Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis
A Randomized Clinical Trial

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IMPORTANCE Synovitis is common and is associated with progression of structural characteristics of knee osteoarthritis. Intra-articular corticosteroids could reduce cartilage damage associated with synovitis but might have adverse effects on cartilage and periarticular bone.

OBJECTIVE To determine the effects of intra-articular injection of 40 mg of triamcinolone acetonide every 3 months on progression of cartilage loss and knee pain.

DESIGN, SETTING, AND PARTICIPANTS Two-year, randomized, placebo-controlled, double-blind trial of intra-articular triamcinolone vs saline for symptomatic knee osteoarthritis with ultrasonic features of synovitis in 140 patients. Mixed-effects regression models with a random intercept were used to analyze the longitudinal repeated outcome measures. Patients fulfilling the American College of Rheumatology criteria for symptomatic knee osteoarthritis, Kellgren-Lawrence grades 2 or 3, were enrolled at Tufts Medical Center beginning February 11, 2013; all patients completed the study by January 1, 2015.

INTERVENTIONS Intra-articular triamcinolone (n = 70) or saline (n = 70) every 12 weeks for 2 years.

MAIN OUTCOMES AND MEASURES Annual knee magnetic resonance imaging for quantitative evaluation of cartilage volume (minimal clinically important difference not yet defined), and Western Ontario and McMaster Universities Osteoarthritis index collected every 3 months (Likert pain subscale range, 0 [no pain] to 20 [extreme pain]; minimal clinically important improvement, 3.94).

RESULTS Among 140 randomized patients (mean age, 58 [SD, 8] years, 75 women [54%]), 119 (85%) completed the study. Intra-articular triamcinolone resulted in significantly greater cartilage volume loss than did saline for a mean change in index compartment cartilage thickness of −0.21 mm vs −0.10 mm (between-group difference, −0.11 mm; 95% CI, −0.20 to −0.03 mm); and no significant difference in pain (−1.2 vs −1.9; between-group difference, −0.6; 95% CI, −1.6 to 0.3). The saline group had 3 treatment-related adverse events compared with 5 in the triamcinolone group and had a small increase in hemoglobin A1c levels (between-group difference, −0.2%; 95% CI, −0.5% to −0.007%).

CONCLUSIONS AND RELEVANCE Among patients with symptomatic knee osteoarthritis, 2 years of intra-articular triamcinolone, compared with intra-articular saline, resulted in significantly greater cartilage volume loss and no significant difference in knee pain. These findings do not support this treatment for patients with symptomatic knee osteoarthritis.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01230424

Symptomatic knee osteoarthritis was estimated to affect more than 9 million individuals in the United States in 2005 and is a leading cause of disability and medical costs, most of which were attributable to arthroplasty. Treatments for osteoarthritis are primarily prescribed to reduce symptoms, with no interventions known to influence structural progression.

Evidence suggests that osteoarthritis is an inflammatory condition. Studies demonstrated the presence of synovitis in osteoarthritic joints accompanied by mononuclear cells and proinflammatory mediators with up-regulation of aggrecanases and collagenases. Clinical and epidemiological studies found that inflammation is common in the knee joints of people with knee osteoarthritis and associated with progression of cartilage damage. These observations suggest that suppression of inflammatory processes by corticosteroids (already in widespread clinical use for knee osteoarthritis) might reduce progression of knee osteoarthritis. This possibility is supported by interventional studies in animal models of osteoarthritis. However, associations of intra-articular corticosteroids with adverse joint outcomes in some observational studies involving people with osteoarthritis, together with their known antianabolic effects on healthy cartilage, have raised questions about their potential to damage joints. A 2-year clinical trial suggested that there were no adverse effects associated with intra-articular corticosteroids but was limited because radiography was used to evaluate osteoarthritis progression. Radiography is insensitive to osteoarthritis progression and does not directly image critical soft-tissue structures or bone marrow lesions. Therefore, a 2-year clinical trial of repeated intra-articular triamcinolone injections was performed to test the benefits and harms of intra-articular corticosteroids in the treatment of knee osteoarthritis, using magnetic resonance imaging (MRI) to evaluate articular structures.

Methods

Overview

This was a 2-year double-blind clinical trial of intra-articular triamcinolone administered every 3 months vs saline for symptomatic knee osteoarthritis with ultrasonic evidence of synovitis. Outcomes were cartilage loss, articular structural damage, pain, and physical function. The study was performed at Tufts Medical Center between June 2011 and January 2015. It was approved by the Institutional Review Board of Tufts Medical Center. (The study protocol is available in Supplement 1.) Adaptive interim monitoring was initially planned but this approach was removed in March 2014 with the approval of the data and safety monitoring board when it became apparent that its disadvantages outweighed any advantages.

Sample

Patients were recruited through clinics and local advertisements. Telephone-administered prescreening was conducted before scheduling an on-site visit that included knee radiographs and blood tests. All participants provided written informed consent. Self-reported race/ethnicity and sex were collected.

Eligibility criteria included age 45 years or older and presence of knee osteoarthritis defined by the American College of Rheumatology classification criteria. These criteria are based on a standardized question about knee pain, and tibiofemoral osteoarthritis evident on posterior-anterior weight-bearing semi-flexed radiographs. Eligibility thresholds were placed for knee pain (score, ≥2 but ≤8 on the weight-bearing questions of the Western Ontario and McMaster Universities [WOMAC] pain subscale, range 0–12) and radiographic severity (Kellgren-Lawrence [KL] grade, 2 or 3). Potential participants had a clinical examination confirming pain from the knee joint and had to be willing to discontinue their analgesic medication for 48 hours before each pain assessment. Eligibility criteria included ultrasonographic evidence of effusion synovitis in the study knee, defined according to established protocols by a suprapatellar pouch depth larger than 2 mm. Ultrasonographic detection of effusion and synovitis is well-validated, and each is associated with prevalent and incident knee osteoarthritis. Exclusion criteria included other disorders affecting the study joint, such as systemic inflammatory joint disease, prior sepsis, osteonecrosis; chronic or recent use of oral corticosteroids, doxycycline, indomethacin, glucosamine, or chondroitin; recent (<3 months) intra-articular corticosteroids or hyaluronic acid; serious medical conditions (like uncontrolled diabetes, HIV infection, or hypertension) that could be contraindications to participation; and any contraindication to undergoing an MRI scan.

Randomization

Randomized treatment assignments were computer generated by the study statistician (M.L.) using SAS software and provided to the research pharmacy at Tufts Medical Center. The randomization was stratified by KL grade and sex, with 1:1 assignments permuted in blocks of 4. The investigative team and participants were blinded to group assignment.

Study Intervention

The active medication was 1 mL of triamcinolone (purchased from Bristol-Myers Squibb), 40 mg/mL, for injection. The...
comparator was 1 mL of 0.9% sodium chloride for injection (Hosperia Inc). Neither was mixed with local anesthetic. Both were administered every 12 weeks for 2 years. Synovial fluid (≤10 mL) was aspirated prior to the injection.

Toxicity Monitoring and Safety Procedures
At each visit, information on adverse effects was collected, vital signs obtained, including standard measurement of blood pressure, and blood was obtained for the hemoglobin A1c (HbA1c) assay. Knee MRI scans were screened for avascular necrosis or subchondral fracture. Oversight of treatment-specific results was provided by a National Institute of Arthritis and Musculoskeletal and Skin Disease-appointed data and safety monitoring board, which met in closed sessions.

Masking of Treatment Assignment
The research pharmacist prefilled the syringes and masked the contents using opacified labels and 3-way stopcock. Ultrasound guidance was used for the injection, but, after placement of the needle, the probe was removed to prevent visualization of medication. The clinician who performed the injections was not involved with outcome assessments in the study.

Concomitant Analgesic Use
Participants were asked to discontinue concomitant analgesics 2 days before each assessment to avoid masking symptoms of pain. Participants were advised to take acetaminophen only if needed.

Study Assessments
Following the screening visit, there were 9 visits scheduled at 3-month intervals over the 24-month period. Assessments included a knee examination; blood pressure measurement; WOMAC version 3.1 questionnaire (pain subscale range, 0 [no pain]-20 [extreme pain]; minimal clinically important improvement was a 3.94-difference in pain score; the stiffness subscale range, 0 [no stiffness]-8 [extreme stiffness]; function subscale range, 0 [no difficulty with daily activities]-68 [extreme difficulty], minimal clinically important improvement was a 6.66-difference in score)23; global knee pain assessment (range, 0 [no pain]-100 [extreme pain]), adverse event ascertainment; medication review; and serum HbA1c levels. Objective measures of functioning tests (timed 20-m walk and chair-stand test) every 6 months, and the 36-Item Short Form Health Survey (SF-36) were collected at baseline and at 12 and 24 months.

Magnetic Resonance Imaging
Participants underwent MRI scans at months 0, 12, and 24 (Achieva X-Series 3.0 Tesla scanner, Philips) operating sequences as follows: (1) for cartilage volume, 3-dimensional sagittal gradient echo with cartilage excitation, 3D_WATSc_SENSE: parallel imaging in right-left and anterior-posterior; recovery time, 20 ms; echo time, 7.6 ms; and field of view, 160 × 160 × 120 mm; matrix, 512 × 512; voxel size, 0.3 × 0.3 × 1.0 mm; flip angle, 12°; (2) for trabecular fast-field echo sequence, 3-dimensional T1 fast-field echo coronal recovery time, 20 ms; echo time, 4.92 ms; field of view, 120 mm; matrix, 51 × 512; voxel size, 0.2 × 0.2 × 1.0 mm; and flip angle, 50°; and (3) for the morphology sequence, proton density fat-suppressed in 3 planes, recovery time 3000 ms; echo time, 30 ms; field of view, 120 mm; matrix, 480 × 325; voxel size, 0.25 × 0.35 × 2.5 mm; flip angle, 90°.

Knee Joint Ultrasonography
Knees were scanned according to a standardized protocol19 in the longitudinal plane with the joint in 30° flexion using a LOGIQe Ultrasound machine and a 13.0-MHz transducer (both by General Electric).

Dropout is defined as not attending the 24-month visit.

a Patients who scored neither a Kellgren-Lawrence (KL) grade of 2 nor 3 were excluded.

b Patient scored 2 or higher on the weight-bearing question or 8 or less on the weight-bearing pain score according to the Western Ontario and McMaster Universities (WOMAC) index.
Bone Marrow Lesion and Effusion Volume Measurement

A validated semiautomated approach was used to measure bone marrow lesion volume using the sagittal proton density fat-suppressed images (intraterster reliability, >0.90). Effusion volume was measured using thresholds with predefined perimeters based on anatomic landmarks on the sagittal proton density fat-suppressed knee images. Intraterster reliability was good for effusion-synovitis volume (0.81).

Semiquantitative Assessment of Cartilage Damage

One reader (J.B.D.) evaluated MRIs for cartilaginous intrasubstance signal change, denudation, fissures, delamination, and superficial fibrillations, defined as fraying of the articular surface that appeared as a fine velvety surface or an indistinct articular margin. The intraterster agreement was good with a prevalence and bias-adjusted κ for progression of intrasubstance signal change of 0.80 and 0.55 for denudation. Fissures, delamination, and superficial fibrillations were uncommon. When present, these were reviewed with a musculoskeletal radiologist (R.J.W.) to reach consensus.

Analytic Plan

Coprimary outcomes were change in knee cartilage volume in the index compartment, assessed using cartilage thickness, and change in pain, assessed using the WOMAC pain subscale. All other outcomes were secondary and considered exploratory. Intention-to-treat analyses were used for all outcomes. Multiple imputation using the fully conditional specification method was performed to fill in missing values for the outcomes. For structural outcomes, KL grade, sex, age, self-reported race/ethnicity, and baseline and nonmissing values of the outcomes from other measurement points were used to impute missing values by treatment group. Pain and function outcomes were imputed similarly but with the addition of analgesia for breakthrough pain and without age. All analysis models were adjusted for randomization stratification factors of KL grade and sex. The pain and function outcomes were also adjusted for use of analgesia. Mixed-effects regression models were used with a random intercept for longitudinal repeated measures. Acetaminophen use was analyzed using logistic regression with the generalized estimating equations correction for repeated measures. All analyses were performed using SAS version 9.4 (SAS Institute Inc). All testing was 2-sided with P values <.05 considered significant. No adjustment was made for multiple comparisons.

Sample Size Calculation

Based on the original adaptive trial design and allowing for a 25% dropout rate, enrollment of 70 participants per group was selected to allow 80% power to detect a treatment difference of 90 mm³ in change cartilage volume over 2 years. There is no established minimally clinically important difference for cartilage volume loss. However, this corresponds to an effect size of 0.4 SDs using an anticipated SD of 224 mm³ as previously observed. This number also provided 80% power to detect a treatment difference of 2.3 units in WOMAC pain (range, 0-20) with an anticipated SD of 4.1.
Results

One hundred forty participants (70 to each group) were randomized from 445 in-person screening visits (Figure 1). The group assigned to receive triamcinolone injections was slightly older (Table 1) but otherwise comparable in demographic and clinical characteristics with the group randomized to receive saline injections (Table 1 and Table 2). Fifty-nine patients (84%) in the triamcinolone group and 60 (86%) in the saline group completed the final visit, with 990 of the possible 1120 intra-articular injections (88%) administered. In the mixed-model analyses, 408 imputations were made for structural outcomes (ie, 12% of 3360 possible data points). Adherence to washout protocol was 99%; use of medication for breakthrough pain was 7%.

The rate of cartilage loss in the index compartment was greater in the triamcinolone group for cartilage thickness (−0.21 vs −0.10 mm; between-group difference, −0.11 mm; 95% CI, −0.20 to −0.03 mm), and for the secondary cartilage damage index (mean change, −133.66 μm3; 95% CI, −177.39 to −89.93 μm3; between-group difference, −61.25 μm3; 95% CI, −121.78 to −0.72 μm3; Table 2). There were no significant differences between the 2 groups in progression of cartilage denudation, bone marrow lesion, effusion volume (Table 2), or in trabecular morphology. There were no significant differences between the 2 groups in change in subchondral tibia or in hip and in bone mineral density. Results of a completers’ analysis are presented in the eTable in Supplement 2. Semiquantitative cartilage abnormalities were not significantly different, except for superficial fibrillation, which was more common in the saline group (34% vs 13%; between-group difference, 21%; 95% CI, 7%–35%).

The decrease in knee pain did not significantly differ across treatment groups: −1.2 units in the triamcinolone vs −1.9 in the saline group; between-group mean difference, −0.64; 95% CI, −1.6 to 0.3). Also, there were no significant differences in any of the secondary patient-reported or objective clinical end points (Figure 2 and Table 3). Both groups exhibited a nonsignificant increase in high-sensitivity C-reactive protein (0.2 vs 0.1 mg/L; between-group mean difference, −0.1 mg/L; 95% CI, −0.4 to 0.2 mg/L). At the final visit, 45% of participants guessed their treatment assignment correctly.

There were more adverse events in the saline group (63 vs 52 participants, P = .02; 182 vs 131 events, P = .02). Eight were classified as treatment related, 3 in the saline group (1 cellulitis, 2 injection site pain) and 5 in the triamcinolone group (1 facial flushing, 4 injection site pain).

There were no significant differences in serious adverse events (P value = .06). One was classified as related (cellulitis, saline group). The incidence of new or worsening hypertension was not greater in the triamcinolone group (1 vs 2 events), and there were no instances of osteonecrosis or subchondral fracture. Hemoglobin A1c levels declined in the triamcinolone but increased in the saline group (−0.1% vs 0.2%; between-group difference, −0.2; 95% CI, −0.5 to −0.007, with adjustment for KL grade, sex, and body mass index).

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<th>Table 2. Treatment Effect on Structural Outcomes of Knees With Osteoarthritis</th>
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<td><strong>Mean (95% CI)</strong></td>
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*Higher natural log values for bone marrow lesions and effusion denote greater volumes affected by these findings. The natural log transformation was used for these measures due to pronounced skewness.†Index compartment indicates compartment with greatest joint space narrowing.
In this clinical trial investigating the benefits and risks of intra-articular corticosteroids, 40 mg of triamcinolone administered every 3 months over 2 years into knees with osteoarthritis and inflammation resulted in significantly greater cartilage volume loss and no significant difference in knee pain than did saline injections. These results contrast with a previous smaller trial that tested a similar regimen and found no difference in the rate of radiographic joint space loss and detected a benefit on knee pain in some secondary (but not primary) end points. The use of MRI in this study enabled direct quantitation of cartilage and soft-tissue structures and showed more cartilage loss in the triamcinolone group than in the saline group. Radiography does not image cartilage directly and is insensitive to change, so it may not have detected the small changes in cartilage loss measured on the MRIs in this study.

The 2-year change in the index compartment cartilage thickness was greater in the triamcinolone group with a between-group difference of −0.11 (95% CI, −0.20 to −0.03), which corresponds to a moderate effect size of 0.46 mm. A value for the amount of change in cartilage loss that would represent a minimally clinically important difference is not established; however, this change was smaller in magnitude than the cross-sectional differences between one KL grade measured in a prior natural history study (eg, 0.35 mm between grades 2 and 3). Increased progression was not detected in other osteoarthritis features, structurally or clinically. In fact, superficial fibrillation worsened more frequently in the saline group, although this may have been due to chance since secondary and semiquantitative structural measures showed no difference between groups. The effects that were detected on cartilage loss were statistically significant and consistent across different measurements. In vivo and clinical evidence show catabolic effects of corticosteroids. Although the cartilage loss was not associated with worsening of symptom outcomes, rates of cartilage loss have been associated with higher rates of arthroplasty, raising the possibility of potential for long-term adverse consequences on the health of the joint. Cartilage structure should be evaluated in any future clinical studies of similar therapeutics.

The hypothesis that intra-articular corticosteroids might reduce the rate of cartilage loss and other structural manifestations of osteoarthritis was based on recognition of the role of inflammation in its pathogenesis, and reduced structural progression observed in vivo. Suppression of inflammation could attenuate catabolic effects of inflammation and reduce articular damage. However, these results showed greater progression of knee cartilage volume loss and no sustained effect on intra-articular inflammation as indicated by persistence of effusion. As a proof-of-concept study, the results raise questions about the role of inflammation in osteoarthritis progression.

It has been suggested that intra-articular saline injection might have a therapeutic effect in osteoarthritis.
a hypothesis based on clinical trial results in which saline was used as a comparator with apparent symptomatic improvement.36 However, there is a strong placebo response to intra-articular injection, and no prior trials included a sham injection. Also, the rate of cartilage loss in this study was commensurate with that observed in prior natural history studies, so it is likely that the difference in cartilage loss rates between groups was due to an adverse effect of intra-articular corticosteroids on cartilage rather than a benefit from intra-articular saline.

Limitations
This study has several limitations. First, symptom ascertainment took place every 3 months with the goal of measuring long-term effects on these outcomes. Pain was not measured within the 4-week period after each injection, during which benefits are known to occur.37 Thus, any transient benefit on pain ending within the 3-month period between each injection could have been missed by these methods. Second, participants were permitted to continue their usual medications during the trial, which might have attenuated any between-group differences in symptom outcomes even though participants were asked to discontinue nonsteroidal anti-inflammatory drugs prior to each assessment, and the
use of analgesics taken for breakthrough pain was also adjusted for in the multivariate models. Third, high expectations and large placebo responses could also have affected assessments of effects, although these appeared modest compared with typical osteoarthritis trials. Fourth, this study was targeted at osteoarthritic knees that had some degree of inflammation, determined using ultrasonography. It is possible that this imaging technique lacks specificity in identifying inflammation, or that pain from knees with osteoarthritis and features of inflammation are paradoxically less likely to respond to triamcinolone, as was found in a previous study. Alternatively, although the dose regimen tested was consistent with clinical practice guidelines, it is possible that the dose or frequency was insufficient to generate sufficient anti-inflammatory effect to reduce pain in the long term.

Conclusions
Among patients with symptomatic knee osteoarthritis, 2 years of intra-articular triamcinolone, compared with intra-articular saline, resulted in significantly greater cartilage volume loss and no significant difference in knee pain. These findings do not support this treatment for patients with symptomatic knee osteoarthritis.

REFERENCES


