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Minerva Medica 2019 mese;110(0):000–000
DOI: 10.23736/S0026-4806.19.06190-1

ORIGINAL ARTICLE

Ultrasound-guided intra-articular injection: efficacy of hyaluronic acid compared to glucocorticoid in the treatment of knee osteoarthritis

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ABSTRACT

BACKGROUND: Osteoarthritis (OA) is a degenerative joint disease which causes pain and functional impairment in adults over 50 years old with consequent important disability. Unfortunately, there is no definitive cure for OA, thus the approach is characterized by multiple treatments that can manage its symptoms. Even though data from randomized controlled trials and meta-analyses indicate that intra-articular hyaluronic acid (IAHA) offers the best benefit/risk balance among the various pharmacologic treatments to improve OA-related knee pain, there is a lack of agreement among national and international guidelines about such uses of IAHA for the medical management of symptomatic knee OA. To minimize confounding factors and biases, the aim of our study was to evaluate the efficacy of the different weight and concentration of IAHA treatment in patients suffering from knee OA comparing to glucocorticoids (GC) joint injections. Furthermore, to make the procedure more accurate and assessment more objective, we use ultrasonography (US) with power Doppler (PWD) to help us differentiate between active and inactive inflammation within joints and periarticular soft tissues.

METHODS: We performed a retrospective evaluation of a cohort of patients with knee OA, diagnosed according to the ACR criteria, treated by US-guided joint injection of HA and GC. The patients were catalogued according to the type of treatment they underwent: group A, patients treated with HA (1.5%) >1500 kDa (three US-guided knee injections one week apart); group B, patients treated with HA (2%) 800-1200 kDa (three US-guided knee injections one week apart); group C, patients treated with glucocorticoids (three US-guided knee injections of triamcinolone acetate 40 mg one week apart). All patients were monitored for 6 months, evaluating: subjective pain using a 10-cm Visual Analogue Scale; pain, stiffness, and functionality using the Western Ontario and McMaster Universities Arthritis Index (WOMAC); the concomitant intake of anti-inflammatory and/or analgesic drugs through a questionnaire; and US results by grey scale and PWD.

RESULTS: A total of 171 patients affected by knee OA were evaluated (women 72.3%) with a mean age of 69.3±4.1 years. All the subjects analyzed showed a pain reduction at 6 months after treatment (group A: -39.5; group B: -36.9; group C: -30.8). The difference between the three groups was statistically significant (Kruskall-Wallis P=0.001) and in particular between group A and group C (P=0.000) and between group B and group C (P=0.005), but not between A and B (P=0.258). WOMAC was statistically significantly improved from baseline in all groups examined (group A: -11.9; group B: -14.9; group C: -11.2). The PWD score showed a statistically significant improvement in group B (-0.64) even after 6 months (P=0.004). All patients in the different groups showed a statistically significant reduction of concomitant therapy compared to baseline with respect to paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)/COX2 therapy, while only group B showed a statistically significant reduction for opioids.

CONCLUSIONS: This study demonstrated the efficacy of OA treatment with medium molecular weight HA in favor of the higher concentration of HA that may affect the reduction of pro-inflammatory mediators. Furthermore, US monitoring allowed to evaluate aspects related to synovial involvement, which cannot be appreciated with standard imaging.

(*Cite this article as:* Parisi S, Ditto MC, Priora M, Borrelli R, Laganà A, Peroni CL, *et al*. Ultrasound-guided intra-articular injection: efficacy of hyaluronic acid compared to glucocorticoid in the treatment of knee osteoarthritis. Minerva Med 2019;110:000–000. DOI: 10.23736/S0026-4806.19.06190-1)

KEY WORDS: Osteoarthritis; Hyaluronic acid; Intra-articular injections; Doppler ultrasonography.

Osteoarthritis (OA) is a degenerative joint disease which causes pain and functional impairment in adults over 50 years old.[1] OA is a progressive disease with different degrees of severity, and it is a major cause of disability worldwide.[2] Today, unfortunately, there is no definitive cure for OA, thus the approach is characterized by multiple treatments that can manage its symptoms. Among the prescribed drug therapies, we include paracetamol, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs), especially the latter having a significant toxicity and poor tolerability by OA patients.[3-6] These patients are frequently of advanced age with many comorbidities and they are receiving multiple medications; consequently, intra-articular (IA) therapy is often preferred by both OA patients and their physicians.[7] Many scientific societies, including the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR), the American Academy of Orthopedic Surgeons (AAOS), the Osteoarthritis Research Society International (OARSI), and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommend nonpharmacologic treatments as first-line therapy.[8-12] Even though data from randomized controlled trials (RCTs) and meta-analyses indicate that intra-articular hyaluronic acid (IAHA) offers the best benefit/risk balance among the various pharmacologic treatments to improve OA-related knee pain,[13-15] there is a lack of agreement among national and international guidelines about such uses of IAHA for the medical management of symptomatic knee OA.[12, 16]

Hyaluronic acid (HA) is the main constituent of synovial fluid and cartilage, where it plays an important role in regulating joint homeostasis.[17] Under natural conditions it is a metabolically active polymer, involved in the processes of communication, migration and cellular differentiation.[18] When administered by joint injection, HA restores viscous and elastic characteristics while acting like lubricant and shock absorber.[19] In this way, it performs a chondroprotective action, as well as possibly showing anti-inflammatory and analgesic properties.[20] The chemical composition of human HA has been exactly defined: it is a complex glycosaminoglycan which consists of different disaccharide units (D-glucuronate β1.4) with a molecular weight ranging from 100 to 10,000 kDa in non-pathological tissue.[21] Its distribution in the human body is very wide albeit mainly located in the extracellular matrix and in body fluids. It represents the major constituent of synovial fluid and cartilage, where it plays an important role in regulating joint homeostasis. Inside the articular cavity, HA is mainly synthesized by type B synovial cells. The molecules tend to aggregate in extensive macromolecular formations, thus giving typical resistance and viscoelasticity properties.[22] In conditions of adequate hydration, it is a structure with viscoelastic properties; during slow joint movements, HA behaves like a viscous fluid, while acting as an elastic structure in fast movements in order to absorb the mechanical impact.[23] HA is also involved in the processes of communication, cell migration and cell differentiation, in the regulation of the extracellular matrix and in the activation of the metabolism of different cellular structures.[24] IAHA has been found to stimulate the endogenous synthesis of HA and extracellular matrix components by synovial fibroblasts, to promote chondroprotection by mitigating proteoglycan loss in cartilage and apoptosis of chondrocytes, to reduce HA degradation by decreasing the production of pro-inflammatory cytokines, and to low the induction of pain mediators.[25] Evidence of the numerous mechanisms by which HA acts on joint structure and function provides support that IAHA may be clinically beneficial in knees affected by OA not only by providing pain relief but also by delivering potential disease-modifying effects.[26] To date, there are no reliable data on the best type of HA to use. Some studies have shown a better efficacy while using an intermediate weight when compare to high-weight molecules;[27] other elements failed to show significant differences between average and high-weight molecules.[28] One metanalysis compared a high-molecular-weight HA formulation to a low-molecular-weight HA and it did not identify any differences on efficacy; however, it reported a higher rate of acute post-injection flares with the high-molecular-weight HA.[29]

Conventional radiography is the traditional

tool for the imaging of joints with OA and it has been proved to be readily available, inexpensive and reliable.[30, 31] However, it gives only a two-dimensional image of a three-dimensional joint site, it cannot detect inflammation and soft-tissue abnormalities and it exposes patients to ionizing radiations.[32] Musculoskeletal ultrasound (MUS) is an imaging tool with an increasing role in the assessment of OA.[33] It has been demonstrated to show findings related to both inflammation and structural damage.[34, 35] In addition, it is characterized by a wide set of advantages beyond its imaging modalities, such as being safe, easily accessible, relatively cheap, not invasive and lacking any contraindications.[36] Moreover, Doppler modalities are able to differentiate between active and inactive inflammation within joints and periarticular soft tissues.[37] MUS is an easy non-invasive procedure with minimal discomfort for patients, and it seems useful in evaluating joint effusion and synovitis as elements of inflammation.[31] There are a few studies which have demonstrated the correlation of sonographic findings, such as suprapatellar effusion (SPE) and medial meniscus protrusion (MMP), and symptomatic OA.[32, 38]

To minimize confounding factors and biases, the aim of our study was to evaluate the efficacy of the different weight and concentration of IAHA treatment in patients suffering from knee OA comparing to glucocorticoids (GC) joint injections.

Materials and methods

We performed a retrospective evaluation of a cohort of patients with knee OA, diagnosed according to the ACR criteria,[39] with a grade 2-3 of the Kellgren-Lawrence classification,[40] belonging to the Unit of Rheumatology, at Città della Salute e della Scienza of Turin, from January 2017 to January 2019, and treated by ultrasound- (US) -guided joint injection of HA and GC.

The patients were catalogued according to the type of treatment they underwent, as stated by the following groups:

• group A: patients treated with HA (1.5%) >1500 kDa (three US-guided knee injections one week apart);

• group B: patients treated with HA (2%) 800-1200 kDa (three US-guided knee injections one week apart);

• group C: patients treated with glucocorticoids (three US-guided knee injections of triamcinolone acetate 40 mg one week apart).

All patients were monitored for 6 months, evaluating at timepoints T_0 (baseline) and T_1 (after 6 months) the following measurements:

• subjective pain, using a 10-cm Visual Analogue Scale (VAS);

• pain, stiffness, and functionality using Western Ontario and McMaster Universities Arthritis Index (WOMAC);

• the concomitant intake of anti-inflammatory and/or analgesic drugs about one week before first joint injection and about one week before the check-up at 6 months, through a questionnaire administered to patients;

• grey scale (GS) and power Doppler (PWD) through US; in all cases, the examination was performed using a MyLab70 XVG (Esaote Biomedica, Genoa, Italy) machine equipped with a linear multifrequency (4-13 MHz) transducer, operating at a frequency of 13 MHz; in addition, PD modality was applied (PRF 750 Hz, gain 50%, frequency 6.3 MHz). The same settings were used in all cases. At the beginning of each scanning session, a focus was placed at the level of the region of interest. Color gain was adjusted below the degree that caused the appearance of noise artefacts.[41] US scans were carried out following a protocol based on European League Against Rheumatism (EULAR) guidelines for musculoskeletal ultrasonography.[42] The application of US gel to the skin to provide an acoustic interface, examinations were started paying attention not to apply probe pressure on the anatomical structures under examination. During the same scanning session, US was initially performed in B-mode in order to detect morphological changes and then PWD techniques were immediately used to search for synovial abnormal vascularization. Patients were examined in the supine position with the knee flexed at 30°. The US evaluation and the US-guided knee injections were performed by a single operator.

Patients suffering from inflammatory rheumatisms (*e.g.* rheumatoid arthritis or psoriatic ar-

thritis) or patients with microcrystalline arthritis and patients with neurological diseases were not included.

Ethics Committee's approval and written informed consent for the anonymous use of personal data was obtained from every patient, in compliance with Legislative Decree 196/2003. This study complies with the ethical standards laid down in the 1975 Declaration of Helsinki.

Statistical analysis

Data are presented as mean and standard deviation for continuous variables, and number and proportion for categorical data. Non-parametric and parametric tests (Kruskal-Wallis test, Mann-Whitney U-test and χ^2 test) were properly used to compare subgroup characteristics (clinical characteristics, clinical assessment, US assessment at T_0 and T_1). A $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS statistical software v. 20.0 (SPSS, Chicago, IL, USA).

Results

A total of 171 patients affected by knee OA were evaluated (women 72.3%) with a mean age of 69.3±4.1 years. We performed 110 bilateral and 61 unilateral injections for a total number of 843.

Group A was composed of 61 patients treated with HA (1.5%) >1500 kDa (three US-guided infiltrations one week apart); group B was composed of 58 patients treated with HA (2%) 800-1200 kDa (three US-guided infiltrations one week apart); group C was composed of 52 patients treated with glucocorticoids (three US-guided infiltrations of triamcinolone acetate 40 mg after one week).

There were no statistically significant differences between the groups examined (Table I). Pain VAS scores, WOMAC overall scores, and US assessment (GS and PWD) scores at T_0 and T_1 are provided in Table II. All the analyzed subjects showed a pain reduction at 6 months after treatment (group A: -39.5; group B: -36.9; group C: -30.8). The difference between the three

TABLE I.—*Characteristics of the three study groups (group A treated with HA 1.5% >1500 kDa, group B treated with HA 2% 800-1200 kDa, group C treated with triamcinolone acetate 40 mg).*

Characteristics	Group A	Group B	Group C	P value
Age, years	67.8±3.8	70.9±2.1	69.1±4.1	0.942
Gender, female	72.3%	70.5%	74.2%	0.521
BMI, kg/m^2	27.4±4.2	26.2±3.8	26.7±4.3	0.870
Duration of OA symptoms, years	5.8±4.7	5.1±4.2	5.5±5.1	0.684
Kellgren-Lawrence grade of OA				0.767
II	66%	70%	68%	
III	34%	30%	32%	

Data provided as mean±SD or as percentage of patients, unless stated otherwise.
BMI: Body Mass Index; OA: osteoarthritis.

TABLE II.—*Clinical assessment of the study groups (group A treated with HA 1.5% >1500 kDa, group B treated with HA 2% 800-1200 kDa, group C treated with triamcinolone acetate 40 mg).*

Parameters	Group A		Group B		Group C	
	T_0	T_1	T_0	T_1	T_0	T_1
Pain VAS, mm	70.3±11.6	30.8±10.1	70.0±12.5	33.1±10.7	69.1±9.8	38.3±11.2
P value	0.000		0.000		0.000	
WOMAC overall score	52.4 (48.8-58.2)	40.5 (29.3-47.2)	53.1 (41.8-60.2)	38.2 (29.3-47.2)	52.4 (40.4-61.2)	41.2 (29.1-46.8)
P value	0.002		0.001		0.003	
Grey scale (SPS)	1.23±0.43	1.14±0.35	1.14±0.47	1.04±0.37	1.27±0.45	1.09±0.29
P value	0.504		0.631		0.307	
Power Doppler	1.13±0.64	0.95±0.57	1.04±0.65	0.40±0.50	0.91±0.68	0.72±0.63
P value	0.395		0.004		0.429	

Data provided as mean±SD or as median (95% CI), unless stated otherwise.
VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; SPS: suprapatellar synovitis.

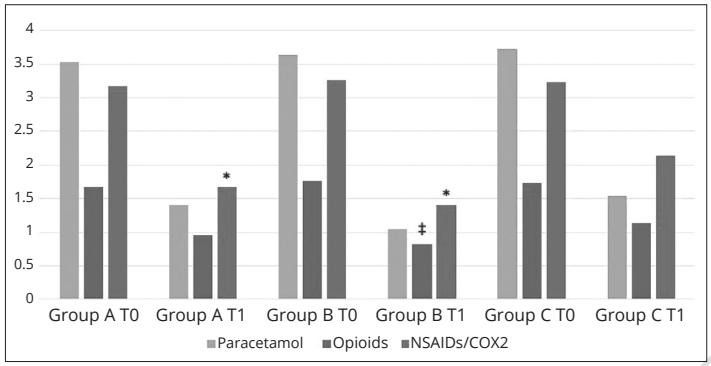

Figure 1.—Therapy in the three study groups: HA 1.5% >1500 kDa in group A, HA 2% 800-1200 kDa in group B, and triamcinolone acetate 40 mg in group C.
NSAIDs: non-steroidal anti-inflammatory drugs; COX2: cyclooxygenase 2 inhibitor; T_0: baseline; T_1: 6 months.
‡Statistically significant reduction only in group B; *statistically significant reduction in groups A and B compared to group C.

groups was statistically significant (Kruskall-Wallis P=0.001) and in particular between group A and group C (P=0.000) and between group B and group C (P=0.005), but not between group A and group B (P=0.258). WOMAC score was statistically significantly improved from baseline in all groups examined (group A: -11.9; group B: -14.9; group C: -11.2) but such a difference was not found between groups (Kruskall-Wallis P=0.856). The GS score improved in the three groups of patients without showing statistically significant differences, while the PWD showed a statistically significant improvement in group B (-0.64) even after 6 months (P=0.004). All patients in the different groups showed a statistically significant reduction of concomitant therapy compared to baseline with respect to Paracetamol and NSAIDs/COX2 therapy, while group B showed a statistically significant reduction also for opioids. Furthermore, group A and group B showed a statistically significant reduction in NSAIDs intake compared to group C (Figure 1).

Discussion

The ESCEO and ACR guidelines recommend IAHA for knee OA in patients whose symptoms persist despite previous treatment with paracetamol, NSAIDs and slow acting symptomatic drugs for OA (SYSADOA) or other analgesics.[9, 12] Paracetamol is widely prescribed as first-line therapy for OA although its efficacy is poor and has no effect on physical function and joint stiffness in patients with knee OA.[43, 44] Furthermore, recent data on the safety profile of paracetamol raise doubts about the systematic and chronic use of the drug at the upper limit of standard analgesic doses (>3 g/day), since it has been associated with higher gastrointestinal (GI) events, liver toxicity and cardiovascular events.[5, 45] A recent meta-analysis of 137 studies including 33,243 participants showed that the most effective treatment compared to the oral placebo was IAHA, while the least effective treatment was paracetamol.[46] Oral NSAIDs have moderate efficacy on pain and a recent meta-analysis found out that diclofenac 150 mg/day was the most effective for reducing pain.[47] Regardless of their efficacy, all selective or non-selective oral NSAIDs increase the risk of GI and CV events[48, 49] and renal failure.[50] These risks tend to increase with age, and they are even more likely to appear in patients treated for OA.[51] A meta-analysis showed that IAHA efficacy was not significantly different from continuous oral NSAIDs at 4 and 12 weeks in terms of pain, function and joint stiffness.[52] Opioid analgesics are recommended for the treatment of moderate to severe OA that does not respond to first-line treatments. Opioids significantly reduce the intensity of short-term pain and have minimal benefits on joint function compared to placebo in patients with OA.[53] Despite their effectiveness, the risk for opioids to cause adverse events is high, as well as the risk of developing addiction.[53] Another treatment used in knee OA, is GC joint injections, especially where there is evidence of joint effusion.[54] A Cochrane review of 27 studies involving 1767 participants only found a low-grade evidence that IA corticosteroids are more useful for pain and function than

control group.[55] Current evidence suggests that IA GC may offer only a short-term effect on pain compared to IAHA.[56] Even a recent meta-analysis has shown that IAHA is more effective than long-term IA corticosteroid (up to 6 months).[57] McAlindon *et al.* assessed the safety and efficacy of triamcinolone acetonide compared to placebo over a two-year period.[58] No significant difference in pain reduction was observed between placebo and active treatment when measured at 3 months after each injection. Given the favorable safety profile of IAHA compared to NSAIDs, IAHA could be a preferable alternative to oral NSAIDs for knee OA, especially for older patients with greater risks of systemic events[46] and could similarly prove to be a safer alternative for patients who are taking opioids. In the literature, data show that the addition of HA leads to a significant reduction of both matrix metalloprotease (MMP) -13 and the expression of MMP-1 by more than 60%.[59] These results are comparable with the reported effect of HA on the expression of MMPs under catabolic stimulation of IL-1β;[60, 61] furthermore, it suggests that HA mediated inhibition of MMP-13 expression leads to a decrease in the degradation of proteoglycans.[62] Interestingly, clinical studies suggest a greater effect after HA administration in patients with moderate OA.[63, 64] The potential therapeutic value of HA suppression of MMP-13 expression has been demonstrated by Little *et al.*.[65] By studying surgically-induced OA in a murine MMP-13 knockout model, they identified MMP-13 as one of the major contributors to progression. Evidence has shown that subchondral bone changes in OA are intimately involved in cartilage degradation, and the relationship between osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) may be implicated.[66] HA could modulate osteoclast activation by modulating the expression of these molecules. With the addition of HA, the expression of OPG mRNA was increased by 19% whilst RANKL expression appeared to be reduced by 49% in mouse osteoblasts leading the assumption that HA could increase the OPG/RANKL mRNA ratio.[67] Mladenovic *et al.* showed that, in an inflammatory context, HA inhibits the production of MMPs and the expression of A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) -4 and ADAMTS-5 as well as RANKL. IAI-HA can prevent cartilage degeneration by inhibiting the resorption of the subchondral and protective bone microarchitecture by inducing MMP-13 levels suppression.[67] It can act by regulating expression of MMP-13 in subchondral bone, therefore the inhibition of MMP-13 in subchondral bone may be a new approach for OA treatment. The beneficial effect of HA in OA may be due to its action on the cartilage and subchondral bone.[67]

Our preliminary study suggests the potential role of medium molecular weight HA with 2% of concentration in decreasing local inflammation and pain of knee OA. A significant clinical improvement was obtained and detected observing the decrease in VAS pain after 6 months of HA or GC treatment; such a result may be influenced by the US guidance injection. Based on these findings and since an accurate needle

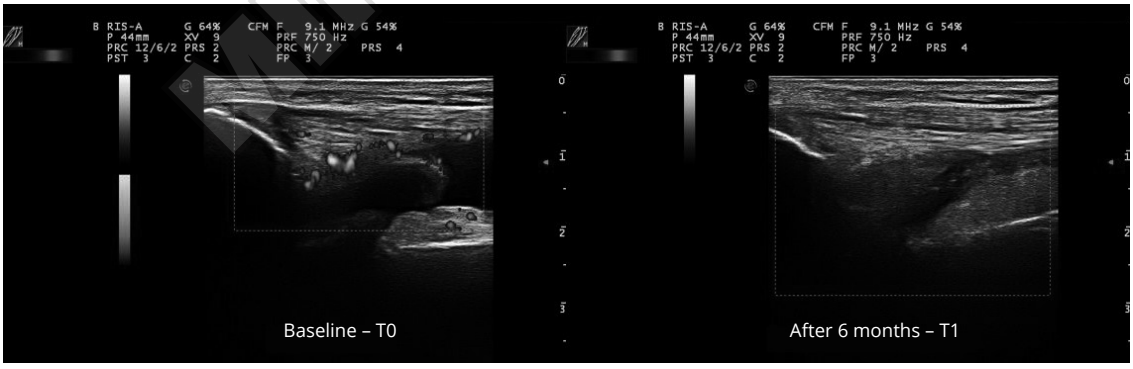

Figure 2.—Decrease of the US-PD signal after treatment with HA (2) 800-1200 kDa (Group B).

placement is necessary for therapeutic injections, we performed US-guided injections. US provides an alternative means to ensure accurate needle placement whilst having several noteworthy advantages as well due to its lack of contraindications, radiation exposure for both the patient and the operator and it does not require contrast.[68, 69] A recent meta-analysis has shown how the use of the imaging guide, particularly ultrasonography, improves the accuracy of intra-articular injection, including the knee. Furthermore, intra-articular injections of the knee guided by ultrasound improve clinical outcomes and come with cheaper costs.[70] Moreover, US can detect short-term synovial response in knee OA. Specifically, PWD score may be both responsive to and associated with pain and could be useful in evaluating the effectiveness of therapy.[71] To the best of our knowledge, this is the first study in which US examination analyzing inflammatory parameters (*i.e*. synovial hypertrophy and PWD) of the knee OA was performed in all the subjects at baseline and during the follow-up period. According to previous findings, no adverse events occurred in our study. Even if the use of intra-articular HA displays some disadvantages, such as the need of multiple injections and higher cost than steroids, its use does not induce increase in blood glycemia, ligament or capsule weakening or cutaneous side effects (Figure 2).

Limitations of the study

Because a retrospective study is burdened by major limitations, such as the inclusion of a relatively small number of patients, the lack of a control group and random allocation, the results should be interpreted with caution. Our preliminary study suggests that, in the long-term, US-guided injections for knee OA with medium molecular weight HA are effective in decreasing local inflammation and pain, probably because a higher concentration of HA (2%) has a more powerful anti-inflammatory effect.

Conclusions

This study demonstrated the efficacy of OA treatment with medium molecular weight HA in favor of the higher concentration of HA that may affect the reduction of pro-inflammatory mediators. Furthermore, US monitoring allowed to evaluate aspects related to synovial involvement, which cannot be appreciated with standard imaging.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: June 11, 2019. - Manuscript received: May 31, 2019.