Poster #399

Preclinical Efficacy Evaluation for TL1A Antibody-Related Drug on TNBS-Induced Acute Colitis Model in Transgenic Humanized Mice

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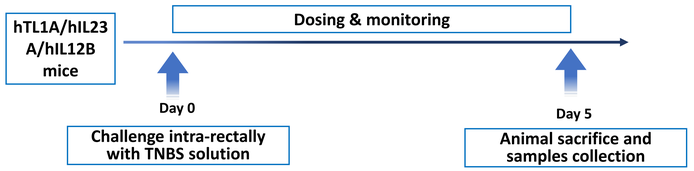
Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's diseases (CD), is recognized as an autoimmune disorder characterized by chronic inflammation of the digestive tract. Long-term inflammation can lead to fibrosis, intestinal stenosis, and obstruction, and sometimes requiring surgical intervention. It has been reported that Tumor Necrosis Factor-like Ligand 1A (TL1A) binds to its receptor DR3, amplifying immune responses and accelerating fibrosis associated with IBD. In addition, targeting TL1A can effectively inhibit the excessive immune activity of the body, delay disease progression, and improve the prognosis of patients.

Experimental Design

Study Procedure



Animal grouping and dosing regimen

Group	N	Treatment	TNBS treated (Y/N)	Dose (mg/kg)	Dosing Route
1	10	Sham	N	--	IP, Day -1, 2
2	10	Vehicle	Y	--	IP, Day -1, 2
3	10	Tulisokibart (anti-human TL1A)	Y	10 mg/kg	IP, Day -1, 2
4	10	Risankizumab (anti-human IL23p19)	Y	10 mg/kg	IP, Day -1, 2
5	10	Tulisokibart + Risankizumab	Y	10 mg/kg + 10 mg/kg	IP, Day -1, 2

TNBS solution was instilled into the colon lumen of B-hTL1A/hIL23A/hIL12B mice (female, 8-10 weeks-old, n=10). On Day 0, the control group (Sham) received intrarectal injections of 50% ethanol. The treatment groups received 10 mpk anti-human TL1A antibody Tulisokibart, 10 mpk anti-human IL23p19 antibody Risankizumab, alone or in combination. Body weight and DAI score were recorded daily. On Day 5, the mice were sacrificed, and colon length and weight were recorded. Colon tissue was later used for H&E staining and Masson's trichrome staining. The blood and colon tissue were collected for cytokines detection. One-way ANOVA and Two-way ANOVA were used for statistical analysis (*, p<0.05; **, p<0.01, ***, p<0.001, ****, p<0.0001). Error bars represented Standard Error of Mean (SEM).

Results

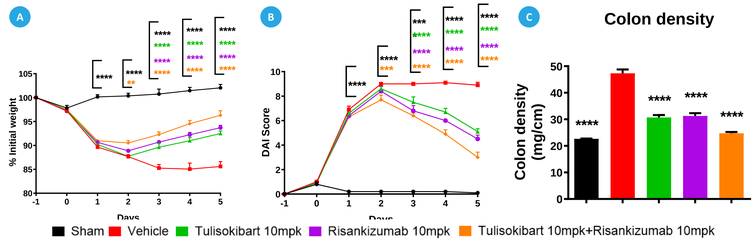


Figure 1. Characterization of TNBS induced acute colitis in B-hTL1A/hIL23A/hIL12B mice model
A) Body weight change, B) DAI score and C) colon index of the TNBS induced acute colitis in B-hTL1A/hIL23A/hIL12B mice. Tulisokibart, Risankizumab and the combination ameliorated the body weight loss and downregulated the DAI score of TNBS induced colitis in mice.

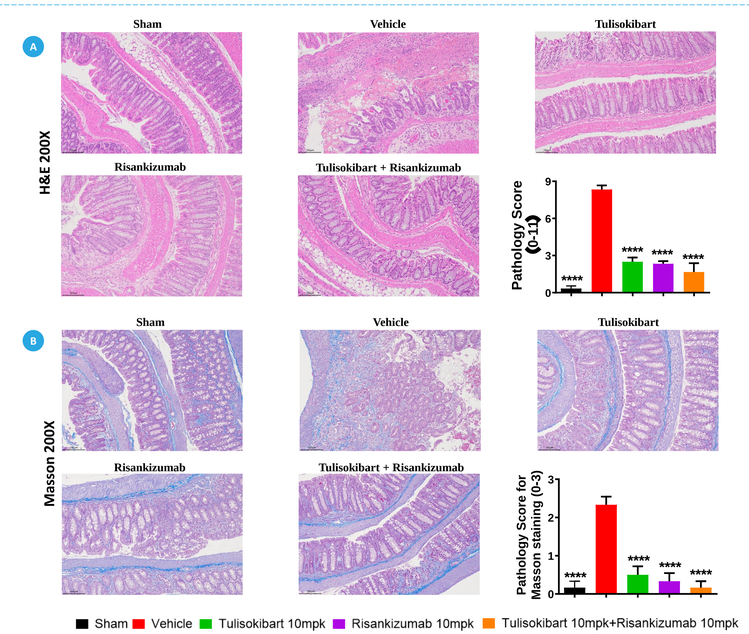


Figure 2. Histopathological staining results
A) H&E staining and B) Masson trichrome staining. Tulisokibart, Risankizumab and the combination ameliorated crypt architecture, inflammatory cell infiltration, muscle thickening, goblet cell depletion absent, crypt abscess and fibrosis in mice with colitis.

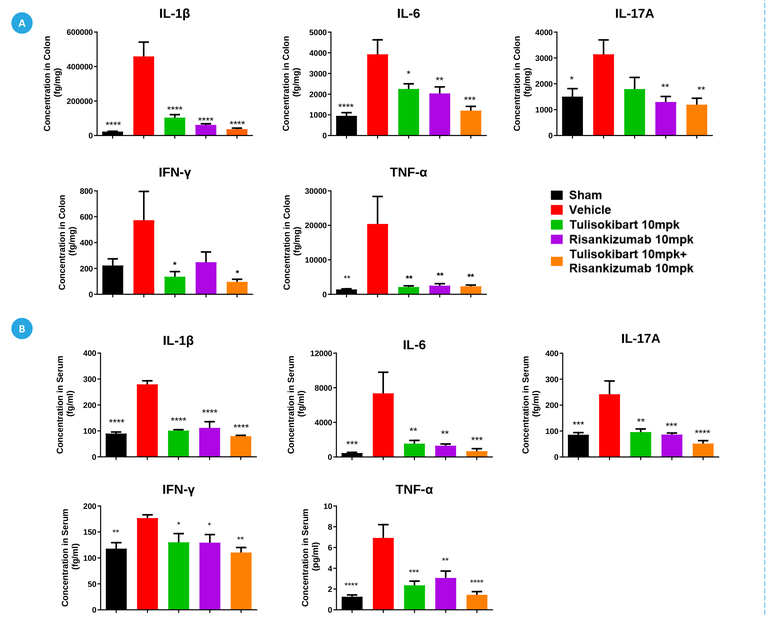


Figure 3. Expression of inflammatory cytokines
IL-1β, IL-6, IL-17A, IFN-γ, and TNF-α expression levels in A) colon mucosa and in B) serum detected by ultrasensitive CBA kits Tulisokibart, Risankizumab and the combination ameliorated inflammatory cytokines release in both colon mucosa and serum.

Summary

In this study, we successfully established a TNBS-induced colitis model, evidenced by significant weight loss and elevated DAI scores in Vehicle mice. We showed that treatment with Tulisokibart (anti-human TL1A), Risankizumab (anti-human IL23p19), or their combination reduced weight loss, DAI scores, and release of inflammatory cytokines. Histological analysis showed reversal of inflammatory cell infiltration, crypt damage and fibrosis in all treatment groups. These findings highlight the potential of targeting TL1A to become a "Best-in-Class" therapy for IBD treatment.

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