Olorinab (APD371), a Peripherally Restricted, Highly Selective, Full Agonist of the Cannabinoid Receptor 2 (CB2), Reduces Colitis-Induced Visceral Hypersensitivity in Rats

Joel Castro, 1 Jessica Maddern, 1 Sonia Garcia-Caraballo, 1 Beatriz Lindstrom, 2 John Adams, 2 Stuart M. Brierley 1

1 Visceral Pain Research Group, Flinders University, SAHMRI, Adelaide, SA, 5000, Australia; 2 Arena Pharmaceuticals, Inc, San Diego, CA, USA

INTRODUCTION
Colitis is ulcerative colitis, collectively known as an inflammatory bowel disease (IBD), are chronic relapsing gastrointestinal disorders with an increasing prevalence worldwide.
Abdominal pain is reported by up to 60% of patients with IBD, is associated with lower quality of life, and is currently among the most challenging aspects of the disease.

The cannabinoid CB2 receptor (CB2) is expressed throughout the gastrointestinal tract and is an effective target for IBD.

Olorinab (APD371) has been shown to reduce gastrointestinal pain in preclinical studies.

METHODS

Studied designs

Animals of the mice were administered in mouse or colitis models of colitis and in healthy control animals.

Olorinab was administered orally or by intraperitoneal injection before instillation of TNBS.

Volumes of 2.5 ml 40% TNBS were administered to each mouse or rat by colonoscopy.

Control groups included healthy and colitis animals treated with vehicle or olorinab (30 mg/kg). Treatment was continued on day 3 following instillation of TNBS (APD371).

Animal models of colitis

Gastroparesis induced by chronic constriction injury (CCI) and in Sprague-Dawley rats by rectal administration of TNBS, as described in Hughes et al.

In each mouse, 2.0 ml 40% TNBS in 30% ethanol was administered via enema at a volume of 100 µL.

RESULTS

Increased colonic compliance

Colitis animals displayed significant colonic inflammation (increase in myeloperoxidase activity) compared with healthy control animals.

Olorinab (nM)

Colitis animals + vehicle (n = 18)

Healthy animals + olorinab 30 mg/kg (n = 9)

Healthy animals + vehicle (n = 11)

Colitis animals + olorinab 30 mg/kg (n = 9)

Healthy + vehicle versus healthy + olorinab: not significant. GEE, LSD post hoc test.

Colonic nociception

Olorinab prevents colitis-induced visceral hypersensitivity, suggesting an antinociceptive role for CB2 receptors in visceral sensory pathways.

Vascular inflammation

Olorinab treatment with or without colitis significantly reduced vascular inflammation, as measured by MPO activity.

REFERENCES


ACKNOWLEDGMENTS

Medical writing assistance was provided by ApotheCom, San Francisco, CA, and was funded by Arena Pharmaceuticals, Inc. Stuart Brierley is an NHMRC R.D Wright Early Career Researcher. 1. Brierley SM et al. Summit; March 2006; 17:1-2.