Inflammatory Characteristics on Ultrasound Predict Poorer Longterm Response to Intraarticular Corticosteroid Injections in Knee Osteoarthritis

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ABSTRACT. ***Objective.*** To assess whether inflammation on ultrasound is predictive of clinical response to intraarticular (IA) corticosteroid injections in patients with knee osteoarthritis (OA).

Methods. Patients with symptomatic knee OA were randomized to receive either an IA injection of 40 mg triamcinolone acetonide in the treatment group or 1 cc 0.9% saline in the placebo group. Clinical response was assessed by changes in baseline Western Ontario and McMaster Universities (WOMAC) index scores and physician global assessment at 4 and 12 weeks. Ultrasounds were performed at each visit. Patients and assessors were blinded to treatment status.

Results. Seventy-nine patients were enrolled into the study. Four-week data were available for 67 patients in the primary analysis comparing change in WOMAC pain score from baseline to 4 weeks. There was almost no change in the WOMAC pain subscale score from baseline to 4 weeks in the control group, but there was a significant improvement in WOMAC pain subscale score from 10.8 (SD ± 3.2) at baseline to 8.75 (SD ± 4.0) at 4 weeks in the treatment group (adjusted p = 0.001). Of the 34 patients in the treatment group; 16 (47%) had inflammatory disease and 18 (53%) had noninflammatory disease as determined by ultrasound. There was no difference in the change in WOMAC pain score between the inflammatory and noninflammatory patients in the treatment group at 4 weeks. There was a statistically significant greater improvement in pain subscale scores among noninflammatory patients than among inflammatory patients at 12 weeks.

Conclusion. Intraarticular corticosteroid injections are an effective short-term treatment for symptomatic knee OA compared to placebo. Patients with noninflammatory characteristics on ultrasound had a more prolonged benefit from IA corticosteroids compared to inflammatory patients. (First Release Jan 15 2010; J Rheumatol 2010;37:650–5; doi:10.3899/jrheum.090575)

Key Indexing Terms:
OSTEOARTHRITIS ULTRASOUND CORTICOSTEROIDS
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Osteoarthritis (OA) is the leading cause of rheumatic complaints in the United States, affecting nearly 27 million people. Symptomatic knee OA in particular is estimated to affect 12.1% of the population aged 60 years and older and is a significant source of morbidity and economic burden in the growing aging population[1]. Despite the high prevalence of OA, its pathogenetic mechanisms are unclear. Although OA was once thought to be a noninflammatory degenerative disease, it is now recognized that inflammation plays a role in its pathogenesis. However, it is unclear to what extent inflammation affects the natural history of OA. In addition, given the heterogeneity of the disease, it is unclear if inflammation may have a more prominent role in disease pathogenesis in certain subpopulations.

Intraarticular (IA) corticosteroid injection therapy has been used for over 50 years as a treatment option for symptomatic knee OA. Although originally used for inflammatory arthritis, it has been found to have clinical efficacy in some patients with OA. Studies in OA have produced conflicting results regarding the clinical predictors of response to IA corticosteroids; it has been suggested that they are most effective in patients with evidence of inflammation on physical examination. However, no study has examined ultrasound characteristics of patients prior to IA corticosteroid treatment. We examined whether evidence of inflammation on ultrasound is predictive of clinical response to IA corticosteroids in knee OA.

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MATERIALS AND METHODS

Patients were recruited from the musculoskeletal and arthritis clinics at the San Diego Veterans Affairs (VA) Hospital and the University of California San Diego (UCSD) Medical Center. Our study was approved by the UCSD Human Research Protections Program. Written informed consent was obtained from all patients.

All patients had radiographs of the affected knee within 1 year of enrollment. Patients with knee pain who met American College of Rheumatology (ACR) criteria[2] for knee OA were included in the study. Patients taking oral corticosteroids, who had a primary inflammatory connective tissue disease, or who had received IA corticosteroids in the affected knee within 3 months of study entry were excluded.

All patients had grayscale ultrasound examination of the affected knee at baseline. Patients were then randomized to receive an injection of either 1 cc of 40 mg/ml triamcinolone acetonide or 1 cc of 0.9% saline, which were drawn into a syringe covered with opaque tape prior to the patient encounter. Injections were given using a 22-gauge, 1.5-inch needle via an anterior lateral approach with the patient in an upright 90˚ position by a non-blinded physician who did not participate in the clinical assessments or ultrasound examinations. Repeat ultrasounds were performed at 4 and 12 weeks. Clinical change was assessed by the Western Ontario and McMaster Universities OA (WOMAC) index, physical examination, and physician global assessment. All patients and assessors were blinded. The clinical assessor was distinct from the physician performing ultrasounds and was blinded to ultrasound images and interpretations. The primary endpoint of our study was improvement in WOMAC pain subscale score at 4 weeks. A secondary endpoint was improvement in WOMAC pain subscale score at 4 weeks in patients with inflammatory characteristics on ultrasound compared to patients without inflammatory characteristics on ultrasound. Other secondary endpoints included WOMAC total pain score at 4 and 12 weeks, and physician global assessment using a visual analog scale (VAS) at 4 and 12 weeks for the treatment and control groups.

Thirteen consecutive patients had blood drawn for biomarker analysis at the baseline visit prior to randomization.

Ultrasound imaging. Patients who were randomized underwent grayscale ultrasonography of the affected knee at baseline, 4 weeks, and 12 weeks. At the VA Hospital, ultrasounds were performed with a 14-MHz linear transducer for the first two-thirds of the study, and an 8-MHz linear transducer for the last third of the study, when a different assessor was introduced (Acuson Sequoia 512). At the UCSD Medical Center, ultrasounds were performed with a GE Logiq e12 MHz linear transducer (GE Healthcare, Little Chalfont, UK) by the same assessor performing ultrasounds at the VA. All ultrasounds were performed by a rheumatologist experienced in the performance of musculoskeletal ultrasonography and blinded to the patients' treatment group status. Longitudinal and transverse views of the suprapatellar pouch of the affected knee were obtained. Saved static images were interpreted by an assessor experienced in the interpretation of musculoskeletal ultrasonography who was blinded to the treatments as well as the dates the images were obtained.

Inflammatory disease was defined *a priori* by the presence of synovial hypertrophy with or without effusion. We chose to use a dichotomous definition of inflammatory disease rather than a semiquantitative scoring system for synovial thickening because of the small patient subset. A pathologic effusion was defined by an effusion of ≥ 5 mm.

Biomarker analysis. Multiplex cytokine and chemokine analysis [interleukin 1ß (IL-1ß), IL-4, IL-6, IL-8, IL-10, IL-12 (p70), granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant proteins, macrophage inflammatory protein, tumor necrosis factor-α, and regulated on activation, normal T expressed and secreted] of inflammation biomarkers was performed on serum collected by venipuncture at the baseline visit prior to corticosteroid injection using Luminex technology (Luminex, Austin, TX, USA). Assays were performed with Bio-Plex reagents and measured on a Bio-Plex System (Bio-Rad, Hercules, CA, USA) according to the manufacturer's instructions. Serum pro-matrix metalloprotease (MMP) 1, pro-MMP-3, and C-reactive protein (CRP) levels were assayed by high sensitivity ELISA (R&D Systems, Minneapolis, MN, USA).

Statistics. Baseline characteristics were compared between treatment groups using either chi-squared or Fisher's exact tests for categorical factors and t-tests or Wilcoxon rank-sum tests for continuous factors. Primary and secondary comparisons of differences in WOMAC scores (pain or total) were performed using linear regression models, adjusting for baseline scores. Assumptions of normality and homogeneity of variances were checked using Shapiro-Wilk and Cook-Weisberg tests. Influence statistics were examined to determine whether any individual observations or small groups of observations had substantial influence on estimated measurements. Two-sided tests were used for all statistical analyses. P values were not adjusted for multiple comparisons because the tests performed could not be assumed to be independent and a Bonferroni correction was considered to be too conservative.

RESULTS

Baseline characteristics. Eighty patients were screened. Of these, 79 were randomized to receive an injection of either 40 mg triamcinolone acetonide (n = 40) or 1 cc of 0.9% saline (n = 39). A chart of the participation process according to Consolidated Standards of Reporting Trials guidelines is provided in Figure 1.

At 4 weeks, data from 67 patients were available for the primary analysis. Descriptive statistics are presented for the primary analysis cohort in Table 1. There were 65 men and 2 women, with an average age of 64.3 years (SD 11.9). The median disease duration was 14 years (range 0.3–51 yrs). Average baseline WOMAC pain scores were comparable between the treatment and control groups. Average baseline WOMAC total scores were slightly higher in the treatment group compared to the control group (51.6 vs 45.3; p = 0.10). Within the treatment group, WOMAC pain subscale scores were higher among patients with inflammation at baseline as well as after 4 weeks and 12 weeks (Table 2). However, among both the treatment and control groups, there were no statistically significant differences in baseline WOMAC pain scores between patients with inflammation and without inflammation.

Effect of IA corticosteroids vs placebo. There was a significant difference in improvement of the WOMAC pain subscale score from baseline to 4 weeks comparing the treatment to the control group [–1.9 (± 0.6; p = 0.001) after adjusting for baseline values], with a greater improvement in the treatment group. Changes in WOMAC composite scores were also significantly different between treatment and control groups at 4 weeks, but neither the change in WOMAC pain subscale nor the change in composite score was significantly different at 12 weeks. A decrease in pain subscale and composite scores among the treated group remained after 12 weeks, but this was not statistically significant. Similarly, the change in VAS scores was statistically significantly different between the treatment and control group at 4 weeks (p = 0.03), but not at 12 weeks (Table 3).

Clinical response of IA corticosteroids in inflammatory and

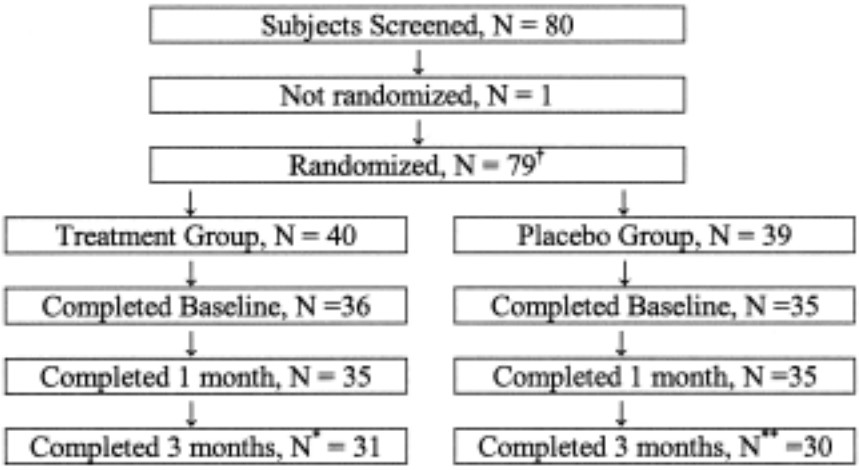

Figure 1. Participation in the study. †Includes 3 patients who were randomized twice; 2 of these were re-enrolled because outcome measures could not be obtained for the first enrollment. It was discovered after randomization that a third patient had participated 3 years before. They are reported here under the randomization with completed baseline assessment. *These include 2 patients in the treatment group who had not completed a 1-month followup visit. **These include 1 patient in the placebo group who had not completed a 1-month followup visit.

Table 1. Descriptive statistics for primary analysis cohort (n = 67). Baseline characteristics were compared between treatment groups using either chi-square of Fisher exact tests for categorical factors and t-tests or Wilcoxon rank-sum tests for continuous factors.

	Control	Treatment	Total	p
N (%)	33 (49)	34 (51)	67	
Sex (%)				0.24
Women	2 (100)	0 (0)	2	
Men	31 (48)	34 (52)	65	
Inflammatory (%)				0.38
Yes	12 (43)	16 (57)	28	
No	21 (54)	18 (46)	39	
Age, yrs, mean (SD)	63.2 (12.4)	65.3 (11.6)	64.3 (11.9)	0.49
	n = 33	n = 34	n = 67	
Disease duration, yrs, median (minimum, maximum)	12.5 (0.3, 40)	18.5 (0.3, 51)	14 (0.3, 51)	0.44+
	n = 30	n = 26	n = 56	
Baseline WOMAC pain score, mean (SD)	10.1 (3.3)	10.8 (3.2)	10.5 (3.2)	0.36
	n = 33	n = 34	n = 67	
4-week WOMAC pain score, mean (SD)	10.0 (3.2)	8.75 (4.0)	9.4 (3.6)	0.16
	n = 33	n = 34	n = 67	
Baseline WOMAC total score, mean (SD)	45.3 (15.6)	51.6 (15.0)	48.5 (15.5)	0.10
	n = 32	n = 33	n = 65	
4-week WOMAC total score, mean (SD)	45.8 (15.9)	42.6 (19.6)	44.1 (17.8)	0.48
	n = 31	n = 32	n = 63	
Baseline VAS score, mean (SD)	4.7 (2.6)	5.0 (2.6)	4.9 (2.6)	0.64
	n = 32	n = 32	n = 64	
4-week VAS score, mean (SD)	4.8 (2.6)	3.7 (2.4)	4.3 (2.5)	0.08
	n = 29	n = 32	n = 61	

WOMAC: Western Ontario and McMaster Universities Index; VAS: visual analog scale, for physician global assessment.

noninflammatory patients. In the treatment group, 16 patients had evidence of synovitis on ultrasound and 18 did not. An example of a patient with inflammatory characteristics on ultrasound is shown in Figure 2. There were no statistically significant differences between presence or absence of synovitis at the baseline, 4-week, or 12-week followup visits (Table 4). At 4 weeks, there was no statistically significant difference in decrease in WOMAC pain subscale scores between inflammatory and noninflammatory patients. However, there was a statistically significant

Table 2. Descriptive statistics by inflammatory status for the treatment group only. Variable patient numbers for each category reflect variable numbers of patients for which data were available at each timepoint.

	Noninflammatory	Inflammatory	Total	p
Baseline WOMAC pain score, mean (SD)	10.2 (3.2) n = 18	11.5 (3.2) n = 16	10.8 (3.2) n = 34	0.25
4-week WOMAC pain score, mean (SD)	7.7 (4.3) n = 18	10.0 (3.3) n = 16	8.8 (4.0) n = 34	0.09
12-week WOMAC pain score, mean (SD)	8.3 (3.7) n = 14	11.1 (3.9) n = 16	9.8 (4.0) n = 30	0.06

WOMAC: Western Ontario and McMaster Universities index.

Table 3. Change in WOMAC and VAS scores from baseline to 3-month and 1-month followup in control and treatment groups. Variable patient numbers for each category reflect variable numbers of patients for which data were available at each timepoint. Values for the control and treatment groups are unadjusted. p values are adjusted for baseline scores.

	Control, mean (SD)	Treatment, mean (SD)	p
WOMAC pain score, mean (SD)			
4 wks	–0.1 (1.9) n = 33	–2.1 (2.6) n = 34	0.001
12 wks	–0.2 (2.2) n = 29	–1.0 (2.8) n = 30	0.35
WOMAC composite score, mean (SD)			
4 wks	1.0 (7.8) n = 30	–8.7 (11.7) n = 31	0.001
12 wks	0.6 (9.9) n = 29	–3.2 (10.2) n = 25	0.21
VAS, physician global assessment, mean (SD)			
4 wks	0.1 (2.0) n = 28	–1.1 (2.4) n = 30	0.03
12 wks	–0.2 (1.5) n = 28	–0.03 (2.0) n = 26	0.54

WOMAC: Western Ontario and McMaster universities index; VAS: visual analog scale.

greater improvement in pain subscale scores among noninflammatory patients than among inflammatory patients at 12 weeks ($p = 0.03$; Figure 3). No difference in response was seen among patients who had no effusion at baseline compared to those who did (data not shown).

Biomarker analysis. Thirteen patients had blood drawn at their baseline visit. Of these 13 patients, 9 had no evidence of inflammation on ultrasound and 4 did. There were no significant differences between inflammatory and noninflammatory patients in baseline levels of inflammatory cytokines, MMP-1, and MMP-3. CRP levels were higher in the noninflammatory patients compared to inflammatory patients; however, the mean values of both groups were within the normal range.

DISCUSSION

This is the first placebo-controlled trial that used ultrasound to predict response to IA corticosteroids in knee OA. Our results confirmed the benefit of IA corticosteroids in symptomatic knee OA and also suggest that patients with synovial hypertrophy on ultrasound have less prolonged benefit from this treatment. In our study, we refer to patients with synovial hypertrophy as "inflammatory," although we recognize that these terms are not equivalent. While the use of power Doppler imaging may have more accurately detected synovitis, in the absence of histologic studies the significance of synovial hypertrophy on ultrasound is uncertain. There are few studies correlating imaging of the synovium with histologic and molecular studies in OA. For the purposes of our study, we used synovial hypertrophy on ultrasound as a possible marker of inflammation, although studies should be pursued to investigate the validity of this in OA.

Previous studies have confirmed the benefit of IA corticosteroids in knee OA. Bellamy, *et al* published a Cochrane review including 28 trials (1973 participants) comparing IA corticosteroids to placebo, and found them to be more effective than IA placebo for pain reduction at 1 week after injection. While there was evidence of benefit between 2 to 3 weeks, there was lack of evidence to demonstrate a benefit 4 to 24 weeks after injection[3]. These analyses confirmed the benefit of IA corticosteroids in reducing pain, and provided evidence of its prolonged benefits at 4 weeks.

The mechanism of the effect of corticosteroids in OA is unclear. This treatment has variable efficacy in OA, and it has been suggested that it may be more effective in a subgroup of patients with evidence of inflammation on physical examination. However, few studies have examined clinical predictors of response to IA corticosteroids in OA. In 1995, Gaffney, *et al* published a single-blinded study in which patients with primary knee OA were randomized to receive either IA triamcinolone hexacetonide or saline[4]. Subgroup analysis of the treatment group revealed that improvement in pain was associated with clinical evidence of effusion ($p < 0.05$), and even more so with aspiration of synovial fluid at the time of injection ($p < 0.01$). However, aspiration of synovial fluid in the placebo group was not associated with a significant decrease in pain. Jones and Doherty subsequently reported results of a double-blinded study comparing IA methylprednisolone acetate and saline in 60 patients with knee OA. No clinical predictors of response were identified[5]. A study by Pendleton, *et al* also examined ultrasound as a

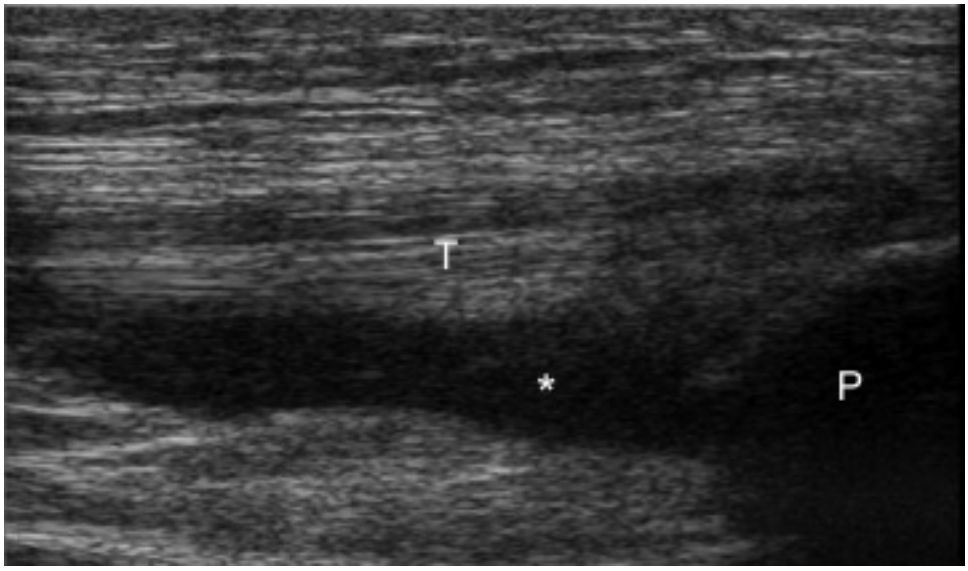

Figure 2. Longitudinal view of the suprapatellar pouch in a patient at baseline. *Synovial fluid and hypertrophic synovium. T: quadriceps tendon; P: patella.

Table 4. Presence of inflammation at baseline, 4-week and 12-week followup visits. Data are number of patients (%).

	Control	Treatment	Total	p
Baseline	13/35 (42)	18/36 (58)	31/71 (44)	0.20
4 weeks	14/33 (42)	16/33 (48)	30/66 (45)	0.40
12 weeks	12/27 (44)	11/24 (46)	23/51 (45)	0.57

clinical predictor of response to IA corticosteroids in knee OA[6]. In that study, there was no placebo arm, but the patients and assessors were blinded to ultrasound findings. Power Doppler imaging was used in addition to grayscale ultrasound. In that study, synovitis on ultrasonography did not predict response to IA corticosteroids at either 1 or 6 weeks.

Our study demonstrated similar efficacy of IA corticosteroids in inflammatory and noninflammatory patients in the short term. However, at 12 weeks there appeared to be a persistent benefit from treatment in noninflammatory patients, while pain levels approached baseline in inflammatory patients. This is contrary to a common notion that IA corticosteroids have greater benefit in patients with clinically evident inflammation. A possible explanation may be that there is a subset of patients who are prone to have a persistently aggressive inflammatory component to their disease. While they may derive initial benefit from temporary antiinflammatory treatments, the benefit may wane more quickly as the inflammatory response recurs. It is also possible that inflammatory processes in OA can be subclinical and even subradiographic, such that patients without synovitis on ultrasound still derive benefit from antiinflammatory treatments. In fact, lack of synovitis on ultrasound may even be a good prognostic sign that symptoms may be controlled more easily with such treatments. Another possibility is that the effects of corticosteroids are mediated through other mechanisms besides decreasing synovial inflammation. Because pain in knee OA is multifactorial, patients may derive benefit from its effects on other structures such as menisci and the subchondral bone.

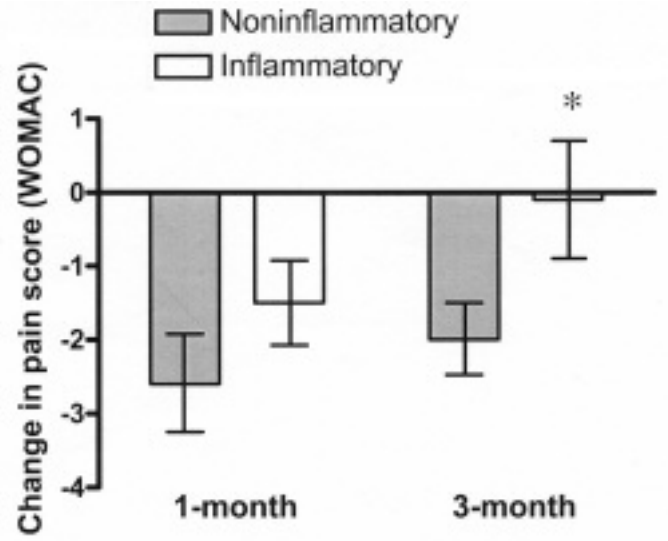

Figure 3. Change in Western Ontario and McMaster Universities index (WOMAC) pain subscale score in inflammatory and noninflammatory patients after corticosteroid injections. *p = 0.03.

There is compelling evidence of a substantial prevalence of detectable synovitis in OA that needs further characterization. The 2005 European League Against Rheumatism report on the prevalence of inflammation in OA said that of the 600 patients with symptomatic knee OA studied with grayscale ultrasound, 16 (2.7%) had synovitis alone, 85

(14.2%) had both synovitis and effusion, 177 (29.5%) had joint effusion alone, and 322 (53.7%) had no inflammation[7]. Hill, *et al* examined magnetic resonance images of 270 subjects with symptomatic knee OA over 30 months and found that the majority of patients had synovitis at baseline[8]. Histologic studies have found a high prevalence of synovitis in all grades of OA, although it is not clear whether synovitis is more prominent in early- or late-stage disease[9,10]. Studies have also suggested that inflammation in OA may be a risk factor for disease progression[11-13]. Despite the plethora of imaging studies in OA, there are few that have correlated radiographic evidence of synovitis with histological characteristics, and no study to our knowledge has correlated imaging with the inflammatory cytokine profile of the synovium[14]. Despite a study correlating serum levels of high-sensitivity CRP with levels of inflammatory cell infiltrate in synovium in OA patients[12], we did not find such correlation of any serum inflammatory cytokine with synovitis detected on ultrasound. While serum biomarkers are an attractive candidate, their accuracy in identifying a subset of patients with an inflammatory phenotype of OA remains to be established. Further, while musculoskeletal ultrasound has allowed us to visualize variable degrees of synovitis in OA, future studies correlating ultrasound findings with both histology and cytokine profiling should be performed.

Our study, as well as others, demonstrated that patients often have variable degrees of inflammation at varying timepoints. There were patients in our study who did not have inflammatory disease at baseline, but did have evidence of inflammation by 12 weeks. What remains to be defined in a longitudinal study is whether there is a subset of OA patients who have higher levels of inflammatory activity during their disease course. This group may be a potential target for aggressive antiinflammatory therapies such as disease-modifying drugs.

There are several weaknesses to our study. The first is the small patient subset. In addition, ultrasound examinations were not performed in real time, but were saved as images for a second assessor to interpret. However, this did allow for blinding of the second assessor as to the timepoints the images were obtained, and interpretation was performed by a single person. We also limited the ultrasounds to the suprapatellar pouch, which may have decreased the sensitivity for detecting synovitis in the knee. Power Doppler imaging was not used because it was not part of our standard ultrasound protocol at the time the study was initiated, and we did not change our methods afterward to remain consistent. However, we recognize that power Doppler imaging may have added more specificity in detecting active synovial inflammation. In addition, there was a small subset of patients undergoing baseline biomarker analysis, especially ones with inflammatory disease, making the results difficult to interpret. Finally, the majority of the patients were men because most of the patient recruitment occurred at the VA hospital.

Intraarticular corticosteroid injections appear to be effective in reducing pain in knee OA regardless of the degree of synovial inflammation. As patients with less inflammation appear to have more prolonged benefit from intraarticular corticosteroids, the burden of inflammation in patients with more significant synovitis may override the efficacy of corticosteroids. Further studies are needed to correlate clinical characteristics with imaging as well as histopathologic and molecular characteristics of synovitis in OA to determine the existence of clinically distinct phenotypes that have different outcomes and responses to tailored treatments.

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