Modeling Hepatitis E infection in immunocompromised patients using a new pig model

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Nancy León-Janampa[1], Céline Barc[2], François Darrouzain[3], Philippe Gatault[4], Mickaël Riou[2], Anne Pinard[2], Jérémy Pezant[2], Ignacio Caballero-Posadas[5], Christelle Rossignol[5], Catherine Gaudy-Graffin[1], Denys Brand[1], Julien Marlet[1]

1 INSERM U1259, Université de Tours, France
2 INRAE, UE-1277 Plateforme d'Infectiologie expérimentale, Centre Val de Loire, F-37380, Nouzilly, France
3 Service de Pharmacologie médicale, CHRU de Tours, France
4 Transplantation rénale – Immunologie clinique, CHRU de Tours, France
5 INRAE, Université de Tours, UMR ISP, Centre Val de Loire, F-37380, Nouzilly, France

BACKGROUND

HEV genotypes 3 and 4 circulate in animals (pigs, wild boar) and are associated with chronic hepatitis in immunocompromised patients (1).

The pathogenesis of this chronic hepatitis E infection remains unclear and current treatment strategies are limited.

Our objective was to develop a new pig model of hepatitis E virus (HEV) infection in immunocompromised (IC) patients, using immunosuppressive strategies similar to those used in solid organ transplant patients.

METHODS

Six piglets (7 weeks old, Large White) were separated into three groups: control group (IC-/HEV-), immunocompromised (IC+/HEV-) and immunocompromised infected with HEV (IC+/HEV+) (Fig. 1). Since day 0, pigs in groups IC+/HEV- and IC+/HEV+ were treated with a combination of tacrolimus (0.8 mg/kg/d), mycophenolic acid (MPA, 25 mg/kg/d) and prednisolone (0.5 mg/kg/d). After two weeks of treatment, pigs in group IC+/HEV+ where infected with genotype 3i HEV (9.10^7 IU/mL) by i.v injection. HEV RNA and residual concentration (C_0) levels of tacrolimus and MPA were monitored weekly. Tacrolimus dosage was adjusted weekly to reach target concentrations between 5 and 10 ng/mL. Immune response profiles (IL-2, IL-4, IL-10, IFN-γ and TNF-α ELISA cytokine assays), blood count and biochemical hepatic markers (ALT, bilirubin) were compared between the different groups overtime. After six weeks (four weeks post infection), the animals were necropsied and the HEV RNA was quantified in biopsies of liver, small intestine, colon, spleen, kidney and in the fluids of intestinal tract. All procedures were performed in accordance with ethical standards for handling laboratory animals and ethical guidelines for clinical studies.

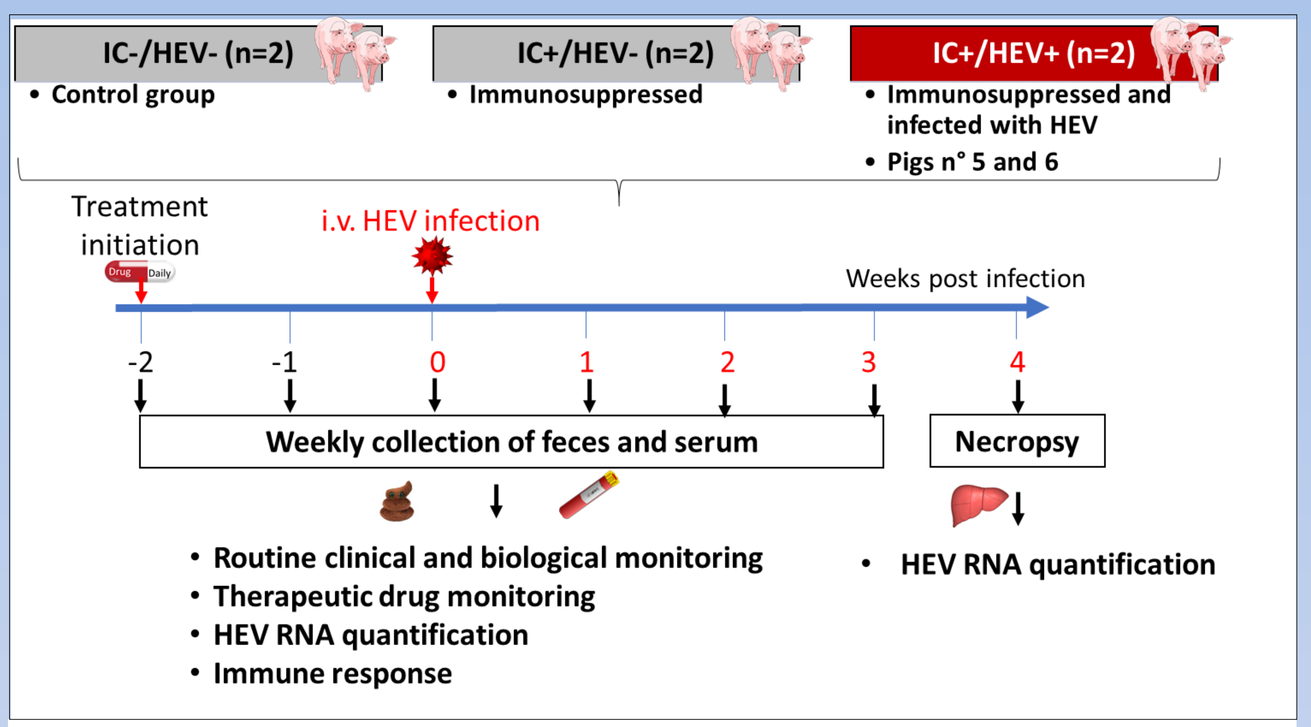

Figure 1. Experimental design of HEV infection in immunocompromised pigs

RESULTS

Acute HEV infection in pigs treated with tacrolimus, MPA and prednisolone was mostly asymptomatic. ALT, γGT and bilirubin levels were similar between the three groups. Diarrhea and lower weight (32 vs 42 kg at week 5) was observed in pigs treated with immunosuppressive drugs. One pig (group 2) was euthanized early due to acute kidney failure in a context of tacrolimus overdose. HEV RNA was detected in pig's sera (group 3) since week 1 after inoculation (10^3 IU/mL). It reached a peak at week 2 (10^4 IU/mL) and stayed at this plateau until the end of the study. HEV RNA levels were higher in feces with a plateau at 10^7 IU/mL (Fig. 2). HEV RNA levels were high in the liver and intestinal fluid (10^7 IU/mL) and in the colon (10^5-10^6 IU/mL). They were lower in the spleen and in the small intestine (10^2-10^5 IU/mL) (Fig. 3). IL-2 levels were similar between the three groups and tended to decrease over time.

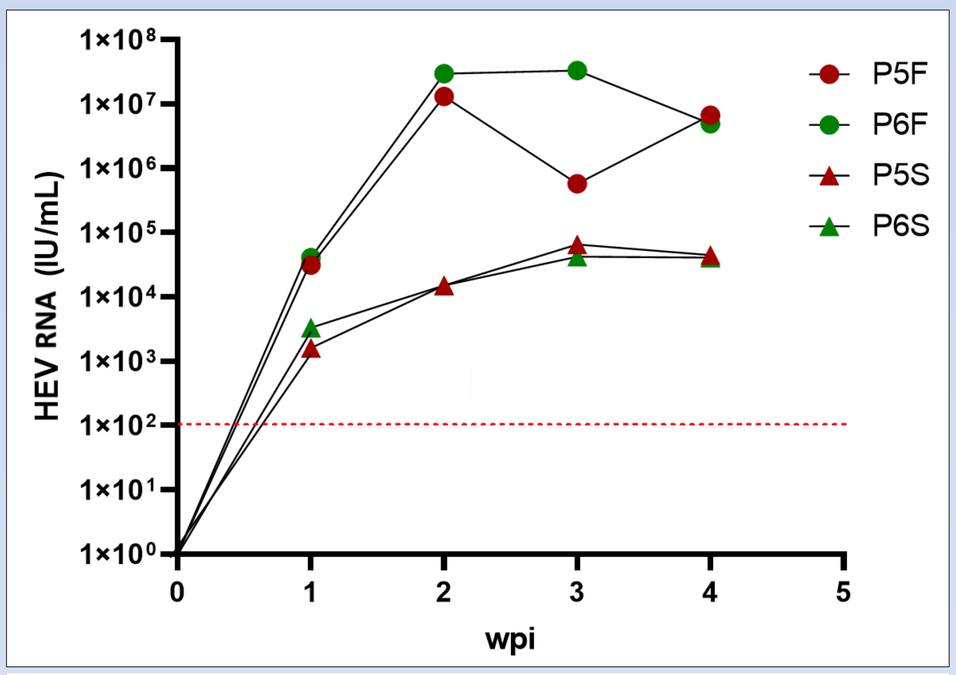

Figure 2. Quantification of HEV RNA in feces and sera of immunosuppressed and infected pigs. P5: Pig 5, P6: Pig 6, F: feces and S:sera; wpi, weeks post infection

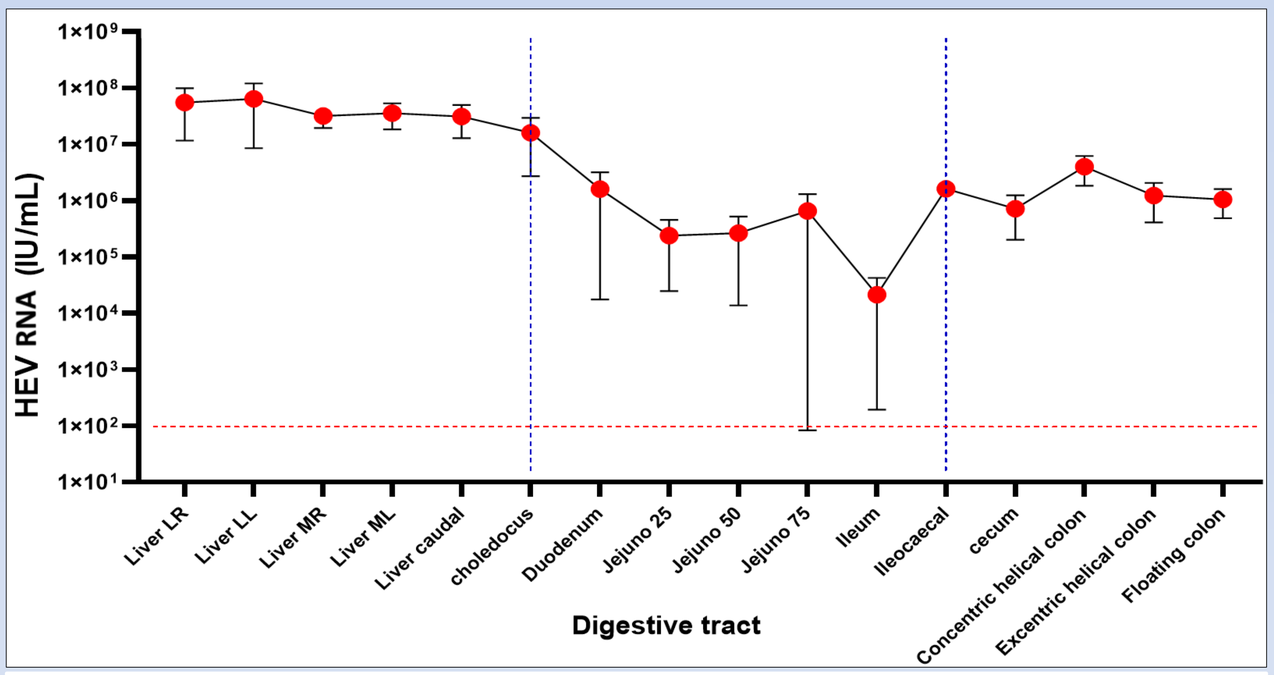

Figure 3. Quantification of HEV RNA in the digestive tract of immunosuppressed and infected pigs. LR: lateral right, LL, lateral left, MR: medial right, ML: medial left.

CONCLUSIONS

This pig model allowed the establishment of an HEV infection in animals treated with tacrolimus and MPA. Similar to infection in humans, infection in pigs was mostly asymptomatic. Levels of HEV RNA in the colon were close to levels seen in the liver and intestinal fluid, suggesting that this part of the digestive tract might play an important role in the physiopathology of HEV infection. HEV infection in this model lasted at least 4 weeks. This model could be used to study the physiopathology of chronic HEV infection (>8 weeks) and to identify or validate new therapeutic strategies for chronic HEV infection.

1. Izopet J, Tremeaux P, Marion O, Migueres M, Capelli N, Chapuy-Regaud S, Mansuy JM, Abravanel F, Kamar N, Lhomme S. Hepatitis E virus infections in Europe. J Clin Virol. 2019; 120:20-26.