The current and update in management of pre-core mutant hepatitis B virus

Essay
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Index

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List of Contents

Contents (Cont.)

Chapter 3: HBV MANAGEMENT

List of Abbreviations

AASLD	:	The American Association for the Study of Liver Disease.
HBV	:	Hepatitis B Virus.
CHB	:	Chronic Hepatitis B.
HCC	:	Hepato_Cellalur Carcinoma.
HBeAg	:	Hepatitis B envelop (early) Antigen.
HBsAg	:	Hepatitis B surface antigen
AFP	:	Alpha fetoprotein
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
CccDNA	:	Covalently closed circular DNA
CDC	:	The Center of Disease Control & Prevention
CTL	:	Cytotoxic T-lymphocyte
DR	:	Direct repeats
E	:	Core
GRE	:	Glucocorticoid-responsive element
HAI	:	Histologic activity index
HBCAb	:	Hepatitis B Core Antibody
HBeAg	:	HepatitisB e antigen
HBIG	:	Hepatitis B immunoglobulin
HBsAg	:	Hepatitis B surface antigen
HBV	:	Hepatitis B virus
HBx	:	Hepatitis B virus X protein
HCC	:	Hepatocellular carcinoma
HDV	:	Hepatitis D virus
HIV	:	Human Immunodeficiency Virus
IFNs	:	Interferons
Ig	:	Immunoglobulin
MS	:	Multiple sclerosis
NAs	:	Nucleotide analogs
NAT	:	Nuclric acid testing
ORF	:	Open reading frame
P	:	Promoters
PCR	:	Polymerase chain reaction
Peg	:	Pegylated
Pg	:	Pregenomic
rc	:	Relaxed
RIA	:	Radioimmunossay
RNaseH	:	The ribonuclease
RT	:	Real-time
RT	:	The reverse transcriptase
SOI	:	Secondary occult infection
TCR	:	T-cell repertoire
Th	:	T- helper cell
TP	:	Terminal protein

List of Tables

List of Figures

Introduction
and
Aim of the study

Introduction:

HBV infection is a common global public health problem which affects over 400 million people worldwide. It does not only lead to a wide spectrum of liver disease ranging from acute hepatitis (including fulminant hepatic failure) to chronic hepatitis, but also the main reason of fatal complications including decompensated cirrhosis and CHB-related HCC that cause up to one million HBV carriers dying of HBV associated liver disease annually. **(Zhang et al., 2011)**

HBV is the prototype member of the family Hepadnaviridae, with a compact genome of approximately 3.2 kb arranged in a circular, partially double-stranded DNA molecule. Hepatitis B virus exists in ten different genotypes (A-j) and its prevalence differs with geography and ethnicity. Genotype D has a worldwide distribution but predominates in the Mediterranean area. **(Cho et al., 2011)**

The natural progression of the chronic HBV in individual patients varies according to the pace at which they go through the four phases of CHB infection, namely immune tolerant, immune clearance, inactive and reactivation phases. This is largely determined by the HBV genotype and host immune characteristics. **(Leungn, 2011)**

In the natural course of chronic HBV infection, the loss of HBeAg expression and the appearance of antibodies directed against it (Anti-HBe) are usually accompanied by cessation of viral replication leading to inactive carrier state. Hepatitis B early antigen (HBeAg) is produced from expression of precore gene. Certain mutations in the precore gene will abolish HBeAg production. Hepatitis B virus (HBV) carrying such mutated gene is called precore mutant. **(Chook et al., 2011)**

This mutation results in an inability of the hepatitis B virus to produce HBeAg, even though the virus is actively reproducing. This means that even though no HBeAg is detected in the blood of people with the mutation, the hepatitis B virus is still active in these persons and they can infect others. Most hepatitis B virus persons at early stage are carrying precore wild-type (not mutant) virus. As time goes by, our body immune system fight back on the precore wild-type virus, and the precore mutant is selected out during the battle. **(Chook et al., 2011)**

The frequent genomic mutation that leads to HBeAg negativity is the mutation of the nucleotide (NT) 1896 from G to A (G-A). This mutation converts codon 28 of the precore sequence to a termination codon (TGGTTAG) and thus prevents HBeAg from being expressed. Analysis of nucleotide 1858 showed presence of thymine in the patients with genotypes C and D. This nucleotide was closely related to the presence of precore mutants. Pre-core variants are more common among patients with genotype D. **(Alfaresi et al., 2010)**

ALT and HBV DNA levels are significantly lower in e-antigen negative patients than in e-antigen positive patients. However, spontaneous recovery is rarer, long-term prognosis is poorer, and histological lesions are more severe in HBeAg-negative patients than in HBeAg-positive patients. Necrotic inflammatory activity is almost identical in both HBeAg-negative and positive patients. However, fibrotic activity is higher in e-antigen negative patients than in e-antigen positive patients. The estimated annual incidence of cirrhosis is 2%-6% in HBeAg positive CHB patients and 8%-10% in HBeAg negative CHB patients. The higher incidence of cirrhosis in HBeAg-negative patients is related to age and fibrosis stage, suggesting that HBeAg-negative chronic hepatitis can progress to cirrhosis and HCC in the natural history of HBV infection rather than de novo infection with HBV variants that do not produce HBeAg. **(Shi and shi, 2009)**

Eradication of hepatitis B virus (HBV) is not a realistic goal of hepatitis B treatment. But the goal is the permanent suppression of viral replication to reduce the long-term complications of CHB as the development of cirrhosis, liver failure, and hepatocellular carcinoma. Most of the current treatment guidelines for CHB suggest that treatment is indicated in patients with HBV-DNA greater than 20,000 IU/ML for HBeAg-positive CHB and when HBV-DNA is greater than 2,000 IU/ML for HBeAg-negative CHB, together with evidence of active inflammation as reflected by elevated serum ALT or liver histology in the absence of other causes for liver disease. **(Chotiyaputta and Lok, 2010)**

Seven medications have been approved for the treatment of CHB: interferon, pegylated interferon (Peg-IFN), lamivudine, Telbivudine, Adefovir, Tenofovir and Entecavir. Tenofovir is the most effective oral antiviral agentfor HBeAg-negative patients. Tenofovir and entecavir are the most potent oral antiviral agents for HBeAg-positive patients. **(Yuen and Lai, 2011)**

Long-term nucleoside analogue treatments are required to maintain the persistent suppression of HBV replication with the potential risk of drug resistance. **(Yuan and Lee, 2011)**

Aim of the study:

The aim of this study is to review the literature for the current and the latest update as regards to the natural history, epidemiology, diagnosis and treatment of pre-core mutant hepatitis B.