ARP Rheumatology 2024;2:101-105
https://doi.org/10.63032/NJOL3215

ORIGINAL ARTICLES

Predictors of efficacy of ultrasound-guided intra-articular glucocorticoid injection in knee osteoarthritis: a prospective study

Slimani S[1], Aissoug A[2], Aouidane S[1], Ghodbane NE[1], Ladjouze-Rezig A[3]

ABSTRACT

Background: Intra-articular glucocorticoid injection (IAGI) is widely used for treatment of knee osteoarthritis (OA) flares. Response rates are generally around 70%. Several studies have tried to identify predictors of good response, but response to ultrasound (US)-guided injection has not yet been investigated. This study aimed to identify the predictors of response to IAGI performed under US guidance in patients with primary knee OA.

Materials and methods: A total of 116 patients (116 knees) presenting with unilateral or bilateral primary knee OA were enrolled for this prospective single-center study. All were aged >40 years and met the American College of Rheumatology (ACR) criteria for knee OA. Demographic, clinical, laboratory, and imaging data were collected, injection was performed using US guidance, and tolerance was assessed. The primary efficacy endpoint was ≥40% reduction in total WOMAC score (WOMAC40). Univariate and multivariate logistic regression analyses were conducted to identify the predictors of response.

Results: The mean age of the patients was 64.2 ± 9.4 years and mean BMI was 29.9 ± 3.8 kg/m^2. Total WOMAC40 response rate was 61.2%. In multivariate analysis, the independent predictors of response were BMI <30 kg/m^2 (OR = 0.38 [0.16 – 0.89], p = 0.025) and ESR <20 mm (OR = 0.27 [0.08 – 0, 90], p = 0.033).

Conclusion: Knee OA patients with BMI <30 kg/m^2 and/or ESR <20 mm have higher chance of having satisfactory response to US-guided IAGI. Clinical and radiographic severity and age do not seem to affect the probability of response.

Keywords: Predictive factors; Intra-articular injection; Ultrasound guidance; Glucocorticoids; Knee osteoarthritis.

KEY MESSAGES

- Intra-articular glucocorticoid injection is widely used for treatment of knee osteoarthritis (OA) flares. Response rates are generally around 70%.
- Response to ultrasound (US)-guided injection has not yet been investigated. This study aimed to identify the predictors of response to IAGI performed under US guidance in patients with primary knee OA.
- Knee OA patients with BMI <30 kg/m2 and/or ESR <20 mm have higher chance of having satisfactory response to US-guided IAGI. Clinical and radiographic severity and age do not seem to affect the probability of response.

[1] University of Batna 2, Algeria; [2] Rheumatology Clinic, cité des enseignants Ennasr, Batna, Algeria; [3] University of Algiers 1, Algeria

Submitted: 27/06/2023
Accepted: 28/12/2023

Correspondence to: Sami Slimani
E-mail: slimani@dr.com

INTRODUCTION

Intra-articular glucocorticoid injection (IAGI) is a widely used treatment for flare-ups of knee osteoarthritis (OA). Scientific societies such as ACR, EULAR, OARSI, and ESCEO recommend IAGI as the first-line treatment for a painful or swollen osteoarthritic knee and as the second-line treatment for severe knee OA[1-4]. A systematic literature review has shown that IAGI is superior to viscosupplementation for relieving pain in knee OA over the short term, but that this superiority is not evident after 4-6 weeks. Thus, IAGI may only be appropriate for the treatment of painful inflammatory flares. An update of the Cochrane review published in 2015 showed that the benefit of IAGI in knee OA could last for up to 6 weeks, with a standardized mean difference of –0.41[6].

The response to IAGI varies from one study to another, but the rates are generally around 70%[7]. Advanced identification of the indicators of good response would allow clinicians to optimize the use of this therapy. Previous studies have demonstrated that IAGI shows better efficacy in non-obese patients without severe radio-

graphic knee OA[8-13]. However, no study has evaluated the efficacy of IAGI carried out under ultrasound (US) guidance. We hypothesized that US guidance would improve the precision of the procedure, overcome the technical difficulties related to obesity, and thereby increase the efficacy of IAGI. The aims of this study were to identify the predictors of response to IAGI performed under US guidance in patients with primary knee OA and to assess the tolerance of the procedure and the overall response rate at 4 weeks.

MATERIALS AND METHODS

Design

This prospective single-center study was conducted at our hospital between January 2015 and December 2017.

Patients

Consecutive patients presenting with unilateral or bilateral primary knee OA were enrolled. Patients were eligible for inclusion if they 1) satisfied the ACR criteria for knee OA[14]; 2) were ≥40 years old; 3) were on a stable dose of analgesic treatments for at least 2 weeks; and 4) had been recommended IAGI by the treating rheumatologist because of presence of local inflammatory signs and/or pain visual analog scale (VAS) score >40/100. The exclusion criteria were 1) secondary knee OA (due to inflammatory disease or a major architectural defect of the lower limbs); 2) mental illness that would interfere with data collection; 3) allergy to glucocorticoids; 4) dermatosis of the knee; 5) osteosynthesis of the knee; 6) coagulation deficiency with INR >3; or 7) history of glucocorticoid and/or hyaluronic acid injection during the previous 6 months. When a patient presented with bilateral symptomatic knee OA, only the knee with the more severe symptoms was injected and evaluated. During the whole duration of the study, patients were asked to remain under the same oral medication, with the same dosage, either analgesics or NSAIDs.

Ethics

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Batna. Before enrollment, all patients received information on the aims and procedures of the study and were included only after they expressed their willingness to participate.

Methods

Four visits were scheduled for each patient. At the first visit—the inclusion visit (V1, investigator AA)—the indications for IAGI were confirmed; satisfaction of inclusion criteria was checked; and baseline demographic, clinical, laboratory, and imaging data were collected; the data included age, sex, height, weight, BMI, duration of disease, knee to be injected, current and past treatments, comorbidities, presence of other osteoarthritic sites, VAS pain score, extent of effusion and joint stiffness, axis of lower limbs, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, Kellgren and Laurence radiographic stage, location of joint space narrowing and osteophytes on anteroposterior and lateral radiographs, and the 24 parameters for calculation of the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, in its French translation. The second visit—the injection visit (V2, investigator SS)—was less than 24 hours after V1; during this visit, US parameters were recorded (presence, location, and dimensions of intra-articular effusion, synovial hypertrophy, cartilage thinning, osteophytes, Baker cyst, and bursitis; intrasynovial Doppler; and meniscus pathology). IAGI was performed under US guidance, and immediate tolerance of the procedure was recorded. Synovial puncture was only performed when there was significant intra-articular effusion. The third visit—the clinical follow-up visit (V3, investigator AA)—was 4 weeks after V2. Late tolerance data were collected, and the clinical parameters were reassessed. The fourth visit—the control visit (V4, investigator SS)—was within 24 hours of V3; during this visit, the US parameters collected during V2 were reassessed. It should be noted that investigators AA and SS did not have access to each other's data during the study.

Intra-articular injection

US of the knee (at V2 and V4) was performed using an Esaote MyLab 50 machine equipped with a 6-18 MHz multifrequency linear probe, with power Doppler set to a pulse repetition frequency (PRF) of 750 Hz (for slow blood flow), frequency < B-mode and maximum gain before motion noise appearance. At V2, 40 mg triamcinolone acetonide was injected into the intra-synovial cavity under US guidance, using a suprapatellar lateral approach.

Evaluation of efficacy and tolerance

The primary efficacy endpoint of the study was a decrease in total WOMAC score by at least 40% between V1 and V3. The secondary endpoints were a decrease in WOMAC pain score by 40%, and a decrease in total WOMAC and WOMAC pain by 20%. US response was defined as the disappearance of the intra-articular effusion (from >5 mm thick at V2 to <5 mm thick at V4) and/or disappearance of synovial hypertrophy.

Tolerance was classified as immediate tolerance (adverse events occurring within 24 hours after injection

but excluding expected transient worsening of pain) and late tolerance (assessed at V3; especially skin reactions, disturbance in diabetes control, and infection).

Statistical analysis

Calculation of sample size was according to the method of Soper *et al.*[15]. To detect an effect-size (f^2) of 0.15, with probable number of predictive factors set at 4, and alpha risk of 0.05 and statistical power of 90%, we estimated that a minimum of 108 knee joints would be necessary.

Data were summarized according to their nature: quantitative variables as means ± standard deviation or as medians (range), and categorical variables as percentages. The Student's *t* test was used to compare mean WOMAC scores between V1 and V3, and mean VAS pain scores and US parameters between V2 and V4. The chi-square test was used for qualitative variables and the Goodman–Kruskal gamma test for ordinal variables. Patients were classified into two groups: responders (WOMAC decrease >40%) and non-responders. Univariate analysis was performed to identify the demographic, clinical, radiographic, and US variables associated with therapeutic response. Factors significantly associated (at $p < 0.2$) with good response in univariate analysis were entered into multivariate analysis, using an automated binary logistic regression model (stepwise). SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Statistical significance was at $p < 0.05$.

RESULTS

A total of 116 knees (in 116 different patients; 101 women, 15 men; sex ratio, 0.15) were included in this study. Mean age was 64.2 ± 9.4 years (range, 40-85 years), mean BMI was 29.9 ± 3.8 Kg/m^2, and mean duration of disease was 14.1 ± 14.8 years. The main comorbidities in the study population were arterial hypertension (55 patients, 47.4%) and diabetes (28 patients, 24.1%). Ninety-one patients (78.4%) had osteoarthritis affecting other locations also, mainly the spine and the hands.

Among the 116 injected knees, 70 (60.3%) were right knees. Mean VAS pain score was 84.0 ± 12.1. Clinical joint swelling was seen in 75% of knees. Mean total WOMAC score was 73.3 ± 11.8. Main treatments being taken at time of inclusion were acetaminophen (88.8%), nonsteroidal anti-inflammatory drugs (85.3%), opioids (76.7%), and slow-acting anti-arthritic drugs (9.5%). Biological parameters (ESR and CRP) were available for 102 patients; mean ESR was 14.1 ± 8.9 mm and mean CRP was 3.1 ± 2.8 mg/L. Kellgren and Lawrence radiographic grading was available for all patients; 35 knees were grade 2, 48 knees were grade 3, and 33 knees were grade 4. Table I summarizes the US data. Only 5 joints have been punctured before injection, because of a significant amount of synovial fluid.

Comparison of data collected at enrollment and at 4 weeks after IAGI showed significant overall improvement, with mean pain VAS score decreasing from 8.40 ± 1.21 to 3.49 ± 2.10, WOMAC index from 73.3 ± 11.8 to 38.8 ± 20.7, and intra-articular effusion height from 7.4 ± 3.0 mm to 5.8 ± 3.1 mm (all $p < 0.001$). Total WOMAC40, total WOMAC20, pain WOMAC40, and pain WOMAC20 responder rates were 61.2% (71 patients), 81.9%, 65.5%, and 82.8%, respectively. Intra-articular effusion disappeared at 4 weeks in 29 (32.9%) patients. There were no major immediate or delayed adverse events; a few patients had transient increase of pain in the injected joint, but it could not be attributed to IAGI.

Univariate analysis found several clinical and paraclinical parameters to be associated with total WOMAC40 response (Table II). However, in multivariate analysis, the only independent predictors of good response were BMI <30 kg/m^2 (OR = 0.38 [0.16–0.89], $p = 0.025$) and ESR <20 mm (OR = 0.27 [0.08–0.90], $p = 0.033$). Table III shows the estimated response rate according to the presence or the absence of these two predictive factors.

DISCUSSION

In this prospective study, the researchers aimed to evaluate the predictors of a good response to US-guided intra-articular glucocorticoid injection (IAGI) in knee osteoarthritis (OA). The study identified two independent predictors of a good response: a body mass index (BMI) less than 30 kg/m² and an erythrocyte sedimen-

TABLE I. Ultrasound abnormalities found during the inclusion scanning.

Abnormality	Number (percentage) N = 116
Effusion	114 (98.3 %)
Synovial hypertrophy	80 (69.0 %)
Doppler signal	5 (4.3 %)
Baker cyst	15 (12.9 %)
Infra-patellar bursitis	5 (4.3 %)
Enthesopathy	46 (39.7 %)
Medial meniscus extrusion (> 3mm)	77 (66.4 %)
Lateral meniscus extrusion (> 3mm)	15 (12.9 %)
Osteophytes	90 (77.6 %)

TABLE II. Characteristics of responders versus non-responders, for total WOMAC 40 at 4 weeks. Only elements with a p < 0.2 are shown

	Responders N = 71	Non responders N = 45	OR (CI 95%)	p
Diabetes (n, (%))	14 (19.7%)	14 (31.1%)	0.86 (0.68 – 1.08)	0.162**
Osteoarthritis of dorsal spine (n, (%))	1 (1.4%)	3 (6.7%)	0.20 (0.02 – 1.98)	0.130**
Opioids intake (n, (%))	57 (83.8%)	32 (72.7%)	1.94 (0.77 – 4.90)	0.119**
Oral NSAIDs intake (n, (%))	62 (91.1%)	37 (84.1%)	1.95 (0.61 – 6.24)	0.199**
Weight (kg) (mean ± SD)	76.7 ± 11.4	81.0 ± 10.6	-	0.046*
BMI (Kg/m^2) (mean ± SD)	29.1 ± 3.5	31.0 ± 4.0	-	0.011*
BMI > 30 Kg/m^2 (n, (%))	26 (36.6%)	27 (60%)	0.38 (0.18 – 0.83)	0.014**
Intercondylar distance (cm) (mean ± SD)	0.9 ± 1.5	1.6 ± 2.0	-	0.014*
Genu varum (n, (%))	23 (32.4%)	21 (46.7%)	0.55 (0.25 – 1.18)	0.123**
Intermalleolar distance (cm) (mean ± SD)	0.4 ± 0.9	0.6 ± 1.4	-	0.027*
ESR (mm) (mean ± SD) &	12.9 ± 8.7	15.9 ± 8.8	-	0.090*
ESR > 20 mm (n, (%))	5 (8.2%)	11 (26.8%)	0.24 (0.07 – 0.77)	0.011**
Lateral femoro-tibial osteophytes on X-rays (n, (%))	34 (47.9%)	28 (62.2%)	0.56 (0.26 – 1.20)	0.126**
Presence of US synovial hypertrophy (n, (%))	45 (63.4%)	35 (77.8%)	0.50 (0.21 – 1.16)	0.102**
Medial meniscal extrusion (mm) (mean ± SD)	3.8 ± 2.3	4.7 ± 3.1	-	0.063*
Medial femoral osteophytosis (mm) (mean ± SD)	2.3 ± 2.2	3.0 ± 2.3	-	0.118*
Medial tibial osteophytosis (mm) (mean ± SD)	1.3 ± 1.5	1.9 ± 1.9	-	0.088*
Lateral femoral osteophytosis (mm) (mean ± SD)	1.2 ± 1.7	1.7 ± 1.7	-	0.130*

BMI, body mass index; ESR, erythrocyte sedimentation rate; NSAIDs, Non-steroidal anti-inflammatory drugs; OR (IC 95%), Odds Ratio (95% confidence interval); SD, Standard deviation. * Student's t test. ** Chi-square test. & data available for 102/116 patients

TABLE III. Response rate according to the presence and the number of predictive factors.

Number of predictive factors	Total WOMAC 40's response rate (%)
0 factor	25.0
1 factor	66.7
2 factors	73.3

tation rate (ESR) less than 20 mm. The presence of both predictors increased the probability of a WOMAC40 response to 73%, while their absence lowered the probability to 25%. This predictive model could help clinicians select patients who are most likely to respond favorably to US-guided IAGI.

The study also showed that US-guided IAGI was highly effective, resulting in a mean decrease of 58% in pain intensity and 47% in WOMAC score at 4 weeks. Furthermore, the treatment was well tolerated, with no patients experiencing local or systemic adverse events such as allergies, intra-articular infection, or disturbance of diabetes control.

In our literature review we found six previous studies that have attempted to determine the predictors of good response to IAGI in patients with knee OA. These studies had several limitations. In all six studies, the injections were administered using anatomical landmarks guidance[8,13]. Moreover, the sample sizes were small (<100). While three of the studies were placebo-controlled clinical trials, the other three were open-label studies with designs comparable to ours. Biological data were not recorded in any of the six, and only three studies reported radiographic grade[10,12,13]. Only three studies—all carried out after 2007—included US evaluation[10-12]. The response rate in our study (61%) is similar to that in the previous studies, where the rate varied between 42% and 78%. However, the different studies are not directly comparable with regard to the primary endpoint, given the heterogeneity of the chosen endpoint (WOMAC50%, VAS 15%, VAS 20%, and VAS <4/10). Multivariate analysis to identify the independent predictors of response was carried out in only two studies; one study, by Jones *et al.*, found no independent predictive factors[9], while the other, by Bevers *et al.*, identified three independent predictors: use of analgesics, female sex, and presence of prepatellar bursitis[12].

The impact of obesity on the effectiveness of treatment of knee OA has already been demonstrated by previous studies, as also the positive impact of weight loss on the evolution of the disease[16-29]. Obesity has been highlighted as a factor for poor response to viscos-

upplementation, but our study is the first to show that this parameter has a negative impact on the response to IAGI.

Our study has some limitations. First, we chose to administer the injection using US guidance rather than the more commonly used anatomical landmarks guidance; therefore, we cannot claim that our results apply to current practice in most rheumatology centers. We opted for US guidance because of its accuracy and higher efficiency, which we anticipate will ensure its wide adoption by rheumatologists in the future. Second, this was an open-label study, and so the level of evidence is inferior to that derived from clinical trials. Third, we did not examine the effect of clinical parameters such as the Lequesne index and anxiety and depression scores. We chose the WOMAC index since it is more comprehensive and more often used in modern clinical trials and international cohort studies.

In conclusion, our study suggests that in patients with primary knee OA, a BMI less than 30 kg/m² and an ESR less than 20 mm are predictive of a probability of response to US-guided IAGI. Clinical and radiographic severity and age do not seem to affect the probability of response. Similar studies on other populations should be conducted to confirm our results.

REFERENCES

1. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheum 2020;72(2). doi: 10.1002/art.41142.
2. Zhang W, Doherty M. EULAR recommendations for knee and hip osteoarthritis: a critique of the methodology. Br J Sports Med 2006;40(8):664e9. doi: 10.1136/bjsm.2004.016840.
3. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the nonsurgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27(11):1578e89. doi: 10.1016/j.joca.2019.06.011.
4. Bruyère O, Honvo G, Veronese N, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019 Dec;49(3):337-350. doi: 10.1002/art.24925.
5. Bannuru RR et al. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis & Rheumatism 61, 1704– 1711 (2009)
6. Jüni P et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev CD005328 (2015). doi:10.1002/14651858.CD005328.pub3
7. Robinson P, Keenan AM, Conaghan PG. Clinical effectiveness and dose response of image-guided intra-articular corticosteroid injection for hip osteoarthritis. Rheumatology (Oxford) 2007;46(2):285e91. doi: 10.1093/rheumatology/kel217.
8. Gaffney K, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. Ann Rheum Dis 1995;54:379–81. doi: 10.1136/ard.54.5.379.
9. Jones A, Doherty M. Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. Ann Rheum Dis 1996;55:829–32. doi: 10.1136/ard.55.11.829.
10. Pendleton A, Millar A, O'Kane D, Wright GD, Taggart AJ. Can sonography be used to predict the response to intra-articular corticosteroid injection in primary osteoarthritis of the knee? Scand J Rheumatol 2008;37:395–7. doi:10.1080/03009740802050738.
11. Chao J, Wu C, Sun B, Hose MK, Quan A, Hughes TH, et al. Inflammatory characteristics on ultrasound predict poorer long term response to intraarticular corticosteroid injections in knee osteoarthritis. J Rheumatol 2010;37:650–5. doi:10.3899/jrheum.090575.
12. Bevers K, Zweers MC, Vriezekolk JE, Bijlsma JWJ, den Broeder AA. Are ultrasonographic signs of inflammation predictors for response to intra-articular glucocorticoids in knee osteoarthritis? Clin Exp Rheumatol 2014;32:930–4.
13. Matzkin EG, Curry EJ, Kong Q, Rogers MJ, Henry M, Smith EL. Efficacy and Treatment Response of Intra-articular Corticosteroid Injections in Patients With Symptomatic Knee Osteoarthritis. J Am Acad Orthop Surg. 2017 Oct;25(10):703-714. doi: 10.5435/JAAOS-D-16-00541.
14. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49. doi: 10.1002/art.1780290816.
15. Soper D. A-priori Sample Size for Multiple Regression. https://www.danielsoper.com/statcalc/calculator.aspx?id=1. Accessed July 5, 2017.
16. Wills AK, Black S, Cooper R, Coppack RJ, Hardy R, Martin KR, et al. Life course body mass index and risk of knee osteoarthritis at the age of 53 years: evidence from the 1946 British birth cohort study. Ann Rheum Dis 2011;71:655–60. doi:10.1136/ard.2011.154021.
17. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004;50:1501–10. doi:10.1002/art.20256.
18. Hunter DJ, Beavers DP, Eckstein F, Guermazi A, Loeser RF, Nicklas BJ, et al. The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. Osteoarthr Cartil OARS Osteoarthr Res Soc 2015;23:1090–8. doi:10.1016/j.joca.2015.03.034.
19. Eymard F, Chevalier X, Conrozier T. Obesity and radiological severity are associated with viscosupplementation failure in patients with knee osteoarthritis. J Orthop Res. 2017 Oct;35(10):2269-2274. doi: 10.1002/jor.23529.