CROSS RESISTANCE AND ITS IMPACT ON CLINICAL MANAGEMENT

Fabien Zoulim
Hepatology Department and INSERM Unit 871, Lyon, France

Chronic hepatitis B is a major health problem worldwide: 360 million people are estimated to be chronically infected with hepatitis B virus (HBV) and a substantial proportion will ultimately develop severe liver disease and complications such as cirrhosis and hepatocellular carcinoma\(^1\). In the past decade, the therapeutic landscape has changed with the increased availability of nucleos(t)ide analogues\(^2\). However, the major issue that may prevent the successful long-term control of the disease is replication of drug-resistant antiviral species, which can occur within the first few years of antiviral therapy\(^3\). Drug resistance leads to treatment failure and progression of liver disease\(^4\).

Resistance-associated mutations can be distinguished as primary or secondary\(^5\). The first category refers to amino acid changes resulting in reduced susceptibility to an antiviral drug. Secondary mutations are compensatory mutations that restore functional defects associated with primary drug resistance (such as loss of fitness)\(^5\). Cross-resistance occurs when drug-resistance mutations selected by one agent affect the susceptibility of the virus to other nucleos(t)ide antivirals\(^5\).

Several nucleos(t)ide-resistance pathways have been identified clearly showing that cross-resistance can compromise future treatment options if the selection pressure of a drug is maintained once resistance has emerged\(^5\). The rtM204V/I pathway is responsible for resistance to several nucleosides, such as lamivudine, telbivudine, clevudine and entecavir, whilst the rtN236T pathway is responsible for resistance to adefovir and tenofovir\(^5\). It has recently been recognised that the rtA181T/V pathway is shared for lamivudine and adefovir\(^5\).

Prevention of resistance is the optimum treatment strategy. The European Association for the Study of the Liver Clinical Practice Guidelines issued in 2008\(^6\) recommend the use of a potent nucleos(t)ide analogue with a high genetic barrier to resistance as first-line therapy in treatment-naïve patients. In order to prevent subsequent resistance, adding a second drug with no cross-resistance is recommended if HBV DNA remains detectable (>10-15 IU/mL) after 48 weeks of treatment. In patients who developed resistance to any of the available anti-HBV drugs, monotherapy is not an option. An appropriate rescue therapy should be considered with the most effective antiviral effect and the minimal risk to induce multiple drug-resistant strains\(^6\). Adding-on a second drug without cross resistance is the only efficient strategy\(^6, 7\).

References