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Lamivudine resistance in children with chronic hepatitis B

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Abstract

Currently, although lamivudine (LAM) has a low genetic barrier, only interferon-alpha and LAM are available as a first-line treatment in children with chronic hepatitis B (CHB). LAM is a potent inhibitor of hepatitis B virus-deoxyribonucleic acid (HBV-DNA) polymerase replication by termination of the proviral HBV-DNA chain. LAM has a good safety and tolerability profile in CHB patients with hepatic decompensation. However, the main disadvantages of this HBV reverse transcriptase inhibitor are: (1) pre-existing covalently closed circular DNA cannot be eradicated by LAM, thus relapse after therapy withdrawal is frequent; and (2) although the longer LAM treatment induced the higher seroconversion rate, the risk of viral resistance increased through the selection of YMDD (tyrosine, methionine, aspartate, aspartate) motif. Insufficient suppression of viral replication leads to the emergence of resistant strains that could result in virological breakthrough which is usually followed by biochemical breakthrough. Mutant strains affects additional resistance and cross resistance, leading to drug resistance in a significant number of CHB patients. In this case, efficacy of more powerful anti-viral agents with higher genetic barrier against development of resistance is diminished. Furthermore, strains that are resistant to LAM could bring about vaccine escape mutants, decreasing the efficacy of HBV vaccine. A more potent drug with a high genetic barrier to resistance needs to be approved as the first-line treatment option for CHB in children.

Key words: Children; Chronic hepatitis B; Lamivudine; Lamivudine-resistant mutants; *YMDD* mutation

Core tip: In present day, antiviral drugs with higher genotypic barrier to resistance cannot be used for children with chronic hepatitis B since these drugs are not covered by the general health insurance in many countries. Therefore, lamivudine (LAM) which is not used for adults due to its many drawbacks has been used as a first-line of treatment for children out of necessity. Even though long term treatment results with LAM appear to be good, long term treatment increases the possibility of occurrence of resistant strains. These strains which are resistant to LAM could develop cross resistance to other anti-viral agents.

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INTRODUCTION

Approximately 400 million human are globally affected by chronic hepatitis B virus (HBV) infection. There is a high risk of developing serious complications such as cirrhosis and liver cancer in these people. Despite the development of new therapies using antiviral agents fighting chronic hepatitis B (CHB) remains to be a major clinical challenge. Interferon-alpha (IFN-α), lamivudine (LAM), adefovir, entecavir and lately tenofovir are all amongst the approved drugs for medical care of children affected by CHB. IFN-α for 12 mo and older children; LAM initiating at 3 years of age; adefovir and tenofovir in children 12 years and older; and entecavir initiating from 16 years of age are used[1]. Even though LAM is the primary antiviral drug officially accepted in present day for children with CHB less than 12 years old, use of antiviral drugs with a high genetic barrier against the emergence of resistance (such as entecavir and tenofovir) are not practiced for children with HBV because these drugs are not covered by the general health insurance in many countries.

CLINICAL ASPECTS OF LAM RESISTANCE IN CHILDREN

LAM, a nucleoside analogue has been officially accepted for treatment of CHB infection by United States Food and Drug Administration in 1998. LAM is found to be effective in suppression of HBV-DNA, normalizing aminotransferase values and improving histologic activity index. However, hepatitis B e antigen (HBeAg) seroconversion is not always resulted from LAM treatment[1,2]. Choe *et al*[3] found that HBeAg seroconversion developed in 34% of children with CHB within one year after initiation of LAM treatment. The probability of response to LAM treatment increases with high aminotransferase levels and high histologic activity index at baseline. Hom *et al*[4] found out that there is no significance of age, gender, previous IFN therapy, baseline weight, HBV-DNA, and body mass index in prediction of response to LAM treatment in children with CHB. However, Hong *et al*[5] showed that high aminotransferase levels affect the HBeAg seroconversion as well as younger age in children with long-term LAM treatment. Figlerowicz *et al*[6] reported that pretreatment serum HBV-DNA level is related to seroconversion of HBeAg and sustained viral response rate. Although LAM is a potent antiviral drug in the treatment of HBV, it does not help to purify liver from covalently closed circular DNA integrated into the cell nuclei. Covalently closed circular DNA brings about continued presence of HBV in liver cells[1,2]. Therefore, after stopping LAM treatment HBV replication may return to pretreatment levels. In fact, it has been reported that relapse rates varied from 19% to 62% after cessation of treatment with LAM[7]. Kansu *et al*[8] reported that relapse rates of 6.8% in children treated with combined IFN-α2a and LAM. Jonas *et al*[9] determined a relapse rate of 17.5% in a placebo controlled LAM trial in children. Hagmann *et al*[10] found relapse rate of 25% after cessation of LAM treatment. It is likely that duration of LAM treatment would be a culprit for the variations in relapse rates. Choe *et al*[3] reported long term LAM treatment increased HBeAg seroconversion rates more than IFN treatment. This is especially seen in pre-school children. High relapse rates have been observed when LAM treatment is discontinued before and right after HBeAg seroconversion. Because of this, treatment should continue possibly 12 mo after HBeAg seroconversion is observed. Nevertheless, major limitation of prolonged LAM therapy is formation of resistant mutants[1,5]. It is recognized that resistance to LAM develops as a result of emerging mutations which are formed in catalytic part of the reverse transcriptase YMDD [(Y) tyrosine, (M) methionine, (D) aspartate, (D) aspartate]. In *YMDD* mutation formations, methionine is replaced with valine (rtM204V), isoleucine (rtM204I) or rarely serine (rtM204S). In these mutations, rtM204V is always together with rtL180M which is a compensating mutation. This mutation partially restores replication fitness of HBV. However, it has been shown that rtM204I differentiation is independent from rtL180M. In addition, rtV173L differentiation which is found in some samples resistant to LAM, increased replication capacity of HBV[11]. Resistance to LAM causes absence of HBV-DNA suppression and eventually advancement of liver disease. However, replication capacity of *YMDD* mutants is less than the wild virus. Because of this, lower aminotransferase and HBV-DNA levels can be found in YMDD mutant virus infections[12]. Hartman *et al*[13] showed that 54% of the *YMDD* mutants were maintained normal aminotransferase values. After development of LAM resistance, usually serum HBV-DNA becomes positive (virologic breakthrough) and then serum alanine aminotransferase level increases (biochemical breakthrough). Mutant strains generally emerge after 6 mo of therapy with LAM. Resistance rates of 38%, 49% and 65% have been reported at 2, 3 and 5 years of therapy with LAM[14]. In a multicenter trial carried out by Jonas *et al*[9], the *YMDD* mutation was detected in 19% of children who had undergone LAM therapy for 52 wk. No LAM resistance mutations were identified in the placebo group during the first year of this study. Sokal *et al*[15] found YMDD mutation rates of 49% and 64% in second and third year of treatment, respectively. Hartman *et al*[16] found LAM resistant mutants in 11 of 17 (65%) children at the end of the first year of LAM treatment. Interestingly, *YMDD* mutation rate of this study was extremely higher than other studies. Hagmann *et al*[10] reported development of clinical resistance to LAM in 3 children (19%) in the first year of therapy. Furthermore, in this study, frequency of drug resistance is found to be low in children with high HBV-DNA suppression level. Hong *et al*[5] reported breakthrough in 25.9% (21 out of 81) of patients treated with LAM. These patients were followed up for more than 1 year. Lee *et al*[17] reported viral breakthrough in 12 children (27%) during the therapy and documented

YMDD mutation in 11 children (25%). In this study, average time for development of mutation was 22.7 mo. Ni *et al*[18] found mutant strains in 34% of the children after 12 mo of therapy with LAM. In this study, higher resistance rates were found compared to other studies. Akman *et al*[19] reported YMDD mutants in 58.4% of the total 24 children treated with LAM for 30 ± 10 mo. Choe *et al*[3] found viral breakthrough developed 10% in the first year and 23% in the second year of LAM treatment. In this study, *YMDD* mutation was found in 9 of 11 patients who have developed breakthrough. Liberek *et al*[20] determined mild and temporary aminotransferase increase in 4 out of 59 children with CHB and 2 children with *YMDD* mutation between third and twelfth months of LAM treatment. Koh *et al*[21] reported breakthrough and relapse rates in 10% and 3.3% of children with CHB after 52 mo with LAM therapy. In this study, although the exact reason of lower breakthrough and relapse rates are not known, clinical characteristics of patients and differences in treatment schedule could be reasons for this phenomenon.

Resistance to LAM increases with longer treatment periods. Therefore, LAM therapy should be discontinued 6 mo after HBeAg seroconversion or appearance of *YMMD* mutations[1]. On the other hand, higher proportion of LAM resistance is associated with higher viral load after first 6 mo of therapy[22]. It has been shown that complete virologic response reduces the risk of resistance to LAM. Yuen *et al*[23] established a relationship between high HBV-DNA level and alanine aminotransferase level at beginning with the emergence of YMDD mutations. Paik *et al*[24] determined a significant relationship between the *YMDD* mutations emerging at three months with viral breakthrough. In another study, after 12 mo of LAM treatment, Yuen *et al*[25] showed no significant differences exist in virologic response and *YMDD* mutant rates between patients with genotypes B and C. Contrary to this study, Kobayashi *et al*[26] showed development of *YMDD* mutants was influenced by HBV genotypes in patients with CHB. Numerous studies have been performed to determine whether a combination regimen with LAM and IFN-α prevents or delays the emergence of *YMDD* mutants. There are conflicting results in literature regarding this matter. In accordance with a study conducted by Chan *et al*[27], a lower LAM resistance was found in combination treatment with pegylated-IFN and LAM (21%) compared with LAM monotherapy (40%). However, Marrone *et al*[28] showed risk for emergence of LAM resistance was not reduced with IFN and LAM combination treatment. It is possible that older patients and moderately high aminotransferase levels prior to treatment in the study of Chan *et al*[27] could have caused the differences between these two studies. Furthermore, results may have been affected in favor of the combination therapy since Chan *et al*[27] conducted combination of LAM with IFN eight weeks longer than monotherapy with LAM. Ozgenç *et al*[29] determined high breakthrough incidence in children with partial response to long-term LAM therapy. In this study, reported breakthrough rates of LAM were 13.3%, 69.4%, and 82.4% in 1, 2, and 3 years, respectively. Kansu *et al*[8] reported breakthrough rates of 17.9% in simultaneous therapy group and 24.6% in sequential therapy group. Yilmaz *et al*[30] did not find breakthrough in any patient that could suggest *YMDD* mutation. Selimoglu *et al*[31] reported breakthrough in 11 (23.4%) children treated with IFN-α and LAM combination therapy. In another combination treatment of IFN-ɑ and LAM, Dikici *et al*[32] demonstrated no viral breakthrough with the exception of one patient during the follow-up period after the treatment. The viral breakthrough for this child was accepted as an *YMDD* mutation. Kuloğlu *et al*[33] reported breakthrough and *YMDD* mutant rates of 65.8% and 55.2% respectively with combined IFN-α and long term LAM therapy. Saltik-Temizel *et al*[34] provided no information about viral breakthrough rates in their article on combination therapy with LAM and high-dose IFN-α. Results from different treatment regimens are presented in Table 1.

In accordance with the results of these studies, avoiding unnecessary use of antiviral drugs can help to reduce resistance. Therefore, LAM should be prescribed only for patients with good predictors of response. If there is no finding for resistance to LAM, children should be treated for one year. However, there may be a need for longer treatment[35]. Although the optimal duration of therapy is not well-established, patients should be treated for at least six more months after HBeAg seroconversion[36]. Treatment may be discontinued in those who have HBV-DNA replication or mutant strains[37]. High HBV-DNA load before treatment was shown to be an important factor causing virologic breakthrough. Early suppression of viral replication plays a key role for prevention of LAM resistance. Insufficient response to LAM therapy with persistence of viremia can increase the resistance[38]. On the other hand, an elevated pretreatment alanine aminotransferase level (more than twofold the upper normal limit) is a key factor reducing the LAM resistance[39]. Patients who have not achieved a complete virologic response (partial response) to LAM at week 24, switching to a more potent antiviral agent or add-on another antiviral agent without cross-resistance profile is the only useful treatment approach[40]. Treatment guidelines for children have not been established yet. However, in case of failure with LAM therapy, addition of adefovir or switching to either adefovir or entecavir therapies should be considered in older children.

LAM RESISTANCE IN PREVIOUSLY UNTREATED PATIENTS WITH CHB

Because HBV polymerase lacks of proofreading mechanism, spontaneous polymerase mutations occur naturally[1,2]. Therefore, YMDD motif variants can develop not only as secondary to LAM usage, but also

Table 1 Outcomes of different therapeutic regimens in children with chronic hepatitis B

Ref.	Therapeutic regimen	Duration of treatment	HBeAg seroconversion rate (%)	Relapse rate (%)	Breakthrough rate (%)
Jonas *et al*[9]	LAM	52 wk	26	18	19
Hagmann *et al*[10]	LAM	12[6] mo	50	25	19
Sokal *et al*[15]	LAM	24 mo	25	11	49
		36 mo	35	0	64
Hartman *et al*[16]	LAM	12[6] mo	18	0	65
Hong *et al*[5]	LAM	12 mo	60.5	NA	25.9
Lee *et al*[17]	LAM	12 mo	60	0	27
Ni *et al*[18]	LAM	12 mo	38	0	34
Akman *et al*[19]	LAM	32.3 ± 8.3 mo	20.8	NA	58.4
Choe *et al*[3]	LAM	12[6] mo	65	4	10[3]
					23[4]
Liberek *et al*[20]	LAM	12 mo	27.1	NA	3.38
Koh *et al*[21]	LAM	12[6] mo	42	3.3	10
Kansu *et al*[8]	LAM + IFN	6 m IFN	60.2[1]	6.8[1]	17.9[1]
		24 mo LAM	39.4[2]	0[2]	24.6[2]
Ozgenç *et al*[29]	LAM + IFN	6 mo IFN	15.6[3]	6.8[3]	13.3[3]
		12-36 mo	5.6[4]		69.4[4]
		LAM	0[5]		82.4[5]
Dikici *et al*[32]	LAM + IFN	6 mo IFN	37	3.7	3.3
		12 mo LAM			
Kuloğlu *et al*[33]	LAM + IFN	6 mo IFN	34.2	NA	65.8
		12[6] mo LAM			
Saltik-Temizel *et al*[34]	LAM + IFN	6 mo IFN	60	NA	NA
		12 mo LAM			

[1]Simultaneous therapy; [2]Sequential therapies; [3]First year; [4]Second year; [5]Third year; [6]Until HBeAg seroconversion or evidence of resistance. NA: Information was not given in the study; IFN: Interferon; LAM: Lamivudine; HBeAg: Hepatitis B e antigen.

it can naturally occur with a relatively high incidence in previously untreated patients with CHB[41]. Recently, the incidence of *YMDD* mutants in previously untreated patients from eight countries was found to be 12.2%[42]. It is important to investigate these mutations in primary LAM-nonresponsive patients. Although some correlation between virologic breakthrough during LAM therapy and previously presence of LAM-resistant mutants in untreated patients has been found, its clinical significance during LAM therapy is still unknown. However, there is a small possibility for these mutants to be dominant during HBV infection and CHB can effectively be treated with LAM. Lee *et al*[43] indicated that previously presence of LAM resistant mutants was rapidly cleared with LAM therapy in untreated CHB patients. Further researches are necessary to evaluate the influence of LAM-resistant mutants in previously untreated patients with CHB.

CROSS-RESISTANCE

Presently, medications such as adefovir, entecavir and, recently, tenofovir have been used for the treatment of adolescents with CHB[1]. However, only IFN-α and LAM are still available as a first-line treatment especially in young children at this time. In patients with LAM-resistance, sufficient suppression of HBV-DNA is not obtained and the incidence of resistance to adefovir is increased. It has been observed that adding adefovir to continued LAM therapy is found to be linked with lower adefovir resistance rates. Because only one additional substitution at T184, S202, and/or M250 is enough to emergence of entecavir resistance, the development of entecavir resistance occurs more easily in LAM-resistant patients than treatment-naïve patients[11]. After two years therapy, the resistance rates of entecavir have been increased (8%) in LAM-resistant patients[1]. Tenney *et al*[44] reported a low rate of entecavir resistance (0.8%) and a high rate of entecavir resistance (43%) in LAM-resistant patients after five years of therapy.

TREATMENT OF LAM-RESISTANT CHB IN CHILDREN

In case of virologic breakthrough, to avoid the emergence of cross resistance, a second antiviral agent without cross-resistance is added to LAM[1]. There have been no beneficial effects of using adefovir in children between 2 and 12 years of age. Therefore, adefovir was licensed for use in adolescents. Jonas *et al*[45] reported that early virologic response was a good predictor for emergence of resistance against adefovir. Both the combination of LAM with adefovir and entecavir monotherapy were found to be more effective by Chu *et al*[46] in suppressing HBV replication compared to adefovir monotherapy in LAM-resistant children. Ryu *et al*[47] reported that high baseline viral load was rapidly declined with entecavir monotherapy in LAM refractory children. However combination of LAM with adefovir was more effective in suppressing the viral load than entecavir.

LAM-ASSOCIATED VACCINE-ESCAPE MUTATIONS

Currently, there are two types of LAM-associated HBV mutants with antigenically modified HBsAg. In the genome organization of HBV, surface and polymerase genes overlap; and changes in the polymerase reverse transcriptase which involve LAM resistance substitutions may cause mutations [first type hepatitis B surface antigen (*HBsAg*) mutant] in the surface gene of HBV. A triple substitution pattern (V173L + L180M + M204V) of LAM resistance is associated with the changes (sE164D + sI195M) in the overlapping surface gene[48]. These mutants may act as a vaccine escape mutants (sG145R). As a result, those viruses which have mutated cannot be recognized and eliminated by existing monoclonal antibodies (anti-HBs). Because of the prolonged viral suppression with LAM treatment, the second type *HBsAg* mutants are emerged from the selection of surface antigen escape mutants[49]. The development of LAM resistant and HBsAg escape mutants is associated with decreased attachment of anti-HBs antibodies to HBsAg[50]. LAM-resistant *HBV* mutants with the capability to escape from anti-hepatitis B surface antibodies have the ability to infect individuals both vaccinated and unvaccinated for HBV. Therefore, it is imperative that physician weigh up the possible benefits and harms of treatment with LAM carefully.

CONCLUSION

Currently, LAM monotherapy is not used in adults because of very high recalcitrance rates. Similarly, most potent antiviral agents with optimal resistance profile should be used as first-line therapy in children. It is important to monitor early detection of virologic breakthrough and determine genotypic resistance to decide the optimal intervention. Monitoring the levels of HBV-DNA and determination of types of resistant strains would be necessary to establish therapeutic strategies. Because the LAM resistant viruses appear to be more prevalent in population, these mutants may become a potential serious public health problem.

In conclusion, there is a need to conduct further studies and new arrangements in general health insurance policies for use of the antiviral drugs which have strong antiviral effects and low resistance rates as first-line treatment in children with CHB.

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