EUROPEAN JOURNAL OF INFLAMMATION Vol. 11, no. 3, 847-853 (2013)

THE EFFECT OF INTRA-ARTICULAR HYALURONIC ACID (SINOVIAL® ONE) ON KNEE OSTEOARTHRITIS: A PRELIMINARY STUDY

A. POLACCO[1], B. BEOMONTE ZOBEL[2], M. POLACCO[2], S. SCARLATA[3], F. GASPARRO[4], R. DEL VESCOVO[2] and L. SCARCIOLLA[2]

[1]*Geriatric Joint Pathologies Department;* [2]*Diagnostic Imaging Department;* [3]*Geriatrics Department;* [4]*Physiotherapy Department, Università Campus Bio-Medico, Rome, Italy*

Received September 5, 2013 – Accepted October 29, 2013

Intra-articular injections of hyaluronic acid are a valid treatment option for patients with osteoarthritis. Differences in purity, origin, and molecular weight may influence the efficacy and safety of hyaluronic acid products, therefore, we evaluated the safety, efficacy, and duration of improvements following a single intra-articular injection of a low-medium molecular weight hyaluronic acid product of bacterial synthesis, Sinovial® One, on patients with osteoarthritis of the knee. The double-blind study enrolled 21 patients (24 knees) with symptomatic knee osteoarthritis, classified into moderate, severe and very severe osteoarthritis using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain functional Index and the Kellgren and Lawrence scales. At four months there was improvement in measured clinical parameters in 77.6% of the 24 treated knees, particularly in patients with moderate and severe osteoarthritis (improvement in 100% and 66.7%, respectively). No local or systemic adverse events were observed. These preliminary findings suggest that Sinovial® One is safe and effective for patients with knee osteoarthritis, providing long-lasting improvement in clinical parameters.

The use of hyaluronic acid (viscosupplementation) is accepted as a safe and valid therapeutic approach in the treatment of the human arthritic knee, where systemic side effects and short-lived therapeutic results may limit the use of analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids (1, 2). Hyaluronic acid, the major component of synovial fluid, is a long chained mucopolysaccharide of the glycosaminoglycan (GAG) family involved in governing the endurance and normal metabolism of joint cartilage (2). A number of animal models and human studies have shown that intra-articular administration of hyaluronic acid may reduce pain, decrease the consumption of NSAIDs, and improve function by encouraging normalization of cartilage homeostasis and improving the viscoelastic and protective properties of synovial fluid in joints compromised by trauma or degenerative pathology (1, 2). Two recent systematic reviews and meta-analyses of the efficacy of intra-articular hyaluronic acid for knee osteoarthritis found that, although steroids were more effective in providing immediate pain relief, their effects were short-lived (3), whereas hyaluronic acids reached peak effectiveness at week eight, were more effective than corticosteroids beyond eight weeks of treatment (3), and had long-term residual effectiveness at 24–26 weeks (3, 4).

A number of hyaluronic acid preparations with different origins and molecular weights (MW) are available. The ideal MW of hyaluronic acid has

Key words: osteoarthritis, treatment, hyaluronic acid, knee, intra-articular, Sinovial® One

Mailing address: Prof. Antonio Polacco,
Patologia Articolare dell'Anziano,
Università Campus Bio-Medico di Roma,
Via Alvaro del Portillo, 5
00128 Roma, Italy
Tel.: +39 622541650 Fax: +39 622541663
e-mail: a.polacco@unicampus.it

1721-727X (2013)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

been suggested to be in the range of 1000–1200 kDa (5), and there are indications that intermediate MW (800–1500 kDa) hyaluronic acids are more effective than low MW (500–730 kDa) hyaluronic acids in the symptomatic treatment of knee osteoarthritis, with a similar safety profile (6). However, although intermediate (low-medium) MW and cross-linked high MW hyaluronic acids appear to be similarly effective (7), the risk of local reactions and symptom flares may be greater with high MW hyaluronic acids (8).

Furthermore, in addition to the MW, the origin (animal, specifically rooster comb, extraction or bacterial synthesis), intermolecular links (cross-linked or non-linked), degree of purity, spatial molecular shape (linear or spherical), concentration and quantity of the individual dose, and the possible concurrent presence of two molecules with different MWs may influence the activity, efficacy, and safety of hyaluronic acids.

Sinovial® One 2% (50 mg hyaluronic acid per 2.5 mL) is a new long-acting formulation of an intermediate (low-medium) MW hyaluronic acid of bacterial synthesis, which may be less likely to cause acute allergic reactions that can be encountered with hyaluronic acids of animal extraction origin. Sinovial® One is administered as a single injection per cycle of treatment, rather than weekly administration for 3 or 3–5 weeks, as required with conventional intra-articular formulations of hyaluronic acid. This simple and convenient dosage schedule may contribute to improved patient acceptance.

The objective of this preliminary study is to evaluate the safety, efficacy and duration of the effects of a single intra-articular injection of Sinovial® One in patients with symptomatic knee arthritis.

MATERIALS AND METHODS

This was an open label, double-blind, single center study of 21 adult patients (13 women and 8 men, for a total of 24 knees) with symptomatic knee osteoarthritis, treated with a single intra-articular injection of Sinovial® One. To ensure blinding, the clinical evaluation of the patients was performed by a physician who was unaware of the substance used, and the operator was unaware of the clinical conditions of the patient. Nor were patients informed as to the nature of the injected product. The study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki, and written informed consent was obtained from all participants.

Patients were classified according to the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (9) and the Kellgren and Lawrence X-ray scale (10) to determine eligibility and establish baseline clinical and radiological parameters. Sinovial® One was administered in accordance with the manufacturer's recommendation as a single dose injection of 2.5 mL (50 mg). To ensure optimal distribution within the joint, following administration of a local anesthetic (mepivacaine 2%), the hyaluronic acid was injected into two different sites; a lateral site (25 mg; half a syringe) between the between the upper third and the middle third of the patella, and the remainder (25 mg) into a front-medial site between the medial femur condyle and tibial plate. In the presence of any joint effusion, arthrocentesis was performed prior to injection of the hyaluronic acid.

Inclusion and exclusion criteria

Adult patients who had the main pathology of knee osteoarthritis were eligible for the study. The exclusion criteria included: use of general corticosteroids or systemic slow acting drugs for osteoarthritis (glucosamine, etc.) within the previous 3 months; a systemic active sepsis or inflammatory condition; a septic knee arthritis within the previous 3 months; inflammatory arthritis (rheumatoid, rheumatic, and infective); metabolic diseases affecting the joints (gout, etc.); and intra-articular injections of corticosteroids or hyaluronic acids in the past 3 months.

Outcome measures

The study comprised three main objectives, the first being to assess the efficacy of the drug in knee arthritis, the second to assess the safety, and the third to evaluate the duration time of improvements obtained. Data were evaluated for total WOMAC score (the mean of pain score 0–20, stiffness score 0–8, physical function 0–68); the total score of WOMAC ranges from 0 to 96. A 0–10 cm VAS scale was used.

In the secondary outcomes, improvements were evaluated by extrapolating five parameters out of the total WOMAC scale: 1) lack of pain at rest; 2) painless walking distance increase; 3) joint range increase; 4) walking up stairs, and 5) walking down stairs. These parameters were given a grading scale from 0 to 4, with 0 representing the highest degree of improvement and 4 meaning a complete lack of improvement; the score ranges from 0 (best result) to 20 (worst result).

The patients were evaluated according to the Bellamy criteria (2002) which integrate the pain Visual Analogue Scale (VAS) as well as the WOMAC score (11). In order

to facilitate a better and more objective comparison with the baseline data, the final results were evaluated according to the same WOMAC parameters as those used to divide the patients into osteoarthritis severity groups. Patients were assessed clinically at 30, 60, 90, and 120 days. We analyzed the safety, the efficacy and the duration of the clinical benefits during and after the infiltration of Sinovial® One.

Statistical analysis

Statistical analysis to determine the variation of the clinical outcome was performed using the Student *t*-test applied to the WOMAC and VAS values at baseline, and at 30, 90, and 120 days after treatment. The percentage variation between VAS and WOMAC values before and after infiltration of Sinovial® One were also assessed as follows: $\Delta V\% = 100 \cdot (V4-V0)/V0$, where V0 is the mean of the index in the group pre-treatment and V4 the mean of the index in the post-treatment group after 4 months.

RESULTS

Of the 21 patients included in the study, three were treated bilaterally, for a total of 24 knees. Baseline demographical and clinical characteristics are presented in Table I.

The patients were divided into three groups according to knee osteoarthritis severity (Table II): Group A, moderate arthritis (16 knees), with a Kellgren and Lawrence Grade II-III and a total WOMAC score between 0 and 15, mean 8.8. Group B, severe arthritis (6 knees), with a Kellgren and Lawrence Grade III and a total WOMAC score between 16 and 31, mean 21.8. Group C, very severe arthritis (2 Knees), with a Kellgren and Lawrence Grade IV and a Total WOMAC score between 38 and 42, mean 40.

Overall, the majority of patients were overweight or obese, almost all had significant comorbidities and/or had undergone surgical procedures for a range of coexisting conditions. Only five patients undertook regular sporting activities, and their occupational backgrounds covered a range from sedentary (office workers) to energetic (farmer, bricklayer). Nine

Table I. *Patient demographics at baseline.*

	Number Patients (n = 21) Number Knees (n=24)	Osteoarthritis Severity†		
		Moderate (n = 16)	Severe (n = 6)	Very severe (n = 2)
Mean age, years ±SD	72.7±2.61	71.93±3.25	70.66±3.10	78.6±2.44
Gender, Female/Male (n=21)	13:8	7:6	5:1	1:1
Mean duration of osteoarthritis, years	4.5	3.6	4.1	5.8
Bilateral treatments, no.	3	3	0	0
Caucasian race, %	100	100	100	100
Body mass index (kg/m^2), mean ±SD (% pts)				
Normal weight‡	21.75 (12.5)	24.36±0.4 (12.5)	19.70±0 (16.6)	0
Overweight‡	27.5 (37.5)	27.12±1.4 (37.5)	25.60±0.64 (33.3)	27.05±0.93 (50.0)
Obese‡	32.75 (50.0)	33.49±1.78 (50.0)	34.28±2.62 (50.0)	32.75±1.35 (50.0)
Comorbidities, no. (%)				
Any‡	21 (100.0)	12 (92.3)	5 (83.3)	2 (100.0)
Hypertension	16	12	2	2
Diabetes	3	0	2	1
Fibromyoma	3	1	1	1
Prior surgery, no. (%)§	17 (81.0)	11 (84.6)	4 (66.7)	2 (1000).

†*Severity was assessed using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain functional Index and the Kellgren and Lawrence X-ray scale.* ‡*Normal weight: Body Mass Index (BMI) 18.5–25.0 kg/m^2, Overweight: BMI 25.0–30.0 kg/m^2, Obese: >30 kg/m^2.* ‡ Other *comorbidities included breast cancer, cardiac arrhythmia, cerebrovascular ischemia, goiter, and hepatitis C.* § *Some patients had undergone more than one surgical procedure. SD: standard deviation*

Table II. *Improvement in clinical parameters during treatment with Sinovial® One.*

	Overall (n = 24 knees)	Osteoarthritis Severity†		
		Moderate (n = 16)	Severe (n = 6)	Very severe (n = 2)
WOMAC score (mean)				
Baseline	14.7 (SD)	8.8 (3.2)	21.8 (3.3)	40.0 (2.8)
4 months	7.9 (SD)*	4.6* (2.4)	11.5* (3.0)	24.0* (5.3)
VAS score (mean)				
Baseline	5.5	5.4	6.3	5.9
4 months	3.1*	3.0*	4.1*	3.0*
Clinical improvement‡ (%)	77.6	100	66.7	66.2

†*Severity was assessed using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain functional Index and the Kellgren and Lawrence X-ray scale.* ‡*According to the following WOMAC parameters: 1) lack of pain at rest; 2) painless walking distance increase; 3) joint range increase; 4) walking up stairs and 5) walking down stairs. Numbers refer to knees (total of 24 knees in 21 patients).* * $p<0.01$ *vs baseline.*

patients had synovial effusion.

Efficacy

VAS and WOMAC scores improved after a single administration of Sinovial® One, with an overall improvement in measured clinical parameters in 77.6% of treated knees (n = 24). Improvement was observed in 100% of treated knees in patients with moderate osteoarthritis, 66.7% in patients with severe osteoarthritis, and 66.25% in patients with very severe osteoarthritis (Table I). A steady and durable decline in WOMAC and VAS scores occurred over time (Fig. 1). This was apparent even in patients with very severe knee osteoarthritis. Furthermore, NSAID consumption decreased in all groups during the study.

Secondary efficacy outcomes

All treated patients with moderate osteoarthritis (16 knees; Group A) reported substantial improvements in symptoms after treatment. The mean symptoms score, assessed on the 5-item subscale extrapolated from the WOMAC index, decreased from 5 at baseline to 0 after treatment. Also the VAS score decreased from 5.4 to 3. Specifically, all patients with moderate arthritis reported absence of pain at rest, walked more easily and for a longer distance, acquired a greater joint range, and walked up or down stairs more easily. These 5 parameters decreased from 5 to 0.

Similar improvements were seen in Group B (patients with severe arthritis; 6 knees), with a decrease in mean symptoms score from 9 to 3. A similar result was obtained in WOMAC index from 21.8 to 11.5 and in VAS score from 6.3 to 4.1. Finally, patients with very severe arthritis (Group C; 2 knees) also had improvements in symptoms after injection with Sinovial® One, with a decrease in mean symptoms score from 15 to 7. This improvement was confirmed by WOMAC score (from 40 to 24) and VAS score (from 5.9 to 3).

Duration of improvements

Mean values of VAS and WOMAC continued to decrease over time in the 21 patients available for follow-up at 120 days. The percentage variation between baseline (pretreatment) and 120 days was approximately –43% (Fig. 1). We also compared mean WOMAC and VAS values in patients with moderate arthritis versus severe arthritis. In this case the percentage variation between baseline and 120

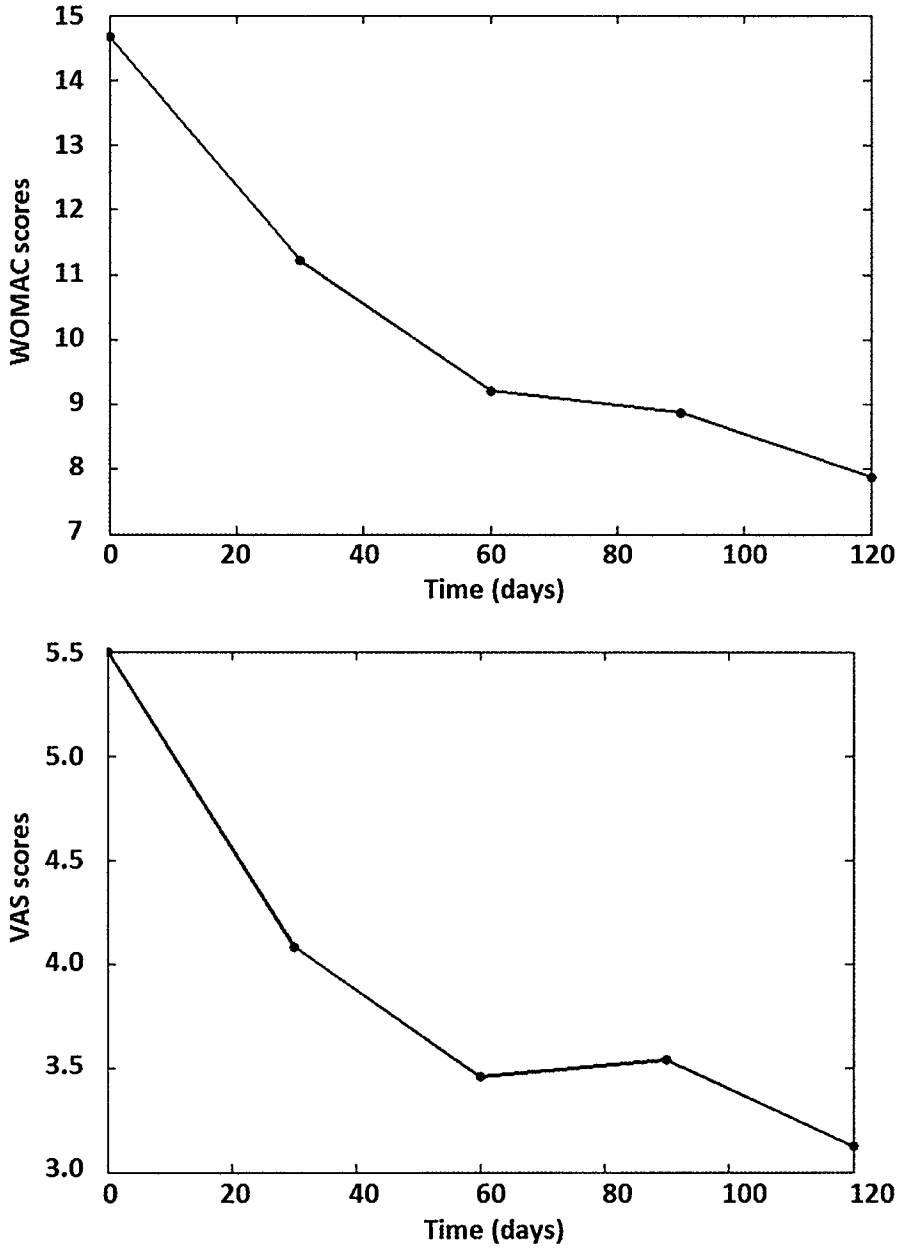

Fig. 1. *Change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Visual Analog Scale (VAS) scores over time after a single intra-articular treatment of the knees of 21 patients (24 knees).*

days was approximately –46%.

Safety

Sinovial® One was well tolerated. There were no reports of local or systemic allergic reactions, and there were no general or systemic adverse events, joint effusions, or hemorrhagic complications at injection points. Concomitant anticoagulant therapy, administered to some patients, did not interfere with the therapy.

DISCUSSION

Although the small number of subjects (21 patients, 24 knees) does not allow us to arrive at definitive conclusions, Sinovial® One was well

tolerated in these patients with knee arthritis and there were positive indications of efficacy. Furthermore, our thorough and methodical approach to recording patient clinical characteristics, physical and occupational activities, and response to treatment allows some conclusions to be drawn. Benefits in pain relief were observed in all patients, with improvements in the ease and distance of walking, greater autonomy, increases in knee joint movement, and decreases in NSAID consumption. We were able to observe that occupation, even heavy work such as bricklaying or farming, seemed to have a negligible effect on the benefits of treatment and the duration of improvements obtained. In addition, although 87.5% of patients were overweight or obese, this did not appear to influence the results, although this condition would be considered an important risk factor for the progression of osteoarthritis. The benefits of treatment were sustained, with an improvement still apparent in 77.6% of treated knees four months after the single administration of Sinovial® One.

Patients with very severe osteoarthritis are normally excluded from clinical research. However, our study included a small number of such patients, and benefits were observed even in these patients.

The treatment was very well tolerated, with no reports of adverse side effects, even in subjects consuming concomitant anticoagulants, indicating that the hyaluronic acid formulation utilized in the study was very safe. No local complications were observed after injection, such as pseudoseptic reactions or severe acute inflammatory reactions, which have been reported with a cross-linked high MW hyaluronic acid (12). We feel this can be explained by the source of Sinovial® One, which is a highly-purified product of bacterial synthesis, rather than a hyaluronic acid of animal extraction more likely to cause general and local allergic reactions in subjects sensitive to bird proteins or who suffer from other allergies. Furthermore, we found the simplified dosage schedule convenient to administer.

Our study has some limitations, in particular the small number of patients, lack of a control group, and a follow-up limited to 4 months. However, our proposal will be to evaluate all 21 patients at 6 months.

In conclusion, our preliminary findings suggest that the three main objectives of the study were achieved, and that a single intra-articular injection of Sinovial® One is safe, effective and associated with a prolonged duration of activity in the arthritic knee. Additional larger, controlled studies with a longer follow-up appear warranted to confirm these findings.

ACKNOWLEDGEMENTS

We thank Dr. Emiliano Schena of the Bioengineering Dept. of Università Campus Bio-Medico di Roma for his help in statistical analysis, and Jennifer E. Miller for language corrections. We also thank Ray Hill, an independent medical writer, who provided assistance with language editing, technical revisions, and journal styling prior to submission. This assistance was funded by IBSA.

REFERENCES

1. Abate M, Salini V. Hyaluronic Acid in the Treatment of Osteoarthritis: What is New. In Osteoarthritis - Diagnosis, Treatment and Surgery. Q. Chen Q, ed. InTech 2012; p. 23.
2. Hameed F, Ihm J. Injectable medications for osteoarthritis. PM & R 2012; 4(S):75-81.
3. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009; 61(12):1704-11.
4. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis. Osteoarthritis Cartilage 2011; 19(6):611-19.
5. Balazs EA. The physical properties of synovial fluid and the special role of hyaluronic acid. In Disorders of the Knee. A. Helfet, ed., ed. JB Lippincott, Philadelphia, 1974; p. 61-74.
6. Berenbaum F, Grifka J, Cazzaniga S, et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis

2012; 71(9):1454-60.

7. Pavelka K, Uebelhart D. Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial®) *vs* hylan G-F20 (Synvisc®) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study. Osteoarthritis Cartilage 2011; 19(11):1294-300.
8. Reichenbach S, Blank S, Rutjes AW, Shang A, King EA, Dieppe PA, Juni P, Trelle S. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum 2007; 57(8):1410-18.
9. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15(12):1833-40.
10. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16(4):494-502.
11. Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. J Rheumatol 2002; 29(12):2473-76.
12. Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementation: diagnosis and treatment. Clin Orthop 2004; (419):130-37.