Acute and chronic infections caused by RNA and DNA viruses constitute a major public health crisis affecting millions of people. A limited arsenal of antiviral agents exists, mostly directed against a specific viral target such as the polymerase or protease characteristic of each virus. There is also rapid emergence of resistance to direct-acting antiviral drugs and dose-limiting toxicity. Therefore, new anti-viral drugs are urgently needed. Ideally, compounds with novel mechanisms of action that have a broader spectrum of antiviral activity and are agnostic to viral genotypes and resistant mutants will be needed. SB 9200, an oral dinucleotide designed to target the liver, is a potent antiviral agent against HBV, HCV, RSV, and Norovirus. Results of a Phase 1 clinical trial of SB 9200 in HCV-infected patients was recently reported (Thompson et al., EASL, 2015, AASLD, 2015).

**BACKGROUND**

SB 9200 is an orally bioavailable dinucleotide that activates the cellular viral sensors RIG-I and NOD2 causing the induction of IFN signaling cascade for antiviral defense. In efficacy studies in WHV-infected woodchucks, SB 9200 was shown to cause significant reductions of viral DNA and surface antigens in serum and liver (Menne et al., EASL, 2015). Reported here is the evaluation of the induction and expression of interferon-stimulated genes (ISGs) including RIG-I, NOD2, and STING, as well as an interferon regulatory transcription factor, IRF3, and antiviral cytokines associated with the antiviral activity of SB 9200.

**OBJECTIVE**

To evaluate the immune-stimulating and direct antiviral properties of SB 9200 in woodchucks chronically infected with woodchuck hepatitis virus (WHV) by daily, oral dosing with SB 9200 at 15 and 30 mg/kg for 12 weeks.

**METHODS**

Two groups of five chronically WHV-infected woodchucks were treated orally with SB 9200 at 15 and 30 mg/kg/day for 12 weeks. Both groups were monitored for 8 weeks post-treatment. Cytokine production and ISG expression associated with treatment were determined by changes in RNA transcript levels of IFN-β, IP-10, IL-6, ISG15, OAS1 in blood and liver using RT-PCR. Samples from woodchucks were also analyzed for changes in expression levels of ISGs including RIG-I, NOD2, STING, and IRF3 by RT-PCR and immunohistochemistry.

**RESULTS**

SB 9200-treatment induced dose-dependent and long-lasting expression of type I IFNs and ISGs, and antiviral cytokines in blood and liver of woodchucks. SB 9200 treatment also induced the expression of RIG-I, NOD2, STING, and IRF3 in liver compared to pretreatment levels. The expression of all genes was significantly induced during treatment and follow-up.

**CONCLUSIONS**

Our studies demonstrate that anti-viral activity of SB 9200 in woodchucks is associated with activation and induction of host-immune response genes.

- Peak plasma levels of SB 9200 correlated with peak viral load decline.
- SB 9200 treatment resulted in a dose dependent reduction in hepatic levels of WHV nucleic acids.
- SB 9200 treatment resulted in long lasting expression of type I IFNs and ISGs.

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