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

B

= PD-1  = Other inhibitory receptors  = Immunosuppressive signals in the liver  = HBV antigens

HBV DNA

NA treatment

Time

HBV DNA

NA treatment

Time

van Bömmel F, Berg T. Hepatol Comm 2021
Frequency of HBV DNA relapses

Rate of HBV DNA relapses

weeks after NA discontinuation

patients (n) 184 182 178 150 41 24
Response to NA Discontinuation Runs Through Different Phases

- **Treatment phase** (> 3 years)
- **Lag-phase** (<1-12 months)
- ** Reactivation phase** (~ 3 months)
- **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%) |

- **HBV DNA levels**
- **HBsAg levels**
- **ALT levels**

Kapitel | Titel der Veranstaltung

van Bömmel F, Berg T. Hepatol Comm 2021
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

Van Bömmel F, et al. ILC 2020
STOP-NUC: HBsAg levels in control arm
STOP-NUC: Re-treatment

Curves: All, Events: 11, N: 79

Proportion without re-treatment vs. Time to re-treatment [weeks]

N at Risk
All: 79, 77, 75, 74, 73, 73, 70, 70, 61
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)
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 ≥ 2.0 seconds from baseline with appropriate vitamin K levels and elevated ALT
3. Confirmed elevated ALT 10× ULN with or without associated symptoms
4. ALT 2× ULN and ≤ 5× ULN persisting for ≥ 84 days (12 weeks) as well as an HBV-DNA relapse ≥ 20,000 copies/mL
5. ALT 5× ULN and ≤ 10× ULN persisting for ≥ 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

![Graph showing cumulative probability of HBsAg loss over weeks after therapy cessation for Asian and Non-Asian individuals. The graph includes a table with the number of individuals at risk (N° at risk) for each category at different time points.]

|          | Non-Asian | 64 | 33 | 30 | 30 |
|----------|-----------|----|----|----|----|
| Asian    | 1,101     | 925| 809| 744| 684|

*P < 0.001
Influence of HBsAg levels on HBsAg loss

N° at risk:
- HBsAg <10: 64, 31, 25, 21, 16
- HBsAg 10-100: 192, 150, 126, 108, 96
- HBsAg >100: 960, 808, 691, 645, 602
Influence of HBcrAg levels on HBsAg loss

Sonneveld MJ, et al. J Hepatol 2022
# Safety of NUC discontinuation

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

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

- 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!