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Science Changing Life



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BACKGROUND

Liver fibrosis

- Prevalent pathological feature of chronic hepatic injuries
- Accumulation of collagen with inflammation and scarring as clinical sign
- Limited treatment options available for human patients
- Cyclophilins, a family of proteins, has been shown to contribute to the development of fibrosis and later stages (hepatocellular carcinoma)

CRV431

- Pan-cyclophilin inhibitor showing reduction of collagen deposition in CRV431treated mice with damaged pancreatic cells and nourished with high-fat diet Same trend observed in CRV431-treated mice exposed to carbon tetrachloride
- (CCL_4)

Aim: Examine if CRV431 affects the development of fibrosis induced by both chemical and diet in male C57BL/6J mice; obeticholic acid (OCA) as comparator

EXPERIMENTAL DESIGN

Time 0 6 Weeks						
Group 1 (n=10)						
Group 2 (n=10)		Vehicle daily				
Group 3 (n=8)		50mg/kg CRV431 daily				
Group 4 (n=10)		10mg/kg OCA daily				
Group 5 (n=10)		CRV431 and OCA combination (COMBO				

RESULTS

	Serum					Liver Histology Score		
Group / Detections	Glucose (mg/dL)	Alanine Transaminase (nmole/min/mL)	Aspartate Transaminase (nmole/min/mL)	Alpha Fetoprotein (ng/mL)	Cholesterol (mg/dL)	Inflammation	Steatosis	Ballooning
Negative Control	264.5	9.739	51.35	69.09	202.4	0	0	0
Vehicle	344.4	43.55	79.52	116.2	255.1	3.4	3	2
CRV431	284.1	44.53	79.16	114.7	237.7	3	3	2
OCA	552.5	18.12	64.26	95.45	254.6	2.9	3	2
COMBO	284.6	28.7	76.65	114.6	205.9	2.6	2.8	1.9

CRV431 does not affect glucose and protein levels in serum • Treatment did not affect levels detected in serum. Bonferroni's multiple comparison tests (two-tailed) were conducted.

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CRV431 decreases diet- and chemical-driven fibrosis in livers of mice





stained with Sirius Red

- - extent of CRV431



CONCLUSIONS

CRV431 is a potent agent against diet- and chemical-driven fibrosis. This result is consistent with our previous findings and suggests that cyclophilin inhibition can protect the liver from induced injuries.





CRV431 reduces body weight of mice

- CRV431 alone and COMBO lowered body weight compared to vehicle
- CRV431 or OCA alone did not
- decrease liver weight
- Decreased liver weight was seen in COMBO-treated mice