


Optimizing Osteoarthritis Management – Therapeutic Efficacy and Evaluation of Intra-Articular Triamcinolone Acetonide Injection

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Abstract: Osteoarthritis (OA) is a common degenerative joint disease that often leads to pain and diminished quality of life in patients. For end-stage osteoarthritis, surgical intervention remains the only effective treatment. However, for the majority of patients, surgery is not the initial consideration. The management of osteoarthritis primarily focuses on alleviating associated clinical symptoms, and rational non-surgical conservative treatment is the recommended approach for patients in the early to middle stages. Intra-articular injection therapy represents one of the most effective non-surgical treatment options, second only to oral analgesics and anti-inflammatory medications, with a lower incidence of systemic complications. Compared to surgery, it is more cost-effective and less invasive. Among these, intra-articular corticosteroid injection is a widely adopted non-surgical treatment by rheumatologists for osteoarthritis. Numerous studies have demonstrated that intra-articular corticosteroid injections can provide short-term pain relief in osteoarthritis. Triamcinolone Acetonide (TA) is one of the commonly used corticosteroids, valued for its notable anti-inflammatory and analgesic effects. It is extensively applied in intra-articular injections for osteoarthritis to alleviate pain and potentially delay disease progression. The purpose of this paper is to review the mechanism of action of Triamcinolone Acetonide, its current applications and efficacy in osteoarthritis, safety profile, and future directions, thereby providing a theoretical foundation and practical guidance for clinical management strategies in osteoarthritis.

Keywords: osteoarthritis, intra-articular injection, pharmacology, triamcinolone acetonide, ultrasound

Introduction

OA is a highly prevalent condition worldwide and represents one of the most common musculoskeletal disorders leading to disability. According to a 2019 Lancet study, approximately 250 million people globally were affected by OA. By 2025, new research has found that this number has increased to over 500 million. The high prevalence of OA imposes a substantial socioeconomic burden. On an individual level, the pain and functional impairment associated with the disease pose significant challenges to quality of life and healthcare expenditure.¹⁻³ Historically, OA was regarded as a condition resulting merely from mechanical wear and tear. However, emerging evidence indicates that OA is a whole-joint disorder, characterized by structural damage involving the articular cartilage, subchondral bone, ligaments, joint capsule, synovium, and periarticular muscles. Previously considered a mere consequence of mechanical wear, osteoarthritis is now recognized as a whole-organ disease involving structural damage of the articular cartilage, subchondral bone, ligaments, joint capsule, synovium, and periarticular muscles.⁴ Its pathogenesis also involves dysregulation of the innate immune system, cytokine networks (IL-1 β , TNF- α), synovial inflammation, and an imbalance in cartilage metabolism.^{5,6} Corticosteroid have anti-inflammatory effects for systemic application and can act on the entire body, which is consistent with the multi-site and multi-structural onset of OA.

Previous studies have indicated that patients with OA may continue to experience pain symptoms even after undergoing joint replacement surgery.^{7,8} In addition, a series of complications may also arise. Firstly, periprosthetic

fractures occur at a rate of 0.3% to 2.5% following arthroplasty. This is often due to improper prosthesis positioning, excessive bone resection during surgery, or excessive postoperative activity, leading to localized stress concentration and subsequent fracture. As more arthroplasty cases are included in research, an increasing number of postoperative periprosthetic fractures have been identified and reported.^{9,10} Secondly, patients may develop Metal deposition syndrome within a period ranging from 6 weeks to 26 years after the initial implantation, resulting from wear or dislocation of the metal components.¹¹ Additionally, one case study reported postoperative septic metal intoxication.¹² It has been observed that the majority of patients in clinical practice seek treatment only when the disease has reached an end-stage or when the pain symptoms become unbearable. At this point, surgical intervention often becomes the last resort. However, the aforementioned studies demonstrate that even after joint replacement surgery, pain relief may not be fully achieved, studies indicate that as high as 25% of patients still report pain and mobility difficulties one year after surgery,^{13,14} and a range of complications may still arise. Consequently, a growing number of researchers have focused on investigating the pathogenesis of OA to identify non-surgical interventions that may delay disease progression. It is now widely recognized that OA develops as a chronic, prolonged process, progressing through mild to moderate stages before reaching the end phase. With advances in research, increasing evidence indicates that the mild to moderate stages represent a critical window for therapeutic intervention. Targeting the early phases of OA with proactive and tailored non-surgical management is considered a first-line treatment strategy. Such approaches can alleviate the disease burden before OA progresses to severe osteophyte formation, joint space narrowing, cartilage destruction, significant functional impairment, and persistent chronic pain.^{15–18} Current non-surgical treatment strategies include foundational therapies, topical agents, oral medications, intra-articular injections, and biologics. Among these, intra-articular injections are widely utilized in early to moderate OA due to their low systemic adverse effects, potent localized action, cost-effectiveness compared to surgery, and minimal invasiveness. This modality has proven to be a highly effective approach for managing OA. Commonly injected agents include hyaluronic acid, stem cells, platelet-rich plasma (PRP), and corticosteroids.¹⁸

However, among the aforementioned therapies, hyaluronic acid has been demonstrated in studies to provide only a modest reduction in pain compared to placebo, while also increasing the risk of serious adverse events, suggesting that the perceived pain relief by patients lacks clinical significance,^{19,20} studies also suggest that intra-articular injection of corticosteroid not only provides short-term analgesic effects compared with intra-articular hyaluronic acid, but also demonstrates more pronounced efficacy in patients with severe pain.^{21,22} The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group recommends that intra-articular hyaluronic acid should be avoided when patients have contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) or continue to experience symptoms despite NSAIDs use.²³ PRP is limited by insufficient durability of efficacy, unclear advantages in safety, and low cost-effectiveness. Furthermore, it is not suitable for all OA patients or disease stages, and the definition of the optimal candidate population remains unclear.²⁴ Stem cell therapy, as an emerging treatment modality, is constrained by high costs, uncertain therapeutic outcomes, and potential adverse effects such as pain, swelling, and immune reactions.^{25–28} In comparison, corticosteroid injections have the longest history of use,²⁹ and intra-articular and periarticular glucocorticoid injections are common in sports medicine.³⁰ According to the ESCEO 2019 algorithm, intra-articular corticosteroids serve as an effective alternative to oral NSAIDs and are particularly suitable for patients with knee joint effusion (though evidence remains limited).³¹ It is recommended that injections be administered no more than 2–3 times per year, with intervals between injections not shorter than 3–6 months.³² Studies have shown that intra-articular corticosteroid injections can rapidly alleviate pain within two weeks and exhibit a range of anti-inflammatory mechanisms. Their application is not only historically validated but also meets patients' needs for symptomatic pain relief, while their anti-inflammatory effects align with the pathogenesis of OA. For OA patients, pain is often the most typical clinical symptom. Corticosteroids such as TA, methylprednisolone acetate, prednisolone acetate, and betamethasone are used in the treatment of OA patients and demonstrate favorable anti-inflammatory effects. However, studies indicate that TA is more effective and has a longer duration of action in terms of analgesia compared to other corticosteroids.^{33,34} Therefore, TA is frequently employed in OA management.

This article provides a systematic review of the pharmacodynamics, pharmacokinetics, clinical efficacy, and safety of TA and its sustained-release formulations in the treatment of systemic OA. It also explores the potential for their combination with other therapeutic agents, aiming to offer an evidence-based foundation for clinical practice.

Pharmacological Properties of Triamcinolone Acetonide

Chemical Structure

The molecular structure of TA is derived from hydrocortisone through several chemical modifications. These include the introduction of a fluorine atom at the C9 α position, the formation of a double bond between C1 and C2, and the addition of a 16- α -hydroxyl group (Figure 1). The fluorine atom and hydroxyl group enhance the compound's binding affinity to hormone receptors, while the double bond further strengthens receptor interaction and retards metabolic clearance.^{35,36} As a result of these structural modifications, TA exhibits prolonged anti-inflammatory and analgesic effects compared to other corticosteroids, which is attributed to its altered pharmacokinetic profile.^{33,34}

Mechanism of Pharmacological Action

Anti-Inflammatory Effect: Inhibits Inflammatory Mediator Production and Reduces Inflammatory Cell Infiltration

The beneficial effects of glucocorticoid (GC) injections are thought to be primarily attributable to their anti-inflammatory properties.³⁷ As a potent anti-inflammatory agonist, GCs act on immune cells by stimulating the bone marrow to increase granulocyte production, while simultaneously inhibiting neutrophil apoptosis and their migration through the vasculature to sites of inflammation or infection. Additionally, GCs suppress the activity of other immune cells such as monocytes, lymphocytes, and mast cells.^{36,38} In terms of inflammatory mediators, GCs inhibit phospholipase A₂, thereby reducing the release of pro-inflammatory derivatives of arachidonic acid, including interleukin-1 (IL-1), IL-2, interferon- γ , and tumor necrosis factor (TNF). They also diminish the synthesis of prostaglandins and leukotrienes, contributing to their anti-inflammatory effects.^{36,39} As a synthetic glucocorticoid, TA exerts anti-inflammatory actions similar to those of

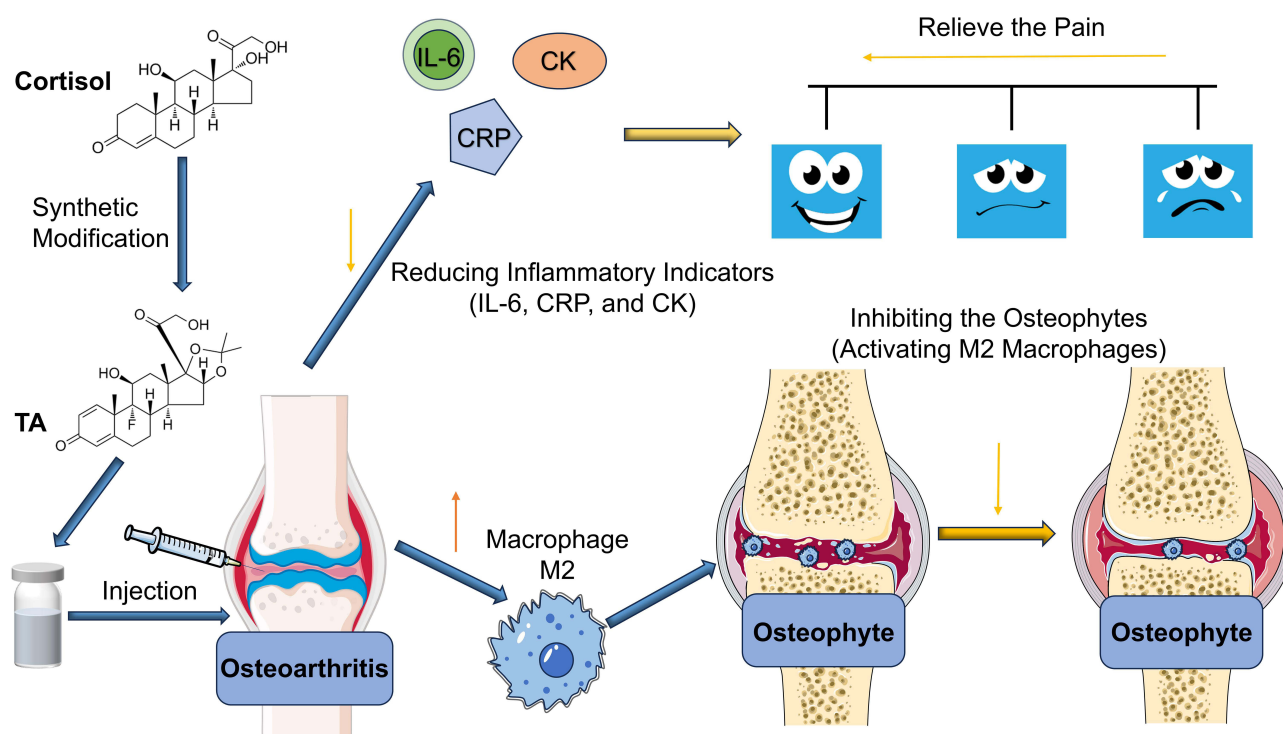


Figure 1 The molecular structure of triamcinolone acetonide is based on that of hydrocortisone, with specific chemical modifications. When formulated and injected into the human knee joint, it alleviates pain by reducing inflammatory indicators and also decreases osteophyte formation through increasing the population of M2 macrophages.

other corticosteroids. Upon binding to and activating the glucocorticoid receptor, TA induces an anti-inflammatory response characterized by downregulation of pro-inflammatory cytokine expression, inhibition of prostaglandin and leukotriene synthesis, and suppression of arachidonic acid release. Concurrently, it activates anti-inflammatory transcription factors such as lipocortin-1.^{35,40} Previous studies have indicated that lipocortin-1 can be induced by glucocorticoids, suppresses the production of the inflammatory mediator nitric oxide in synovial macrophages, thereby alleviating arthritis inflammation, and plays a significant anti-inflammatory role in neutrophil-mediated joint inflammation by regulating their migration and activation. Moreover, lipocortin-1 is not only a key mediator of glucocorticoid action but also possesses intrinsic anti-inflammatory functions, its effect may be mediated through cellular surface receptors or external secretion signaling pathways.^{41,42} However, the cited studies are relatively dated, and recent research on the impact of lipocortin-1 on the pathophysiological mechanisms of osteoarthritis remains limited. We hope that future studies will provide further supplementation and more detailed explanations in this regard. TA exerts an inhibitory effect on synovial inflammation but does not significantly affect synoviocytes. Sherman was the first to systematically evaluate the response of synovial cells to pharmacological treatment by culturing synovial explants in medium containing TA. Observations at 1 and 7 days revealed no significant decrease in synovial explant viability, indicating that TA did not markedly influence synoviocyte viability or metabolic activity.⁴³

Furthermore, TA exhibits analgesic effects through anti-inflammatory mechanisms. Previous studies have reported that OA can trigger the release of IL-6, leading to local inflammation at the injury site, along with elevated levels of C-reactive protein (CRP), a key inflammatory marker.^{44–46} Serum CRP levels have also been associated with the severity of pain in OA.⁴⁷ Creatine kinase (CK), an energy-producing enzyme located in mitochondria and predominantly found in muscle tissue, has been demonstrated to increase in response to muscle inflammation or injury.⁴⁸ A single-center retrospective cohort study revealed that patients treated with TA injections exhibited lower levels of CRP and CK compared to those who did not receive such treatment.⁴⁹ Therefore, it can be concluded that TA, as a systemic therapeutic agent, alleviates OA-related pain and mitigates inflammatory progression by reducing these inflammatory biomarkers (Figure 1).

Immunosuppressive Effect: Inhibits Osteophyte Formation

Macrophages are critically involved in osteophyte formation, as studies have shown that selective depletion of synovial macrophages in two collagenase-induced mouse osteoarthritis models significantly reduces the formation of joint osteophytes.^{50,51} The polarization of synovial macrophage subtypes plays a critical role in the progression of OA.⁶ Studies have demonstrated that the three subtypes of M2 macrophages exhibit an anti-inflammatory phenotype and contribute to tissue repair and remodeling.^{52,53} Previous transgenic studies in mice with polarized M1 and M2 macrophages revealed that M1 macrophages accelerate OA progression, whereas M2 macrophages attenuate disease development.⁵⁴ M1 macrophages secrete pro-inflammatory cytokines (such as TNF- α , IL-1 β), exacerbating inflammation and cartilage destruction; whereas M2 macrophages promote tissue repair by secreting TGF- β , IL-10, and other factors. When macrophages are biased toward the M1 phenotype, it leads to an imbalance in polarization, resulting in persistent inflammation, cartilage degeneration, and osteophyte formation, thereby further exacerbating the symptoms and structural damage of osteoarthritis.⁵⁵ In an in vitro study, Utomo demonstrated that corticosteroids suppress M1 macrophage polarization by downregulating pro-inflammatory cytokines such as interferon- γ and TNF- α , while promoting M2 macrophage polarization through the upregulation of anti-inflammatory cytokines including IL-4 and IL-10.⁵⁶ In a combined in vivo and in vitro study, TA was shown to induce macrophage activation and differentiation, thereby inhibiting osteophyte formation. Siebelt quantified macrophage activation via intra-articular TA injection in a rat OA model and complemented these findings with in vitro assays characterizing M1 and M2 polarization through surface receptor expression. In vitro macrophage cultures demonstrated that TA strongly induces monocyte differentiation into CD163⁺ and FR β ⁺ regulatory macrophages. Furthermore, TA-stimulated M2 macrophages exhibited enhanced IL-10 expression at the mRNA level (Figure 2). Comparative analyses between TA-injected experimental groups, untreated healthy controls, and normal saline (NS)-injected groups indicated that only TA specifically activated M2 macrophages, leading to suppression of osteophyte formation.³³

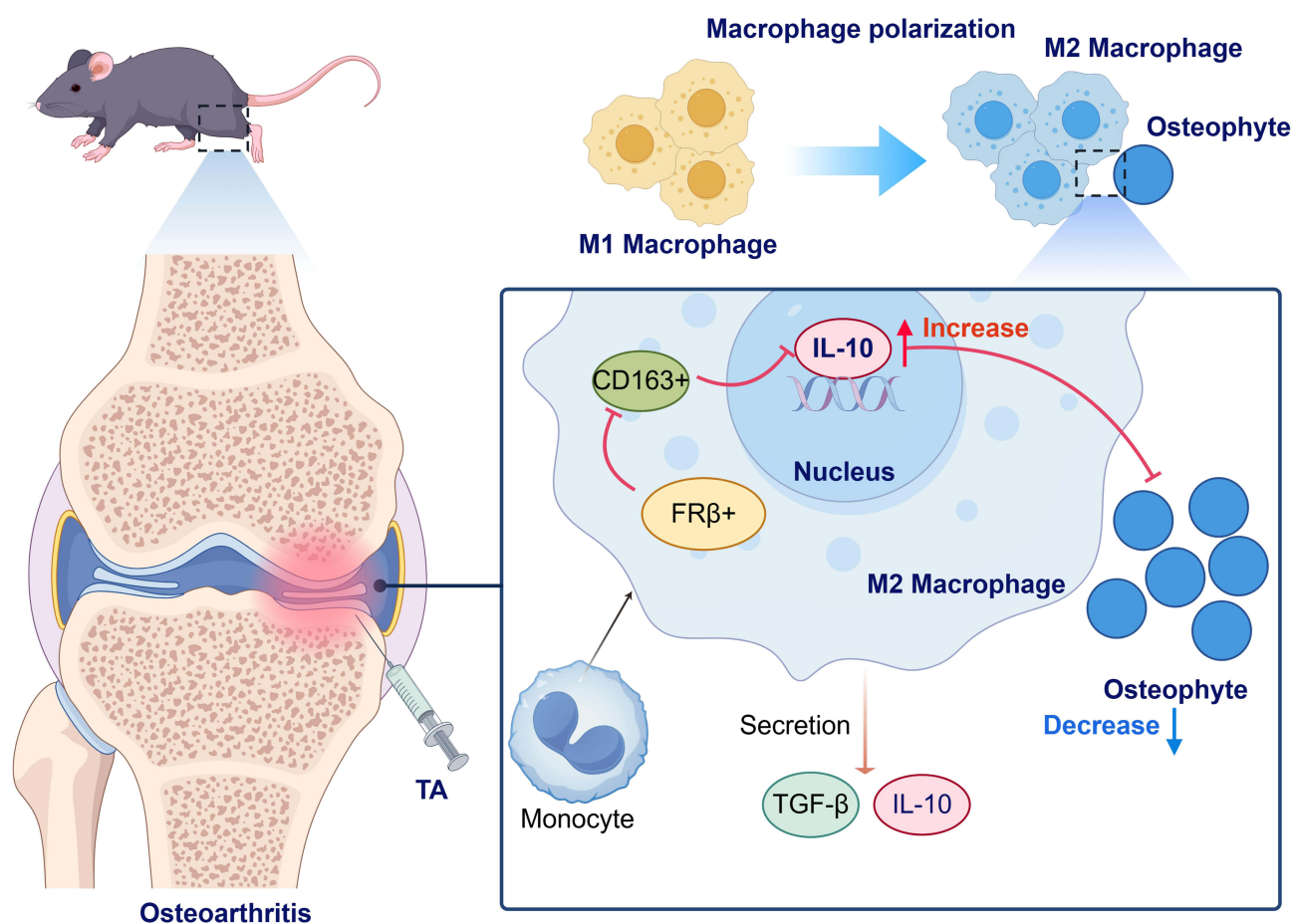


Figure 2 After intra-articular injection of triamcinolone acetonide into the mouse knee joint, a robust induction of monocyte differentiation into CD163+ and FR β + regulatory macrophages was observed. Furthermore, TA-stimulated M2 macrophages exhibited enhanced IL-10 expression at the mRNA level, and these M2 macrophages suppressed osteophyte formation. In addition, M2 macrophages promoted tissue repair through the secretion of TGF- β and IL-10.

Analgesic Effect: Animal Studies

Preclinical studies conducted in both small and large animal models have demonstrated that TA exerts certain analgesic effects in animals with OA. In rats subjected to OA induced by medial meniscectomy, joint pain was characterized using a dynamic weight-bearing test during jumping. The right/left hind paw pressure ratio significantly decreased to approximately 66% beginning on postoperative day 7 and remained at this level through day 90. However, in the group of OA-induced rats treated with the triamcinolone acetonide extended-release microsphere formulation FX006 (Zilretta), the pressure ratio recovered to 96% at 15 days post-surgery (8 days post-administration), showing no significant difference compared with that of the healthy control group.⁵⁷ These findings reveal its capacity to elicit analgesic effects within a short-term period. In a canine model of intra-articular hip injection, Alves observed that administration of TA (n=20) resulted in significantly greater improvements in weight-bearing, pain (with sustained relief lasting 118.6 days vs 8.4 days), and functional outcomes over a 6-month period compared with NS (n=20). The anti-inflammatory effect of TA was supported by a marked reduction in synovial fluid IL-1 β levels at 8 days post-injection (P=0.04) and lower joint temperatures as measured by thermography (P<0.01). However, possibly due to the generally higher physical activity levels in dogs, the duration of therapeutic benefits—including weight-bearing capacity, pain relief, and joint function—was limited to 90 days in canines, in contrast to the sustained effects of up to 7 months reported in human studies.⁵⁸ Despite these interspecies variations, the findings collectively indicate that intra-articular TA injection can ameliorate pain and improve joint function in both animal and human subjects. In horses with distal tarsal joint osteoarthritis, intra-articular administration of TA resulted in short-term improvement of lameness attributable to osteoarthritis.^{59,60} In another in vivo equine study, pain responses to passive flexion and joint effusion of the

metacarpophalangeal joint were assessed using a 4-point grading scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Although TA was assigned to the control group in this study, intra-articular injection of TA into the metacarpophalangeal joint yielded significantly lower effusion scores at the one-week follow-up compared to baseline ($p < 0.001$), and passive flexion scores were significantly reduced at both one week ($p < 0.001$) and two weeks ($p < 0.001$) post-injection.⁶¹

Effects on Cartilage

Plasma serine protease-activated protein C (APC) has been demonstrated to be synthesized by human chondrocytes at sites of pathological cartilage fibrillation. In vitro studies have shown that APC acts synergistically with IL-1 β to promote the degradation of articular cartilage, an effect that can be inhibited by corticosteroids.⁶² Porter and his team further corroborated these findings through in vivo experiments, in which cartilage was harvested from the femoral condyles and patellar groove of the knee joints of young healthy cattle (1–2 months old). IL-1 β was employed to simulate acute or persistent inflammation, and the effects of physiological doses of TA (1 nM–200 μ M) on cartilage metabolism were evaluated. The results indicated that, in the short term (2 days), TA did not affect chondrocyte viability or proliferation, irrespective of the presence of IL-1 β . While short-term treatment with IL-1 β alone reduced glycosaminoglycan (GAG) synthesis by 30% and collagen synthesis by 60%, treatment with any physiological dose of TA neither inhibited the rate of GAG synthesis nor accelerated it in inflamed cartilage. Instead, TA rescued IL-1 β -induced GAG loss, thereby preventing degradation of the cartilage extracellular matrix. Even under long-term treatment (10–14 days), TA exhibited no effect on chondrocyte viability or the synthesis of GAG or collagen. This experiment demonstrates that, although physiological doses of TA are unable to restore cartilage synthesis, they can mitigate matrix degradation in an inflammatory environment through anti-catabolic mechanisms. Moreover, both short-term and long-term TA treatments are relatively safe, with no evident chondrotoxicity.⁶³ In Klocke's study, a cohort of 80 patients with symptomatic knee osteoarthritis (KOA) who received an intra-articular injection of 40 mg TA combined with 4 mL of 1% lidocaine, comparisons were made between baseline and 3-week post-injection levels of urinary C-terminal telopeptide of type II collagen (uCTX-II), a biomarker of cartilage metabolism, and serum cartilage oligomeric matrix protein (sCOMP), another cartilage metabolic marker. The results showed a significant reduction in uCTX-II at 3 weeks post-injection (349.9 vs 306.3 ng/mmol, $p = 0.002$), along with a downward trend in sCOMP. The decrease in these cartilage catabolic biomarkers suggests that intra-articular TA may potentially inhibit cartilage degradation in the short-term following injection.⁶⁴

Previous studies have demonstrated that intra-articular application of TA exerts toxic effects on cartilage from three perspectives: chondrocyte viability, oxidative stress, and gene expression. TA was shown to reduce chondrogenic gene activity in a dose-dependent manner. Measurements taken at 7 and 14 days after injection of 1, 5, and 10 mg/mL of TA revealed cartilage viability rates of 75.43%/70.10%/66.07% and 78.30%/68.55%/66.05%, respectively. Furthermore, TA induced oxidative stress, as indicated by a significant increase in the ratio of oxidized glutathione to total glutathione with rising TA concentrations. In terms of gene expression, TA significantly upregulated the mRNA levels of P21, GDF15, and c-Fos, suggesting that its toxic effects may be mediated through pathways involving cell cycle regulation and apoptosis. However, when comparing the total glutathione levels measured with TA treatment alone versus those with additional vitamin C at concentrations of 0 mg/mL (0.087 \pm 0.025 vs 0.089 \pm 0.023), 1 mg/mL (0.394 \pm 0.12 vs 0.129 \pm 0.048), and 5 mg/mL (0.517 \pm 0.135 vs 0.123 \pm 0.031, $P=0.025$), it was found that the application of antioxidants such as vitamin C could ameliorate TA-induced cartilage damage.⁶⁵ This provides insights that such an approach may potentially serve as a remedial measure, though further experimentation is required for comprehensive summarization and validation. Dragoo utilized a bioreactor equipped with a continuous infusion pump simulating synovial fluid metabolism to administer a single dose of 5 mg of TA to human chondrocytes in vitro. In an experimental setup where the duration of exposure was individually determined for TA and four other corticosteroid groups, TA exhibited a mean exposure time of 14 days. Compared to the 14-day medium control, this single TA dose resulted in a significantly reduced chondrocyte viability (10.2% \pm 1.3% vs 4.8% \pm 0.9%; $P = 0.0049$), demonstrating significant cytotoxic effects. To account for the potential influence of culture duration on cell survival, a subsequent experiment standardized the exposure time to 14 days for all five corticosteroid groups. Under these uniform conditions, TA showed only a trend towards cytotoxicity (9.2% \pm 3.4% cell death vs 4.6% \pm 2.4% cell death; $P > 0.05$), which was not statistically significant. The authors suggest

that this lack of significance may be attributed to increased variability when comparing multiple drugs concurrently, potentially diluting the effect. Nevertheless, Drago's findings indicate that, although the effect may be weaker under controlled conditions, the toxic effect of TA on chondrocytes is authentic.⁶⁶ Taken together, the role of the agent in modulating chondrocytes remains contentious based on the aforementioned mechanistic studies, with dosage and duration of administration emerging as two critical factors underlying the controversy. However, discrepancies among study findings preclude a unified conclusion regarding the optimal dosing and timing, underscoring the need for further investigation.

Another study has reported an association between cartilage defects and joint pain. The researchers utilized magnetic resonance imaging (MRI) to observe cartilage morphological features in 294 participants initially free of radiographic knee osteoarthritis (KOA) over a six-year period. They assessed both full-thickness cartilage loss and loss of cartilage area, and correlated these findings with the Knee Injury and Osteoarthritis Outcomes Score (KOOS) questionnaire. The results indicated that each one-point increase in the score for full-thickness cartilage loss was associated with a 1.04-point decrease in the KOOS score. Full-thickness cartilage defects were found to be associated with joint pain, whereas cartilage area loss showed no significant correlation.⁶⁷ Ishijima conducted molecular biomarker testing on serum and urine samples from 30 patients with Kellgren-Lawrence Grade (KL) 1 and 16 patients with KL grade 2 knee osteoarthritis. The serum biomarkers included the Serum Cartilage Type II Collagen Cleavage by Collagenase (sC2C, a marker of degradation) and the Serum Cartilage Type II Procollagen Carboxy Propeptide (sCPII, a marker of synthesis). Urinary biomarkers measured were uCTX-II (indicating cartilage degradation) and Urinary Bone N-terminal Crosslinking Teloepitope of Type I Collagen (uNTx, a marker of bone resorption). When patients were stratified by the presence of pain, irrespective of KL grade, levels of sC2C, sCPII, and uCTX-II were significantly elevated, suggesting that pain is associated with increased cartilage metabolism and enhanced bone resorption. Upon stratification by both KL grade and pain status, KL grade 1 patients with pain exhibited significantly higher sC2C and sCPII levels, whereas KL grade 2 patients with pain showed significantly elevated uCTX-II levels and an increased uCTX-II/sCPII, suggesting that pain at different stages of KOA may be associated with distinct patterns of tissue metabolic abnormalities. However, cartilage has no nerves, the authors propose that pain may arise indirectly through cartilage structural changes leading to alterations in joint mechanics and stress at the bone-cartilage interface, which subsequently stimulate nerve endings and result in pain perception.⁶⁸ This provides us with new insights, suggesting that cartilage regeneration may be associated with pain relief, which could offer a novel therapeutic direction for OA pain management. However, more comprehensive trials are needed to provide evidence-based support for clinical application. Additionally, while the analgesic effect of TA is well-established, its potential chondrotoxicity remains controversial, indirectly indicating that its pain-relieving effect is primarily mediated through anti-inflammatory mechanisms rather than direct action on cartilage.

Pharmacokinetic Characteristics

Understanding the pharmacokinetics of intra-articular TA administration is crucial for assessing its efficacy and safety in OA treatment.

Blood Concentration and Time to Onset After Administration

In the equine intercarpal (IC) and sacroiliac (SI) joints, 18 mg of TA was administered respectively. It was observed that the peak plasma concentration in the IC group was significantly higher than that in the SI group (1.61 vs 0.70 ng/mL, $p < 0.01$), although both groups reached peak concentrations at 8 hours. Furthermore, TA concentrations in the IC group remained significantly higher than those in the SI group from 8 to 36 hours.⁶⁹ Similarly, in equine studies conducted by Soma et al, it was demonstrated that TA exhibits distinct pharmacokinetic profiles depending on the route of administration—intravenous (IV), intramuscular (IM), and intra-articular (IA). The study indicated that TA follows a three-compartment model for both IM and IA administration, while a two-compartment model applies to IV administration. Regarding half-life: the median distribution half-life after IV administration was 0.50 hours (range: 0.24–0.67 hours), whereas the transfer half-life of TA from the joint to plasma following IA administration was 5.2 hours (range: 0.49–7.3 hours). In terms of elimination half-life, IA administration resulted in a significantly longer duration compared to IV administration (23.8 hours vs 6.1 hours). As for maximum plasma concentration (C_{max}): the C_{max} after IA

administration was 2.0 ng/mL (range: 0.94–2.5 ng/mL), achieved at 10 hours (range: 8–12 hours), while IM administration yielded a C_{max} of 0.34 ng/mL (range: 0.20–0.48 ng/mL), reached at 13.0 hours (range: 12–16 hours).⁷⁰ These differences suggest that IA administration may result in a longer duration of action in the body compared to IV administration, while demonstrating a more potent concentration efficacy relative to IM injection. In light of these comparisons, IA administration is the more preferable approach for the treatment of OA. Although the experimental data presented above were not directly derived from human studies, findings from other mammalian species may still offer valuable translational insights.

Metabolism and Clearance within the Joint

Following intra-articular injection of 40 mg TA into the shoulder joint, a significant decrease in urinary TA concentration was observed starting 1 week post-injection, becoming nearly undetectable by day 45.⁷¹ Triamcinolone Hexacetonide (THA), an ester of TA, is frequently administered via the intra-articular route. Even if a small fraction of the administered dose reaches the systemic circulation, plasma esterases are expected to rapidly hydrolyze THA into TA. Coll et al investigated the elimination of THA and its metabolites in human urine and plasma following a single intra-articular hip injection, with the detection of TA metabolites in urine representing a novel exploration. In OA patients (n=8) receiving a single 40 mg THA injection, urinary elimination of THA peaked at 48 hours and remained detectable until day 23; plasma concentrations peaked between 24 and 28 hours and were detectable until day 10. After intra-articular THA administration, only TA metabolites (not THA or new metabolites) were detected in urine, whereas both THA and TA were detected in plasma, leading to the consideration that plasma THA serves as direct evidence of intra-articular administration.⁷² When comparing plasma samples collected over the same timeframe after intra-articular injections of TA (10 mg, 20 mg, and 40 mg) and THA (20 mg and 40 mg), the terminal half-life of THA was determined to be 4.6 days, while that of TA ranged between 3.2 and 6.4 days. Regarding systemic clearance, the total clearance for TA at 10 mg, 20 mg, and 40 mg doses was 66.7 L/h, 38.8 L/h, and 62.9 L/h, respectively. For THA, the total clearance was 75.0 L/h and 67.5 L/h at the 20 mg and 40 mg doses, respectively. Both TA and THA were completely absorbed, albeit with slightly different absorption rates; approximately 35% to 40% of THA was absorbed from the joint within 3 days of intra-articular administration, compared to 58% to 67% for TA. The mean residence time within the joint also differed, being only 3.2–4.3 days for TA compared to 6 days for THA^{35,73} (Table 1). This longer intra-articular residence time of THA underscores its potential for intra-articular therapy in the management of osteoarthritis.

Efficacy of Novel TA-Loaded Formulations

In recent years, there has been increasing exploration and application of novel formulations of TA. When FX006, an extended-release microsphere formulation of TA, was administered via intra-articular injection into the knee at doses of 16 mg and 32 mg, the median time to onset of analgesic effect was similar for both doses (Day 4) and occurred earlier than that observed with saline placebo (Day 8). The maximum analgesic effect for both FX006 16 mg and 32 mg was achieved at Weeks 4–5.⁷⁴ In a Phase IIa clinical study, eligible patients with bilateral knee osteoarthritis received simultaneous unilateral injections of either TA extended-release (TA-ER) 32 mg or conventional TA 40 mg into each knee. The time to peak plasma concentration was 4.5 hours for TA compared to 6.5 hours for TA-ER. Furthermore,

Table 1 Comparison of TA and THA Metabolism and Clearance Within the Joint

Drugs	Sample	Terminal Half-Life ($t_{1/2\beta}$)	Absorption Rates of 3 Days Post-Injection	Dose	Total Clearance (CL)	Mean Residence Time Within the Joint
TA	Blood plasma	3.2 to 6.4 days	58% to 67%	10mg 20mg 40mg	66.7L/h 38.8L/h 62.9L/h	3.2 to 4.3 days
THA	Blood plasma	4.6 days	35% to 40%	20mg 40mg	75.0L/h 67.5L/h	6 days

Abbreviations: TA, Triamcinolone acetoneide; THA, Triamcinolone hexacetonide.

systemic exposure, as measured by the area under the concentration-time curve (AUC), was lower for TA-ER than for TA.⁷⁵ Following intra-articular injection into the hip, the maximum plasma concentration of TA-ER was significantly lower than that of triamcinolone acetonide crystalline suspension (TAcS) (geometric mean: 890.4 pg/mL vs 5549.4 pg/mL). Systemic exposure (AUC) was also significantly lower for TA-ER compared to TAcS. TA-ER demonstrated a more stable plasma concentration profile and a longer mean residence time.⁷⁶

FX006 was developed by Flexion Therapeutics in 2017 (development code: FX006, trade name: Zilretta) and received FDA approval for marketing (National Drug Code: 70801-003-01, Flexion Therapeutics, Burlington, MA, USA).⁵⁷ However, the prescribing information (FDA-approved labeling) for FX006 (Zilretta) does not list Kellgren-Lawrence (KL) grade as an absolute restriction for its use. The sustained-release properties of the novel TA-loaded material prolong intra-articular drug retention, enabling longer-lasting symptomatic improvement, reduced injection frequency, and minimized systemic exposure, thereby supporting its potential as an optimized non-surgical therapeutic option for OA.

Clinical Application of TA in Osteoarthritis

Commonly Injected Joints (Hip, Knee, Hand, Shoulder) and Clinical Efficacy Assessment (Figure 3)

Efficacy of Hip Joint Intra-Articular Injection

In a six-month comparative trial conducted by Kigozi, patients with hip OA were allocated to either basic conservative treatment (BCT) alone (n=66) or BCT combined with ultrasound-guided intra-articular injection of 40 mg TA and 4 mL

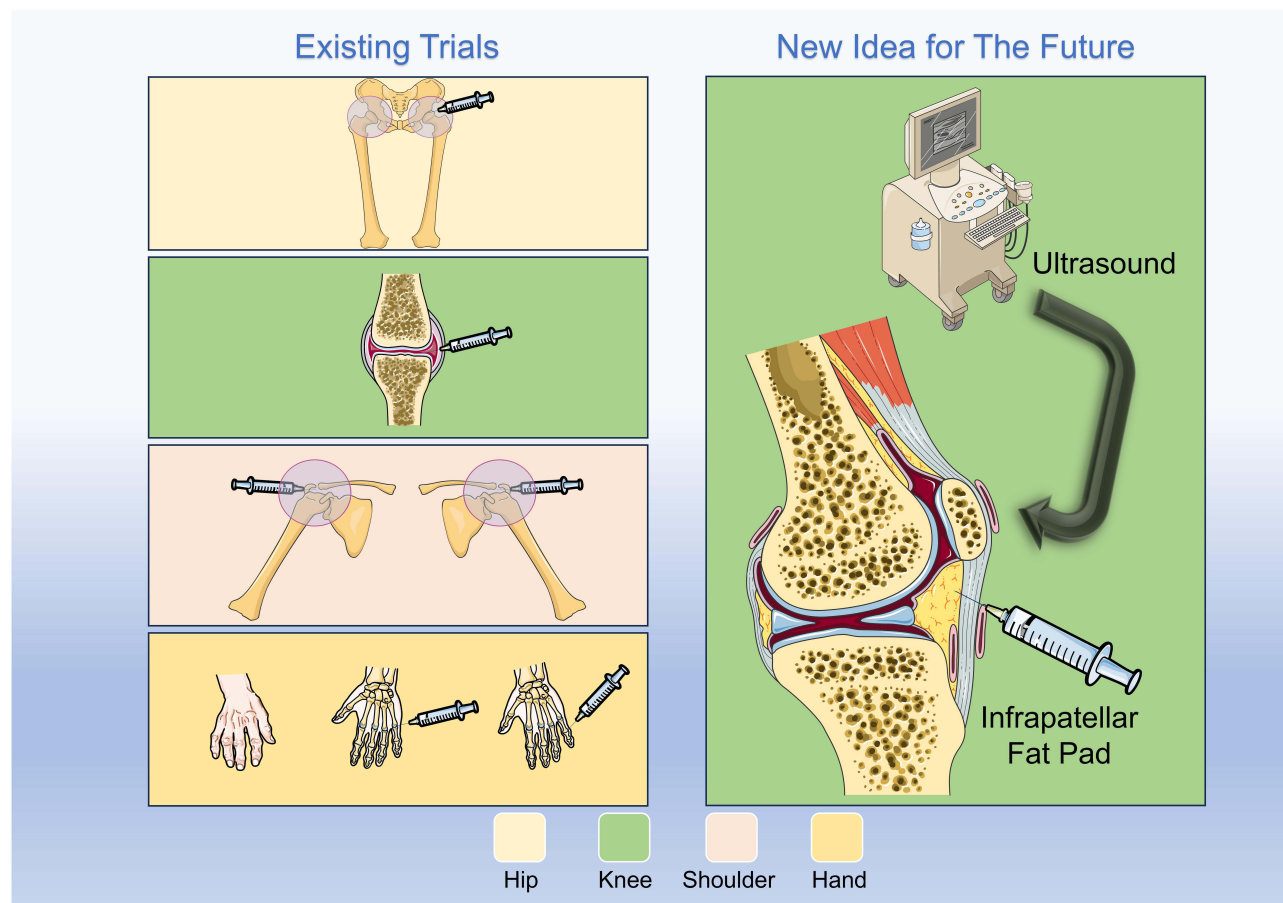


Figure 3 This article discusses the efficacy of triamcinolone acetonide injections in the Hip, knee, shoulder, and hand joints. Future research could explore ultrasound-guided injections into the infrapatellar fat pad for the knee joint.

of 1% lidocaine (BCT+US-T) (n=67). The study revealed that the BCT group required a greater number of specialist consultations (+0.14 visits) and private physiotherapy sessions (+0.33 sessions), and underwent more hip surgeries (2 vs 0) compared to the BCT+US-T group. Additionally, the mean number of sick leave days due to hip pain was significantly higher in the BCT group than in the BCT+US-T group (6.25 days vs 1.39 days). The average cost of treatment interventions was also greater in the BCT group (£327.5) relative to the BCT+US-T group (£165.8).⁷⁷ In conclusion, this trial demonstrates that the combined BCT and US-T approach resulted in superior therapeutic outcomes and lower costs, indicating that TA injection significantly improves pain relief and functional outcomes in patients with hip OA.

In addition to its ability to alleviate pain in patients with hip OA prior to surgery, a single-center retrospective cohort study has also highlighted the significance of TA administration during total hip arthroplasty.⁴⁹ In the periarticular analgesic injection (PAI) group, a 41-mL mixture comprising 20 mL of 5 mg/mL levobupivacaine, 1 mL of 40 mg/mL TA, and 20 mL of NS was injected into 87 hip joints after prosthesis implantation and before wound closure. In contrast, 113 hip joints in the control group underwent total hip arthroplasty without PAI intervention. The PAI group exhibited significantly lower Numerical Rating Scale (NRS) scores than the control group on both the first and second post-operative days (3.8 vs 4.7 and 2.2 vs 2.3, respectively). Although the potential confounding effect of local anesthetics on pain reduction must be considered, previous studies have reported that PAI with levobupivacaine and/or epinephrine did not significantly reduce postoperative pain following total hip arthroplasty,^{78,79} underscoring TA's role in rapid analgesia. Importantly, on postoperative day 7, D-dimer levels were significantly lower in the PAI group (3.9±1.8 vs 6.3±2.1), suggesting corticosteroid PAI might promote early mobilization, thereby prevent elevated D-dimer levels and potentially reduce deep vein thrombosis risk⁴⁹ (Table 2).

In reality, the actual cost of TA is relatively low. According to the analysis of Kigozi's trial, the BCT+US-T group of patients maintained longer working periods while saving £450 in societal productivity costs.⁷⁷ Hashimoto's study demonstrated that the use of TA during total hip arthroplasty provides rapid postoperative analgesia and helps prevent thrombosis.⁴⁹ Furthermore, the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Rheumatology (ACR) support the use of intra-articular corticosteroid injections for the hip—preferably under ultrasound guidance.⁴ These findings represent highly positive outcomes: TA administration in hip osteoarthritis patients can improve their quality of life and reduce both societal and individual economic burdens.

Efficacy of Knee Joint Intra-Articular Injection

Theoretically, OA can affect any joint in the body; however, the knee joint is one of the most commonly involved sites, with KOA accounting for approximately 43% of all OA cases. The condition predominantly affects the elderly and obese populations, with an estimated prevalence of 10% to 13% among older adults, which may be associated with long-term mechanical loading and cumulative wear of the knee joint.^{1,16,80} In addition to the dietary and physical activity

Table 2 Summary of the Efficacy of TA Hip Joint Intra-Articular Injection

Authors, Publication Year	Sample Size (pts)	Intervention	Follow-Up Duration	Injection Guidance	Outcomes Evaluated	Results
Kigozi et al ⁷⁷ (2025)	67	Group I: BCT Group II: 40mg TA + 4mL 1% lidocaine	6 months	Ultrasound	Surgeries, average cost of treatment	Group II provided superior outcomes at lower cost
Hashimoto et al ⁴⁹ (2021)	200	Group I: PAI Group II: total hip arthroplasty	7 days	None	NRS pain (0–10), D-dimer levels	Group I both postoperative day 1 and day 2 with lower NRS, postoperative day 7 with lower D-dimer levels

Note: PAI: 20mL 5mg/mL levobupivacaine, 1mL 40 mg/mL TA, 20mL saline (41mL mixture).

Abbreviations: TA, Triamcinolone acetonide; BCT, basic care (education and advice); NRS, Numerical Rating Scale.

modifications recommended by clinical guidelines, we aim to experimentally demonstrate the therapeutic efficacy of intra-articular administration of TA in patients with KOA.

For patients with KOA, the administration of corticosteroids prior to exercise therapy provided no additional benefit, regardless of OA severity. No significant differences were observed between the intra-articular corticosteroid group (n=50) and the placebo group (n=50) in the Knee injury and Osteoarthritis Outcome Score (KOOS) (+13.6 vs +14.8, $p=0.64$). Similarly, lower extremity muscle strength, walking distance, and functional outcomes were comparable between the two groups.⁸¹ In contrast, the use of TA during total knee arthroplasty (TKA) was associated with reduced postoperative pain and a rapid onset of action by the second day after surgery. Compared with the control group, patients in the TA group achieved straight-leg-raising earlier (2.3 days vs 2.8 days) and demonstrated better knee function improvements within six months, along with greater range of motion.⁸²

Conaghan first conducted a randomized, double-blind, placebo-controlled, multicenter phase IIb trial, in which patients were assigned to receive either 16 mg (n=102) or 32 mg (n=104) of the extended-release TA microsphere formulation (FX006), or a saline placebo (n=104). The 32 mg FX006 group exhibited a longer duration of analgesia compared to the 16 mg group (9 weeks vs 3 weeks). Although the reduction in average daily pain (ADP) at week 12 did not reach statistical significance between the 32 mg FX006 and placebo groups (-3.1 vs -2.5 , $p=0.08$), the 32 mg FX006 group demonstrated significant improvements over placebo at most time points in the McMaster Universities Osteoarthritis Index (WOMAC) pain and function subscales, as well as in the Patient Global Impression of Change (PGIC) score. The incidence of adverse events was similar across groups, with the majority being mild to moderate in severity. This trial provided the basis for subsequent Phase III clinical trials.⁷⁴ Subsequently, a phase III randomized controlled trial was conducted, where patients received an intra-articular injection of either 5 mL FX006 (n=161), 1 mL (40 mg) of standard TAcS (n=162), or 5 mL saline placebo (n=163). At week 12, the FX006 group showed a 50% improvement in ADP, which was significantly greater than that in the placebo group (-3.12 vs -2.14 , $p < 0.0001$), but not significantly different from the TAcS group. However, according to the WOMAC and the KOOS, the FX006 group exhibited significantly greater improvements in pain and physical function compared to the TAcS group at 12 weeks post-injection ($P < 0.05$).⁸³ In a study involving bilateral KOA patients who received TA-ER injections (n=70), significant pain improvement from baseline was observed: the NRS scores decreased by 4.7 ± 0.3 at 6 weeks, 3.4 ± 0.3 at 12 weeks ($p < 0.0001$), and 1.1 ± 0.3 at 24 weeks ($p < 0.0011$)⁸⁴ (Table 3).

International associations have issued specialized guidelines on intra-articular corticosteroid injections for patients with KOA. Although the American Academy of Orthopaedic Surgeons (AAOS) maintains a neutral stance, several societies—such as the American College of Rheumatology (ACR), the European Alliance of Associations for

Table 3 Summary of The Efficacy of TA Knee Joint Intra-Articular Injection

Authors, Publication Year	Sample Size (pts)	Intervention	Follow-Up Duration	Injection Guidance	Outcomes Evaluated	Results
Sean et al ⁸² (2011)	100	Group I: total knee arthroplasty Group II: 40mg TA + total knee arthroplasty	24 months	None	VAS pain (0–10), ROM, straight-leg raise, knee function	Group II enabled faster straight-leg raise, lower pain and better knee function
Conaghan et al ⁷⁴ (2017)	310	Group I: FX006 16mg Group II: FX006 32mg Group III: placebo	24 weeks	None	WOMAC, PGIC, ADP	Group II had longer analgesic duration than Group I, the overall effects of both were better than Group III

(Continued)

Table 3 (Continued).

Authors, Publication Year	Sample Size (pts)	Intervention	Follow-Up Duration	Injection Guidance	Outcomes Evaluated	Results
Conaghan et al ⁸³ (2018)	486	Group I: FX006 5mL Group II: 1mL TAcS Group III: placebo	24 weeks	None	ADP, KOOS, WOMAC	At week 12, Group I and Group II have similar effect in ADP, Group I better than Group II in KOOS and WOMAC, both better than Group III
Segal and Alm ⁸⁴ (2022)	70	TA-ER 32mg	24 weeks	Ultrasound	NRS	NRS scores decreased than baseline

Abbreviations: KOOS, Knee injury and Osteoarthritis Outcome Score; ROM, range of motion; VAS, Visual Analogue Scale; FX006, Triamcinolone acetonide microsphere sustained-release agent; WOMAC, McMaster Universities Osteoarthritis Index; PGIC, Patient Global Impression of Change; ADP, average daily pain; TAcS, standard TA crystal suspension; TA-ER, TA extended-release.

Rheumatology (EULAR), and the Osteoarthritis Research Society International (OARSI)—support the use of intra-articular injections.⁴ In summary, evidence from specific clinical trials to guidelines issued by internationally recognized authorities indicates that intra-articular TA injection is an effective and acknowledged treatment for KOA patients. Moreover, TA-ER demonstrates superior efficacy compared to conventional TA formulations in the management of KOA. However, attention must be paid to the timing of administration: injection prior to exercise training appears to offer little benefit, in severe osteoarthritis, total knee arthroplasty remains an effective option for alleviating pain and functional symptoms. Beyond this, adjunctive intraoperative and postoperative therapeutic strategies can be explored; for instance, continuous cold flow (CCF) therapy has been proposed as an effective intervention by some researchers.⁸⁵ The aforementioned findings in this study indicate that, analogous to hip arthroplasty, the application of TA in knee arthroplasty also ameliorates pain. Therefore, future consideration may be given to administering additional combined TA injections for patients with poor pain tolerance undergoing joint replacement surgery.

Efficacy of Shoulder Joint Intra-Articular Injection

OA affecting the shoulder joint has a reported prevalence ranging from 15% to 75%, which is comparable to that of the knee. The interplay among periarticular structures—including muscles, ligaments, tendons, and bursae—often contributes to the pathology, and these structures are frequently implicated as sources of pain in shoulder OA.^{1,86} This review summarizes three randomized controlled trials that evaluated the efficacy of intra-articular TA injections in the shoulder. Two of these trials were dose-comparison studies, designed as single-blind (n=61) or triple-blind (n=136), while the third investigated the effect of injection volume (n=90).

Carroll and Hong investigated the efficacy of intra-articular TA at doses of 20 mg and 40 mg in patients with shoulder pain (n=61 vs n=136). Despite differences in follow-up time points (3 days/3 weeks/6 weeks vs 2/4/8 weeks), both studies reported similar outcomes, indicating no significant differences in shoulder pain scores and functional improvement between the 20 mg and 40 mg TA groups. However, both doses demonstrated superior efficacy compared to placebo.^{86,87}

In addition to the aforementioned trials using TA injection dosage as the independent variable, Klontzas also designed a study from a volumetric perspective, in which 40 mg of TA was administered in volumes of 1 mL and 10 mL, respectively, into the subacromial-subdeltoid bursae of two subject groups (n=90). At follow-up time points of 30 minutes, 3 weeks, 3 months, 6 months, and 1 year, the 10 mL TA injection group demonstrated significantly improved Visual Analogue Scale for Pain (VAS) pain scores compared to the 1 mL group (2.6 / 2.2 / 2.0 / 1.6 / 1.0 vs 7.3 / 4.7 / 3.2 / 2.5 / 1.8). This led to the conclusion that injection volume is the critical factor for achieving both early and long-term pain relief (Table 4). Hong suggested that these outcomes may be attributed to the 10 mL mixture (corticosteroid combined with anesthetic—the latter intended to mitigate irritation caused by high-volume triamcinolone acetonide

Table 4 Summary of the Efficacy of TA Shoulder Joint Intra-Articular Injection

Authors, Publication Year	Study Design	Sample Size (pts)	Intervention	Follow-Up Duration	Injection Guidance	Outcomes Evaluated	Results
Hong et al ⁸⁷ (2011)	Randomized controlled trial, triple-blind	61	Group I: TA 20mg Group II: TA 40mg	8 weeks	Ultrasound	VAS pain (0–10), SDQ, AROM	Both of them have similar effect
Carroll et al ⁸⁶ (2018)	Randomized controlled trial, single-blind	136	Group I: TA 20mg Group II: TA 40mg	6 weeks	None	QuickDASH score, subject-reported pain, adverse events	Both of them have similar effect and improved at 2, 4, 8week
Klontzas et al ⁸⁸ (2020)	Randomized controlled trial	90	Group I: 1mL TA (40mg) Group II: 1mL TA (40mg) + 2mL 1% lidocaine + 7mL 0.25% Bupivacaine, total: 10mL	12 months	Ultrasound	VAS pain (0–10)	The VAS of the high-volume group was significantly lower than that of the low-volume group

Abbreviations: SDQ, Shoulder Disability Questionnaire; AROM, active range of motion; VAS, Visual Analogue Scale; QuickDASH score, a shortened version of the Disabilities of the Arm, Shoulder, and Hand (DASH) Outcome Measure.

injection) sufficiently distending the bursa, disrupting adhesions, and promoting uniform drug distribution, thereby facilitating early and sustained pain alleviation.⁸⁸

Based on the above trials, it can be concluded that TA is an extended-release formulation. However, its therapeutic efficacy is dose-independent, with 20 mg and 40 mg of TA demonstrating comparable effectiveness. This supports the selection of a lower dose for initial TA therapy to minimize unnecessary drug utilization in clinical practice.

Efficacy of Hand Joint Intra-Articular Injection

OA affecting the hand is relatively common and can be further categorized into radiographic OA (prevalence: 21–92%) and symptomatic OA (prevalence: 3–16%).¹ Long-standing erosive hand osteoarthritis (EHOA) is considered a variant of hand OA, characterized by severe local inflammation and progressive joint degeneration.⁸⁹

In a novel approach, Spolidoro administered intra-articular injections of THA 20 mg/mL combined with 2% lidocaine (LID) into the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the hand. A comparative analysis between the experimental group (THA + LID, n=30) and the control group (LID alone, n=30) revealed that at the 1-, 4-, 8-, and 12-week follow-ups, the experimental group showed significant improvements in movement-induced pain (VASm) (mean values: 3.9, 2.8, 1.8, 2.2 vs 4.1, 3.0, 4.0, 4.0; P=0.014) and joint swelling (VASs) (mean values: 2.0, 1.4, 0.7, 1.1 vs 2.1, 2.0, 1.8, 2.0; P=0.022). The treatment was well tolerated, with no between-group differences observed in transient discomfort or increased pain within 48 hours post-injection.⁹⁰

In a study by Favero evaluating the efficacy of ultrasound-guided intra-articular injection of 40 mg/mL TA in 12 patients with EHOA, targeting both the DIP and PIP joints, significant reductions in joint effusion, capsular distension, and synovial hypertrophy were observed at 1-, 3- and 6-months post-injection. The proportion of joints achieving a VAS pain score of 0 was 48.38%, 42.86%, and 22.58% at 1-, 3- and 6-months, respectively. At the 6-month follow-up, the prevalence of joint effusion decreased from 66.7% at baseline to 19.4%; synovial thickening declined from 92.3% to 29.0%; and capsular distension was reduced from 96.6% to 41.9%. Regarding safety, Favero highlighted favorable post-injection outcomes with no reported serious adverse events. Following the 2018 EULAR recommendations, which support the consideration of intra-articular glucocorticoid injections for painful interphalangeal joints with clear

inflammatory features, this study provides evidence for an effective localized treatment strategy utilizing ultrasonography to target inflammation in EHOA—a relatively uncommon disorder.⁹¹

Despite the relatively small sample size, the findings nevertheless demonstrate the local efficacy and tolerability of intra-articular TA injections at this specific anatomical site.

Exploring Standardized Use and Personalized Protocols in the Era of Precision Medicine

Common Doses

In a 12-week multicenter, double-blind, randomized controlled trial, Popma investigated the efficacy of intra-articular knee injections of 40 mg (n = 49) versus 80 mg (n = 48) of TA in patients with KOA. A significant reduction in the Likert burden score and VAS pain score was observed in both groups as early as the first week post-injection. However, no statistically significant difference was found between the 40 mg and 80 mg groups in terms of the rate of good response (defined as an improvement of ≥ 2 points on the Likert burden scale) over the 12-week period (49% vs 55%). Similarly, there were no significant differences in VAS pain scores, arthritis activity, swelling reduction, or functional improvement between the two doses.⁹² In line with these findings, studies by Carroll and Klontzas also reported no significant differences in pain relief or functional improvement between 20 mg and 40 mg TA injections in the shoulder joint.^{86,88} Additionally, it has been reported that the use of TA at doses exceeding recommended levels (> 40 mg per month) or with frequent administration may lead to adverse effects. For instance, a 34-year-old female developed typical iatrogenic Cushing's syndrome following monthly injections of 100 mg TA.⁹³

The aforementioned controlled trial indicates that intra-articular TA injection does not exhibit a dose-dependent effect in terms of clinical efficacy. A 20 mg dose of TA provides pain relief and functional improvement comparable to that of a 40 mg dose post-injection, and a similar relationship is observed between 40 mg and 80 mg doses. Moreover, long-term administration of higher doses may lead to adverse events such as iatrogenic Cushing's syndrome. These findings offer critical insights for clinical practice: to minimize both pharmaceutical waste and the incidence of adverse reactions, it is estimated that the recommended dosage for intra-articular injection of TA is 20 to 40mg. Nevertheless, the precise optimal dose within this range warrants further investigation and validation in future studies.

Importance of Ultrasound Guidance for Accurate Injection

Ultrasound, as a well-established two-dimensional imaging technique, offers the advantages of being non-invasive, cost-effective, and capable of repeated examinations.⁹⁴ It can be used both for localizing inflammatory sites and for guiding needle insertion, thereby enabling “precision-guided” drug delivery, which is of significant importance in facilitating intra-articular injections. In a study by Soh, the efficacy of ultrasound-guided versus blind corticosteroid shoulder injections was evaluated. At six weeks post-injection, the ultrasound-guided group demonstrated significant improvements in both pain and shoulder function, with a mean difference of 2.23 in the VAS pain score and 1.09 in the Constant-Murley shoulder score. Moreover, the ultrasound-guided group experienced fewer adverse events.³⁷ In the treatment of OA, ultrasound guidance allows for precise localization and anti-inflammatory drug injection into the affected site, which can further delay disease progression and lead to improved therapeutic outcomes.

Efficacy Evaluation of Combination with Hyaluronic Acid (HA)

Intra-articular TA, as a monotherapy for OA, often proves insufficient for adequate symptom relief and quality-of-life improvement. Under these circumstances, combining TA with other pharmacotherapies, such as hyaluronic acid (HA), presents a viable therapeutic strategy. The superior efficacy of this combination approach will be demonstrated through references to three prospective clinical trials.

In a 26-week follow-up study of patients with KOA (n=98), Petrella found that combined intra-articular administration of TA (Hydros-TA, HA + 10 mg TA) provided more rapid pain relief compared to HA (Hydros, Hyaluronic acid-based hydrogen gel suspended in a hyaluronic acid solution) alone, with significant pain improvement observed within 2 weeks (WOMAC difference: 12.4 mm, p = 0.04). By week 26, the Hydros-TA group showed a 30.0 mm improvement in WOMAC function scores. Moreover, the tolerability of Hydros-TA was comparable to that of Hydros, with no

additional adverse events reported.⁹⁵ Tammachote et al evaluated knee pain, function, and range of motion over 6 months (n=99) and reported no statistically significant differences between the HA-only (cross-linked) and HA+TA groups at the 6-month endpoint. However, the HA+TA combination demonstrated superior pain relief at 1 week and functional improvement at 2 weeks.⁹⁶ A prospective observational study investigated pain and functional outcomes as well as adverse events following intra-articular HA (cross-linked) +TA injection in the hip over 6 months (n=100). Among the 91 patients who completed follow-up, the mean VAS pain score improved by 19.2 points. Sixteen patients no longer required analgesic medication after treatment. Positive hip impingement test rates decreased from 85.3% to 62.8% for anterior impingement and from 56.8% to 30.8% for posterior impingement. All HOOS function subscales showed significant improvements (pain: 12.7 points; activities of daily living: 10.9 points; quality of life: 13.5 points; etc., $p < 0.001$). Hip flexion range improved from 103.3° to 115.4° in 78 patients with bilateral involvement. The adverse event rate was 9.5% (9/91), mostly transient pain (5.3% lasting <7 days). Serious events included three arthroplasty cases (1 fracture, 2 due to OA progression), deemed unrelated to the injection.²⁹

The aforementioned three sets of trials demonstrate that, compared with HA injection alone, intra-articular injection of HA combined with TA provides enhanced short-term rapid analgesic effects in patients with osteoarthritis, with sustained improvements in joint pain and function lasting up to six months. Moreover, the combination therapy was associated with no serious adverse events, indicating a relatively safe treatment option. These findings may assist in the development of additional individualized non-surgical management strategies for OA patients, tailored to their specific needs. Clinicians can consider patients' pain levels, functional status, and overall health status to design combined interventions that address individual requirements.

Previous studies have indicated that intra-articular injection of HA can reduce the concentration of matrix metalloproteinase (MMP)-9 in synovial fluid.⁹⁷ Since MMPs can promote chondrocyte degradation, HA is considered to exert a chondroprotective effect.⁹⁸ Although glucocorticoid injections exhibit potent anti-inflammatory properties, they may also cause some degree of cartilage damage. Therefore, it is hypothesized that the combination of HA and TA in intra-articular injections may allow HA to counteract the cartilage damage induced by TA, while TA could compensate for the limitations of HA in terms of pain relief and anti-inflammatory efficacy, thereby resulting in superior therapeutic outcomes. However, all three prospective trials discussed here are limited by small sample sizes and the absence of placebo-controlled groups. Moreover, the potential chondrotoxic effects of TA were not assessed. Thus, the proposed hypothesis has not been fully validated. Further studies with improved methodological rigor are warranted to substantiate these findings.

Safety and Adverse Reactions

Local Adverse Reactions

Intra-articular TA injection for the treatment of OA has been demonstrated to induce several localized dermatological adverse effects, with transient facial flushing being the most frequently reported.³⁵ Case reports have described systemic allergic dermatitis manifesting as symmetrical drug-related intertriginous and flexural exanthema and erythema multiforme-like eruptions.⁹⁹ Additionally, rare ischemic reactions in the feet have been observed in the absence of ischemia, temperature changes, or diminished pulses.¹⁰⁰ Atrophic linear plaques accompanied by hyperpigmentation and cutaneous atrophy have also been documented; however, these must be differentiated from linear scleroderma, which requires immunosuppressive therapy.¹⁰¹

But the aforementioned studies indicate that these adverse effects subside spontaneously after drug discontinuation. This observation, to some extent, provides supporting evidence for the safety profile of intra-articular TA in the local treatment of OA, suggesting an absence of severe local adverse reactions.

Systemic Adverse Reactions

Transient Hyperglycemia

Following intra-articular injection of 18mg TA into either the intercarpal joint (n=10) or the sacroiliac joint (n=10), both groups exhibited significant elevations in blood glucose levels starting at 1-hour post-injection, which persisted for up to

72 hours.⁶⁹ The rapid egress of corticosteroids from the joint space may lead to high systemic peak concentrations of TA after conventional TA (TAc) injections in human joints, resulting in several days of hyperglycemia following administration. In contrast, the extended-release characteristics of TA-ER result in lower systemic exposure, with peak plasma concentrations approximately 80% lower than those observed with TAc, thereby significantly attenuating glycemic fluctuations and minimizing the impact on blood glucose levels.¹⁰² Both animal studies and clinical trials have demonstrated transient acute hyperglycemia following intra-articular TA injection. Notably, approximately 30% of patients with type 2 diabetes also suffer from KOA.¹⁰² Consequently, particular attention to glycemic variability is warranted when performing intra-articular TA injections in OA patients with comorbid diabetes.

Hypothalamic-Pituitary-Adrenal Axis (HPAA) Suppression

A notable and potentially serious side effect associated with TA use is the suppression of the hypothalamic-pituitary-adrenal axis (HPAA), which may lead to secondary adrenal insufficiency (SAI).^{71,103} A systematic review encompassing 3753 patients found that intra-articular corticosteroid injections were associated with the highest incidence of SAI (52.2%) compared to other routes of administration.¹⁰⁴ In a comparative study, 40 mg of methylprednisolone acetate (MA) and the same dose of TA were administered via intra-articular injection into the shoulder joint. Due to differences in pharmacokinetics, cortisol recovery was significantly slower in the TA group at 7 days post-injection compared to the MA group ($P < 0.0001$). Moreover, 24-hour urinary free cortisol levels remained below baseline at 45 days post-injection, indicating that TA-induced HPAA suppression persisted throughout the 45-day observation period. Although none of the patients in this trial exhibited clinical symptoms, the findings suggest that subclinical HPAA suppression is common.⁷¹ Therefore, caution is warranted when administering intra-articular TA injections in patients with OA.

Psychiatric Abnormalities

While the psychiatric impact of systemic corticosteroids may be more widely recognized, Malladi reported a particularly rare case of intra-articular corticosteroid injection inducing neuropsychiatric adverse effects. A 51-year-old female received three sequential intra-articular injections of 40mg TA for KOA. Following the first injection, she exhibited suicidal behavior requiring hospitalization within 10 days. The second injection precipitated extreme agitation, delusions, and suicidal ideation within 3 days, necessitating police intervention and involuntary psychiatric admission. After the third injection, the patient discontinued long-term psychiatric follow-up and was lost to follow-up. Notably, the patient maintained psychiatric stability prior to each episode, with no documented history of suicidality or prior psychiatric hospitalizations.¹⁰⁵

Clinical Implications for Cartilage

Although debates persist regarding the toxicity of TA toward chondrocytes from a mechanistic perspective, its adverse effects on cartilage in clinical trials involving intra-articular injections are significant enough that clinicians cannot afford to overlook them.

According to clinical trial findings, six months after intra-articular TA injection in 12 patients with knee osteoarthritis (KOA), histological analysis of eight knee samples per patient revealed cartilage degeneration in 16.67% of the subjects, whereas no such degeneration was observed in the untreated control group.³⁴ A randomized, double-blind, placebo-controlled trial was conducted in which the experimental group received intra-articular injections of TA (40 mg/1 mL) every 12 weeks over a period of 2 years ($n = 70$), while the control group received saline injections (1 mL) on the same schedule ($n = 70$). The results showed a greater reduction in the inter-space cartilage thickness index in the TA group compared to the control group, with a mean change of -0.21 mm versus -0.10 mm, respectively—a difference of 0.11 mm. This indicates that TA was associated with significantly greater cartilage loss compared to saline, suggesting that long-term use of TA may have adverse effects on cartilage integrity.¹⁰⁶

Conclusion and Future Perspectives

This article provides a comprehensive review of the mechanism of action of triamcinolone acetonide, its current clinical applications in osteoarthritis, therapeutic efficacy, and post-administration safety profile (Figure 4). TA, as a long-acting

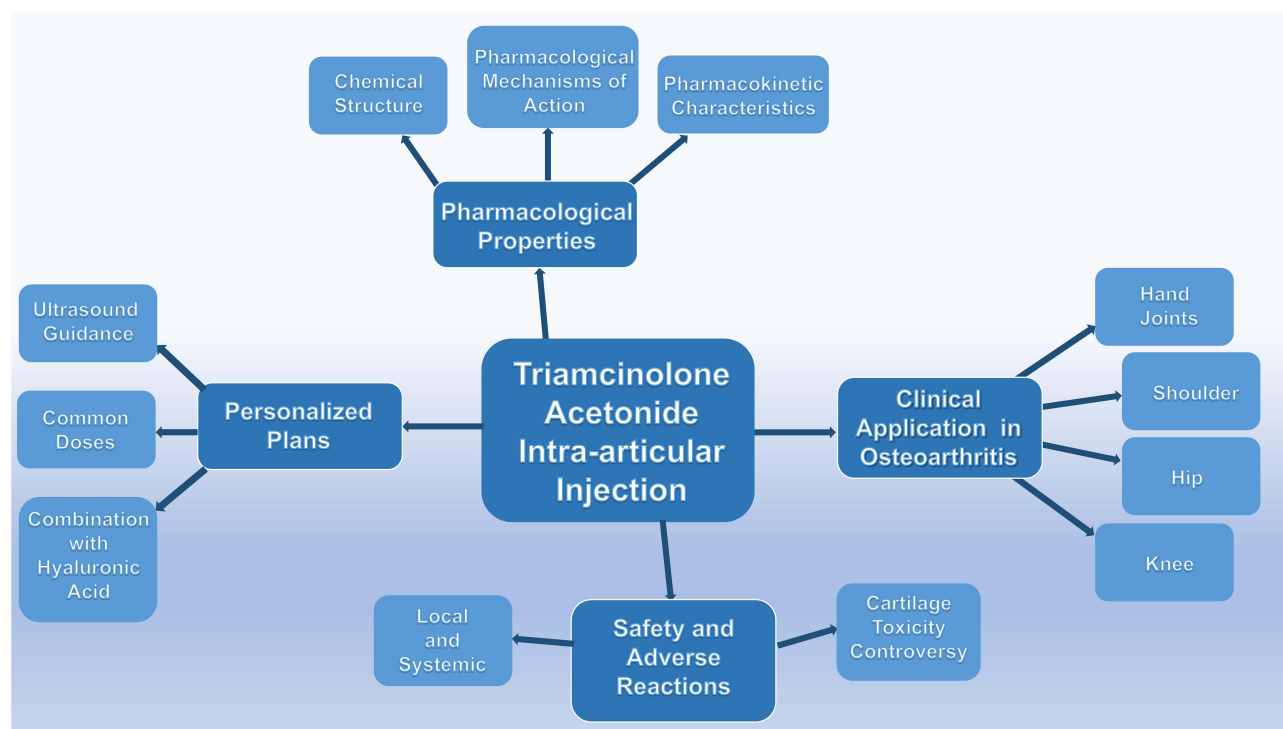


Figure 4 This article focuses on the intra-articular injection of triamcinolone acetonide, providing a detailed elaboration and discussion across four key aspects: pharmacological properties, personalized treatment plans, clinical application in osteoarthritis, and safety profile and adverse reactions.

glucocorticoid, continues to be a valuable agent in clinical practice. Despite being a well-established drug, it has garnered renewed widespread attention in the non-surgical management of OA due to its potent anti-inflammatory and immunomodulatory effects. Its ability to concurrently address both inflammation and analgesia allows it to achieve therapeutic goals for OA at two levels: targeting the underlying pathological mechanisms and alleviating clinical symptoms, making it an effective tool for OA symptom management. However, its use requires careful consideration. Firstly, because intra-articular injection can cause significant discomfort for patients, it often needs to be co-administered with a local anesthetic such as lidocaine. Secondly, although the overall post-injection efficacy profile of TA is generally safe, it can still induce certain adverse effects in patients, including rare dermatological and psychiatric symptoms, which clinicians must differentiate from other conditions. Furthermore, studies in both animal models and human trials have indicated that TA administration can impact the endocrine system, leading to transient hyperglycemia and suppressed cortisol levels. Therefore, clinical application must take into account the patient's individual health status. Finally, the potential impact of TA on articular cartilage remains a subject of debate, necessitating further long-term, large-sample clinical studies to clarify its chondrotoxic safety profile. Recent studies have demonstrated that the introduction of sliding-ring polyrotaxane and conductive polypyrrole esters into hydrogel microspheres through supramolecular engineering and microfluidic techniques, enabling the construction of stress-electrically coupled hydrogel microspheres, as well as the application of precise cellular electrical stimulation therapy using these electro-mechanically active hydrogel microspheres, can promote cartilage healing. These combined approaches can be utilized for the repair of cartilage injuries.^{107,108}

With the advancement of the era, ultrasound and other imaging technologies can provide targeted guidance for injections, which to some extent reduces the incidence of complications and improves therapeutic efficacy. The novel sustained-release material loaded with TA demonstrates lower systemic exposure and longer-lasting efficacy without inducing additional adverse events, making it worthy of promotion and application. Future studies may further explore treatment strategies involving TA in combination with drugs other than HA to investigate potential synergistic effects between therapeutic agents. Furthermore, another study has demonstrated that the application of ultrasound-responsive

piezoelectric analgesic microspheres, constructed using ultrasound and piezoelectric nanomaterials in rats, can significantly improve pain-related behaviors and joint pathological damage. Further in-depth validation is warranted in the future to demonstrate their therapeutic efficacy for pain and joint damage associated with human osteoarthritis.¹⁰⁹

For OA, emerging research advancements indicate that it is frequently associated with extensive effects on periarticular structures, including cartilage degradation, ligament injury, subchondral bone remodeling, and inflammatory manifestations involving the synovium.¹ Due to their anatomical proximity and functional interconnections and interdependence, if one periarticular structure is traumatized or inflamed, others may also be affected. In the knee joint, the infrapatellar fat pad (IFP, also known as Hoffa's fat pad) is a particularly important and unique anatomical structure compared to those in other joints throughout the body. Adjacent to the synovium, it serves specific mechanical roles by providing cushioning to protect the knee joint and is believed to contribute to the blood supply—via the genicular rete arteriosum—to the anterior cruciate ligament, patella, and patellar tendon. However, with ongoing research, the IFP has been found to play a dual role in the pathogenesis of OA,¹¹⁰ being closely associated with pain and inflammation in KOA. It involves not only immune cells, typically represented by mast cells, but also a range of cytokines including interleukins, natural killer cells, substance P, and calcitonin gene-related peptide, in addition to being richly innervated.^{18,111} Whether anti-inflammatory therapy targeting the IFP can alleviate KOA symptoms and disease progression is increasingly attracting researchers' attention. This paper has already discussed the application and superior efficacy of TA in systemic OA. In the future, leveraging TA's anti-inflammatory and analgesic mechanisms, ultrasound-guided injection of TA-loaded novel materials into the IFP could be utilized to explore whether this approach can effectively delay the progression of KOA (Figure 3).

With the application of novel biomaterials and precise targeting techniques, we believe that TA holds great promise in the future management of OA. It may serve as a non-surgical intervention to delay disease progression and alleviate symptoms, thereby reducing healthcare expenditures and optimizing medical resources for both patients and society, while simultaneously enhancing social satisfaction and workforce productivity.

Despite its contributions, this review has several limitations. First, from a methodological standpoint, our search strategy focused exclusively on peer-reviewed journals indexed in the PubMed, potentially excluding relevant findings from books and conference proceedings (methodological limitation). Second, this article, due to its focus on the use of TA in the treatment of osteoarthritis, predominantly highlights its therapeutic efficacy when compared to alternative treatments. However, many other therapies have also demonstrated positive outcomes through research, which, owing to space constraints, are not as prominently featured in this text—potentially leading to a subtle bias (theoretical limitation).

Abbreviations

APC, Serine Protease-activated Protein C; AUC, The Area Under the Concentration-time Curve; AAOS, the American Academy of Orthopaedic Surgeons; ACR, the American College of Rheumatology; ADP, Average Daily Pain; BCT, Basic Conservative Treatment; CRP, C-reactive Protein; CK, Creatine Kinase; DIP, Distal Interphalangeal; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis; EULAR, European Alliance of Associations for Rheumatology; EHOA, Erosive Hand Osteoarthritis; GC, Glucocorticoid; GAG, Glycosaminoglycan; HA, Hyaluronic Acid; HPAA, Hypothalamic-pituitary-adrenal Axis; IL, Interleukin; IC, Intercarpal; IV, Intravenous; IM, Intramuscular; IA, Intra-articular; KOA, Knee Osteoarthritis; KOOS, the Knee injury and Osteoarthritis Outcome Score; KL, Kellgren-Lawrence Grade; LID, Lidocaine; MRI, Magnetic Resonance Imaging; MMP, Matrix Metalloproteinase; MA, Methylprednisolone Acetate; NSAIDs, Non-Steroidal Anti-inflammatory Drugs; NS, Normal Saline; NRS, Numerical Rating Scale; OA, Osteoarthritis; OARSI, Osteoarthritis Research Society International; PRP, Platelet-rich Plasma; PAI, Periarticular Analgesic Injection; PGIC, Patient Global Impression of Change; PIP, Proximal Interphalangeal; sC2C, Serum Cartilage Type II Collagen Cleavage by Collagenase; sCPII, Serum Cartilage Type II Procollagen Carboxy Propeptide; SI, Sacroiliac; SAI, Secondary Adrenal Insufficiency; sCOMP, Serum Cartilage Oligomeric Matrix Protein; TA, Triamcinolone Acetonide; TNF, Tumor Necrosis Factor; THA, Triamcinolone Hexacetonide; TA-ER, TA Extended-release; TAcS, Triamcinolone Acetonide Crystalline Suspension; uCTX-II, Urinary C-terminal Telopeptide of Type II Collagen; uNTx, Urinary Bone N-terminal Crosslinking Telopeptide of Type I Collagen; US, Ultrasound; VAS, Visual Analogue Scale for Pain; WOMAC, McMaster Universities Osteoarthritis Index.

Ethics Approval

This narrative article contains no original data, so issues of ethics, informed consent, and patient confidentiality do not apply.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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