AASLD The Liver Meeting®

TARGETING CCL24 RESTORES MST1 EXPRESSION: A MECHANISTIC INSIGHT FROM THE SPRING TRIAL

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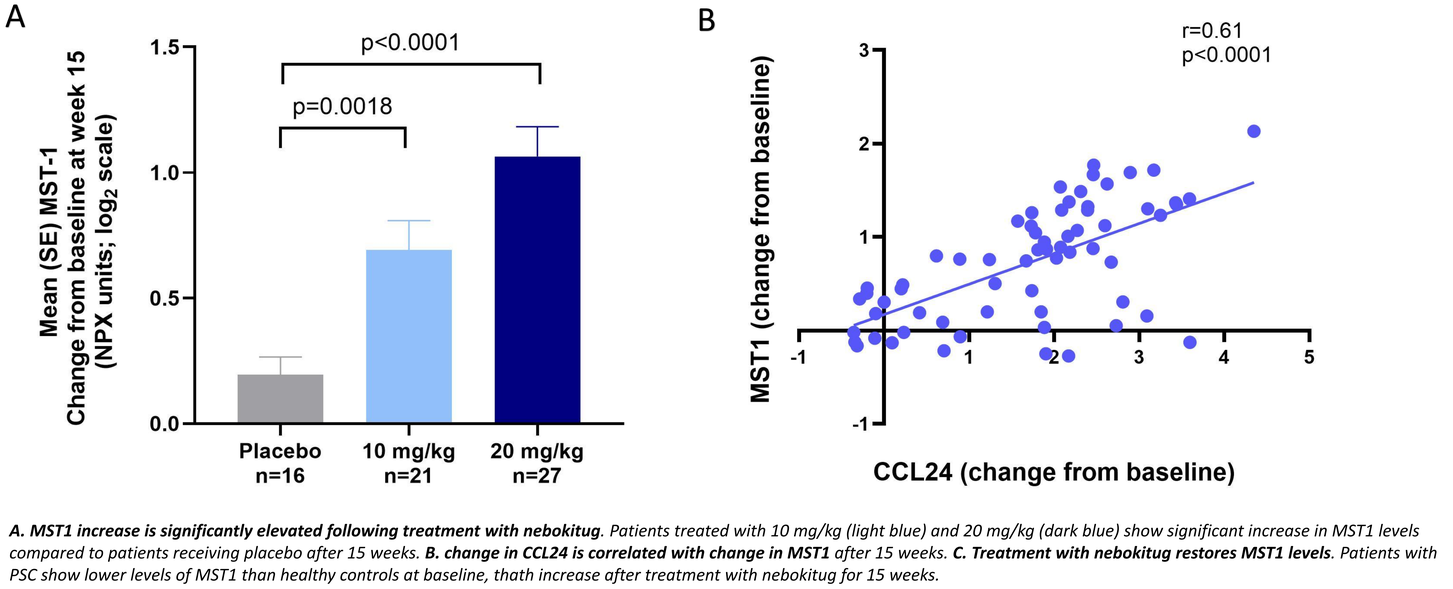
INTRODUCTION & AIM

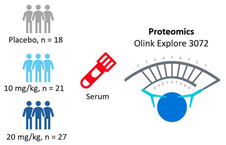
Macrophage Stimulating 1 (MST1) acts as a negative regulator of macrophage-associated inflammation. In patients with primary sclerosing cholangitis (PSC), a disease characterized by inflammation and fibrosis of the bile ducts, MST1 function is impaired due to a disease-associated single nucleotide polymorphism, and its expression in the liver is significantly lower in PSC compared to healthy individuals. Nebokitug, a monoclonal antibody targeting CCL24, has shown promising modulation of inflammation and fibrosis related markers in the Phase 2 SPRING trial (NCT04595825). Here, we evaluated the association between CCL24 blockade and MST1 as a disease relevant pharmacodynamic (PD) marker.



***A. MST1 increase is significantly elevated following treatment with nebokitug**. Patients treated with 10 mg/kg (light blue) and 20 mg/kg (dark blue) show significant increase in MST1 levels compared to patients receiving placebo after 15 weeks. **B. change in CCL24 is correlated with change in MST1** after 15 weeks. **C. Treatment with nebokitug restores MST1 levels**. Patients with PSC show lower levels of MST1 than healthy controls at baseline, thath increase after treatment with nebokitug for 15 weeks.*

METHOD

The SPRING phase 2 study is a randomized, double-blind, placebo-controlled study in PSC patients treated with nebokitug (10 or 20 mg/kg IV) or placebo every 3 weeks for 15 weeks. Serum MST1 levels were assessed by Olink® proteomics at baseline and week 15. Associations between MST1, CCL24 and changes in liver stiffness measurement (LSM) were evaluated. MST1 levels were also evaluated in nebokitug–treated metabolic dysfunction-associated steatohepatitis (MASH) patients (5 mg/kg SC Q2W for 16 weeks) and in two relevant preclinical models: Mdr2-/- and TAA-induced liver fibrosis.



RESULTS

- Serum levels of MST1 in PSC patients were found to be reduced compared to healthy individuals.
- In the SPRING study, nebokitug induced a dose-dependent increase in MST1 (10 mg/kg p=0.0018; 20 mg/kg p<0.0001), with no change in the placebo group.
- A significant correlation was observed between change in MST1 and CCL24 (Pearson R=0.62, p=3.9e−08), supporting MST1 as a downstream marker of CCL24 blockade that is also relevant to liver diseases.

Notably, MST1 increase was associated with a greater reduction in LSM. MASH patients treated with nebokitug showed a 1.6–1.85-fold increase in MST1 by week 15, detectable as early as week 2. In addition, in preclinical models, liver MST1 mRNA expression was increased by approximately two-fold in mice treated with a anti CCL24 mAb, compared to vehicle controls, consistent with the clinical observations.

CONCLUSIONS

Nebokitug treatment in PSC patients leads to a significant dose-dependent increase in MST1, correlating with CCL24 target engagement and reductions in LSM.

These results from the SPRING trial suggest that MST1 may serve as a PD biomarker of nebokitug activity and further support its anti-inflammatory mechanism of action.