In Vitro Colonic Nociception Study Design

• Olorinab causes a CB2-mediated mechanosensory protein expression in cultured mouse colonocytes (Figure 1).
• Olorinab prevents colonic hyperalgesia in response to colonic distension in vitro without affecting baseline mechanics (Figure 2).

In Vivo Visceromotor Response Study Design

• Male 13-week-old C57 BL/6 mice were administered an intracolonic enema of 2,4,6-trinitrobenzene sulfonic acid (TNBS) 12 mg in 30% ethanol (0.1 mL) administered rectally (time of CVH) (see Figure 3).
• CVH mice + olorinab 3 mg/kg (N = 12) vs. CVH mice + vehicle (N = 12).

Pain Assessment In Vivo

• Visceromotor response was assessed in vivo by quantifying visceromotor responses (VMR) to colonic distension (CRD; 0 to 80 mm Hg) (Figure 4).

Assessment of Colonic Mechanosensory In Vitro

• Single- and multi-unit recordings from spinal cord to colonic afferent nerves were performed as previously described (Figure 5).

Colonic Nociceptor Mechanosensory Recordings in the Mouse Model of Colitis

• Olorinab mediates a significant reduction in colonic nociception in in vivo models of IBD and IBS (Figure 6).

RESULTS

Colonic Inflammation in the Rat Model of Colitis

• Olorinab significantly attenuates colonic inflammation (increased myeloperoxidase activity) compared with controls (P < 0.01, N = 5, Figure 8).

Visceral Hypersensitivity and Colonic Compliance in the Rat Model of Colitis

• Olorinab significantly decreases visceral hypersensitivity in response to colonic distension without changing colonic compliance (P < 0.001, N = 5, Figure 9).

Colonic Nociceptor Mechanosensory Recordings in the Mouse Model of Colitis

• Olorinab significantly reduces colonic mechanical hyperalgesia in in vivo models of IBD and IBS (Figure 10).

CONCLUSIONS

• Olorinab significantly reduces visceral hypersensitivity in animal models of IBD and IBS but not in healthy controls, suggesting that CB2 receptor agonists may target visceral sensitivity pathways in models of IBD and IBS.

ACKNOWLEDGMENTS

This work was funded by Arena Pharmaceuticals, Inc. F.A.P. is a consultant for Arena Pharmaceuticals, Inc. F.A.P. and Arena Pharmaceuticals, Inc. received a research grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

FUNDING

This work was funded by Arena Pharmaceuticals, Inc.