SRT-015, best-in-class apoptosis signal-regulating kinase 1 inhibitor, demonstrates preclinical efficacy in acute models of liver injury

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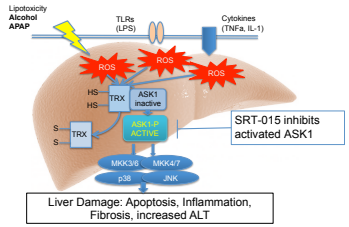
Introduction

Acute liver toxicity can be induced in vivo by multiple agents including acetaminophen (APAP; paracetamol) overdose and excessive alcohol consumption. APAP is a widely used pain reliever and fever reducer in the US and Europe. Although it is considered safe at therapeutic doses, APAP overdose causes severe liver injury, contributing to around 70,000 hospitalizations and 50% of cases of acute liver failure each year in the US. In the US approximately 5 million individuals develop acute alcoholic hepatitis (AH), a syndrome of progressive inflammatory liver injury; however, no pharmacological therapies for AH are approved.



The kinase apoptosis signal-regulating kinase 1 (ASK1) is activated by the oxidative state induced by both APAP and acute alcohol treatments resulting in acute liver damage.

SRT-015, a best-in-class ASK1 inhibitor, has already demonstrated preclinical efficacy and target engagement in a chronic therapeutic DIO-NASH mouse model with biopsy verifed steatosis and fibrosis (1,2). In vitro studies have demostrated dose-dependent direct anti-apoptotic, anti-inflammatory and anti-fibrotic effects with SRT-015 treatment (1). Additionally, clinical safety was demonstrated and human pharmacokinetic profile was established in Phase 1 trials with oral SRT-015 (3).

Aim

We have previously demonstrated in vivo efficacy in a chronic DIO-NASH mouse model with oral SRT-015. Here we evaluate the efficacy and target engagement of SRT-015 in two acute preclinical models of liver injury for acetamenophen (APAP) overdose and alcoholic hepatitis (AH).

Method

C57BL/6 male mice were used for both APAP and AH models.
In the acute hepatotoxic APAP model, overdose was induced with APAP (300 mg, i.p.) and 1 hr. later SRT-015 (0.3-10 mg/kg, p.o.) or vehicle administered (N = 6) . Six hours after APAP treatment serum ALT was determined and liver analyzed for mitogen-activated protein kinases (MAPK) including ASK1, p38 and JNK by Western blots. Statistical analysis was performed with GraphPad Prism using one-way ANOVA.
In the acute AH model, pyrazole induces high cyp2E1 levels emulating the effect of alcohol and LPS administration the gut bacterial toxins. Cyp2E1 was induced by two consecutive days of pyrazole administration (150 mg/kg, i.p.). On day 3 LPS (4 mg/kg i.p.), vehicle or SRT-015 (1,3,10 mg/kg, BID p.o.) was administered (n = 6-9/group). Serum ALT was measured 24 hr. post LPS treatment. Additional details of model mechanisms in results section.

References

1 Elias et al, Hepatology 2020
2 Elias et al, NASH-TAG 2023
3 Burge et al, Hepatology 2022
4 Du et al, Expert Opin Drug Metab Toxicol. 2015

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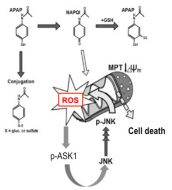
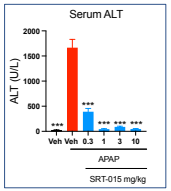
Results

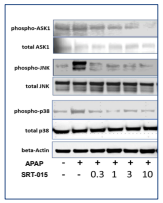


APAP Mechanism: At therapeutic doses, most APAP is conjugated and excreted with only a small amount converted to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). However, after an overdose, excess NAPQI binds to proteins leading to oxidative stress which activates signaling pathways converging on ASK1 and JNK. Activated JNK (pJNK) increases the mitochondrial oxidative stress resulting in matrix swelling and cell death (4).

APAP Model

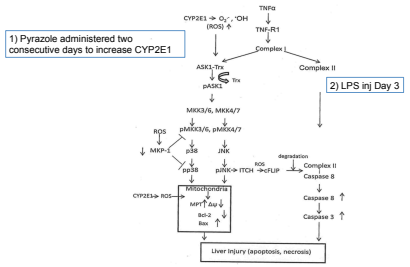


Effect of SRT-015 on serum ALT activities measured at 6h after APAP administration in mice. All the values are expressed as mean ± SEM (n=6). ***p<0.001 vs APAP

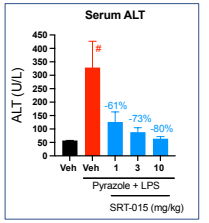


Western blot analysis of effect of therapeutic dosing of SRT-015 (0.3-10 mg/kg) on JNK, p-JNK, p38 and p-p38, ASK1 and p-ASK1 in the liver samples collected at 6 h after APAP administration.

AH Model



AH model: Pyrazole administered for 2-days to induce CYP2E1 (instead of ethanol), prior to SRT-015 and LPS administration. On day 3, SRT-015 was administered by oral gavage twice (12 hours apart) and LPS 30 min after the second dose of SRT-015. LPS administration emulates the inflammation by gut bacteria penetrating the intestinal wall following binge drinking. 24 h after LPS administration, serum was collected for ALT.



Serum ALT was evaluated as a marker of liver injury 24 h after LPS treatment (n = 12-13). SRT-015 (1, 3 and 10 mg/kg, p.o. via gavage, BID) demonstrated 61%, 73%, and 80% decreases in ALT levels from Pyrazole + LPS group, respectively. The minimum efficacious dose of SRT-015 was 1 mg/kg.

Conclusions

SRT-015 treatment significantly, and dose-dependently, decreased the liver injury marker ALT in two models of acute hepatotoxicity demonstrating efficacy. SRT-015 treatment also demonstrated target engagement by dose-dependently decreasing APAP-induced ASK1-JNK/p38 signaling in the APAP model.

These data indicate that SRT-015 is a promising therapeutic for both APAP overdose and AH and support the advancement of SRT-015 to chronic AH models.

Acknowledgements

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