SI-RNA-MEDIATED HBSAG REDUCTION AND IMMUNE-BASED THERAPY IN CHRONIC HEPATITIS B

ABSTRACT 53

A REVIEW OF EMERGING CLINICAL EVIDENCE

Sreethu Sreekantan Geetha[1], Tanishka Muraleedharan[2], Kavya Chowdary[3], Vaishnavi Voruganti[4], Yash Dave[5], Dr. Srijamya[6]

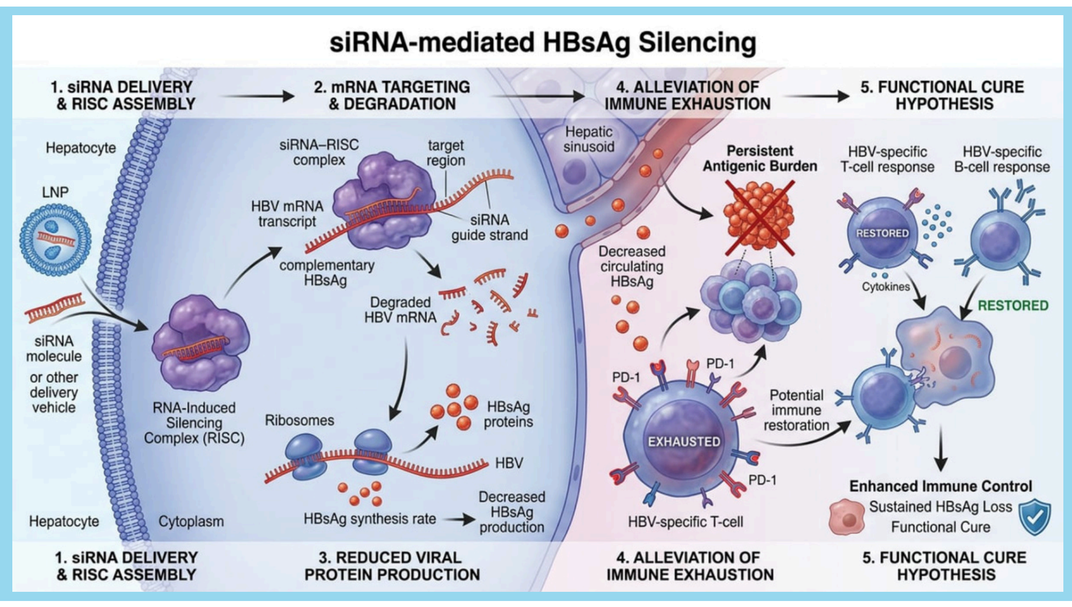
[1] Tbilisi State Medical University, Georgia [2] ACS Medical College and Hospital, Chennai [3] PES Institute of Medical Sciences and Research, India [4] Meenakshi Medical College Hospital and Research Institute, Chennai [5] Baroda Medical College, Vadodara [6] Autonomous State Medical College, Uttar Pradesh

BACKGROUND

- Chronic hepatitis B virus (HBV) infection affects an estimated 2.9% of the global population and remains a leading driver of cirrhosis, liver failure, and hepatocellular carcinoma.
- Current antiviral therapy (nucleoside analogues, interferon) suppresses HBV replication but rarely achieves functional cure - sustained HBsAg loss.
- Persistently high hepatitis B surface antigen (HBsAg) is thought to impair host HBV-specific immune responses, sustaining a self-reinforcing state of immune dysfunction.
- This has encouraged combination strategies pairing antigen-reducing agents (e.g. siRNA) with immune-based therapies (therapeutic vaccination, immunomodulators)

OBJECTIVE

To review clinical evidence on siRNA and therapeutic-vaccine and immunomodulator combination therapy for improving HBV-specific immune responses and functional cure rates.



METHODOLOGY

DATABASES
Pubmed, Google Scholar, Scopus, etc

EVIDENCE
Clinical trials + relevant preclinical studies

FOCUS
siRNA, HBsAg reduction, Therapeutic vaccination, Immune modulation, Functional cure

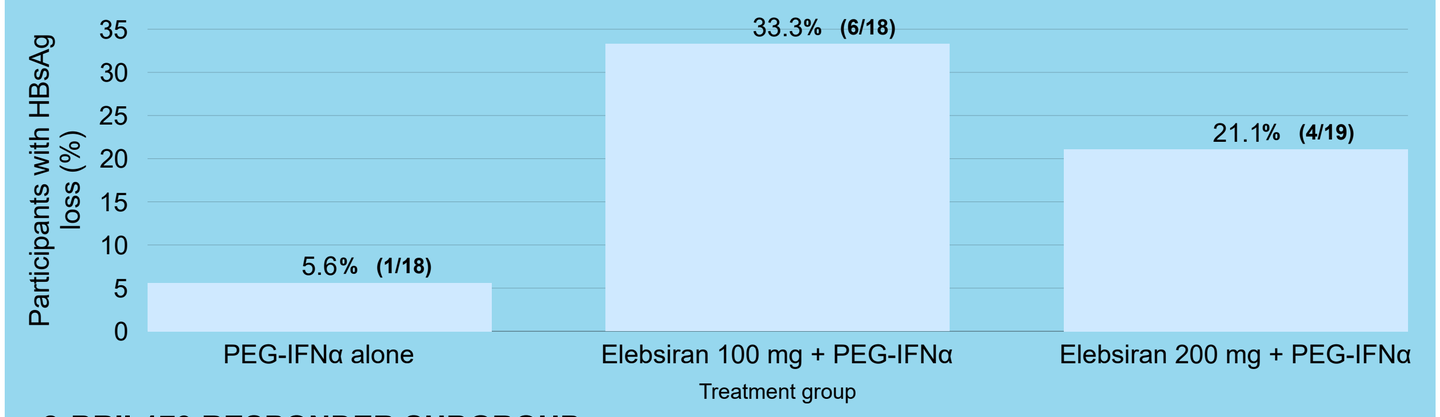
SYNTHESIS
HBsAg outcomes, HBV-specific immune responses, HBsAg seroconversion/loss, Clinical implications

EMERGING CLINICAL EVIDENCE

1. ENSURE: PRIMARY EFFICACY

- In the ENSURE phase 2 trial, HBsAg loss at 24 weeks post-treatment was observed in 1/18 participants (5.6%) receiving PEG-IFNα alone, compared with 6/18 (33.3%) receiving elebsiran 100 mg plus PEG-IFNα and 4/19 (21.1%) receiving elebsiran 200 mg plus PEG-IFNα.
- The combination groups therefore demonstrated higher sustained HBsAg-loss rates than PEG-IFNα monotherapy in this study.

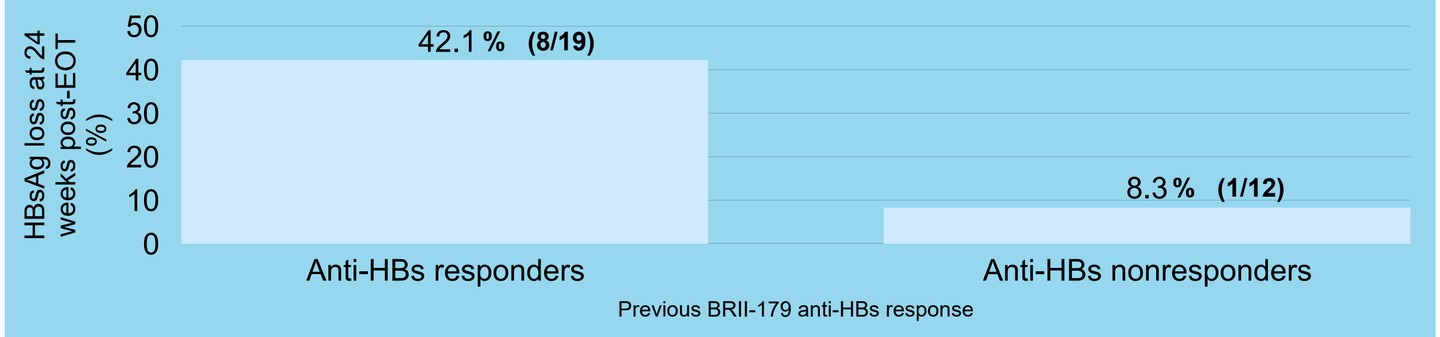
Figure 1. HBsAg loss at 24 weeks post-EOT in ENSURE Part I. Percentages represent participants achieving HBsAg loss in each treatment cohort.



2. BRII-179 RESPONDER SUBGROUP

- In ENSURE cohort 4, participants who had previously demonstrated an anti-HBs response to the therapeutic vaccine BRII-179 subsequently received elebsiran 100 mg plus PEG-IFNα.
- At 24 weeks post-treatment, sustained HBsAg loss occurred in 8/19 (42.1%) previous anti-HBs responders compared with 1/12 (8.3%) nonresponders.

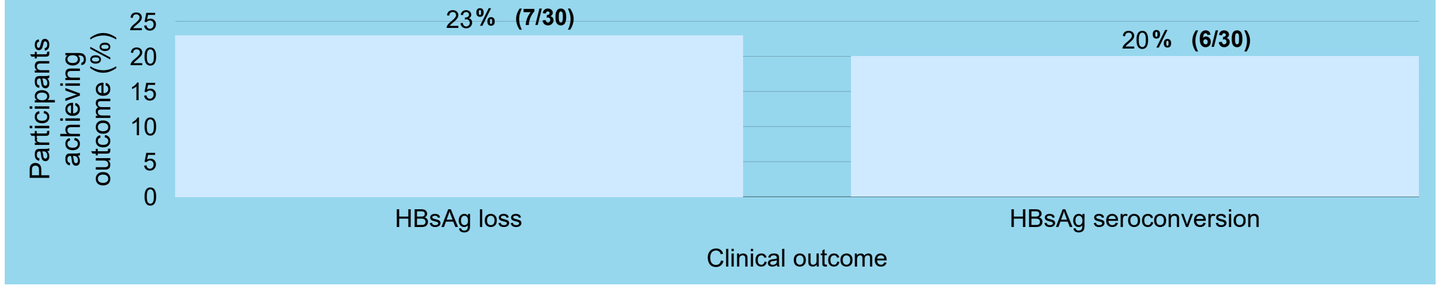
Figure 2. Sustained HBsAg loss at 24 weeks post-EOT according to previous BRII-179 anti-HBs response status in ENSURE cohort 4. All participants subsequently received elebsiran 100 mg plus PEG-IFNα.



3. PIRANGA

- In PIRANGA, xalnesiran 200 mg plus PEG-IFNα (group 4) achieved HBsAg loss in 23% of participants at 24 weeks post-EOT, while HBsAg seroconversion occurred in 20%.
- HBsAg loss with or without seroconversion occurred only among participants with screening HBsAg levels below 1,000 IU/mL

Figure 3. HBsAg loss and seroconversion at 24 weeks post-EOT in PIRANGA group 4 receiving xalnesiran 200 mg plus PEG-IFNα.



CLINICAL IMPLICATIONS

- siRNA-mediated HBsAg reduction may create a more favorable immunological environment for subsequent immune-based intervention.
- Across ENSURE and PIRANGA, HBsAg loss was observed predominantly among participants with lower baseline HBsAg levels.
- The higher sustained HBsAg-loss rate among previous BRII-179 anti-HBs responders in ENSURE supports further investigation of immunological profiling as a patient-selection strategy.
- The current evidence supports continued clinical development rather than replacement of established HBV management strategies.

EVIDENCE GAPS AND FUTURE DIRECTIONS

LARGER RANDOMIZED TRIALS	Confirm efficacy and safety in broader populations
LONGER FOLLOW - UP	Establish durability of HBsAg loss and sustained functional cure
PATIENT SELECTION	Define baseline virologic and immune characteristics associated with benefit
OPTIMAL COMBINATION	Clarify sequencing, dosing and complementary immune strategies

CONCLUSION

- siRNA-mediated HBsAg reduction may create a more favorable immunological environment for subsequent immune-based intervention.
- Across ENSURE and PIRANGA, HBsAg loss was observed predominantly among participants with lower baseline HBsAg levels.
- The higher sustained HBsAg-loss rate among previous BRII-179 anti-HBs responders in ENSURE supports further investigation of immunological profiling as a patient-selection strategy.
- The current evidence supports continued clinical development rather than replacement of established HBV management strategies.

REFERENCES

- Wong GLH, Yuen MF, Lin B, et al. Elebsiran and PEG-IFNα for chronic hepatitis B infection: a partially randomized, open-label, phase 2 trial. Nature Medicine. 2026;32(1):151–159. doi:10.1038/s41591-025-04049-z.
- Hou J, Zhang W, Xie Q, et al.; Piranga Study Group. Xalnesiran with or without an Immunomodulator in Chronic Hepatitis B. New England Journal of Medicine. 2024;391(22):2098–2109. doi:10.1056/NEJMoa2405485.
- Ji Y, Le Bert N, Lai-Hung Wong G, et al. The Impact of Hepatitis B Surface Antigen Reduction via Small Interfering RNA Treatment on Natural and Vaccine (BRII-179)-Induced Hepatitis B Virus-Specific Humoral and Cellular Immune Responses. Gastroenterology. 2025;169(1):136–149. doi:10.1053/j.gastro.2025.02.016.
- Ma H, Lim TH, Leerapun A, et al. Therapeutic vaccine BRII-179 restores HBV-specific immune responses in patients with chronic HBV in a phase Ib/IIa study. JHEP Reports. 2021;3(6):100361. doi:10.1016/j.jhepr.2021.100361.