Do I treat my HBV immunotolerant patients?

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Do I treat my HBV immunotolerant patients?

No

Except for a few
Who are the “HBV immunotolerant patients”?

- Patients with chronic HBV infection and immune tolerance specifically to HBV

- Hyporesponsive HBV specific T cells: anergy, deletion, altered maturation of HBV specific effector cells & expansion of regulatory T cells (Park JJ et al. GE 2015, Dec 9, Epud ahead of print)

- HBeAg positive

- High serum HBV DNA levels (usually >10^7 IU/mL)

- Persistently normal ALT
Natural History of Chronic HBV Infection

Replicative/Immune tolerant phase | HBeAg clearance phase*
---|---
HBeAg(+) | Low-replicative phase

HBeAg(-)/anti-HBe(+) | Replicative/reactivating phase*
---|---
HBeAg(-)CHB | Immune reactive phases

Serum HBV DNA, log_{10} IU/mL

ALT ULN

HBeAg clearance phase is not always effective

**Effective**
- HBeAg (+)
- Anti-HBe
- HBV DNA/HBsAg declining prior to the peak of ALT

**Ineffective**
- HBeAg (+)
- HBV DNA/HBsAg increasing or stable

Natural History of HBeAg(+) Chronic HBV Infection

- Immune tolerant phase
- Immune reactive phase
- Immune tolerant phase
- Immune reactive phase
- Immune tolerant phase

Serum HBV DNA, $\log_{10}$ IU/mL

- ALT
- ULN

- HBeAg(+)
Natural History of HBeAg(+) Chronic HBV Infection

- Immune tolerant phase
- Immune reactive phase
- Immune tolerant phase
- Immune reactive phase
- Immune tolerant phase

Serum HBV DNA, log_{10} IU/mL

- Immuno-tolerant phase
- HBeAg-pos. CHB phase
- Immuno-tolerant phase
- HBeAg-pos. CHB phase
- Immuno-tolerant phase

ALT
ULN
Types of HBeAg-positive chronic HBV patients

A. Areas with high HBV prevalence – vertical transmission
   (East Asian countries – genotypes B & C)
   Low (5%) mean annual rate of HBeAg seroconversion –
   Substantial proportion of adults: HBeAg+

   Predictors of HBeAg seroconversion:
   older age, higher ALT, lower HBV DNA, HBV genotypes A (vs D), B (vs C)


B. Areas with intermediate HBV prevalence – horizontal transmission
   (Mediterranean & Middle East countries – genotypes D>A)
   High (10-15%) annual rate of HBeAg seroconversion – <10-20% of adults: HBeAg+

C. Areas with low HBV prevalence – transmission among high-risk adults
   (Western countries in the past – genotype A)
   Not many data for HBeAg seroconversion rates (probably high) –
   HBeAg+ adults with short duration of HBV infection

Predictors of HBeAg seroconversion:
   older age, higher ALT, lower HBV DNA, HBV genotypes A (vs D), B (vs C)
Main arguments favoring treatment initiation in HBV immunotolerant patients

• Maintenance of high HBV replication: increasing numbers of infected hepatocytes
  - Risk of progression of liver lesions
  - Increasing HCC risk

• High risk of HBV transmission
  (NAs may be required in the third trimester of pregnancy of HBV immunotolerant women, not any more in infancy/childhood due to universal vaccination programs)
Liver histological lesions in chronic HBV patients by ALT levels

Overall 37% of patients in the normal ALT group had significant necroinflammation or fibrosis.


Limitations - Both HBeAg+ & HBeAg- patients, PNALT: ≥2 normal ALT determinations ≥6 months apart, Older age: independent risk factor for advanced fibrosis
Severity of liver fibrosis according to HBeAg status and ALT

PNALT: persistently normal ALT, PIEALT: persistently or intermittently elevated ALT

Limitations – Representative sample? (PNALT/PIEALT: 73/530 for HBeAg+, 116/686 for HBeAg- patients); PNALT: 3 normal values within 12 months

Multiple Logistic Regression for Prediction of Significant Fibrosis (≥F2)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline HBV DNA, cp/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 log</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 log</td>
<td>1.859</td>
<td>1.184-2.917</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>ALT status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNALT</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIEALT</td>
<td>4.304</td>
<td>2.870-6.452</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>0.933</td>
<td>0.698-1.247</td>
<td>0.640</td>
</tr>
<tr>
<td>40-49</td>
<td>1.134</td>
<td>0.919-1.570</td>
<td>0.447</td>
</tr>
<tr>
<td>≥50</td>
<td>1.663</td>
<td>1.131-2.446</td>
<td>0.010</td>
</tr>
</tbody>
</table>

PNALT: persistently normal ALT, PIEALT: persistently or intermittently elevated ALT

Liver stiffness in Chinese HBeAg-positive chronic HBV patients

Insignificant fibrosis: LSM ≤6/7.5 kPa for patients with normal/elevated ALT
Advanced fibrosis: LSM >9/12 kPa for patients with normal/elevated ALT

Age>35 yrs & ALT>0.5xULN (ALT>29 IU/L): the only factors independently associated with advanced fibrosis

Histological findings in immune tolerant chronic HBV adult patients in France

40 patients with 2 consecutive normal ALT determinations within 6 months & HBV DNA >10⁷ cp/ml - median age: 29 years (range: 17-59)

Born in – Asia: 87%, sub-Saharan Africa: 7%, France: 5% (1/2 Asian mother)

<table>
<thead>
<tr>
<th>Histological stage of fibrosis¹</th>
<th>All patients (n = 40)</th>
<th>Alanine aminotransferase level &lt;0.5 ULN (n = 12)</th>
<th>Alanine aminotransferase level 0.5–1 ULN (n = 28)</th>
<th>Age &lt;40 y (n = 36)</th>
<th>Age &gt;40 y (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>20</td>
<td>4</td>
<td>16</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>F1</td>
<td>20</td>
<td>8</td>
<td>12</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic grade of activity²</th>
<th>All patients (n = 40)</th>
<th>Alanine aminotransferase level &lt;0.5 ULN (n = 12)</th>
<th>Alanine aminotransferase level 0.5–1 ULN (n = 28)</th>
<th>Age &lt;40 y (n = 36)</th>
<th>Age &gt;40 y (n = 4)</th>
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</thead>
<tbody>
<tr>
<td>A0</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>A1</td>
<td>29</td>
<td>9</td>
<td>20</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>A2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

¹Metavir score.

Loss of tolerance [ALT>ULN or HBeAg(-) or HBV DNA<10⁵ cp/ml]: 12/31 (38%) during 38 months follow-up

Natural history of immune tolerant chronic HBV in Chinese adult patients – Histological follow-up

9/57 (16%) ALT elevation (ALT>ULN on 3 consecutive determinations 6 months apart) during 5 years of follow-up

<table>
<thead>
<tr>
<th>Stage of fibrosis</th>
<th>Initial liver biopsy</th>
<th>Follow-up liver biopsy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>15</td>
<td>16</td>
<td>0.58</td>
</tr>
<tr>
<td>F1</td>
<td>33</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Histological findings in the 48 patients who remained immunotolerant

Median Modified HAI score: Initial biopsy 3 (1-6) vs. Follow-up biopsy 3 (1-5)

Main arguments favoring treatment initiation in HBV immunotolerant patients

• Maintenance of high HBV replication:
  - increasing numbers of infected hepatocytes
  - Risk of progression of liver lesions
  - Increasing HCC risk

• High risk of HBV transmission
  (NAs may be required in the third trimester of pregnancy of HBV immunotolerant women, not any more in infancy/childhood due to universal vaccination programs)
REVEAL cohort: the role of serum HBV DNA levels on HCC and cirrhosis development

Cumulative Incidence of HCC at year 13 follow-up (N = 3653)

Cumulative Incidence of Cirrhosis at year 13 follow-up (N = 3582)

Baseline HBV DNA (cp/mL) measured using the Roche COBAS assay

REVEAL-HBV study: Baseline factors for HCC development (2762 HBsAg carriers/33,847 person-years)

**Host**

- M: 57%; Age 30-65
- ALT <15 U/L: 60%; 15-44: 34%
- Cirrhosis: 2.5%

**Viral**

- HBV-DNA <10^4: 36.7%; >10^5: 36.4%
- HBeAg (-): 81%

**Genotype**

- A1762T/G1764A: 0.34, 1, 2.35, 4.42
- Precore 1896: 0, 2, 4, 6

**Other factors**

- Older age & Cirrhosis: the strongest HCC risk factors
- ALT <15 U/L: no increased HCC risk
- Normal ALT patients: 85% HBeAg-neg. with a mean age of 45
- No careful longitudinal data for liver disease progression

* P<0.001

Yang HI et al. JNCI 2008;100:1134-42.
### 5 year cumulative HCC in HBeAg-negative patients: complete responders under NA(s) vs inactive cases

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>5-year cumulative HCC incidence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete responder</td>
<td>316</td>
<td>6.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>under NA(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive cases</td>
<td>884</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete responder</td>
<td>223</td>
<td>15.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>under NA(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive cases</td>
<td>130</td>
<td>6.0%</td>
<td></td>
</tr>
</tbody>
</table>

**Complete responders under NA(s):** HBV DNA <2000 IU/ml on therapy  
**Inactive cases:** persistently HBV DNA<2000 IU/ml without treatment  

Efficacy of current treatment options in HBV immunotolerant patients

(Peg)-IFNα

ETV, TDF
TBV, LAM, ADV

Very limited data, usually from subgroup analyses of HBeAg-positive CHB patients with normal or slightly increased ALT levels at baseline
(Peg-)IFNa therapy in HBeAg-positive CHB

Higher HBeAg seroconversion rates in patients with

- Higher ALT levels (usually >2xULN)
- Lower HBV DNA levels


Prednisone Withdrawal Followed by Recombinant Alpha Interferon in the Treatment of Chronic Type B Hepatitis: A Randomized, Controlled Trial.
ETV or TDF therapy in HBeAg-positive CHB

1 year: HBV DNA undetectability 65-75%

HBeAg seroconversion: 20%

(Higher baseline ALT = higher HBeAg seroconversion rate)

≥4 years: HBV DNA undetectability >90-95%

HBeAg seroconversion: >30-35%

0-1% HBV resistance

TDF vs TDF+FTC x192 weeks in HBeAg+ patients with normal ALT and high HBV DNA

Mean age: 33 years; 89% Asians, 93% gen. B/C, mean HBV DNA: 8.4 log_{10} IU/mL

<table>
<thead>
<tr>
<th>Outcome at week-192</th>
<th>TDF (N=64)</th>
<th>TDF+FTC (N=62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;69 IU/ml</td>
<td>55%</td>
<td>76%</td>
<td>0.016</td>
</tr>
<tr>
<td>HBV resistance</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>5%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
</tbody>
</table>

ALT >ULN & HBV DNA >2,000 & Biopsy ≥A2/F2

Immunotolerant phase: Persistently ALT ≤ULN
  • No Biopsy – No therapy – Follow-up if age ≤30 years
  • Biopsy or even therapy if age >30 years and/or family history of HCC, cirrhosis

Potential additional treatment indications
  • Immunosuppression/Chemotherapy
  • Professional reasons
  • Last trimester of pregnancy

Management of immunotolerant patients
HBeAg+ patients with high HBV DNA (>20,000 IU/mL) and PNALT

- Age >40 years: treatment
- Age 30-40 years: decisions individualised - liver biopsy
- Age <30 years: follow-up (ALT /3-6 months, HBeAg/anti-HBe /6-12 months)
- Positive family history for HCC: reduce the age limit for treatment initiation
- Clinical or laboratory indications of advanced liver lesions (eg low PLT, high gamma-globulins, splenomegaly, spiders, palmar erythema, advanced fibrosis by noninvasive markers etc): liver biopsy even in patients <30 years

Potential additional treatment indications
- Immunosuppression/Chemotherapy
- Professional reasons
- Last trimester of pregnancy

Immunotolerant phase: persistently ALT ≤30/19 IU/L for M/F

- No Biopsy – No therapy – Follow-up every 6 months if age ≤40 years
- Therapy if age >40 years and HBV DNA ≥10^6 IU/mL and significant necroinflammation or fibrosis

HBeAg-positive immunotolerant patient

ALT monthly for ≥3 months

- ALT >ULN and/or clinical signs of advanced disease
- Persistently ALT≤ULN & HBV DNA >20,000
- Persistently ALT<ULN & HBV DNA ≤20,000 IU/mL

Liver biopsy and/or Non-invasive assessment of fibrosis and/or Treatment

ALT, HBeAg, HBV DNA

Persistently ALT≤ULN & HBV DNA >20,000 IU/mL

≥Moderate lesions

Treatment

Age >40

<30 years

≥Moderate lesions

Liver biopsy and/or Non-invasive assessment of fibrosis

Follow-up

Do I treat my HBV immunotolerant patients?

No

Except for a few