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**Lamivudine resistance in children with chronic hepatitis B**

KasırgaE. Clinical importance of lamivudine resistance

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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). Lamivudine is a potent inhibitor of hepatitis B virus-deoxyribonucleic acid (HBV-DNA) polymerase replication by termination of the proviral HBV-DNA chain. Lamivudine 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 (cccDNA) cannot be eradicated by lamivudine, 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 hepatitis B virus 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

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**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 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 lamivudine appear to be good, long term treatment increases the possibility of occurrence of resistant strains. These strains which are resistant to lamivudine 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 moand 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 LAMIVUDINE RESISTANCE IN CHILDREN**

Lamivudine, 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, 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 cccDNA 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. Ozgenc *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. Selimoğlu *et al*[31] reported breakthrough in 11 (23.4 %) children treated with IFN-α and LAM combination therapy. In another combination treatment of IFN-α 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. Kuloglu *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.

**LAMIVUDINE RESISTANCE IN PREVIOUSLYUNTREATED PATIENTS WITH CHRONIC HEPATITIS B**

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 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 LAMIVUDINE-RESISTANT CHRONIC HEPATITIS B 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.

**LAMIVUDINE-ASSOCIATED VACCINE-ESCAPE MUTATIONS**

Currently, there are two types of lamivudine-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 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]. Lamivudine-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.

**REFERENCES**

1 **Williams JN**. A window on the future: can computerization help your practice? *Ky Dent J* 1990; **42**: 8-9 [PMID: 2370736 DOI: 10.1016/j.jhep.2013.05.016.7]

2 **Palumbo E.** Lamivudine for chronic hepatitis B in children. *Infect Dis Clin Prac* 2008; **16**: 13-15 [DOI: 10.1097/ipc.obo13e31815aa2dd]

3 **Choe BH**, Lee JH, Jang YC, Jang CH, Oh KW, Kwon S, Hyun MC, Ko CW, Lee KS, Lee WK. Long-term therapeutic efficacy of lamivudine compared with interferon-alpha in children with chronic hepatitis B: the younger the better. *J Pediatr Gastroenterol Nutr* 2007; **44**: 92-98 [PMID: 17204960 DOI: 10.1097/01.mpg.0000243439.47334.4e]

4 **Hom X**, Little NR, Gardner SD, Jonas MM. Predictors of virologic response to Lamivudine treatment in children with chronic hepatitis B infection. *Pediatr Infect Dis J* 2004; **23**: 441-445 [PMID: 15131468 DOI: 10.1097/01.inf.0000126412.93562.f5]

5 **Hong SJ**, Kim YH, Choe BH, Park HJ, Tak WY, Kweon YO. Current role of Lamivudine regarding therapeutic response and resistance in children with chronic hepatitis B. *Pediatr Gastroenterol Hepatol Nutr* 2013; **16**: 80-88 [PMID: 24010111 DOI: 10.5223/pghn.2013.16.2.80]

6 **Figlerowicz M**, Kowala-Piaskowska A, Filipowicz M, Bujnowska A, Mozer-Lisewska I, Słuzewski W. Efficacy of lamivudine in the treatment of children with chronic hepatitis B. *Hepatol Res* 2005; **31**: 217-222 [PMID: 15799860 DOI: 10.1016/j.hepres.2005.02.003]

7 **Lok AS**, McMahon BJ. Chronic hepatitis B. *Hepatology* 2001; **34**: 1225-1241 [PMID: 11732013 DOI: 10.1053/jhep.2001.29401]

8 **Kansu A**, Doğanci T, Akman SA, Artan R, Kuyucu N, Kalayci AG, Dikici B, Dalgiç B, Selimoğlu A, Kasirga E, Ozkan TB, Kuloğlu Z, Aydoğdu S, Boşnak M, Ertekin V, Tanir G, Haspolat K, Girgin N, Yağci RV. Comparison of two different regimens of combined interferon-alpha2a and lamivudine therapy in children with chronic hepatitis B infection. *Antivir Ther* 2006; **11**: 255-261 [PMID: 16640106]

9 **Jonas MM**, Mizerski J, Badia IB, Areias JA, Schwarz KB, Little NR, Greensmith MJ, Gardner SD, Bell MS, Sokal EM. Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; **346**: 1706-1713 [PMID: 12037150 DOI: 10.1056/NEJMoa012452]

10 **Hagmann S**, Chung M, Rochford G, Jani M, Trinh-Shevrin C, Sitnitskaya Y, Neumann AU, Pollack H. Response to lamivudine treatment in children with chronic hepatitis B virus infection. *Clin Infect Dis* 2003; **37**: 1434-1440 [PMID: 14614664 DOI: 10.1086/378739]

11 **Zoulim F**, Locarnini S. Management of treatment failure in chronic hepatitis B. *J Hepatol* 2012; **56** Suppl 1: S112-S122 [PMID: 22300461 DOI: 10.1016/S0168-8278(12)60012-9]

12 **Lai CL**, Dienstag J, Schiff E, Leung NW, Atkins M, Hunt C, Brown N, Woessner M, Boehme R, Condreay L. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis* 2003; **36**: 687-696 [PMID: 12627352 DOI: 10.1086/368083]

13 **Hartman C**, Berkowitz D, Shouval D, Eshach-Adiv O, Hino B, Rimon N, Satinger I, Kra-Oz T, Daudi N, Shamir R. Lamivudine treatment for chronic hepatitis B infection in children unresponsive to interferon. *Pediatr Infect Dis J* 2003; **22**: 224-229 [PMID: 12634582 DOI: 10.1097/01.inf.0000055062.64965.2e]

14 **Lok AS**, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; **125**: 1714-1722 [PMID: 14724824 DOI: 10.1053/j.gastro.2003.09.033]

15 **Sokal EM**, Kelly DA, Mizerski J, Badia IB, Areias JA, Schwarz KB, Vegnente A, Little NR, Gardener SD, Jonas MM. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. *Hepatology* 2006; **43**: 225-232 [PMID: 16440364 DOI: 10.1002/hep.21020]

16 **Hartman C**, Berkowitz D, Eshach-Adiv O, Hino B, Rimon N, Satinger I, Kra-Oz T, Shamir R. Long-term lamivudine therapy for chronic hepatitis B infection in children unresponsive to interferon. *J Pediatr Gastroenterol Nutr* 2006; **43**: 494-498 [PMID: 17033525 DOI: 10.1097/01.mpg.0000235982.34323.67]

17 **Lee EH,** Jang JY, Kim KM. Efficacy of lamivudine therapy for chronic hepatitis B in children. *Korean J Pediatr Gastroenterol Nutr* 2008; **11**: 130-136

18 **Ni YH**, Huang FC, Wu TC, Kong MS, Jeng YM, Chen PJ, Tsuei DJ, Chen HL, Hsu HY, Chang MH. Lamivudine treatment in maternally transmitted chronic hepatitis B virus infection patients. *Pediatr Int* 2005; **47**: 372-377 [PMID: 16091071 DOI: 10.1111/j.1442-200x.2005.02101.x]

19 **Akman SA**, Kose S, Halicioglu O. Lamivudine and adefovir resistance in children and young adults with chronic hepatitis B. *Int J Infect Dis* 2010; **14**: e236-e239 [PMID: 19665408 DOI: 10.1016/j.ijid.2009.04.002]

20 **Liberek A**, Szaflarska-Popławska A, Korzon M, Łuczak G, Góra-Gebka M, Łoś-Rycharska E, Bako W, Czerwionka-Szaflarska M. Lamivudine therapy for children with chronic hepatitis B. *World J Gastroenterol* 2006; **12**: 2412-2416 [PMID: 16688835 DOI: 10.3748/wjg.v12.i15.2412]

21 **Koh H**, Baek SY, Chung KS. Lamivudine therapy for korean children with chronic hepatitis B. *Yonsei Med J* 2007; **48**: 927-933 [PMID: 18159582 DOI: 10.3349/ymj.2007.48.6.927]

22 **Hong SJ,** Choe BH. Strategy to overcome drug resistance that develops during treatment of chronic hepatitis b in children. *Pediatr Gastroenterol Hepatol Nutr* 2012; **15**: 63-73 [DOI: 10.5223/pghn.2012.15.2.63]

23 **Yuen MF**, Sablon E, Hui CK, Yuan HJ, Decraemer H, Lai CL. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. *Hepatology* 2001; **34**: 785-791 [PMID: 11584376 DOI: 10.1053/jhep.2001.27563]

24 **Paik YH**, Han KH, Hong SP, Lee HW, Lee KS, Kim SO, Shin JE, Ahn SH, Chon CY, Moon YM. The clinical impact of early detection of the YMDD mutant on the outcomes of long-term lamivudine therapy in patients with chronic hepatitis B. *Antivir Ther* 2006; **11**: 447-455 [PMID: 16856618]

25 **Yuen MF**, Wong DK, Sablon E, Yuan HJ, Sum SM, Hui CK, Chan AO, Wang BC, Lai CL. Hepatitis B virus genotypes B and C do not affect the antiviral response to lamivudine. *Antivir Ther* 2003; **8**: 531-534 [PMID: 14760886]

26 **Kobayashi M**, Suzuki F, Akuta N, Suzuki Y, Arase Y, Ikeda K, Hosaka T, Sezaki H, Kobayashi M, Iwasaki S, Sato J, Watahiki S, Miyakawa Y, Kumada H. Response to long-term lamivudine treatment in patients infected with hepatitis B virus genotypes A, B, and C. *J Med Virol* 2006; **78**: 1276-1283 [PMID: 16927289 DOI: 10.1002/jmv.20701]

27 **Chan HL**, Leung NW, Hui AY, Wong VW, Liew CT, Chim AM, Chan FK, Hung LC, Lee YT, Tam JS, Lam CW, Sung JJ. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. *Ann Intern Med* 2005; **142**: 240-250 [PMID: 15710957 DOI: 10.7326/0003-4819-142-4-200502150-00006]

28 **Marrone A**, Zampino R, Portella G, Grimaldi M, Durante-Mangoni E, Santarpia L, Ruggiero G, Utili R. Three-phase sequential combined treatment with lamivudine and interferon in young patients with chronic hepatitis B. *J Viral Hepat* 2005; **12**: 186-191 [PMID: 15720534 DOI: 10.1111/j.1365-2893.2005.00619.x]

29 **Ozgenç F**, Arikan C, Sertoz RY, Nart D, Aydogdu S, Yagci RV. Effect of long-term lamivudine in chronic hepatitis B virus-infected children. *Antivir Ther* 2004; **9**: 729-732 [PMID: 15535410]

30 **Yilmaz A**, Akcam M, Gelen T, Artan R. Lamivudine and high-dose interferon alpha 2a combination treatment in naïve HBeAg-positive immunoactive chronic hepatitis B in children: an East Mediterranean center's experience. *Eur J Pediatr* 2007; **166**: 195-199 [PMID: 16944240 DOI: 10.1007/s00431-006-0220-2]

31 **Selimoglu MA**, Aydogdu S, Unal F, Zeytinoglu A, Yüce G, Yagci RV. Alpha interferon and lamivudine combination therapy for chronic hepatitis B in children. *Pediatr Int* 2002; **44**: 404-408 [PMID: 12139566 DOI: 10.1046/j.1442-200X.2002.01589.x]

32 **Dikici B**, Bosnak M, Kara IH, Dogru O, Dagli A, Gürkan F, Haspolat K. Lamivudine and interferon-alpha combination treatment of childhood patients with chronic hepatitis B infection. *Pediatr Infect Dis J* 2001; **20**: 988-992 [PMID: 11642634 DOI: 10.1097/00006454-200110000-00013]

33 **Kuloğlu Z**, Kansu A, Erden E, Girgin N. Efficacy of combined interferon alpha and long-term lamivudine therapy in children with chronic hepatitis B. *Turk J Pediatr* 2010; **52**: 457-463 [PMID: 21434529]

34 **Saltik-Temizel IN**, Koçak N, Demir H. Lamivudine and high-dose interferon-alpha combination therapy for naive children with chronic hepatitis B infection. *J Clin Gastroenterol* 2005; **39**: 68-70 [PMID: 15599215]

35 **Chen EQ**, Tang H. Optimization therapy for the treatment of chronic hepatitis B. *World J Gastroenterol* 2014; **20**: 5730-5736 [PMID: 24914334 DOI: 10.3748/wjg.v20.i19.5730]

36 **Paganelli M**, Stephenne X, Sokal EM. Chronic hepatitis B in children and adolescents. *J Hepatol* 2012; **57**: 885-896 [PMID: 22634122 DOI: 10.1016/j.jhep.2012.03.036]

37 **Jonas MM**, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, Narkewicz MR, Rosenthal P, Schwarz KB, McMahon BJ. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. *Hepatology* 2010; **52**: 2192-2205 [PMID: 20890947 DOI: 10.1002/hep.23934]

38 **Della Corte C**, Nobili V, Comparcola D, Cainelli F, Vento S. Management of chronic hepatitis B in children: an unresolved issue. *J Gastroenterol Hepatol* 2014; **29**: 912-919 [PMID: 24863185 DOI: 10.1111/jgh.12550]

39 **Choe HJ**, Choe BH. What physicians should know about the management of chronic hepatitis B in children: East side story. *World J Gastroenterol* 2014; **20**: 3582-3589 [PMID: 24707141 DOI: 10.3748/wjg.v20.i13.3582]

40 **El Sherbini A**, Omar A. Treatment of children with HBeAg-positive chronic hepatitis B: A systematic review and meta-analysis. *Dig Liver Dis* 2014; **46**: 1103-1110 [PMID: 25195086 DOI: 10.1016/j.dld.2014.08.032]

41 **Akarsu M**, Sengonul A, Tankurt E, Sayiner AA, Topalak O, Akpinar H, Abacioglu YH. YMDD motif variants in inactive hepatitis B carriers detected by Inno-Lipa HBV DR assay. *J Gastroenterol Hepatol* 2006; **21**: 1783-1788 [PMID: 17074014 DOI: 10.1111/j.1440-1746.2006.04567.x]

42 **Tan Y**, Ding K, Su J, Trinh X, Peng Z, Gong Y, Chen L, Cui Q, Lei N, Chen X, Yu R. The naturally occurring YMDD mutation among patients chronically infected HBV and untreated with lamivudine: a systematic review and meta-analysis. *PLoS One* 2012; **7**: e32789 [PMID: 22479339 DOI: 10.1371/journal.pone.0032789]

43 **Lee SH**, Kim HS, Byun IS, Jeong SW, Kim SG, Jang JY, Kim YS, Kim BS. Pre-existing YMDD mutants in treatment-naïve patients with chronic hepatitis B are not selected during lamivudine therapy. *J Med Virol* 2012; **84**: 217-222 [PMID: 22170540 DOI: 10.1002/jmv.23191]

44 **Tenney DJ**, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, Wichroski MJ, Xu D, Yang J, Wilber RB, Colonno RJ. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology* 2009; **49**: 1503-1514 [PMID: 19280622 DOI: 10.1002/hep.22841]

45 **Jonas MM**, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, Mondou E, Rousseau F, Sokal E. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to & lt; 18 years) with chronic hepatitis B. *Hepatology* 2008; **47**: 1863-1871 [PMID: 18433023 DOI: 10.1002/hep.22250]

46 **Chu M**, Cho SM, Choe BH, Cho MH, Kwon S, Lee WK. Virologic responses to add-on adefovir dipivoxil treatment versus entecavir monotherapy in children with lamivudine-resistant chronic hepatitis B. *J Pediatr Gastroenterol Nutr* 2012; **55**: 648-652 [PMID: 22688509 DOI: 10.1097/MPG.0b013e318262a737]

47 **Ryu HJ**, Lee JM, Ahn SH, Kim do Y, Lee MH, Han KH, Chon CY, Park JY. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *J Med Virol* 2010; **82**: 1835-1842 [PMID: 20872709 DOI: 10.1002/jmv.21898]

48 **Sheldon J**, Soriano V. Hepatitis B virus escape mutants induced by antiviral therapy. *J Antimicrob Chemother* 2008; **61**: 766-768 [PMID: 18218641 DOI: 10.1093/jac/dkn014]

49 **Yeh CT**. Development of HBV S gene mutants in chronic hepatitis B patients receiving nucleotide/nucleoside analogue therapy. *Antivir Ther* 2010; **15**: 471-475 [PMID: 20516567 DOI: 10.3851/IMP1552]

50 **Sayan M**, Akhan SC. Antiviral drug-associated potential vaccine-escape hepatitis B virus mutants in Turkish patients with chronic hepatitis B. *Int J Infect Dis* 2011; **15**: e722-e726 [PMID: 21784687 DOI: 10.1016/j.ijid.2011.05.019]

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**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 | 126 mo | 50 | 25 | 19 |
| Sokal *et al*[15] | LAM | 24 mo36 mo | 2535 | 110 | 4964 |
| Hartman *et al*[16] | LAM | 126 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 | 126 mo | 65 | 4 | 103234 |
| Liberek *et al*[20] | LAM | 12 mo | 27.1 | NA | 3.38  |
| Koh *et al*[21] | LAM | 126 mo | 42 | 3.3  | 10 |
| Kansu *et al*[8] | LAM + IFN | 6 m IFN 24 mo LAM | 60.2139.42 | 6.8102 | 17.9124.62 |
| Ozgenc *et al*[29] | LAM + IFN | 6 mo IFN12-36 moLAM | 15.635.6405 | 6.83 | 13.3369.4482.45 |
| Dikici *et al*[32] | LAM + IFN | 6 mo IFN12 mo LAM | 37 | 3.7 | 3.3 |
| Kuloğlu *et al*[33] | LAM + IFN | 6 mo IFN126 mo LAM | 34.2 | NA | 65.8 |
| Saltik-Temizel *et al*[34] | LAM + IFN | 6 mo IFN12 mo LAM | 60 | NA | NA |

1Simultaneous therapy; 2Sequential therapies; 3Firstyear; 4Secondyear; 5Thirdyear; 6Until HBeAg seroconversion or evidence of resistance; NA: Information was not given in the study. IFN: Interferon; LAM: Lamivudine.