SB 9200, a novel agonist of innate immunity, shows potent antiviral activity against resistant HCV variants

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BACKGROUND

New direct-acting antiviral (DAAs) agents for chronic HCV infection have substantially increased the rates of sustained virological response (SVR). However, relapse after antiviral therapy remains a significant problem, especially in patients with cirrhosis, and salvage therapy with new therapeutic agents remains the only viable option. SB 9200 is a novel, first-in-class oral modulator of innate immunity via its activation of RIG-I and NOD2 pathways in virally infected cells.

MATERIALS & METHODS

Patient sera from treatment naïve, responders or treatment failures (with either DAA (Sofosbuvir and Ledipasvir or pegIFN/RBV +/- DAAs) were tested in a capture-fusion assay. THP-1 cells were exposed to donor serum, fused with Huh7 derivative cells and treated with differing concentrations of SB 9200 before qPCR assessment of HCV replication. Dose response curves were used to calculate the IC50 values.

RESULTS

SB 9200 demonstrates pan-genotypic anti-HCV-activity

Replication of HCV from sera of patients infected with G1-6 was inhibited by SB 9200 in a dose-dependent manner.

Activity of SB 9200 against Sofosbuvir-resistant HCV variants

Serum from a HCV g3 patient who failed Sofosbuvir/Daclatasvir treatment was shown to be insensitive to Sofosbuvir. However, the serum was sensitive to SB 9200.

The activity of SB 9200 against serum from g1a patients who subsequently failed Sofosbuvir/Ledipasvir treatment was evaluated. Sequencing analysis revealed the presence of several HCV variants associated with poor response to current NS5A inhibitors. SB 9200 demonstrated antiviral activity against the known NS5A RAVs L31M and Q30H. Although 3/5 samples were insensitive to IFN, 4/5 were shown to be sensitive to SB 9200.

CONCLUSIONS

SB 9200 inhibits the replication of all tested HCV genotypes. Activity of SB 9200 is not influenced by previous treatment exposure. Given the potent activity of SB 9200 against HCV resistant variants (including pegIFN/RBV or DAA treatment failures), its clinical evaluation in combination with DAAs for patients requiring salvage therapy is warranted.

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