Corticosteroid injections for knee osteoarthritis are supported by the literature: in the affirmative

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Nicolas S. Piuzzi and Michael A. Mont

Knee osteoarthritis constitutes a public health concern of immense dimensions, and places a burden on society similar to few other conditions.[1,2] Emphasis has been placed on the development of disease-modifying approaches that can revert or at a minimum delay the progression of the disease.[3] However, to date, no such treatment has been proven nor is any available for patients. Despite much hype and reports of novel regenerative treatments, which include cell-based therapies and other orthobiologics, these are still yet to be proven or remain unavailable for the vast majority of patients suffering from knee osteoarthritis.[4,5] Therefore, current knee osteoarthritis treatments are centered upon symptom-modifying approaches in an attempt to reduce pain and to improve function while the disease pursues its almost inevitable progressive course.

In addition to 'standards of care', such as weight loss, physical therapy, analgesics, activity modification, and strengthening exercises, intra-articular corticosteroids remain one of the mainstays of treatment utilized in clinical practice.[1] Most patients (~80%) with symptomatic knee osteoarthritis show a therapeutic response to intra-articular injections of corticosteroids, therefore, the debate is centered upon the longevity of symptom relief.[6] The relatively short effect is probably related to rapid systemic absorption from the joint, which not only limits the extent of local anti-inflammatory effects, but also can lead to undesirable cardiovascular and metabolic systemic reactions.[7,8] A recent article published in *JAMA* stated that 'until more data becomes available there is no good reason to use' a novel Food and Drug Administration-approved microsphere-based extended-release formulation of synthetic corticosteroid triamcinolone acetonide (Zilretta, Flexion).[6] Respectfully, we have reservations regarding this strong statement and believe that further consideration of this issue is needed based on the available evidence.

The clinically important benefits of intra-articular corticosteroids have long been challenged.[9] A Cochrane systematic review concluded that the clinically important benefits of intra-articular corticosteroids remain unclear, especially after 1–6 weeks after administration.[10] In a later review, Jüni *et al.* reported that despite the overall quality of the evidence being limited by considerable heterogeneity between trials, and evidence of small-study effects, when stratifying results according to length of follow-up, benefits seemed to be moderate at 1–2 weeks after end of treatment (standardized mean difference [SMD] −0.48, 95% confidence interval [CI] −0.70 to −0.27), small to moderate at 4–6 weeks (SMD −0.41, 95% CI −0.61 to −0.21), small at 13 weeks (SMD −0.22, 95% CI −0.44 to 0.00), and no evidence of an effect was seen at 26 weeks (SMD −0.07, 95% CI −0.25 to 0.11).[11] Therefore, in this setting, the new Food and Drug Administration-approved drug Zilretta (Flexion) proposed for intra-articular injection for osteoarthritic knee pain appears quite attractive for the treatment of these patients. An encouraging pharmacokinetic phase II open-label study that enrolled 81 patients compared intra-articular triamcinolone acetonide delivered as an extended-release, microsphere-based formulation (FX006) (n = 63) *versus* a crystalline suspension (n = 18) in patients with knee osteoarthritis. Interestingly, triamcinolone acetonide concentrations following FX006 were quantifiable through week 12, whereas in the crystalline suspension, only two of eight patients had quantifiable values at week 6.[12] In addition, triamcinolone acetonide delivered as an extended-release, microsphere-based formulation had diminished peak in plasma levels, and thus reduced systemic exposure to corticosteroids compared with crystalline suspensions. Also, the largest phase III, multicenter, double-blinded, 24-week study, which randomized 484 patients (40–85 years old), who had moderate-to-severe knee osteoarthritis

Correspondence to:
Nicolas S. Piuzzi
Department of Orthopaedic Surgery, Cleveland Clinic, 9500 Euclid Avenue, ND2, Cleveland, Ohio 44195, USA Instituto Universitario del Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
piuzzin@ccf.org; nspiuzzi@gmail.com

Michael A. Mont
Department of Orthopaedic Surgery, Lenox Hill Hospital, New York, USA

pain to receive triamcinolone acetonide extended release (ER) 32 mg, saline placebo, or a standard crystalline suspension of triamcinolone acetonide (TAcs) 40 mg (active control), had pivotal results. Overall, triamcinolone acetonide ER significantly reduced the average daily pain intensity score at week 12 compared with placebo (−3.12 *versus* −2.14, primary endpoint; $p < 0.0001$).[13] These results are encouraging, however, when compared with TAcs; triamcinolone acetonide ER did not have significant differences in average daily pain change from week 1 through 12 despite performing more favorably with respect to exploratory end points, as evidenced by greater improvements in The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale scores for pain ($p \leqslant 0.0475$), stiffness ($p \leqslant 0.0182$), and physical function ($p \leqslant 0.0111$) and the Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QOL) subscale score ($p \leqslant 0.0256$) at weeks 4, 8, and 12.

Partnerships between industry and academia can certainly produce high-quality patient-oriented research and are becoming more relevant in the context of reduced federal funding for research.[14] If safeguards are set in place to avoid bias and maintain appropriate research ethics, such relationships may lead to important advancements for patient with knee osteoarthritis in the near future. The efficacy of injections therapies for the treatment of knee osteoarthritis, and the potentially decreasing effect after subsequent injections are delivered continues to be a matter of debate. There is certainly a need for further cost/benefit analyses to establish the new corticosteroid-suspension agent's value versus traditional formulations. Future research will define if widespread use of novel formulations such as these microsphere-based extended-release formulations of triamcinolone acetonide in clinical practice are further justified. In the meanwhile, there are no reasons why these injections should not be offered to patients in light of the results of these recent reports.

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ORCID iD

Nicolas Santiago Piuzzi https://orcid.org/0000-0003-3007-7538

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