INTRAARTICULAR HYALURONATE EFFICACY AND SAFETY IN THE KNEE OA TREATMENT

INGRID MÖLLER, CARMEN MORAGUES, NURIA MARTÍ, JUAN J ALEGRE. INSTITUTO POAL DE REUMATOLOGÍA. BARCELONA

INTRODUCTION

Sodium Hyaluronate is a glycosaminoglycan which is widely distributed in the connective tissues of animals, presenting a disaccharide structure: N-acetyl-D-glucosamine and sodium D-glucuronate linked together by alternating 1-3 and 1-4 glucosidic bonds. Intra-articular injections of sodium hyaluronate (1%, 2ml) of bacterial origin (Streptococcus zooepidemicus, m.w. = 1.200 KDa) have been used in the treatment of knee osteoarthritis for several years,

Study Objectives:

- To evaluate the efficacy, and the duration of efficacy, of treatment with intra-articular injections of 2ml sodium hyaluronate (1% solution - Ostenil®), administered once a week for 5 consecutive weeks, in the treatment of grade 2-3 knee OA (Kellgren-Lawrence classification), under actual clinical conditions with 6 months follow-up period.
- To confirm the absence of deleterious effects on cartilage or any toxicity for the patient.

MATERIAL AND METHODS

STUDY DESIGN

Prospective, open study, with a 6-month follow-up period including 40 patients with grade 2-3 knee OA (Kellgren-Lawrence classification).

The treatment consisted of 1 i.a. injection of HA into the knee joint per week for five consecutive weeks.

Patients were evaluated at baseline, before the start of treatment, at Week 4 and Months 1 and 6 after the end of the treatment.

Patients underwent standard haematology and clinical chemistry tests at inclusion and at the end of treatment. This included: full haemogram, ESR, hepatic and renal biochemistry.

PATIENTS

Inclusion criteria

- Patients with symptomatic OA grade 2-3 rated by the Kellgren-Lawrence classification.
- Age: 37-75 years old.
- Weight: 40-95 Kg (BMI: 18-30).

Exclusion criteria

- Patients suffering from other inflammatory diseases or any other joint problems.
- Patients with primary or secondary neoplasms.
- Patients presenting metabolic bone diseases or other metabolic disease.
- Patients undergoing different treatments such as intra-articular corticosteroids, NSAIDS, SYSADOA, or osteoporosis treatment during the 3 months prior to recruitment.
- Pregnant women
- Valgus and/or varus as well as congenital acquired articular deformities.

PARAMETERS ASSESSED

The following parameters were assessed at baseline (Day 0), at Week 4 of the study and then one and six months after the end of treatment.

Primary efficacy parameter: Lequesne Algofunctional Index of the knee.

Secondary efficacy parameters:

- Pain on the Visual Analogue Scale (VAS: 0-10 cm).
- Presence of joint effusion in the target joint.
- Subjective evaluation of treatment efficacy by the patient.
- Evaluation of tolerability (local or general adverse effects, haematology and clinical chemistry parameters).
- Knee X-rays (specialised radiological evaluations on high quality standard patellofemoral X-rays taken with knee positioned at 45º and antero-posterior X-rays taken in a weight-bearing monopodal position) were taken at baseline and 6 months after the end of the treatment.

STATISTICAL ANALYSIS

The statistical evaluation was performed by Biométrica, Spain, using the SPSS® Statistical software version 10. All the data were assessed according to the intention-to-treat analysis (ITT analysis). The statistical methods used were non-parametric methods such as the Friedman test, Cochran Q test, the Wilcoxon and McNemar test, with a level of significance set at p<0.05.

RESULTS

Lequesne Index values at baseline

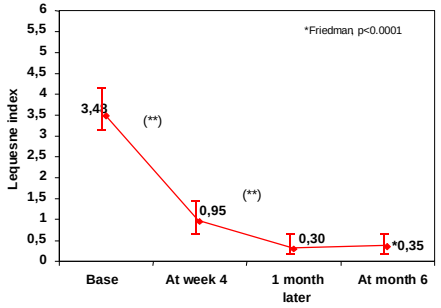
ISK values	N	%
0	1	2,5
1	3	7,5
2	3	7,5
3	15	37,5
4	8	20,0
5	7	17,5
6	3	7,5
Total	40	100,0

VAS values at baseline (cm)

VAS Score (10 cm)	N	%
4	4	10,0
5	16	40,0
6	10	25,0
7	7	17,5
8	2	5,0
NC	1	2,5
Total	40	100,0

Evolution of the Lequesne Index

	Mean	SD	I.C. (95%)	Median	Max
Baseline	3,48	1,4	(3,04; 3,92)	3,00	6,00
At Week 4	0,95	1,0	(0,63; 1,27)	1,00	4,00
1 month later	0,30	0,6	(0,11; 0,49)	0,00	2,00
At Month 6	0,35	0,7	(0,13; 0,57)	0,00	2,00

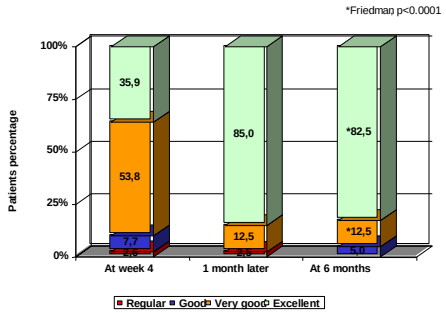


(**) Wilcoxon statistically significative (p<0.001)

Evolution of pain on the VAS

	Mean	SD	Median	Min	Max
Baseline	5,67	1,06	5,00	4,00	8,00
At Week 4	2,38	1,27	3,00	0,00	6,00
1 month later	0,88	1,14	1,00	0,00	6,00
At 6 months	0,83	1,17	0,00	0,00	4,00

Patients' global evaluation of efficacy



EFFICACY

At baseline, 87.5% of the patients presented at least total incapacity for one of the activities of the Lequesne Index. At the end of the study, the efficacy variables showed an absolute improvement in 97.5% of the patients. Only 2.5% of the patients were totally unable to perform at least one of the activities. For every variable measured, statistically significant results were obtained at the end of the visits (Friedman test: p<0.001, for all comparisons). The patients expressed a favourable opinion of the treatment from week 4 onwards. Six months after the end of the treatment, 95% of the patients evaluated treatment efficacy as very good or excellent (p<0.0001).

TOLERABILITY

The tolerability was excellent. There were no changes in the laboratory safety parameters evaluated at baseline and at the end of the study.

CONCLUSION

The weekly i.a administration of 2ml (1%) HA solution (OSTENIL®), for 5 consecutive weeks is efficacious in controlling symptomatic knee OA as shown both by the parameters evaluated by the investigators (p<0.001) and the subjective evaluation by the patient (p<0.0001). The treatment is efficacious in men and women of any age and weight, however, younger and lighter patients obtained better results (which did not reach statistical significance).

- Ostenil® is well tolerated by patients with grade 2-3 knee OA (Kellgren and Lawrence criteria), and does not exhibit adverse local or systemic effects.
- The effect of the treatment was maintained during the whole follow-up period, demonstrating that its long-term efficacy lasts for more than 6 months after the end of the treatment.
- No radiological changes were noted 6 months after the end of the treatment when the treated and non treated knees were compared, given that all patients had bilateral knee OA.
- The good results obtained with OSTENIL® are based on both its efficacy and the correct selection of the indication to be treated (inclusion/exclusion criteria of the patients).

BIBLIOGRAFÍA

1. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. Arthritis Rheum 1995; 38: 1541-1546.
2. Huskisson EC, Donnelly S, Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology 1999: 38; 602-607.
3. Huskinson EC, Donnelly SM, Editorial: Hyaluronic acid in osteoarthritis. Eur J Rheumatol Inflamm 1995: 15(1): 1-2.
4. Lequesne M, Brandt K, Bellamy N, Moskowitz R, Menkes CJ, Pelletier JP. Guidelines for testing slow acting drugs in osteoarthritis. J Rheumatol 1994; 21 (suppl. 41): 65-73.
5. Menkes CJ. Intraarticular treatment of osteoarthritis and guidelines to its assessment. J Rheumatol 1994; 21: 74-76.
6. Möller Parera I, Larrea Gayarre A, Roig Escofet D, García Iborra JR, Sampedro Álvarez J et al. Un estudio de seguimiento multicéntrico en pacientes con gonartrosis tratados con inyecciones intraarticulares de ácido hialurónico. Rev Esp Reumatol 2000; 27: 337-345.
7. Simon LS. Viscosupplementation therapy with intraarticular hyaluronic acid: fact or fantasy? In: Brandt KD, editor, Rheumatic disease clinics of North America. Filadelfia: WB Saunders Company, 1999; 25: 155-163.