As assessing the in vitro anti-HBV activity of combinations including CRV431, TXL, and prototype capsid assembly modulators

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Background and Aims:

It is expected that a functional cure for chronic HBV infection will require drug combinations targeting the viral life cycle at multiple, complementary stages. CRV431, a cyclophilin inhibitor, blocks HBV interactions with host cyclophilins (cyp) essential for viral replication and chronicity. CRV431 reduces HBV DNA, suppresses HBsAg, inhibits viral uptake via NTCP and blocks HBx-cypA and HBsAg-cypA binding, as shown in vitro and in mouse models. TXL, a novel tenofovir (TFV) prodrug in Phase 2 clinical development, inhibits HBV polymerase and is designed to deliver high intra-hepatic tenofovir (TFV) concentrations, while minimizing off-target effects of high circulating TFV blood levels. Capsid assembly modulators (CAMs) block several HBV replication steps, including pre-genomic RNA packaging and cccDNA formation. The aim of our current studies was to investigate the antiviral activity of combinations of TXL, CRV431, and prototype CAMs (BAY41-4109, DVR-56).

Method:

Combinations of TXL and CRV431, TXL and CAMs, as well as CRV and CAMs were tested in cell lines supporting HBV replication: AD38, DE19, and DES19. Drug concentrations tested bracketed the EC50 of the individual drugs. The endpoints measured for antiviral effect varied according to the cell lines and included intracellular HBV DNA, extracellular HBV DNA, extracellular HBsAg and HBeAg. Endpoints were quantitated according to published methods. Drug concentrations versus antiviral effect were evaluated using Prichard-Shipman MacSynergy and Chalice.

Results:

As measured by the suppression of HBV DNA, synergy scores for combinations of CRV431 and TXL, CRV431 and CAMs, TXL and CAMs, ranged from additive to synergistic. None of the combinations tested showed any evidence of antagonism. Cells were viable within the ranges of drug concentrations tested.

Conclusion:

These studies extend previous observations of synergy between CRV431 and TXL. Our data demonstrate that novel combinations of antivirals interrupting the HBV life cycle at multiple, previously untested, targets, were additive to synergistic. Importantly, none of the combinations showed antagonism. Two drug classes are currently approved for chronic HBV treatment, nucleoside analogs and alpha interferons. Innovative drugs and treatment strategies will be essential for achieving the HBV functional cure. These results lay the foundation for therapeutic strategies including TXL and/or CRV431 as the basis of drug combinations for the functional cure.