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Transaminase flares during HBsAg reduction to < 1 IU/mL are correlated with the establishment of functional cure of HBV following NAP-based combination therapy

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INTRODUCTION

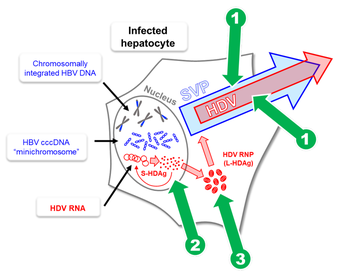
Nucleic acid polymers (NAPs) inhibit the assembly and secretion of HBV subviral particles and interact with small and large forms of the hepatitis delta antigen (Figure 1). An analysis of all 52 participants in the REP 301 and REP 401 studies was conducted to examine the correlation between HBsAg clearance, transaminase flares and therapeutic outcome for HBV (rebound, virologic control or functional cure) reported for these studies.

Figure 1. Antiviral effects of REP 2139:

(1) Inhibition of HBV SVP assembly / secretion and HDV envelopment.

(2) Potential inhibition of HDV RNA synthesis via interaction with S-HDAg.

(3) Potential inhibition of HDV RNP formation via interaction with L-HDAg.



MATERIAL & METHODS

All 52 participants from the REP 301 (NCT02233075) and REP 401 (NCT02565719) were included. Variables analyzed included on therapy HBsAg and anti-HBs response, maxima and area under the curve (AUC) for ALT, baseline characteristics, and therapeutic outcomes (based on 48-week follow-up in the REP 401 study and 3.5-year follow-up in the REP 301-LTF study).

Table 1. Baseline and on therapy flare characteristics in participants with different therapeutic outcomes.

		Outcome during treatment free follow-up			p-value
		Rebound (HBV DNA > 2000 IU/mL) (n=15)	Virologic control (HBV DNA ≤ 2000 IU/mL, normal ALT) (n=20)	Functional cure (HBV DNA TND, HBsAg < LLOQ, normal ALT) (n=17)	
Age ($\bar{x}$ / median)		39.5 / 44	37.2 / 37	37.7 / 39	0.750
Sex	Male	12	16	14	0.979
	Female	3	4	3	
HBV genotype	A	1	1	0	0.922
	D	10	14	14	
	ND (HDV dominant)	4	5	3	
Baseline HBsAg (IU/mL, $\bar{x}$ ± SD)		$1.67x10^4 \pm 8.23x10^3$	$1.12x10^4 \pm 7.03x10^3$	$1.13x10^4 \pm 1.38x10^3$	0.274
Baseline HBV DNA (IU/mL, $\bar{x}$ ± SD)		$9.66x10^6 \pm 2.28x10^7$	$3.73x10^6 \pm 1.57x10^7$	$3.46x10^7 \pm 1.40x10^8$	0.494
Baseline transaminases (U/L, $\bar{x}$ ± SD)	ALT	76.1 ± 69.2	96.4 ± 72.4	88.4 ± 66.0	0.695
	AST	46.5 ± 30.8	57.0 ± 38.0	51.9 ± 25.6	0.635
	GGT	31.4 ± 24.6	33.1 ± 16.4	39.6 ± 25.6	0.531
Baseline LMS (kPa)	≤ 7	6	10	7	0.942
	7 - 9	5	5	5	
	9 - 11	1	3	0	
	11 - 18	2	2	3	
	>18	0	0	2	
Transaminase flare during therapy (> 3x ULN)	ALT	11	16	14	0.733
	AST	6	9	13	
	GGT	4	10	11	0.248
	Any	11	17	17	

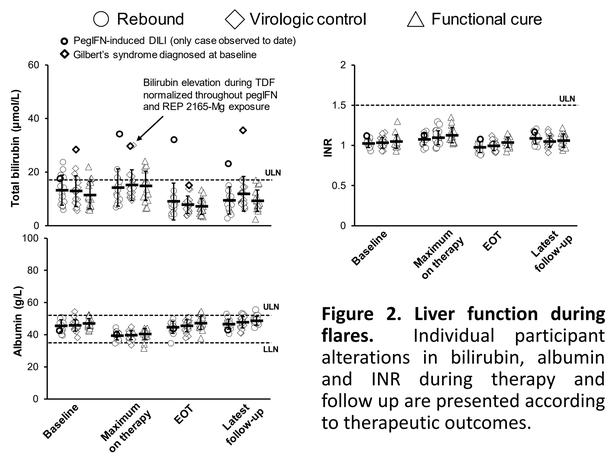


Figure 2. Liver function during flares. Individual participant alterations in bilirubin, albumin and INR during therapy and follow up are presented according to therapeutic outcomes.

RESULTS

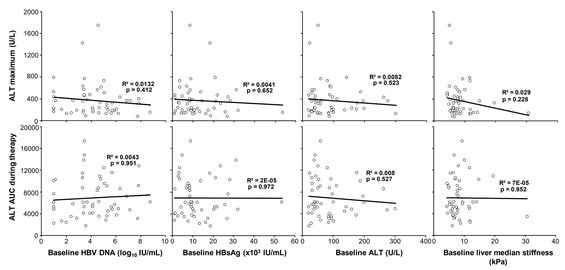


Figure 3. Effect of baseline characteristics on ALT elevations. No correlation exists between between ALT maxima or ALT AUC during therapy and baseline HBV DNA, HBsAg, ALT or LMS.

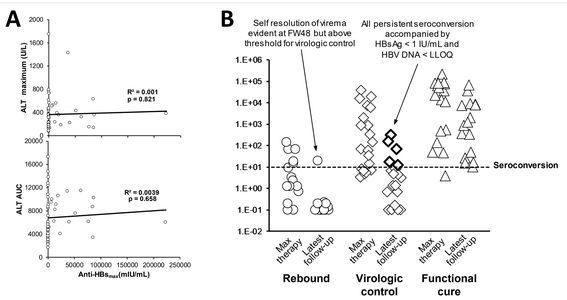


Figure 4. Effect of anti-HBs on ALT elevations. No correlation exists between between ALT maxima or ALT AUC during therapy and evolution of anti-HBs. Seroconversion during therapy is correlated with positive therapeutic outcomes but only persists with functional cure or "strong" virologic control.

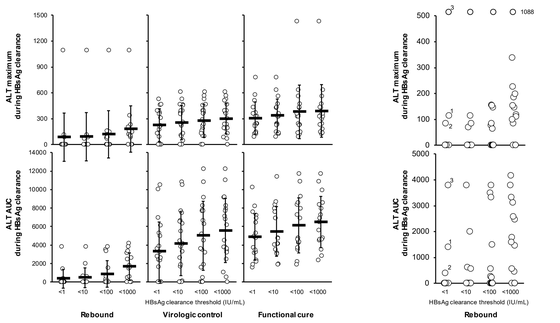


Figure 7. Relationship between ALT flare activity at various HBsAg clearance thresholds and therapeutic outcome. (A) ALT maxima (top) and ALT AUC (bottom) during therapy at different HBsAg clearance thresholds for therapeutic outcomes are indicated. (B) Expanded scale in the viral rebound group. ALT flare activity at all HBsAg clearance thresholds was statistically different between therapeutic outcome groups ($p < 0.05$).

DISCLOSURES

MB and AV are employees of and shareholders in Replicor. The Institute for Virology, University Hospital Essen received support from Replicor for the virologic testing. All other authors have no conflicts of interest to declare.

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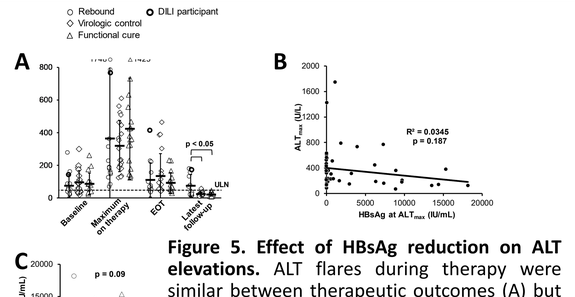

Figure 5. Effect of HBsAg reduction on ALT elevations. ALT flares during therapy were similar between therapeutic outcomes (A) but only universally normalized during follow-up with positive therapeutic outcomes. Overall ALTmax during therapy was not influenced by HBsAg reduction (B) but HBsAg reductions at ALT max were lower in virologic control or functional cure groups (C).

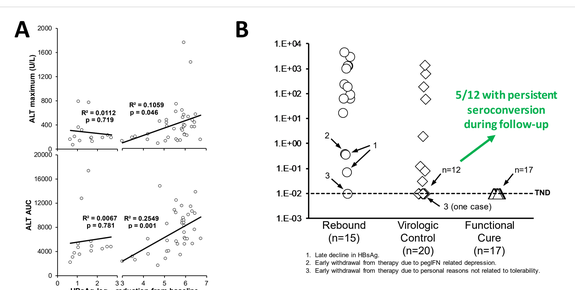

Figure 6. Extent of HBsAg reduction influences ALT flare activity and therapeutic outcome. Intensity and duration of ALT elevation during therapy were correlated with HBsAg reduction > 3 $\log_{10}$ from baseline (A). Undetectable HBsAg (0.00 IU/mL) during therapy was present in 60% of participants with virologic control and 100% of participants with functional cure (B).

Table 2. Incidence of flares during therapy at various HBsAg levels versus therapeutic outcome

Transaminase elevation during HBsAg reduction	Incidence (%) in different therapeutic outcome groups			p-value
	Rebound (n=15)	Virologic control (n=20)	Functional cure (n=17)	
< 1000 IU/mL	73	95	100	0.194
< 100 IU/mL	47	85	100	0.066
< 10 IU/mL	27	80	100	0.001
< 1 IU/mL	20*	70	100	< 0.001

*all withdrew early from therapy or had late HBsAg decline during therapy (see Figure 7)

Table 3. Utility of various on-therapy milestones to predict therapeutic outcome

Milestone during therapy		PPV	NPV	Sensitivity	Specificity
Transaminase elevation during HBsAg clearance	No functional cure (R + VC) vs functional cure				
	< 1 IU/mL	50	100	100	51
	< 10 IU/mL	46	100	100	43
	< 100 IU/mL	41	100	100	31
	< 1000 IU/mL	36	100	100	14
	No clinical benefit (R) vs clinical benefit (VC + FC)				
	< 1 IU/mL	84	80	91	66
	< 10 IU/mL	89	73	89	73
	< 100 IU/mL	92	53	83	72
	< 1000 IU/mL	97	27	77	80
HBsAg < LLOQ	No functional cure (R + VC) vs functional cure				
		59	100	100	66
	No clinical benefit (R) vs clinical benefit (VC + FC)				
		100	65	78	100
HBsAg seroconversion (> 10 mIU/mL)	No functional cure (R + VC) vs functional cure				
		44	94	94	43
	No clinical benefit (R) vs clinical benefit (VC + FC)				
		86	62	84	67

R = rebound, VC = virologic control, FC = functional cure

CONCLUSIONS

- **Transaminase flares are common during combination therapy with NAPs and pegIFN:**
  - Occur during therapy (96% of participants) regardless of baseline characteristics or therapeutic outcome
  - Are not accompanied by alteration in liver function and are otherwise asymptomatic
  - Cumulative flare activity during therapy is correlated with HBsAg reduction > 3 $\log_{10}$ from baseline
- **All participants with HBV functional cure experience HBsAg 0.00 IU/mL and transaminase elevation while HBsAg is < 1 IU/mL during therapy**
  - Both these milestones appear to be required to achieve functional cure
  - **Also associated with functional cure of HDV**
- **The presence of transaminase flares while HBsAg is < 1 or < 10 IU/mL predict clinical benefit after therapy (virologic control or functional cure)**
  - Higher HBsAg thresholds (> 10 IU/mL) have relatively poor predictive value
- **HBsAg specific immune function likely plays an important role in establishing virologic control and functional cure**
- ***Should functional cure include HBsAg < 1 IU/mL, HBV DNA < LLOQ and normal ALT if HBsAg seroconversion is present?***