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Editorial

What Are the Main Differences in the Treatment of Chronic Hepatitis B between Korean Children and Adults?

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▸ See the article "A Multicenter Study of the Antiviral Efficacy of Entecavir Monotherapy Compared to Lamivudine Monotherapy in Children with Nucleos(t)ide-naïve Chronic Hepatitis B" in volume 33, e63.

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The most common misconception among physicians is that chronic hepatitis B (CHB) in children can be monitored without treatment until they become adults. The risk of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) in Asian children is higher than that of western children, which can occur after suffering moderate to severe hepatitis for a prolonged period during active hepatitis (immune-clearance or immune-reactive phase), even in childhood. Therefore, timely treatment in the immune-reactive phase is crucial as delayed or no treatment in this phase results in increased incidences of liver cirrhosis (LC) or HCC.[1] However, the duration of the immune-tolerance phase (hepatitis B e antigen [HBeAg] positive chronic HBV infection) is unpredictable. It may exceed three decades in patients vertically infected by HBeAg-positive mothers. Furthermore, almost 90% of children remain HBeAg-positive by the age of 10–15 years. In Korea, where genotype C is predominant, the proportion of CHB patients entering the initial period of immune-reactive phase was 11.7% in younger children < 12 years and 39.7% in children < 18 years, respectively.[2] This indicates that every child with HBV will not remain a HBV carrier, and a 'wait and see' option could be dangerous in 2/5 of children.

In the current issues of *Journal of Korean Medical Science*, Choe et al.[3] and Lee et al.[4] have reported the antiviral efficacy of tenofovir monotherapy and entecavir monotherapy in Korean children. Considering that the prevalence rate of pediatric hepatitis B has decreased from 2%–3% to 0.1%–0.2% during the past 20 years, results from these multi-center studies are noteworthy, despite the small number of enrolled children. Limitations arise from the retrospective design of these studies, which leads to difficulty in accurately comparing the cut-off values of virologic suppression between non-concurrent groups. Meanwhile, a positive aspect is that tenofovir is expected to be covered by national health insurance in the same way as entecavir in children over 2 years of age.

Entecavir was approved by the FDA in 2014 for children with CHB over 2 years of age. Tenofovir was approved for children with CHB aged 12 years or older in 2012. However, it was not until 2015 when both drugs were covered by the national health insurance for Korean children. Tenofovir and tenofovir alafenamide are currently being studied in phase 3 global clinical trials for approval of usage in children over ages of 2 and 12 years, respectively.

Currently, lamivudine is no longer the first-line drug as a result of high rates of antiviral drug resistance, though it was estimated to be effective in Korean children aged 6 years or younger before the introduction of entecavir.[5] Choe et al.[5] reported that 2 years of treatment with lamivudine was significantly effective in achieving HBeAg seroconversion and HBsAg clearance when compared with 6 months of treatment with interferon-α. This superiority in efficacy was observed especially in children under 6 years, despite the fact that they were all infected vertically.

Another misconception among physicians is that patients with high HBV DNA levels and positive HBeAg titers should be treated, despite normal hepatic enzyme levels. Treatment indications should be carefully evaluated in children with CHB. Treatment should not be considered in patients in the immune-tolerance phase. Pretreatment serum alanine aminotransferase (ALT) levels must exceed two times the upper limit of the normal value to achieve a better clinical response. If ALT levels are persistently elevated in an eligible patient, other hepatic related situations that can cause this elevation should be excluded. One example is in cases of reactive hepatitis, which could be associated with pneumonia or urinary tract infection. For obese children with CHB, it would be very difficult to differentiate whether the cause of the elevated liver enzyme is attributable to an HBV-related active hepatitis or a fatty liver disease. Thus, if such patients fail to reduce their body weight, liver biopsies should be conducted in order to determine whether to start an antiviral treatment.

A treatment strategy is also important to prevent treatment failure. Inadequate drug compliance is one of the major causes of treatment failure in children. Physicians should educate the patients and parents that it is important to take medicines every day on all counts. Another crucial point that physicians should remember is to not quit medication several months after achieving clinical response and HBeAg seroconversion. As part of a consolidation therapy, an additional treatment period is required after HBeAg seroconversion to prevent relapse.[1] It is desirable to continue the nucleos(t)ide analogues for two additional years after complete remission (HBeAg seroconversion and HBV DNA clearance) is achieved. Furthermore, a longer consolidation period may be required, if HBeAg seroconversion is delayed or HBV DNA is detected again and remains positive by very low levels after complete remission.[6]

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