Oral treatment with PBI-4050, a novel first-in-class anti-fibrotic compound, reduces hepatic fibrosis and hepatocellular carcinoma

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INTRODUCTION AND PURPOSE

Hepatic fibrosis is an outcome of many chronic liver diseases, including hepatitis B virus, hepatitis C virus, alcoholic liver disease and non-alcoholic steatohepatitis. Liver fibrosis is characterized by the excess accumulation and alteration of extracellular matrix molecules, including collagen, in the tissue. Liver fibrosis can progress to liver cirrhosis, liver failure, and portal hypertension. Moreover, fibrosis may accelerate experimental hepatocarcinogenesis. Liver transplantation is the only treatment available for patients with advanced stage of fibrosis. Therefore, alternative methods are required to develop new strategies for anti-fibrotic therapy. It was thus desired to evaluate the effect of PBI-4050 on murine CCl_4-induced liver fibrosis.

METHODS

CCl_4-induced liver fibrosis study design:

IP injection of 2 ml/kg of CCl_4 10% in corn oil, twice a week for 7 or 16 weeks

C57BL6/J male

DAY 1
Oral administration of vehicle or PBI-4050 (200 mg/kg, day 1 to 113)

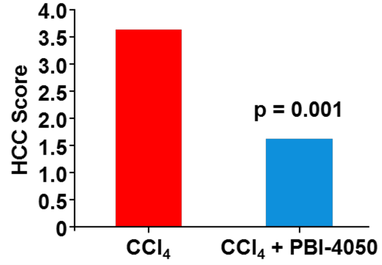
DAY 59
Euthanasia and fibrosis evaluation
or
DAY 113
Euthanasia and HCC evaluation

RESULTS

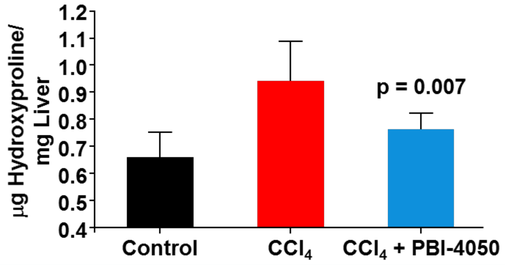
PBI-4050 reduces the percentage of animals with hepatocellular carcinoma (HCC). A significant reduction of HCC score and metastasis is also observed.

	% of Animal with HCC	HCC Score
Sham	0	0
CCl_4	100	3.63
CCl_4 + PBI-4050	75	1.63

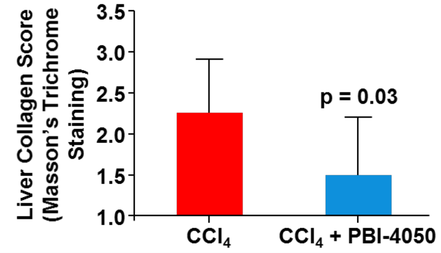
HCC score:
1 = few HCC (less than 3)
2 = less than 10 HCC
3 = more than 10 HCC
4 = more than 10 HCC and metastasis on diaphragm



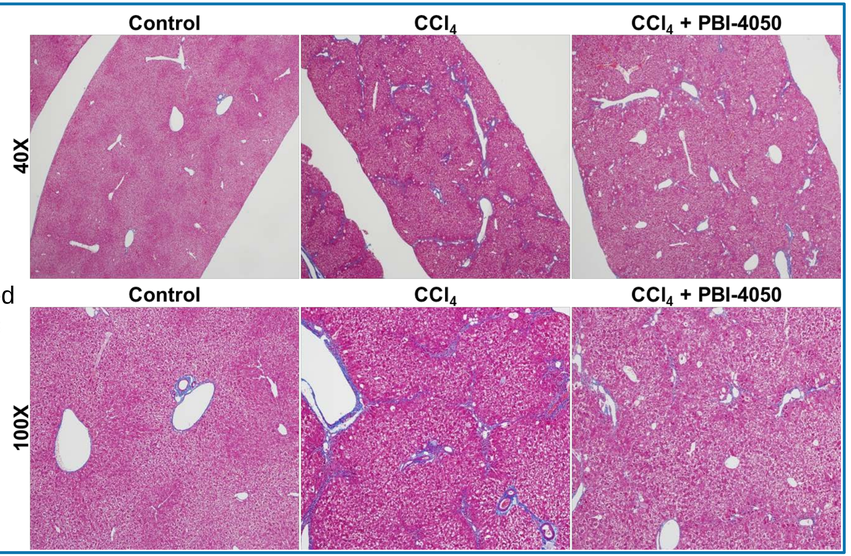
PBI-4050 significantly reduces hepatic concentration of hydroxyproline.



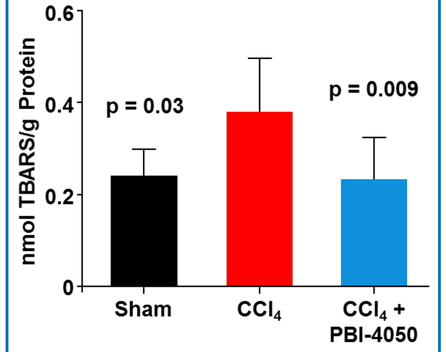
PBI-4050 significantly reduces the collagen score in liver (Masson's Trichrome staining).



PBI-4050 significantly reduces histological lesions in CCl_4-induced liver fibrosis (Masson's Trichrome staining).



CCl_4 induces hepatorenal injury via oxidative stress and biochemical alterations. In kidney, PBI-4050 significantly reduces TBARS (lipid peroxidation).



CONCLUSIONS

PBI-4050 significantly reduces:

- **fibrosis in liver;**
- **the number of animals developing HCC;**
- **HCC metastasis;**
- **lipid peroxidation in kidney.**

These results suggest that PBI-4050 offers the potential as a novel therapy for the treatment of liver fibrosis and hepatocellular carcinoma.