Background: Upregulation of the innate immune response via the activity of Toll-like receptors and the NLRP3 inflammasome have been suggested as initiating events that can drive fibrosis in systemic sclerosis (SSc) (Pharmacol Ther. 2018;192:163). Lenabasum, a cannabinoid receptor type 2 agonist, is known to activate the resolution phase of acute human innate immune responses triggered through Toll-like receptor activation, favoring production of pro-resolving lipid mediators, reducing inflammatory infiltrates, and increasing bacterial clearance (Clin Pharmacol Ther. 2018;104:675). Given the potential importance of inflammasome activation in the pathogenesis of SSc, the question remained whether lenabasum inhibits inflammasome activation.

Objectives: Assess effects of lenabasum on IL-1β and IL-18 production induced by inflammasome activation.

Methods: Primary human macrophages were derived from monocytes, stimulated with LPS and ATP to activate inflammasomes and cultured with lenabasum. Levels of IL-1β and IL-18 were measured in cell supernatants by ELISA. Separately, human PBMC were activated with 0.1 µg/ml LPS ± 10 µM lenabasum for 24 hours, and effects of lenabasum on the levels of IL-1β and other pro-inflammatory cytokines were measured.

Results: Lenabasum significantly inhibited IL-1β and IL-18 secretion by monocyte-derived macrophages, with IC50 = 66.73 ± 3.92 nM and 349.23 ± 21.27 nM, respectively. A control inflammasome activation inhibitor, MCC950, which showed IC50 = 18.33 ± 1.22 nM for IL-1β inhibition and IC50 = 21.43 ± 0.81 nM for IL-8 inhibition.

Conclusion: Lenabasum inhibits inflammasome activation, which could contribute to potential therapeutic efficacy in SSc and other autoimmune diseases.

References: