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PRACTICAL ISSUES AND UPDATES

Towards intra-articular therapies for more than just symptom management in osteoarthritis

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Abstract
Osteoarthritis is a chronic condition that causes pain and loss of joint function. While currently recommended intra-articular therapies (e.g. corticosteroids and hyaluronic acid) can alleviate some of the symptoms of osteoarthritis, they are currently unable to alter the course of disease progression, and the duration of symptom relief is generally short-term. New therapies are under evaluation for treatment of osteoarthritis; these aim to reverse the pathological structural changes associated with the disease and provide longer-lasting pain relief. This article summarises recent guideline recommendations for intra-articular therapies and highlights some of the new therapies currently in clinical evaluation.

Osteoarthritis is a condition involving inflammation and structural changes in the joint

Osteoarthritis is one of the most common chronic health conditions, and its incidence is on the rise [1]. It is common in older patients, with symptomatic osteoarthritis occurring in 10% of men and 18% of women aged ≥ 60 years [1]. Osteoarthritis is a chronic condition that progresses over many years [2]. It commonly occurs in one or more joints of the knee, hip, hand or foot [1]. The symptoms of osteoarthritis include pain, swelling and a loss of joint function [3]. Osteoarthritis can be caused by pathological changes in the bone, cartilage or synovium [2]. Typically, loss of bone is common in early osteoarthritis and reduced bone reabsorption is seen in late-stage disease. Loss of cartilage is also associated with osteoarthritis and can lead to cartilage softening, fibrillation, and fissuring of superficial layers. Inflammation of the joint synovium, with associated increase infiltration of immune cells and release of inflammatory cytokines, is also common in patients with this disease [2].

Treatments currently used in the clinic focus on symptom management; none of the currently approved treatments for osteoarthritis are effective in delaying or reversing structural damage to the joint [2]. Most guidelines strongly recommend exercise and educational approaches for patients with osteoarthritis [4–6]. In addition to these treatments, pharmacological therapies are often required. Nonsteroidal anti-inflammatory drugs (NSAIDs) are strongly recommended, with topical preferred over oral administration due to the risk of adverse events (AEs). If adequate pain relief is not achieved with NSAIDs, or if patients have pre-existing comorbidities which preclude their use, intra-articular therapies involving corticosteroids or hyaluronic acid are often recommended [4, 6].

Ideally, therapy for osteoarthritis involves not only pain relief but also prevention of further joint damage [3]. A number of intra-articular therapies currently in clinical evaluation aim to repair damage to the joint by correcting pathological changes in bone and cartilage remodelling. These approaches will be of more benefit to some patients than others, and tools that can stratify patients with osteoarthritis into subgroups to identify likely responders are sorely needed [7]. Additionally, new intra-articular therapies designed for longer-term pain relief are also being evaluated [3].

This article briefly summarises the intra-articular therapies currently used in the clinic and the recommendations for their use according to recent guidelines, including from the American College of Rheumatology (ACR) [4]; the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [5]; and the Osteoarthritis Research Society International (OARSI) [6], and highlights the new intra-articular therapies

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currently being evaluated in clinical trials for treatment of osteoarthritis as reviewed by Assi et al. [3].

Consider intra-articular therapies for treatment of osteoarthritis ...

Intra-articular corticosteroids and hyaluronic acid have a long history of use in the clinic for treatment of osteoarthritis [8, 9]. The advantage of intra-articular therapies is that they directly deliver drugs to the joint [3]; this can be quite effective given that osteoarthritis is typically a localised disease. Furthermore, this has the effect of limiting off-target systemic effects of treatment [3]. There is a small but significant risk of infection with intra-articular injection, particularly with corticosteroids [10], as well as technical difficulties in accessing some joints (e.g. hip and small joints of the hand) [3] and requires a skilled practitioner to administer. For injections into the hip, the ACR recommends use of ultrasound to guide the injection [4]. In the clinic, approximately 38% of patient with knee osteoarthritis receive intra-articular corticosteroids and approximately 13% receive intra-articular hyaluronic acid [11].

There is also recent interest in platelet-rich plasma as an intra-articular therapy for osteoarthritis and there is some evidence to support its efficacy [12]; however, the ACR [4] and the OARSI [6] guidelines strongly recommend against its use in knee and hip osteoarthritis due to inconsistencies in its formulation and because the evidence to support its efficacy come from low quality trials. There is no recommendation on the use of intra-articular platelet-rich plasma for hand osteoarthritis due to lack of data [4].

...including corticosteroids...

Guideline recommendations for intra-articular corticosteroids in knee, hip and hand osteoarthritis are mixed, but generally favours its use in these indications (Table 1). Most studies of intra-articular corticosteroids have been in the knee [3]. The evidence supports the use of intra-articular corticosteroids for short-term pain relief in knee and hip osteoarthritis but not in hand osteoarthritis (Table 1). The effect size and duration of effect of intra-articular corticosteroids in knee osteoarthritis varied between trials [10, 13, 14]; differences in the formulation (water soluble, insoluble, slow-release) and dose of corticosteroids may account for some of these variations [10, 14]. The class of corticosteroid used is not thought to have a large impact on efficacy [3]. There have been reports of rapid destructive osteoarthritis following intra-articular corticosteroid injection but there is insufficient evidence that this is linked to use of intra-articular corticosteroids and may instead be due to underlying disease [10, 13].

...and hyaluronic acid

Hyaluronic acid is the main component of the synovial fluid and cartilage matrix; it provides lubrication to joints and protects cartilage from mechanical degradation [15]. Guideline recommendations for use of hyaluronic acid in knee osteoarthritis is mixed, while limited guidance is available for other joints (Table 1). The evidence generally supports the use of intra-articular hyaluronic acid for reducing pain in patients with osteoarthritis (Table 1) [15–17]. There is heterogeneity between study outcomes [17] and some controversy as to whether the effect size is clinically relevant [4, 18]. Variability in study protocols including frequency of administrations and type of hyaluronic acid used (e.g. differences in molecular weight, animal or recombinant in origin, whether or not it is conjugated to other active drugs) may also contribute to the heterogeneity in the efficacy of intra-articular hyaluronic acid [16].

A number of new intra-articular therapies are being investigated in osteoarthritis

New intra-articular therapies for treatment of osteoarthritis are currently undergoing clinical evaluation (Table 2). A better understanding of the pathology behind osteoarthritis and advances in new methods of delivery of therapeutic substances are driving the development of new classes of treatments for the disease [2, 3]. Identification of key proinflammatory cytokines that are involved in pain and destruction of joint tissue has aided in the development of many immunomodulatory therapies; additionally, the signalling involved in bone and cartilage remodelling have also been targeted [3]. Slow-release formulations are being evaluated to develop therapeutic options with longer durations of effect. Similarly, gene therapies allow for release of therapeutic signalling molecules for longer durations of time [3]. The evidence for efficacy of these new intra-articular therapies currently under investigation is summarised in Table 2.

The primary endpoint in most studies was statistically significant benefit but whether improvements were clinically significant was not assessed (Table 2). Identifying intra-articular therapies with significant clinical responses can be challenging given the large effect size and interpatient variability of placebo responses with this mode of drug administration [21]. Notably, studies that involve multiple injections and with a longer duration (≈12 weeks or more) are more prone to placebo responses [21].

Table 1 Intra-articular therapies used in the clinic for treatment of osteoarthritis

Therapies	Comments
Anti-inflammatory	
Corticosteroids (e.g. triamcinolone, methylprednisolone, fluticasone, dexamethasone)	*Recommendation*: recommendations are generally in favour of its use for pain relief in OA, with strong recommendations in favour of its use for knee and hip OA and a conditional recommendation for hand OA in the ACR guidelines [4], a weak recommendation in favour of its use for knee OA in the ESECO guidelines [5], a conditional recommendation in favour of its use in knee OA and no recommendation for hip OA in the OARSI guidelines [6]; may be used ahead of NSAIDs in older pts and pts at risks of cardiovascular or GI AEs according to the ESCEO and OARSI guidelines [5, 6]
	Evidence: in meta-analyses of clinical trials, ↓ pain and improved function compared with placebo in pts with knee [13, 14] and hip OA [10] but lacked evidence of efficacy in hand OA [19]; pain relief was generally short-term, with pain relief up to 16 weeks reported in knee OA [13, 14] and 1–3 months in hip OA [10]; safety was rarely reported in knee OA studies [13, 14], with some reports of transient redness [13]; in hip OA the most common AE was post injection flare [10]
Slow-release corticosteroids (e.g. FX006, Cingal)	*Recommendation*: recommendations are the same as for use of intra-articular corticosteroids in general; there are currently insufficient data to recommend slow-release formulations over other formulations [4]
	Evidence: FX006 ↓ pain compared with placebo in the short-term in pts with knee OA in phase 3 clinical trials; Cingal is approved in Europe and other countries worldwide but its approval is on hold in the USA after it failed to ↓ pain compared with placebo in pts with knee OA in a phase 3 trial [3]
Viscosupplementation	
Hyaluronic acid	*Recommendation*: a mix of recommendations for its use in OA, with conditional recommendations against its use for hand and knee OA and a strong recommendation against its use for hip OA in the ACR guidelines [4], a weak recommendation in favour of its use in knee OA in the ESCEO [5], a conditional recommendation in favour of its use for knee OA and no recommendations for hip OA in the OARSI guidelines [6]; may be used ahead of NSAIDs in older pts and pts at risks of cardiovascular or GI AEs according to the ESCEO and OARSI guidelines [5, 6].
	Evidence: ↓ pain compared with placebo for ≈3–6 months in pts with knee OA in meta-analyses of clinical trials [15–17]; provided a small but statistically significant reduction in pain and improvement in function compared with oral NSAIDs according to one meta-analysis [20]; safety is not often reported in these trials but in those that do, arthralgia and joint swelling are the most common AEs [15]

ACR American College of Rheumatology, *AE* adverse event, *GI* gastrointestinal, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OA* osteoarthritis, *pts* patients, ↓ reduce(d)

Short-term pain relief and improved function may be achieved with anti-inflammatory and immunomodulatory therapies

Intra-articular therapies targeting inflammation, include new slow-release formulations of corticosteroids, NSAID-hyaluronate conjugates, as well as drugs that target specific immunological pathways which can reduce inflammation but may also modify structural aspects of disease (Table 2). In clinical trials, slow-release corticosteroids (EP-104IAR, TLC599) reduced pain in the short-term, as did the intra-articular NSAID-hyaluronate conjugate (Table 2).

A number of new therapies modulate specific immune pathways [interleukin (IL)-10, transforming growth factor (TGF)-β1, IL-1, tumour necrosis factor (TNF)] and can reduce inflammation but may also improve joint structure [2, 3]. Gene therapy to promote expression of IL-10 was efficacious in reducing pain and improving function (Table 2). Cell and gene therapy with TissueGene-C, involving intra-articular injection of TGF-β1-expressing cells, also successfully reduced pain and improved function, and these improvements were observed up to 12 months after administration (Table 2). Although TissueGene-C was briefly approved in South Korea, this approval has since been withdrawn due a discrepancy between the cell type that was provided and what was written in the product manufacturing data [3]. The evidence supporting use of anti-TNF and anti-IL-1 therapies are still limited (Table 2).

Structure modifying therapies may have long-term effects on disease

Intra-articular structure-modifying drugs aim to slow decline or reverse joint damage in patients with osteoarthritis and

Table 2 Intra-articular therapies under investigation for treatment of osteoarthritis [3]

Therapies	Comments
Anti-inflammatory and immunomodulatory	
Slow-release corticosteroids (e.g. EP-104IAR, TLC599)	TLC599 significantly[a] ↓ pain and improved function at 24 weeks compared with placebo in pts with knee OA in a phase 2 trial [22]
	There was a trend towards ↓ pain over 12 weeks with EP-104IAR compared with placebo in pts with knee OA in a phase 1 trial [23]
Diclofenac-hyaluronate conjugate (SI-613)	Significantly[a] ↓ pain over 12 weeks compared with placebo in pts with knee OA in a phase 3 trial [24]
TGF-β1 expression with cell and gene therapy (TissueGene-C)	Significantly[a] ↓ pain and improved function at 6 months to 12 months after injection compared with placebo in pts with knee OA in a phase 3 trial [25]; associated with a higher incidence of AEs compared with placebo [25]
Anti-TNF (adalimumab, infliximab, etanercept)	Limited pain relief in pts with knee and hand OA in small clinical trials; not recommended in ACR guidelines due to the potential of serious AE [4]
IL-10 expression with gene therapy (XT-150)	Provided pain relief in pts with knee OA in a phase 1 trial [3]; significantly[a] improved function compared with placebo on day 120 and 180 in pts with knee OA in phase 2 trials [26]; has 2021 FDA Fast Track designation for OA
Anti-IL-1 (anakinra, canakinumab)	Did not ↓ pain in pts with OA in clinical trials; ongoing studies of these drugs as structure modifying-treatments and efficacy in preventing OA progression in early onset OA; not recommended in ACR guidelines due to the potential of serious AE [4]
IL-1Ra expression with gene therapy (FX201)	Pain relief in two out of five pts with knee OA in a phase I trial
Structure-modifying	
Recombinant FGF18 (sprifermin)	Increased changes in femorotibial cartilage thickness compared with placebo after 2 years in pts with knee OA who were at risk of further OA progression in a phase 3 trial [27]; pain was not significantly ↓ compared with placebo [27]
Wnt signalling modulator (lorecivivint, LNA043)	Lorecivivint did not ↓ pain or promote structural changes in the joint (joint space width) compared with placebo in pts with knee OA at week 13 in phase 2 trials [28] but did significantly[a] ↓ pain and improve function at week 52 in pts with unilateral OA knee pain [28] and at week 12 and 24 in pts with a pain score of < 4 on the NRS pain scale in the untreated knee [29]
	LNA043 significantly[a] improved cartilage regeneration for up to 28 weeks in pts with OA associated with femoral articular cartilage lesions in early clinical trials [30]; LNA043 has 2021 FDA Fast Track designation for OA
MEPE peptide (TPX-100)	Significantly[a] ↓ pathological bone changes compared with placebo at 6 and 12 months in pts with knee OA in a phase 2 trial [31]
Kartogenin mimetic (KA-34)	There was a trend towards ↓ pain, stiffness and physical function in pts with knee OA in a phase 1 trial
Pain	
TRPV-1 channel agonist (CNTX-4975, MTX-071)	CNTX-4975 significantly[a] ↓ pain at week 12 and 24 compared with placebo in pts with knee OA in phase 2 trials [32] but efficacy failed to reach significance in phase 3 trials; has 2018 FDA Fast Track designation for OA [3]
	MTX-071 ↓ pain for 6–12 months and improved function in pts with knee OA in early clinical trials

ACR American College of Rheumatology, *AE* adverse event, *FDA* US Food and Drug Administration, *FGF18* fibroblast growth factor 18, *IL* interleukin, *IL-1Ra* interleukin-1 receptor antagonist, *MEPE* matrix extracellular phosphoglycoprotein, *NRS* numerical rating *OA* osteoarthritis, *pts* patients, *TGF-β1* transforming growth factor β1, *TNF* tumour necrosis factor, *TRPV-1* transient receptor potential cation channel subfamily V member 1, ↓ reduce(d)

[a] $p < 0.05$ vs. placebo or comparator

involves drugs that reduces loss or promotes growth of cartilage as well as drugs that reduce pathological bone changes associated with osteoarthritis [2]. In clinical trials, cartilage thickness was improved with sprifermin and LNA043, and pathological bone remodelling was reduced with TPX-100 (Table 2). Functional improvements and pain relief in a subset of patients receiving lorecivivint were also reported (Table 2). Although structural improvements are observed with many of these treatments it is not currently clear if these changes will translate into symptomatic improvements

(Table 2). In the trials where pain is reduced (e.g. with lorecivivint), this was only seen in long-term follow-up (Table 2).

Long-term pain relief may be achieved with therapies targeting pain receptors

Therapies aiming to reduce pain have largely centred around the transient receptor potential vanilloid-1 (TRPV-1) channel, which is expressed on pain receptors in joints and transmit nociceptive signals to the brain [3]. CNTX-4975 and MTX-071 bind to TRPV-1 and prolongs channel opening and results in desensitisation or loss of these neurons [3]. This leads to reduced pain in patients with osteoarthritis in clinical trials (Table 2). Notably, the pain relief with MTX-071 appears to be long-lasting in some patients (Table 2).

Take home messages

- Osteoarthritis can involve pathological changes to the bone, cartilage and/or synovium of joints.
- Recommend exercise and educational therapies to all patients with osteoarthritis.
- Consider intra-articular corticosteroids and hyaluronic acid in patients where NSAIDs are not appropriate or have failed to achieve adequate benefit.
- Be aware of the new intra-articular therapies for treatment of osteoarthritis currently under investigation, including immunomodulatory therapies, structure modifying therapies and therapies that directly target pain receptors.

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