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 flare occurs infrequently in patients with chronic HBV infection or HBV/HDV co-infection. This has led to doubts over the nature of these flares as they may signify hepatocellular or even invasive mediated clearance of liver cells.

The nucleic acid polymer REP 2139 blocks the assembly of Hepatitis B and HBV and inhibition of release of HBsAg from hepatocytes or converted HDV DNA. When combined with pegIFN, REP 2139 has a unique ability to rapidly clear both HBV and HDV RNA. This combination effectively recruits REP 2139 (REP 2139 study) and REP 401 (REP 401 study) have demonstrated a remarkable safety and tolerability profile when treatment is also accompanied by transaminase flares in almost all patients (USD2 patients combined from both studies).

This unique behavior provides an opportunity to examine the safety and tolerability of transaminase flare on wide range of intensity, duration and different flare patterns.

METHODS

Available treatment efficacy data from the 52 patients enrolled in REP 2139 2017 and REP 401 studies were analyzed. REP 2139 was the only patient from these two studies to experience pegIFN-induced D2V as previously reported.

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 baseline HBsAg (standardize to 2000 IU/mL with normal ALT and MHS at least 24 weeks after therapy removal).

Regression analysis of the relationship between transaminase maxima (top row) and median hepatic stiffness (MHS, right) Individual data points for all participants in the analysis dataset as well as regression analysis are color coded according to the legend at the top right.

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:

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 log10 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 dectectable HBsAg from the blood (0.00 IU/mL) during therapy.

REFERENCES

1. Blanchem et al., Antiviral Research 2019; in press

DISCLOSURES

All authors are shareholders and employees in Replicor Inc.

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