CRV431, a Cyclophilin Inhibitor, Reduces Fibrosis and Tumor Burden in Mice with Hepatocellular Carcinoma

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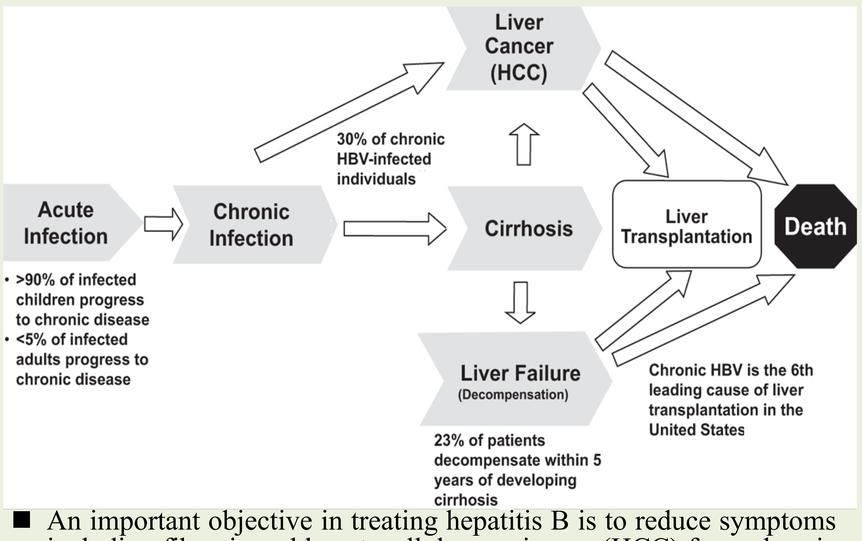
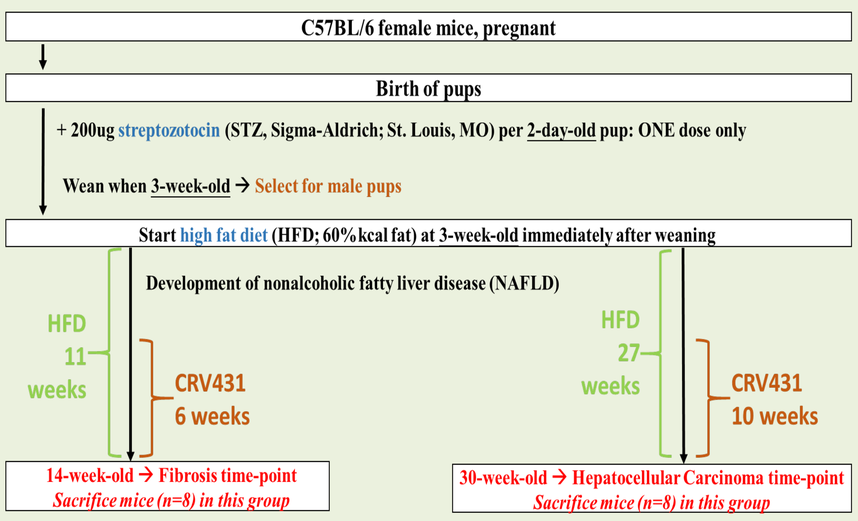
PREMISE



- An important objective in treating hepatitis B is to reduce symptoms including fibrosis and hepatocellular carcinoma (HCC) from chronic hepatitis B virus (HBV) infection.
- More than 300 million humans have chronic HBV infections worldwide. Over 750,000 HBV-infected individuals die each year, with 300,000 cases due to HCC.
- Previous studies show that cyclophilin isomerases contribute to disease progression, including that by HBV infection.
- CRV431, a cyclophilin inhibitor and non-immunosuppressive cyclosporine A analogue, demonstrates preclinical anti-HBV activities and has completed a Phase 1 clinical trial. Using a non-alcoholic steatohepatitis murine model with many similar pathogenic outcomes compared to chronic HBV infection, we aimed to assess ***whether CRV431 affects inflammation, fibrosis, and HCC.***

METHODS

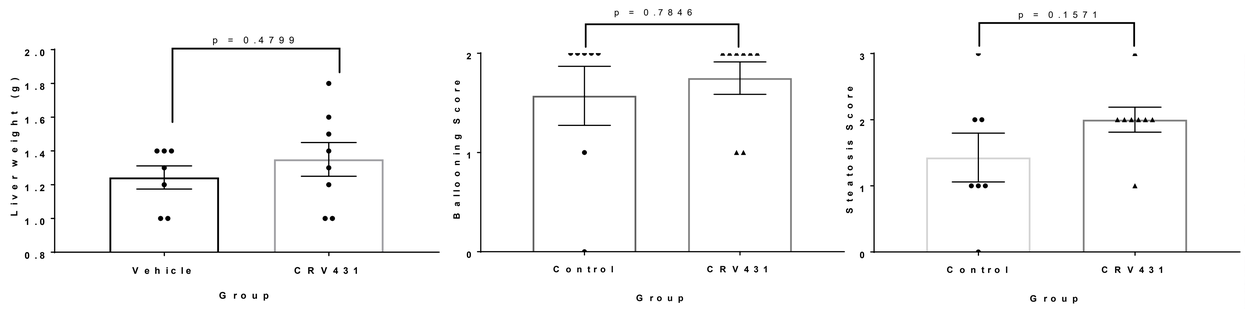


CONCLUSION

- **CRV431 is a well-tolerated and potent candidate for chronic HBV treatment. Our findings suggest that the therapeutic activity of CRV431 may extend to reductions of fibrosis and HCC development or progression.**
- **Future studies include determining the mechanisms of action of CRV431 on decreasing fibrosis and tumorous nodule formation, and testing CRV431 efficacy in a viral hepatitis-induced HCC model.**

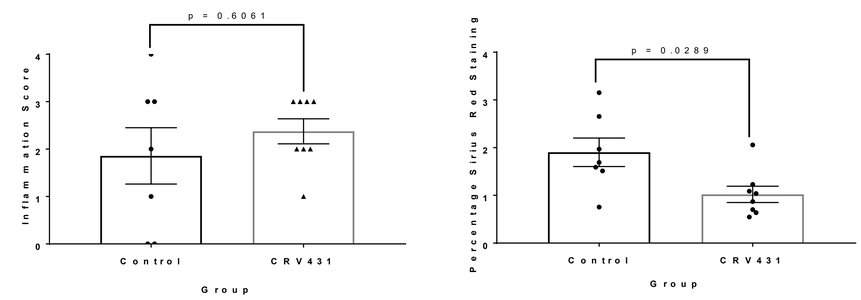
RESULTS

CRV431 DID NOT AFFECT LIVER WEIGHT, BALLOONING, AND STEATOSIS OF MICE WITH NASH SYMPTOMS



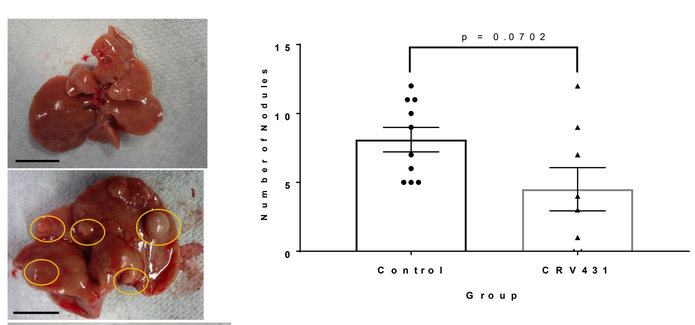
- Representative hematoxylin and eosin staining with livers of vehicle- (n=7) and CRV431-treated 14-week-old mice (n=8). Bar indicates 100μm.
- Liver weight was measured with digital scale. The following ratings for NAFLD activity [33] were used for ballooning: 0 (no histopathological changes), 1 (few balloon cells), and 2 (many prominent balloon cells; for steatosis: 0 (<5% steatosis), 1 (5-33%), 2 (33-66%), and 3 (>66% steatosis). Error bars indicate ± standard error of the mean. Two-tailed statistical Mann-Whitney nonparametric analyses, with alpha value set at 0.05, were conducted with GraphPad Prism.

CRV431 REDUCED FIBROSIS BUT NOT INFLAMMATION



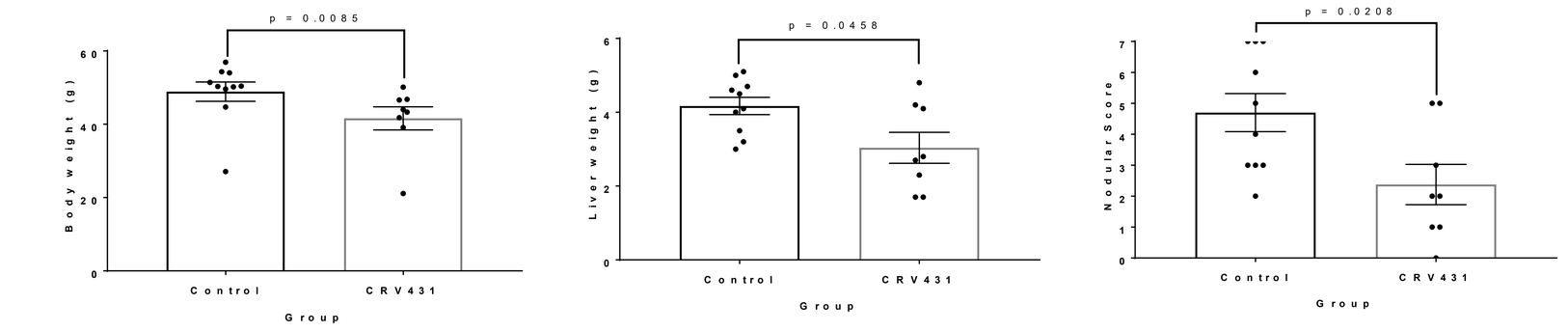
- Livers of 14-week-old mice were stained with hematoxylin and eosin. Inflammation scores (combining portal and lobular) included the following: 0 (no histopathological changes), 1 (minimal infiltration of leukocytes with no major inflammatory foci in the liver), 2 (mild with <2 inflammatory clusters), 3 (moderate with 2-4 foci of leukocytes), and 4 (severe infiltration of leukocytes with >4 inflammatory clusters)
- Livers were also stained with Sirius Red, with percentage of stained collagen obtained from Image J.

CRV431 DECREASED NUMBER OF HCC TUMORS



- Number of tumorous nodules in entire livers of vehicle- (n=10) and CRV431-treated (n=8) 30-week-old mice.
- Representative photos of livers with or without nodules. Nodules are circled in yellow. Bar indicates 1cm.

CRV431 REDUCED LIVER WEIGHT, BODY WEIGHT, AND TOTAL TUMOR BURDEN



- Liver and body weights of vehicle- and CRV431-treated 30-week-old mice were measured with digital scale.
- Our scoring system for tumor burden considered nodules detectable with a diameter of >0.1cm. Nodules with diameter not exceeding 0.5cm were categorized as small, where that of medium-sized nodules was less than 1.0cm. Nodules with diameter ≥1.0cm were considered large. Scores included 0 (no detectable nodules), 1 (no more than 4 small nodules with no larger nodules), 2 (more than 4 small nodules with no larger nodules), 3 (no more than 2 medium-sized nodules with no larger nodules), 4 (3 or more medium-sized nodules with no larger nodules), 5 (no more than 1 large nodule), 6 (no more than 2 large nodules), and 7 (3 or more large nodules).

DISCLOSURES

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