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**Long-term hepatitis B surface antigen response after finite treatment of ARC-520 or JNJ-3989**

*Mak L, Wooddell C, Lenz O, et al. Long-term hepatitis B surface antigen response after finite treatment of ARC-520 or JNJ-3989. Gut 2025; 74: 440-450. doi: 10.1136/gutjnl-2024-333026.*

Nucleos(t)ide analogues are standard of care for patients with chronic hepatitis B (CHB), however annually only 1-4% of patients on-treatment will achieve functional cure, defined as loss of HBsAg for ≥6 months. Small interfering RNAs (siRNAs) regulate transcription by inducing degradation of the target sequence, and have been studied as a potential cure for CHB in Phase 2 clinical trials. Authors recruited patients from three existing trials using two different siRNAs (ARC-520 and JNJ-3989) for long-term follow-up (LFU) in order to study long-term outcomes of siRNA treatment.

The trials were heterogeneous in design, delivering between 8-12 weeks of an siRNA at different doses and frequencies, and in one trial without a control arm. 58 participants were recruited for LFU for up to 6 years: 53 received siRNA and 5 placebo. All were of Chinese ethnicity and remained on NUC.

Only 1 participant (siRNA treated) achieved HBsAg clearance. The siRNA group saw greater reduction in HBsAg levels compared to placebo in both the short-term (1.58 log and 0.53 log respectively) and the long-term (0.85 log and 0.52 log respectively). At LFU, 49% of the siRNA group sustained HBsAg levels <100 IU/ml compared to 0% in the placebo group. No safety concerns were raised.

This study has many limitations, including significant heterogeneity in the original trials, small numbers and few controls. Nevertheless, siRNA appears to have promise and further work is needed to understand their long-term mechanism of action as well as explore optimal dosing regimens