Anti Hepatitis B Therapy

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To understand how different therapeutic strategies aim to control chronic hepatitis B infection, it is helpful to have functional knowledge of the replicative cycle of the virus. In the HBV replicative strategy, genomic DNA is synthesized from a pregenomic RNA template by reverse transcription.

The nucleoside analogues, which specifically block HBV DNA replication, are making a significant impact on the management of HBV infections, especially in those clinical situations where the benefit of IFN-α therapy was marginal or contraindicated. Lamivudine is now registered in many countries. There are several new nucleoside analogues in phase I/II/III development and many undergoing preclinical evaluation.

Antisense oligodeoxynucleotides (ODN) consist of DNA or RNA sequences designed to specifically bind an RNA target, resulting in the formation of an RNA-RNA(Antisense RNA) or RNA-DNA(Antisense DNA) hybrid, which brings about inhibition of RNA replication, reverse transcription, and translation. Antisense ODNs have been developed that inhibit HBV replication *in vitro.*

Under normal circumstances of infection, the HBV is not cytopathic and in both acute and chronic infections most of the liver damage seen with HBV is essentially immunemediated. The major immune modulating agents are the interferons.

Nuclear factor-κB (NF-κB) signaling pathway is an important regulating pathway in liver diseases, including hepatocellular carcinoma. Immunohistochemical analysis showed that NF-κB–inducing kinase (NIK), an upstream kinase of IκB kinases, nuclear localization occurs only in liver tissues obtained from hepatitis B surface antigen (HBsAg)(+) patients but not in tissues from HBsAg(-) patients. HBV induced NIK-dependent NF-κB activation. However, interferon (IFN)-γ induced NIK nuclear localization and inhibited NF-κB activation in HepG2.2.15 cells and in HepG2 cells transfected with pHBV1.2x. When NIK nuclear localization was inhibited by deletion of nuclear localization signal on NIK, IFN-γ did not induce the NIK nuclear localization and did not inhibit NF-κB activation. IFN-γ selectively inhibits HBV-mediated NF-κB activation. This inhibition is accomplished by NIK nuclear localization, which is a novel mechanism of NF-κB inhibition.