HBsAg, anti-HBs and ALT kinetic characterization during NAP-based combination therapy of HBeAg negative chronic hepatitis B infection

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INTRODUCTION

- Achieving a functional cure from Hepatitis B is rare with current therapy. Nucleic acid polymers (NAPs) are a new class of antiviral drugs (Fig. 1) which, when used in combination therapy, result in HBsAg loss with high rates of functional cure [1,2].
- The interplay among serum hepatitis B surface Antigen (HBsAg), anti-HBs, and alanine aminotransferase (ALT) kinetics during combination therapy with REP 2139-Mg or REP 2165-Mg, pegylated interferon alpha-2a (IFN) and tenofovir disoproxil fumarate (TDF) has not been analyzed in detail.
- Clinical markers for tracking and predicting the probability of successful treatment need to be identified.

AIM

To characterize HBsAg, anti-HBs and ALT kinetics during 48-week NAP-based triple therapy and identify their relationships with the treatment outcome.

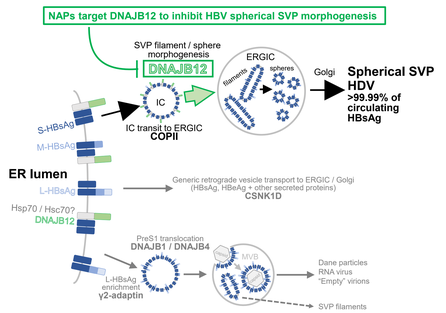

Figure 1: Mechanism of NAPs-based antiviral drugs. NAPs block the production and secretion of subviral particles (SVPs) by hepatocytes, significantly reducing the amount of HBsAg in circulation.

METHODS

- Twenty chronic HBV-infected, HBeAg negative participants received 24 weeks of tenofovir disoproxil fumarate (TDF) monotherapy.
- Participants then received 48 weeks of triple therapy including REP-2139-Mg or REP-2165-Mg, pegylated interferon alpha-2a (IFN), and TDF as described in [1].
- Serum HBsAg (Abbot Architect) and anti-HBs (Abbot Architect) were measured every two weeks, and serum ALT was measured weekly.
- Participants received follow-up testing for 48 weeks after end of therapy (EOT).

METHODS (CONT.)

Analysis Methodology

- HBV DNA was not analyzed since it reached ≤2.1 log IU/mL in 19/20 participants during TDF monotherapy and remained low/undetectable throughout triple therapy.
- Distinctions between HBsAg phases were defined as at least a 2-fold change in slope.
- A single-phased decline was defined as monophasic, and two-phased declines were defined as biphasic.
- Patients with an overall reduction from baseline in HBsAg <1 log at EOT were defined as non-responders (NR).

CONCLUSIONS

- **Monophasic HBsAg kinetic pattern may predict successful treatment with NAPS triple therapy.**
- **Non-monophasic HBsAg kinetic pattern was associated with 100% NPV for achieving functional cure.**
- **Concomitant ALT flare and anti-HBs seroconversion with a rapid decline in HBsAg suggest that NAP-based therapy might lead to specific anti-HBV immune responses yet to be identified.**

ACKNOWLEDGEMENTS

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[2] Bazinet et al., Journal Viral Hepatitis 2021 May;28(5):817-825.

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RESULTS

Three HBsAg kinetic patterns identified

- Three HBsAg kinetic patterns were found NR (n=4), monophasic decline (n=12), and biphasic decline (n=4). (Figure 3)
- HBsAg decline was delayed in NR (9±2 wk) relative to monophasic and biphasic declines (3±3 wk, p = 0.001).
- Rate of HBsAg decline in monophasic patients was 0.52±0.22 log IU/mL/week, all reaching <LLoQ by week 18±8.
- The 1st phase of decline in biphasic participants (0.25±0.15 log IU/mL/week) was slower (p=0.02) relative to monophasic participants, followed by a second phase decline of 0.03±0.02 log IU/mL/week with only one patient reaching HBsAg <LLoQ at EOT.
- There were no difference in kinetic patterns between REP 2139-Mg and REP 2165-Mg.

Anti-HBs seroconversion highly associated with HBsAg monophasic decline pattern

- Early anti-HBs seroconversion (14±5 wk) accompanied 11 out of 12 HBsAg monophasic responders and 1 of 4 biphasic responders.

ALT flares coincided with HBsAg monophasic decline pattern

- ALT flared to a 12.0±10.4-fold peak above mean baseline, coinciding with HBsAg decline and anti-HBs seroconversion (for monophasic declines).

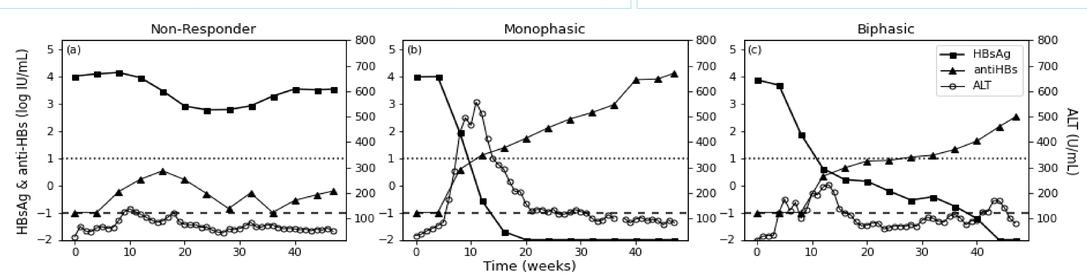

Figure 2: Representative figures for the three identified viral kinetic patterns. Dotted line represents anti-HBs seroconversion. Dashed line represents HBsAg LLoQ.

Outcomes- Monophasic HBsAg kinetic pattern associated with successful treatment

- As defined in [1] participants achieved either functional cure, partial cure, or virological rebound at follow-up
- The distribution of outcomes for each HBsAg kinetic pattern is shown in Figure 3.
- Positive and negative predicted values (PPV and NPV) associated with a monophasic viral kinetic pattern, and functional cure (FC) at follow-up are shown in Table 1
  - 100% of patients who exhibited FC had a monophasic HBsAg kinetic pattern (NPV)
  - Monophasic patients with FC had shorter (p=0.065) mean time to HBsAg LLoQ (17 wk) compared to monophasic non-FC patients (27 wk).

PPV	NPV	Sensitivity	Specificity
67%	100%	100%	67%

Table 1: Positive predictive values (PPV) and negative predictive values (NPV) for the probability that a monophasic HBsAg kinetic pattern during NAPs triple therapy results in functional cure after 48-week follow-up.

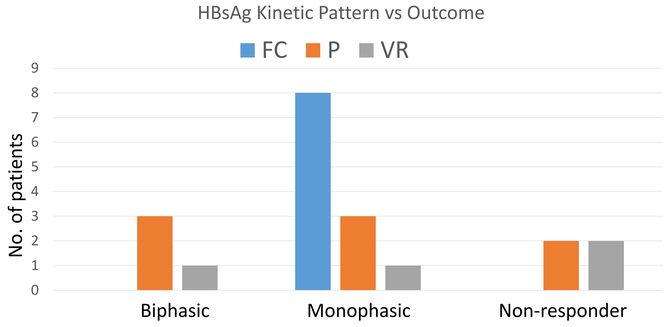

Figure 3: Distribution of outcomes for each HBsAg kinetic pattern. FC=Functional Cure, P=Partial Cure, VR = Virological Rebound