Medical Management of Hepatitis B

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Outline

• Efficacy of approved treatment
• Limitations of approved treatment
  – Low rate of HBsAg loss
  – Risk of HCC decreased but not eliminated
  – Long-term / lifelong treatment required
• When to start and when to stop treatment
• Feasibility of cure
Goals of HBV Treatment

- Eradication of HBV
- Resolution of hepatic inflammation
- Reversal of liver fibrosis
- Prevention of cirrhosis, liver failure, and hepatocellular carcinoma
Approved HBV Treatments

- **Interferons (IFN)**
  - Standard IFN alfa - 1992
  - Pegylated IFN alfa - 2005

- **Nucleos(t)ide analogues**
  - Lamivudine (Epivir) - 1998
  - Adefovir (Hepsera) - 2002
  - Entecavir (Baraclude) - 2005
  - Telbivudine (Tyzeka) - 2006
  - Tenofovir (Viread) - 2008
Decrease in Serum HBV DNA after 1 Year of Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Log_{10} Decrease in HBV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM</td>
<td>-5.5</td>
</tr>
<tr>
<td>ADV</td>
<td>-3.5</td>
</tr>
<tr>
<td>ETV</td>
<td>-6.9</td>
</tr>
<tr>
<td>TBV</td>
<td>-6.5</td>
</tr>
<tr>
<td>TDF</td>
<td>-6.2</td>
</tr>
<tr>
<td>PEG-IFN</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

Not head-to-head comparison, results from various trials combined

LAM=lamivudine, ADV=adefovir, ETV=entecavir, TBV=telbivudine, TDF=tenofovir, PEG-IFN=peginterferon

6 log = 1 million
HBeAg Seroconversion after 1-5 Years of Treatment

At 1 Year

- Peg IFN @: 32%
- LMV: 16-21%
- ADV: 12-18%
- ETV: 21%
- TBV: 22%
- TDF: 21%

> 1 Year

- Peg IFN ^: ~35%
- LMV #: ~50%
- ADV #: 48%
- ETV #: 41%
- TBV *: 42%
- TDF #: 40%

Legends:
Peg = peginterferon
LMV = lamivudine
ADV = adefovir
ETV = entecavir
TBV = telbivudine
TDF = tenofovir

@ 6 months off Rx
^ 3 years off Rx
# 5 years on Rx
* 4 years on Rx
HBsAg Loss after 2-7 Years of Treatment

HBeAg+ Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>HBsAg Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg ^</td>
<td>11</td>
</tr>
<tr>
<td>LMV #</td>
<td>3</td>
</tr>
<tr>
<td>ADV #</td>
<td>2</td>
</tr>
<tr>
<td>ETV #</td>
<td>5</td>
</tr>
<tr>
<td>TBV *</td>
<td>1.3</td>
</tr>
<tr>
<td>TDF @</td>
<td>11.8</td>
</tr>
</tbody>
</table>

HBeAg- Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>HBsAg Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg ^</td>
<td>8</td>
</tr>
<tr>
<td>LMV #</td>
<td>1</td>
</tr>
<tr>
<td>ADV #</td>
<td>5</td>
</tr>
<tr>
<td>ETV</td>
<td>0.5</td>
</tr>
<tr>
<td>TBV *</td>
<td>0.3</td>
</tr>
<tr>
<td>TDF @</td>
<td>0</td>
</tr>
</tbody>
</table>

Peg = peginterferon
LMV = lamivudine
ADV = adefovir
ETV = entecavir
TBV = telbivudine
TDF = tenofovir

^ 3 years off Rx
# 4-5 years on Rx
* 2 years on Rx
@ 7 years on Rx
Reversal of Fibrosis and Cirrhosis
Tenofovir Phase III Trial: Biopsies at Year 0, 1 & 5

- 348/641 (54%) had liver biopsy at baseline and Year 5
- 71/96 (74%) with cirrhosis (Ishak Score ≥5) at baseline no longer had cirrhosis at Year 5

Marcellin, P, Lancet 2013; 381: 468
Antiviral Therapy Prevents Disease Progression

Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml

% with disease progression

Increase CTP score, liver failure or HCC

Liaw YF, NEJM 2004; 351:1521
Antiviral Therapy Decreases Incidence of HCC

651 pts, bridging fibrosis or cirrhosis, HBeAg+ and/or HBV DNA >0.7 MEq/mL

Time to diagnosis (months)

P=0.047

After exclusion of cases in yr 1: HR=0.47; P=0.052

Liaw YF, NEJM 2004; 351:1521
Efficacy of Currently Available HBV Therapies

- Potent viral suppression
- Reverse hepatic fibrosis / cirrhosis
- Prevent progression to liver failure

**BUT**

- Low rate of HBsAg loss
- Decrease but not eliminate risk of HCC
Low Rate of HBsAg Loss

• IFN treatment
  – HBsAg loss rare in genotype non-A and in Asians

• Nucleos(t)ide analogue treatment
  – Slow decline in HBsAg titer, particularly for genotype non-A
  – Estimated time to HBsAg loss, after median 52.2 (IQR: 30.8-142.7) years continuous treatment¹

¹Chevaliez S, J Hepatol 2013; 58: 676
PEG-IFN +/- Lamivudine in HBeAg+ Patients

172 patients followed x mean of 3.5 years after end of treatment
Low rate of HBsAg loss in genotype B or C infection

Buster E, Gastroenterol 2008; 135: 459
# Phase 3 Trial of Tenofovir

**HBsAg Loss by Week 144 in HBeAg+ Patients**

HBsAg loss in tenofovir trial only in non-Asians and HBV genotypes non B or C

<table>
<thead>
<tr>
<th></th>
<th>HBsAg+ (N=243)</th>
<th>HBsAg- (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), year</strong></td>
<td>32 (18-63)</td>
<td>37 (20-64)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>94 (39)</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>118 (49)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Black</td>
<td>17 (7)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>167 (69)</td>
<td>16 (80)</td>
</tr>
<tr>
<td><strong>HBV genotype, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>46 (19)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>B</td>
<td>34 (14)</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>68 (29)</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>78 (33)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>E/F</td>
<td>12 (5)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

*Heathcote EJ, Gastroenterol 2011; 140: 132*
Most common HBV genotypes in N America: B&C

1625 adults with CHB not receiving antiviral therapy enrolled 1/2011 – 8/2013

Does HBsAg Loss Equal Cure?

- **HBV DNA**
  - Undetectable in serum in most patients
  - Detected in liver in majority of patients

- **Liver histology**
  - Inflammation and fibrosis decreased but not completely gone

- **Clinical outcomes**
  - Risk of liver failure and mortality decreased
  - Risk of HCC decreased but not eliminated
Outcomes After Spontaneous HBsAg Loss

- 298 patients spontaneous HBsAg loss
- HBV DNA detected in serum in 13.4% of 142 patients within 1 year and in 3.7% of 27 patients >10 years after HBsAg loss
- HCC in 7 patients, none in those who lost HBsAg before age 50
Cumulative Probability of Survival in Patients with Compensated Cirrhosis who did or did not Clear HBsAg

- Liver-related deaths
- 1 (3%) patient who cleared HBsAg – HCC
- 55 (20%) patients who did not clear HBsAg: HCC (19) and liver failure (36)

Fattovich G, Am J Gastroenterol 1998; 93: 896
Cumulative Probability of HCC in Patients with Compensated Cirrhosis who did or did not Clear HBsAg

HCC in 1/32 (3%) who cleared and in 30/277 (11%) who did not clear HBsAg

Fattovich G, Am J Gastroenterol 1998; 93: 896
Strategies to Increase Rate of HBsAg Loss Combining Existing Therapies

- Combining 2 NUCs
- Combining NUC and IFN
  - Simultaneous start
  - Add on: IFN or NUC first, second drug added after a few weeks or a few years
  - Switching therapy, NUC first, stop after viral suppression and switch to IFN
De Novo Entecavir + Tenofovir Did not Increase HBsAg Loss Compared to Entecavir Alone

HBeAg seroconversion, %

HBsAg loss, %

HBV genotypes

Lok A, Gastroenterol 2012; 143: 619
Combination of Tenofovir and Peg-IFN Increases Rate of HBsAg Loss Compared to Monotherapy

- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk → TDF 32 wk])
- 5/7 had ≤1 week of therapy after HBsAg loss

Marcellin P, Gastroenterol (in press)
Combination of Tenofovir and Peg-IFN Increases HBsAg Loss Only in Genotype A

<table>
<thead>
<tr>
<th>Group</th>
<th>A= TDF+PEG x 48 wk</th>
<th>B= TDF+PEG x 16 wk + TDF x 32 wk</th>
<th>C= TDFx120 wk</th>
<th>D= PEGx48 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Marcellin P, Gastroenterol 2015 (in press)
Adding Pegylated Interferon to Entecavir for HBeAg+ Chronic Hepatitis B: ARES Study

Response?

PEG-IFN 180μg/week

Yes**
N=16

ETV 0.5mg/day

Follow-up
N=14

No
N=69

ETV 0.5mg/day

Randomization 1:1
N=90

Yes**
N=9

ETV 0.5mg/day

Follow-up
N=8

No
N=81

ETV 0.5mg/day

Weeks

*Response was defined as HBeAg loss with a HBV DNA <200 IU/mL (primary endpoint at week 48)

**Responders were to stop ETV therapy at week 72 and thus received at least 24 weeks of consolidation therapy. Two responders assigned add-on and 1 responder assigned monotherapy continued ETV monotherapy (protocol violation)
Adding Pegylated Interferon to Entecavir for HBeAg+ Chronic Hepatitis B: ARES Study

Peg-IFN add on:
- ~0.3 log decline in HBsAg
- Only 1/85 HBsAg seroconversion

Brouwer WP, Hepatology 2015; 61: 1512
Switching from Entecavir to PEG-IFN in HBeAg+ Patients (OSST Trial)

- HBeAg+ patients on ETV with HBV DNA <1000 c/mL and HBeAg <100 PE IU/mL
- Randomized to switch to Peg-IFN x 48 weeks with 8 weeks ETV overlap or to continue ETV

HBeAg-positive subjects receiving ETV 0.5 mg QD for 9-36 months with HBV DNA <1000 copies/ml + HBeAg <100 PE IU/ml (N = 200).

Peginterferon alfa-2a 180 µg/week (n = 97)

ETV 0.5 mg QD (n = 100)

Randomisation 1:1

Ning Q, J Hepatol 2014; 61: 777
Switching from Entecavir to PEG-IFN in HBeAg+ Patients (OSST Trial)

PEG-IFN group higher rate of HBeAg seroconversion and HBsAg loss but also higher rate of AEs and ALT flares

P = 0.047

Ning Q, J Hepatol 2014; 61: 777
Does Antiviral Therapy Prevent HCC Development?

- Is risk of HCC decreased?
- Is risk in CHB patients with maintained viral suppression during antiviral therapy same as in inactive carriers?
- Does risk of HCC continue to decline with longer duration of viral suppression?
Decrease in Number of HBV Patients Listed for Liver Transplant for ESLD in the U.S. but Not in Number Listed for HCC

ESLD: endstage liver disease

Approval of lamivudine
Patients with HBV DNA Suppression During Oral Antiviral Therapy Retain a Higher Risk of HCC Than Patients with Inactive Disease

- HCC incidence of NUC treated patients compared to historic inactive controls
- Complete response (CR) defined as HBV DNA continuously <2000 IU/mL
- Incidence of HCC in CR calculated from time when HBV DNA <2000 IU/mL

LC: Cirrhosis
CHB: Chronic hepatitis B

Cho JY, Gut 2014;63:1943
Risk of HCC Remains After Five Years of ETV or TDF Therapy in Caucasian CHB Patients

794 adult Caucasian CHB patients

**Cumulative HCC Incidence in Relation to Presence of Cirrhosis**

- **No Cirrhosis**
  - Yearly incidence rate: 3.27%
  - Cumulative incidence: 15.04% (P=0.45)

- **Cirrhosis**
  - Yearly incidence rate: 1.07%
  - Cumulative incidence: 12.11% (P=0.818)

**Cumulative HCC Incidence**

- Yearly incidence rate: 1.22%
- Cumulative incidence: 17.96% (P=0.086)

HCC risk seems to be decreasing after the first 5 years of ETV/TDF therapy in CHB patients, especially in those with compensated cirrhosis at baseline.

Late HCC development mainly in older patients (>55 years) at start of treatment.
HBV Treatment: When to Start?

TREAT NOW

TREAT NOW OR MONITOR?

MONITOR & DEFER TREATMENT UNTIL INDICATED

Risk of Cirrhosis, Liver Failure and HCC
Clear Cut Cases in Which Treatment Should be Initiated Now

- Life-threatening liver disease
  - Fulminant hepatitis B
  - Severe exacerbations of chronic hepatitis B
  - Decompensated HBV cirrhosis
- High risk of liver failure/HCC in the near future
  - Compensated cirrhosis and high serum HBV DNA
- HBsAg+ patients who will be starting immunosuppressive therapy
- Non-cirrhotics at high risk of progressive liver disease
When to Initiate Treatment in Non-Cirrhotics?

- **HBeAg**
- **Anti-HBe**

- **HBV DNA**
- **ALT**

- **Immune tolerant**
- **Immune clearance HBeAg-positive chronic hepatitis**
- **Inactive carrier state**
- ** Reactivation HBeAg-negative chronic hepatitis**

Years:
- 0
- 20
- 40
- 60
HCC Can Occur at any Age, during HBeAg+ or HBeAg- Phase, with or without Cirrhosis
High Viral Load is Associated with Increased Incidence of HCC

REVEAL Study (n=3,653), mean age 43

Cumulative incidence of HCC (% subjects)

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)

Log rank test of trend
p<0.001

Tenofovir vs. Emtricitabine + Tenofovir x 4 Years
Immune Tolerance Phase
HBeAg+, HBV DNA ≥8 log10 c/mL, ALT ≤ULN

Response at Week 192

Universal relapse when treatment stopped

Chan H, Gastroenterol 2014; 146: 1240
## Which Treatment? Interferon or Nucleos(t)ide Analogue?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Interferon</th>
<th>Nucleos(t)ide Analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>Finite duration ~ 12 mos</td>
<td>Long duration, yrs to life long</td>
</tr>
<tr>
<td><strong>Antiviral activity</strong></td>
<td>Modest , also immunomodulatory effects</td>
<td>Potent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ETV/TDF/TBV  &gt; LAM  &gt; ADV</td>
</tr>
<tr>
<td><strong>HBsAg loss</strong></td>
<td>1-3% after 1 yr</td>
<td>Rare, 0-1% after 1 yr</td>
</tr>
<tr>
<td><strong>Resistance mutations</strong></td>
<td>None</td>
<td>0-25% after 1 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LAM &gt; TBV &gt; ADV &gt; ETV/TDF</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Frequent</td>
<td>Rare</td>
</tr>
</tbody>
</table>

ADV: adefovir, ETV: entecavir; LAM: lamivudine, TBV: telbivudine; TDF: tenofovir
Can HBV Antiviral Therapy be Stopped?

Risk of hepatitis flare
Loss of benefit
Price of long-term treatment
## Guideline Recommendations Regarding When to Stop Nucleos(t)ide Analogues

<table>
<thead>
<tr>
<th></th>
<th>AASLD 2015</th>
<th>APASL 2012</th>
<th>EASL 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg+</strong></td>
<td>HBeAg seroconversion and UD HBV DNA + ≥12 mo consolidation</td>
<td>HBeAg seroconversion and UD HBV DNA ≥12 mos</td>
<td>HBeAg seroconversion + ≥12 mo consolidation</td>
</tr>
<tr>
<td><strong>HBeAg-</strong></td>
<td>HBsAg loss?</td>
<td>HBsAg loss or Rx ≥2 yr with UD HBV DNA ≥3 occasions 6 mo apart</td>
<td>HBsAg loss?</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>DO NOT STOP</td>
<td>?</td>
<td>DO NOT STOP</td>
</tr>
</tbody>
</table>

**Notes:**
- HBeAg: Hepatitis B e-Antigen
- UD: Undetectable
- Rx: Treatment

**References:**
- Terrault N, Hepatology 2015 (in press); Liaw YF Hepatol Int 2012; 6: 531; EASL J Hepatol 2012; 57: 167
Duration of Nucleos(t)ide Analogue Therapy
Adverse Effects of HBV Treatment

• Interferon
  – SC injections
  – ‘flu-like symptoms, fatigue, mood changes, depression, bone marrow suppression, unmask or exacerbate autoimmune illnesses

• Nucleos(t)ide analogs
  – Lactic acidosis, rare
  – Adefovir and tenofovir – nephrotoxicity
  – Tenofovir – decrease bone mineral density
  – Telbivudine – myopathy, peripheral neuropathy
## Tenofovir (TDF) vs. Tenofovir + Emtricitabine (FTC/TDF) in Patients with Lamivudine Resistance: Safety Through 5 Years

<table>
<thead>
<tr>
<th>n, (%)</th>
<th>TDF (N=141)</th>
<th>FTC/TDF (N=139)</th>
<th>Total (N=280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs leading to study drug discontinuation</td>
<td>4 (2.8)</td>
<td>5 (3.6)</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (2.1)</td>
<td>4 (2.9)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs*</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Confirmed renal events†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCr ≥0.5 mg/dL above baseline</td>
<td>2 (1.4)</td>
<td>0</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td><strong>SCr ≥0.3 mg/dL above baseline</strong></td>
<td><strong>13 (9.2)</strong></td>
<td><strong>8 (5.8)</strong></td>
<td><strong>21 (7.5)</strong></td>
</tr>
<tr>
<td>PO$_4$ &lt;2 mg/dL</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>CL$_{Cr}$ &lt;50 mL/min</td>
<td>10 (7.1)</td>
<td>9 (6.5)</td>
<td>19 (6.8)††</td>
</tr>
</tbody>
</table>

*AE judged by the investigator as study drug-related  
† SCr = serum creatinine, PO$_4$ = serum phosphate, CL$_{Cr}$ = creatinine clearance (Cockcroft-Gault)
On baseline DEXA scan, osteopenia and osteoporosis were present in 34% and 7% of patients in spine, and 23% and 1.4% in hip.

Mean total BMD declines of 1% and 3% were seen at Week 240 in spine and hip, respectively.

Fractures were reported in 7 patients (TDF 3; FTC/TDF 4) – 6 were trauma-related, no information available for 1 patient.

Fung S, AASLD 2015, abs 2004
Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF; * Cumulative probabilities of resistance taken; † Naïve HBeAg (+); ‡ Naïve HBeAg(-); N/A not available.

Adherence to HBV Nucleos(t)ide Analogs: Analysis of pharmacy claims database in 3 cohorts of patients treated in the US in 2007, 2008 and 2009

20% patients <80% adherence (% of days in that year in which patients have medications in their hands)
Cost of HBV Treatment

- Medications
  - Retail price for entecavir or tenofovir
    - 30 days ~$1000
    - 5 years ~$60,000
- Physician visits
- Monitoring labs
Is HBV Eradication Possible?

Can treatment accomplish what nature can’t?

HBV persists in persons who have recovered from acute hepatitis B with HBsAg to anti-HBs seroconversion

- Reactivation of HBV replication during potent immunosuppressive therapy
- Transmission of HBV when livers are transplanted
- Long-lasting rigorous immune response to HBV after “recovery”
Barriers to Eradicating HBV

- ccc DNA
- Integrated HBV DNA
- Impaired immune response
- Existing therapies target only a few steps in HBV lifecycle

Diagram showing the lifecycle of HBV with arrows indicating viral entry, vesicular transport, receptor uncoating, nuclear import, replication, transcription, translation, assembly, budding, and vesicular transport. The diagram highlights the replenishment of cccDNA.
Combination of Antiviral and Immune Modulating Therapies May Achieve Functional Cure

Viral targets
- Entry inhibition
- cccDNA
  - formation
  - stability / destruction
  - epigenetic regulation
- Viral core functions
- Other viral targets

Immune modulation
- Stimulate innate responses
  - Specific ligands
- Stimulate adaptive responses
  - Co-inhibitory signals
  - Co-stimulatory signals
- Therapeutic vaccination

Functional cure
- HBsAg loss
- Sustained suppression of HBV replication with finite course of therapy
Current Status of Hepatitis B Treatment

- Effective in long-term suppression of HBV replication but not eradication of HBV
- Maintenance of viral suppression reverses liver fibrosis, decreases risk of HCC
- Long-term (lifelong) treatment necessary to maintain clinical benefit
- Definitive cure of hepatitis B may not be feasible but strategies to increase HBsAg loss (functional cure?) should be encouraged