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Intra-articular treatment combining sustained release Colchicine encapsulated in microspheres, and ropivacaine, is effective in inflammatory arthritis in rats

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Background

Gout is a common disease with a prevalence and incidence on the rise worldwide. However, approved treatments to treat acute gout flares have slow and insufficient effectiveness and are associated with poor safety profiles. There is therefore a clear unmet medical need for a more effective product against acute pain, with a rapid onset of action and a good safety profile in patients suffering from gout flare. We developed a treatment that could be used intra-articularly (IA). We evaluated this treatment in rats in a model of acute inflammatory arthritis.

Methods

This treatment (PKM-01) combines an anesthetic, ropivacaine (ROPI) HCL, with colchicine (COL), formulated within a biodegradable poly (lactic-co-glycolic acid) (PLGA) polymer matrix. COL was encapsulated within microspheres of PLGA polymer to allow for sustained release over the duration of the flare, typically lasting 7-10 days. Concurrently, the anesthetic, ROPI, was incorporated for immediate release. PLGA polymer, known for its safety in drug delivery applications, degrades into lactic and glycolic acids, which are naturally metabolized by the body, ensuring that the degradation products do not pose any harm. The microspheres were designed with a size distribution, ranging from 5 to 50 µm. To evaluate the effect of this treatment, we adapted a model of IA carrageenan (CAR) induced arthritis in knees or ankles. 50 µL CAR 3% was injected IA in Sprague Dawley rats, and acute arthritis occurred in the hours following injection, mimicking a flare of any inflammasome-induced acute arthritis. Treatments were IA administered less than one minute delay after CAR IA injection: PBS, ROPI, dexamethasone (DXM), ROPI, COL, encapsulated COL, or PKM-01. Pain was evaluated with von Frey filaments on soles of hind paws. Joint inflammation and destruction were evaluated by histological semi-quantitative scores. All experiments were blinded. Groups of 8 animals were used and experiments were repeated 2-3 times. Pharmacokinetic assays were also performed.

Results

All control animal (CAR injected, receiving PBS) developed acute painful and destructive arthritis. DXM exerted a significant effect on pain, inflammation and joint destruction. ROPI was effective on pain and not on inflammation or destruction. PKM-01 (combination of COL and ROPI) was effective on these 3 parameters. PKM-01 exerted a strong analgesic effect (first evaluation: 2 hours) in comparison to control groups and showed anti-inflammatory properties, that were histologically detected as soon as 24 hours on joint inflammation and destruction. These effects were more complete than those observed with COL alone or encapsulated, or with DXM. Results were comparable if CAR induced arthritis was performed either in knees or ankles. COL assays during 72 hours in blood after ankle injections showed low levels and below threshold of toxicity.

Conclusion

Taken together, these data showed in this murine model that PKM-01 could be an option for gout flare in humans, since oral treatments with COL are limited by toxicity. It could be useful also in case of co-morbidities when first line treatment are contra-indicated, and to provide rapid antalgic effect in patients. A clinical trial is planned in gout flare population.