

Strategy to Overcome Drug Resistance That Develops during Treatment of Chronic Hepatitis B in Children

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Development of antiviral resistance to lamivudine is the most important factor for the treatment failure. It is necessary to establish proper guidelines to overcome drug resistance for children with chronic hepatitis B. Primary treatment with lamivudine should be considered if patients are in immune-clearance phase and have persistently elevated ALT levels more than twice the upper limit of normal value. Before initiating the therapy, careful consideration of the patient's status is required to exclude abnormal liver function tests due to other causes. The treatment option should be carefully decided to suppress the viral replication effectively. To obtain good compliance, clinicians should educate patients and their parents. Appropriate monitoring for virologic breakthrough and genotypic resistance is important in deciding to change the treatment plan. Sequential monotherapy should be avoided and a combination of drugs in other categories is recommended. New antiviral agents, such as entecavir and tenofovir, which have high potency and high genetic barrier, are soon expected to be available for use with children. (**Pediatr Gastroenterol Hepatol Nutr** 2012; 15: 63~73)

Key Words: Chronic hepatitis B, Antiviral agents, Drug resistance, Children

INTRODUCTION

The rate of HBsAg positivity in Korean children in 2007 was 0.2% of preschool children and 0.44% of early teenaged students [1]. Currently, the therapeutic options for childhood chronic hepatitis B infection include the nucleoside analog lamivudine. Lamivudine treatment results in the development of mutant strains, leading to drug resistance in a significant number of patients with chronic hepatitis B

infection. For adult patients, lamivudine is not recommended as the first-line treatment because of its high incidence of viral resistance [2]. However, entecavir, which is more potent and has lower frequency of resistance than lamivudine, has not been covered in children younger than 16-years-of-age by medical insurance in Korea.

As the development of mutant virus affects additional resistance and cross resistance, prevention and control strategies are important. Studies on the treat-

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ment of chronic hepatitis B in children are insufficient globally, so that it is necessary to establish proper guidelines to overcome drug resistance for children.

WHY TREAT?

In Korea, childhood chronic hepatitis B infection occurs mainly due to maternal perinatal transmission. Most children with chronic hepatitis B who are infected at birth are in an immune-tolerant phase, with high viral replication, positive HBeAg, high hepatitis B virus (HBV) DNA levels, and normal levels of aminotransferases before becoming active hepatitis (Fig. 1). Infected children may stay in the immune-tolerant phase until adulthood, but nearly half go into immune-clearance phase during childhood [3].

Most children with chronic hepatitis B are asymptomatic or in good clinical course. But, in contrast to cases infected in adults, they are likely to experience persistent infection or have chances to develop long-term serious sequelae such as liver cirrhosis and hepatocellular carcinoma (HCC) [4]. Many Asian countries have reported the cases of HCC in young children [5,6]. They may have experienced severe, protracted active hepatitis because their laboratory data shows that they are in late immune-clearance phase or inactive carrier state. Our center experienced a case of a 14-year-old boy who died of hepatoma rupture. One Korean study about primary hepatic tumor of childhood has reported that HBsAg

was positive in 13% of hepatoblastoma cases and 80% of HCC cases [7]. According to a report of 99 patients with chronic hepatitis B patients in a long-term follow-up, HCC developed in two patients, with an age at onset of 9 and 16 years [8].

We investigated the cumulative proportion of the transition to immune-clearance phase, and found that 40% of patients had proceeded to active hepatitis before the age of 18 years [3]. Therefore, proper management should be considered in children with chronic hepatitis B in the early immune-clearance phase.

WHO TO TREAT?

The therapeutic target of chronic hepatitis B is the patient in an immune-clearance phase with active viral replication and inflammation with fibrosis (Fig. 1) [4,9-11]. If the immune-clearance phase is longer or severe, the clinical course would be worse [12]. We believe that early management is necessary to reduce necroinflammation and fibrosis during active hepatitis [13].

Antiviral medication was not or less effective in the patients with normal or slightly elevated ALT [11,14], whereas patients with high aminotransferase level ($>2 \times$ upper limits of normal value, ULN) had good clinical outcome with antiviral treatment [15-17]. In addition, these patients had lower lamivudine resistance rate than patients with low aminotransferase level ($<2 \times$ ULN) [18]. So, treatment in the immune-tolerant phase is ineffective and unnecessary,

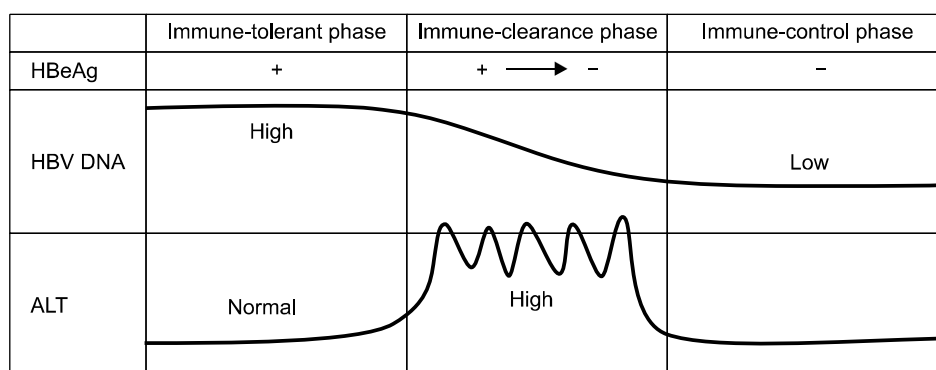


Fig. 1. The natural course of chronic hepatitis B virus infection. The figure is modified from one presented in reference [78].

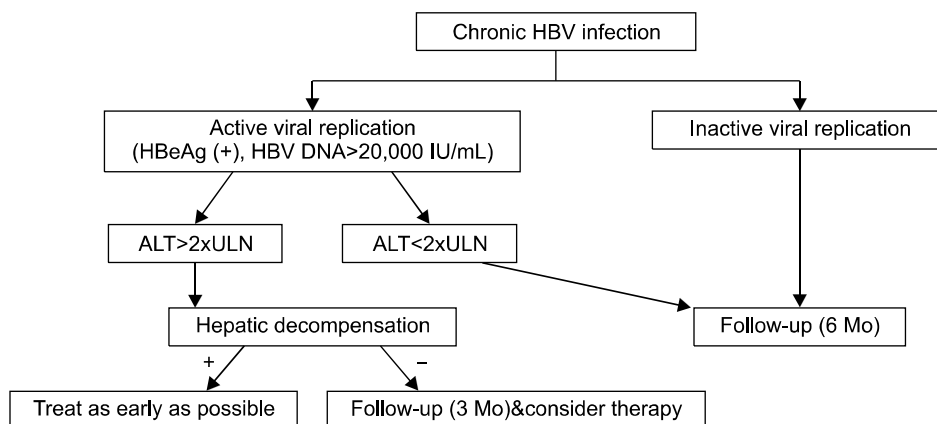


Fig. 2. Recommended flow of initial treatment of chronic hepatitis B in children. The figure has been adapted from reference [4]. ULN denotes upper limits of normal value.

which eventually results in drug resistance.

If the ALT level has been elevated continuously in children with immune-clearance phase, serum HBV DNA should be checked to confirm the level of viral replication. The patient with positive HBeAg should be considered to be treated if their ALT level is higher ($>2 \times \text{ULN}$) and HBV DNA is more than 20,000 IU/mL [4]. Very high serum ALT level ($>5 \times \text{ULN}$) with low HBV DNA may result in natural HBeAg seroconversion, so that observation for 3 months may be permitted if there is no evidence of hepatic decompensation. However, patients with hepatic decompensation should be treated as soon as possible (Fig. 2) [4].

Although treatment is recommended for patients with moderate to severe necroinflammation or having worse than periportal fibrosis, liver biopsy is not considered to be essential in children. But, it could be performed to determine the exact histologic status and to exclude other etiologies of hepatitis [4].

In obese children, ALT levels can be elevated due to non-alcoholic fatty liver disease [19], and reactive hepatitis associated with systemic infections including pneumonia, bronchiolitis, and urinary tract infection can be a cause of elevated ALT level. Wilson disease, muscle disease, drugs, and herbs also can cause abnormal ALT level [20,21]. Evaluation and close follow-up of elevated ALT is required to avoid treating children in immune-tolerant phase who have elevated liver enzymes associated with other causes.

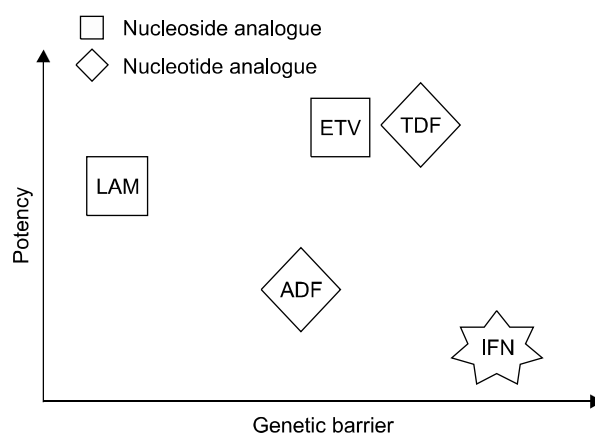


Fig. 3. Antiviral potency and genetic barrier of antiviral drugs. LAM: lamivudine, ETV: entecavir, TDF: tenofovir, ADF: adefovir.

WHAT TO TREAT WITH?

Key factors to consider in making treatment decisions are efficacy, durability, safety, tolerability, cost, barrier to resistance, genotype, hepatic synthetic function, and resistance/mutation profile, as some characters and so on [22].

As a first-line treatment, adult guidelines recommend using pegylated interferon alpha-2a or a nucleos(t)ide analogue, which have potent antiviral effects and low resistance rate, such as entecavir or tenofovir. However, only interferon alpha and lamivudine are available as a first-line treatment in children, although lamivudine has a low genetic barrier (Fig. 3). Entecavir is only used for adolescents over

16-years-of-age [23-25].

Lamivudine monotherapy in Korean children

In one study, lamivudine was superior to interferon in children in year 2 after the initiation of treatment (HBeAg seroconversion rate 65% versus 37%) [20]. Although lamivudine is safe and effective in children, it is quite hampered by a high frequency of development of resistance. Interferon has some limitations because it has many adverse events and is less effective in genotype C [26].

In a Korean adult study, cumulative HBeAg seroconversion rate at months 12, 24 and 36 after the initiation of lamivudine treatment was 30.2%, 38.8%, and 42.4%, respectively [27].

In children with chronic hepatitis B, the HBeAg seroconversion rate was 65% at 2 years after the initiation of treatment (89% in children with age < 7 years, 43% with age ≥ 7 years) [20]. Other studies in Korean children showed similar results. HBeAg seroconversion (mean follow-up duration 23.8 months) was 42% in one study (60% in children with age < 6 years, 38% at age ≥ 6 years) [28], and 48% in another study (mean follow-up duration 35.0 months; 46% in children with age < 7 years, and 50% with age ≥ 7 years) [29].

In terms of HBsAg seroconversion, we have demonstrated that 20% of children had seroconversion at 2 years after the initiation of treatment (42% in children with age < 7 years, 0% with age ≥ 7 years) [20]. Another Korean study also revealed similar results. In a mean follow-up duration of 35.0 months, 14% of the total children had HBsAg seroconversion (23% in children with age < 7 years, 0% with age > 7 years) [29]. The results indicate that the younger the patients are, the better therapeutic effect we can expect.

Combination therapy

Combination therapy in adults conducted until now has been shown to be not superior to monotherapy [30-34]. Lamivudine + adefovir combination therapy was not more effective than monotherapy [35]. Likewise, interferon + lamivudine combination therapy was not superior to interferon monotherapy

[30-34], as well as in studies for children [36,37]. There are few reports about lamivudine + adefovir combination therapy for children. Until now, combination therapy has not been recommended for first-line treatment of chronic hepatitis B [2].

Combination therapy for initial treatment can be useful in special circumstances, such as for patients with high risk of emergence of viral resistance (chronic infection, presence of viral resistance before the initiation of treatment) or the patients whose life could be threatened by aggravation of hepatitis (i.e., patients with liver cirrhosis or post-liver transplantation state) [38].

WHEN TO STOP?

After the occurrence of HBeAg seroconversion, additional antiviral therapy is needed for at least one more year to prevent relapse in HBeAg positive chronic hepatitis B [39].

In HBeAg negative chronic hepatitis B patients, it is recommended to treat with an oral antiviral agent until HBsAg loss occurs, because the moment of HBeAg seroconversion does not appear [2]. Practically, we can consider stopping treatment after 2 ~ 3 years of additional treatment if there is no breakthrough after clearance of serum HBV DNA, because HBsAg loss rarely occurs [40].

HOW TO TREAT LAMIVUDINE RESISTANCE?

Rescue therapies for lamivudine-resistance involve adding the second drug without cross-resistance or switching to a more potent drug.

If virologic breakthrough develops despite good compliance with therapy, the resistance mutation test should be performed and the treatment regimen needs to be changed according to the result [41]. To avoid the development of cross resistance, nucleotide analogs are added to nucleoside analogs, and vice versa. This kind of combination therapy can reduce the possibility of the development of additional drug resistance [2].

Virologic breakthrough is the first noticeable sign to detect the antiviral resistance during nucleos(t)ide analogue treatment. As HBV DNA level of patient continues to increase, it is usually followed by biochemical breakthrough [42].

If early suppression of viral replications are not satisfactory, resistant strains emerges because of long lasting high viral load, which requires long-term treatment, that could result in virologic breakthrough [43]. Once resistant strain is developed, additional treatment should be given as early as possible to interrupt viral replication. Treatment strategy should be changed immediately if biochemical breakthrough develops [44]. Monitoring for HBV DNA level is recommended every 3 months during treatment.

On treatment monitoring

It is well known that drug resistance is associated with HBV DNA titer at week 24 after the initiation of lamivudine treatment [45-47]. Yuen et al. studied the positive relationship between lamivudine resistance and HBV DNA level for 159 Chinese HBeAg positive patients. This study revealed that the resistance incidence 2 years later was 8%, 13%, 32%, and 64% in the group of < 200 copies/mL, $200 \sim 10^3$ copies/mL, $10^3 \sim 10^4$ copies/mL, and 10^4 copies/mL of HBV DNA at 24 weeks, respectively [46]. Therefore, the treat-

ment response at 24 weeks is crucial to decide further treatment strategy.

The patient with complete virologic response has a very low risk of resistance [45-47]. In that case, the clinician should treat with the same regimen and monitor the response every 3 ~ 6 months [48,49].

In primary non-response, virologic breakthrough or partial virologic response, resistance testing has to be performed. If a resistant strain develops, combination therapy using drugs without cross-resistance is recommended. If not, treatment should be switched to the more potent antiviral agent with the lowest resistance rate (Fig. 4) [50,51]. Unfortunately, the Korean National Medical Insurance does not approve funding of treatment change depending on the response at week 24. The insurance program allows drug-change only if virologic breakthrough or resistance is confirmed [25].

Adefovir add-on therapy

Adefovir can be added to lamivudine in the rescue therapy of lamivudine resistance [52-54]. Several studies for adult patients with lamivudine resistance showed that switching to adefovir monotherapy induced the high incidence of adefovir resistance (18% at 1 year, 65% at 5 years) [55,56]. Later studies reported that lamivudine + adefovir combination therapy reduced the incidence of adefovir resistance and

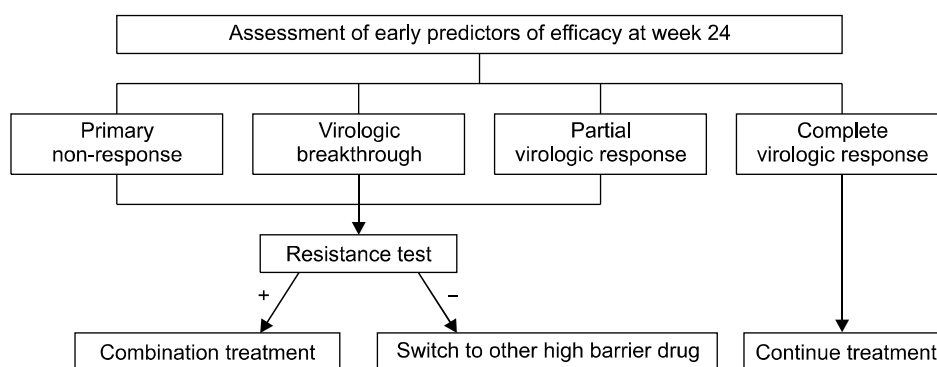


Fig. 4. Recommending flow of lamivudine treatment in adults. The figure is modified from reference [2]. Primary non-response is defined as a decrease in serum HBV DNA $< 2 \log_{10}$ (IU/mL) after 6 months of therapy. Virologic breakthrough is defined as an increase in serum HBV DNA of more than $1 \log_{10}$ (IU/mL) compared to lowest value. Partial virologic response is defined as a decrease in serum HBV DNA of more than $2 \log_{10}$ (IU/mL) but detectable HBV DNA by real-time PCR assay. Complete virologic response is defined as a decrease in serum HBV DNA to undetectable level by real-time PCR assay.

was more effective than adefovir monotherapy in the suppression of HBV replication [22,57-61]. Our study for children also have revealed the same results [43]. Low HBV DNA level at the time of start of the combination therapy was a good predictor for better results [61,62]. Recent studies have also shown that lower basal viral load is associated with complete virologic response [57,61,63]. Moreover, early intervention is associated with the low incidence of lamivudine resistance [45-47]. Yuen et al. reported that resistance rate was 12% in the group of ≤ 3 log as basal HBV DNA level, whereas it was 64% in the group of ≥ 4 log [46].

Switch therapy to entecavir

Entecavir is a more potent and effective drug, with a high genetic barrier to resistance in nucleoside-naïve patients [23,63-66]. As cross-resistance exists between entecavir and lamivudine, a high dose of entecavir is required for the rescue therapy.

The development of entecavir resistance is explained as a two-hit mechanism. Entecavir resistance develops when the lamivudine resistant HBV with two mutations (rtL180M, rtM204V/I) acquires an additional mutation [67-69]. Considering wild-type HBV suppression, the results of entecavir treatment in children were more potent than the suppression in adults [58,70,71].

However, a high incidence of entecavir resistance in lamivudine-refractory patients has been documented. Tenny et al. reported that entecavir resistance rate in 5-year treatment was only 0.8% in nucleoside-naïve patients, but 43% in lamivudine-refractory patients [43]. These results suggested that entecavir is inappropriate for treatment of patients with lamivudine-resistance. Nevertheless, Chu et al. revealed that the virologic response rate for children, of whom the majority had one mutation, was 37.5% at 24 weeks and 50% at 48 weeks, compared with 7.7 ~ 33.3% at 24 weeks and 22.0 ~ 54.5% at 48 weeks for adult patients, although the children had higher baseline HBV DNA load than adults [43].

Lamivudine + adefovir combination therapy has been proven to have a more potent antiviral effect than entecavir monotherapy [71,72]. Even though

entecavir has a good effect on initial viral suppression, entecavir alone has a relatively high resistance rate in lamivudine-resistant patients and is considered to be less effective than lamivudine + adefovir combination therapy. Therefore, entecavir monotherapy is not optimal in patients with lamivudine resistance [2].

Rescue therapy in children

As rescue therapy for lamivudine resistant cases, adding-on adefovir or tenofovir or switching to truvada (a combination pill containing emtricitabine and tenofovir) is recommended by adult guidelines (Table 1). However, guidelines for children have not been established. Moreover, tenofovir and emtricitabine are not approved yet for children with chronic hepatitis B by the Food and Drug Administration (FDA).

We have also shown that lamivudine + adefovir combination therapy is more effective than adefovir monotherapy in children with lamivudine-resistant chronic hepatitis B infection [43]. These results were similar to those in adults [57,58,70].

An expert meeting report concluded that rescue therapy for children with lamivudine-resistant chronic hepatitis may be decided according to the severity of liver disease. Clinicians could stop the treatment for the non-severe cases and monitor flare-up, while for children with severe hepatitis, second drug such as adefovir should be added or switching to in-

Table 1. Treatment Guidelines in Lamivudine Resistance

KASL 2011	Add ADV or TDF Switch to TDF or PEG-IFN
EASL 2009	Add TDF (ADV if TDF not yet available)
AASLD 2009	Add ADV or TDF Switch to Truvada*
APASL 2008	Add ADV Switch to ETV or IFN-based therapy

*Truvada, a combination pill containing emtricitabine and tenofovir. KASL: The Korean Association for the Study of the Liver, EASL: European Association for the Study of the Liver, AASLD: American Association for the Study of the Liver Disease, APASL: Asian Pacific Association for the Study of the Liver, ADV: Adefovir, TDF: tenofovir, IFN: interferon, ETV: entecavir.

interferon-alpha considered [19].

HOW TO PREVENT NUCLEOS(t)IDE ANALOGUE RESISTANCE

In adult patients, the resistance rate for lamivudine therapy was 14~32% and 60~70% for 1 year and 5 years, respectively [73,74]. However, in children, the resistance rates were reported as low as 10% at 1 year of treatment and 23% at 2 years of treatment [20]. Other studies in Korean children have shown similar results [29,75]. Most of the children enrolled in these studies had pretreatment baseline ALT > 2×ULN. On the other hand, Sokal et al. have revealed that resistance rates were 49% and 64% in 2-year treatment and 3-year treatment, respectively [76]. These were similar or even higher than those of adults. The reason for the dichotomy may be explained by the inclusion of 51% of children with pretreatment ALT > 2×ULN for the 2-year treatment group and only 11% for the 3-year treatment group. Our studies also have shown that breakthrough rate was higher (60%) in the group of ALT < 2×ULN compared with 17% in the group of ALT > 2×ULN as pretreatment baseline [18]. Moreover, breakthrough was not found in preschool children younger than 6-years-of-age with higher pretreatment baseline ALT > 2×ULN [9]. Therefore, elevated pretreatment ALT level over 2×ULN is regarded as an important factor to reduce drug resistance.

Primary treatment with lamivudine should be considered if patients have persistently elevated ALT levels > 2×ULN, but patients should be in the immune-clearance phase. Before initiating therapy, a thorough evaluation of the patient's status regarding abnormal liver function tests is essential to exclude other causes, such as reactive hepatitis and non-alcoholic steatohepatitis, as two conditions. The treatment should focus on inhibiting viral replication in the early phase of treatment. Appropriate monitoring for early detection of virologic breakthrough and genotypic resistance is essential to decide the optimal intervention. The sequential monotherapy using drugs in the same category should be avoided and

combination therapy with drugs in other categories is recommended.

Approximately 30% of the causes of viral breakthrough are due to poor compliance of patients [77]. Clinicians should educate patients and their parents to maintain good compliance and should adjust the optimal dosage according to body weight as children grow.

CONCLUSION

Currently, the medications for the treatment of children with chronic hepatitis B infections are interferon-alpha and lamivudine. In Korea, a genotype C predominant country, lamivudine is more effective than interferon-alpha. However, development of antiviral resistance to lamivudine is a major problem that is regarded as the most important factor for treatment failure. Therefore, it should be understood that appropriate prevention and rescue therapy of antiviral resistance are critical for improving treatment outcomes. Entecavir and tenofovir need to be approved as the primary treatment option for chronic hepatitis B in children.

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