Supplement material：

Figure S1

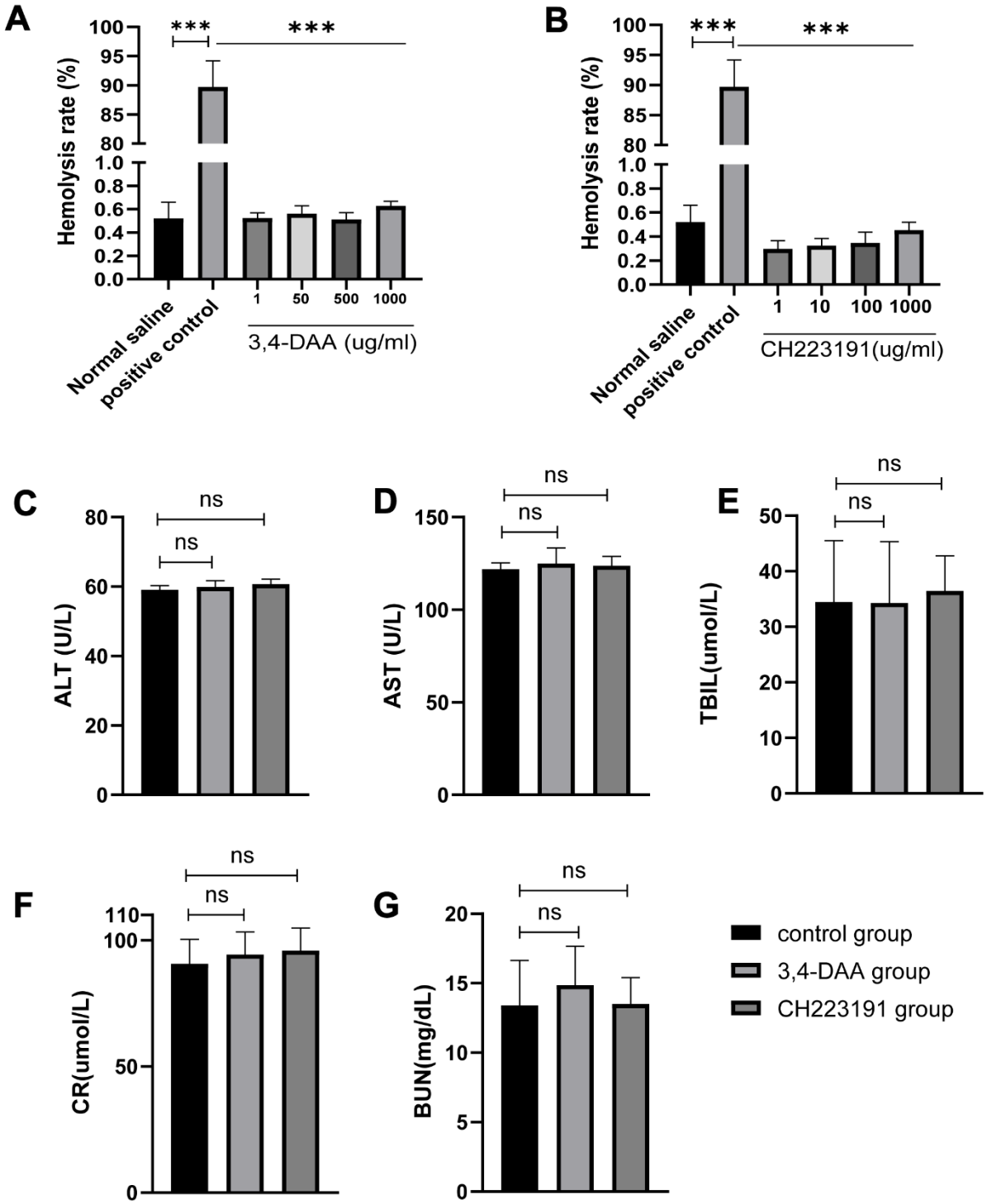

Figure S1 Assessment of the drug toxicity effect.

(A-B) Hemolysis test of 3,4-DAA and CH223191. 2% of the red blood cell suspensions were treated with normal saline (negative control), deionized water (positive control), or two drugs in different concentrations (n=3). (C-D) Wild Lewis rats were randomly assigned to 1mL CMC-Na or 200mg/kg 3, 4-DAA or 10mg/kg CH223191, after 21 days, peripheral blood of each group was taken for analysis and determination of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum total bilirubin (TBIL), urea and creatinine levels by automatic biochemical analyzer (N = 3).

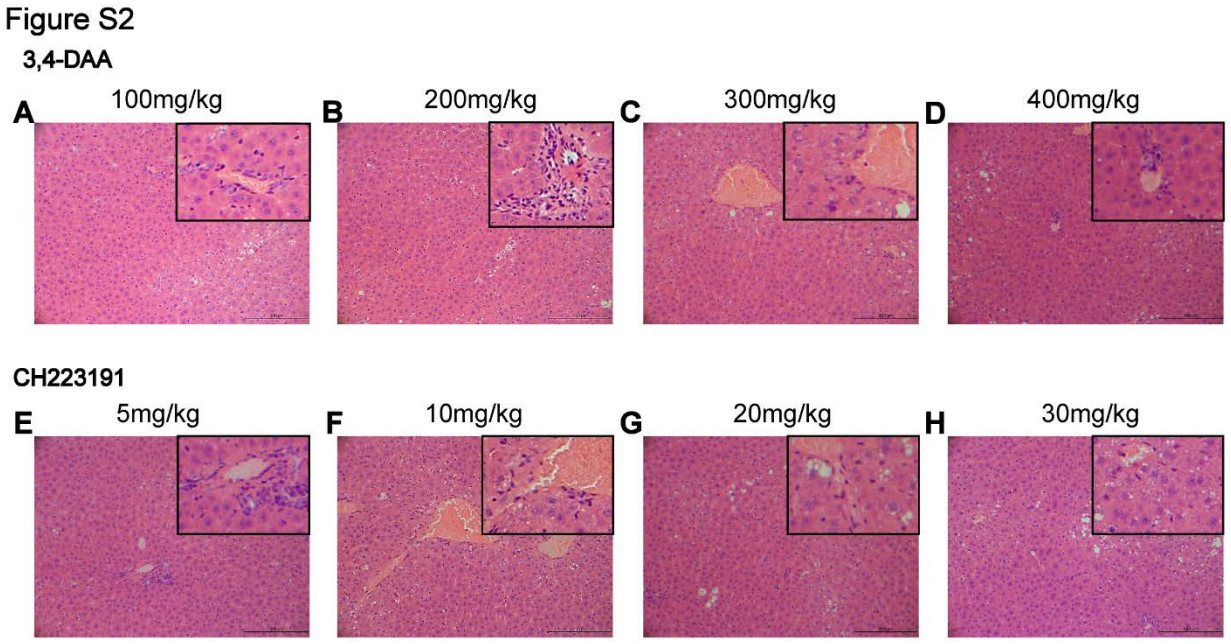

Figure S2 Validation of drug toxicity in liver.

(A-H) Wild Lewis rats were randomly divided into groups and given 1mL CMC-NA, 100mg/kg, 200mg/kg, 300mg/kg and 400mg/kg 3, 4-DAA or 5, 10, 20, 30 mg/kg CH223191. After 21 days, liver of each group was collected for HE staining.

Figure S3

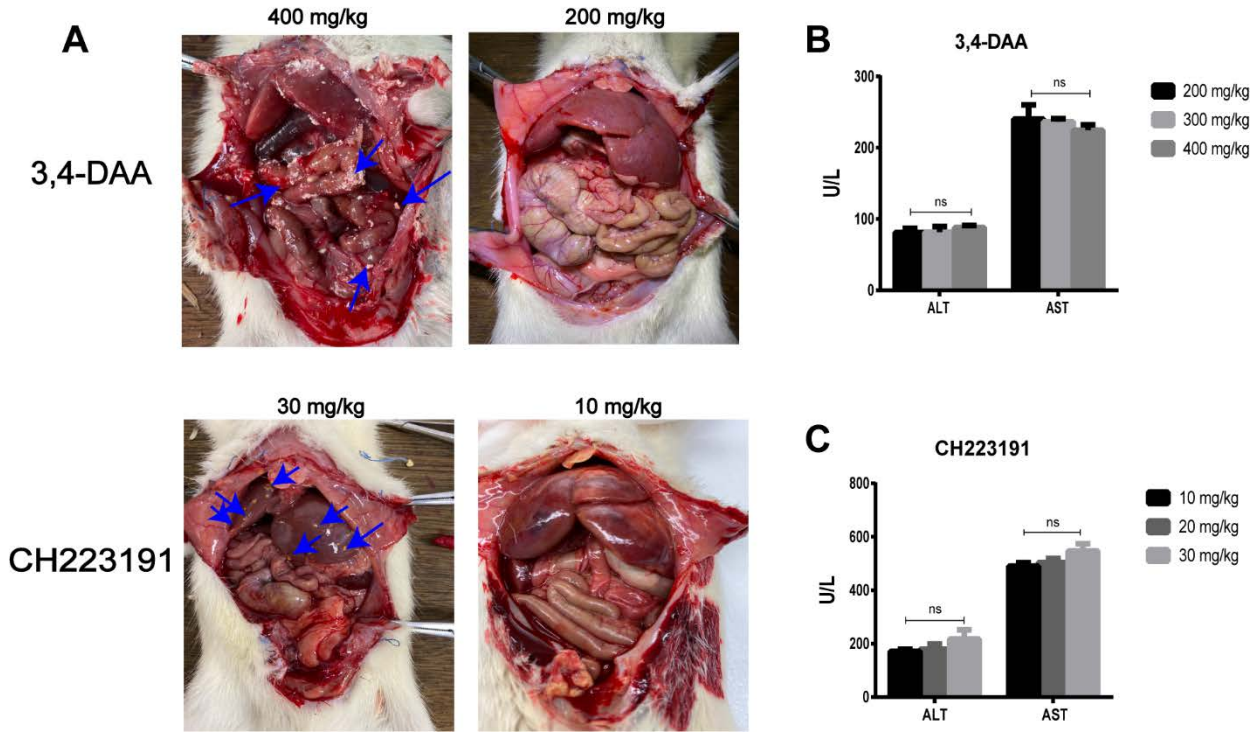

Figure S3 High dose intraperitoneal injection has a problem of dissolution and has little effect on liver function.

(A) The transplanted recipient rats were divided into two groups, and were given 3, 4-DAA or CH223191 at 10 am every day (i.p.), and examined after anesthesia at 5 PM on the third day. The blue arrow shows unabsorbed drug particles. (B-C) On the third day, PB of recipient rats was collected to detect ALT and AST by automatic biochemical analyzer (N=3).

Figure S4

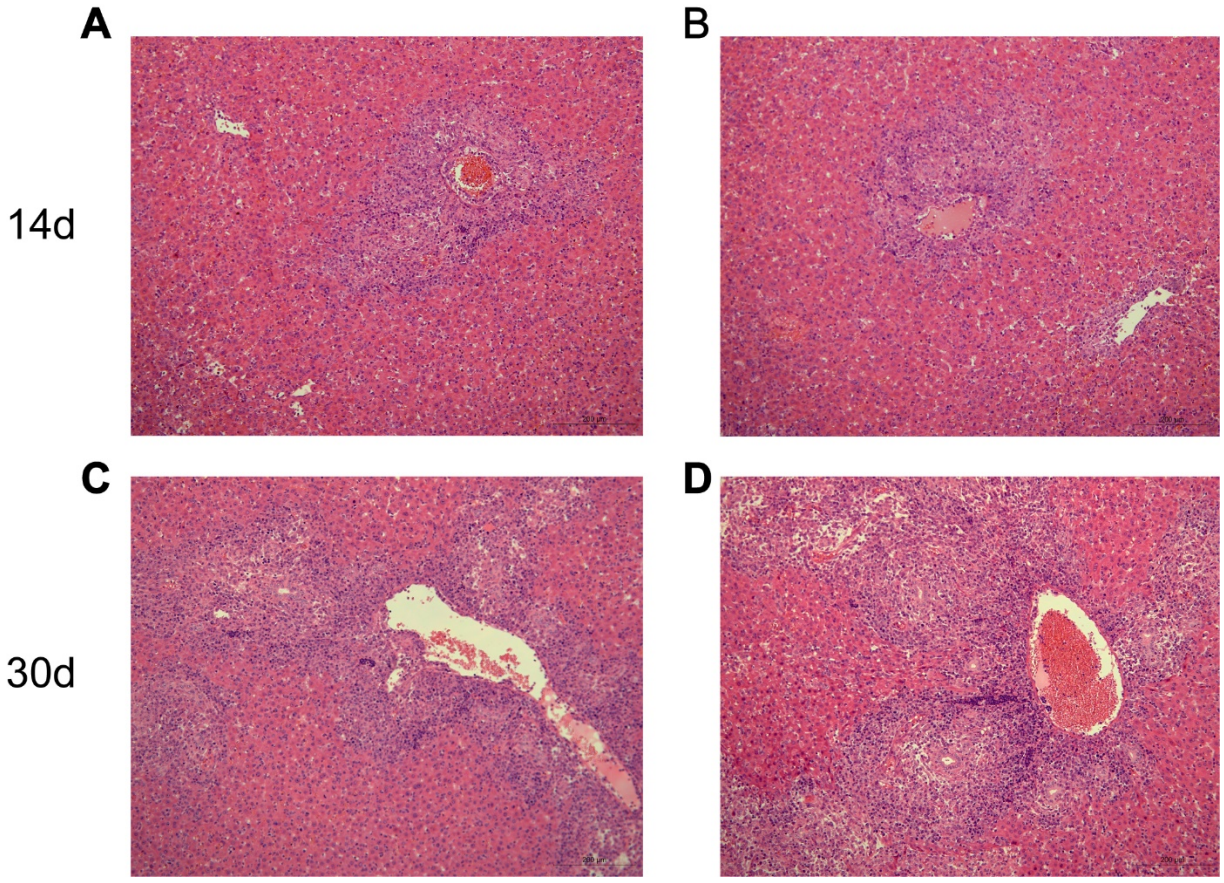

Figure S4 Liver status after discontinuation administration of 3, 4-DAA.

(A-B) HE of rats after continuous administration of 3, 4-DAA on POD 14.(C-D) Liver condition of 3, 4-DAA group rats on POD 30.

Figure S5

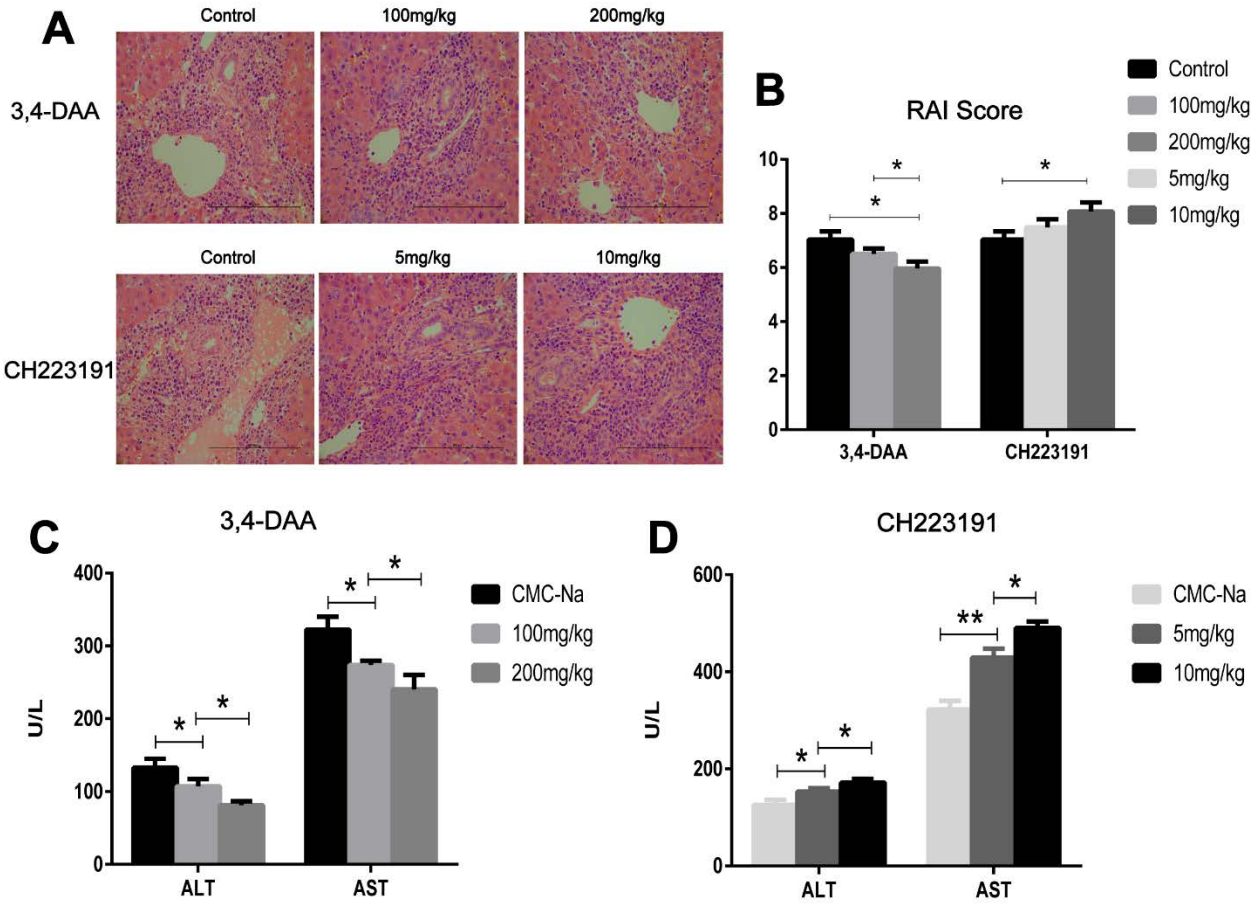

Figure S5 3, 4-DAA and CH223191 alleviated and accelerated immune mediated-liver rejection in a dose-dependent manner at low doses, respectively.

(A-B) Hepatic morphologic changes and RAI scores in low-dose drug-treated recipient rats (100mg/kg and 200mg/kg 3,4-DAA; 5mg/kg and 10mg/kg CH223191). (C-D) On POD 7, PB of recipient rats was collected to detect ALT.

Figure S6

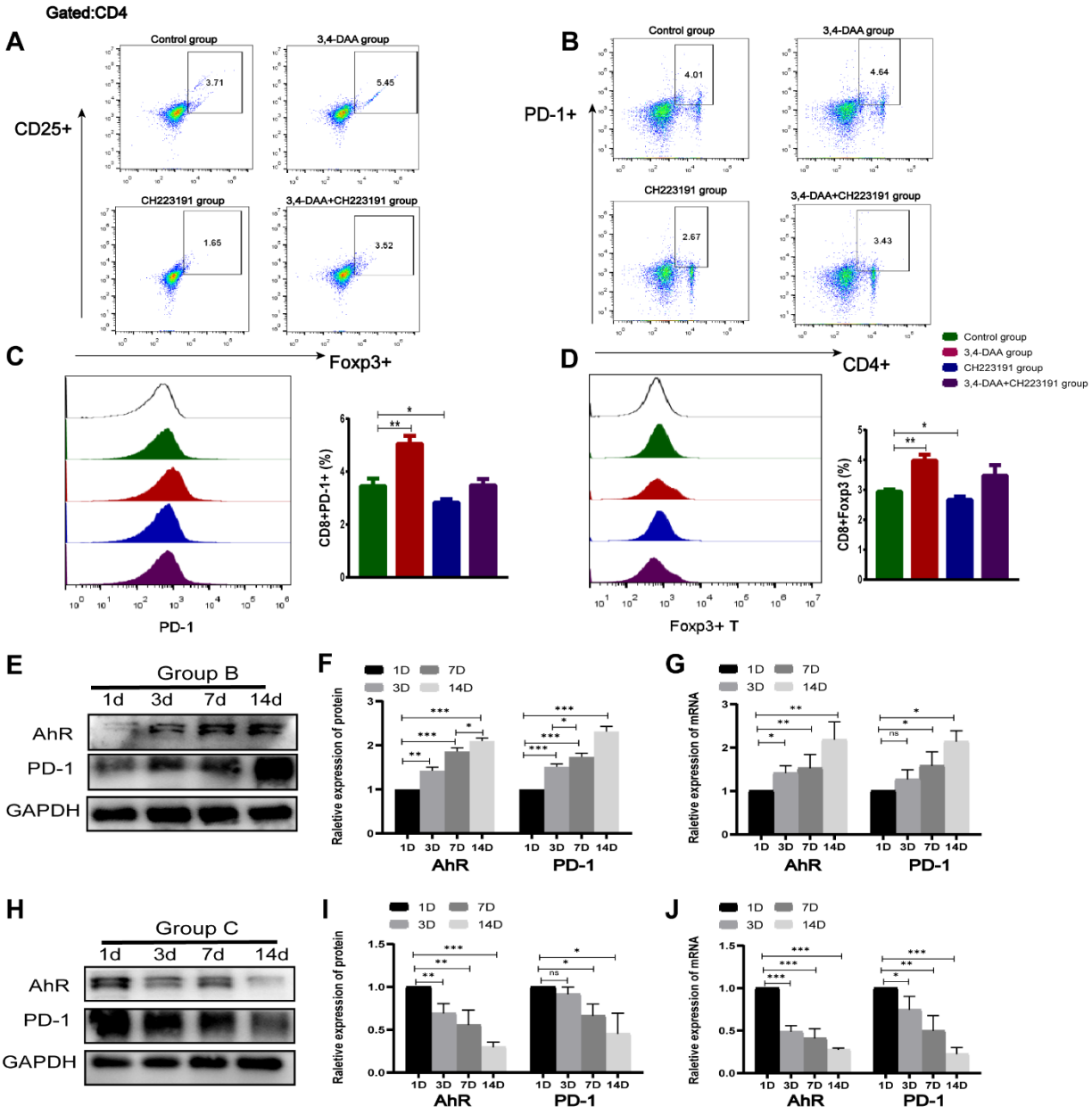

Figure S6 Activation of AhR alleviated rejection by affecting the content of cells infiltrating graft.

(A-D) PB of recipient rats in each group was collected 7d after administration. PBMCs was separated and the content of CD4+CD25+ Foxp3+, CD4+PD-1, CD8+ Foxp3+ and CD8+PD-1 T cells were detected by flow cytometry. (E-J) The expression levels of AhR and PD-1 were detected in the 3,4-DAA-treated group (group B) and CH223191-treated group (group C) by Western blot and RT-PCR, respectively.

Figure S7

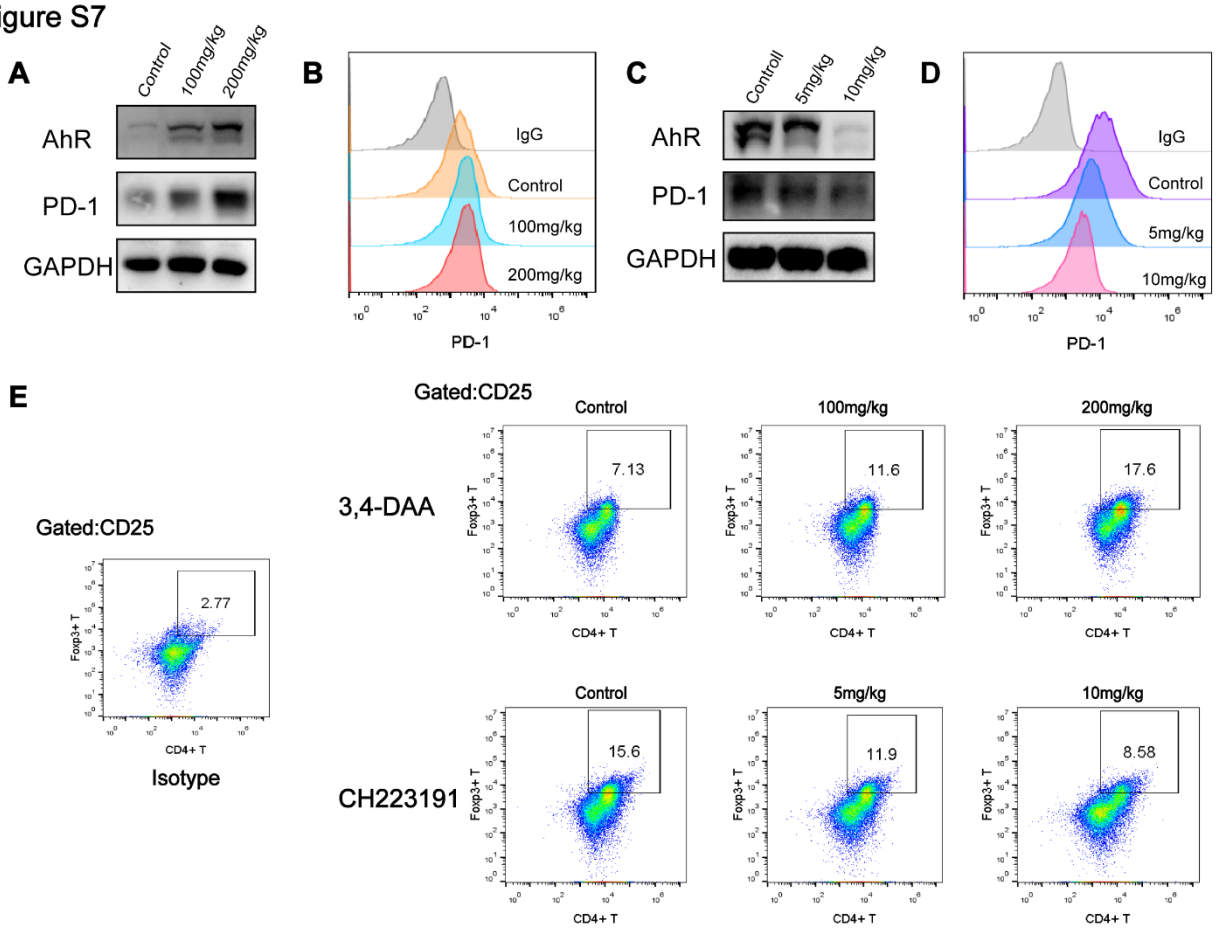

Figure S7 3, 4-DAA and CH223191 alleviated and accelerated immune mediated-liver rejection in a dose-dependent manner, respectively.

(A-B) The expression levels of AhR, PD-1 and the content of CD4+PD-1+ T cells in spleen were detected by flow cytometry and Western Blot.(F) The content of CD4+CD25+Foxp3+ T cells in spleen were detected by flow cytometry.

Figure S8

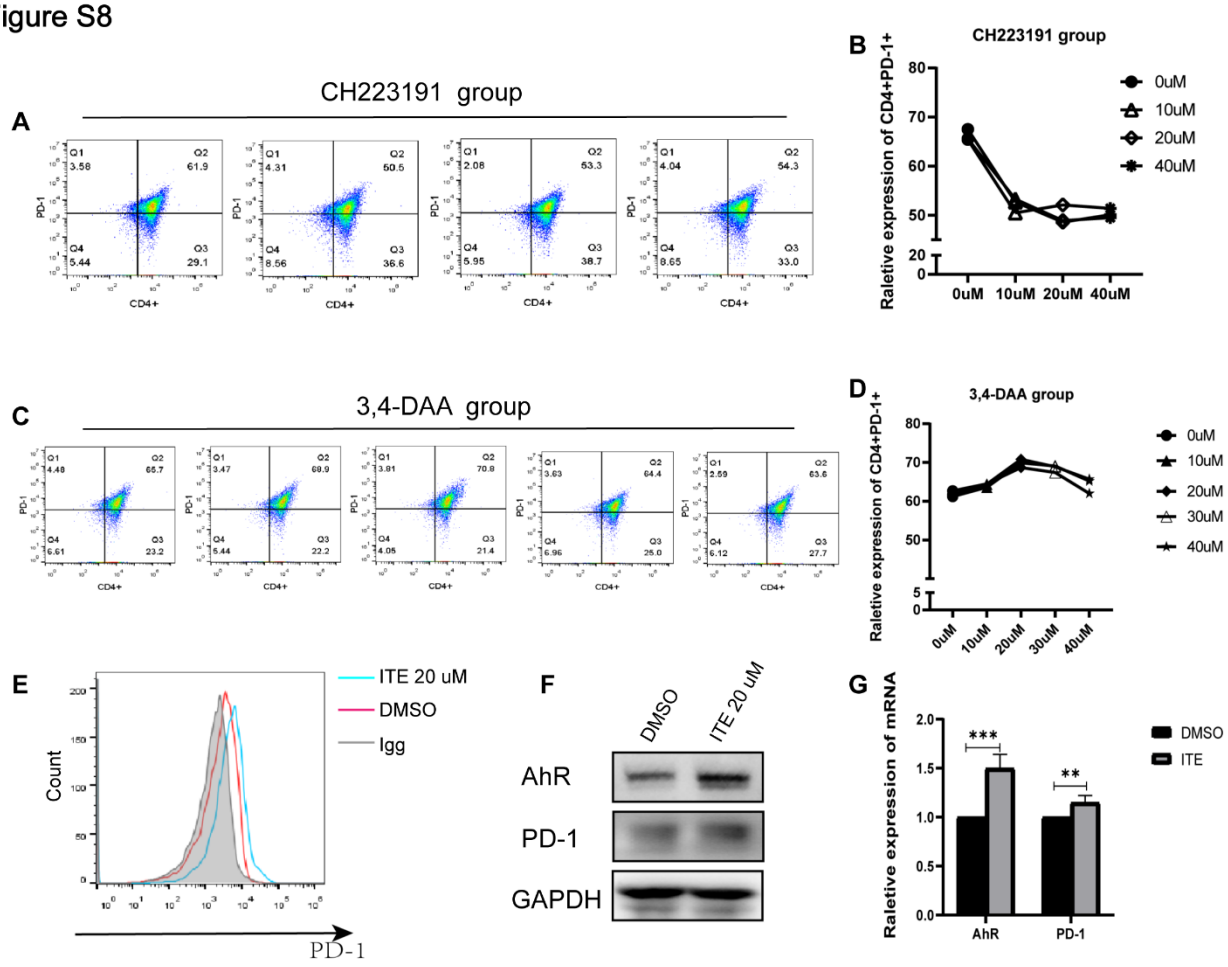

Figure S8 In vitro drug doses were selected and the effect of ITE on AHR was studied

(A-D) Selection of drug dose for in vitro treatment. (E-G) ITE could affect PD-1 expression through AhR.