Progress in the treatment of chronic hepatitis B

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The Hepatitis B Revolution

1965 Australia antigen
1970 Dane particle (EM)
1975 anti-HBc IgM for acute hepatitis B
1981 Plasma-derived HBV vaccine
1982 Hybridization (HBV DNA assay)
1983 HBeAg-negative CHB
1984 Mass vaccination program in Taiwan
1986 recombinant HBV vaccine

1976 Dr. Blumberg 1976 Nobel Prize

1970 HBeAg
1973 HBcAg
1977 HBIG
1979 HBV genome sequenced
1981 Plasma-derived HBV vaccine
1982 Hybridization (HBV DNA assay)
1983 HBeAg-negative CHB
1984 Mass vaccination program in Taiwan
1986 Recombinant HBV vaccine

1986 cccDNA discovery
1988 Relationship to HCC, Genotype
1989 Pre-core / core mutation

Hepatitis B virus (HBV)

- DNA virus (3.2 kb), overlapping 4 ORFs: S, C, P and X genes
- Replicate via an RNA intermediate (Pregenomic RNA)
- Reversely transcribed into HBV DNA by virus-encoded polymerase (error prone RT activity)
- Variation rate: 1.4-3.5x10^-5/site/year
- The reverse transcription step accounts for the majority of point mutations and deletions or insertions observed in HBV genome
  - Genotype / subgenotype
  - Recombinant
  - Variant / mutant
  - Quasispecies

The HBV in Taiwan

- HBsAg carrier rate before mass vaccination: 15% to 20%, one of the highest in the world.
- The infection is attributed to perinatal transmission from mothers to infants in 40% of Taiwanese HBsAg carriers.
- Mass vaccination program in Taiwan since July 1, 1984
- National viral hepatitis therapy program in Taiwan since Oct 1, 2003

Geographic Distribution of Chronic Hepatitis B infection Worldwide (As measured with HBsAg, 2006)

www.cdc.gov

• HBV carrier: >350 million worldwide, 75% in A-P region
• >780,000 per year die due to the consequences of hepatitis B

Three Phases + One Variant Phase of CHB

- Immune tolerant phase
- Immune clearance phase
- Inactive residual phase (immune control)
- Reactivation (immuneescape)

Liver Histology: Minimum
Hepatocyte expression of liver-HBsAg
- Active hepatitis
- Nucleus/lymph
- Absent

Factors contribute to CHB progression

Host Factors
- Age: > 40 y/o
- Gender: M > F
- Immune status: Frequency of ALT flare

Other Factors
- Alcohol
- Smoking
- Aflatoxin
- HCV, HDV, HIV coinfection

HBV Factors
- Viral Load
- Genotype: C > B
- D > A
- Mutations: BCP, Pre-S

High baseline HBV DNA associated with increased risk of cirrhosis and HCC

Goal of treatment for CHB

Short-term vs. Long-term

- HBsAg(+) patients
- Anti-HBe gain
- HBsAg loss

Initiation of treatment
- Permanently suppress HBV replication

TIME
- Initial response
- HBV DNA undetectable
- ALT normalization
- Durable response
- Prevent complications
- Prolong survival

The Hepatitis B Revolution

1990
- 1991 Interferon

1995

2000
- 2002 Adefovir; Sensitive PCR
- 2003/10 慢性B型及C型肝炎治療試辦計畫

2005
- 2005 *Entecavir
- *Peg-IFN α-2a
- 2006 Telbivudine

2010
- 2010

2015
- 2015

New NAs (TAF, Besifovir...)
- Myrcludex-B, REP 9AC', Isothiafludine
- TLR7 agonist, anti-PD-1 mAb
- Therapeutic vaccine (Tarmogen)
- siRNA, APOBEC3A/B (cccDNA degradation)...

* Preferred agents in APASL guideline 2012


Liaw and Chu. Lancet 2009


Chen CJ, et al. JAMA 2006

Main respective advantages and disadvantages of IFN and NAs in the treatment of CHB

<table>
<thead>
<tr>
<th>Effects</th>
<th>(PEG-)IFN</th>
<th>Nucleos(t)ide analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>• Finite duration</td>
<td>• Pure antiviral</td>
</tr>
<tr>
<td></td>
<td>• Higher rate of anti-HBe and anti-HBs seroconversion rate within 12 mo therapy (higher sustained response; off-therapy immune control)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Absence of resistance</td>
<td></td>
</tr>
<tr>
<td>Disadvantages</td>
<td>• Moderate antiviral effect</td>
<td>• Indefinite duration</td>
</tr>
<tr>
<td></td>
<td>• Inferior tolerability</td>
<td>• Risk of resistance</td>
</tr>
<tr>
<td></td>
<td>• Risk of adverse events</td>
<td>• Unknown long-term safety</td>
</tr>
<tr>
<td></td>
<td>• Subcutaneous injections</td>
<td></td>
</tr>
</tbody>
</table>

Interferon

- In 1991, conventional IFN α-2a trice weekly was the first successful treatment approved for CHB with widespread use.
- In 2005, Peg-IFN α-2a replaced standard IFN due to improved pharmacokinetic properties and a less demanding injection schedule with comparable efficacy.

Highest response rates of post-treatment with PEG-IFN α-2a 180 μg/48 weeks (NEPTUNE study)

HBeAg seroconversion rate increases over time in HBeAg-positive CHB treated with PEG-IFN

- Long-term follow-up (mean duration 6 years)
- 85 HBeAg-positive CHB treated with PEG-IFN α2b at a dose of 1.5 μg/kg weekly for 32 weeks

HBsAg clearance increases post-treatment in both HBeAg-positive and HBeAg-negative CHB treated with PEG-IFN

HBsAg clearance – Improves survival

Survival in compensated cirrhosis with and without HBsAg seroconversion

Retrospective study of 309 patients over mean follow-up of 5.7 years

Survival %

With HBsAg clearance

No HBsAg clearance

P<0.001

Fattovich et al. Am J Gastroenterol 1998

Buster et al. Gastroenterology 2008

MarcoFin et al. Hepatol Int 2012

Liaw YF et al. Hepatology 2011

VWS Wong et al. Hepatology 2010
Long-term impact of IFN-based therapy

- HBeAg seroconversion and HBsAg clearance increase over time

- Cirrhosis reduced 35%
- HCC reduced 41% (49% in cirrhotics)
  Yang YF et al. JVIH 2009

- Overall hepatic events (cirrhotic complications, HCC, and liver-related mortality) reduced 45%
- Liver-related mortality reduced 37% (80% in initial responders)
  Wong GLH et al. Aliment Pharmacol Ther 2010

* Meta-analysis

Pre-treatment predictors of response to PEG-IFN

- IFN treatment benefits, are restricted to a subgroup of patients, 20-30%, and the tolerability is suboptimal

- Baseline predictors of a response for PEG-IFN:
  - High baseline ALT levels
  - Low HBV DNA, low HBeAg level
  - Virus genotype (A>D, B>C)

Limited applicability:
- Someone with same viral factors (VL, genotype) and ALT elevation but divergent IFN response
- ALT and HBV DNA levels are time-dependent
- Weak predictors of response at the individual level
  EASL guideline. J Hepatol 2012

Role of IL28B polymorphisms: Conflicting results

- Base line predictors of a response for PEG-IFN:
  - High baseline ALT levels
  - Low HBV DNA, low HBeAg level
  - Virus genotype (A>D, B>C)

Limited applicability:
- Someone with same viral factors (VL, genotype) and ALT elevation but divergent IFN response
- ALT and HBV DNA levels are time-dependent
  - Weak predictors of response at the individual level
  EASL guideline. J Hepatol 2012

On-treatment HBsAg rather than HBV DNA level CAN distinguish responders from relapsers

- SVR (N=12)
- Relapsers (N=18)

Role of on-treatment qHBsAg decline

- Patients with HBeAg-positive CHB
- % Patients with HBeAg seroconversion
- Mortality cde

Week 12 stopping rule in HBeAg-positive and -negative patients treated with Peg-IFN for 48 wks

- SVR (N=12)
- Relapsers (N=18)

Author (year), HBeAg (No of patients), Genotype, Week, Stopping rule, NPY (%)

- Sonneveld et al (2010), >100 (320), D (35%), A (35%), 12, No HBeAg decline, 97
- Pinterivich and Marcellin (2011), >100 (399), C (55%), B (25%), 12, No HBeAg decline, 82
- Pinterivich et al (2011), >100 (399), C (55%), B (25%), 12, >2000 IU/mL HBeAg, 84
- Lui et al (2011), >100 (114), Most + B, 12, >2000 IU/mL HBeAg, 100
- Rijpstra et al (2013), >100 (112), D (100%), 12, No HBeAg decline and <2 log HBV DNA decline, 100
- Rijpstra et al (2013), >100 (91), D (100%), 12, No HBeAg decline and <2 log HBV DNA decline, 100
**Lamivudine**
- In 1998, first nucleoside analogue reverse transcriptase inhibitor approved by FDA
- A significant risk of resistance
- A major role in the transition CHB treatment and allowed reduction in cirrhosis and risk of HCC to be achieved with some success.

**Adefovir dipivoxil**
- In 2002, first nucleotide analogue approved for the treatment of CHB.
- Had an intrinsic stereoscopic structure which was an important factor against the emergence of viral resistance.
- ADV was highly effective for LAM resistant HBV
- Renal toxicity

**Entecavir**
- A potent polymerase inhibitor with high genetic barrier. The cumulative incidence rate of resistance after 6 years in nucleoside-naïve patients remains low at 1.2%.
- Similar HBeAg seroconversion (21% vs 18%) between ETV & LAM

**5 years ETV monotherapy in NUC naïve HBV**

**Histological outcome**
- 69 patients (50 HBeAg-positive and 19 HBeAg-negative) receiving entecavir at least 3 years
- All patients had HBV DNA level <300 copies/mL (< 50 UI/mL)
- 57 patients with paired liver biopsy (median time of Bx: 6 yrs)
- A ≥1-point improvement in the Ishak fibrosis score occurred in 88% of patients, including all 10 patients with advanced fibrosis or cirrhosis at baseline

**Change in Ishak Fibrosis Scores at Year 5 by Baseline Fibrosis Score**

**Telbivudine**
- In 2006, telbivudine, another nucleoside analogue was approved by the FDA while newer treatments for LAM-resistant disease were still under investigation.
- GLOBE trial: predictors of super-responder in HBeAg+ve CHB: HBV DNA < 9 log_{10} copies/mL or ALT ≥ 2 times the ULN at baseline with undetectable serum HBV DNA at week 24 of therapy.
- High rate of resistance
- Effective and safe for the prevention of mother-to-child transmission of HBV
- Renal protective effect: a trend towards in increased GFR in both compensated and decompensated CHB. The mechanism is unknown.
**Tenofovir**

- In 2008, TDF, the second nucleotide analogue was approved
- Potent antiviral effect with an excellent durability of response
- No resistance detected to date with 5 years of follow up
- First line therapy or Rescue therapy for viral resistance
- A decrease of eGFR has been observed
- Accelerated BMD loss has been reported

**Regression of cirrhosis during treatment with TDF for chronic hepatitis B: a 5-year open-label follow-up study**

Regression of cirrhosis in 74% at 5-year TDF Tx

**Cross-resistance data for the most frequent resistant HBV variants**

<table>
<thead>
<tr>
<th>HBV variant</th>
<th>LVD</th>
<th>LdT</th>
<th>ETV</th>
<th>ADV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M204I/L</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>L180M+M204I/V</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>A181T/V</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>N236T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>A181T/V+N236T</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>L180M+M204I/V+H165T+T184G+S202I+G+M250I/V</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

S= sensitive, I= intermediate/reduced susceptibility, R= resistant

Zoulim & Locarnini Gastroenterology 2009, Liver Int 2013

**Management of HBV Resistance (Early rescue)**

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM resistance</td>
<td>Switch to TDF (add ADV if TDF not available)</td>
</tr>
<tr>
<td>LdT resistance</td>
<td>Switch to or add TDF (add ADV if TDF not available)</td>
</tr>
<tr>
<td>ETV resistance</td>
<td>Switch to or add TDF (add ADV if TDF not available)</td>
</tr>
<tr>
<td>ADV resistance</td>
<td>Switch to ETV or TDF (LAM naive)</td>
</tr>
<tr>
<td>TDF resistance</td>
<td>TDF resistance not detected to date</td>
</tr>
</tbody>
</table>

EASL guideline. J Hepatol 2012

**HBsAg seroclearance with NUCs: rare but important**

5409 CHB patients treated with lamivudine or entecavir
- median follow-up period of 6 years (33,567 patient-years)
- 110 achieved HBsAg seroclearance (0.33% annual seroclearance rate)

Kim GA et al Gut. 2013
A retrospective nationwide study of Taiwan’s NHIRD:
NA therapy is associated with reduced risk of HCC

Wu CY et al. Gastroenterology 2014

Taiwan’s NHIRD (1997/1 – 2010/12)

- Unreated
- Treated (NAs)

Modified log-rank P < .001

HR: 0.37

P < .001

New hepatitis B virus therapeutic strategies

- Direct inhibition (DNA/RNA/peptide)
- Boosting HBV-specific adaptive immunity
- Boosting innate immunity

A. Bertoletti et al. Curr Opin Infect Dis 2014

Significant Reduction in End-stage Liver Diseases Burden through National Viral Hepatitis Therapy Program in Taiwan

CJ Chiang, Chen CJ et al. Hepatology 2014 Accepted manuscript online

肝癌之每十萬人年齡標準化死亡率

肝癌之每十萬人年齢標準化死亡率

New hepatitis B virus therapeutic strategies

TLR-7 agonist
GS-9620

Therapeutic Vaccination
Tarmogen /GS-4774

A. Bertoletti et al. Curr Opin Infect Dis 2014