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Resistance profile of entecavir in patients with chronic hepatitis B

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1. Introduction

Currently, five nucleos(t)ide analogues (NUCs) have been developed and licensed for the treatment of chronic hepatitis B including two L-nucleosides (lamivudine and telbivudine), one deoxyguanosine analogue (entecavir) and two acyclic nucleoside phosphonates (adefovir and tenofovir). Two NUC-treatment strategies have been established: a finite-duration treatment for HBeAg-positive patients who achieve HBeAg seroconversion during treatment, or a long-term treatment for HBeAg-positive patients without HBe seroconversion and for HBeAg-negative patients with the aim of maintaining HBV DNA suppression at undetectable levels [1–3]. However, long-term therapy with NUCs is associated with an increased risk of developing drug resistance. Viral resistance has become the single most important factor of treatment failure and a major challenge in the management of antiviral therapy for chronic hepatitis B [4–6].

2. Hepatitis B virus resistance to antiviral therapy

Hepatitis B virus (HBV) drug resistance is an expected consequence of NUC therapy because of the high viral replication rate (10^{11} virions produced daily) and the high mutation rate caused by the low fidelity of the viral polymerase/reverse transcriptase (RT) (1 error per 10^4 bases copied). The RT also lacks any proofreading activity, and therefore all possible single base mutations can be produced daily [7–9]. Consequently, in each infected individual, the viral population is present as a large pool of genetic variants, including drug resistant mutants. During antiviral treatment, under the selective pressure of the drug, resistant mutants are selected which over time become the dominant viral species.

The reduced susceptibility of resistant mutants to the antiviral activity of NUCs is due to mutations within the Pol-gene, resulting in amino-acid substitutions in the RT defined as primary mutations which reduce the affinity of the enzyme for the antiviral drug in favour of natural substrates (Fig. 1) [10]. Resistance to lamivudine (LAM) is due to an amino-acid mutation at position 204 in the majority of patients, while a mutation at position 181 is present in less than 5% of cases. Both mutations also confer resistance to emtricitabine and telbivudine (LdT). Amino-acid substitution rtA181T/V is associated with resistance to adefovir (ADV) and may be responsible for multi-drug resistance. In patients treated with entecavir (ETV), at least three mutations are simultaneously required: mutations at positions rtL180M + rtM204V (both associated with LAM resistance), plus at least one mutation at either position rt184, rtS202 or rtM250.

Development of antiviral drug resistance is a complex and multistep phenomenon [1,11]. Initially, during antiviral therapy, mutants containing amino-acid substitutions known to confer resistance to the antiviral drug appear. The emergence of resistant mutants is defined as *genotypic resistance* which precedes the *virologic breakthrough,* defined as an increase in serum HBV DNA levels by at least 1

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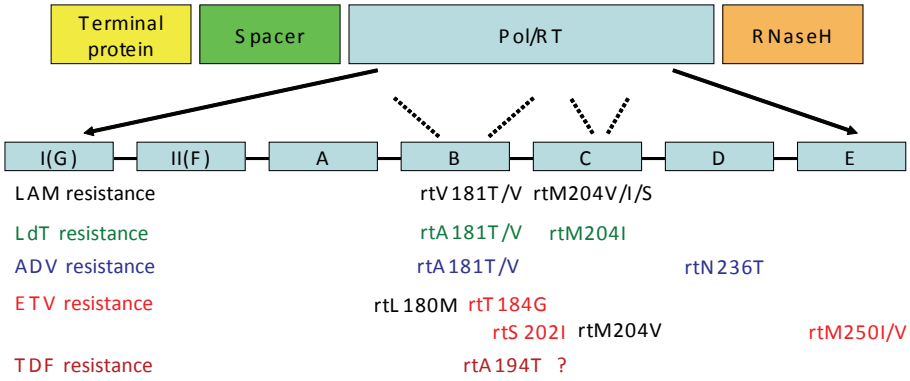

Fig. 1. Primary resistance mutations for lamivudine (LAM), telbivudine (LdT), adefovir (ADV), entecavir (ETV) and tenofovir (TDF). Modified from Locarnini [10].

log10 (10-fold) above nadir confirmed in two consecutive samples 1 month apart, after achieving initial response in a compliant patient. Then, virologic breakthrough is followed by *biochemical breakthrough*, defined as elevation in serum alanine aminotransferase after achieving normalization [12,13]

Development of antiviral drug resistance has important clinical implications as it provokes the loss of clinical benefits acquired during treatment. In fact, when compared to patients who maintain viral suppression, patients infected with drug resistant variants have a reduced rate of HBeAg seroconversion, reversion of histological improvement, and increased risk of progression to cirrhosis and its complications [14,25,16]. In cirrhotic patients, hepatitis flares may also cause hepatic decompensation and death from liver failure [17,18]. Moreover, patients who develop antiviral resistance before transplant have an increased risk of post-transplant HBV recurrence because HBV DNA levels may not be adequately suppressed at the time of transplant, and post-transplant prophylactic therapy may be ineffective unless additional therapy is administered [19]. In addition, antiviral resistant mutations selected with one agent may reduce the efficacy of other NUCs leading to multidrug resistance. With regards to LAM, apart from the cross-resistance to all L-nucleosides, such as telbivudine, emtricitabine and clevudine, a number of compensatory resistance mutations (that is, mutations that restore replication defects associated with primary resistance mutations) can be selected during long-term LAM therapy, thus reducing the efficacy and favoring the development of resistance to other groups of NUCs. Therefore, selection of LAM-R mutants may compromise future rescue options [4].

Lastly, antiviral drug resistance may have a potential impact on public health as transmission of LAM-resistant HBV mutants to seronegative individuals has been reported [20] and, since the Pol-gene overlaps with the S gene, mutations selected in the RT region by antiviral therapy may lead to mutations in the HBsAg that reduce the protective efficacy of HBV vaccine [21].

3. Factors influencing drug resistance development

Antiviral drug resistance depends on a number of factors involving the patient, virus and drug used [22,23]. Among the host factors, a high body mass index and poor adherence are associated with a higher risk of resistance due to an inadeguate drug exposure. The following viral factors may have a role in the emergence of resistance: (1) the previous exposure to NUCs (which may determine the presence of pre-existing antiviral resistant mutations), (2) high serum HBV DNA levels (which reflect a greater pool of viruses and a higher rate of virus replication, thus increasing the likelihood that drug-resistant mutations will be selected), (3) the viral fitness of the drug resistant mutants.

Regarding drug characteristics, the most important factors are potency, the genetic barrier and the pharmacologic barrier. Potency reflects the degree to which viral replication is suppressed during antiviral therapy. Naturally, a complete suppression of viral replication allows little opportunity for resistance to emerge because mutagenesis is replication dependent. The genetic barrier reflects the number of substitutions required to produce a marked decrease in susceptibility to the antiviral drug. Resistance to LAM and ADV requires only one amino-acid substitution, while resistance to ETV requires three amino-acid substitutions (two LAM-resistance substitutions and at least one ETV-resistance substitution) representing a genetic barrier which may be more difficult for the virus to overcome since the likelihood of two or three mutations arising simultaneously is much lower than for a single mutation [24]. The pharmacologic barrier indicates the ratio between the levels of drug exposure and the drug level required for inhibition. When considering all these drug-related characteristics, ETV and TDF appear to have the best resistance profiles [1,3,25].

4. Resistance to current HBV antivirals

Although antiviral drug resistance has been reported for all NUCs used for the treatment of chronic hepatitis B, the rates at which it emerges differ considerably. In fact,