

CR4056, A SELECTIVE IMIDAZOLINE-2 LIGAND, IMPROVES OSTEOARTHRITIS (OA) PAIN IN THE RAT MEDIAL MENISCAL TEAR MODEL.

Eleonora Comi^{1,2}, Flora Ferrari¹, Dario Tremolada¹, Marco Lanza¹, Gianfranco Caselli¹, Lucio C. Rovati¹

¹ Rottapharm Biotech Srl, Monza (MI), ITALY

² PhD program in Neuroscience, University of Milano-Bicocca, Monza (MI), ITALY

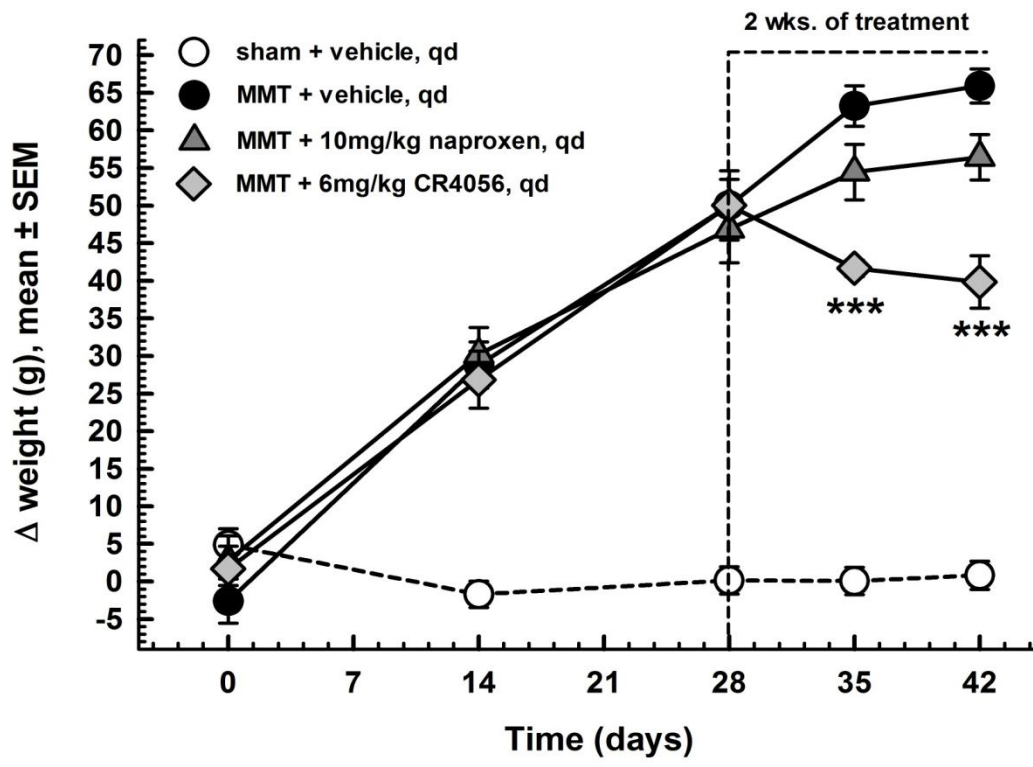
Purpose: Joint pain is the cardinal symptom of OA although it poorly correlates with OA joint structure changes. Interestingly, OA pain is driven by both nociceptive and neuropathic mechanisms.

The analgesic efficacy of CR4056, an I₂ receptor ligand currently in phase II clinical trials, was previously reported in the OA pain model obtained by the intra-articular injection of monosodium iodoacetate (MIA) in the rat knee. Moreover, CR4056 evidenced a remarkable analgesic activity in several animal models of inflammatory, neuropathic and postoperative pain. The aim of this study was to evaluate the effect of CR4056 in a well-established model of surgically-induced OA able to mimic the structural and painful components of human OA.

Methods: OA was induced in male Sprague Dawley rats (335–370 g) by transection of the medial collateral ligament and medial meniscus of the femoro-tibial right joint (MMT model). Hind paw weight bearing distribution was assessed as indirect measure of spontaneous pain by using an incapacitance tester (2Biological Instruments Snc, Besozzo, Italy), prior to surgery and 14, 28, 35 and 42 days post-surgery. Control rats were subjected to sham surgery, while treatments after MMT consisted of 6 mg/kg CR4056, or 10 mg/kg naproxen as an active control, or vehicle (9 animals/group) and they were administered orally as subacute treatment from 28 to 42 days after surgery. Statistical analysis was performed by Two-way RM ANOVA, followed by Tukey's multiple comparisons test.

Results: MMT surgery resulted in a significant development of right-left hind paw weight bearing imbalance at each experimental time point, compared with the sham group (data expressed as difference of weight bearing between contralateral and ipsilateral paw). The difference in weight bearing distribution between sham and MMT rats gradually increased throughout the study, reaching its peak 42 days post-surgery in animals receiving vehicle (mean \pm sem, 0.83 ± 1.87 vs. 65.92 ± 2.26 , respectively). Subacute oral administration of 6 mg/kg CR4056 for 2-weeks from 28 to 42 days after surgery induced a significant reduction of right-left hind paw weight bearing imbalance, compared with the MMT control group treated with vehicle (42 days post-surgery mean \pm sem, 39.84 ± 3.47 vs. 65.92 ± 2.26 , respectively), as illustrated in the Figure. Conversely, 10 mg/kg naproxen was devoid of noticeable effect on weight bearing imbalance after 2-weeks subacute treatment.

Conclusion: The data presented here further evidence that the imidazoline I₂ receptor ligand CR4056 could represent a new highly effective analgesic treatment option for OA pain.



*** p<0.001 vs. MMT control; Tukey's multiple comparisons test