CLINICAL APPLICATIONS of HBsAg QUANTIFICATION

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CASE - 1

• 25 Years Old Patient

• HBsAg (+)    HBeAg (-)    HBeAb (+)

• HBV DNA = 380 U/mL    HBsAg = 260 U/mL

• ALT = 26 U

• Abdominal US Normal
Diagnosis?

1. HBV Inactive Carrier
2. Mutant - Type Chronic HBV Infection
3. Immune Clearance Phase of HBV Infection
4. Immune Tolerance Phase of HBV Infection
Management?

1. Start PEG-IFN Injections
2. Start Oral Treatment (TDF or ETV)
3. Follow-up Every 3 - 6 Months
4. No Need for Follow-up
HBV Infection: Natural History

- **Anti-HBe**
- **HBV DNA**
- **ALT**
- **Immune tolerant**
- **Immune clearance HBeAg (+) CHB**
- **Inactive CHB**
- **Reactivation HBeAg (-) CHB**
After spontaneous HBeAg seroconversion, 67% to 80% of carriers remain in inactive carrier phase. 4% to 20% of inactive carriers have reversion back to HBeAg positive. 10% to 20% have reactivation after years of quiescence disease. Serial testing is necessary during the "inactive carrier state".

Lok AS et al. Hepatology 2009
Inactive Carrier: Monitoring

• A minimum follow-up of 1 year with ALT levels at least every 3-4 months and HBV DNA levels is required before classifying a patient as inactive carrier

• Inactive carriers should be followed up for life with ALT determinations at least every 6 months after the first year and periodical measurement of HBV DNA levels

EASL Guidelines. J Hepatol 2012
HBV Life Cycle
# HBV DNA & HBsAg: Different Meanings

<table>
<thead>
<tr>
<th></th>
<th>HBV DNA</th>
<th>HBsAg</th>
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</thead>
<tbody>
<tr>
<td><strong>Virology</strong></td>
<td>Dane particle</td>
<td>Dane particle and subviral particles</td>
</tr>
<tr>
<td><strong>Natural history</strong></td>
<td>Reduced after HBeAg seroconversion but relapse on immune escape</td>
<td>Very slow reduction over time regardless of HBV DNA levels or disease activity</td>
</tr>
<tr>
<td><strong>Implication</strong></td>
<td>Viral replication</td>
<td>Immune clearance of infected hepatocytes</td>
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Moucari et al. Liver Int. 2011
Role of qHBsAg in Inactive Carrier Status

- Single Point Quantification of
  - HBsAg (< 1000 IU/mL) &
  - HBV DNA (< 2000 IU/mL)
- Negative Predictive Value: > 96%
- Positive Predictive Value: > 88%
- Accuracy > 90%

CASE - 2

- 40 Years Old Patient
- HBsAg (+)  HBeAg (-)  HBeAb (+)
- HBV DNA = 145,000 U/mL  HBsAg = 3460 U/mL
- Genotype D
- ALT = 118 U
- Abdominal US Normal
- Liver Biopsy: A2F1
Management?

1. Start PEG-IFN Injections
2. Start NUCs (TDF or ETV)
3. No Treatment - Mild Fibrosis (F1)
4. No Treatment - Difficult Genotype
Treatment Indications in HBeAg (-) Patients

- Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy showing moderate to severe active necro-inflammation and/or at least moderate fibrosis.

- Patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy.

EASL Guidelines. J Hepatol 2012
Treatment Endpoints in HBeAg (-) Patients

- The ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs

- Induction of sustained off-therapy virological (HBV DNA < 2000 U/mL) and biochemical response (Normal ALT) is a satisfactory end point

- A maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy is the next desirable endpoint
Treatment Modalities in HBeAg (-) Patients

• A finite duration treatment with of PEG-IFN can be used: the only option that may offer a chance for sustained off-treatment response

Versus

• A long term treatment with NUCs

EASL Guidelines. J Hepatol 2012
Case - 2: On-Treatment (PEG-IFN)
HBV DNA Pattern

![Graph showing HBV DNA pattern over time from Day 0 to Week 48. The graph shows a decrease in HBV DNA levels from Day 0 to Week 48.]
Case - 2: On-Treatment (PEG-IFN)
HBV DNA Pattern

Day 0
Week 12
Week 24
Week 48
Week 72

0
2
3
5
6

HBV DNA

0 1 2 3 4 5 6
Day 0 Week 12 Week 24 Week 48 Week 72
Case - 2: On-Treatment (PEG-IFN)
HBsAg Pattern
qHBsAg in HBeAg (-) Patients Treated with PEG-IFN: Responders Vs. Relapsers & NR

Moucari et al. Hepatology 2009
qHBsAg: Predictor of Response in HBeAg (-) Patients Treated with PEG-IFN

230 patients with HBeAg-negative CHB treated with peg-IFN alfa 2a ± lamivudine*

Week 12

<table>
<thead>
<tr>
<th>HBV DNA ≤10,000 copies/mL</th>
<th>1 year post-treatment (%)</th>
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<tbody>
<tr>
<td>≥10%</td>
<td>47%</td>
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<tr>
<td>&lt;10%</td>
<td>16%</td>
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Week 24

<table>
<thead>
<tr>
<th>HBV DNA ≤10,000 copies/mL</th>
<th>1 year post-treatment (%)</th>
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</thead>
<tbody>
<tr>
<td>≥10%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>13%</td>
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</tbody>
</table>

Marcellin et al. Hepatol Int. 2013
qHBsAg: Predictor of Response in HBeAg (-) Patients Treated with PEG-IFN

WEEK 12

Any HBsAg decline
No
N=54
Yes
N=48

HBV DNA decline (copies/mL)
<2 log
N=20
≥2 log
N=34
<2 log
N=20
≥2 log
N=28

Chance of sustained response*
0/20 (0%)
8/34 (24%)
5/20 (25%)
11/28 (39%)

CASE - 2

- Patient Decide to Start Oral Therapy with ETV 0.5 mg / day
- At Treatment Week 24: HBV DNA < LLD
- At Treatment Week 48: HBV DNA < LLD
- At Treatment Week 96: HBV DNA < LLD
Treatment Duration?

1. Life - Time Treatment
2. 5 Years of HBV DNA Undetectability
3. HBsAg Loss
4. HBsAg Decline < 200 U/mL
Long-term treatment with ETV / TDF is necessary for patients who are not expected to achieve a sustained off-treatment virological response

- HBeAg-positive patients who do not develop anti-HBe seroconversion

&

- HBeAg-negative patients
Sustained Response in HBeAg (-) Patients Treated with NUCs

- 33 HBeAg (-) Patients
- ADV for 5 Years
- 55% SVR
- Lower HBsAg Level

Hadziyannis et al. Gastroenterology 2012
qHBsAg Predictor of SVR in HBeAg (-) Patients Treated with NUCs

- 105 HBeAg (-) Patients
- Lamivudine for 52 - 243 weeks
- FUP: 12 - 157 months
- Relapse Rate: 43.4%, 60.1% & 68.4% at years 1, 3 & 6
- HBsAg < 200 U/mL had a PPV 93.3% for SVR

Chen et al, J. Hepatol 2014
CASE - 3

- 32 Years Old Patient
- HBsAg (+)    HBeAg (+)    HBeAb (-)
- HBV DNA = 12 650 000 U/mL    HBsAg = 11 460 U/mL
- Genotype A
- ALT = 142 U
- Abdominal US Normal
Management?

1. Start PEG-IFN Injections - Good Genotype
2. Start NUCs (TDF or ETV) - High HBV DNA
3. Combination PEG-IFN + NUC
Treatment Indications in HBeAg (+) Patients

• Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy showing moderate to severe active necro-inflammation and/or at least moderate fibrosis

• Patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy
Treatment Endpoints in HBeAg (+) Patients

- The ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs

- Induction of sustained off-therapy virological (sustained HBe seroconversion, HBV DNA < 2000 U/mL) and bio-chemical response (Normal ALT) is a satisfactory end point

- A maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy in patients who do not achieve anti-HBe seroconversion is the next desirable endpoint
Treatment Modalities in HBeAg (+) Patients

- A 48-week course of PEG-IFN is mainly recommended for patients with the best chance of anti-HBe seroconversion (Genotypes A & B, Low HBV DNA and High ALT)

- A Finite-duration treatment with a NA is achievable for HBeAg-positive patients who seroconvert to anti-HBe on treatment. Once anti-HBe seroconversion occurs during NA administration, treatment should be prolonged for an additional 12 months

EASL Guidelines. J Hepatol 2012
Case - 3: On-Treatment (TDF) HBV DNA Pattern
Case - 3: On-Treatment (TDF) HBV DNA Pattern
Case - 3: On-Treatment (TDF) HBV DNA Pattern

HBe Serconversion

HBe Reversion
Case - 3: On-Treatment (TDF) HBsAg Pattern
qHBsAg: Predictor of SVR in HBeAg (+) Patients Treated with NUCS

112 HBeAg (+) Patients
ETV for 26 - 40 Months, including at Least 12 Months after HBe Seroconversion
ETV Was Stopped with Post-Treatment FUP of 52 Weeks

Relapse Rate = 48.2%. HBsAg level of 2.5 log10 IU/ml at HBeAg seroconversion had a PPV = 95% for SVR
Qiu et al, JID 2014
Case - 3: On-Treatment (PEG-IFN)
HBV DNA Pattern

Day 0
Week 12
Week 24
Week 48

HBV DNA
Case - 3: On-Treatment (PEG-IFN) HBV DNA Pattern
Case - 3: On-Treatment (PEG-IFN) HBsAg Pattern
qHBsAg: Predictor of SVR in HBeAg (+) Patients Treated with PEG-IFN

Take Home Messages

HBsAg: Different than HBV DNA

qHBsAg: May Reflect the Number of Infected Hepatocytes

qHBsAg: Clinically Relevant Marker

In combination with HBV DNA may help to:

determine the stage of the disease (Inactive Carrier Vs. Active Hepatitis)

predict sustained off-treatment response to PEG-IFN & NUCS

tailor the treatment duration & generate stopping rules