Natural History of Chronic Hepatitis B

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Outline

• Phases of chronic HBV infection
• New perspective on immune tolerance phase
• Factors affecting disease progression
• Role of quantitative HBsAg in identifying inactive carriers and in predicting risk of HCC in HBeAg- patients
• Risk of HCC after HBsAg clearance
HBV Disease Progression

- Acute infection
- Chronic infection
- Cirrhosis
- Liver Failure
- HCC
- Liver Transplantation
- Death
Pathogenesis of HBV-related Liver Disease

HBV is not a cytopathic virus
Liver injury is immune mediated
High Viral Load is Associated with Increased Incidence of HCC

REVEAL Study (n=3,653)

Baseline HBV DNA level, copies/mL

- ≥10^6 (n=627)
- 10^5–<10^6 (n=349)
- 10^4–<10^5 (n=643)
- 300–<10^4 (n=1,161)
- <300 (n=873)

Cumulative incidence of HCC (% subjects)

Year of follow-up
Hepatitis B
Factors affecting disease activity and progression

**VIRUS**
- HBV Genotype
- Molecular Variants
- Viral load
- HCV, HDV, HIV

**HOST**
- Gender, Age
- Immune Response
- Genetics
- Obesity, DM

**ENVIRONMENT**
- Alcohol
- Carcinogens
Course of Chronic HBV Infection is Characterized by Remissions and Relapses
Disease Phases in the Hepatitis B Research Network Cohort Study
1390 adults not on treatment in N America

More than 1/3 of patients had an indeterminate phase of disease; 3 different indeterminate profiles identified

Data shown for women, ULN for ALT 20 U/L
HBsAg Levels During Different Phases of Chronic HBV Infection

- IT = immune tolerance
- IC = immune clearance
- LR = inactive carrier
- ENH = HBeAg- chronic hepatitis

220 patients

*Nguyen T, J Hepatol 2010; 52: 508*
Quantitative HBsAg Levels in the Natural Course of Chronic HBV Infection

- Immune tolerance
- Immune clearance (HBeAg+ CHB)
- Inactive carrier
- Reactivation (HBeAg- CHB)

HBeAg → Anti-HBe

HBsAg

HBV DNA

ALT

cccDNA

Integrated HBV DNA

Lok A, Nat Rev Gastroenterol Hepatol. 2011
Cornberg M, J Hepatol (in press)
New Concept of Immune Tolerance Phase
Inflammatory vs. Non-inflammatory NOT
Immune Tolerance vs. Immune Clearance

Proposed representation of non-inflammatory and inflammatory phases of CHB

- HBV-specific T cells are present more in the young patients but do not cause recruitment of inflammatory cells
- monocytes
- granulocytes
- T-cells

Pro-inflammatory events mainly present in adults

Bertoletti A, Cell Mol Immunol 2015;12:258
Patients in the Immune Tolerance Phase Have Weaker Immune Response to HBV: HBRN Cohort Study

A

- IT (n = 21)
- IA+ (n = 58)
- IA- (n = 66)
- IC (n = 45)

P = 0.33  P = 0.53  P = 0.32  P = 0.002  P = 0.97  P = 0.79  P = 0.12  P = 0.01

B

IT: immune tolerance, IA+: HBeAg+ immune active, IA-: HBeAg- immune active, IC: inactive carrier
Incidence and Predictors of HBeAg Clearance

431 HBeAg+ patients in REVEAL study, 47% ≥40 years old, followed for mean of 7 years, 187 had spontaneous HBeAg clearance, 6.2%/year

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Multivariate adjusted rate ratio (95% CI)</th>
<th>P value</th>
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<td>HBV DNA (log c/mL)</td>
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Delayed HBeAg Clearance is Associated with Significantly Higher Risk of Progression to Cirrhosis

% of patients with progression to cirrhosis

Age at time of HBeAg seroconversion (years)

Chu & Liaw J Viral Hepat 2007; 14: 147
Phases of Chronic HBV Infection
Predictors of HBeAg- CHB after HBeAg Seroconversion

- 434 HBeAg+ children: 359 spontaneous and 75 antiviral HBeAg seroconversion
- Median fu 14.4 years after HBeAg seroconversion
- HBeAg- CHB defined as ALT>2x ULN x 6 months with HBV DNA >2000 IU/mL
- Predictors of HBeAg- CHB: HR (95% CI)
  - Age at seroconversion ≥18: 2.46 (1.07-5.64)
  - Male: 3.15 (1.06-9.32)
  - Genotype C vs. B: 4.40 (1.40-9.98)
Liver-related Mortality is Rare in HBeAg- Carriers with Persistently Normal ALT

4376 HBeAg-carriers with ALT <2x ULN fu x 13.4 (3-29) years
HBsAg Levels Combined with HBV DNA and ALT Levels Predict Disease Progression in Patients with Low HBV-DNA

1068 Taiwanese HBeAg- persons with HBV DNA <2000 IU/mL followed for a mean of 13.0 years

Tseng T, Hepatology 2013;57:441
Prediction of Risk of HCC Among Inactive Carriers Identified at Baseline or after Serial Follow-up

REVEAL study: 2952 HBeAg-
1-time assessment: HBeAg-, HBV DNA <2000 IU/mL, HBsAg <1000 IU/mL similar to serial testing in predicting risk of HCC
Spontaneous Clearance of HBV Markers and Subsequent Risk of HCC

REVEAL study 2964 HBsAg+, no cirrhosis

Hazard ratio for HCC after seroclearance during follow up
- HBeAg 0.63
- HBV DNA 0.24
- HBsAg 0.18

after adjustment for age, gender ALT

Among HBeAg- lifetime cumulative incidence of HCC for those with seroclearance of
- Both HBV DNA and HBsAg 4.0%
- HBV DNA only 6.6%
- Neither 14.2%
Incidence of HCC after HBsAg seroclearance

Independent predictors of HCC
- Liver cirrhosis (hazard ratio [HR]: 10.80)
- Male gender (HR: 8.96)
- Age 50 years at the time of HBsAg clearance (HR: 12.14)
Non-invasive Tests Can Predict Survival

Consecutive cohort n= 600, fibrosis assessed with liver stiffness, APRI, FIB-4, Fibrotest or liver biopsy, followed for 5 years

- Survival significantly decreased in patients diagnosed with severe fibrosis, whatever the non-invasive method used, or liver biopsy

*de Ledinghen V, Aliment Pharmaol Ther 2013; 37: 979*
Cumulative HCC incidence based on Liver Stiffness Measurement (LSM)

1,130 adults with CHB (HBeAg+36%, detectable HBV DNA 32%)
Course of Chronic HBV Infection is Characterized by Remissions and Relapses

- HBeAg
- Anti-HBe
- HBV DNA
- ALT

Occult HBV
- HBsAg-
- Anti-HBc+
- Serum HBV DNA+/-
- Hepatic HBV DNA+

Years
0 20 40 60

Immune tolerant
Immune clearance HBeAg-positive chronic hepatitis
Inactive carrier state
Reactivation HBeAg-negative chronic hepatitis
Natural History of Chronic HBV Infection

• Staging provides useful concept for clinical management
• Progression from one stage to another can occur after varying time
• Reversion to an earlier stage can also occur
• Host and viral factors driving transitions remain to be determined
• Lifelong monitoring to prevent adverse outcomes