In the past 10 years, significant progress has been achieved in the understanding of the development of HBV drug resistance. The use of in vitro phenotypic assays has been crucial for the characterization of newly identified resistant mutants and to determine their cross-resistance profile. Results allowed to understand the different mechanism of viral resistance to lamivudine and adefovir, the mechanism of primary failure to adefovir therapy, the unique mechanism of entecavir resistance, and to characterize the emergence of multidrug-resistant strains in patients receiving sequential antiviral therapy. The cross-resistance profile for the main resistant mutants was determined which allowed to provide recommendation to clinicians for treatment adaptation based on molecular virology data. The role of infectivity and viral fitness in the process of selection of drug-resistant mutants was studied in HBV susceptible HepaRG cells. It was shown that mutations in the viral polymerase gene conferring drug resistance may also induce mutations in the overlapping envelope gene and in turn may alter viral infectivity. These results may be highly relevant for the development of clinical strategies aiming at preventing drug resistance or at selecting variants with impaired fitness.

The understanding of the development of HBV drug resistance has allowed to significantly improve the management of antiviral resistance and to design better treatment strategies to prevent resistance. The current standard of care relies on treatment initiation with antivirals combining a strong antiviral potency and a high barrier to resistance. A precise virologic monitoring is required to measure antiviral efficacy, and to diagnose partial response or viral breakthrough at an early stage. This allows to adapt antiviral treatment preferably using an add-on strategy with

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Fabien Zoulim

Hepatology Department and INSERM Unit 871, Lyon, France
a drug having a complementary cross-resistance profile. This strategy has been shown to be efficient in controlling viral replication and preventing liver disease progression in the majority of patients\textsuperscript{6,18}. The future challenge will be to determine whether de novo combination of nucleoside analogs belonging to the new generation of drugs will provide an added benefit in terms of drug resistance and prolonged viral suppression. The identification of new antiviral targets will be important in that respect to develop more potent combination strategies.

References


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