Treatment of Chronic Hepatitis B in an HBeAg Positive Patient

Adrián Gadano, MD
Chief, Liver Unit - Hospital Italiano
President, Fundación Icalma
Buenos Aires - Argentina
Case 1: History

- 52-year-old man.
- Referred from a gastroenterologist for HBeAg + CHB.
- Diagnosis established 3 years before, when donating blood (HBsAg positive).
- Possible route of transmission: high-risk sexual contacts during adolescence.
- No family history of HBV. Alcohol use occasional.
- Asymptomatic. Physical exam unremarkable.
- He had received 2-year therapy with lamivudine after diagnosis with unknown outcome…
Current presentation

• Serological and biochemical status at baseline:
  • ALT level: 112 IU/L (ULN: 40 IU/L).
  • AST level: 87 IU/L (ULN: 40 IU/L).
  • HBsAg: positive.
  • HBeAg: positive / anti-HBe: negative.
  • HBV DNA level was 7.8 log10 copies/mL.
  • Albumin 3.7 mg/dL, total bilirubin 1.0 mg/dL, platelet count 198,000/mm3, INR 1 and serum creatinine 1.0 mg/dL.
  • HCV and HIV were negative.
  • Ultrasound: mild heterogeneous liver architecture with no focal lesions.
Current presentation

• Liver biopsy (3 years before): moderate inflammation and fibrosis extending outside the portal tracts (Metavir A2, F3).

• Fibroscan: 9.1 KPa
Natural History of Chronic Hepatitis B

**HBsAg +**

- **HBeAg +**
  - Normal liver or mild hepatitis
  - Periportal or lobular inflammation
  - Integrated DNA?

- **HBeAg -**
  - Immuno-tolerance
  - Immune-active
  - Inactive phase
  - Immune-active

**ALT**

**HBV DNA**

**Replication**

- ++++
- +++
- +/-
- ++

Lok ASF  New Engl J Med 2002
Decision-making process and outcome

• Treatment with tenofovir was started at the dose of 300 mg/day.
• TDF was well-tolerated.
• After 12 months of therapy, HBV DNA level was undetectable and ALT was normal. HBsAg and HBeAg remained positive.
TDF 300 mg

Fibroscan 9.1 KPa

HBeAg pos

HBsAg pos

ALT (IU/L)

Months

0 6 12 24 36 48 60

0 10 20 30 40 50 60 70 80 90 100 110 120
TDF 300 mg

Fibroscan 9.1 KPa

Fibroscan 7.1 KPa

Creatinine 1.4 mg/dl

HBsAg pos

HBeAg pos

ALT (IU/L)

Fibroscan

0 6 12 24 36 48 60

Months
What would you recommend at this time?

a. Stop tenofovir and start entecavir
b. Stop tenofovir and start PEG IFN alfa 2a
c. Add PEG IFN alfa 2a
d. Continue with tenofovir
Treatment of Chronic Hepatitis B in an HBeAg Negative Patient

Adrián Gadano, MD
Chief, Liver Unit - Hospital Italiano
President, Fundación Icalma
Buenos Aires - Argentina
Case 2: History

- 56-year-old woman.
- Diagnosis established 6 months before.
- Possible route of transmission: Family history of HBV (husband).
- Asymptomatic.
Current presentation

• ALT level: 86 IU/L (ULN: 40 IU/L).
• AST level: 77 IU/L (ULN: 40 IU/L).
• HBsAg: positive.
• HBeAg: negative / anti-HBe: negative.
• HBV DNA level: 6.8 log10 copies/mL.
• HBV genotype: A
• Albumin 3.8 mg/dL, total bilirubin 1.1 mg/dL, platelet count 144.000/mm3, INR 1.1 and serum creatinine 0.8 mg/dL.
• HCV and HIV were negative.
• Ultrasound revealed heterogeneous liver architecture with no focal lesions.
Natural History of Chronic Hepatitis B

**HBsAg +**

- **HBeAg +**
  - Normal liver or mild portitis
  - Immuno-tolerance
- **HBeAg -**
  - Integrated DNA?
  - Inactive phase
  - Immune-active

**HBV DNA**

**ALT**

- Replication ++++
- Replication +++
- Replication +/-
- Replication ++

*Lok ASF  New Engl J Med 2002*
Decision-making process and outcome

• Treatment with entecavir was started at the dose of 0.5 mg/day.
• ETV was well-tolerated.
• After 12 months of therapy, HBV DNA level was undetectable and ALT was normal. HBeAg remained negative and HBsAg remained positive.
• After 60 months of therapy, ETV was discontinued.
Hepatitis B: CASE 2

- Entecavir 0.5 mg

Fibroscan 10.2 KPa

Fibroscan 7.6 KPa

ALT < 26

HBsAg > 250

Months

0 6 12 24 36 48 60

HBeAg neg

HBsAg pos

Fibroscan 7.6 KPa
Hepatitis B: CASE 2

**Fibroscan 10.2 KPa**

Entecavir 0.5 mg

ALT < 26

HBsAg > 250

Fibroscan 7.6 KPa

Fibroscan 6.5 KPa

**Fibroscan 6.5 KPa**

HBsAg 100-250

HBeAg neg

HBsAg pos

0 6 12 24 36 48 60

Months
What would you recommend at this time?

a. Stop entecavir?
   - According to HBsAg levels? Below which threshold?
   - According to fibrosis stage?

b. Start PEG IFN alfa 2a?
   - Taking into account HBsAg levels?
   - Taking into account fibrosis stage?
   - Switch or add-on?
   - For how long?
Realistic goal → a “functional cure”:

- HBV DNA not detectable after a finite treatment
- Loss of HBsAg
- Regression of fibrosis
- Minimization of hepatocellular carcinoma risk

To accomplish this goal, a combination of antiviral drugs that target different steps in the HBV life cycle or immunomodulatory therapies to restore host immune response to HBV might be needed…
HBV: Improving therapeutic options…

Cure of HBV infection: Is it possible?

- New strategies with known drugs
- New drugs with different targets
New Strategies with Known Drugs…

- Given the two classes of anti-HBV agents that are currently available, combination therapy consist of an NRTI (TDF or ETV) plus PEG-IFN.

- NRTI and PEG-IFN may be combined simultaneously, sequentially, starting with either drug first, or as an add-on strategy with either drug first.
Combined Antiviral and Immune-stimulating strategy

Treatment with NA

Decrease in HBV DNA and HBsAg

Entry inhibitors?

T Cell stimulation

Exhausted T Cells

FUncionality of T cells

Recovered T Cells
Combined Antiviral and Immune-stimulating strategy

Chronic HBV infection

ETV-TDF

Peg IFN

Peg IFN + AN

Restoration of immune response

Robert Thimme, Maura Dandri  Journal of hepatology 2013
Combined Antiviral and Immune-stimulating strategy

Decrease and loss of HBsAg
Peg-INF in patients previously treated with NA

PEGON study

HBeAg +

DNA-HBV <2000 UI/ml

ETV or TDF

48 Weeks Peg IFN

ETV or TDF

N:39

ETV or TDF

Follow-up

ETV or TDF

N:38

ETV or TDF

Follow-up

ETV or TDF

Median duration: 2.4 years

Chi et al, AASLD 2015
Seroconversion of HbeAg to anti-Hbe in patients with HBV DNA < 200 U/ml

Chi et al, AASLD 2015

* p = 0.06
HBV: Improving therapeutic options...

Cure of HBV infection: Is it possible?

New strategies with known drugs

New drugs with different targets
Experimental HBV Therapeutics in late preclinical or clinical phase

• Entry inhibitors: Myrcludex B, cyclosporine A…
• HBV capsid inhibitors: AT-130, Bay 41-4109…
• Inhibition of HBV gene expression.
• Inhibitors of HBV cccDNA formation and stability.
• Immune mechanisms of HBV control:
  • TLR agonists
  • PD-1 and other coinhibitory blockers
• Engineered T cells.
• Therapeutic vaccines…

Liang et al, Hepatology 2015
Back-up slides
Myrcludex B pre S1
Tratamiento contra HBV y HDV
Asociación de IFN más AN
85% ETV-TDF

N: 183 ptes
86% : Hombres
HBsAg © 3520 UI/ml
DNA-HBV: ND
Duración : 48 semanas

Pérdida de HBsAg %

<table>
<thead>
<tr>
<th></th>
<th>1%</th>
<th>7/90</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN</td>
<td>1/93</td>
<td></td>
</tr>
<tr>
<td>AN + IFN-P</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

p< 0.05