PFR455

Olorinab (APD371), a Peripherally Restricted, Highly Selective, Full Agonist of the Cannabinoid Receptor 2 (CB_2), Reduces Colitis-Induced Visceral Hypersensitivity in Rats

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INTRODUCTION

- Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD), are chronic relapsing gastrointestinal disorders with increasing prevalence worldwide[1]
- Abdominal pain is reported by up to 60% of patients with IBD, is associated with lower quality of life, and is severe enough to require pain treatment in the majority of cases[2]
- The cannabinoid 2 (CB_2) receptor is expressed throughout the gastrointestinal tract and is an attractive target for IBD[3,4]
- Olorinab (APD371) has been shown to activate endogenous CB_2 receptors in primary rat splenocytes, human HL-60 cells, and primary human B cells[5]
  - Olorinab exhibited >1000-fold selectivity for the CB_2 receptor over the CB_1 receptor and sustained efficacy in several animal models of chronic pain[5,6]
  - No adverse psychotropic effects were seen in healthy volunteers who received olorinab[7]
- Olorinab is in a phase 2 trial for visceral pain associated with Crohn's disease[6,7]

OBJECTIVE

- To investigate the potential analgesic effect of olorinab in animal models of colitis

METHODS

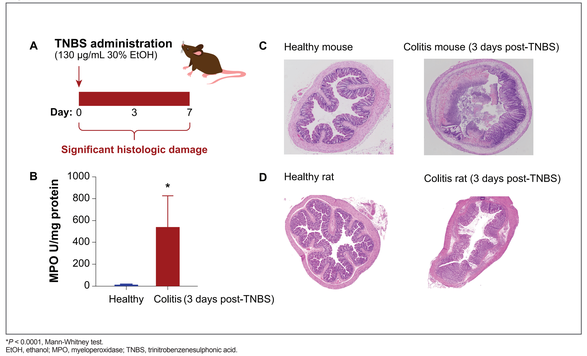
Study design

- Olorinab or vehicle was administered in mouse and rat models of colitis and in healthy control animals
- Olorinab was administered twice daily by oral gavage for 5 days, starting 1 day before induction of colitis
- Measurements of in vivo colonic pain and ex vivo colonic afferent mechanosensitivity were conducted on day 5 following instillation of trinitrobenzenesulphonic acid (TNBS)

Animal models of colitis

- Colitis was induced C57B/L6J mice and in Sprague Dawley rats by rectal administration of TNBS, as described in Hughes et al[8] (**Figure 1**)
  - In each mouse 3.81 mg TNBS in 30% ethanol was administered via enema at a volume of 100 µL
  - In each rat 12 mg TNBS in 35% ethanol was administered via enema at a volume of 300 µL

Figure 1. Animal models of colitis: mouse and rat.



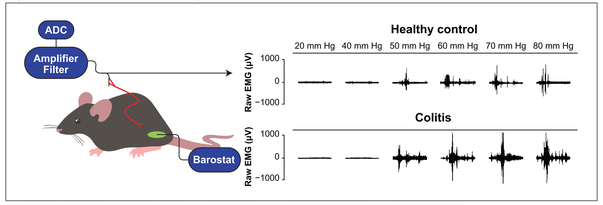
*P < 0.0001, Mann-Whitney test.
EtOH, ethanol; MPO, myeloperoxidase; TNBS, trinitrobenzenesulphonic acid.

METHODS *Cont.*

Pain assessment in vivo

- Noxious distension of the colorectum triggers the visceromotor response (VMR), a nociceptive brainstem reflex consisting of the contraction of the abdominal muscles,[9] used as an indicator of pain
- After TNBS treatment in rats, colorectal distension (CRD) was induced using a barostat, and VMR was measured using an amplifier connected to an analog-to-digital converter (**Figure 2**)

Figure 2. Pain assessment in vivo by VMR response to CRD in rats.

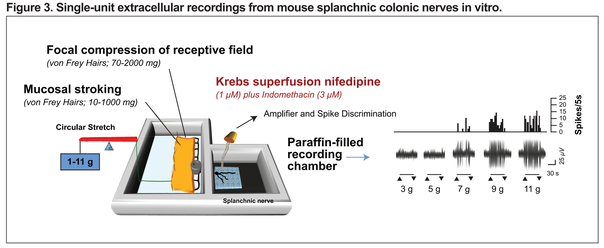


ADC, analog-to-digital converter; CRD, colorectal distension; EMG, electromyogram; TNBS, trinitrobenzenesulphonic acid; VMR, visceromotor response.

Assessment of colonic mechanosensitivity in vitro

- Single-unit extracellular recordings from splanchnic colonic afferent nerves were performed as previously described[8,10,11] (**Figure 3**)

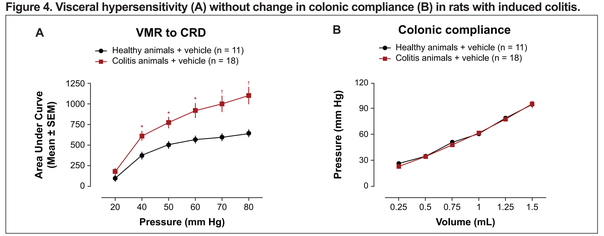
Figure 3. Single-unit extracellular recordings from mouse splanchnic colonic nerves in vitro.



RESULTS

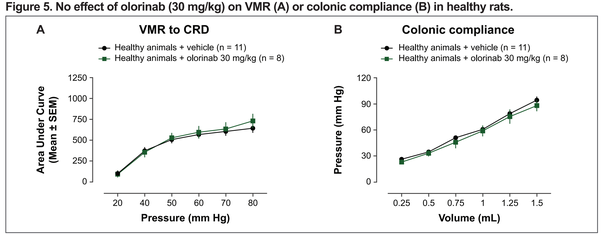
Visceral hypersensitivity and colonic compliance

Figure 4. Visceral hypersensitivity (A) without change in colonic compliance (B) in rats with induced colitis.



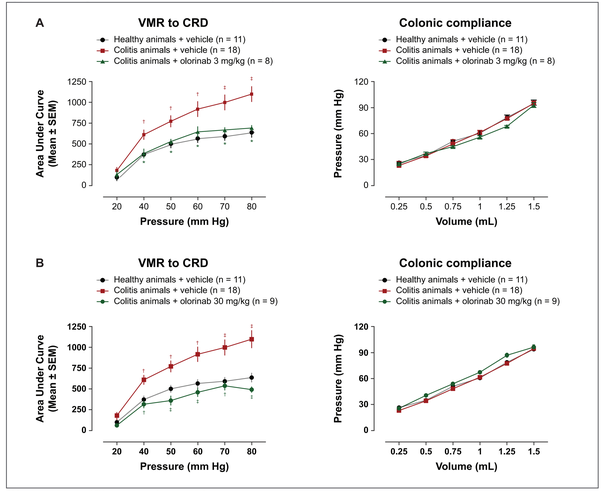
CRD, colorectal distension; GEE, generalized estimating equation; LSD, least significant difference; SEM, standard error of the mean; VMR, visceromotor response.
Healthy + vehicle versus colitis + vehicle: *P < 0.001 and †P < 0.0001, GEE, LSD post hoc test.

Figure 5. No effect of olorinab (30 mg/kg) on VMR (A) or colonic compliance (B) in healthy rats.



CRD, colorectal distension; GEE, generalized estimating equation; LSD, least significant difference; SEM, standard error of the mean; VMR, visceromotor response.
Healthy + vehicle versus healthy + olorinab: not significant. GEE, LSD post hoc test.

Figure 6. Treatment with 3 mg/kg olorinab (A) and 30 mg/kg olorinab (B) in rats with colitis prevents visceral hypersensitivity without an effect on colonic compliance.

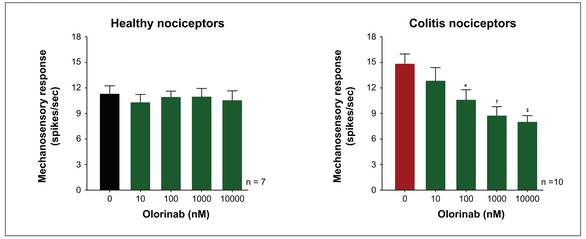


CRD, colorectal distension; SEM, standard error of the mean; VMR, visceromotor response.
*P < 0.01; †P < 0.001; ‡P < 0.0001. Healthy + vehicle versus colitis + vehicle: gray symbols; colitis + vehicle versus colitis + olorinab: maroon symbols. All post hoc generalized estimating equation using least significant difference.

RESULTS *Cont.*

Colonic mechanosensory nociceptor recordings

Figure 7. Nociception of mechanical stimuli in the colon is heightened in colitis animals and reduced after treatment with olorinab.



*P < 0.05, †P < 0.01, ‡P < 0.001. 1-way analysis of variance with Bonferroni post hoc tests.

SUMMARY

Visceromotor response to colorectal distension

- Vehicle-treated colitis animals displayed visceral hypersensitivity, as indicated by significantly elevated VMR to CRD
- Healthy control rats treated with olorinab (30 mg/kg) did not show altered visceral sensitivity to CRD
- Colitis animals displayed significant colonic inflammation (increase in myeloperoxidase activity) compared with healthy control animals
- Colitis rats administered olorinab (3 mg/kg and 30 mg/kg) had significantly reduced VMR to CRD compared with vehicle-treated colitis rats (with VMR normalized to healthy control levels)

Colonic nociception

- Colonic nociceptors from colitis animals are hypersensitive to mechanical stimuli compared with healthy colonic nociceptors
- Olorinab reverses colonic nociceptor hypersensitivity in colitis animals with no effect on healthy colonic nociceptors

CONCLUSIONS

- Olorinab prevents colitis-induced visceral hypersensitivity, suggesting an antinociceptive role for CB_2 receptors in visceral sensory pathways
- Olorinab, through its selectivity, may provide a novel therapeutic treatment for IBD-associated abdominal pain without psychotropic effects and therefore without the potential for dependence or abuse

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