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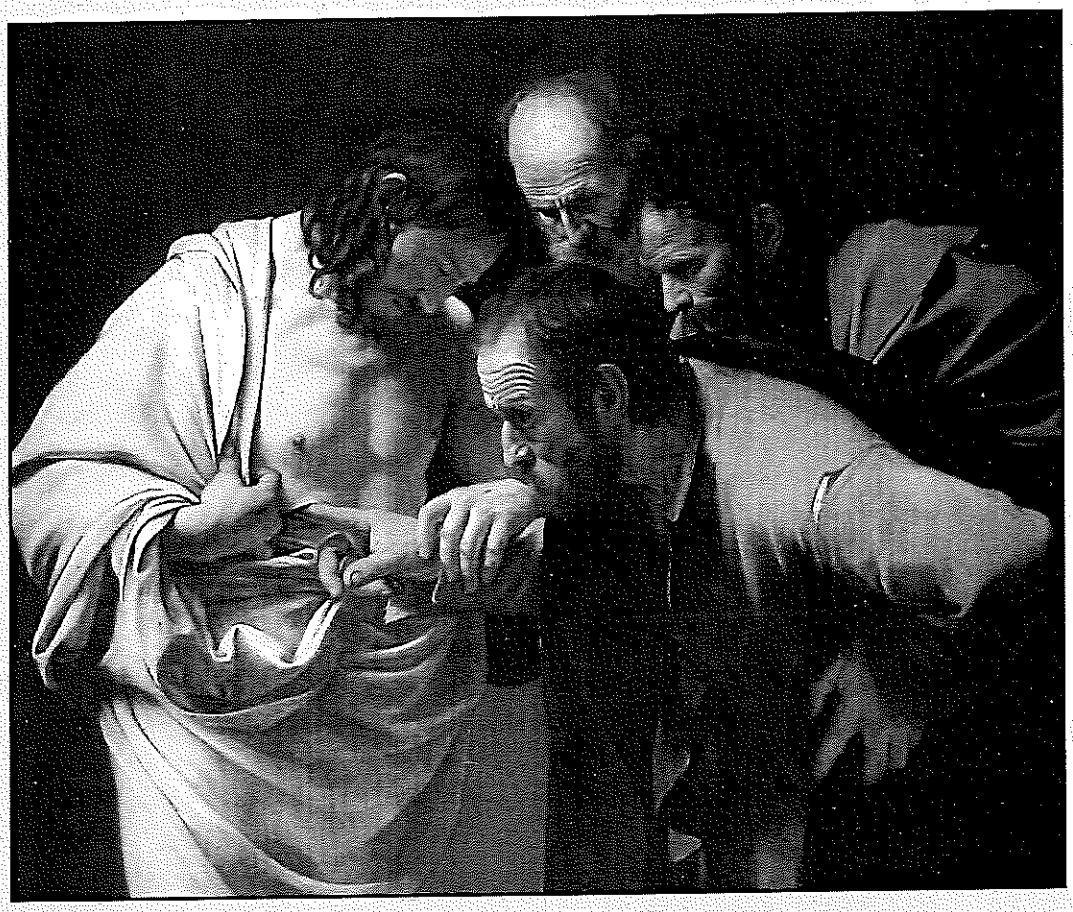
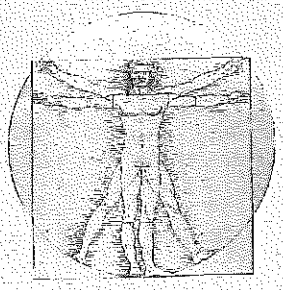


Caravaggio "*Incredulità di San Tommaso*"



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PAIN RELIEF AND FUNCTIONAL RECOVERY OVER A SIX-MONTH PERIOD AFTER INTRA-ARTICULAR INJECTION WITH SODIUM HYALURONATE (MW 1500 - 2000 KDA) IN OSTEOARTHRITIS OF THE KNEE

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The present study aimed to evaluate the effects of a single intra-articular injection of a high molecular weight (MW) (1500-2000 kDa) naturally linear hyaluronic acid (HA) in patients suffering from knee osteoarthritis (OA). One hundred and sixty-eight patients with mild to moderate OA of the knee were enrolled to receive one ultrasound-guided intra-articular (IA) injection of 4ml Sodium Hyaluronate (HyalOne®) and were followed up for 24 weeks. The primary efficacy outcome was the change from baseline to week 24 in patients' pain perception using a 100 mm visual analogue scale (VAS). Additional outcomes included the Western Ontario McMaster Universities Arthritis score (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS) assessed at 4, 12 and 24 weeks. The patients enrolled showed a significant improvement from baseline in all symptomatic outcome measures. Pain significantly decreased after treatment. VAS pain decreased from the baseline mean value of 77.7 mm (SD 8.8, range: 60-90) to the mean value of 13.8 mm (SD 4.9, range: 10-20) at week 24. The analysis of variance for repeated measures conducted on VAS, on each WOMAC subscale, on the total WOMAC score and on each KOOS subscale score showed a significant reduction in all scores at each study point (week 4, 12 and 24) ($p < 0.001$). Comparisons between week 4 and week 12 scores and week 12 and week 24 scores showed a significant and progressive improvement ($p < 0.05$, Wilcoxon test) during the study. The present study suggests that a single IA injection of linear high MW HA in patients suffering from knee OA is well tolerated and provides relief from pain. Benefit to knee function was confirmed by both the WOMAC and the KOOS scores. The patients' overall health status also improved as demonstrated by the high scores registered at the post-treatment KOOS Function in daily Living, Quality of Life and Function in Sport and Recreation subscales.

Osteoarthritis (OA) is the most common joint disorder; in Italy the estimated prevalence is between 10% and 18.3% (1). It is a chronic arthropathy of an entire joint characterised by disruption and potential loss of joint cartilage with other joint changes, including bone hypertrophy (osteophyte formation). Symptoms include gradually developing pain aggravated or triggered by activity, stiffness relieved less than 30 minutes after activity and occasional joint swelling.

Overall, the knee is the most commonly affected joint and the impact on disability attributable to knee OA is similar to that due to cardiovascular disease and greater than that caused by any other medical conditions in the elderly (2).

There is no known cure for OA and there are no specific pharmacologic therapies that can prevent the progression of joint damage secondary to OA. The

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search for disease-modifying agents for OA that can prevent radiographic joint space narrowing, indicative of progressive articular cartilage loss, is being addressed through ongoing research (3-5).

The current goal of patient management of OA is to control pain and swelling, minimize disability, improve quality of life and educate the patient. Management is individualized based on patient expectations, level of function and activity, the joints involved, the severity of the disease, occupational and vocational needs and the nature of any coexisting medical problems.

Relevant Treatment Guidelines and Consensus Statements and information from the literature demonstrate that HA may be administered to treat pain associated with OA of the knee (6). A typical HA treatment cycle consists of five injections, 1 injection per week for 5 weeks (7, 8). Some patients report benefit following three-weekly injections (9, 10).

Synovial fluid contains high concentrations of high molecular weight hyaluronic acid which protects the synovial membrane, acts as a filter between haemolymphatic circulation and synovial liquid (11), has beneficial anti-inflammatory, anti-catabolic and pro-anabolic effects and stimulates repair processes (12). In osteoarthritis, both the concentration and molecular weight of HA are reduced (13), leading to a loss in viscoelasticity of the synovial fluid.

Several studies on osteoarthritis of the knee have demonstrated the effectiveness of viscosupplementation, the intra-articular (IA) injection of hyaluronic acid products, in restoring the viscoelasticity of the synovial fluid, improving joint mobility and reducing pain (14–18). The most recent meta-analysis available, published in September 2013 and including 29 randomized studies involving more than 4,500 patients with knee osteoarthritis, found that intra-articular hyaluronic acid (HA) injections provided significant improvement in pain and function compared to saline injections (19). The therapeutic effects of IA HA generally appear to have a slower onset but a longer duration than IA steroids and may be useful in the long term management of this chronic disease (20, 21).

Many hyaluronan preparations, differing in concentration and molecular weight, have been approved for use around the world (22).

HyalOne® (Hyalubrix 60 Italian brand) is a sterile, non-pyrogenic, viscoelastic solution manufactured with hyaluronic acid sodium salt, obtained by bacterial fermentation from a fraction of high molecular weight with a range of 1,500–2,000 kDa.

The present study aimed to evaluate the use of a single ultrasound-guided intra-articular injection of HyalOne® in patients suffering from knee OA in alleviating symptoms and improving knee functionality in order to delay more aggressive pharmacological approaches to the disease and surgical procedures.

MATERIALS AND METHODS

This was a single-site, investigator-initiated, open, cohort study to assess the efficacy of a single ultrasound-guided IA injection of HyalOne® in reducing pain and improving knee functionality conducted in patients referred to the Centro Medico Mantia Clinic, Palermo, Italy, for knee OA between November 2011 and November 2012.

The study protocol, including informed consent documentation, was approved by the hospital Ethics Committee and the study was carried out in accordance with the International Conference on Harmonization (ICH) Guidelines and the Declaration of Helsinki. Informed Consent was obtained from all patients prior to participation.

The main inclusion criteria were: male or female patients aged 40 years or older with an active lifestyle who had been referred to the clinic for OA pain in one knee and scoring >50 and <90 mm on a 100 mm OA pain visual analogue scale (23, 24) where 0 mm = no pain and 100 mm = worst possible pain; tibiofemoral OA (ACR criteria) (25), Kellgren–Lawrence grade II or III (26) diagnosed by standard X-rays taken within 3 months prior to enrolment; no surgical intervention planned in the study knee in the subsequent 6 months. If taking analgesics, NSAIDs or cyclooxygenase-2 inhibitors, patients were required to comply with a washout period of 1–3 weeks depending on the half-life of the medication. The main exclusion criteria were: patients with bilateral symptomatic knee OA or predominantly patello-femoral involvement of the study knee; knee OA flare with obvious tense effusion at the study knee, diagnosed by clinical examination; clinical symptoms of meniscal instability or significant valgus/varus that required corrective osteotomy; significant ligamentous instability; any prior viscosupplementation therapy or history of sepsis in the study knee; systemic or intra-articular injection of corticosteroids in any joint within 3 months of enrolment; chondrocalcinosis and microcrystal-mediated arthritis, concomitant inflammatory or other rheumatologic, neurological or cardiovascular diseases which could affect the evaluation of knee pain.

Although various imaging modalities such as fluoroscopy, magnetic resonance imaging and computed tomography may be used to assist in injection delivery, the use of musculoskeletal ultrasound (US) guidance is becoming more and more widespread. Not only is its use rapid, safe and simple (27), it also improves accurate delivery of the injected product and clinical outcome (28, 29). Furthermore, studies have found that US guidance is particularly effective in the knee joint in improving accurate needle placement and clinical outcome as well as leading to lower healthcare costs (30, 31).

Ultrasound-guidance is the technique chosen in this study and in our clinical practice to perform injections and ensure accurate delivery inside the target joint. This is particularly important in hyaluronic acid injections given its direct protective effect on joint fluid.

HyalOne® was provided in prefilled syringes each containing 60 mg /4 ml of hyaluronic acid sodium salt for intra-articular injection. The treatment consisted in a single ultrasound image-guided injection into the articular site. The ecoguided treatment used an anterior approach with a 20-Gauge needle after betadine preparation. The ultrasound examination (Technos MPX, Esaote Spa, Genoa, Italy) was performed in all patients by the same radiologist, with a linear transducer (13 MHz) and 45° grades guide, also assessing the capsule with colour power Doppler for blood flow. Injections were performed with the patient in a supine position. Excessive weight bearing and strenuous activity were discouraged for 48 hours after each injection.

Patients received the injection at baseline (T0) and were followed-up at 4 (T1), 12 (T2) and 24 (T3) weeks after the first injection. Safety and efficacy were assessed at each patient visit.

Efficacy assessment

In order to assess the efficacy of HyalOne® in reducing pain and improving knee function the following variables were assessed at each study time point.

The primary efficacy outcome measure was the change from baseline to week 24 in patients' pain perception using a 100 mm Visual Analogue Scale (VAS) where 0 mm = no pain and 100 mm = worst possible pain. At each visit, the patients were asked to respond in terms of their pain "at the present time" by indicating their perceived pain on the VAS.

The secondary endpoints were the improvement in pain, stiffness and functional impairment as measured by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC™) (32) and the patient's assessment of their knee pain and other associated problems as measured by the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire at each visit (33).

The WOMAC questionnaire consists of three subscales: the WOMAC pain scale (5 questions), the WOMAC stiffness scale (2 questions) and the WOMAC physical function scale (17 questions). In the Likert 3.0 of the WOMAC, the version adopted in the study, the patient's response to each of the 24 questions was measured on a 5-point Likert scale with higher scores indicating greater symptom severity (0=none, 1= slight, 2=moderate, 3=severe and 4=extreme).

The KOOS questionnaire consists of 5 subscales: Pain, Other symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee-related Quality of Life (QOL). Patients were asked to refer to the previous week when answering the questions. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale

Safety assessment

The target knee and systemic adverse events (AE) were monitored throughout the study.

Statistical methods

The primary efficacy hypothesis was evaluated by the change from baseline to the week 24 evaluation in the patient's assessment of target knee OA pain during the previous 48 hours on VAS. The secondary endpoints, WOMAC total score, pain, stiffness and physical function sub-scores and KOOS subscale scores were analysed similarly.

Performance data were analysed using descriptive analysis and the appropriate per pair data analysis (Analysis of variance for repeated measures (MANOVA) or Wilcoxon test).

RESULTS

One hundred and sixty-eight patients (168) were enrolled in the study, 104 female (61.9%) and 64 male (38.1%) with a mean age of 54 years (SD 8.82, range: 40 – 69 years old).

All 168 patients received one ultrasound-guided IA injection at the baseline visit.

Treatment with HyalOne® resulted in a statistically significant improvement from baseline to week 24.

Before treatment patients reported intense pain: the mean VAS value was 78 mm (SD 8.8, range: 60-90); the mean WOMAC pain score was 16.7 (SD 1.80, range: 14-20) and the mean KOOS pain score was 23.6 (SD 11.66, range: 5.56 – 41.68) as well as intense knee stiffness: mean WOMAC score of 6.7 (SD 1.04, range: 5 – 8). Knee functionality was moderately compromised: the WOMAC total score presented a mean value of 79.8 (SD 8.08, range: 64 – 96), the KOOS Function in daily living (ADL) a

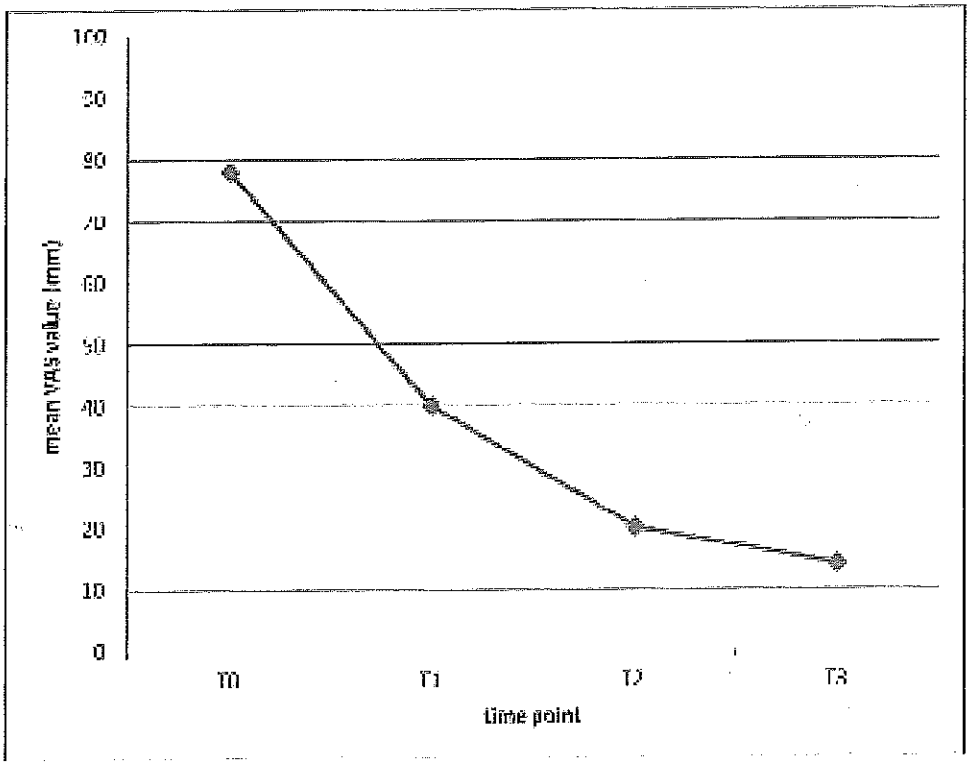

Fig. 1. *Decrease in VAS pain (mm) at each study time point following a single baseline IA HA injection.*

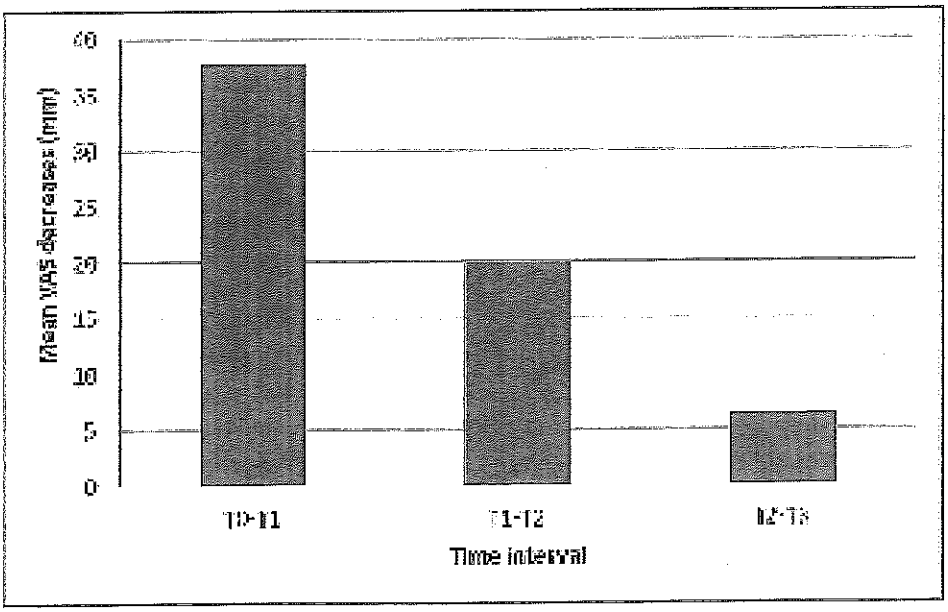

Fig. 2. *Incremental decrease in VAS pain (mm) between study time points following a single baseline IA HA injection.*

mean score of 26.8 (SD 8.06, range: 11.76 – 38.24) and the KOOS sport/recreation a mean score of 19.0 (SD 9.40, range: 5 - 35).

The baseline mean VAS value significantly and progressively decreased at each study time point ($p < 0.001$ at the analysis of variance for repeated measures) (Figure 1).

All patients (100% of subjects) reported a

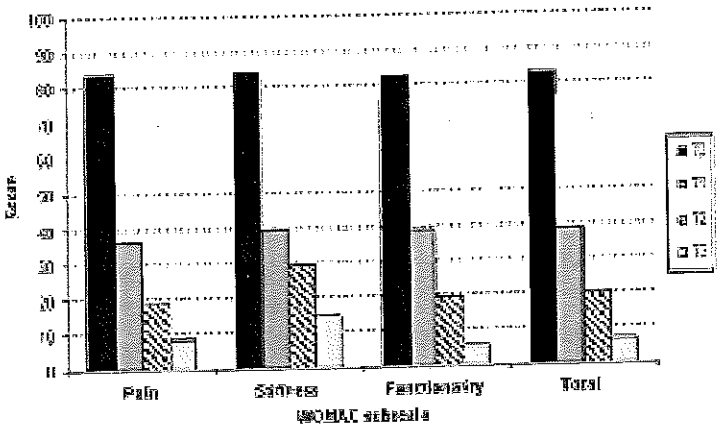

Fig. 3. *Decrease in WOMAC subscale scores at each study time point following a single baseline IA HA injection.*

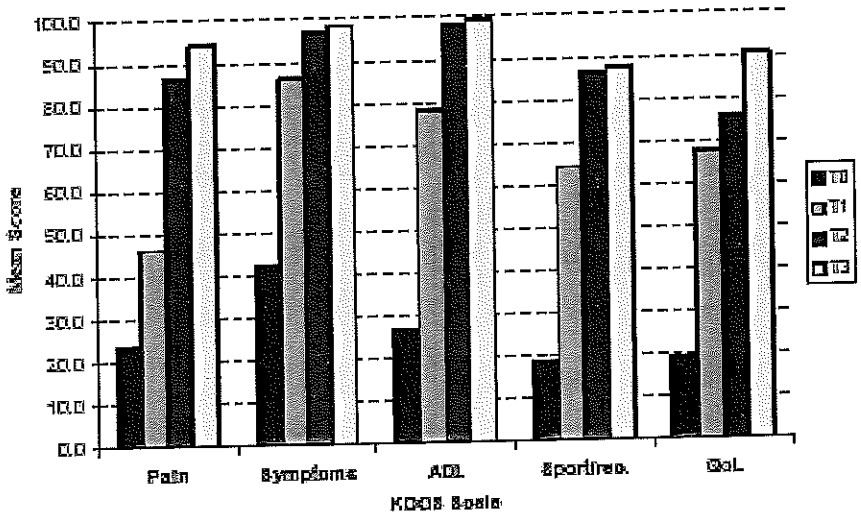

Fig. 4. *KOOS subscale score at each study time point*

reduction in pain at T1 and a further reduction at T2, while at T3 more than half of the treated patients (87 patients, 52%) reported an additional reduction in pain compared to T2. Pain perception at T3 compared to T2 was unchanged in the remaining 48% of patients.

Patients reported an initial decrease in VAS of 37.6 mm (SD 8.9, range 20 – 50) that subsequently decreased by a further 19.9 mm (SD 5.9, range 10 - 30) at T2 and 6.4 mm (SD 7.0, range 0 - 20) at T3 (Figure 2).

During the study the WOMAC normalised pain score decreased from the mean value of 83.7 registered at T0 (SD 8.98, range: 70 – 100) to a mean score of 8.7 (SD 3.28, range: 5-15) at T3.

The stiffness score decreased from a mean value of 84.2 at T0 (SD 12.99, range: 63 – 100) to a mean score of 14.8 at T3 (SD 8.83, range: 0-25); the functionality score decreased from a mean value of 82.8 at T0 (SD 9.16, range: 65-100) to a mean value of 5.7 (SD 4.41, range: 3 – 12) at T3.

Consequently, the total WOMAC score also decreased from the T0 mean value of 83.1 (SD 8.41, range: 67 – 100) to a T3 mean value of 7.1 (SD 1.86, range: 4-11). The results are summarised in Figure 3.

The analysis of variance for repeated measures conducted on each WOMAC subscale and on the total

WOMAC score showed a significant reduction in pain and stiffness and an increase in knee functionality at each study point (T1, T2 and T3) after treatment ($p< 0.001$). Comparisons between T1-T2 score and T2–T3 score evidenced a significant and progressive improvement in pain, stiffness and functionality ($p< 0.001$, Wilcoxon test) during the study.

Mean baseline values of all KOOS subscales progressively increased at each study time point to reach the highest value at T3 .

The analysis of variance for repeated measures conducted on each KOOS subscale showed a significant improvement against baseline in all scales (pain, symptoms, daily activities, sport/recreation and quality of life) at T1, T2 and T3 ($p< 0.001$) (Figure 4).

The comparison between post-treatment time points (T1-T2 and T2-T3) also showed a progressive improvement over time ($p<0.05$, Wilcoxon test).

Safety

The treatment was well tolerated.

Mild transient adverse events were reported in 5 patients. These device-related local AE's consisted mostly of mild or moderate post injection pain and swelling which resolved spontaneously after a few days. Patients' daily activities were unaffected by these events.

No serious adverse events were reported by the patients during the treatment.

DISCUSSION

Currently published data mainly refer to the use of HyalOne® in hip OA, where the product proved to be effective and well tolerated (34-36); however, HyalOne® differs only in volume from Hyalubrix, an IA Hyaluronan product which is marketed in several European countries and although it is indicated for the treatment of all joints, it has been used largely in the treatment of knee OA. Two post-marketing studies on patients suffering from knee OA supported its clinical efficacy, safety and tolerability in reducing pain and improving mobility and quality of life in patients with OA (35, 37). In another study, the use of Hyalubrix after arthroscopic meniscectomy led to a significantly more favourable post-operative clinical outcome, both in terms of function and pain symptoms, as compared with the same procedure performed without this treatment (38). Other authors reported improvement in clinical findings in most gait analysis parameters after IA injection of Hyalubrix in the knee (39).

The present study aimed to provide evidence supporting the effectiveness and safety of a single IA injection of Hyaluronic Acid (HyalOne®) in alleviating pain and improving knee function in patients suffering from knee OA.

The mono-injection strategy is a HyalOne® characteristic that exposes patients to a lower risk of administration–related site effects (e.g. pain at injection site, infection) and requires a lower number of patient visits to the clinic, resulting in a money-saving opportunity for the patients (fewer visits and decrease in loss of working days).

Results from this study demonstrate that treated patients reported significant pain reduction as early as 1 month after treatment and that pain continues to decrease up to 6 months from the single administration.

In real practice HyalOne® treatment seems to cause a statistically significant reduction in algofunctional indices at 6 months after the injection; all patients (100% of subjects) reported a reduction in pain at T1 and a further reduction at T2, while at T3 more than half of treated patients (87 patients, 52%) registered an additional reduction in pain compared with T2. These results were confirmed with a similar trend in the assessment with the functional scales (WOMAC and KOOS).

Improved knee functionality is also confirmed by both the WOMAC and the KOOS scores, as well as an improvement in patients' general health status as demonstrated by the high scores recorded at the post treatment KOOS ADL, QoL and sport/recreation subscales.

These results may be maintained over time through cyclical and personalized repetition of US guided injections, at least one injection every 6 months.

A key result of the study was the complete absence of drop-outs, probably due to the single injection treatment, the rapid decrease in pain and the results persisting over time. It is also easy to repeat the treatment in case of need.

Although this study confirms the effectiveness of HyalOne® in knee OA, limitations in the study design (open-label study with no control group) prompt suggestions for further randomized controlled studies to be carried out comparing HyalOne® to a similar

product/placebo to confirm the results from this study.

In conclusion, these study data demonstrated that HyalOne® may be an effective alternative treatment option in the management of knee OA.

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