

Clinical Issues in Antiviral Resistance in Chronic Hepatitis B

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Introduction

Antiviral therapy of chronic hepatitis B has changed in the last decade with the development of nucleoside analogs. However, due to the slow kinetics of viral clearance and especially that of intrahepatic cccDNA, and to the spontaneous viral genome variability, the efficacy of long-term administration of these antiviral agents is hampered by the emergence of drug-resistant mutants.^{1,2}

Clinical Definitions of HBV Drug Resistance

The clinical definition of drug resistance to anti-HBV agents requires standardization to allow the comparison of resistance data across the different clinical trials and to improve the standard of care for patients failing therapy.^{2,3} It can follow three different levels: 1) the detection of mutation(s) in the HBV genome that have been found to develop specifically during antiviral therapy and to confer resistance to the antiviral agent may be named genotypic resistance; with nucleoside analogs it currently corresponds to the detection of specific mutations in viral polymerase gene; 2) the rise in serum HBV DNA levels during therapy, following the development of genotypic resistance, is usually named virologic breakthrough; it is usually defined by a confirmed increase of 1log₁₀ copies/mL compared to the lowest value during therapy, which is not related to a compliance issue; 3) the clinical breakthrough corresponds to the elevation in serum ALT levels and worsening of liver disease following virologic breakthrough.

More sophisticated laboratory investigations are required to fully characterize resistance to antiviral agents. Phenotypic resistance corresponds to a decreased susceptibility to inhibition by antiviral drugs associated with HBV genome mutations in tissue culture experiments. Phenotypic analysis is mandatory to characterize resistance mutations to new antivirals. These assays also allow determination of the cross resistance profile of the mutants.^{4,5}

Incidence of HBV Drug Resistance in Nucleoside-Naive Patients

Figures may vary depending on the definition used across the trials. With lamivudine, genotypic resistance is observed in approximately 20% of patients per year, reaching 70% after 4 years of therapy.^{6,7} Interestingly, in some trials where resistance was defined by a virologic breakthrough confirmed by sequencing data, the incidence of lamivudine resistance was approximately two-fold lower. The incidence of genotypic resistance to adefovir has been reported in patients treated for HBeAg-negative chronic hepatitis B; it was found to be lower, but 29% of patients had adefovir resistance mutations after 5 years of therapy.⁸ With entecavir administration, genotypic data are available for HBeAg negative and positive patients. Some amino acid substitutions were found but were not responsible for drug resistance in phenotypic assays.⁹⁻¹¹ With telbivudine, resistance data are reported as a virologic breakthrough confirmed by genotypic analysis; 4.5% of patients were found to have resistance after 48 weeks of therapy.¹²

Incidence of HBV Drug Resistance in Lamivudine-Resistant Patients

The incidence of resistance seems to be increased in patients who are treated for a previous lamivudine failure, as suggested by some reports with adefovir therapy. Entecavir administration in lamivudine-resistant patients is associated with the development of resistance in 10% of patients after 96 weeks of therapy leading to the emergence of strains that are resistant to both lamivudine and entecavir.^{13,14}

Biochemical, Histological, and Clinical Correlates of HBV Drug Resistance

After the emergence of drug resistance, clinical deterioration has been shown to occur in the majority of patients who were maintained with lamivudine, as no other option was available.^{15,16}

Some patients may show a rapid deterioration with acute exacerbation of the disease and sometimes liver failure. These severe exacerbations are more frequent when patients had pre-existing liver cirrhosis and a pre-core mutant infection.^{17,18} In the other cases, deterioration of liver disease starts progressively after the development of viral drug resistance. In a large Asian study of cirrhotic patients, lamivudine resistance led to a loss of the clinical benefit as more patients developed liver decompensation and hepatocellular carcinoma.¹⁵ Furthermore, it was shown that patients who develop adefovir resistance may also present with liver decompensation.¹⁹ All these data strongly suggest that a careful monitoring of antiviral efficacy is required to adapt antiviral therapy prior to the deterioration of the disease.

Predictive Factors of Resistance at Baseline

Several baseline predictive factors of resistance have been characterized for lamivudine in clinical trials and cohort studies. High serum HBV DNA levels was the factor independently associated with resistance that was found in all studies.²⁰⁻²² Other factors such as high body mass index and high histology activity index have been found in some studies.^{20,21} For the other antiviral agents, little information is available regarding the prediction of resistance at baseline.

Clinical Consequences of Persistent Viremia

Several large-scale studies have shown the impact of persistent viremia during antiviral therapy. With lamivudine and telbivudine, the persistence of serum HBV DNA levels greater than 3log₁₀ copies/mL after 6 months of therapy is associated with a significant risk of development of resistance at year 1 of therapy.^{23,24} With adefovir dipivoxil administration in HBeAg negative chronic hepatitis patients, a viral load higher than 3log₁₀ copies/mL after 1 year of therapy was associated with a significant risk of developing resistance by year 5 of treatment.²⁰

Approaches to management of HBV resistance have changed with the availability of new anti-HBV agents. The main published reports are on the treatment of patients with virological and clinical breakthroughs. Clinical trials with adefovir dipivoxil have shown its antiviral efficacy in patients with lamivudine failure, which was accompanied by improvement of biochemical tests.^{26,27} The treatment endpoints were, however, analyzed after 1 year of therapy, which did not allow a conclusion regarding whether a switching or an add-on strategy is the best treatment option. However, longer term studies and evidence for the lack of cross resistance between the two drugs, at least with the most common mutants, suggest that the add-on strategy should be recommended. Clinical trials with entecavir have shown its antiviral efficacy in patients with lamivudine resistance, but cases of multiple drug resistance were observed in 10% of patients after 2 years of therapy,²⁸ because lamivudine and entecavir have some level of cross-resistance. The clinical management of HBV drug resistance is now evolving towards the treatment of patients with virologic breakthrough but without clinical manifestations to prevent the progression of the disease, and towards the management of patients with persistent viremia to prevent viremia relapse. These latter aspects deserve evaluation within clinical trials.

The future directions are to design and evaluate new strategies for the prevention of resistance, i.e. *de novo* combination therapy versus very early add-on therapy. Several strategies can be envisioned because of the availability of new drugs with a better resistance profile such as adefovir, entecavir, telbivudine, and tenofovir. A first strategy would be to combine *de novo* two drugs with a different profile of cross resistance to minimize the risk in resistance in the long-term. A second strategy, based on a very early add-on regimen, would be to start with a drug having a very low rate of resistance and then add a second drug if viremia levels do not decline below a threshold exposing to further resistance. These strategies should be evaluated in clinical trials in terms of efficacy, i.e., prevention of drug resistance, and in terms of cost/benefit ratio.

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