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Focus on:

**ASKOT STUDY: Effectiveness
and safety of a 1-shot injection
of sodium Hyaluronate for knee
osteoarthritis treatment**

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ASKOT STUDY: Effectiveness and safety of a 1-shot injection of sodium Hyaluronate for knee osteoarthritis treatment

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ABSTRACT

Purpose: Evaluation of the effectiveness and safety in real-life conditions of a viscoelastic solution of hyaluronic acid for intra-articular one-shot injection in Osteoarthritis.

Patients and methods: An international multi-centre, non-interventional, observational study with 411 patients who were attending rheumatology/orthopaedics units for pain due to knee osteoarthritis. Three visits were performed to register general data and specific information for OA history and current treatment. Pain at rest and pain at walking was evaluated based on a Analogic Visual Scale in each visit, as well as the Lequesne functional index for quality of life impact of OA. Adverse events were registered during the follow up. Efficacy of the injection was evaluated in terms of the functional impact on knee osteoarthritis, using patient self-evaluation.

Results: Population average age and time since OA diagnosis were 62 and 3.64 years, respectively. Both knees affectation were found in 23% of patients and pharmacological treatment was indicated in the last year for 73% overall studied population. Pain was the most relevant symptom. After injection, mean VAS pain at rest was significantly lower 3 and 6 months after treatment in comparison to baseline VAS score (mean [SD]: 18.97 [19.37] vs. 30.79 [22.93]; $p < 0.001$ and 18.50 [19.46] vs. 30.79 [22.93]; $p < 0.001$). Significantly lower Lequesne mean overall score at 3 and 6 months compared to baseline (7.25 [4.37] vs. 10.60 [4.07]; $p < 0.001$ and 6.85 [4.45] vs. 10.60 [4.07]; $p < 0.001$) was also found. Overall, 86.7% of patients declared an improvement in their health at 3-months post-injection and a lower number and intensity of pain exacerbations between baselines (65.2% at 3 months) of patients and (48.8% between 3 and 6 months).

Conclusion: Treatment with an intraarticular 1-shot injection of viscoelastic solution of hyaluronic acid is effective in providing clinically relevant pain relief over a period of at least 6 months in patients suffering from knee osteoarthritis.

Keywords: osteoarthritis, hyaluronic acid, safety, effectiveness, intraarticular injection

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INTRODUCTION

Osteoarthritis represents actually a relevant cause of pain and disability for people over 50 years of age [1], in which the knee is the most common joint affected. Mechanical factors (such as tibiofemoral deformities), history of trauma or obesity are known as risk and maintenance factors [2].

Cartilage disruption and osteophyte formation are the basic anatomical alterations of the affected joint [8] and are related to biochemical and rheological modifications of the synovial fluid [3-7], causing chronic inflammation.

The therapeutic concept of visco-supplementation through intra-articular injections has been proposed as a useful resource to decrease pain symptoms and improve patients' functionality, in order to restore synovial fluids rheological with exogenous Hyaluronic Acid (HA) or its derivatives. [8]

Hyaluronic Acid is considered as a main component of the synovial fluid, with an important role on its rheological and lubricant properties [8]. The Affection on quantity and quality of hyaluronic acid of the joint causes an insufficient protection of weight-bearing joints, increase cartilage breakdown and synovial inflammation [3].

Multiple studies have evaluated the benefit of visco-supplementation in the management of knee osteoarthritis. Randomized double-blind, placebo-controlled studies report significantly reductions on painful symptoms, functional disability and analgesic or NSAID intake [9-12] after intra-articular injection of HA, with optimal benefits around the fourth week of treatment, that may be prolonged up to 26 weeks after the last injection [11].

Efficacy of visco-supplementation has been reported as comparable to classic pharmacologic therapy [13] and with a proper safety profile. According to the American College of Rheumatology OA guidelines [14], is a useful resource in

OA management for patients with high GI risk of upper gastrointestinal adverse effects.

The mechanism of action of hyaluronic acid is not fully understood, and probably multifactorial. Its prolonged therapeutic effects beyond its intra-articular life-time (with a mean value of 10 to 18 hours) suggests that it may have one or more pharmacological actions [15] in addition to evidence of improvement of the rheological parameters of the synovial fluid. Several hypotheses on ancillary non mechanical actions have been suggested [15-17]:

- A self-induction effect on the endogenous hyaluronic acid production and the reaggregation of proteoglycan molecules [18].
- An analgesic effect by inhibition of articular nociceptive receptors [18-20].
- A direct anti-inflammatory action on synoviocytes by inhibiting the release of arachidonic acid and by blocking prostaglandin-E2 synthesis [21].
- A protective effect on the superficial layer of cartilage [22]. An arthroscopic follow-up study showed that the clinical benefit of visco-supplementation was correlated with a significant reduction in the deterioration of cartilage [23].
- A lubricating and control effect on cell membrane permeability [24].

Prolonged effects of intra-articular HA on the OA knee have encouraged reconsidering not only traditional doses regimens, but in regards, a reduction on the number of injections [25].

On this line, a single shot presentation (SUPLASYN® 1-shot) is available as a prefilled syringe containing 60 mg/6 ml of sodium hyaluronate in a viscoelastic solution. Administered as a single injection HA has shown to be safe and effective in providing clinically relevant pain relief over 26 weeks [26], and also suggested as efficacious and well tolerated as a regimen of 3 x 2 ml one week apart [8].

This study aimed to verify that results produced in other clinical trials were transferable

to the beneficiary population (i.e. the population which is effectively managed and treated under the most realistic conditions possible).

PATIENTS AND METHODS

An international multicentre, non-interventional, observational study was carried out between May 2010 and March 2011 at rheumatology/orthopaedics units in Germany, Spain, Czech Republic and Slovakia.

Patients over 18 years old who were attending to rheumatology/orthopaedics units due to knee pain related to osteoarthritis and whom physician decided to perform a 1-shot injection of HA were included. Prior informed consent was necessary for the inclusion in the study. A sample size of 300 was planned to detect any event occurring at an incidence of 1/100 with an alpha error of 0.05.

All patients received an intra-articular injection of SUPLASYN® 1-shot (60 mg/ 6ml of sodium hyaluronate), while half overall studied population received concomitant treatment with analgesics and/or anti-inflammatory medication.

The evaluations were performed at inclusion visit and three follow up visits (at seven days, three months and six months after). Information collected at baseline included general data, history of knee osteoarthritis, pharmacological and non pharmacological treatment of knee osteoarthritis in the last 12 months, integrated care pathway for knee osteoarthritis in the past 3 months, local interventions on the knee, severity of symptoms (using VAS pain at rest and walking from 0 to 100) and their impact on daily life (Lequesne index). Also the last x ray report with the Kellgren-Lawrence grade from the last X ray report was included.

Any adverse event were registered in every visit, as well as Global Impressions related to the clinical course of OA, including number of symptomatic exacerbations of knee osteoarthritis since last assessment and evaluation of Pain

at rest and *at walking* according to a Visual Analogue Scale. The changes on VAS scores and the time necessary to obtain these changes were evaluated on repeated measures to perform analysis of variance using Dunnett's test.

To assess pain influence on functionality related to knee OA, the Lequesne functional index was evaluated. This specific evaluation is composed of 11 questions divided between three questionnaires that evaluate the *intensity of the discomfort and/or pain* in various situations (at night, morning stiffness, when standing, walking, and standing up from a seated position), the *length of maximal walking distance* and the *impact of knee osteoarthritis on daily activities* (going up and down stairs, crouching down, walking on uneven surfaces).

Effectiveness of the injection was evaluated in terms of the functional impact on knee osteoarthritis, using a patient self-evaluation.

Statistical analysis

Main data analysis was processed using SAS version 8.0. Quantitative variables were described with their sample size, mean, standard deviation, median, extreme values and missing data. Qualitative variables were described with their sample size, percentage and missing data. Two-sided 95% confidence intervals were calculated for relevant criteria.

RESULTS

Four hundred and eleven patients with a mean (SD) age of 62 (13.8) years, were included. 64% of the patients were women and 36% men. Patients had a mean body mass index (BMI) of 28.1 (4.7) kg/m², with 2.2% of the population having a BMI <20 kg/ m², 22.7% having a BMI between 20 and 25 kg/ m², 47% between 25 and 30 kg/m², and 28% having a BMI of at least 30 kg/m² (Table 1). Most participants were retirees or unemployed (55%).

All patients had a diagnosis of either unilateral or bilateral knee osteoarthritis (38% right knee, 39% left knee and 23% both knees), with a mean of 3.64 (4.25) years since diagnosis, and an average of 28.6 (81.1) cases of breakthrough pain per patient annually (Table 1).

Overall, 73% of patients had received at least one pharmacological treatment (analgesics and/or NSAIDs) during the 12 months prior to study entry, and 40% had undergone non-pharmacological therapy (massage, physical therapy, etc.). During the 3 months prior to study entry,

51.2% of patients had visited their GP at least once, 92% of patients had consulted a rheumatologist/orthopedist.

Prior treatment included surgery in 6% of patients, arthroscopy in 26%, arthrocentesis in 10% and joint lavage in 3%. Overall, 41% of patients had received at least one intra-articular injection of corticosteroids and 29% had at least one intra-articular injection of hyaluronic acid (Table 1).

Clinical symptoms present at study entry are shown in Table 2.

Table 1. Characteristics of the Study Population (n = 411)

<i>General Sample Characteristics</i>	<i>Mean Age (SD)</i>	62 (13,8) years
	n (%)	
	Female	263 (64%)
	Male	148 (36%)
	Mean (SD)	
	<i>Mean Body mass index (BMI)</i>	28,1 (4,7)
	<i>Body mass index groups</i>	n (%)
	< 20	9 (2,2%)
	20 - 25	93 (22,7%)
	25 - 30	192 (46,8%)
	>30	116 (28,3%)
OA Characteristics		
<i>Affected Knee</i>	n (%)	
	Left	160 (38,9%)
	Right	156 (38%)
	Both	95 (23,1%)
<i>OA History</i>	Mean (SD)	
	Time since first diagnosis (year)	3,64 (4,25)
	Painful episodes / year	28,6 (81,1)
<i>Previous treatment</i>	n (%)	
	At least one pharmacological treatment (last 12 months)	298 (73,2%)
	At least one non-pharmacological treatment (last 12 months)	165 (40,1%)
	Intra-articular corticosteroids injection	166 (40,8%)
	Intra-articular hyaluronic acid injection	116 (29,3%)
<i>Local intervention on the knee</i>	Surgery	24 (6%)
	Arthroscopy	106 (25,9%)
	Arthrocentesis	40 (9,9%)
	Joint lavage	12 (2,9%)

Table 2. Current Condition at Inclusion Visit

Symptoms	Severity	n (%)
Pain	None	2 (0.5%)
	Mild	134 (32.9%)
	Moderate	211 (51.8%)
	Severe	60 (14.7%)
Stiffness	None	83 (20.4%)
	Mild	178 (43.7%)
	Moderate	134 (32.9%)
	Severe	12 (2.9%)
Swelling	None	129 (31.9%)
	Mild	200 (49.5%)
	Moderate	68 (16.8%)
	Severe	7 (1.7%)
Kellgren-Lawrence	Grade 1	48 (12,3%)
	Grade 2	174 (44,5%)
	Grade 3	141 (36,1%)
	Grade 4	28 (7,2%)

Radiographic evaluation was performed using results obtained a mean of 7.28 (12.1) months prior to study entry. According to the stage of development of knee osteoarthritis (Kellgren-Lawrence grading system), 12.3% of patients had grade 1 osteoarthritis, 44.5% grade 2, 36.1% grade 3 and 7.2% grade 4 osteoarthritis.

The mean (SD) VAS pain at rest in the beginning of the study was 30.84 (23.05) and mean VAS pain at walking was 57.6 (19.32). Overall,

Lequesne score was 10.64 (4.08), with 4.46 (1.70) points in the pain and discomfort questionnaire, 2.09 (1.78) for the maximum distance walked questionnaire and 4.04 (1.63) for the activities of daily living questionnaire.

Safety of the injection

Nine patients (i.e., 2.2% of the treated population) reported having at least one adverse event. AEs of seven patients were related or possibly related to the injection, which three of them were related to local adverse events: post injection pain (n = 1), local swelling (n = 1) and sensation of hot knee (n = 1) (Table 3). All the events related to product administration resolved within a few days (0-5 days).

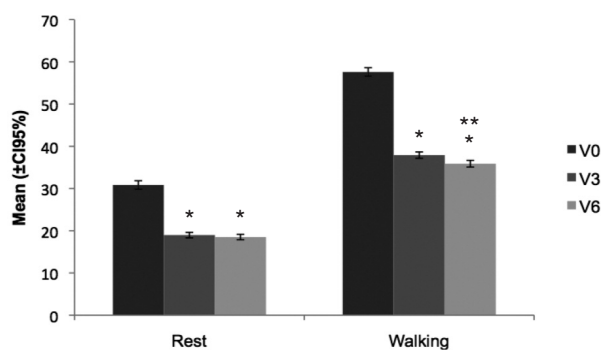
Pain Scores

Mean VAS pain at rest was significantly lower 3 and 6 months after treatment compared to the baseline (18.97 [19.37] vs. 30.79 [22.93]; $p < 0.001$ and 18.50 [19.46] vs. 30.79 [22.93]; $p < 0.001$). Also, patients had a significantly lower mean VAS pain while walking after 3 and 6 months compared to baseline (37.91 [22.76] vs. 57.56 [19.36]; $p < 0.001$ and 35.87 [24.17] vs. 57.56 [19.36]; $p < 0.001$). The evolution of VAS score through the study is presented in Figure 1.

Table 3. Adverse Events

Patient N°	Description	Time delay *	Event duration (days)	Relation to treatment	Symptomatic treatment	Outcome
10018	« Hot knee » sensation	1	3	Certain	None	Resolved
10091	Joint pain	0	1	Possible	None	Resolved
10111	Knee pain and swelling	2	1	Possible	NSAIDs + ice	Resolved
30408	Joint pain	0	0	Certain	None	Resolved
30408	Swelling of the knee	1	0	Certain	None	Resolved
30433	Knee pain and swelling	0	3	Possible	None	Resolved
40249	Swelling of the knee	1	5	Possible	None	Resolved

*Interval between injection and start of event (days)



V0: Pre-treatment visit, V3: 3 months visit, V6: 6 months visit.

*p < 0.001 vs V0. **p < 0.05 V6 vs V3

Figure 1. Evolution of VAS Pain Score

Lequesne algofunctional index

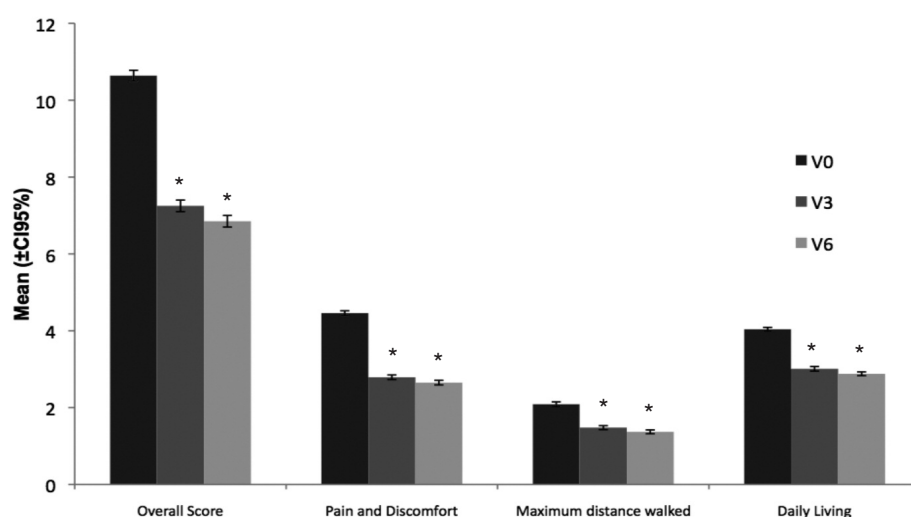
Patients had a significantly lower Lequesne mean overall score at 3 and 6 months compared to baseline (7.25 [4.37] vs. 10.60 [4.07]; $p < 0.001$ and 6.85 [4.45] vs. 10.60 [4.07]; $p < 0.001$). Furthermore, the mean sub score pain and discomfort was significantly lower at baseline compared with the sub score at 3 and 6 months respectively (2.79 [1.83] vs. 4.47 [1.70]; $p < 0.001$ and 2.65 [1.87] vs. 4.47 [1.70]; $p < 0.001$). The walking distance sub score improved signifi-

cantly after 3 and 6 months of treatment compared with baseline (1.48 [1.55] vs. 2.10 [1.78]; $p < 0.001$ and 1.37 [1.43] vs. 2.10 [1.78]; $p < 0.001$). Also, the daily activities sub score decreased significantly after 3 and 6 months of treatment compared with baseline (3.01 [1.76] vs. 4.05 [1.62]; $p < 0.001$ and 2.88 [1.82] vs. 4.05 [1.62]; $p < 0.001$)(Figure 2).

Exacerbations

Overall, 86.7% of patients declared an improvement in their health at 3-months post-injection (14.7 % very strong improvement, 39.1% strong improvement, 32.9% slight improvement, 11.8% no change, 1.2% slight worsening and 0.2% strong worsening); 80.6% declared an improvement at 6-months post-injection (16 % very strong improvement, 37.2% strong improvement, 27.4% slight improvement, 17.2% no change, 2% slight worsening and 0.2% strong worsening) (Table 4).

Improvement in clinical status measured at 3 and 6 months was accompanied by a decrease in the number and intensity of pain exacerbations between baseline and 3 months for 65.2% of patients and between 3 and 6 months in 48.8% of patients.



V0: Pre-treatment visit, V3: 3 months visit, V6: 6 months visit.

*p < 0.001 vs V0.

Figure 2. Lequesne Functional Index 3 and 6 months post treatment

Table 4. Improvement on severity of symptoms comparison: 3 and 6 Months post injection

Data	3 months post-treatment N (%)	6 months post-treatment N (%)
Improvement on Severity of Symptoms		
Very strong improvement	60 (14.7%)	64 (16.0%)
Strong improvement	159 (39.1%)	149 (37.2%)
Slight improvement	134 (32.9%)	110 (27.4%)
No change	48 (11.8%)	69 (17.2%)
Slight worsening	5 (1.2%)	8 (2.0%)
Strong worsening	1 (0.2%)	1 (0.2%)

DISCUSSION

This study, performed in four European countries in patients suffering from knee osteoarthritis confirmed the safety profile and effectiveness of the therapy with hyaluronic acid with a dosing regimen of one administration of 6 mL.

The increased volume of administration (three times more than a conventional injection) did not have any effect on the safety of the injection. The adverse events reported, which were restricted to minor and transient local events, did not require specific treatment and occurred with less frequency to that described in the literature for this dosing regimen and for the 2 mL dosing regimen [8, 26].

All the parameters used to measure the efficacy of the treatment (pain, quality of life) were significantly improved after 3 months and 6 months of treatment. An overall decrease in the Lequensne-index greater than 2 is considered clinically meaningful [27]. In our study, more than half of the patients had a clinically meaningful decrease in the Lequensne-index; the mean overall decreases were 3.35 and 3.75 after 3 and 6 months respectively.

In addition, the study results confirm the efficacy of a single injection and maintenance of the therapeutic benefit over a period of at least 6 months.

These findings are relevant for the physician in daily practice, because decreasing the number of injections into the osteoarthritic joint decreases the risk of infection associated with any intra-articular procedure and improves patient compliance and convenience. Also, there is significant economic benefit to be gained from reducing the number of injections required to complete the treatment as physician time, patient time, clinic overheads, and medical disposable costs could all be reduced [8].

Finally, the results presented here argue in favor of this “natural compound” treatment for knee osteoarthritis over prolonged treatment with NSAIDs. It is particularly suitable given that the target population is generally older and largely susceptible to tolerance issues and poor treatment compliance.

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