GS-008

The combination of therapeutic vaccination with siRNA-mediated silencing of HBV and PD-L1 effectively breaks HBV-specific immunotolerance in high-titer HBV carrier mice

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Background and aims: High levels of hepatic HBV antigens prevent a successful therapeutic vaccination. Reducing HBV levels before vaccination by HBV-specific siRNAs (siHBV) enhanced the immunogenicity and antiviral efficacy of our clinical candidate protein-prime/MVA-boost therapeutic vaccine, TherVacB, in higher-titer HBV-carrier mice. Non-responsiveness to vaccination was associated with high PD-1 expression on vaccine-elicited hepatic CD8 T-cells. Consequently, silencing PD-1 ligand-1 by liver-targeted siRNA (siPD-L1) also improved the TherVacB-mediated therapeutic effects. We hypothesized that combining siHBV with siPD-L1 could further broaden the applicability of TherVacB in high-titer, persistent HBV infection settings.
Method: We established high-titer persistent HBV infection in C57BL/6J mice using AAV-HBV, resulting in over 80% of HBV-positive hepatocytes, HBsAg of 5500 IU/ml and HBeAg of 330 PEI U/ml We pretreated five mice per group for eight weeks with siHBV before TherVacB and applied siPD-L1 during the two protein priming immunizations. We followed up with the mice for 7.5 months after the MVA boost.
Results: Groups of mice receiving TherVacB and TherVacB+siPD-L1 demonstrated only a minor decrease in serum HBsAg and HBeAg levels shortly after treatment. Without vaccination, siHBV+siPD-L1 reduced HBsAg and HBeAg, as expected, but the antigen load eventually returned baseline values, and no induction of HBV-specific immunity was observed. Combining siHBV+TherVacB reduced HBsAg to undetectable levels for eight weeks, but a partial relapse finally resulted in only a 1-log10 decrease compared to the initial values. By contrast, mice receiving siHBV+TherVacB+siPD-L1 cleared HBsAg for 24 weeks. 3/5 mice remained negative for 7.5 months. Overall, the siHBV+TherVacB+siPD-L1 treatment resulted in a ≥3-log10 reduction in serum HBsAg, a 70% reduction in HBeAg, and, on average, a 90% reduction in intrahepatic HBV-DNA. A strong vaccine-elicited immunity accompanied this impressive antiviral effect.
Conclusion: Our data demonstrate that complementary siRNA-mediated silencing of HBV and the immune checkpoint PD-L1 helps to further enhance the efficacy of therapeutic vaccination in high-titer HBV carriers.

GS-009

Efficacy and safety of carvedilol in cirrhosis patients with uncomplicated ascites without high-risk esophageal varices-a randomized controlled trial [NCT05057572]

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Background and aims: Carvedilol is effective in preventing bleeding in patients with cirrhosis and high-risk varices. Although it reduces drivers of clinical decompensation (portal pressure, systemic inflammation and bacterial translocation), the data on carvedilol use for prevention of ascites related complications (SBP, HRS-AKI, refractory ascites or severe hyponatremia) are limited.
Method: Consecutive patients presenting with uncomplicated new-onset ascites and low risk esophageal varices were randomized to receive carvedilol (at the starting dose of 3.125 mg BD) (Group A) or placebo (Group B) in addition to ST (diuretics with or without albumin). The composite primary outcome was incidence of complicated ascites (any of refractory ascites, HRS AKI, SBP, severe hyponatremia) at 1 year. The secondary outcomes include need for paracentesis, change in HVPG, CTP and MELD score and mortality at 1 year.
Results: Of 302 consecutive patients screened, 104 patients were randomized into two groups. Baseline characteristics were comparable between two groups. In both groups, MAFLD was the most common etiology (overall 41.3%) followed by ethanol (21.2%) with comparable comorbidities. Patients in Group A had lower incidence of complicated ascites at 1 year (39.4% vs. 66.7% $p = 0.026$), mainly related to reduction of incident HRS AKI (33.3% vs 63.6% $p = 0.014$). Patients in Group A also had less frequent need for large volume paracentesis as compared to Group B at 1 year (27.3% vs 57.6% $p = 0.013$). Better resolution of ascites (66.6 vs 39.4% $p = 0.06$). Despite comparable at baseline, MELD (18.9 ± 1.3 vs. 15.34 ± 1.38; $p = 0.06$) and CTP score (9.36 ± 1.43 vs. 8.15 ± 1.7 vs $p = 0.003$) were higher in Group B as compared to Group A at the end of one year. Overall, the change in HVPG at one year among responders showed significant reduction from 14.89 to 11.86 mmHg ($p = 0.042$). Use of carvedilol was associated with lesser mortality at one year (9.1% vs 24.2% $p = 0.05$). None had treatment related severe adverse effects requiring discontinuation of therapy.
Conclusion: Carvedilol use in patients with cirrhosis with uncomplicated ascites and low risk varices is safe and prevented further complications, less frequent need for large volume paracentesis and improved survival.

GS-010

Early liver transplantation for severe alcohol-related hepatitis: long-term data of the french-belgian controlled study (QuickTrans)

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Background and aims: The QuickTrans study showed similar survival at 2 years in patients transplanted for alcohol-related hepatitis (AH) compared to alcohol-related cirrhosis but failed to demonstrate non-inferiority of alcohol relapse between the two groups. Long-term data are needed for early liver transplantation (LT) for AH.
Method: Patients were followed-up according to each center local practice after the 2-year end point of the QuickTrans study and our primary end point was alcohol relapse 5 years thereafter (i.e. at 84 months). Secondary end points were survival at 84 months and analysis of alcohol consumption pattern. End points were analyzed