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ORIGINAL RESEARCH

Intra-articular sustained-release colchicine is efficacious in an inflammatory arthritis rat model

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ABSTRACT

Objectives Gout is a common disease causing excruciatingly painful and disabling flares. Although currently approved treatments for gout flares are generally effective, their use is restricted in many patients who present contraindications. There is a clear unmet need for treatments, with a rapid onset of action and a good safety profile. This study evaluates the efficacy of intra-articular (IA) colchicine (COL)-loaded microspheres enabling sustained-release colchicine (SR-COL), and of a combination of SR-COL with an anaesthetic (Ropivacaine HCl, ROPI) (PKM-01) in a rat model of acute inflammatory arthritis.

Methods PKM-01 combines ROPI with SR-COL, prepared using a polylactic-co-glycolic acid matrix polymer. A model of IA carrageenan (CAR)-induced arthritis in knees or ankles was adapted for this study. Treatments (phosphate buffer saline, dexamethasone, SR-COL, ROPI or PKM-01) were administered intra-articularly immediately following the CAR injection. Pain was assessed using Von Frey filaments or weight-bearing tests. Histological scores assessed joint inflammation and destruction.

Results All animals experienced acute painful and destructive arthritis following CAR injection. ROPI effectively alleviated pain but had no significant impact on inflammation or joint destruction. SR-COL demonstrated efficacy in reducing pain, inflammation and joint destruction across all parameters. PKM-01 provided a strong and rapid analgesic effect and exhibited anti-inflammatory properties, as evidenced by histological analysis of joint inflammation and destruction. Blood levels of COL after ankle injections were significantly below toxicity thresholds.

Conclusions These data indicate that PKM-01 may serve as an effective and safe treatment option for acute inflammatory arthritis. A clinical trial is planned in gout flare patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The currently approved treatments for acute gout flares are generally effective with a pain relief expected within the first 1–2 days; however, their systemic nature may limit their use in many patients.

WHAT THIS STUDY ADDS

⇒ Intra-articular sustained release of colchicine associated with ropivacaine (PKM-01) demonstrated efficacy in the carrageenan-induced arthritis model, showing a rapid analgesic effect and significantly preventing joint inflammation and destruction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A Phase II clinical study to test PKM-01 is planned in patients with gout flares.

INTRODUCTION

Gout is a common condition with a prevalence and incidence on the rise worldwide. Population-based studies from Asia, Europe and North America have reported incidence rates between 0.6 and 2.9 per 1000 person-years, and prevalence rates between 0.8% and 3.90% in adults,[1] with a much higher prevalence in Maori and Polynesian.[2] Gout occurs more frequently in men than in women, with population-based studies from Europe and North America indicating a male/female ratio up to 4:1.[1] Gout results from the deposition of monosodium urate (MSU) crystals in both articular and non-articular structures. Hyperuricaemia is the primary risk factor for developing gout. Although presenting as an intermittent flaring condition, gout is a chronic disease. Clinical manifestations include episodes of severely painful arthritis, known as gout flares, which are characterised by massive infiltration of polymorphonuclear neutrophils and monocytes following detection of MSU crystals by resident macrophages.[3 4] This early inflammatory phase is characterised by interleukin (IL)-1β production, which induces the release of different chemokines, cytokines adhesion

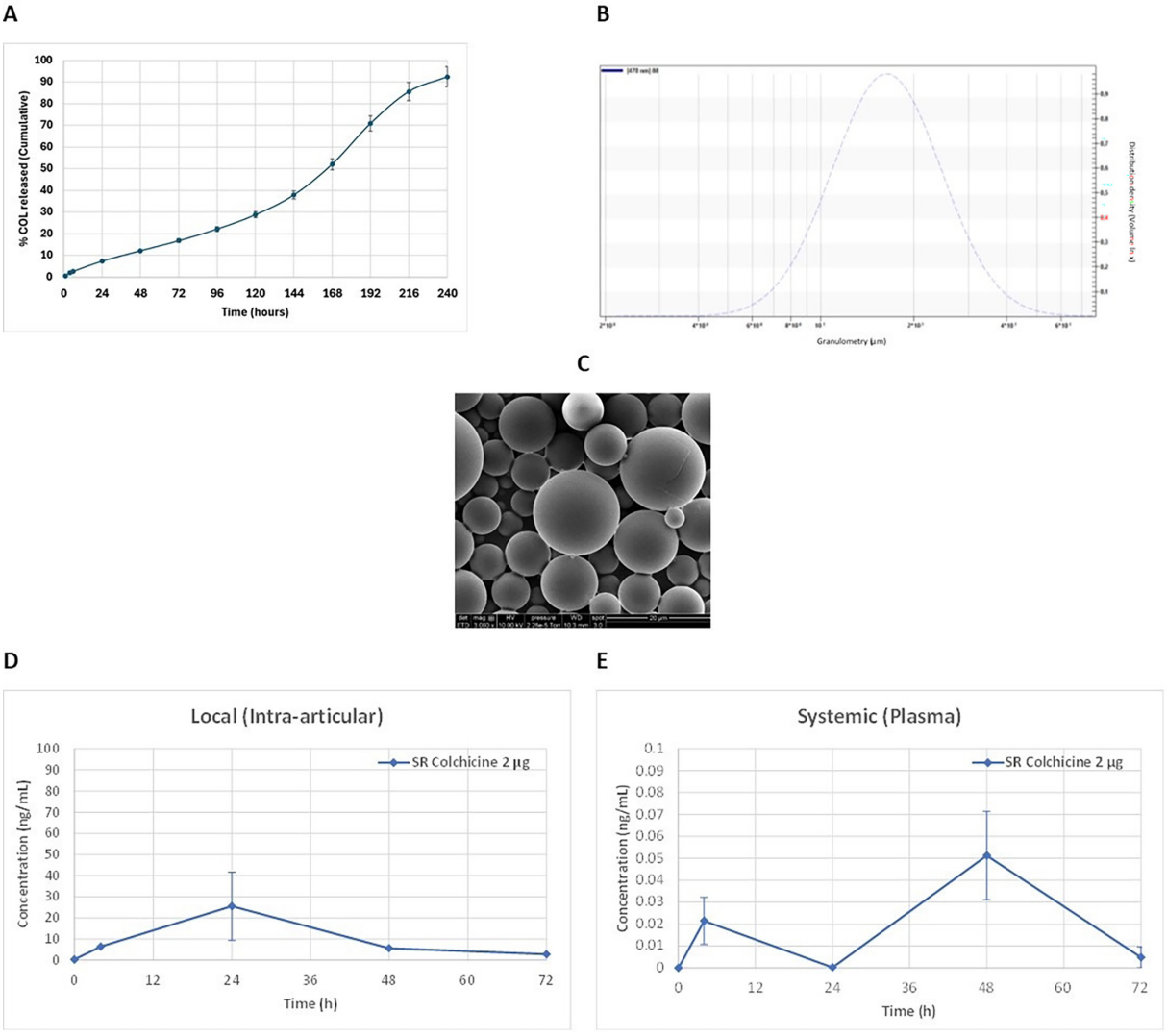

Figure 1 (A) In vitro release profiles of SR-COL microspheres. (B) Particle size distribution of SR-COL microspheres (µm). (C) Example of SR-COL microsphere under scanning electron microscope. (D) Mean COL intra-articular concentrations (y-axis range: 0–100 ng/mL) (mean±SD). (E) Mean COL plasma concentrations (y-axis range: 0–0.1 ng/mL) (mean±SD). SR-COL, sustained-release colchicine.

molecules which, in turn, increments cell infiltration.[5] The release of IL-1β is driven by NOD-like receptor family pyrin domain containing-3 (NLRP3) inflammasome activation induced by MSU crystals in myeloid cells.[6 7] The resulting pain is excruciating and severely alters the quality of life of gout patients. Inflammatory pain may result from the direct action of inflammatory cytokines and the activated inflammasome on nociceptive neurons, lowering their excitability threshold and causing hyperalgesia.

The central strategy for effective management of gout is long-term urate-lowering therapy to reverse hyperuricaemia, which leads to the dissolution of MSU crystals and long-term prevention of gout flares. Flares are treated with the goal of rapid pain resolution and restoration of function. Recommended first-line therapies should be individualised on the basis of coexisting conditions and include oral colchicine (COL), non-steroidal anti-inflammatory drugs, glucocorticoids which can be administered orally or by intra-articular (IA) injection and IL-1β blockers.[8 9] The currently approved treatments for acute gout flares have limited and slow efficacy; indeed, only 33%–50% of patients experience a pain reduction of more than 50% after 1–3 days.[10] Additionally, these treatments are associated with safety concerns, since 50%–66% of gout patients present at least one strong contraindication to COL.[10–12]

The primary mechanism of action of COL is its capacity to bind to tubulin, disrupting microtubules and leading to the down-regulation of multiple inflammatory pathways as well as modulation of innate immunity. Its effectiveness as a treatment for gout has been attributed to its ability to block neutrophil-mediated inflammatory responses induced by MSU crystals in synovial fluid by disrupting the function of the neutrophils' cytoskeleton and interfering with microtubulin assembly. This results in the prevention of activation, degranulation, adhesion and migration of neutrophils to sites of inflammation.[13]

However, COL is a Narrow Therapeutic Index drug characterised by significant gastrointestinal adverse events at the therapeutic dose and by life-threatening overdoses. In addition, toxicity can occur in patients with severe kidney disease, severe liver disease and with concomitant use of strong P-glycoprotein 1 (ABCB1) inhibitors, CYP3A4 inhibitors or both (eg, ciclosporin, ketoconazole, clarithromycin and verapamil).[1 14] According to the existing American and European guidelines, the recommended oral COL dosing is based on a 1 mg to 1.2 mg immediate administration followed by 0.5 mg to 0.6 mg an hour later and 0.5 mg or 0.6 mg up to 2–3 times a day on the following days, until flare resolution.[15–17] Increasing the dose level, for treating a flare, to more than 2 mg/day might be effective, but is not recommended due to the high risk of toxicity.

Therefore, there is a significant need for a more effective treatment option that provides rapid pain relief and has a favourable safety profile. We developed an IA sustained-release form of colchicine (SR-COL) to maintain high local joint concentration during gout flares, enhancing efficacy and minimising systemic toxicity through low plasma levels.

Carrageenan (CAR) is currently used as a trigger for acute inflammation in various tissues. CAR-induced arthritis in rodents has been studied as a model for acute arthritis.[18 19] The pathophysiology of CAR-induced arthritis involves inflammatory cytokines such as IL-1β and is characterised by a stimulation of inflammasome.[20–22] This model of hyper-acute inflammation mimics crystal arthritis (gout or calcium pyrophosphate deposition (CPPD)) disease that can occur in humans. It has been widely used to test anti-gout compounds and anti-inflammatory agents.[22–24] CAR-induced inflammation has previously been shown to be responsive to corticosteroid or COL administration.[25] First, we aimed to demonstrate in a pharmacokinetic study in rats the ability of our approach to achieve high and sustained COL concentrations in the synovial fluid while maintaining low plasmatic concentrations. Subsequently, we sought to evaluate the efficacy of local SR-COL therapy, with or without anaesthetic (ROPI), using the CAR-induced arthritis model in rats.

METHODS

Manufacturing and characterisation of SR-COL microspheres

The manufacturing and the characterisation, including the pharmacokinetic and safety profile of the SR-COL microspheres administration in MSU-induced arthritis in rats are presented in online supplemental material.

CAR-induced arthritis in rats

Arthritis induction and treatments in rats

Experiments were performed in 4 weeks old male Sprague-Dawley (Janvier, Le Genest-Saint-Isle, France) weighing 150 g at study initiation. Anaesthetised rats were injected with 50 µL of Sigma λ-CAR 2% intra-articularly either in one ankle or one knee (batch ref. 22 049-56 F) via 300 µL syringe set with 30G needle. Treatments were administered intra-articularly, 1 min after CAR.

Rats received IA treatments in CAR injected joints. The injected dose, depending on the experiment, was 2 µg of SR-COL injectable microspheres suspensions in a volume of 50 µL, or a combination of 2 µg SR-COL microspheres and 250 µg ROPI in a volume of 50 µL. The positive control group was dexamethasone (DXM) 100 µg (0.7 mg/kg) (Mylan, 4 mg/mL). The negative control group was phosphate buffer saline (PBS). Depending on the groups, the number of rats was between 8 and 10.

Clinical arthritis evaluation

A blinded procedure was used to monitor clinical arthritis before the CAR injection (day 0; D0) to serve as baseline reference. Then clinical arthritis was blindly evaluated at different time points depending on the experiment. For each rat, the clinical severity of arthritis was scored using a scale as 0: normal; 1: slightly swollen or red; 2: noticeably swollen or deformity; 3: extremely swollen or marked deformity. The mean arthritic score on each day of clinical observation was calculated for each group of treatment. Swelling measurements of the joints were performed using an electronic calliper (Mitutoyo, Japan) measuring transversal diameter. The measure was validated when contact was obtained with the skin with no pressure.

Pain evaluation

Pain was evaluated before the CAR injection (day 0; D0) to serve as baseline reference. Then pain was evaluated at different time points depending on experiments, for all groups. An allodynia test was performed using von Frey hairs (Bioseb, France) using the 'ascending stimulus' method.[26] The Von Frey hairs were presented perpendicular to the plantar surface with sufficient force to cause slight buckling against the paw and held for approximately 5 s. Stimuli were presented at intervals of several seconds, allowing for apparent resolution of any behavioural responses to previous stimuli. A positive response was noted if the paw was sharply withdrawn. Flinching immediately on removal of the hair was also considered a positive response. A result showing lower values means a pain induction with smaller filament. Analgesic effect appears as a higher value.

A static weight bearing test was used to evaluate the spontaneous pain.[27] The rat was placed on an inclined holder with the hind paws resting on two separate pressure sensors. The weight distribution between the hind paws is recorded. A result showing lower values means more painful instability resulting from pain. The analgesic effect appears as a higher value with a certain degree of bias in this model (bilateral hind paw arthritis results in unpredictable effects on static weight bearing).

Histological analysis

Paws were dissected out for histological examination of the ankle or the knee. Samples were placed each in a dedicated numbered cassette and immersed in 10% formalin overnight. The next day, decalcification was performed for 5 hours in RDO (Eurobio) then 48 hours in EDTA 0.5M. Then, samples were dehydrated in an automat and embedded in paraffin. Sections of 4 µm are made and stained in H&E. Observation was blindly performed, with an inflammation and synovial involvement scored on a 0–3 scale basis as follows: 0: Normal; 1: Moderate synovial thickening and/or sparse inflammatory cells; 2: Noticeable thickening and/or several focuses of inflammatory cells and 3: Involvement of whole synovium with severe thickening or diffuse infiltration by inflammatory cells, and with a cartilage destruction score as follows: 0: Normal; 1: Limited destruction or notches or indentation of cartilage surface; 2: Severe destruction or many notches or slimming of cartilage and 3: Complete destruction.[28 29]

Statistical analysis

The main analysis for pain evaluation was performed in respect to intent-to-treat principles. According to data distribution, a parametric test (analysis of variance (ANOVA), Student test) or a non-parametric test (Kruskal-Wallis, Mann-Whitney U) with appropriate post hoc comparisons was used to compare data across the different groups. Clinical score curves were compared with ANOVA. A p value of <0.05 was considered statistically significant. Correlations used the non-parametric Spearman test. All statistical analyses were performed using Prism software.

RESULTS

SR-COL microspheres exhibit a sustained-release profile

COL was entrapped within a matrix of polylactic-co-glycolic acid polymer to form microspheres allowing for sustained release of the drug over the duration of the flare. In vitro release testing demonstrated that the drug release from the microspheres was consistent over time and lasted for about 10 days (figure 1A).

The particle size distribution and morphology of the microspheres were analysed to assess their suitability for suspension and precision in dosing through a 26G needle. Particle size distribution data showed a d10 of 10 µm, a median particle size (d50) of 16 µm, and a d90 of 35 µm, confirming a narrow size distribution and suitability for injection through a 26G needle (inner diameter of 0.13 mm) (figure 1B). The scanning electron microscopy image of SR-COL microspheres depicts the uniform morphology of the microspheres, highlighting consistent particle shape and size (figure 1C). These characteristics ensure that each dose administered from the syringe contains a precise amount of the active ingredient, thus confirming the accuracy and reliability of the injected dose in vivo.

Bioburden and endotoxin testing were conducted on the microspheres. The measured endotoxin levels were low (0.007 EU/mg). Microbial contamination was evaluated using the total aerobic microbial count and total yeast and mould count, with both counts found to be below 2 CFU per unit (data not shown).

Pharmacokinetics of IA administration of SR-COL was evaluated. COL concentrations in IA lavage of the ankle at 4, 24, 48 and 72 hours after inflammation induction varied between 10 and 25 ng/mL, with a peak of COL in situ at 24 hours post-injection (figure 1D). Systemic COL concentrations in plasma at similar time points demonstrated that most of the samples were below the limit of quantitation (0.05 ng/mL) although the value at 48 hours was slightly above this level (figure 1E). The COL area under curve (AUC) in rat after IA injection of SR-COL was measured below 2 ng*h/mL. In both cases, the release over 3 days with a plateau phase is characteristic of a sustained-release profile and, very importantly, without burst release or lag-time. Furthermore, the ratio between IA and plasma could be estimated at least between 200 to 500, confirming the strong COL dilution from the joint to the whole body, leading to negligible systemic levels.

SR-COL microspheres demonstrated both local and systemic safety

The safety of administering SR-COL microspheres (2 µg COL dose level) and empty microspheres (same polymer dose level) into the ankle of healthy rats was compared with a group of naïve animals, both at local and systemic levels. At the local level, the animals were observed for 28 days following the IA administration of both items. The assessment of the injury score, which includes swelling/oedema, discolouration, mobility and limb functionality on a scale from 0 to 8, indicated no significant effect for both products, with scores remaining close to 0 and similar to the naïve group, throughout the observation period. In addition, the histopathological observations of the tissues collected from the joints are comparable to the naïve group, demonstrating the local innocuity of SR-COL at the injected dose levels. At the systemic level, clinical chemistry, haematology and coagulation panels, along with the histopathological analysis of the collected organs, indicated no modifications when compared with the naïve group. Overall, these findings confirm the absence of systemic effects associated with SR-COL microspheres.

IA SR-COL microsphere administration exerted anti-inflammatory and analgesic effects on CAR-induced arthritis

As anticipated, arthritis developed in the rats injected with CAR (figure 2A). Compared with the control group treated with PBS, the administration of SR-COL microspheres significantly reduced the clinical score 2 hours post-injection (H2). Six hours after the injection (H6), arthritis scores were similar to the control group, but we then observed a decrease which was maintained and

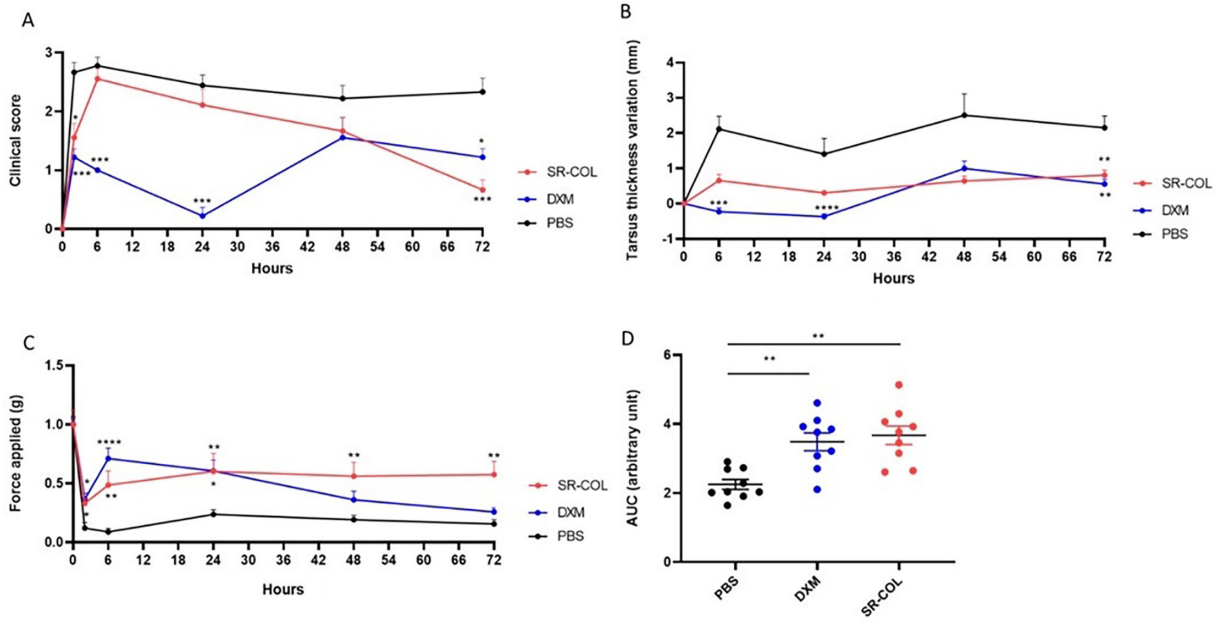

Figure 2 Evaluation of SR-COL intra-articular administration on clinical arthritis score (A) and tarsus thickness variation (B). Von Frey pain evaluation scores (C) and area under curve (AUC) of the Von Frey pain evaluation (D) in SR-COL, DXM and phosphate buffer saline (PBS) groups. Kruskal-Wallis test was performed. *p≤0.05, **p≤0.01, ***p≤0.001. Animals received intra-articular carrageenan and either PBS, dexamethasone (DXM) or sustained-release colchicine (SR-COL).

statistically significant at day 3 (D3) (figure 2A). Moreover, a marked decrease of tarsus thickness was observed at D3 with SR-COL compared with PBS (figure 2B). Finally, the IA administration of high doses of DXM resulted in a major anti-inflammatory effect and thereby validated the model.

Allodynia was evaluated using the Von Frey filaments test (the lower values correspond to the higher pain) on the ankle joint. Both DXM and SR-COL microsphere administration demonstrated a rapid analgesic effect, observed from the first time point of evaluation (figure 2C). For the SR-COL group, pain was statistically significantly reduced at H2 and H6 and remained distinctly and statistically improved over 3 days (figure 2C), while this was not the case for DXM-treated rats. This result was consistent with the AUC representation of pain evaluation (figure 2D).

SR-COL microspheres prevent histological arthritis

Histological evaluation showed statistically significant effect of SR-COL in terms of synovitis or perisynovitis (figure 3A–C). The evaluation of osteo-cartilaginous destructions showed an early joint destruction in rats receiving CAR, as early as 24 hours after induction (data not shown). SR-COL and DXM IA administrations were able to prevent the destruction and the inflammation of the joints analysed at D2.

Addition of ROPI to SR-COL microspheres exerted an anti-inflammatory, analgesic and protective effect on arthritis

With the perspective of potential further development in humans, we refined the treatment by adding ROPI to enhance the analgesic effect of SR-COL microspheres and to achieve a more rapid onset of action. In this experiment, CAR injection was performed in knees and the analgesic effect was evaluated using the weight-bearing method. As expected, DXM significantly reduced spontaneous pain, histological inflammation and joint destruction (figure 4A–D). ROPI administration decreased pain, but did not affect histological inflammation or destruction. PKM-01 (combination of SR-COL and ROPI) was effective on all three parameters (figure 4A–D). Indeed, the PKM-01 combination demonstrated a rapid and strong analgesic effect from H2 along with anti-inflammatory properties detected after 24 hours on the joint inflammation and destruction histological analysis (figure 4C and D, online supplemental figure 1).

DISCUSSION

In this study, we demonstrated that IA local treatment with PKM-01 (combination of SR-COL and ROPI) is effective and well tolerated in rats with CAR-induced inflammatory arthritis. PKM-01 exhibited statistically longer pain efficacy as compared with DXM, reduced clinical signs of arthritis and prevented histological joint inflammation and cartilage destruction.

At the initial stage of a gout flare, MSU crystals trigger the early inflammatory response by activating the NLRP3 inflammasome, resulting in joint inflammation and pain.[8] This stimulation leads to the production of inflammatory cytokines, including IL-1β and metalloproteinases, and to an influx of neutrophils. These phenomena, observed in crystal arthritis, especially in gout and CPPD disease, are also reported in CAR arthritis model.

The primary mechanism of action of oral COL, one of the first-line treatments for gout flares, is its ability

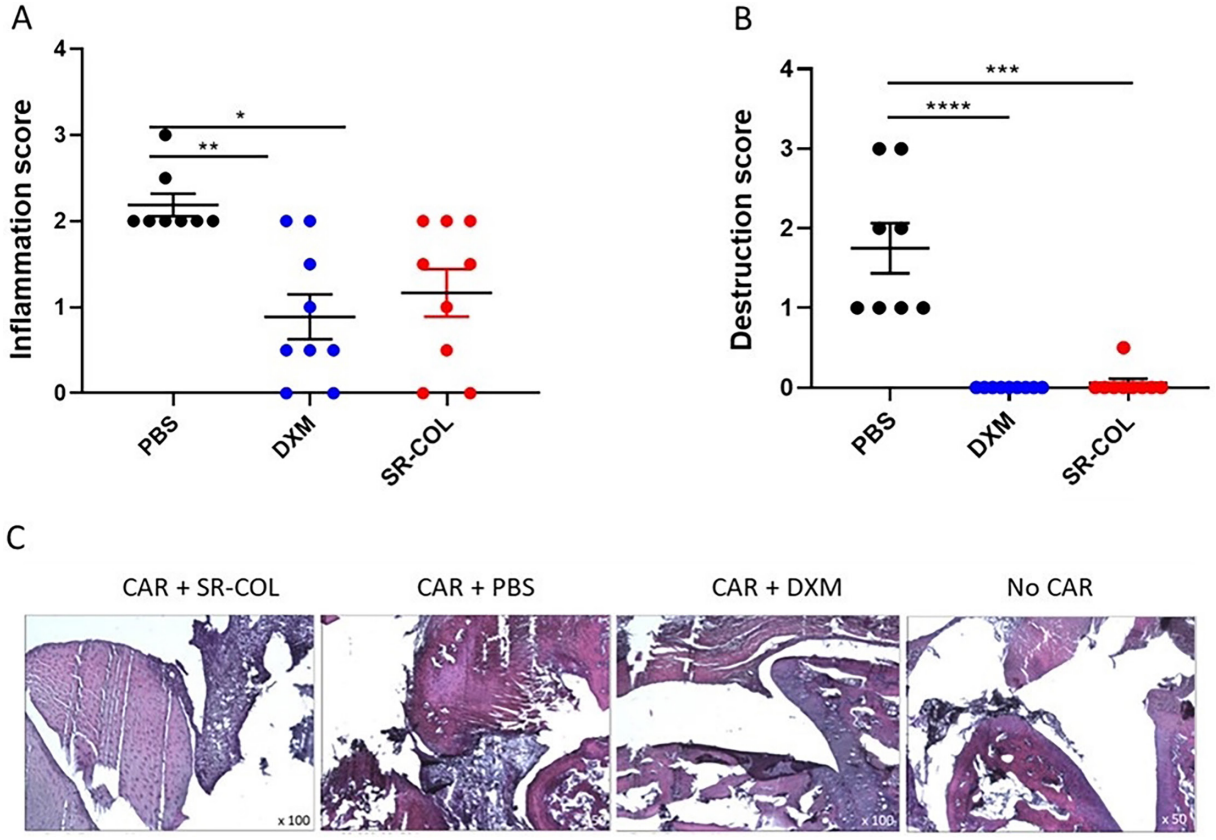

Figure 3 Histological inflammation (A) and destruction (B) scores at D2. (C) Histological characterisation of ankles from representative rats in the different conditions of treatment (H&E stain evaluation). Kruskal-Wallis test. *p≤0.05, **p≤0.01, ***p≤0.001. Animals received intra-articular carrageenan and either phosphate buffer saline (PBS), dexamethasone (DXM) or sustained-release colchicine (SR-COL). CAR, carrageenan.

to inhibit neutrophil-mediated inflammatory responses triggered by MSU crystals in the synovial fluid. This is achieved through disruption of the function of the neutrophil cytoskeleton and interference with microtubulin assembly. This results in the prevention of neutrophil activation, degranulation, adhesion and migration to the sites of inflammation.[13] However, oral COL has a delayed onset of action, limited efficacy, a narrow therapeutic index and clinically significant drug interactions, particularly in patients with renal insufficiency that could be fatal. In this context, a local approach aiming to maximise local COL efficacy while minimising systemic safety risks would represent a valuable option for patients. These polymeric microspheres progressively release COL over a period of 10 days, followed by the gradual biodegradation of the polymeric matrix into its endogenous metabolites (ie, lactic acid and glycolic acid) in less than 3 months.[30] SR-COL microspheres have been engineered to remain within the joint by being sufficiently large, typically exceeding 10 µm in diameter, to prevent entry into the synovial microvasculature even from inflamed joint.[31] Additionally, SR-COL microspheres are specifically designed to gradually release COL over a period of 7–10 days thereby avoiding burst effects or lag time in drug delivery to maximise safety and efficacy. The IA administration of these microspheres enables sustained release of COL within the joint, maintaining a local concentration of up to several tens of ng/mL over days and inducing a strong effect on pain, joint inflammation and joint destruction in the CAR arthritis model.

The significant efficacy observed for SR-COL in the CAR arthritis model may be attributed to the high local concentration of COL, as compared with oral COL, where the local IA Cmax is estimated to be approximately 3 ng/mL.[13] In contrast, the achieved local IA COL concentration range with the IA injection of SR-COL microspheres (of 10 ng/mL to 100 ng/mL) has been reported to alter neutrophil adhesion, prevent neutrophil recruitment[13] and reduce neutrophil deformability and motility.[32] Furthermore, the rapid onset of action observed in the CAR arthritis, as early as 2 hours after the administration of SR-COL, is clinically more favourable than the average 24 hours for oral COL administration in humans[33] and may be attributed to the sustained and high exposure to COL over time. This is consistent with reported findings,[34] where maximum intracellular loading of COL is reached faster with higher extracellular COL concentration and prolonged time exposure. Interestingly, SR-COL appears to exert a quicker effect on pain than on clinical inflammation, with a significant reduction observed as early as 2 hours after injection, whereas its impact on clinical arthritis becomes significant only at D3. This

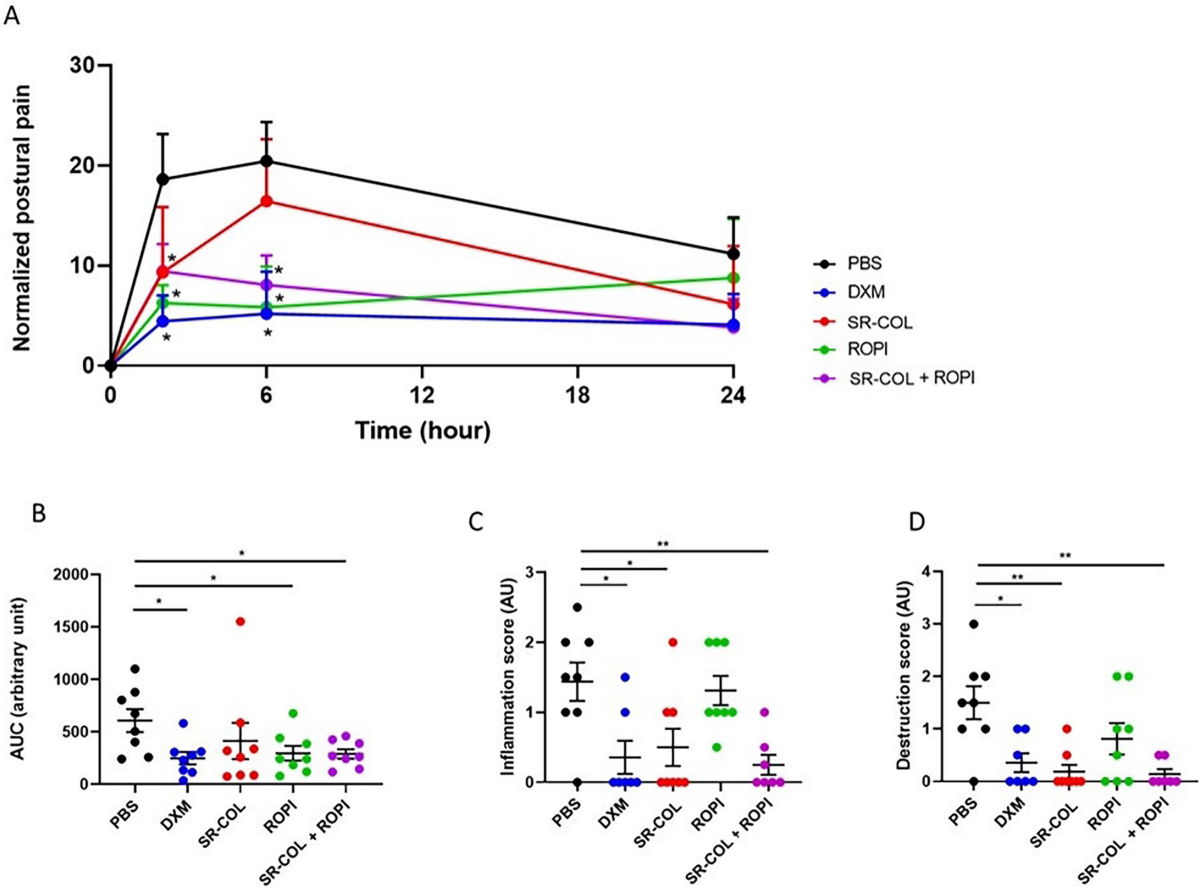

Figure 4 Postural pain evaluation scores along the study (A) and area under curve (AUC) (B). Histological inflammation (C) and destruction (D). Kruskal-Wallis test was performed. *p≤0.05, **p≤0.01, ***p≤0.001. Animals received intra-articular administration of carrageenan (CAR) and sustained-release colchicine (SR-COL), and/or dexamethasone (DXM), and/or phosphate buffer saline (PBS), and/or ropivacaïne (ROPI) associated with SR-COL in knees.

suggests a potentially distinct mechanism of action on pain pathways, which may precede the modulation of joint inflammation.

Following its release into the joint from SR-COL microspheres and subsequent dilution throughout the body, COL reaches negligible levels in the systemic compartment. In rat experiments, the local to systemic dilution factor is estimated to range between 200 and 500. By comparing PK data after administration of efficacious IA dose levels in rat and efficacious systemic dose levels in human, we observed that systemic concentration values in rats following IA injection were equal to or less than 0.05 ng/mL, which is significantly lower than the concentration achieved through the approved oral COL in humans (approximately 6 ng/mL Cmax). Similarly, the COL AUC in rats after IA injection of SR-COL was measured below 2 ng*h/mL, a low value compared with 50 ng*h/mL after the approved human oral COL dose.[33]

We did not observe any local detrimental effects after the administration of SR-COL microspheres, either alone or in combination with ROPI (PKM-01), into the joints of healthy rats at the effective dose level defined by the CAR arthritis model. Furthermore, consistent with the anticipated outcomes of the negligible systemic COL concentrations, there were no indications of systemic toxicity. If confirmed in humans, these negligible systemic COL concentrations could permit the reassessment of existing contraindications or dose adjustments for oral COL administration related to drug interactions or comorbidities. Based on these preclinical results, PKM-01 could be a rapidly efficacious and safe option to treat acute pain in microcrystalline arthritis, particularly for gout flares and potentially acute CPPD disease arthritis, in which treatment options are also limited.[35 36]

While this study provides valuable insights, certain limitations must be acknowledged. First, it was conducted in animal models as part of a proof-of-concept study. Clinical trials are planned for the treatment of gout flares in humans. Second, the model employed does not use urate crystals to accurately replicate gout flares but rather serves as a general model of acute arthritis, triggered by inflammasome activation. However, this CAR-induced model is relevant for drawing conclusions about diseases with similar mechanisms, such as urate or CPP crystal-induced arthritis,[37] particularly considering that literature on urate crystals models is scarce with regards to pain assessment.[38–40] Moreover, there is no model yet replicating CPPD disease, and the air pouch

model only replicates the inflammatory response and not the potential effects on cartilage.[41] Finally, the findings related to cartilage pathology should be confirmed in dedicated models such as other models of inflammatory arthritis or osteoarthritis models.

In conclusion, this study establishes proof-of-concept for the efficacy of IA SR-COL treatment combined with ROPI, in an acute arthritis model, providing support for further development to test its efficacy in crystalline arthritis.

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Contributors All authors contributed to the manuscript. JG, FM, LS, NB, CS, GP and M-CB were responsible for conception and design. JG, RH and ER were responsible for statistical analyses. All authors were responsible for data collection and analysis. JG, FM, GP, ER and M-CB wrote the first version of the manuscript. All authors were responsible for the interpretation of data and approved the final version of the manuscript. M-CB and GP are the guarantors.

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Competing interests JG, FM, CS, GP and PP are employees of PK MED. M-CB and H-KE received research grants from PK MED.

Patient consent for publication Not applicable.

Ethics approval All animal care and experimental procedures were conducted in compliance with the principles and guidelines of the European Union (2010/63/UE) and the French government regulations (referral #32645).

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