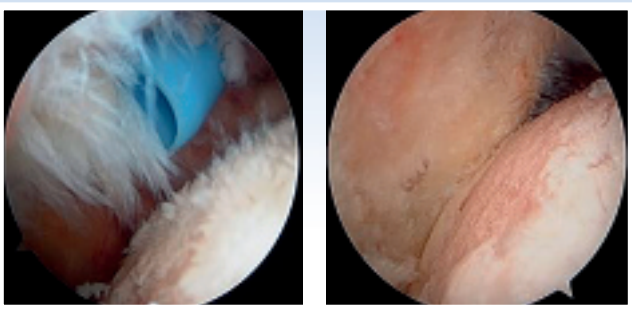
SECTION

2

General Orthopaedics



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CHAPTER

11

Nonsurgical Management of Osteoarthritis of the Knee: What You Should Be Injecting Now and in the Future

Andrew I. Spitzer, MD, FAAOS • Jack M. Bert, MD, FAAOS • Jason L. Dragoo, MD • Rahman Kandil, MD • John C. Richmond, MD, FAAOS

ABSTRACT

Osteoarthritis of the knee affects many Americans. With the aging of the population and increasing comorbidities (eg, obesity, diabetes, hypertension, heart disease), the use of oral or topical NSAIDs is often contraindicated. Injectable treatment options are advantageous because of the ability to decrease or avoid the unwanted systematic adverse effects of NSAIDs. Injectable treatment options for osteoarthritis of the knee go back to the 1950s, beginning with corticosteroids, which remain widely used despite concerns that they may have adverse effects on articular chondrocytes and short duration of efficacy. The recent (FDA approval in 2017) introduction of a sustained-release corticosteroid (triamcinolone acetonide extended-release) offers significantly longer benefit than standard cortisone products and with substantially lower concentration levels of chondrocyte exposure to the steroid. Hyaluronic acid was added to the options for intra-articular injection in osteoarthritis of the knee in the late 1990s and remains widely used despite some controversy over its efficacy. Although guidelines for the use of hyaluronic acid for management of osteoarthritis of the knee have varied widely, careful analysis of the data and patient's perceived efficacy indicate its continued and important role in managing osteoarthritis of the knee. Finally, the past 15 years have seen an explosion in the use of biologics including platelet-rich plasma and pluripotential (often termed stem) cells. The science behind their use and efficacy is evolving and continued study is warranted.

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Introduction

Osteoarthritis affects one in three Americans between the ages of 18 and 64 years and is 1.5 times more common in women.[1] The knee is one of the most commonly affected joints, with a lifetime risk of nearly 45%.[2] The prevalence of osteoarthritis of the knee rises with age, limits activities, contributes to multiple medical comorbidities such as diabetes and heart disease, and increases the risk of all-cause mortality.[3] Although total knee arthroplasty (TKA) is an effective surgical management for osteoarthritis of the knee, approximately 20% of patients are not satisfied with their pain and functional outcomes,[4] and up to a third of patients will have persistent symptoms.[5] In addition, patients' perspectives on injection therapy suggest that a major influence on the decision to receive an intra-articular injection is the effect of knee osteoarthritis on their lives, and the perception that if other treatment strategies have failed, that injections could be worth the potential downsides (eg, out-of-pocket cost, potential adverse effects), especially if it could help them avoid surgery or return to the valued activities.[6] Despite the general perception of benefit from and desirability of intra-articular injections among both healthcare providers and patients alike, recommendations from guidelines published from medical organizations such as the American College of Rheumatology and the American Academy of Orthopaedic Surgeons (AAOS) are inconsistent and vary according to the specific injectable administered.[7-9]

Triamcinolone Acetonide Extended-Release

Intra-articular corticosteroid (IACS) injection, first reported in 1951 by Hollander, is a popular treatment option for osteoarthritis.[10] Of those patients undergoing TKA, approximately 30% have received a prior IACS.[6,10-12] The mechanism of action is not entirely understood. It is known that the lipophilic steroid molecule diffuses through the cell membrane; binds to receptors in the cytosol where it may have local effects; and translocates to the nucleus where it may modify transcriptional, posttranscriptional, and posttranslational mechanisms. It ultimately exerts its effect by reducing synovial inflammation by limiting the production of proinflammatory mediators such as metalloproteinases, interleukin (IL) 1 and 6, tumor necrosis factor alpha, collagenases, and arachidonic acid derivatives.[13] The onset of action can be nearly immediate for some of the cytosolic effects; however, the nuclear effects typically take a few days to have a clinical effect.[10,13] Solubility of the steroid determines its residence time, onset, and duration of action, with more crystalline, particulate, fluorinated, less-soluble compounds, such as triamcinolone, having a slower onset and longer duration of action.[13,14]

The steroid-induced reduction in inflammation restores homeostasis to the joint, reducing effusion and pain and improving function, and has been shown to be superior to placebo or no treatment, though less effective in patients with obesity or with advanced osteoarthritis of the knee.[15,16] However, the clinical benefit is short lived, with reviews demonstrating only 1 to 6 weeks of clinical improvement,[17,18] with the short duration of action probably due to rapid clearance and efflux from the joint, which occurs rapidly over approximately 21 days.[19] The short duration of action of IACS is problematic because osteoarthritis of the knee is a chronic disease and IACS is not recommended to be repeated more than once every 3 months. A sustained-release corticosteroid triamcinolone acetonide extended-release(TA-ER) (Zilretta) was approved by the FDA in October 2017. Its novel formulation consists of microspheres of poly(lactic-co-glycolic acid) in which the triamcinolone acetonide is embedded (**Figure 1**). Canine studies have demonstrated that the microspheres reside in the superficial layer of the synovium, do not circulate in the synovial fluid, and are not found in any other local or systemic tissue.[20] Although present in the joint at 4 weeks, by 16 weeks they are no longer visible on histologic sections. On exposure to an aqueous environment

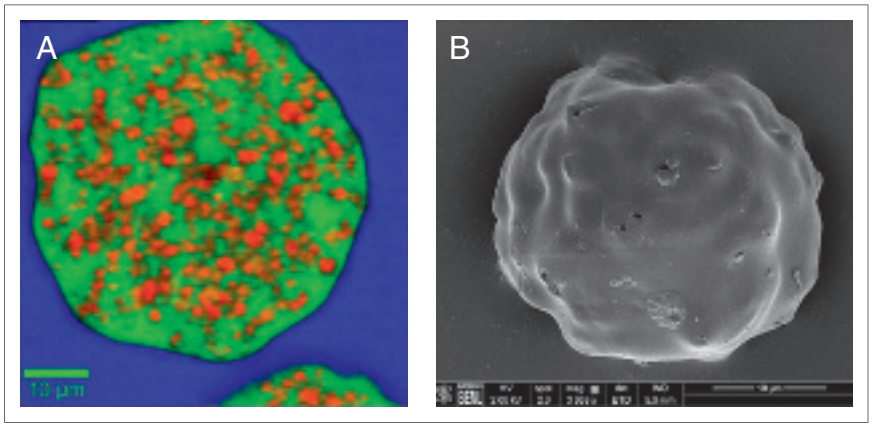

FIGURE 1 Extended-release formulation of triamcinolone acetonide. **A**, Raman image of microsphere cross sections. Within each microsphere, small crystals of triamcinolone acetonide (red) are embedded in a poly(lactic-co-glycolic acid) matrix (green). **B**, Scanning electron microscopy image of a microsphere collected in the initial phase of release. Small channels approximately 500 nm in diameter appear as black dots on the smooth, largely intact surface of the microsphere. (Reproduced with permission from Conaghan PG, Hunter DJ, Cohen SB, et al: Effects of a single intra-articular injection of a microsphere formulation of triamcinolone acetonide on knee osteoarthritis pain: A double-blinded, randomized, placebo-controlled, multinational study. *J Bone Joint Surg Am* 2018;100[8]:666-677. https://www.jbjs.org)

such as the intra-articular space of the knee, the microsphere begins to slowly release the triamcinolone acetonide and degrade over a sustained period. The degraded microsphere is metabolized to CO_2 and H_2O and eliminated by the lungs and kidney.[21]

Pharmacokinetic analysis after injection of TA-ER indicates persistence of clinically relevant levels of triamcinolone acetonide within the synovial fluid of osteoarthritic knees at 12 weeks following administration. By 16 weeks, any triamcinolone acetonide remaining is below the level of quantification. By comparison, when standard triamcinolone acetonide formulated as a crystalline suspension (TAcs) is administered, by 6 weeks, the level of triamcinolone acetonide in the synovial fluid is below the level of quantification.[22] Early systemic absorption of triamcinolone acetonide as measured by plasma concentrations of triamcinolone acetonide after intra-articular TA-ER injection has been shown to be approximately 18 times lower than an intra-articular TAcs injection.[22] As a result, TA-ER causes only a minimal perturbation of glucose control in patients with type 2 diabetes, which is of critical importance. Russell et al[23] studied patients with type 2 diabetes mellitus in good glucose control with demonstrated continuous glucose monitoring levels below 180 mg/dL. After intra-articular injection with standard TAcs, poor glucose control ensued for approximately 72 hours, with plasma peaks in the range of 240 to 260 mg/dL. In contrast, after intra-articular injection of TA-ER, no patient experienced a blood glucose level above 200 mg/dL at any time point[23] (**Figure 2**).

The pharmacodynamic effect and clinical efficacy of TA-ER have been extensively evaluated. In a phase III, multicenter, international, randomized, double-blind, parallel arm trial in 484 patients with moderate to severe osteoarthritis of the knee (Kellgren-Lawrence grade 2 or 3), TA-ER was compared with a placebo control (saline injection) and with TAcs.[24] The primary end point was change in average daily pain (ADP) intensity from baseline to week 12 between TA-ER and placebo. Secondary end points included ADP intensity over time between TA-ER and TAcs, and, for each cohort, time to onset of pain relief; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for pain (A), stiffness (B), and function (C); Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QOl) subscale; and the use of rescue medications during the study. Patients were assessed through 24 weeks.

The primary end point was successfully achieved with a rapid, substantial, and persistent greater than 50% reduction in ADP baseline osteoarthritic knee pain, which was statistically significantly and clinically meaningfully better with TA-ER versus placebo both at 12 weeks and over 12 weeks ($P < 0.0001$), and which persisted through week 16 (**Figure 3**). The median onset

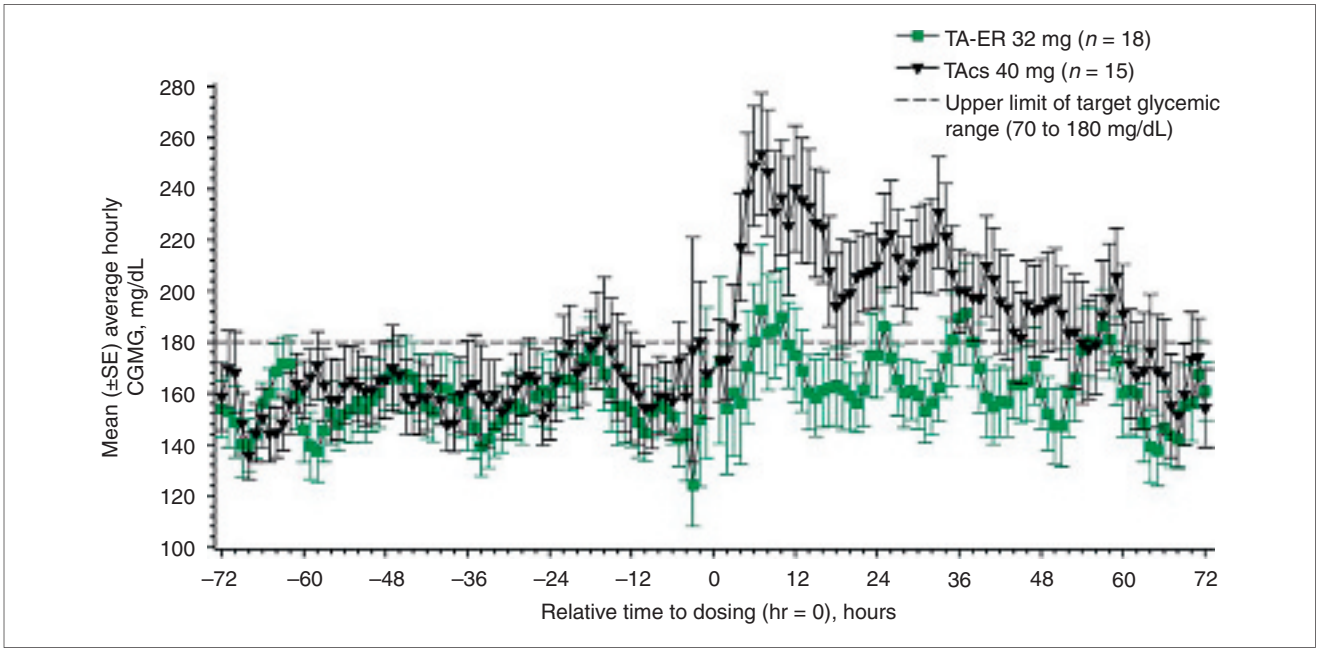

FIGURE 2 Graphical representation of mean average hourly CGMG levels (FAS; *n* = 33) CGMG = continuous glucose monitoring–measured glucose, FAS = full analysis set, LSM = least squares mean, SE = standard error, TAcs = triamcinolone acetonide crystalline suspension, TA-ER = triamcinolone acetonide extended-release. (Russell SJ, Sala R, Conaghan PG, et al: Triamcinolone acetonide extended-release in patients with osteoarthritis and type 2 diabetes: A randomized, phase 2 study. *Rheumatology (Oxford)* 2018;57[12]:2235-2241, with permisssion of the British Society for Rheumatology.)

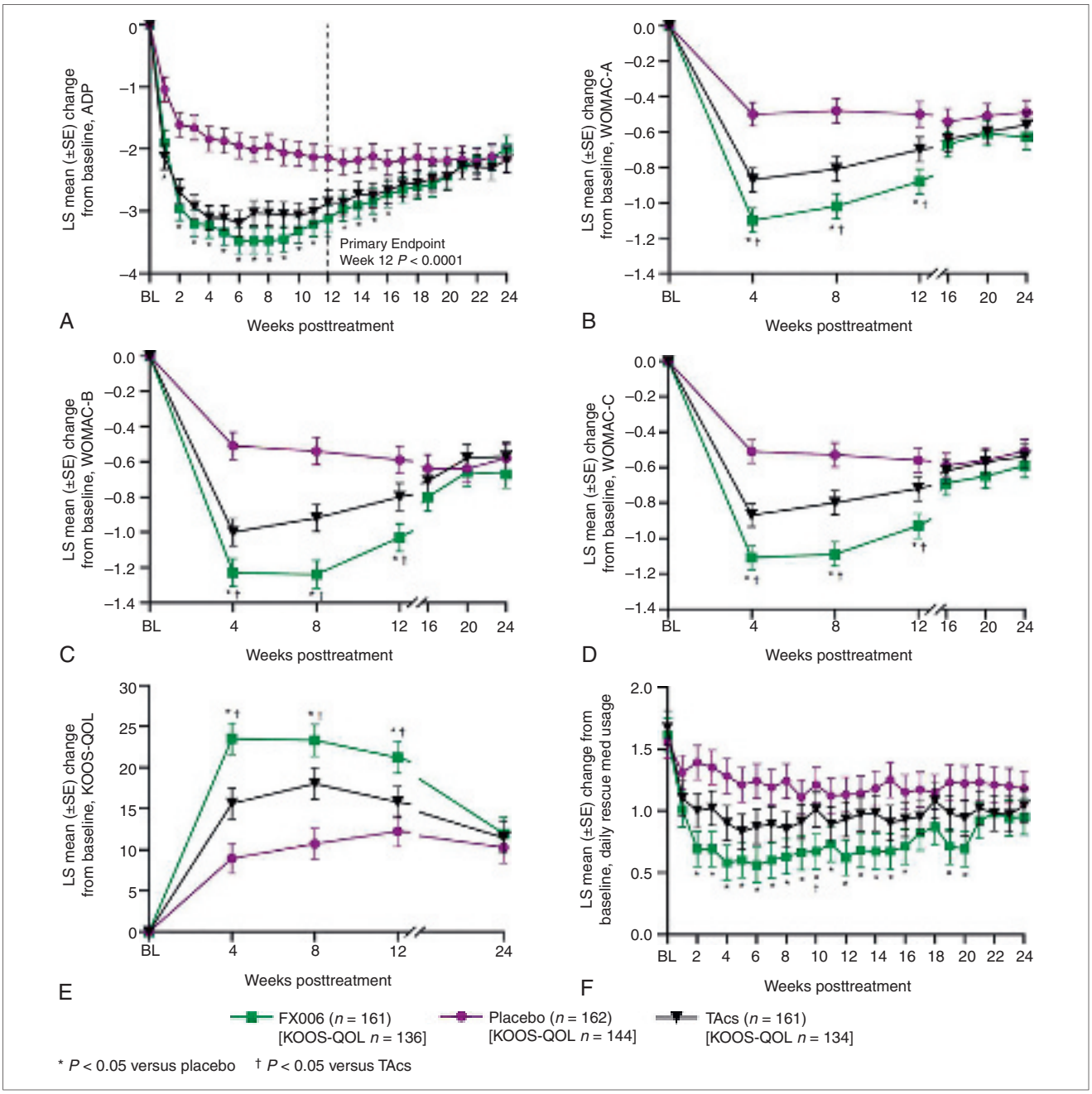

FIGURE 3 Graphical representation of least square (LS) mean change from baseline (BL) (and standard error [SE]) for the efficacy end points of weekly mean average daily pain (ADP) intensity scores (0 to 10 on numeric rating scale) at week 12, the primary end point (n = 484) (**A**); Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-A (pain), WOMAC-B (stiffness), and WOMAC-C (physical function) subscale scores (n = 484) (**B** through **D**); Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QOL) subscale score (n = 414) (**E**); and rescue medication (med) use (mean number of daily rescue medication [500-mg] tablets per week; n = 484) over time in the full analysis set (**F**). Primary and exploratory secondary end point analyses used an analysis of covariance with model parameters for treatment and covariates of baseline pain intensity score and study site. TAcs = triamcinolone acetonide crystalline suspension, placebo = saline solution placebo. (Reproduced with permission from Conaghan PG, Hunter DJ, Cohen SB, et al: Effects of a single intra-articular injection of a microsphere formulation of triamcinolone acetonide on knee osteoarthritis pain: A double-blinded, randomized, placebo-controlled, multinational study. *J Bone Joint Surg Am* 2018; 100[8]:666-677. Copyright © 2018 The Authors. Published by The Journal of Bone and Joint Surgery, Incorporated. All rights reserved. https://www.jbjs.org.)

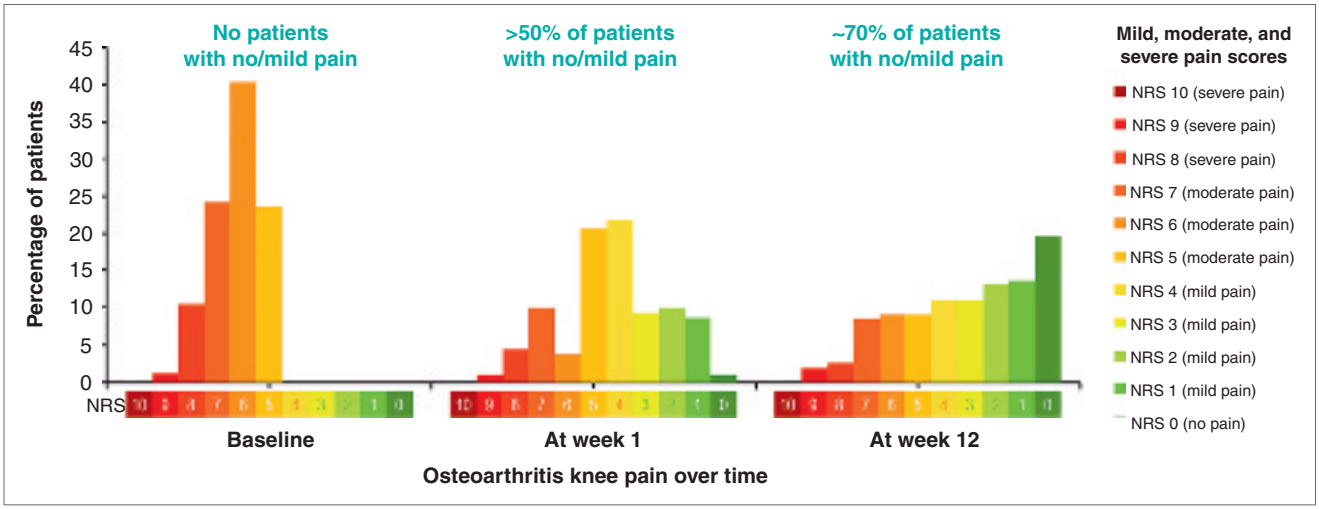

FIGURE 4 Distribution of pain scores on a scale from 0 to 10 at baseline, week 1 postinjection, and week 12 postinjection. NRS = numerical rating scale. (Reproduced with permission from Flexion Therapeutics, Burlington, MA.)

of clinically meaningful pain relief, defined as > 30% pain relief, was 4 days for TA-ER versus 11 days for placebo. At baseline, by inclusion criteria, no patients had mild or no pain. More than 50% of patients had no or mild pain at week 1 postinjection, and nearly 70% had no or mild pain at 12 weeks postinjection (**Figure 4**). The clinical effect demonstrated early onset and sustained duration of action.[24]

TA-ER did not separate from TAcs with regard to ADP statistically, but numerically was superior (**Figure 3**, **A**). However, ADP is known to be a relatively insensitive metric, requiring a choice of a single number between 0 and 10, and not considering patient comorbidities, bilaterality of disease, activity level or desire, or overall patient expectations. It is a necessary outcome to measure, especially with regard to comparison with placebo, but may not be sufficient to differentiate active comparators. In support of this are several post hoc analyses. Approximately 65% of the patients in the original phase III study had bilateral disease, with the index treated knee being most symptomatic. When only patients with unilateral disease were considered, TA-ER statistically reduced ADP ($P < 0.05$) versus TAcs and placebo[25] (**Figure 5**).

With regard to the secondary end points of WOMAC-A (pain), WOMAC-B (stiffness), and WOMAC-C (function); KOOS-QOL; and rescue medication use, TA-ER was statistically significantly ($P \leq 0.05$) superior to TAcs and placebo through week 12. Notably, the WOMAC scores at week 12 were numerically better than the maximal benefit, achieved at 4 weeks, by TAcs, suggesting a powerful clinical impact that surpasses even the early maximal relief from an intra-articular TAcs injection and is sustained to at least 12 weeks (**Figure 3**, **B** through **E**). No important safety signals were identified between the cohorts, with only cough, contusion at the injection site, and sinusitis slightly more common in the TA-ER cohort (2%) in comparison with placebo (1%).[24]

Because osteoarthritis of the knee is a chronic disease with persistent recurrent symptoms, it is important to be able to offer repeated and ongoing treatments for pain. TA-ER has been studied in a phase IIIB open-label, single-arm, repeat administration study consisting of a real-world cohort of 208 patients age 61 years, 56% female, BMI 31 kg/m^2, 8.6 years since diagnosis of moderately symptomatic osteoarthritis of the knee (total WOMAC-A > 6), and with moderate to advanced radiographic findings (Kellgren-Lawrence grade 2—32%, grade 3—38%, grade 4—30%).[26] Patients were eligible for a second injection beginning 12 weeks and until 24 weeks following the index injection when they had recurrence of their symptoms and wanted another injection, and if in the opinion of the investigator and the patient there had been sufficient benefit from the index injection. The patients were then followed up through 52 weeks for any clinical or radiographic adverse events. Ninety-two percent of patients opted for a second injection, 3% still did not need a second injection by 24 weeks, and only 5% dropped out of the study.

The median time to reinjection was 16.6 weeks, with 25.1%, 33.5%, 20.7%, and 20.1% receiving injections at 12, 16, 20, and 24 weeks, respectively. The exploratory end points of WOMAC-A, B, C, and KOOS-QOL all responded as expected and as demonstrated in the phase III study. In addition, the magnitude and duration of the effect of the second injection were essentially identical to the response from the index injection (**Figure 6**). There were no substantial differences in treatment-emergent adverse events between the first and second injections, no significant safety

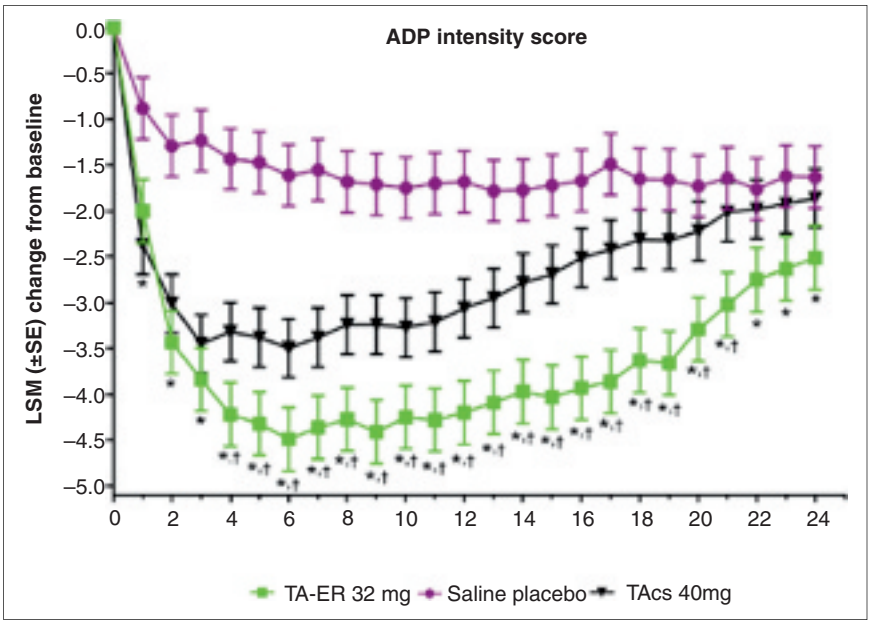

FIGURE 5 Graphical representation of change in ADP intensity score over time in participants with unilateral knee osteoarthritis. *P < 0.05 TA-ER versus placebo. †P < 0.05 TA-ER versus TAcs. ADP = average daily pain, LSM = least squares mean, SE = standard error, TA = triamcinolone acetonide, TAcs = triamcinolone acetonide crystalline suspension, TA-ER = triamcinolone acetonide extended-release. (Adapted by permission from Springer Nature, *Adv Ther*. Efficacy of triamcinolone acetonide extended-release in participants with unilateral knee osteoarthritis: A post hoc analysis. Langworthy MJ, Conaghan PG, Ruane JJ, et al: 2019;36(6):1398-1411.)

signals for the entire study, and no evidence of chondrolysis, osteonecrosis, rapid progression of disease, or other concerning findings.[26]

Administration of TA-ER demands some special considerations. TA-ER must be refrigerated to preserve the shelf life stamped on the package. Once removed from the refrigerator, the product may be stored at room temperature for no longer than 6 weeks. The kit for administration supplies a vial with the powdered microspheres, and a special diluent that must be used for reconstitution. Once reconstituted, the preparation is stable for 4 hours at ambient conditions. The reconstituted TA-ER should be stored in the vial until ready for injection, at which point it can be drawn into the syringe. A fresh 21-gauge needle or larger should be used for injection to prevent clumping of the microspheres, and injection should be carried out under sterile conditions.[27] TA-ER can safely be coadministered with 5 mL of either 1% lidocaine, 0.25% bupivacaine, 0.5% ropivacaine, or an admixture of 2 mL, 1.5 mL, and 1.5 mL of each of the three of them, respectively, without compromise to syringeability, pH, particle size, percentage of free drug, purity, or appearance.[28] However, based on the known toxicity of local anesthetics on chondrocytes,[29] it would be prudent to use separate syringes for the TA-ER and the local anesthetics, and to switch syringes to the same intra-articular needle during the injection procedure and avoid intra-articular injection of the local anesthetic.

There are a number of general concerns about single and repeated steroid injections. Chondrotoxicity, with progressive thinning of the remaining cartilage, has controversially been attributed to repeated IACS; however, the variable effect of the steroid and the local anesthetics coadministered is not well elucidated.[10,13] This has led to the anecdotal but generally accepted recommendation to repeat IACS no more than every 3 to 4 months. Raynauld et al studied radiographic changes after repeated IACS injections but did not demonstrate any deleterious effect.[30] Recently, McAlindon et al[31] evaluated MRI changes in osteoarthritis (Kellgren-Lawrence grade 2-3) after 2 years of repeated IACS injections versus placebo at 3-month intervals. The IACS led to 0.2 mm of cartilage deterioration in contrast to only 0.1 mm for the placebo group.[31] However, this analysis relied on imputed outcomes. When only those who completed the study were included, as was published in the online-only supplemental material, there was no difference between the groups. Even in the worst-case scenario, the clinical significance of these findings, especially in the patient with knee osteoarthritis with advanced radiographic changes and established cartilage loss, is unclear. Furthermore, in vitro data studying cultured bovine chondrocytes exposed to inflammatory mediators and mechanical injury suggest that low concentrations of IACS such as provided by the sustained but slow release of TA-ER may confer some protection from such a toxic milieu as may be seen in osteoarthritis of the knee.[32]

A recent study using the Osteoarthritis Initiative data set and the Multicenter Osteoarthritis Study data set evaluated the rate of radiographic progression of osteoarthritis of the knee and TKA and found that IACS was not associated with a higher rate of radiographic progression or progression to TKA than intra-articular hyaluronic acid injections. The authors further concluded that the risk of disease progression attributed to IACS in earlier studies may reflect the presence of more severe osteoarthritis in those undergoing injections.[33] A recent

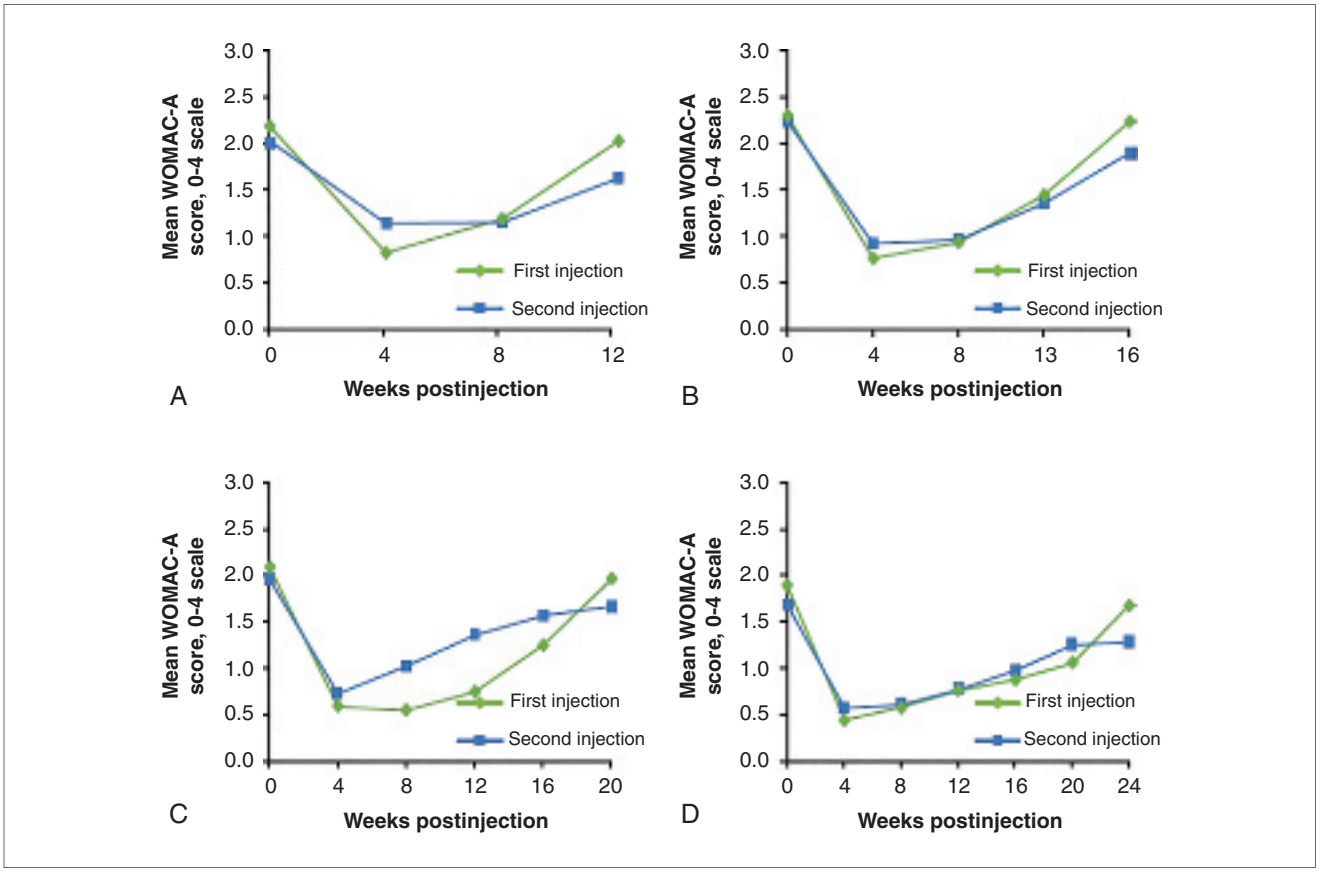

FIGURE 6 Graphical representation of comparison of mean WOMAC-A (pain) scores following the first and second TA-ER injections for patients who received the second injection at (**A**) week 12 (*n* = 45), (**B**) week 16 (*n* = 60), (**C**) week 20 (*n* = 37), or (**D**) week 24 (*n* = 36) (efficacy population). TA-ER = triamcinolone acetonide extended-release, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. (Reproduced with permission from Spitzer AI, Richmond JC, Kraus VB, et al: Safety and efficacy of repeat administration of triamcinolone acetonide extended-release in osteoarthritis of the knee: A phase 3b, open-label study. *Rheumatol Ther* 2019; 6[1]:109-124.)

review by Samuels et al[34] concluded that "there is no definitive evidence that intra-articular glucocorticoids accelerate joint deterioration or hasten the requirements for TKA." Finally, even McAlindon et al,[35] commenting on a case series deeply flawed by bias and poor case documentation and that suggested high risk of damage to the joint tissues from IACS injections, indicated that care should be exercised in the dissemination of information with scientifically spurious conclusions "to avoid excessive concerns about a treatment that most experts view as having a favorable balance of benefit versus harm when used appropriately."

Hyaluronic Acid: Science, Controversy, and Current Role

In 1997, hyaluronic acid was approved for human use. It had been noted that there was a reduction in the molecular weight of synovial fluid as well as intra-articular hyaluronic acid synthesis with aging. Additionally, there was an increase in hyaluronic acid degradation. Because hyaluronic acid is synthesized by hyaluronic acid synthases ranging from lower molecular weight to higher molecular weight (HMW), many of the biologic actions of hyaluronic acid are dependent on the molecular size of the ligand, which is a binding molecule of a protein. Furthermore, several studies found significant differences in HMW hyaluronic acid versus short oligosaccharide chain hyaluronic acid and noted that short oligosaccharide chain hyaluronic acid (lower-molecular-weight hyaluronic acid) can act as ligands that cause a proinflammatory response through mediated receptor signaling pathways and thus molecular weight distribution is important to consider.[36] IAHA provides pain relief by suppressing proinflammatory cytokines and chemokines and promotes the synthesis of anti-inflammatory mediators. It further enhances chondrocyte metabolism, decreases the rate of

chondrocyte apoptosis, and stimulates the synthesis of endogenous hyaluronic acid.[37] Cross-linking of the hyaluronic acid compound can increase residence time (the amount of time hyaluronic acid remains in the knee joint) in trace amounts up to 26 weeks, whereas without cross-linking, excretion of hyaluronic acid will occur in the first 24 hours of administration. Prolonged residence time provided by HMW/cross-linked viscosupplementation results in an increased production of endogenous hyaluronan with increased inhibition of matrix metalloproteinases.[38]

There is good evidence for using hyaluronic acid in the management of osteoarthritis of the knee in that there are multiple studies that confirm a delay in TKA varying between 6 months and 7 years when using HMW/cross-linked hyaluronic acid. In a study of more than 50,000 patients with osteoarthritis of the knee, repetitive doses over 3 years resulted in an increase in the delay of TKA after the initial onset of treatment.[39] There is also some evidence that viscosupplementation slows the progression of cartilage degeneration as noted in a level I prospective study by Wang et al.[40] In the patient group that did not receive HMW viscosupplementation, tibial cartilage volume decreased compared with the group that did receive HMW viscosupplementation with 2-year MRI follow-up in 78 patients. Furthermore, there may be some increase in the proteoglycan content of superficial cartilage subsequent to injection of HMW viscosupplementation based on T1rho MRI at 6 weeks.[41] McIntrye et al[42] noted that there was a significant decrease in the use of opioids subsequent to HMW hyaluronic acid in 152,953 patients with symptomatic osteoarthritis of the knee. In patients with grade II and grade III articular cartilage changes at the time of arthroscopy of the knee, a meta-analysis shows improvement in symptoms in most articles in the literature, with decreased pain, decreased pain on motion, and a decrease in crepitus at 3- and 6-month follow-up.[43]

Thus, if there is a significant amount of data confirming the efficacy of HMW/cross-linked viscosupplementation, why did the AAOS come out with a strong recommendation against its usage for the management of osteoarthritis of the knee in 2013 in the nonarthroplasty guideline for the management of knee osteoarthritis? To answer this question, it is critical to understand that the AAOS clinical practice guidelines (CPGs) only use level I studies when available. Unfortunately, using this criterion, there were fewer than 10 articles available that the committee thought met the criteria for review out of more than 1,000 articles analyzed. In their analysis, the committee thought that the effect size was not clinically significant, which the AAOS defined as a "statistically significant difference in treatment effect where the lower limit of the 95% confidence interval is greater than the minimal clinically important improvement" metric.[44,45] This conclusion may have been based on flawed methodology and interpretation of minimal clinically important differences of patient-reported outcomes.[46] Furthermore, as noted by Vangsness et al,[47] there is no universal standard for calculating minimal clinically important differences because there are as many as nine published methods.

In 2017, the population of the United States was more than 328 million; 182 million lives were commercially insured (employer based), 118.7 million were covered by Medicare or Medicaid, 15.6 million had military insurance, and 28 million remained uninsured. Medicare accounts for more than 54 million lives and covers all approved uses of IAHA injections. However, since the 2013 AAOS CPGs for the nonarthroplastic management of knee osteoarthritis were published, 17 major insurance carriers representing approximately 30% of all private insurance currently covered lives do not pay for IAHA injections.[47] The AAOS CPG on the nonarthroplastic management of knee osteoarthritis is being updated, and a new edition with possible changes is anticipated in 2021.

It has been noted in recent surveys that orthopaedic surgeons from several subspecialty societies have exhibited a lack of compliance with the 2013 AAOS nonarthroplasty knee osteoarthritis published CPG. In a survey of the American Association of Hip and Knee Surgeons, of 345 responses in patients with Kellgren-Lawrence grade 2 and 3 osteoarthritis of the knee, IAHA was the most selected intervention not recommended by the AAOS. This led the authors to state the following: "Apparently, the AAOS guidelines on the treatment of OA have not reached the orthopedic community resulting in lack of treatment consensus and continued use of modalities with no proven patient benefits." They further went on to state that "given the disparity between the recommendations and actual practice, the orthopaedic community needs education re: the efficacy of this modality."[48] In a letter to the editor published in the *Journal of the American Academy of Orthopaedic Surgeons* on February 15, 2018, Spitzer and Bert[49] stated the following in response: "We encourage the authors to further survey their membership to determine the true reason for their non-compliance. We also encourage the AAOS leadership to revisit their Guidelines with inclusion of more data, proper statistical analysis, and conclusions that provide more options for patients suffering with painful Osteoarthritis of the Knee, and the clinicians struggling to treat them." The AAOS mission statement states that the "AAOS will champion the interests of all patients … and advance the highest quality of musculoskeletal health."[49] Lubowitz et al[50] correctly asserted that "…it is not in the interests of ALL patients to recommend against a treatment that is of significant benefit for SOME patients, especially when

that treatment is for a disease that is not preventable, and for which there is no cure."

Since 2013, multiple articles have been published discussing the advantages of HMW viscosupplementation. In a review of 68 randomized studies by Altman et al with a 26-week minimum follow-up, it was concluded that HMW viscosupplementation (>3 million daltons) had greater efficacy than lower-molecular-weight viscosupplementation.[51] In the 2016 *JBJS Reviews*, Johal et al[52] concluded that "recently published articles suggest that VS is a safe option with a clinically important reduction in pain for younger patients with osteoarthritis of the knee in those formulations with HMW or hyaluronic acid cross-linking." In a Cochrane review, Evaniew et al[53] concluded that there were "overall benefits to IAHA in comparison with placebo for pain, function, and patient global assessment score." In a systematic review of 49 trials, Percope de Andrade et al[54] confirmed that the effect size favored hyaluronic acid by 4 weeks and had a residual effect at 24 weeks compared with steroids. Bannuru et al[55] showed that IAHA had a clinical effect size that is two to three times greater than that of standard of care oral pain medication and the effect size is comparable with standard of care NSAIDs. Bhadra et al[56] in 2017 published an article on appropriate use criteria for hyaluronic acid in the management of osteoarthritis of the knee and like Johal et al concluded that hyaluronic acid should be used in patients with mild to moderate osteoarthritis of the knee who have been unsuccessful with pharmacologic or nonpharmacologic therapies.

Patient perceptions of current treatment modalities for mild to moderate osteoarthritis of the knee were published by Posnett et al[57] comparing exercise, physical therapy, acupuncture, magnetic pulse therapy, topical creams and patches, glucosamine chondroitin sulfate, nonnarcotic oral analgesics, NSAIDs, narcotics, steroid injections, HMW viscosupplementation injections, and arthroscopic surgery. This study consisted of more than 2,000 patients in 5 European countries, and the patients simply responded subjectively with the extent of satisfaction occurring when they underwent all these different treatment modalities. They were asked whether they were satisfied with their current treatment strategies and what was the perceived effectiveness of current treatment strategies. HMW viscosupplementation had the highest score of perceived effectiveness of all the treatment modalities at 74%, and 66% were satisfied with the viscosupplementation injection, which again had the highest satisfaction rating among all the other treatment modalities.

The economics of care needs to be addressed when recommending treatment for a disease that has no cure. Cost-effectiveness of a treatment modality can be measured economically by quality-adjusted life-years, which may be as high as $12,800/yr with avoidance of surgery.[58] IAHA may be of greater value than conventional care, with two studies noting that it is less costly and more effective plus it appears to postpone TKA, and thus using a metric termed incremental cost effectiveness ratio may be as high as $38,741/quality-adjusted life year.[59,60] With the new AAOS knee osteoarthritis CPG on the horizon, change may be in the offing.

The Role of Injectable Biologics: Platelet-Rich Plasma and Stem Cells

As a result of the concerns of safety of corticosteroids, the efficacy of hyaluronic acid, and the desire of patients to use the latest biologic treatment strategies, platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and adipose-derived stromal vascular fraction (SVF) have entered the realm of injectables used to manage osteoarthritis of the knee.

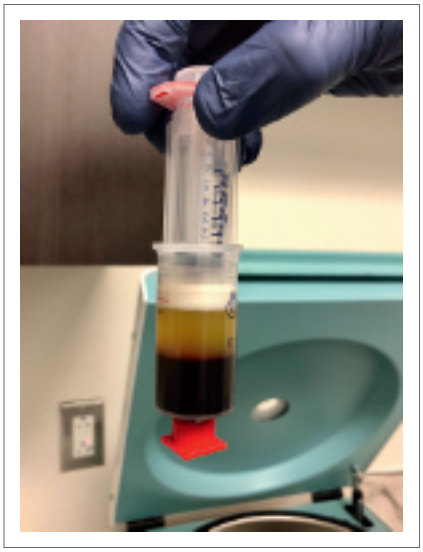

FIGURE 7 Photograph shows a double-syringe system after centrifugation showing separation of blood contents with platelet-rich plasma (above) and red blood cells (below).

Platelet-Rich Plasma

PRP is by far the most studied injectable biologic for osteoarthritis of the knee, and there is emerging evidence that PRP is a safe nonsurgical treatment option. PRP is prepared by drawing autologous blood by venipuncture and then centrifuging the blood and separating the plasma layer from the rest of the blood contents (**Figure 7**). PRP contains a hyperphysiologic concentration of platelets, at least two times the concentration of platelets in blood. Platelets are among the first cells arriving at the site of tissue injury and help release growth factors that play a critical role in regulating inflammation and collagen synthesis.[61] PRP is therefore thought to be capable of enhancing tissue repair because of its high concentration of growth factors. PRP preparations are typically further categorized into leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) preparations. LP-PRP is generally regarded as anti-inflammatory, whereas LR-PRP is more inflammatory.[62] The exact definition of PRP has not been determined

in terms of the concentration of platelets. Most published reports differ in their reporting of PRP concentrations. There is no standard protocol for obtaining and processing PRP. Furthermore, there is variability in the number of injections administered in studies, ranging from a single injection to a series of three weekly injections. The level of evidence ranges from case reports to systematic reviews and meta-analyses. From a reimbursement perspective, most commercial insurance providers and Medicare consider PRP a noncovered service.

Cole et al[63] performed a randomized controlled trial on a total of 111 patients with symptomatic osteoarthritis of the knee who received a series of either LP-PRP or hyaluronic acid injections. No difference was found between hyaluronic acid and PRP at any time point in the primary outcome measure: the WOMAC pain score. However, significant improvements were seen in other patient-reported outcome measures, with results favoring PRP over hyaluronic acid. Belk et al[64] performed a meta-analysis of level I studies looking at PRP versus hyaluronic acid for osteoarthritis of the knee. Mean improvement was significantly higher in the PRP group (44.7%) than the hyaluronic acid group (12.6%) for WOMAC total scores. LP-PRP was associated with significantly better subjective International Knee Documentation Committee scores versus LR-PRP. The authors concluded that patients undergoing treatment for knee osteoarthritis with PRP can expect to experience improved clinical outcomes when compared with hyaluronic acid. A systematic review by Laver et al[65] examined 29 well-designed studies on the management of cartilage degeneration, including 26 studies evaluating osteoarthritis of the knee. PRP was found to have better outcomes than hyaluronic acid. The review concluded that PRP is safe and effective for improvements in pain and function for patients with sustained benefit lasting 12 months. Shen et al[66] performed a meta-analysis looking at 14 randomized controlled trials comparing PRP with various controls including placebo, hyaluronic acid, corticosteroid injections, oral medications, and homeopathic treatment. The meta-analysis showed a significant improvement in WOMAC scores at 3-, 6-, and 12-month follow-up for the PRP group. Subgroup analyses showed PRP to be more effective in patients with mild to moderate osteoarthritis. The authors concluded that intra-articular PRP injections are more efficacious in the management of osteoarthritis of the knee than other alternative injections in terms of pain relief and patient-reported outcomes.

With regard to various PRP formulations, developing orthopaedic literature suggests that LP-PRP is the preferred preparation for osteoarthritis of the knee with variable results found with LR-PRP.

LP-PRP may be better suited for management of knee osteoarthritis because it may increase extracellular matrix repair, reduce inflammation, and slow cartilage degeneration.[67] Kon et al[68] compared a series of three LR-PRP injections with two different preparations of hyaluronic acid. The PRP group showed stronger and longer efficacy than the hyaluronic acid groups. However, when the authors followed with a randomized controlled trial comparing PRP with hyaluronic acid, they did not find superior clinical improvement in the PRP group. Platelets were increased by a factor of 4.6 and leukocytes by a factor of 1.1. Leukocyte differentials were not reported.[69] A meta-analysis by Riboh et al[70] compared LP-PRP and LR-PRP in the management of osteoarthritis of the knee and found that LP-PRP injections resulted in significantly improved WOMAC scores compared with hyaluronic acid or placebo. In contrast, no statistically significant difference was found between LR-PRP preparations and hyaluronic acid or placebo. Filardo et al[69] studied LR-PRP injections and found no statistical difference when compared with hyaluronic acid injections, providing further evidence that LP-PRP may be the preferred preparation for the management of osteoarthritis. The biologic basis for this may be in the relative level of inflammatory versus anti-inflammatory mediators present in LR-PRP and LP-PRP. Inflammatory mediators, tumor necrosis factor alpha, IL-6, interferon gamma, and IL-1β are increased significantly in the presence of LR-PRP, whereas injection of LP-PRP increases IL-4 and IL-10, which are anti-inflammatory mediators.[71,72] In addition to its deleterious effects on chondrocytes, LR-PRP may also fail to help manage osteoarthritic symptoms because of its effect on synoviocytes. Braun et al[62] found that management of synovial cells with LR-PRP or erythrocytes resulted in significant proinflammatory mediator production and cell death.

A large and growing number of well-designed studies in the literature support the notion that intra-articular injection of LP-PRP is a safe treatment for osteoarthritis of the knee. There is level I evidence demonstrating its ability to reduce pain symptoms and increase function in patients in whom knee osteoarthritis is diagnosed with sustained benefit lasting up to 12 months. Larger studies with longer follow-up are needed to determine optimal platelet concentration amounts, number of injections, and its long-term efficacy.

Bone Marrow Aspirate Concentrate

BMAC is another biologic treatment option for osteoarthritis of the knee. BMAC is commonly used to describe a mixture of bone marrow cellular elements such as platelets, white blood cells, red blood cells, and hematopoietic precursors including mesenchymal stem cells (MSCs).[73] Recently, the role of these MSCs in the management of arthritis has been found to be more paracrine in nature, hence the proposed renaming of MSCs from mesenchymal stem cells to medicinal signaling cells.

MSCs are often harvested from bone marrow aspiration, typically from the iliac crest, and centrifuged to isolate cellular components.[74] BMAC is a popular method of delivering MSCs because it is one of the few methods allowed by the FDA to deliver stem cells because of its minimally manipulated nature. At the time of this writing, the evidence is lacking to support the clinical use of BMAC for osteoarthritis of the knee. Although there are small case series supporting its clinical efficacy, there is a paucity of well-designed, level I studies showing its clinical superiority to PRP and other injectable biologics.

A comparative study of the components of PRP and BMAC found that BMAC contains a higher number of cells that will differentiate and a higher concentration of potentially advantageous chemokines.[75] Centeno et al[76] reported on 840 procedures involving BMAC (along with either lipoaspirate or platelet-poor plasma, dextrose, platelet lysate) and found moderate survey response rates, 66% and 74%. The mean numerical pain rating scale score, of a possible 10, decreased from 4.0 to 2.6 and from 4.3 to 3.0 in the two groups. The authors concluded that BMAC injections for osteoarthritis of the knee showed encouraging outcomes and a low rate of adverse events. The addition of an adipose graft to the BMAC did not provide a detectible benefit over BMAC alone. Shapiro et al[77] performed a single-blinded, placebo-controlled study investigating BMAC for osteoarthritis of the knee. Study participants had bilateral knee osteoarthritis and one knee received BMAC, whereas the other knee received saline as a control. At 6 months, the authors found improvement in both groups but no significant difference between BMAC and saline.

Anz et al[78] performed a randomized controlled trial to compare the efficacy of BMAC with PRP for the treatment of osteoarthritis of the knee. They found no statistically significant differences in baseline International Knee Documentation Committee or WOMAC scores between the two groups at different time points up to 12 months. All pain and functional scores for both the PRP and BMAC groups significantly improved from baseline with no difference between PRP and BMC at any time point up to 12 months. BMAC is a more invasive procedure than PRP and is associated with more complications such as infection. Given the lack of strong clinical evidence supporting its superiority to PRP, it cannot be recommended over other biologic injections such as PRP at this time. Further research is needed to evaluate its safety and efficacy as biologic treatment option for osteoarthritis of the knee.

Adipose-Derived SVF

SVF is a biologic treatment option for osteoarthritis of the knee, but it would be inaccurate to call SVF a stem cell therapy. SVF is collected through liposuction to obtain adipose tissue, which is then separated from the extracellular matrix by adding collagenase. The lipoaspirate is then washed with a normal saline solution to remove the collagenase, often followed by centrifugation leading to SVF, which can be injected into the knee.[79] There are a small number of studies looking at the effect of SVF on patients with osteoarthritis of the knee, but all are case series or cohort studies with significant limitations. There are not enough well-designed, level I studies to currently recommend injecting of SVF in patients with osteoarthritis of the knee.

Yokota et al[80] performed a cohort study looking at both SVF and adipose-derived stem cells in patients with osteoarthritis of the knee. There were no major complications. Both groups reported improvements in visual analog scale and KOOS scores. Tsubosaka et al[81] performed a case series consisting of 57 patients injected with SVF for osteoarthritis of the knee. Significant improvements were found in total WOMAC, visual analog scale, and KOOS scores at all time points up to 12 months postoperatively compared with preoperative scores. Panchal et al[82] found significant improvements in pain, quality of life, and function for at least 12 months after the injection of SVF in patients with refractory, severe (Kellgren-Lawrence grade 3 or 4) osteoarthritis of the knee. Di Matteo et al[83] performed a systematic review of 13 articles studying BMAC and SVF in patients with osteoarthritis of the knee. This review was limited by the fact that most studies did not look at knee osteoarthritis only and did not study SVF injection alone. Despite these significant limitations, SVF was found to be a relatively safe procedure with minimal complications and no serious adverse events. The authors found that SVF injection led to positive clinical outcomes with a significant improvement in pain and function. Similar to BMAC, SVF is a significantly more invasive procedure than PRP and is associated with more complications such as effusion, infection, and liposuction adverse events. Given the lack of strong clinical evidence supporting its superiority to other treatment options, it cannot be recommended over other nonsurgical treatment options at this time.

Summary

With the aging of the population and increasing comorbidities, injectable treatment strategies for osteoarthritis of the knee are becoming more attractive. Corticosteroids have been used for this purpose since the 1950s. Standard steroid preparations (soluble or crystalline suspension) have a short duration of efficacy. TA-ER delivered via a novel poly (lactic-co-glycolic acid) microsphere results in rapid onset (4 days) and long duration (16 weeks) of clinically meaningful benefit, which can be repeated when needed. The use of hyaluronic acid to manage osteoarthritis of the knee was not supported by the 2013 CPG of the AAOS. The use of

HMW/viscosupplementation continues because of its safety profile, ability to be repeated on a regular basis, and its substantial benefit, particularly in mild to moderate osteoarthritis of the knee (Kellgren-Lawrence grade 1–3). Its use in more advanced cases (Kellgren-Lawrence grade 3–4) can postpone the need for knee arthroplasty. An updated AAOS CPG on nonsurgical management of knee osteoarthritis is forthcoming. The evidence in support of PRP injections for management of knee osteoarthritis is rapidly expanding with multiple, well-designed randomized controlled trials demonstrating efficacy and clinical superiority to hyaluronic acid and older corticosteroid preparations. There is still an overall lack of quality needed to answer major research questions such as clinical and structural efficacy of PRP, optimal cell dose, number of injections, and specific protocols for cell delivery.[84] There is a significant lack of high-quality evidence to support the routine injection of BMAC, SVF, or any other injectable biologic (except PRP) in patients with osteoarthritis of the knee.

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