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A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis

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Background. **Clinical trials have demonstrated the safety and efficacy of hyaluronic acid-based products for the treatment of synovial joints affected by osteoarthritis (OA), but data from observational studies of normal medical practice are sparse.**

Aim. **This study investigated the safety and efficacy of intra-articular (IA) sodium hyaluronate (MW 1500-2000 KDa; Hyalubrix®) in the treatment of synovial joint OA.**

Design. **This is prospective, and observational study.**

Setting. **This study was carried out at 47 specialist centers for physiatrists, orthopedics and rheumatology in Italy; the enrolled population, 1266 outpatient, was predominantly female (66%, 840/1266), with a mean age of 66 years, and a mean weight of 74 kg.**

Population. **The Participants with OA received IA injections of the study treatment (2 mL) once per week for 3 weeks. The knee was the joint most commonly affected by OA (right knee 802/1266 [63%]; left knee 598/1266 [47%]), and the longest median duration of disease occurred in the carpal joint (right carpal joint 40 months; left carpal joint 60 months).**

Methods. **The primary endpoints were tolerability and details of usage of the IA sodium hyaluronate syringe device. Efficacy parameters included assessment of self-reported pain via the Visual Analogue Scale (VAS), and evaluation of motor function via the Health Assessment Questionnaire (HAQ). Quality of life (QoL) was assessed using the Euro QoL questionnaire (Clinical Trial Registration Number: ISRCTN 42690497).**

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Conflicts of interest.—None declared.

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Results. **Data from 1266 participants were collected. The adverse event (AE) rate was 0.8% (95% CI, 0.4 to 1.5). Thirteen AEs were reported, 12 of which were mild or moderate in severity. Only one participant discontinued study treatment following an AE. No serious adverse events occurred. Coadministration of local anesthetic was required by up to 10% of patients. Statistically significant improvements in VAS, HAQ and EuroQoL were recorded in multiple joints (P<0.0001 for each).**

Conclusion. **The study treatment was safe and well tolerated.**

Clinical rehabilitation impact. **The study treatment reduced pain, improved mobility, and increased QoL in participants with OA.**

KEY WORDS: Osteoarthritis - Hyaluronic acid - Injections, intra-articular - Viscosupplementation - Clinical trial, phase IV.

Osteoarthritis (OA) is a common degenerative musculoskeletal disease, occurring in approximately 10% of people aged 55 years or older.[1] It affects synovial joints, particularly the knees, hips, interphalangeal joints, and spine, and is characterised by loss of articular cartilage and subsequent remodelling of periarticular bone. Patients typically present with pain, inflammation, and/or stiffness occurring in one or more joints, which fluctuates in intensity and localisation over time. Osteoarticular disease reduces the rheological properties of synovial fluid in the various joints affected, increasing the susceptibility of the articular cartilage to damage.[2, 3] Pain and functional disability caused by OA can have a major negative impact on daily living, socioeconomic activity, and quality of life (QoL).[4] OA is one of the main causes of locomotor disability and is a significant burden on healthcare services.

Symptomatic pharmacotherapy for OA primarily consisted of non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular (IA) injections of corticosteroid. However, the associated side-effects of these agents generated interest in developing alternative treatment modalities.[5] One such modality is viscosupplementation, in which IA injection of hyaluronic acid (HA) is used to restore the viscoelastic properties of synovial fluid. The efficacy and tolerability of IA hyaluronan (another term for HA) have been demonstrated in numerous clinical trials carried out over the past 15 years;[6-14] however, data from observational studies designed to evaluate the safety and efficacy of HA products in daily medical practice are sparse. Evaluation of potential differences in the impact on OA disease progression, which has been described for low- to mid-molecular weight (MW) sodium hyaluronate (500-730 kDa),[10, 15-17] is of particular importance.

Hyaluronan (HA) preparations are viscous solutions derived from extracts of rooster combs or bacterial fermentation, and are composed of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. More than 20 types of hyaluronan are now commercially available world-wide. Intra-articular treatment of OA with all currently available commercial hyaluronan preparations is generally well tolerated. The most common adverse event associated with their use is an inflammatory reaction, or flare, at the injection site, which is characterised by pain and swelling.[9, 12, 18] These reactions are typically mild and resolve without treatment. Such local reactions do not necessarily recur with subsequent injections and are often self limiting. Furthermore, discontinuation of treatment generally is unnecessary, as the clinical benefits are often still significant after the local reaction subsides.[19] A recent report by Juni *et al.*[20] stated that a higher incidence (~12%) of local adverse events per patient was recorded after viscosupplementation therapy with hylan GF 20 (MW~6000 KDa), a chemically cross linked product derived from rooster comb and treated with formaldehyde and vinylsulphone to increase its average molecular weight. A lower incidence (~8.5%) was obtained with non-chemically modified (*i.e.* 100% natural) sodium hyaluronate derived from rooster comb.[20]

Moreover, there is growing evidence to suggest that cross linked hyaluronan may be associated with an increased incidence of pseudo-septic arthritis, also termed severe acute inflammatory reaction (SAIR), which is clinically distinct from the local inflammatory reactions seen with all hyaluronan preparations, or the flares associated with most IA injections.[21] Although there are numerous accounts of SAIR in the literature,[22-28] these are not usually associated with naturally-derived sodium hyaluronates, suggesting a possible link between SAIR/pseudo-sepsis and chemical modification of the hyaluronan molecule.

Hyalubrix® (Fidia Farmaceutici SpA, Italy) is a naturally derived, high MW (1500-2000 KDa) sodium salt of HA, and is indicated for the treatment of degenerative and mechanical arthropathies.

On the basis of the available clinical trial data, expected adverse reactions related to the use of Hyalubrix® would be those typical to HA products, namely

TABLE I.—*Details of secondary endpoint evaluations: Health Assessment Questionnaire, Visual Analogue Scale, and European Quality of Life Questionnaire.*

Evaluation tool	Details
Health Assessment Questionnaire [30-32]	• Self-administered • Assesses difficulty in performing basic daily activities during the previous week • Each item is scored from 0 to 3: 0=no difficulty, 3=impossible to perform task • Widely used to assess physical function • Sensitive to change • Comparable to disease-specific Western Ontario and McMaster Universities Osteoarthritis Index, WOMACa
Visual Analogue Scale (VAS)	• Self-administered • Used to assess characteristics or attitudes that range across a continuum and cannot easily be measured directly • Line (horizontal or vertical) with 100 mm scale, anchored at either end by descriptors: e.g. 0=no pain, 100=worst pain imaginable
European Quality of Life Questionnaire (EuroQoL) [33, 34] • Utility score • EuroQoL VAS	• Measures current health status • Five dimensions: mobility, personal care, usual activities, pain, anxiety/depression • The utility score obtained from the five 'dimension scores' represents an index for overall quality of life • Overall score decreases the more the patient perceives his/her quality of life to be far from full health • Overall score can be negative if health status is perceived by patient as 'worse than death' • EuroQoL VAS, 100 mm vertical scale: 0=best health state imaginable 100=worst health state imaginable

inflammatory reaction of the injected joint (*e.g.* pain, swelling, redness). Following the recommendations of European Commission (EC) postmarketing guidance for medical devices, which recommends the development of studies focussed on adverse event registration,[29] the aim of this study was to investigate the use of IA sodium hyaluronate (MW 1500-2000 KDa; Hyalubrix®) in daily medical practice in patients with OA, particularly regarding tolerability.

Materials and methods

This prospective, observational study was carried out at 47 specialist centres for physiatrists, orthopaedics and rheumatology in Italy. Men and women aged from 54-to-78-year-old with radiologically diagnosed OA (located in the knee, hip, shoulder, tibio-tarsal joint, and trapezio-metacarpal joint), suitable for treatment with injectable HA, were admitted to the study. The presence of infection in the treatment area, and/or an established sensitivity to HA excluded participation in the study. Enrolment occurred between August 2006 and January 2008. Clinical Trial Registration Number: ISRCTN 42690497.

All participants received IA HA, administered via a pre-filled syringe device (Hyalubrix®, Fidia Farmaceutici SpA, Italy) containing sodium hyaluronate solution (1.5%; 2.0 mL) for IA injection, into one or more joints, as required, once per week for three consecutive weeks. The participants were then assessed at a follow up visit occurring two weeks after the third (final) injection.

The primary endpoint of this study was to evaluate the use of IA sodium hyaluronate (MW 1500-2000 KDa; Hyalubrix®) according to EC guidelines for medical device registration, with particular reference to tolerability, which was assessed via adverse event reporting. Treatment administration details were also recorded by the investigator. Secondary endpoints included mean variation in pain score compared with the score at baseline. The severity of pain was evaluated at each visit using a continuous 100-mm Visual Analogue Scale (VAS, to assess the global level of pain in the target joint), and the Health Assessment Questionnaire (HAQ),[30, 31] which was validated for use in Italian patients.[32] The effect of treatment on the participants' QoL was also evaluated at each visit using the European Quality of Life Questionnaire (EuroQoL; also known as EQ-5D).[33, 34] via VAS and utility scores. A synopsis of HAQ, VAS, and EuroQoL is given in Table I. The use of OA-specific pharmacological therapy was also recorded at each study visit. In addition, an evaluation of the effectiveness and tolerability of the IA sodium hyaluronate syringe device was made by physicians and participants at the follow-up visit.

Ethics

This study was conducted in accordance with the Declaration of Helsinki 2000, with pertinent national and international regulatory requirements. All participants provided written informed consent and were free to withdraw from the study at any time. The protocol was approved by local Ethics Committees.

TABLE II.—*Baseline characteristics of the study participants*

Characteristic	Participants (N=1266)	
Age – yr: mean±SD	66±12	
Sex – %:	66 female: 34 male	
Weight – kg: mean±SD	74±11	
Height – cm: mean±SD	164±8	
Number of joints per person affected by OA: mean ±SD	1±1 (range 1 to 8)	
Location of joints affected by OA – N. (%):		
Knee	Right 802 (63)	Left 598 (47)
Hip	Right 85 (7)	Left 69 (6)
Shoulder	Right 63 (5)	Left 45 (4)
Tibio-tarsal joint	Right 14 (1.1)	Left 11 (0.9)
Carpal joint	Right 12 (0.9)	Left 8 (0.6)
Duration of OA in months – median (IQR):		
Knee	Right 24 (12 to 60)	Left 24 (12 to 48)
Hip	Right 27 (12 to 60)	Left 24 (12 to 60)
Shoulder	Right 12 (6 to 15)	Left 12 (6 to 24)
Tibio-tarsal joint	Right 12 (8 to 60)	Left 36 (12 to 48)
Carpal joint	Right 40 (12 to 60	Left 60 (12 to 100)
Concomitant OA medication used at baseline – N. (%):	123 (10)	
NSAIDs	46 (4)	
COX-2 inhibitors	15 (1)	
Corticosteroids	10 (1)	
Hyaluronic acids	48 (4)	
Chondroprotective agents	1 (1)	
Local anaesthetics	41 (3)	
Other analgesics		
Concomitant disease [a] – N. (%):	412 (33)	
Cardiovascular	154 (12)	
Metabolic-endocrine	61 (5)	
Gastric ulcer disease	54 (4)	
Musculoskeletal (not OA)		

a) Occurring in at least 4% of participants; IQR: interquartile range; NSAID: non-steroidal anti-inflammatory drug; OA: osteoarthritis; SD: standard deviation.

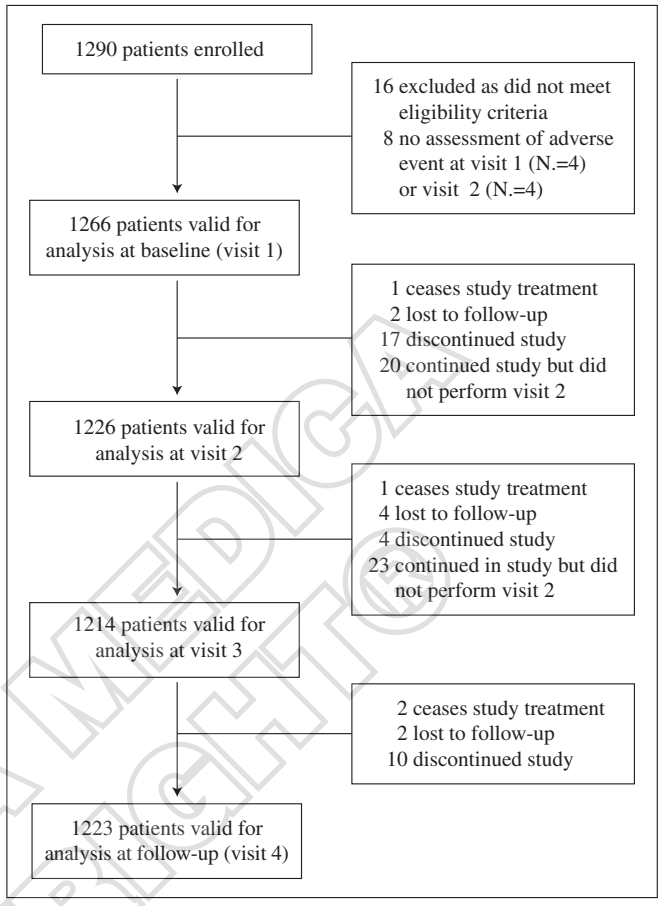


Figure 1.—Diagram showing flow of participants through the study

Statistical analysis

Sample size was determined by using a previous study as a reference and considering the frequency of adverse events reported in that population. Schieb reported eight adverse events occurring in 1523 participants (0.5%) with degenerative or traumatic arthropathies,[35] who were treated with injectable HA administered using the same medical device as that used here. With a planned sample size of 1500 participants, adverse events occurring with a frequency of 0.5% would be observed with an accuracy of ±0.4% and a statistical confidence of 95%, assuming a monthly drop-out rate of 10%.[1]

The analysis population for primary and secondary endpoints consisted of enrolled participants who had received at least one dose of injectable HA and had an assessment of tolerability. No substitution of missing data occurred. As this was an observational study, the analyses were mainly descriptive. Student's t-test was performed on the change from baseline for variables related to the primary objectives. Statistical analyses were carried out using SAS® (version 8.2) software.

Results

A total of 1290 participants were enrolled into the study, of which 1266 were evaluated. Partici-

TABLE III.—*Adverse events reported during the study period.*

Characteristic	Number (%)
Participants reporting ≥1 adverse event:	10 (0.8)
Total adverse events reported:	13
Discontinuations due to adverse events:	1 (0.08)
Severity of adverse events:	
Mild	4 (0.3)
Moderate	8 (0.6)
Severe	1 (0.08)
Occurrence of adverse events:	
Visit 1	6
Visit 2	3
Visit 3	4
Description of adverse events:	
Pain at injection site	6
Swelling at injection site	1
Other	6
Joint affected:	
Knee – right	5 (0.4)
Knee – left	2 (0.2)
Unknown	6 (0.5)

N.=1 266 for safety population.

pant flow through the study is shown in Figure 1. Demographic and baseline characteristics of the study population are presented in Table II. The enrolled population was predominantly female (66%, 840/1266), with a mean age of 66 years, and a mean weight of 74 kg. The knee was the joint most commonly affected by OA (right knee 802/1266 [63%]; left knee 598/1266 [47%]), and the longest median duration of disease occurred in the carpal joint (right carpal joint 40 months; left carpal joint 60 months).

Primary endpoints

The total number of joints treated with the study medication was 1 408 at Visit 1, 1 369 at Visit 2, and 1 354 at Visit 3. The dose administered varied from 4 mL in the treatment of the hip joint (administered as two consecutive IA injections of 2 mL each) to 0.8 mL in the trapezio-metacarpal joint. A total of 125 (10%) participants required co-administration of local anaesthetic at Visit 1. This number decreased to 100 (7.8%) at Visit 2, and to 95 (7.5%) at Visit 3. Lidocaine was the main local anaesthetic agent used (74 treatments, mean dose 3.8 [±2.2] mL).

During the study period, 0.8% (10/1266) of participants experienced at least one adverse event (95% CI, 0.4 to 1.5). In total, 13 adverse events were reported (pain at injection site N=6, swelling at injection site N=1, other N=6), the vast majority of which were mild or moderate in severity (Table III). Only one participant (0.08%) discontinued the study treatment following an adverse event. No serious adverse events occurred.

Secondary endpoints

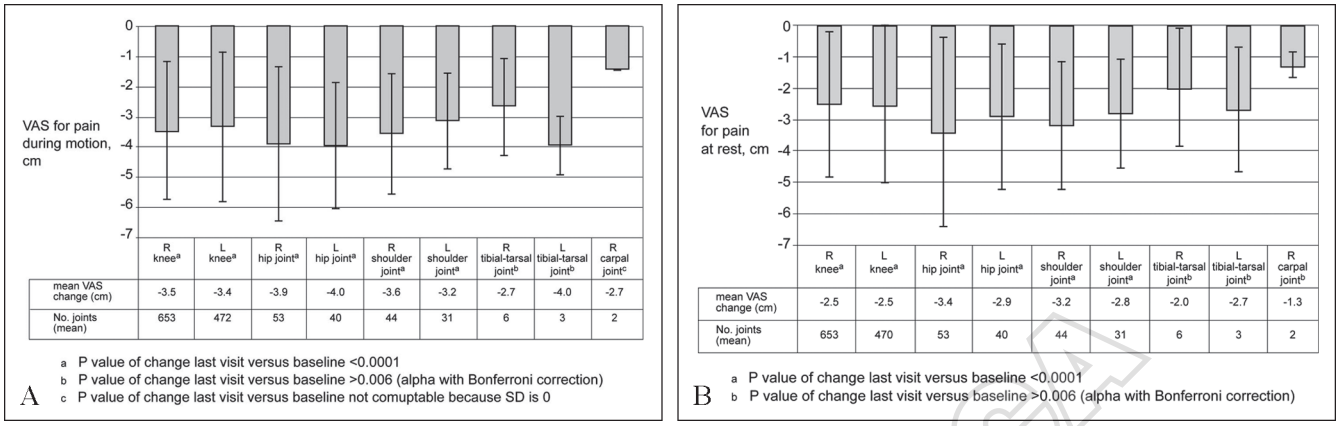
An improvement in joint pain was observed in the study population. VAS ratings for knee pain at rest decreased by 25 mm (±23 SD) from baseline to last visit; for the hip joints, the largest change (-34 mm, ±30 SD) occurred in the right hip. Regarding VAS for pain during motion, the largest difference between baseline and final visit was reported for the hip joints, with a mean change of -40 mm (±30 SD), whereas the mean changes for the right and left knee joints were -35 mm (±23 SD) and -34 mm (±25 SD), respectively.

Mean VAS for joint pain in motion significantly decreased over the study period for all joints (P<0.0001 for knees, hips, and shoulders; P=0.009 for right tibio-tarsal joint, and P=0.02 for left tibio-tarsal joint; P-values were not calculated for the carpal joint) (Figure 2A). A similar trend occurred in VAS for pain at rest (P<0.0001 for knees, hips, and shoulders; and p=0.048 for right tibio-tarsal joint); however, mean VAS for the left tibio-tarsal and right carpal joints were not significant (P=0.15 and P=0.13, respectively) (Figure 2B). Furthermore, the absolute change in VAS for pain at rest was smaller.

The mean absolute change in HAQ over the study period was 0.4 (±0.4), which indicated a significant improvement in motor function (P<0.0001). QoL scores also showed significant improvement over the study period, as indicated by both VAS and utility scores for the EuroQoL questionnaire. The mean absolute change in EuroQoL VAS was 18 (±20) and was 0.3 (±0.3) for EuroQoL utility (P<0.0001 for each).

The number of participants using OA-symptomatic drugs decreased over the study period, falling from 234 (19%) in the period from Visit 1 to Visit 2 to 130 (11%) in the period from Visit 3 to Visit 4. NSAIDs were the most commonly used type of drug, and were taken by 118 (10%) participants in the period after Visit 1 and by 51 (4%) after Visit 3.

Physicians at the 47 study sites and participants



	R knee[a]	L knee[a]	R hip joint[a]	L hip joint[a]	R shoulder joint[a]	L shoulder joint[a]	R tibial-tarsal joint[b]	L tibial-tarsal joint[b]	R carpal joint[c]
mean VAS change (cm)	-3.5	-3.4	-3.9	-4.0	-3.6	-3.2	-2.7	-4.0	-2.7
No. joints (mean)	653	472	53	40	44	31	6	3	2

a P value of change last visit versus baseline <0.0001
b P value of change last visit versus baseline >0.006 (alpha with Bonferroni correction)
c P value of change last visit versus baseline not comuptable because SD is 0

	R knee[a]	L knee[a]	R hip joint[a]	L hip joint[a]	R shoulder joint[a]	L shoulder joint[a]	R tibial-tarsal joint[b]	L tibial-tarsal joint[b]	R carpal joint[b]
mean VAS change (cm)	-2.5	-2.5	-3.4	-2.9	-3.2	-2.8	-2.0	-2.7	-1.3
No. joints (mean)	653	470	53	40	44	31	6	3	2

a P value of change last visit versus baseline <0.0001
b P value of change last visit versus baseline >0.006 (alpha with Bonferroni correction)

Figure 2.—A) Mean change in joint pain during motion over the study period evaluated using the 100 mm Visual Analogue Scale (VAS); B) mean change in joint pain at rest over the study period evaluated using the 100 mm Visual Analogue Scale (VAS). A decrease in VAS score indicates an improvement in pain severity.

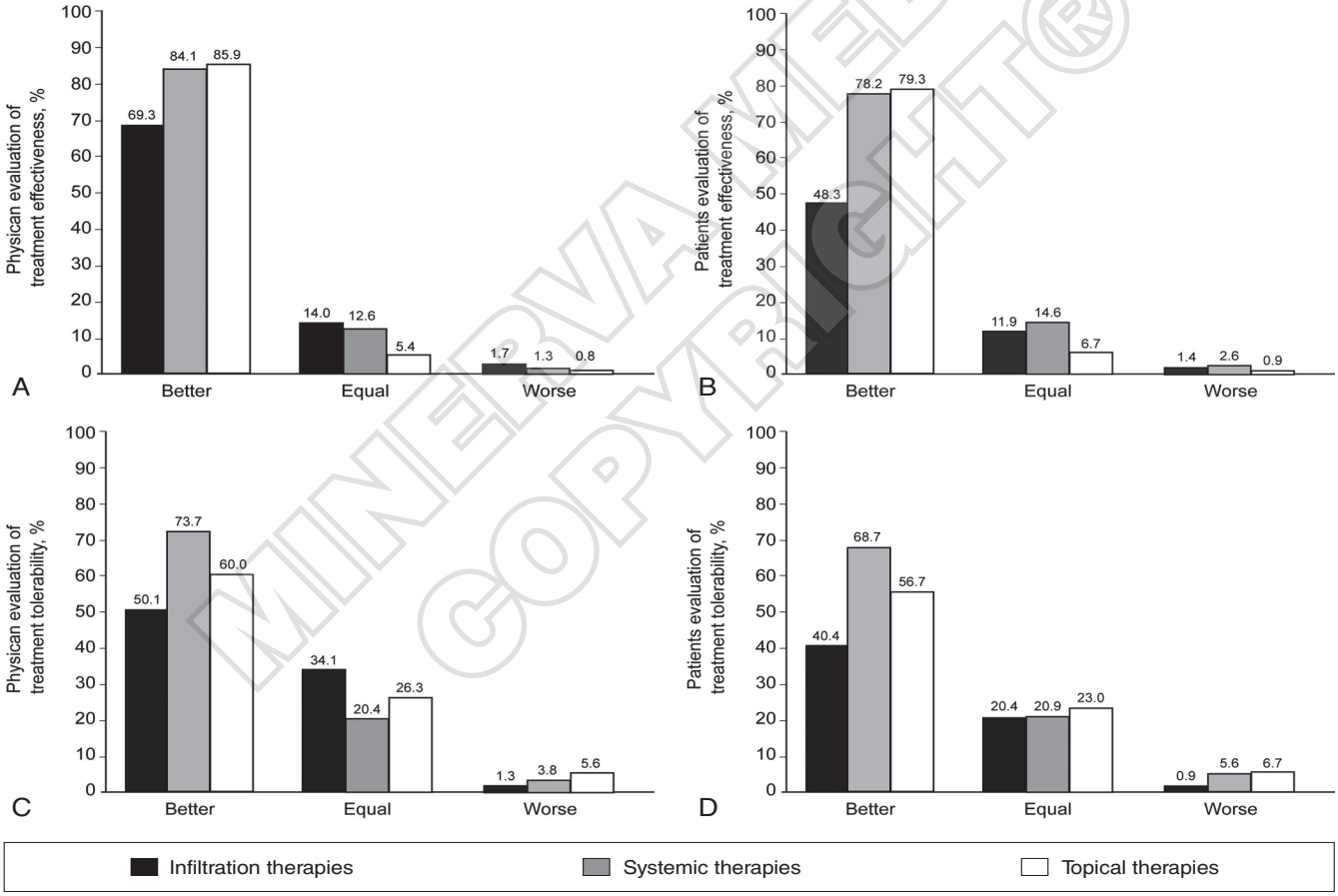


Figure 3.—A-D) Evaluation by physicians and participants (patients) of the effectiveness and tolerability of the intra-articular sodium hyaluronate syringe device used in this study compared to other osteoarthritis therapies. Physician and participant (patient) evaluations of the study treatment compared to other osteoarthritis therapies are summarised here.

valid for analysis at Visit 4 (N=1223) gave a similar assessment of the IA sodium hyaluronate syringe device used in the study: approximately 80% of each group rated the outcome following treatment as either „good" or „excellent", and approximately 6% of each group gave a rating of either „poor" or „no therapeutic effect". Physician and participant evaluations of the study treatment compared to other OA therapies are summarised in Figures 3A-D.

Discussion

This study was designed to evaluate the therapeutic approach and management, efficacy and safety of IA sodium hyaluronate (MW 1500-2000 KDa, Hyalubrix®) in patients with OA in synovial joints. The results of this prospective observational study indicate that the study treatment is safe and effective when used in clinical practice, as measured by VAS for joint pain in motion and at rest over the study period for the joints treated.

IA sodium hyaluronate was found to be generally safe and well tolerated in this study, which is consistent with the favourable safety profile that has been established for this product.[35] Adverse events occurred in 0.8% of treated participants during the study, were mostly of minor clinical relevance (such as injection site reactions), and were consistent with known reactions to HA. Considering the number of IA injections performed during the trial, the estimated risk recorded here equated to approximately three adverse events per 1000 vials injected. The rate of adverse events in other studies using 100% naturally derived injectable HA was also low, for example, Lussier *et al.*[9] recorded a rate of 2.7% (around 40 events in 1500 participants). However, higher rates of adverse events have been reported with chemically modified HA. For example, a trial using Hylan GF 20 recorded an adverse event rate of 5.4%.[12] Moreover, in an extensive retrospective study by Hamburger *et al.*,[36] in which two hyaluronan formulations of diverse molecular weights (Sodium Hyaluronate and Hylan GF 20) were used to treat pain associated with OA of the knee, the authors concluded that hyluronan therapy with either of the formulations was found to be generally safe and well tolerated, and consistent with the favourable safety profile that has been established for these products. However, a report by Goldberg [37] found the use of Hylan GF 20 was associated with SAIR, whereas the use of sodium hyaluronate was not.

Evaluation of the efficacy of the IA sodium hyaluronate used in this study demonstrated statistically significant improvements in pain experienced at rest and while in motion. For pain during motion, the mean change in VAS for the hips was -40 mm, and was -35mm for the knees. In a meta-analysis of nine trials, Arrich *et al.*[1] calculated the weighted variation of VAS ratings for knee pain during motion in HA treated patients over a period of 2 to 6 weeks: this change was -38 mm, which is similar to the observed results in our study.

It is unlikely that the sustained beneficial effects of hyaluronan therapy can be accounted for only by a temporary restoration of synovial fluid lubrication and viscoelasticity. There are at least four potential mechanisms of action for hyaluronan, as described in the literature, that could account for the beneficial effects seen in this trial. The first mechanism is restoration of elastic and viscous properties of the synovial fluid, the second is the biosynthetic-chondroprotective effect,[17, 38, 39-42] anti-inflammatory effects have been observed with hyaluronan and suggest a third potential mechanism,[39, 41, 43] and, finally, there is evidence to support an analgesic effect of hyaluronan.[44-47] Taking these various mechanisms into consideration, it appears reasonable to speculate that hyaluronan products may have a direct effect on reducing joint nociceptor activity, in part due to the role of hyaluronan as a mechanical filter that is associated to its rheological properties, but also to a chemical interaction with inflammatory mediators present in the inflamed joint tissues that reduce their sensitising effect on the nociceptor terminals.

Despite its limitations, this observational study provides a picture of hyaluronan use in clinical practice. Many questions in medical research have been investigated using observational studies,[48] and they have an established role in researching the benefits and risks of medical interventions.[49] For example, observational studies are more suitable for detecting rare or late adverse effects, and are more likely to provide an indication of what occurs in daily medical practice.[50] Many clinicians believe that systematic reviews of observational study data can greatly improve medical practice and public health, just as the Cochrane Collaboration did for systematic reviews of randomised controlled trials. Following a review by the Cochrane Library,[51] administration of IA hy-

aluronan is now included within therapeutic recommendations from the US and Europe.[52-54]

Conclusions

In summary, this study has demonstrated that IA injections of sodium hyaluronate (MW 1500-2000 KDa; Hyalubrix®) are safe and well tolerated. The study treatment reduced pain, improved mobility, and increased QoL in participants with OA. In addition, the study treatment was rated highly by physicians and participants alike. Considering both the efficacy and safety outcomes of this study, together with the body of evidence in the literature, particularly the association of chemically modified HA (but not naturally derived HA) treatment with SAIR, these findings indicate that patients should be fully counselled on the anticipated risks and benefits of the various hyaluronan products when considering treatment options for synovial joints affected by OA.

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