Combination treatment with Entecavir and the TLR7 agonist APR002 produces sustained suppression of viral replication, loss of surface and e antigens, and antibody response to both antigens in woodchucks

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Current HBV therapeutics rarely induce a functional cure due to the immunotolerant status of patients. In this regard, small molecule agonists targeting TLR7 have previously been shown to elicit a functional cure in animal models of HBV, but sometimes with poor tolerability because of immune-related toxicities; therefore, a safer approach is warranted. Here, the safety and antiviral efficacy of the novel TLR7 agonist, APR002, in combination with entecavir (ETV) was evaluated in the woodchuck model of chronic hepatitis B (CHB). APR002 is an oral enterohepatic-restricted TLR7 agonist, designed to act locally in the liver and thereby minimizing systemic immunotoxicity. Chronic WHV carrier woodchucks were dosed orally once daily with ETV for 20 weeks, alone or in combination with oral APR002 at two separate doses administered once weekly for 12 weeks (weeks 4 to 16) and then followed for additional 16 weeks. Treatment with APR002 was well-tolerated based on clinical observations and changes in body weight, hematology, serum chemistry, and histopathology. Antiviral efficacy and pharmacodynamic responses were assessed in serum, blood and liver. ETV treatment markedly suppressed serum viremia and antigenemia and intrahepatic WHV markers. During treatment, the addition of APR002 apparently did not provide additional antiviral benefit regarding the magnitude of reduction in serum WHV DNA, WHsAg, and WHeAg and in intrahepatic WHV DNA, RNA and cccDNA. However, and in contrast to ETV monotherapy where all 5 woodchucks experienced viral relapse during the follow-up, combination treatment with APR002 resulted in durable suppression or undetectability of WHV replication in serum and liver in 4 of 10 woodchucks at the end of the study (week 36). These animals also had detectable antibodies to WHsAg and WHeAg, enhanced expression of important interferon-stimulated genes (ISGs) mainly in blood and transient elevations of liver enzymes. The overall results suggest that treatment with the TLR7 agonist APR002 in combination with ETV can safely and effectively mediate a functional cure in woodchucks with chronic WHV infection, and thus supports further investigation in human CHB.