferon (PEG-IFN) was the only treatment option recommended, it resulted in an unsatisfactory response rate. Several studies have shown that only 25-43% of HDV patients reached undetectable HDV viremia after 48-weeks of PEG-IFN [14, 15], and late HDV relapse was observed [16]. When we studied the treatment outcome of 48 weeks PEG-IFN in 36 patients with chronic hepatitis D, only 22.7% of patients reached undetectable HDV RNA, whereas 5.5% had HBsAg loss at the end of treatment [3]. But during the one-year follow-up, half of the patients who were considered responders had an HDV relapse. On the other hand, patients who had HBsAg loss at the end of the treatment remained negative during the follow-up. Therefore, not only undetectable HDV RNA but also loss of HBsAg in HDV patients was considered a functional cure.

The hepatocyte entry inhibitor bulevirtide (brand name Myrcludex B) was recently approved in the European Union to treat chronic HDV infection in HDV RNA positive adult patients with compensated liver disease. A previous study has shown that 87% of those taking bulevirtide 10 mg once-daily plus PEG-IFN and 40% of those taking bulevirtide 5 mg twice-daily plus tenofovir reached undetectable HDV viral load [17]. Other newly developing drugs such as prenylation inhibitor-lonafarnib, interferon lambda are currently in Phase 2, 3 clinical trials [18].

Since antivirals against HDV, including Peg-IFN and the novel drug bulevirtide, are either inaccessible or unaffordable for most HDV patients in Mongolia, we should be advocating for more effective policy measurements of cost-sharing or reimbursement by Mongolia's National Health Insurance System to achieve better outcomes. At present, only a few Mongolian patients were allowed to participate in phase 3 clinical trials of lonafarnib, but the recruiting process is delayed due to the COVID-19 pandemic.

Many countries are postponing medical services for chronic diseases to reduce the healthcare services burden during the SARS-COV-2 pandemic. Several research articles have been published during the last year covering outcomes of SARS-COV-2 infection in patients with chronic liver diseases. Severe COVID-19 and fatality rate were similar in patients with chronic viral hepatitis [19, 20]. On the other hand, acute hepatic decompensation occurred in 46% of cirrhotic patients who were infected with SARS-COV-2. In addition, the mortality rates were significantly higher in cirrhotic patients than patients with non-cirrhotic liver disease [21]. High-dose corticosteroids for severe COVID-19 may cause acute exacerbation of chronic hepatitis B, and antiviral prophylaxis with nucleoside analogs is recommended in all patients with severe COVID-19 [22]. In these challenging days of the COVID-19 pandemic, healthcare providers are working even harder to maintain continuous medical services, especially for patients with pre-existing chronic diseases using teleconsultation and remote medical care tools.

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