Hepatitis B Virus Progression in Relation to Viral Load, Genotypes, Quasispecies, Host Factors and its Effect on Outcome of Treatment

Essay

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بِسْمِ اللّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

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CONTENTS

List Of Abbreviations

AASLD: American Association for Study of Liver Diseases
ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
Anti-HBc: Hepatitis B core antibody
Anti-HBe: Hepatitis B e antibody
Anti-HBs: Hepatitis B surface antibody
AST: Aspartate aminotransferase
cccDNA: Covalently closed circular DNA
CTLs: Cytotoxic T lymphocytes
DNA: Deoxyribonucleic acid
ELISA: Enzyme linked immunosorbant assay
g/dl: Gram per deciliter
HBcAg: Hepatitis B core antigen
HBeAg: Hepatitis e antigen
HBIG: Hepatitis B Immune Globulin
HBsAg: Hepatitis B surface antigen
HBV: Hepatitis B virus
HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
HDV: Hepatitis Delta virus
HLA: Human leukocyte antigen
IDUs: Injecting Drug Users
Kd: Kilo Dalton
LCF: Liver cell failure
lU/ml: International unit per milliliter
mg/dL: Milligram per deciliter
MHC: major histocompatibility complex
MIU: Million international unit
ng: Nanogram
NK: Natural killer
PBMCs: periphral blood mononuclear cells
PCR: Polymerase chain reaction
Pg: Pico gram
RNA: Ribonucleic acid
STD: Sexually transmitted diseases
WHO: World Health Organization
α-INF: Alpha interferon
µg: Micro gram
µmol/L: Micro mol per liter

The 20 L-α-Amino Acids (Symbol And Name **)**

(the monomer units of proteins)

1) **A** Alanine Ala [A]
2) **C** Cysteine Cys [C]
3) **D** Aspartic acid Asp [D]
4) **E** Glutamic acid Glu [E]
5) **F** Phenylalanine Phe [F]
6) **G** Glycine Gly [G]
7) **H** Histidine His [H]
8) **I** Isoleucine Ile [I]
9) **K** Lysine Lys [K]
10) **L** Leucine Leu [L]
11) **M** Methionine Met [M]
12) **N** Asparagine Asn [N]
13) **P** Proline Pro [P]
14) **Q** Glutamine Gln [Q]
15) **R** Arginine Arg [R]
16) **S** Serine Ser [S]
17) **T** Threonine Thr [T]
18) **V** Valine Val [V]
19) **W** Tryptophan Trp [W]
20) **Y** Tyrosine Tyr [Y]

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) currently affects about 400 million people, particularly in developing countries, and it is estimated that worldwide over 200,000 and 300,000 chronic HBV carriers die each year from cirrhosis and hepatocellular carcinoma (HCC), respectively (***Perz et al., 2006***) .

HBV is highly endemic in sub-Saharan Africa, China and South-East Asia. It is also highly endemic in the Mediterranean basin and it is present at significant levels in most industrialized countries (***Lee et al., 1998***).

Exposure to HBV can cause a broad spectrum in clinical manifestations of human HBV infection that may differ even among family members . The clinical manifestations range from a clinically asymptomatic condition to those with overt pathology that can be acute hepatitis or chronic liver disease (***Thoi et al., 2000***) . The majority of adults with primary HBV infection (90-95%) can successfully clear the virus and only 5-10% of adults become chronic HBV earners. Among the chronically infected individuals , 20-30% leads to liver cirrhosis and about 5% develop hepatocellular carcinoma through a long-term disease progression. On the other hands , more than 90% develop chronic infection in the perinatally transmitted cases. The reasons for this variation in the natural history of HBV infection are not fully understood, but viral and immunological factors (viral load, viral mutations, and host immunity) could play important roles in modulating both the antiviral immune response and host susceptibility to HBV (***Choi, 2004***).

Men seem to be more prone to developing CHB than women, although the reasons for this gender difference are unclear (***Ryder and Beckingham, 2001b***).

The risk of progression to chronic HBV infection is inversely proportional to the age at infection. Up to 50 to 90% of neonates and infants born to HBeAg positive mothers become HBV carriers , as compared to 20 to 30 % among children infected between the age of 1-5

years, and less than 5% among immunocompetent adults (***Thoi et al., 2003***).

High viral load predicts progression of liver disease, cirrhosis, cirrhosis-related complications, and HCC independent of HBeAg, ALT, and cirrhosis (with a threshold of risk starting to rise at an HBV DNA concentration somewhere between 10^4 and 10^5 copies/ml.) (***Iloeje et al., 2006 and Chen et al., 2006***).

The symptoms and complications of HBV infection arise from liver damage. However, HBV does not itself directly damage hepatocytes, as it is not directly cytopathic . Instead, the liver damage and symptoms characteristic of HBV seem to arise from the immune system's attempts to remove the infection. Several types of white blood cell (cytotoxic and natural killer T-cells) fight the virus by killing infected cells, but the immune system also produces chemical messengers (cytokines), such as interferons, which appear to have antiviral affects inhibiting viral replication; reducing proliferation of viruses to infect new cells; and modulating the immune response to the infection (***Ganem and Prince, 2004***).

The importance of the immune system in HBV progression means that immunosuppressed people often show only mild liver damage, despite having high levels of the virus in their blood. Similarly, patients infected early in life are generally asymptomatic and show little liver damage for several decades despite a heavy viral load, as the immune system initially tolerates the infection and therefore causes no damage. Unfortunately this can change in later life, with a sudden activation of the disease process, in the main due to a mutation of HBV (***Ganem and Prince, 2004***).

HBV isolates have been classified into 9 different serotypes according to the antigenic determinants of their HBsAg. However, the classification of HBV by serologic subtype is not rational because a single point mutation at the S gene may result in a change in subtype. Therefore, according to the molecular evolutionary analysis of the genomic DNA

sequence, HBV strains isolated in various countries are classified into 8 genotypes: genotypes A to H (***Arauz-Ruiz et al., 2002***).

HBV is a variable virus, due to the intrinsic properties of the HBV DNA polymerase, the enzyme that ensures viral replication . HBV , like other viruses with error-prone polymerases , such as HIV, hepatitis C virus (HCV) and poliovirus, has a "quasispecies" distribution in infected individuals (***Gunther et al., 1999***).

This means that HBV circulates as a complex mixture of genetically distinct but closely related variants that are in equilibrium at a given time point of infection in a given replicative environment. The quasispecies distribution of HBV is characterized by the coexistence of different viral populations in various proportions. Variant populations are continuously selected by the changing environment in which the virus replicates during human infection. The quasispecies distribution of HBV implies that any newly generated mutation conferring a selective advantage to the virus in a given replicative environment will allow the corresponding viral population to overtake the other variants, following a classical Darwinian evolutionary process (***Domingo and Gomez, 2007***).

Apart from direct biological effects of viral variants, there is a growing consensus that the host immune response, especially the virus-specific T cell response , is the key determinant influencing the course of disease and the onset of liver disease (***Zhou et al., 2003***).

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Studying an update of factors affecting hepatitis B virus progression including viral and host factors.

CHAPTER I

HBV Virology

Hepatitis B Virus

1.1. Epidemiology

(A) Mode of Transmission

HBV is transmitted by percutaneous and mucosal exposure to infectious blood or body fluids. The highest concentrations of virus are found in blood; however, only semen and saliva have been demonstrated to be infectious. HBV remains viable and infectious in the environment for at least 7 days and can be present in high concentrations on inanimate objects, even in the absence of visible blood (***Cindy et al., 2008***).

Persons with chronic HBV infection are the major source of new infections, and the primary routes of HBV transmission are sexual contact, percutaneous exposure to infectious body fluids (such as occurs through needle sharing by injecting drug users (IDUs) or needlestick injuries in health-care settings), perinatal exposure to an infected mother, and prolonged, close personal contact with an infected person (e.g., via contact with exudates from dermatologic lesions, contact with contaminated surfaces, or sharing toothbrushes or razors), as occurs in household contact . No evidence exists of transmission of HBV by casual contact in the workplace, and transmission occurs rarely in childcare settings. Few cases have been reported in which health-care workers have transmitted infection to patients, particularly since implementation of standard universal infection control precautions (***Cindy et al., 2008***) .

(B) HBV worldwide

Worldwide, chronic infection with hepatitis B virus (HBV) currently affects about 400 million people , particularly in developing countries, and it is estimated that 500,000 to 1,000,000 persons die annually of HBV-related liver disease (***Mahoney,2008***).

The prevalence of HBV infection varies markedly in different parts of the world. Approximately 45% of the world's population live in areas where the prevalence of chronic HBV infection is high (8% or more of the population is HBsAg positive), 43% live in areas where the prevalence is moderate (2 to 7% of the population is HBsAg positive),