Review

Evidence and recommendations for use of intra-articular injections for knee osteoarthritis

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A B S T R A C T

Pharmacological treatments are widely recommended in international guidelines for management of osteoarthritis (OA). However, the use of intra-articular (IA) therapies of diverse active drugs remains controversial. We critically reviewed studies of the efficacy and safety of IA injections of corticosteroids (CS), hyaluronic acid (HA), platelet-rich plasma (PRP), and botulinum toxin A (BTA) and evidence-based international recommendations for their use in treating knee OA. The process of article selection was unsystematic. Articles were selected on the basis of authors’ expertise, self-knowledge, and reflective practice. Only studies assessing knee OA were included. IA CS and HA injections were conditionally to fully recommended for treating knee OA. No recommendations have been formulated for IA PRP or BTA. The evidence remains inconsistent and controversial for the use of IA therapies for knee OA. The characteristics of and selection criteria for the OA population that would likely benefit from these therapies need to be identified. Accurately phenotyping and selecting patients is mandatory in future randomized controlled trials. Therefore, efficacy and safety meta-analyses should be performed, as should qualitative and sensitivity analyses of published trial results.

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1. Introduction

Pharmacological treatments, including acetaminophen and non-steroidal anti-inflammatory drugs, are widely recommended in national and international guidelines for managing knee osteoarthritis (OA) in primary care settings [1, 2]. However, patients with knee OA often have comorbidities, which raise concerns about the risk/benefit ratio of these widely prescribed drugs [3]. Therefore, intra-articular (IA) therapies might be an alternative and safe treatment for these patients.

However, the efficacy of IA therapies of diverse active drugs remains controversial among organizations because of important differences in the interpretation of evidence. Indeed, recommendations are usually based on the results of systematic reviews and meta-analysis of randomized controlled trials (RCTs). These reviews are often inconclusive regarding the benefits of these treatments and are limited by the heterogeneity and quality of the included studies. Furthermore, concerns have been raised about the risk/benefit profile of IA drugs.

Here, we review studies of the efficacy and safety of IA injections of corticosteroids (CS), hyaluronic acid (HA), platelet-rich plasma (PRP), and botulinum toxin A (BTA) and evidence-based international recommendations for their use in treating knee OA.

2. Methods

The process of selecting articles related to knee OA for this critical narrative review was not systematic. Individual trials, systematic reviews and meta-analyses included in the latest American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) international guidelines were searched, as was MEDLINE via PubMed from inception to December 2015 for additional guidelines, trials, systematic reviews and meta-analyses. The following MeSH terms were used:
injection, knee osteoarthritis, corticosteroids, hyaluronic acid, platelet-rich plasma, and botulinum toxin. Articles were selected on the basis of authors’ expertise, self-knowledge, and reflective practice.

3. Results

3.1. CS injection

Although OA is generally considered a degenerative joint disorder, there is evidence that a low-grade inflammation also occurs at some phases of the disease [4], which provides sound rationale for the use of drugs targeting local inflammation. CSs are potent anti-inflammatory agents that act by a variety of mechanisms on different cellular levels. IA CS has been used for knee OA for over 50 years [5] and is available in both crystalline and non-crystalline forms. The crystalline triamcinolone and the non-crystalline prednisolone and methylprednisolone are used most frequently. Although the 2012 ACR [1] and 2014 OARSI guidelines [2] both recommend participation in exercise programs as well as weight loss (for overweight patients) as first-line treatments for all patients with symptomatic knee OA, the recommendations largely differ in the use of IA CS [1,2]. ACR guidelines include a conditional, weak recommendation for the use of IA CS in patients unresponsive to basic treatment [1]. Conversely, in OARSI guidelines, IA CS is considered an appropriate treatment, whatever the OA subtype and comorbidities [2]. This recommendation is based on 2 systematic reviews, published before 2010, that supported clinically significant short-term decreases in pain [6,7]. The quality of evidence was rated good. However, no effect size for pain was available [2].

The 2015 update of a 2006 Cochrane review [7] included 14 new trials, for a total of 27 trials [8]. Studies included were RCTs or quasi-RCTs, with a control group receiving sham or no intervention. The median prednisolone equivalent dose across all trials was 50 mg, and the median number of CS injections was one. Trials randomized a median of 76 participants (range 16–205). The meta-analysis found CS more effective for pain reduction than control interventions (standardized mean difference [SMD] = −0.40, 95% CI −0.58 to −0.22), which corresponds to a difference in pain scores of 1.0 cm on a 0–10 visual analog scale (VAS) [8]. When results were stratified by length of follow-up, benefits were moderate at 1–2 weeks (SMD = −0.48, 95% CI −0.70 to −0.27), small to moderate at 4–6 weeks (SMD = −0.41, 95% CI −0.61 to −0.21), and small at 13 weeks (SMD = −0.22, 95% CI −0.44 to 0.00), with no effect found at 26 weeks (SMD = −0.07, 95% CI −0.25 to 0.11) [8]. In addition, CS injection was more effective for improving function than the control intervention (SMD = −0.33, 95% CI −0.56 to −0.09) [8]. Adverse events could not be accurately assessed. Little to no evidence was found for an association with CS dosage, ultrasound guidance, local anesthetic, crystalline preparation, or type of control intervention [8]. However, the authors found a moderate to large degree of between-trial heterogeneity, and most of the identified trials were considered small, and the quality of evidence for the major outcomes was graded “low” [8]. Interestingly, analysis of pain and function stratified by funding source, independent or not of industry, did not show any differences. No hierarchy could be clearly established between corticosteroids in terms of efficacy according to their half-life, onset of action or duration. Therefore, the choice of the corticoid mainly relies on the physician’s practice and the availability of the product.

Finally, a systematic review and network meta-analysis of pharmacological treatment for knee OA that included 129 trials (32,129 participants) [9] found that for treating OA-related knee pain at 3 months, the effect size (ES) was superior for IA CS than IA placebo (ES = 0.33, 95% CI 0.19–0.47), oral placebo (ES = 0.61, 95% CI 0.32–0.89), oral acetaminophen (ES = 0.42, 95% CI 0.12–0.73) and all other oral treatments [9] and was among the highest of all the pharmacological treatments assessed.

3.2. HA injection

The clinical benefit of IA HA on knee OA may rely on 2 mechanisms: [1] mechanical viscosupplementation of the joint (allowing lubrication and shock absorption), and [2] the re-establishment of joint homeostasis by inducing endogenous HA production, which continues long after the exogenous injection has left the joint. However, international guidelines are even more inconsistent for the use of IA HA than IA CS for knee OA. The 2014 OARSI guidelines recommended IA HA injection with a degree of uncertainty for knee-only OA and not appropriate for multiple-joint OA [2]. This recommendation was based on a recent systematic review demonstrating a small but significant efficacy of IA HA for knee OA pain by week 4, with a peak at week 8 (reaching moderate clinical significance) and residual benefit until 24 weeks [10]. Another review found moderate benefits of IA HA for pain and physical function in knee OA [11]. A third review comparing IA HA and IA CS found that IA HA provided greater benefit at 12 and 26 weeks [6]. Conversely, the 2012 ACR guidelines contain no recommendations regarding the use of IA HA as first-line treatment. IA HA injections for knee OA were conditionally recommended only for patients with inadequate response to initial therapy by the technical expert panel [1].

In a systematic review and network meta-analysis of pharmacological treatment for knee OA by Bannuru et al., the ES for IA CS (ES = 0.63, 95% CI 0.39–0.88) was the highest among all the pharmacological treatments assessed [9]. In the most recently updated systematic review and meta-analysis, including only trials considered to have low risk of bias (adequate randomization and concealment, and double-blind design), 8 RCTs (2199 randomized patients) met the inclusion criteria [12]. At 3 months, IA HA significantly reduced pain intensity (SMD = −0.21, 95% CI −0.32 to −0.10) and improved function (SMD = −0.12, 95% CI −0.22 to −0.02) as compared with placebo. The authors concluded that IA HA provided a moderate but real benefit for patients with knee OA [12]. Experimental data suggest a differential action by HA molecular weight (MW). Consistently, some authors found that HA MW may affect its efficacy and safety, with the highest MW more efficient than low MW HA [13]. However, the studies included were heterogeneous, publication bias was high and these conclusions were not supported by other studies. Another meta-analysis even suggested more frequent post-injection reactions with high rather than low MW HA [14]. In clinical practice, HA LW is most commonly used. In trials with low risk of bias, the number of IA HA injections varied from 1 injection for 1 cycle to 5 injections for 4 cycles [12]. However, trials directly comparing different regimens of injections are lacking, and till date, we lack evidence of an effect of number of joint injections. One can assume that increased number of injections might increase the risk for serious adverse events [11]. Seven of the 8 trials included in this meta-analysis received industry funding, and the authors of the meta-analysis disclosed competing interests [12]. However, stratified analysis by funding source has not been performed.

3.3. PRP injection

IA “biological therapies” have generated intense interest as possible modifiers of cartilage biology. PRP derived from autologous blood with a high concentration of activated platelets in a small volume of plasma, which can release a host of mediators and growth factors that act during the initial phase of tissue healing and regeneration. Several growth factors are released, such as
insulin growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular EGF (VEGF), transforming growth factor-β (TGF-β), and others [15]. In vitro, PRP has been shown to have many and complex biological activities, including cellular proliferation, anti-apoptotic activity, cartilage regeneration, collagen synthesis, angiogenesis, and increased vascular permeability [15]. PRP interacts with various tissues, including cartilage, synovial membrane, synovial fluid, and subchondral bone [16]. In vivo, in 2 animal models of OA, treatment with IA PRP was associated with reduced chondrolysis [17,18].

The comparative efficacy and safety profile of IA PRP with other IA drugs for treating knee OA remains controversial. More than 20 open-label studies have been published and have suggested short- to mid-term efficacy in improving both pain and function [19]. The many limitations of these studies included heterogeneity in selected patients and differences in PRP preparations and administration regimens [16]. The most recent comprehensive systematic review of English language, original research RCTs for level I evidence identified only 6 eligible trials [20]; in 5 studies, IA PRP was compared to IA HA [21–25] and in one study to IA saline [26]. Because of the heterogeneity of outcome measures, a meta-analysis could not be performed, and a best-evidence synthesis was used instead [20]. Authors of this systematic review concluded that all but one study [22] showed significant differences in clinical outcomes between PRP and HA, or PRP and saline, in pain and function, with mean post-treatment Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores significantly better for PRP than HA at 3–6 months and 6–12 months [20]. However, many limitations and biases were noted among the 6 studies included, with serious concerns about randomization and blinding procedures; only one of the RCTs used a double-blind approach [24], and in 2 studies, the randomization procedure was not reported [21,26]. Furthermore, the PRP preparation and composition differed and were not standardized, so results were difficult to compare. In the absence of an appropriate blinding, a high placebo effect related to the novelty of the product could not be excluded. Finally, PRP is a blood product that should be submitted to specific regulation. Therefore, the long-term effects of IA PRP with this type of product on the joint (i.e., abnormal cell activation) should be cautiously assessed. Of note, the authors of this review disclosed potential conflicts of interest [20].

After February 2015, 3 supplementary RCTs were published: 2 RCTs comparing IA PRP to IA HA [27,28] and 1 RCT comparing, for the first time, IA PRP to IA CS [29]. The first study randomized 162 patients with different stages of knee OA into 4 groups receiving 3 doses of IA PRP, 1 dose of IA PRP, 1 dose of IA HA or 1 dose of IA saline (control group). Patients were assessed at 6 months. All groups showed improvement on the EuroQol VAS and International Knee Documentation Committee scores as compared with controls. Patients injected with 1 dose of IA PRP or IA HA did not differ in outcome. In the early OA subgroups (Kellgren–Lawrence score I–II), patients who received 3 IA PRP doses showed better clinical results. Patients with advanced OA (Kellgren–Lawrence score III–IV) showed no difference among treatments [28]. The second study randomized 192 knee OA patients (Kellgren–Lawrence score 0–III) to 2 groups: 3 weekly IA PRP or IA HA. Patients were assessed at 2, 6, and 12 months. Post-injection swelling and pain were more frequent with PRP than HA. Both treatments were effective in improving knee functional status and reducing symptoms by the International Knee Documentation Committee (IKDC) subjective score. The 2 groups did not differ at any follow-up time [27]. Finally, in a double-blind RCT, Forough et al. compared, for the first time, a single IA PRP injection to IA CS in 41 participants with knee OA (Kellgren–Lawrence score II–III), at 2 and 6 months. As compared with IA CS, IA PRP decreased joint pain more and for longer than IA CS and improved activities of daily living and quality of life in the short-term [29].

3.4. BTA injection

BTA is a potent neurotoxin produced by the bacterium Closttridium botulinum [30]. BTA inhibits acetylcholine release into the synaptic cleft in cholinergic nerve terminals causing muscle paralysis [31]. In humans, BTA was originally used for its muscle paralyzing effects in neuromuscular disorders, such as spasticity, cervical dystonia and blepharospasm [32,33]. However, growing evidence from RCTs also supports a potent role of IA BTA as a pain modulator in various types of musculoskeletal conditions [34,35]. Consistently, preclinical experimental studies of dogs [36,37] (OA), horses [38] (synovitis) or mice [39,40] with painful joint conditions confirmed an antinociceptive efficacy of IA BTA. The exact mechanisms of pain modulation by BTA in OA remain unclear. Pain in OA involves both nociceptive and neuropathic complex mechanisms and abnormal excitability in peripheral and central pain pathways [41–46]. BTA was suggested to suppress the secretion of neurotransmitters, thus directly decreasing peripheral sensitization and indirectly decreasing central sensitization [47,48]. Recent studies also suggest an inhibitory role of BTA on the release of mediators involved in nociception, such as substance P, calcitonin gene-related peptide and glutamate [49].

Non-randomized trials and RCTs of BTA in various osteoarticular conditions, including OA, were comprehensively reviewed in 2013 [34]. The author of the review declared no financial competing interests directly related to the study [34]. In the Boon et al. study, 60 patients (61–64 years old) with chronic knee pain (symptom duration 6–10 years) were randomized to 3 groups: IA BTA 100 U (n = 20), IA BTA 200 U (n = 20), and IA CS (n = 20). At week 8, the 3 groups showed reduced pain and improved function as assessed by the WOMAC, with no differences between the 3 groups. Quality of life assessed by the Medical Outcomes Survey 36-Item Short Form was improved only in the IA BTA group for the pain index [50]. In the Mahowald et al. study, 42 patients with refractory chronic painful knees (pain duration not provided) were

<table>
<thead>
<tr>
<th>Table 1</th>
<th>International guidelines for the use of intra-articular treatments for knee OA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
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<tr>
<td>Hyaluronic acid</td>
<td>No recommendation</td>
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<td></td>
<td></td>
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<td>Platelet-rich plasma</td>
<td>-</td>
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<tr>
<td>Botulinum toxin A</td>
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</table>

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; LOA, level of agreement; LOE, level of evidence; MA, meta-analysis; OAERS, Osteoarthritis Research Society International; RCT, randomized controlled trial; SOR, strength of recommendation; SR, systematic review.
<table>
<thead>
<tr>
<th>Registration</th>
<th>Date</th>
<th>Phase</th>
<th>RCT</th>
<th>Study population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>NCT01518257</td>
<td>2012</td>
<td>III/II</td>
<td>Yes</td>
<td>Painful OA</td>
<td>A single 200-U dose of IA BTA 100 or 200U of IA BTA</td>
<td>A single 2-ml dose of IA saline 40 mg of IA methylprednisolone</td>
<td>Pain at 4, 8 and 12 weeks</td>
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<td>Allergan</td>
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<td>NCT00279903</td>
<td>2005</td>
<td>I</td>
<td>Yes</td>
<td>Painful OA</td>
<td>Single IA injection of BT 1 or 2 IA injections of BTA</td>
<td>Single IA injection of placebo IA injection of saline</td>
<td>Pain at 8 weeks</td>
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<td>NCT02139319</td>
<td>2014</td>
<td>–</td>
<td>Yes</td>
<td>Knee OA</td>
<td>Single IA injection of PRP</td>
<td>Single IA injection of saline Betamethasone and bupivacaine IA injection</td>
<td>Pain at 2 weeks, 1, 3 and 6 months</td>
<td>Recruiting</td>
<td>Yung-Tsan Wu</td>
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<tr>
<td>NCT02230956</td>
<td>2014</td>
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<td>Yes</td>
<td>Painful OA</td>
<td>One cycle of 3 IA injection of PRGF every 15 days</td>
<td>Single IA injection of HA</td>
<td>WOMAC and Lequesne at 6 months</td>
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<td>Fundacion para la Investigacion Biomedica del Hospital Universitario Principale de Asturias</td>
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<td>NCT02142842</td>
<td>2014</td>
<td>I/II</td>
<td>No</td>
<td>Knee OA Grade 2/3</td>
<td>IA injection of autologous stromal vascular fraction and PRP</td>
<td>–</td>
<td>AEs up to 6 months</td>
<td>Completed</td>
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<td>NCT01697423</td>
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<td>II</td>
<td>Yes</td>
<td>Knee OA Grade I/II</td>
<td>Single IA injection of PRP</td>
<td>Triple IA injections of PRP with an interval of 2 weeks IA HA</td>
<td>WOMAC at 3 and 6, and 3, 6 and 9 months</td>
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<td>NCT02488492</td>
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<td>0</td>
<td>Yes</td>
<td>Knee OA Grade I/II</td>
<td>Single IA injection of PRP</td>
<td>Single IA injection of saline</td>
<td>Biochemical molecular outcomes at 10 days</td>
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<td>NCT01270412</td>
<td>2010</td>
<td>II/III</td>
<td>Yes</td>
<td>Knee OA</td>
<td>Single IA injection of PRGF</td>
<td>Single IA injection of HA</td>
<td>Pain, function, quality of life and activity level at 1 and 2 years</td>
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<td>NCT02588872</td>
<td>2015</td>
<td>III</td>
<td>Yes</td>
<td>Painful knee OA</td>
<td>3 weekly IA injections of PRGF</td>
<td>3 weekly IA injections of HA</td>
<td>IKDC at 6 weeks, 6 months and 1 year</td>
<td>Completed</td>
<td>Rush University Medical Center</td>
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<td>NCT02365142</td>
<td>2014</td>
<td>II</td>
<td>Yes</td>
<td>Knee OA KL ≥ II</td>
<td>3 IA injections of PRP</td>
<td>Single IA injection of 100 million bone-marrow mesenchymal stem cells and 3 IA injections of PRGF</td>
<td>Pain and KOOS at 1, 3, 6 and 12 months</td>
<td>Recruiting</td>
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<td>Yes</td>
<td>Painful OA</td>
<td>3 IA injections of PRP</td>
<td>3 IA injections of PRGF 3 IA injections of PRGF</td>
<td>Pain at 28 days, 3 and 6 months</td>
<td>Completed</td>
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<td>Yes</td>
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<td>3 IA injections of PRP</td>
<td>Acetaminophen (500 mg/8 h)</td>
<td>WOMAC at 6, 12 and 24 weeks</td>
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<td>Yes</td>
<td>Painful OA Grade I/II</td>
<td>Single IA injection of PRP</td>
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<td>Pain and WOMAC at 3 months, cartilage repair at 12 months</td>
<td>Completed</td>
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<td>NCT01923909</td>
<td>2013</td>
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<td>Yes</td>
<td>Painful OA Grade I/II/III</td>
<td>Single IA injection of PRP</td>
<td>Single IA injection of PRP</td>
<td>WOMAC and Oxford Knee Score from 6 weeks to 6 months</td>
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<td>Yes</td>
<td>Painful OA Grade I/II/III</td>
<td>Single IA injection of PRGF and mesenchymal stem cell suspension</td>
<td>Single IA injection of PRP</td>
<td>Pain at 6, 12 and 24 weeks</td>
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<td>Samsung Medical Center</td>
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<td>NCT01985633</td>
<td>2013</td>
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<td>Yes</td>
<td>Painful OA Grade I/II/III</td>
<td>Single IA injection of PRGF</td>
<td>Single IA injection of HA</td>
<td>KOOS at 6 months</td>
<td>Unknown</td>
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<td>NCT00782197</td>
<td>2008</td>
<td>IV</td>
<td>Yes</td>
<td>Painful OA Grade ≤ III</td>
<td>3 IA injections of PRP</td>
<td>3 IA injections of HA</td>
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<td>NCT01747018</td>
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<td>II/II</td>
<td>No</td>
<td>Early OA and degenerative chondropathy Grade ≤ III</td>
<td>Single IA injection of PRP</td>
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<td>Pain at 6 months</td>
<td>Completed</td>
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<td>NCT01670578</td>
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<td>Yes</td>
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<td>3 IA injections of PRP</td>
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<td>IKDC at 12 months</td>
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<td>IV</td>
<td>Yes</td>
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<td>3 IA injections of PRP</td>
<td>3 IA injections of HA</td>
<td>IKDC at 12 months</td>
<td>Recruiting</td>
<td>Istituto Ortopedico Rizzoli</td>
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<td>NCT02012530</td>
<td>2014</td>
<td>III</td>
<td>Yes</td>
<td>Painful knee degenerative cartilage lesions Grade 1–3</td>
<td>Single IA injection of PRGF</td>
<td>Single IA injection of HA and anesthetic</td>
<td>KOOS at 3 months</td>
<td>Not yet open</td>
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AEs, adverse events; HA, hyaluronic acid; IA, intra-articular; IKDC, International Knee Documentation Committee score; KL, Kellgren–Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; RCT, randomized controlled trial; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
randomly assigned to IA BTA 100 U (n = 21) or IA saline (n = 21). At 1 month, the 2 groups were comparable for pain reduction. At 3 months, pain reduction compared to baseline was significant only for the IA BTA group [51]. In these 2 studies, whether knee pain was related to knee OA or to another knee condition was not detailed.

4. Discussion

In our critical review of the latest evidence and evidence-based guidelines, IA CS and HA injections were conditionally to fully recommended for treatment of knee OA. No recommendations have been formulated regarding IA PRP or BTA (Table 1).

In addition to oral treatments, IA HA injections are often used in daily practice for managing knee OA. The effectiveness of IA HA, used for more than 20 years, remains debated. HA is now not recommended by the American Academy of Orthopedic Surgeons [52] and is conditionally recommended by the ACR [1]. OARSI recently provided an uncertain recommendation [2]. To help practitioners in the use of IA HA, a panel of 8 international experts achieved unanimous agreement in favor of the following 9 of 24 statements: “(1) IA HA is an effective treatment for mild to moderate knee OA; (2) IA HA is not an alternative to surgery in advanced hip OA; (3) IA HA is a well-tolerated treatment of knee and other joints OA; (4) IA HA should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs; (5) IA HA is a ‘positive’ indication but not a ‘lack of evidence’ better indication; (6) the dosing regimen must be supported by evidence-based medicine; (7) cross-linking is a proven means for prolonging IA residence time of HA; (8) the best approach to inject accurately knee joint is the lateral mid-patellar one; (9) when IA HA injection is performed under fluoroscopy, the amount of radiopaque contrast agent must be as low as possible to avoid HA dilution” [53].

Despite the long-standing use of IA CS, its effectiveness and safety remains debated. Authors of the 2015 updated Cochrane review of IA CS for knee OA concluded that “it remained unclear whether there were clinically important benefits one to six weeks after CS injection in view of the low quality of the included trials, the large amount of heterogeneity, and the likely presence of small-study effects, that IA CS should therefore be considered experimental in knee OA and not be routinely used until adequately powered and properly designed trials clearly indicate a short- to mid-term benefit”. This apparent discrepancy between practice and evidence could be related to methodological issues but also to patient selection. Indeed, patients included in RCTs might not be the same as those clinicians are likely to treat in “real life.” Obviously, not all knee OA patients could benefit from IA CS.

Most of the RCTs of patients with knee OA support a slightly better symptomatic effect of IA PRP than IA HA [20], IA CS [29] or IA saline [26], especially with early disease [28]. However, the designs of the trials were not always appropriate to demonstrate the superiority of IA PRP, and results should be interpreted cautiously in terms of the strong placebo effect of IA injections in knee OA [9]. In addition, given the large number of mediators and the wide range of joint biological effects, the accurate mechanism of the potent chondroprotective properties of PRP remains unclear [15,16]. The main concerns that preclude the generalizability of experimental and clinical findings are the high variability in composition of PRP, with platelet concentrations varying five-fold across studies, uncontrolled growth factor concentrations among donors, and different IA administration regimen [15,16]. Finally, the safety data suggest low frequency of serious adverse events, including infections and allergic reactions. Post-injection pain may be more common and more severe with IA PRP than other injections [16].

Overall, only 2 small RCTs provided inconsistent evidence of the short-term efficacy of a single IA BTA injection for relieving pain and improving function and quality of life in patients with chronic knee pain related to various musculoskeletal conditions, with no clear superiority over the comparator treatment [50,51]. Although the rationale for pain modulation by IA BTA in OA is promising, till date, evidence is lacking to recommend IA BTA for treating symptomatic knee OA. Therefore, IA BTA is neither included nor considered in any of the national or international guidelines for managing OA. In addition, concerns have been recently raised about the safety of treatment strategies targeting nociceptive mechanisms in OA, such as anti-nerve growth factor (NGF) therapies [54]. The syndrome of rapid progression of OA associated with chondrolysis and bone destruction appears to be a safety signal associated with increasing doses of anti-NGF antibodies [54]. The occurrence of rapidly progressive OA might represent a form of neuropathic arthropathy caused by nerve damage resulting in the loss of ability to feel pain in the joint combined with reduced joint proprioception [55]. This kind of adverse event could theoretically translate to treatments modifying joint pain perception but has not been specifically assessed for IA BTA. RCTs specifically assessing the efficacy and safety of IA BTA in symptomatic knee OA are mandatory. Currently, 4 studies are registered, and 3 of 4 are completed (ClinicalTrials.gov identifiers: NCT01518257 [n = 121], NCT02279903 [n = 62], NCT02139319 [n = 22], NCT02230956 [n = 176]). The results of these studies are not yet available. Ongoing registered studies of IA treatments with PRP and BTA for knee OA are summarized in Table 2.

Overall, IA injections should be considered part of a multi-modal approach to the management of OA, combining both non-pharmacological and pharmacological interventions, as recommended in all the international guidelines.

5. Conclusions

Evidence is rather inconsistent and controversial about IA therapies for the management of knee OA. The most frequently used IA drugs, namely CS and HA, are conditionally to fully recommended. There are no recommendations for the use of PRP and BTA.

One can question the heterogeneity of the OA patient phenotypes included in the studies, which may have precluded the generalizability of the results and may not correspond to patients who would have been treated in “real life.” Indeed, there is a gap between practice and recommendations regarding IA treatments in OA. Efforts should be made to identify the characteristics of and selection criteria for the OA population likely to benefit from these therapies. Accurately phenotyping and selecting patients [56] is mandatory in future RCTs. Therefore, efficacy and safety meta-analyses should be performed, as should qualitative and sensitivity analyses of published trials. Finally, powerful methodological approaches, such as network meta-analyses, have allowed for comparing available pharmacological treatments in OA according to their relative efficacy, safety profiles and relative costs. These approaches may be helpful in formulating evidence-based algorithms.

Disclosure of interest

The authors declare that they have no competing interest.

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knees with early osteoarthritis: a randomized, double-blind, placebo-con-

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