VHPB Technical meeting

Risks and Benefits of Discontinuation of Nucleos(t)ide Analogue Treatment: A Treatment Concept for Patients With HBeAg-Negative Chronic Hepatitis B

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Risks and Benefits of Discontinuation of Nucleos(t)ide Analogue Treatment: A Treatment Concept for Patients With HBeAg-Negative Chronic Hepatitis B

Florian van Bömmel and Thomas Berg
The Concept of NA Withdrawal as an Approach to Achieve a Functional Cure

A

- hepatocyte
- exhausted CD8+ T cell

B

- hepatocyte
- activated CD8+ T cell

NA treatment

HBV DNA

Time

= PD-1
= Other inhibitory receptors
= Immunosuppressive signals in the liver
= HBV antigens
Frequency of HBV DNA relapses

Rate of HBV DNA relapses over weeks after NA discontinuation.
Response to NA Discontinuation Runs Through Different Phases

- **Treatment phase (> 3 years)**
  - Nucleos(t)ide Analog (NA)
  - HBV DNA levels
  - HBV DNA detection limit

- **Lag-phase (<1-12 months)**
  - HBsAg levels
  - HBsAg detection limit

- **Reactivation phase (~ 3 months)**
  - ALT levels
  - ALT upper normal limit

- **Consolidation phase (~ 12 months)**
  - Long-term outcome
    - Outcome categories A-D
    - A) HBsAg loss (~ 20% after 2-3 years of follow-up)
    - B) Sustained virologic response: (true "healthy carrier" state) & HBsAg level decline ~ 40%
    - C) Indeterminate state: not fulfilling immediate re-treatment criteria (~ 20%)
    - D) Chronic hepatitis B requiring re-treatment (~ 40%)

- **Severe flare?**

**TIME**
FINITE-study: endpoints
STOP-NUC: Cessation of nucleos(t)ide treatment in HBeAg-negative chronic hepatitis B: A randomized controlled trial

**NUC treatment according to guidelines with at least 4 years of complete virologic response** (HBV-DNA < 1000 copies/mL, i.e. 172 IU/mL)

- Enrolment eligibility informed consent
- Randomisation 1:1

**NUC treatment discontinuation** (experimental arm)
- Regular assessment of liver function, HBV virology and serology
- Re-treatment in case of severe or chronic hepatitis B reactivation
- Additional visits on week 2, 6, 10
- Bi-weekly safety visits (ASV), if ALT >2 x ULN

**NUC treatment continuation according to guidelines** (control arm)
- Regular assessment of liver function, HBV virology and serology
STOP-NUC: End point HBsAg loss
STOP-NUC: HBsAg levels after stopping NA

Arm A - stop NUC-therapy
STOP-NUC: HBsAg levels in control arm

Arm B - continue NUC-therapy

Van Bömmel F, et al. ILC 2020
STOP-NUC: Re-treatment

Diagram showing the proportion without re-treatment over time to re-treatment in weeks. The x-axis represents time to re-treatment in weeks, ranging from 0 to 108 weeks. The y-axis represents the proportion without re-treatment, ranging from 0.80 to 1.00. The graph includes data points for events and curves, with the number of events and the total number of participants indicated.
Negative effect of early on HBsAg losses

Cumulative HBsAg loss rate in 519 patients with clinical relapse and retreatment (blue line; n = 269) or patients with clinical relapse but no retreatment (yellow line; n = 150)

p<0.0001
TABLE 3. PROPOSED RETREATMENT CRITERIA FOR HBeAg-NEGATIVE PATIENTS AFTER NA DISCONTINUATION\(^{(62)}\)

NA treatment should be immediately re-installed if one of the following criteria is met:

1. Confirmed (i.e., two consecutive central laboratory results) increase in direct bilirubin from baseline and ALT ULN at the confirmatory test
2. Confirmed sustained increase in prothrombin time \(\geq 2.0\) seconds from baseline with appropriate vitamin K levels and elevated ALT
3. Confirmed elevated ALT 10\times\ ULN with or without associated symptoms
4. ALT 2\times\ ULN and \(\leq 5\times\ ULN\) persisting for \(\geq 84\) days (12 weeks) as well as an HBV-DNA relapse \(\geq 20,000\) copies/mL
5. ALT 5\times\ ULN and \(\leq 10\times\ ULN\) persisting for \(\geq 28\) days (4 weeks)
Influence of qHBsAg at NA cessation

Cumulative HBsAg loss rates according to different HBsAg levels at the time point of NA treatment discontinuation (log-rank test, $P < 0.0001$)
Influence of ethnicity on HBsAg loss

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>N at risk</th>
<th>Weeks after therapy cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Asian</td>
<td>115</td>
<td>0</td>
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<tr>
<td></td>
<td>64</td>
<td>50</td>
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<td></td>
<td>33</td>
<td>100</td>
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<tr>
<td></td>
<td>30</td>
<td>150</td>
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<tr>
<td></td>
<td>30</td>
<td>200</td>
</tr>
<tr>
<td>Asian</td>
<td>1,101</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>925</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>809</td>
<td>100</td>
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<tr>
<td></td>
<td>744</td>
<td>150</td>
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<tr>
<td></td>
<td>684</td>
<td>200</td>
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</tbody>
</table>

*p < 0.001*
Influence of HBsAg levels on HBsAg loss

Cumulative probability of HBsAg loss

$\mu < 0.001$

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th>N at risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg &lt; 10</td>
</tr>
<tr>
<td>64</td>
</tr>
<tr>
<td>HBsAg 10-100</td>
</tr>
<tr>
<td>192</td>
</tr>
<tr>
<td>HBsAg &gt; 100</td>
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<tr>
<td>960</td>
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</table>
Influence of HBcrAg levels on HBsAg loss

TABLE 2. RELAPSES, HEPATIC DECOMPENSATION, AND FATAL OUTCOMES IN HBcAg-NEGATIVE PATIENTS AFTER NA DISCONTINUATION (SELECTED STUDIES)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients With Cirrhosis, n</th>
<th>HBV-DNA Relapse, n (%)</th>
<th>ALT Relapse, n (%)</th>
<th>Hepatic Decompensation, n (% Cirrhosis)</th>
<th>Death, n (% Cirrhosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al. (62)  (two case reports)</td>
<td>2</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Jeng et al. (65)</td>
<td>691 (308)</td>
<td>547 (79.2)*</td>
<td>419 (60.6)†</td>
<td>9 (100)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Kuo et al. (66)</td>
<td>22</td>
<td>N/A</td>
<td>82 (68.4)</td>
<td>1 (100)</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

*Increase of HBV DNA > 2,000 IU/mL.  
†increase of ALT > 2× ULN.
Summary

็ด Cessation of NA treatment is a potent tool to induce functional cure in HBeAg negative patients

๏ HBsAg levels < 1000 IU/mL are a strong positive predictor of HBsag loss
  • Role of other bio markers is unclear

๏ Cessation of NA is safe in non-cirrhotic patients
  • patients with liver cirrhosis NA should not be stopped

๏ The long term development of immune control after NA cessation is unclear
Thank you for your attention!