Evaluation of the Safety and Tolerability of Transaminase Flares During Antiviral Therapy in Patients with HBeAg Negative Chronic HBV Infection or HBV/HDV Co-infection

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INTRODUCTION

During treatment with currently approved therapies, transaminase flares occur infrequently in patients with chronic HBV infection or HBV / HDV co-infection. This has led to debate over the nature of these flares: are they signs of hepatotoxicity or signs of immune mediated clearance of infected hepatocytes.

The nucleic acid polymer REP 2139 blocks the assembly of subviral particles, which leads to declines in intracellular HBsAg and inhibition of release of HBsAg from hepatocytes containing cccDNA or integrated HBV DNA[1,2]. When combined with pegIFN, REP 2139 has a unique ability to rapidly clear both HBsAg and HDV RNA. This combination therapy has been used in HBeAg negative mono-infection (REP 401 study) and HBeAg negative chronic HBV/HDV co-infection (REP 301 study), where therapy is also accompanied by transaminase flares in almost all patients (50/52 patients combined from both studies).

This unique dataset provides an opportunity to examine the safety and tolerability of transaminase flares over a wide range of intensity, duration and different flare patterns.

METHODS

Available on-treatment safety and efficacy data from the 52 patients enrolled in REP 301 and REP 401 studies were pooled. REP 301 patient 01-014 was excluded as this patient was the only patient from these two studies to experience pegIFN induced DILI as previously reported[2].

Various liver function data (ALT, AST, GGT, Alk. Phos, bilirubin and median hepatic stiffness as measured by fasted Fibroscan) were subjected to population analysis based on on-treatment HBsAg response and treatment outcome:

Rebound: recurrence of active HBV or HDV infection after removal of therapy.

HBV functional control: **inactive chronic HBV** (HBV DNA < 2000 IU/mL with normal ALT at least 24 weeks after removal of all therapy).
or
HBV functional cure (HBV DNA and HBsAg target not detected with normal ALT at least 24 weeks after removal of all therapy).

HDV functional control: **inactive chronic HDV** (HDV RNA > 2 log reduction from baseline for at least 24 weeks after removal of all therapy).
or
HDV functional cure (HDV RNA target not detected for at least 24 weeks after removal of all therapy).

Area under the curve (AUC) estimations for ALT, AST, GGT and Alk. Phos. during exposure to pegIFN were performed by trapezoidal analysis.

REFERENCES

1. Blanchet et al., Antiviral Research 2019; in press
2. Bazinet et al., Lancet Gastro & Hepatol. 2017; 2:877-889.

DISCLOSURES

MB and AV are employees and shareholders in Replicor Inc.

CONTACT

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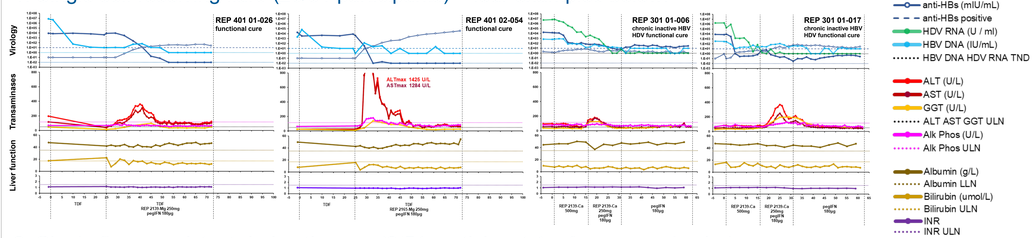
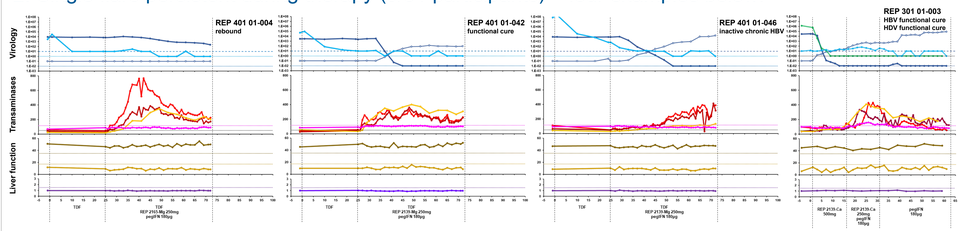
RESULTS

Three distinct flare geometries observed during therapy:

1. Single self resolving flare (26/51 participants) – four examples below:



2. Single flare persistent during therapy (9/51 participants) – four examples below:



3. Multiple flares (14/51 participants) – four examples below:

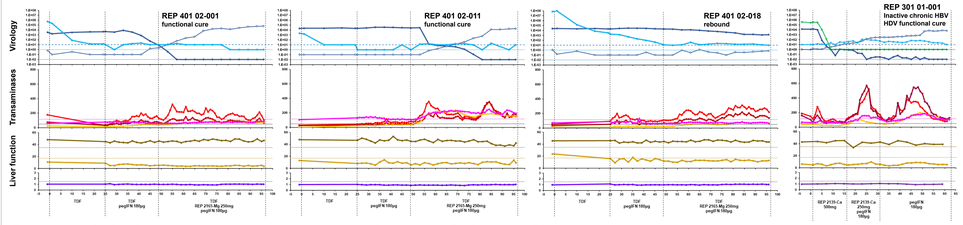


Figure 1. Analysis of transaminase flare geometries and safety in the REP 301 and REP 401 studies.
Global analysis identified flares in 49 of 51 participants in the analysis dataset. Flare geometries could be sorted into three distinct patterns as identified above. Individual, longitudinal virology, transaminase and liver function data throughout therapy are provided for four exemplary participants. Regardless of flare geometry or magnitude of transaminase elevations, alteration in liver function was not observed in any patient and transaminase flare were otherwise asymptomatic

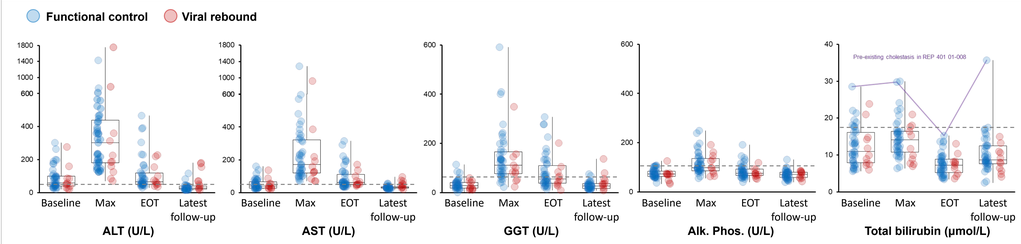


Figure 2. Transaminase and liver function maxima among participants with functional control versus rebound following therapy.
Global population analysis of ALT, AST, GGT, Alk. Phos. and total bilirubin are presented for all 51 participants in the analysis dataset. Individual values at baseline, maxima during therapy (Max), at end of treatment (EOT) and at the latest available follow-up are grouped for participants experiencing functional control (inactive chronic HBV or functional cure) in blue or viral rebound after removal of therapy in red. ALT / AST / GGT elevations experienced during treatment universally normalize off-therapy except in 4/11 patients experiencing viral rebound. Minor elevations in total bilirubin present at baseline were not altered by therapy and bilirubin normalized in all patients by EOT. Transaminase flares are observed whether patients experienced functional control or viral rebound after removal of therapy. Dotted lines indicate upper limit of normal.

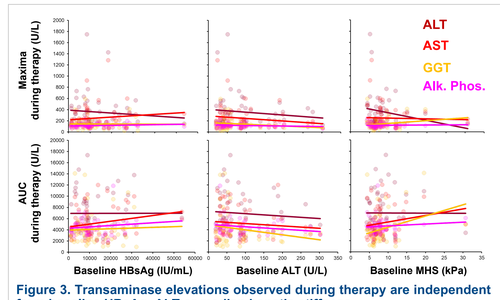


Figure 3. Transaminase elevations observed during therapy are independent from baseline HBsAg, ALT or median hepatic stiffness.
Regression analysis of the relationship between transaminase maxima (top row) and transaminase AUC (bottom row) are presented for baseline HBsAg (left), baseline ALT (middle) and baseline median hepatic stiffness (MHS, right). Individual data points for all participants in the analysis dataset as well as regression analysis are colour coded according to the legend at the top right.

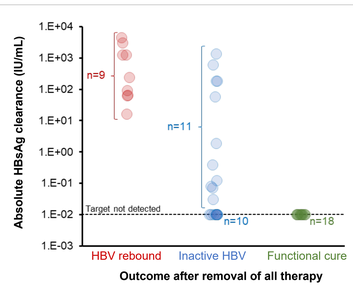


Figure 5. Extent of HBsAg clearance during treatment predicts establishment of functional control after removal of therapy
Population analysis of absolute clearance of HBsAg achieved during treatment versus treatment outcome demonstrates the bulk of functional control off-therapy (23/28 patients) required HBsAg to be < 1 IU/mL. Functional cure is only achieved when HBsAg becomes undetectable during therapy. Analysis dataset includes patients completing therapy and at least 24 weeks of follow-up in the absence of therapy.

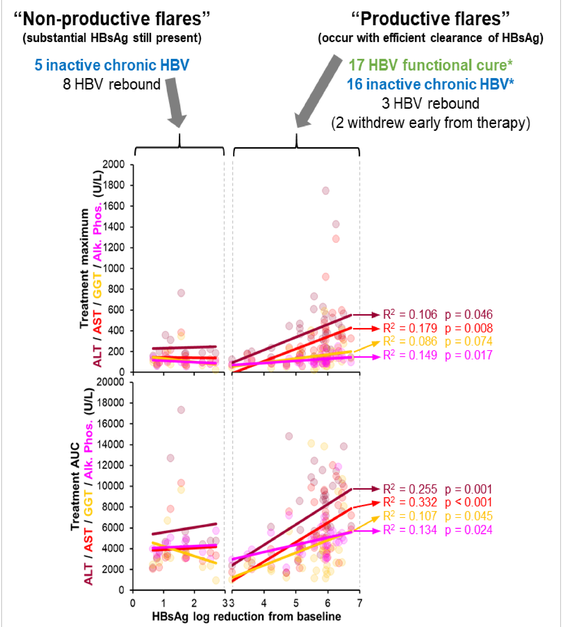


Figure 4. Relationship between transaminase activity and establishment of functional control after removal of therapy
Population analysis of transaminase maxima (top) and AUC (bottom) during therapy for ALT, AST, GGT and alkaline phosphatase reveals two discrete populations. The first population occurs with HBsAg reductions < 3 $\log_{10}$ from baseline, is not correlated with HBsAg clearance and appears to be non-productive in achieving functional cure. The second population occurs with HBsAg reductions > 4 $\log_{10}$ from baseline, is generally correlated with HBsAg declines in this lower range and appears to be productive in establishing functional cure. Correlation between ALT and AST flare activity and HBsAg declines in this lower range (3-7 $\log_{10}$ from baseline) are the strongest and are statistically significant at $p \leq 0.05$. *in this population, one additional patient has HBsAg and HBV DNA TND at 12 weeks of follow-up and another additional patient has HBV DNA target not detected at 12 weeks of follow-up.

CONCLUSIONS

1. Transaminase flares occurred in 50/52 patients with chronic HBV or HBV/HDV infection during REP 2139-based therapy.
2. In the analysis dataset, transaminase flares were not accompanied by any signs of symptoms of liver dysfunction, regardless of flare magnitude or geometry.
3. Transaminase flares could be separated into three distinct patterns, suggesting underlying variability in the immune status of patients at baseline or in the response of patients to pegIFN.
4. Transaminase flares during therapy are not correlated with baseline HBsAg (up to 53,703 IU/mL), ALT (up to 302 U/L) or median hepatic stiffness (up to 30.7 kPa).
5. Transaminase flares are correlated with HBsAg reductions between 3-7 $\log_{10}$ from baseline and these "productive" flares are highly correlated with the achievement of functional cure.
6. Establishment of functional cure of HBV requires elimination of detectable HBsAg from the blood (0.00 IU/mL) during therapy.