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

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Background and Aims: RNA interference has been extensively explored in patients with chronic hepatitis B (CHB) infection. We aimed to characterize the long-term efficacy of small interfering RNA (siRNA) on hepatitis B surface antigen (HBsAg) suppression.

Method: We prospectively followed up subjects with CHB who received short term siRNA treatment, either ARC-520 (4 injections in study Heparc-2002 [NCT02604199] and Heparc-2003 [NCT02604212]) or JNJ-3989 (3 injections in study AROHBV1001 [NCT03365947]), in combination with nucleoside analogue (NUC) in our centre. Subjects enrolled included 15 receiving ARC-520, 38 receiving JNJ-3989 and 5 receiving placebo in previous clinical trials. Serial blood sampling was performed according to the original protocols and upon completion every 24 weeks until last follow-up (LFU; mean duration 52.5+/− 14.4 months). An integer scoring system was used to construct the model score for achieving qHBsAg <100 IU/mL at LFU according to the results of multivariate regression analysis.

Results: Among the 53 NUC+siRNA-treated subjects (mean age 46.8, baseline HBsAg 3.08 log10 IU/mL, 5.7% <100 IU/mL, 83% previously on NUC, 34% HBeAg+), the proportion of patients achieving HBsAg seroclearance or <100 IU/mL at LFU was 1.9% and 31.2%, respectively, compared to 0% for both endpoints for placebo. The mean log10 reductions of HBsAg at LFU in siRNA treated and non-treated subjects were 0.85 and 0.52 respectively (p=0.123). When the two siRNAs were analysed separately, qHBsAg levels were numerically lower at LFU compared to placebo without reaching statistical significance (ARC-520 vs placebo at 72 months: 2.15 vs 2.52 log IU/mL, p=0.503; JNJ-3989 vs placebo at 60 months: 1.86 vs 2.63 log IU/mL, p=0.368). Age was negatively correlated with log reduction of HBsAg at nadir (r = -0.406, p=0.003) and LFU (r = -0.427, p=0.001). Compared to placebo, siRNA led to faster annual decline rate of HBsAg (0.08 vs 0.21 log, respectively, p=0.003). Baseline qHBsAg (OR 0.016, 95% CI 0.001-0.171) and log reduction in HBsAg at nadir (OR 16.979, 95% CI 3.131-92.083) were independently associated with HBsAg <100 IU/mL at LFU. Subjects with siRNA-100 score (derived from these two variables) of 0, 1, 2, 3 and ≥4 had 100%, 80%, 66.7%, 38.5%, and 0% probability of achieving HBsAg <100 IU/mL at LFU.

Conclusion: siRNA treatment suppressed HBsAg expression with a prolonged effect for up to 6 years. The siRNA-100 score consisting of baseline qHBsAg and log reduction at nadir may be indicative of HBsAg level <100 IU/mL at LFU.