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MAKALU: Twelve-week of treatment with Ritonavir-boosted Danoprevir Pluzs Peginterferon and Ribavirin produces 96% SVR12 in HCV Genotype 1-Infected Non-Cirrhotic Chinese Patients

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Background: To evaluate the efficacy and safety of Ritonavir-boosted Danoprevir (DNVr) plus peginterferon and ribavirin in treatment-naive Chinese HCV genotype 1 (GT1) patients without cirrhosis.
Methods: In this multi-center open-label single-arm phase 2 study,70 treatment-naïve, non-cirrhotic HCV GT1 patients were enrolled in China. The treatment protocol involved a combination of DNVr 100 mg/100 mg BID, subcutaneous injection of weekly peginterferon alfa-2a at 180 mcg and oral Ribavirin 1000/1200 mg/day (bodyweight $<75/\geq$ 75 kg) for 12 weeks. The primary endpoint was the rate of sustained virologic response 12 weeks after the end of treatment (SVR12) in these patients.
Result: Of 69 patients completed 12-week treatment, 96% (66/69) patients achieved SVR12. One patient (1.4%, 1/70) discontinued treatment due to serious adverse event (SAE) and no deaths reported. Of danoprevir-related adverse events, only nausea and diarrhea occurred at a rate of >10%. Only grade one ALT and AST increases were related to danoprevir. There was no virologic breakthrough during the treatment. Of 69 patients, only 3 (4%) patients relapsed.
Conclusion: The results show that with 12-week treatment, DNVr plus peginterferon and ribavirin achieved SVR12 rate of 96%. This triple regimen is safe and well tolerated.

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Pre-activation with TLR7 agonist accelerates hepatitis B virus clearance in the mouse model

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Background: Toll-like receptor (TLR) agonists are able to activate cellular signal pathways and induce the production of cytokines. Currently, TLR7 agonist has been shown to be a potent antiviral in the animal models and patients with chronic hepatitis B (CHB). Therefore, activation of TLR7 pathway may promote adaptive immune responses and contribute to HBV control. Here we examined how TLR7 agonist modulates the host immune system and influence adaptive immunity if applied in vivo.
Methods: C57BL/6 mice (male, 6–8weeks) received 20 μg Imiquimod via tail vein injection. Non-parenchymal liver cells (NPC) and splenocytes were isolated and analyzed for their phenotypes at different time points. At day 14 after injection, mice were hydrodynamically injected with 10 μg pAAV/HBV1.2 plasmid. Serum HBV markers were determined up to 3 weeks. The frequencies and phenotypes of different immune cell types in the liver and other organs were analyzed. The frequency and functionality of HBV-specific CD8+ T cells in the liver and spleen were determined by dimer staining and intracellular cytokine staining after stimulation with HBV peptides. Interferon-γ (IFN-γ) production of αCD3/CD28-stimulated splenocytes was detected by specific ELISA.
Result: Imiquimod application itself did not induce significant change in the cell composition in the liver and spleen. However, CD8 T cells from the spleen and NPCs showed a sustainably changed phenotype with up-regulated CD62L expression within 4 weeks of Imiquimod injection. Imiquimod application triggered sustained change of T cell response in mice over 8 weeks. Compared with controls, the IFN-γ production of splenocytes from Imiquimod-treated mice were significantly increased with αCD3/CD28 stimulation ($p < 0.05$ at days 1, 14, and 30). After 28 days of hydrodynamic injection with pAAV/HBV1.2 plasmid, serum HBsAg could be cleared in three of five mice of TLR7 group while the mice of the control group remained HBsAg-positive. The IFN-γ-producing cells in liver lymphocytes with HBV-specific stimulation were significantly increased ($p = 0.009$), and the concentration of IFN-γ in culture supernatant of lymphocytes with αCD3/CD28 stimulation also elevated ($p = 0.029$).
Conclusion: Pretreatment with TLR7 agonist could modulate the host immune status and enhance the HBV-specific T cell responses which facilitate HBV clearance in the mouse model. Thus, the TLR7 agonist may be used for immunotherapeutic strategy to treat chronic HBV infection.

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Augmenter of liver regeneration protects against carbon tetrachloride-induced liver injury by promoting autophagy in mice

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Background: Augmenter of liver regeneration (ALR) exerts strong hepatoprotective properties in various animal models of liver injury, but its protective mechanisms have not yet been explored. Autophagy is a recently recognized rudimentary cellular response to inflammation and injury. The aim of this study was to test the hypothesis that ALR may protect against acute liver injury through the autophagic pathway.
Methods: The level and role of ALR in liver injury were studied in a mouse model of acute liver injury induced by carbon tetrachloride (CCl_4). The effect of ALR on autophagy was analyzed *in vitro* and