European Review for Medical and Pharmacological Sciences 2017; 21: 1635-1644

HyalOne® in the treatment of symptomatic hip OA – data from the ANTIAGE register: seven years of observation

A. MIGLIORE[1], U. MASSAFRA[1], B. FREDIANI[2], E. BIZZI[3], E. SINELNIKOV YZCHAKI[1], G. GIGLIUCCI[1], M. CASSOL[3], S. TORMENTA[4]

[1]Rheumatology Unit, and Research Center, S. Pietro FBF Hospital, Rome, Italy
[2]Medical and Surgical Science and Neuroscience Department, Rheumatology Section, University of Siena, O.U. of Osteo-Articular Diagnostic Procedures, Siena, Italy
[3]Department of Internal Medicine, S. Pietro FBF Hospital, Rome, Italy
[4]Diagnostic Imaging, S. Pietro FBF Hospital, Rome, Italy

Abstract. – OBJECTIVE: Several studies on knee osteoarthritis suggest that the intra-articular administration of hyaluronic acid products may be a relevant option in the management of patients with persistent pain. The aim of this study is to report the data of efficacy of US-guided HyalOne®/Hyalubrix® 60 injections in a large population of patients with hip osteoarthritis, repeated at least 2 times per year for up to seven years.

PATIENTS AND METHODS: This is a prospective, post-marketing, cohort study. Data were collected from the ANTIAGE registry. Values of Lequesne index, pain VAS, NSAIDs intake, global medical and patients assessments were evaluated every six months from the baseline to the end of the follow-up, seven years later. The inclusion criteria were: age ≥18 years, symptomatic hip osteoarthritis of at least 1-year duration, and up to 84 months of follow-up. All the patients received hyaluronic acid injections at least every six months, using ultrasound guidance to ensure accurate placement.

RESULTS: 1022 patients were included in the study. The patients were categorized by age classes, gender, and body mass index (BMI). All the groups show a statistically significant reduction at all time points compared to baseline values of Lequesne index, pain VAS, NSAIDs intake, global medical and patients assessments. There are slight differences in the subgroups of overweighted, obese and over 70 years patients.

CONCLUSIONS: Our study supports the clinical efficacy and safety of HyalOne®/Hyalubrix®60 in patients affected by osteoarthritis. This is the first study, reporting on a large cohort of patients in different categories with a long follow-up on seven years. The data confirm the proper use of ultrasound-guided viscosupplementation (VS) as background therapy in the management of hip osteoarthritis.

Key Words:
Hip osteoarthritis, Viscosupplementation, HyalOne®.

Introduction

OA is the most common cause of joint pain in adults, particularly among the elderly. It is the cause of morbidity and progressively leads to disability and social isolation, especially when the hip and knee are involved. The prevalence of hip OA is about 17% in the white male over the age of 60 years and 9% in the white women of the same age[1]. The aim of the treatment is the relief of pain and the preservation or restoration of joint mobility[2].

Several studies on knee OA suggest that the intra-articular administration of hyaluronic acid (HA) products may be a relevant option in the management of patients with persistent pain. However, some discrepancies can be noted between some guidelines and clinical practice[3]. More recently two expert consensuses have confirmed a positive effect of viscosupplementation (VS) in OA joints[4,5]. 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[6] and is marketed in several European countries. Its residence time in the knee is 120 hours[3]. It is indicated for the treatment of all joints and has been used widely in the treatment of knee OA. A post-marketing study on 1.523 patients suffering from knee OA, supported the clinical efficacy and safety of Hyalubrix in

Corresponding Author: Alberto Migliore, MD; e-mail: migliore.alberto60@gmail.com

pain reduction and functional improvement[7]. A second post-marketing study on 1.266 patients demonstrated the efficacy and tolerability of Hyalubrix®. The study treatment reduced pain, improved joint mobility and increased quality of life in patients with OA[8]. Priano et al[10] in a multicentre randomized controlled trial (RCT) carried out on 100 patients showed that the use of Hyalubrix® after arthroscopic meniscectomy is associated with a significantly more favorable post-operative clinical outcome compared with the non-injected control group. Other authors reported improvement in clinical findings and most Gait analysis parameters after IA injection of Hyalubrix® in the knee[10]. In recent years, there has been an extension of the use of IA HA in hip OA[11-13]. Data of the literature related to hip VS show good safety, with the absence of systemic effects, and a significant efficacy[14-17]. In particular, the use of ultrasound (US) guidance facilitates an improved and accurate delivery of the injected product[18,19].

There are three studies in the literature on the use of HyalOne®/Hyalubrix®60 in hip OA. The first is a study[20] comparing HyalOne® with local anesthetic (mepivacaine) for symptomatic hip OA. The results showed a statistically significant reduction in the Lequesne index at both 3 and 6 months between the two groups in favor of patients treated with HA.

The second study[21] examined the effectiveness and tolerability of intra-articular HyalOne® injections in every day clinical practice. 120 patients with symptomatic OA (Kellgren-Lawrence grade II-IV) were followed-up for 18 months. HyalOne® was administered under US guidance, every 6 months, with the possibility of an additional injection at 3-months intervals on clinical request. The results showed a statistically significant reduction of algofunctional indices as soon as 3 months after HA injection, and at 12 months 80% of patients achieved a decrease of at least 30% in the symptoms. These results were maintained over time by the cyclical repetition of intra-articular injections.

The third study[22] investigated one of the research questions suggested by the EULAR agenda as to whether VS is able to slow the progression of osteoarthritis and/or to delay joint replacement. Six orthopedic surgeons, who do not perform IA hip injections, evaluated independently and retrospectively the indication for Total Hip Replacement (THR) in 176 patients with hip OA previously treated with US-guided injections of HyalOne®. At 24 months 159 of 176 (90%) patients did not undergo THR. At 48 months, 82% of treated patients has avoided arthroplasty. These results seem to indicate that HyalOne® may delay arthroplasty in the context of the global management of OA patients.

The aim of this study is to report the data of efficacy of US-guided HyalOne®/Hyalubrix®60 in a large population of patients with hip OA, repeated at least 2 times per year for up to seven years.

Patients and Methods

Characteristics of the Population Under Observation

Study Design

This is a prospective, observational, open, post-marketing study. All patients treated with IA injections of HyalOne®/Hyalubrix®60 in the hip were included. Data collected from our hospital files were analyzed by descriptive and analytical statistics.

Patient Selection

The records of outpatients affected by symptomatic hip OA and treated with HyalOne®/Hyalubrix® 60 between 2005 and 2013 were analyzed. All patients included in the study were followed with clinical visits performed approximately every 3 months. Data from baseline and control visits were recorded into the ANTIAGE Registry[23].

Inclusion criteria were age $\geq$ 18 years, symptomatic hip OA according to the ACR criteria[24] of at least 1-year duration, and up to 84 months of follow-up. Exclusion criteria were: concomitant use of oral anticoagulant therapy; significant comorbidities (e.g., rheumatologic disease, low back pain, and femoral head osteonecrosis). In December 2015, a group of investigators (comprised of three rheumatologists) selected records by extracting data from the registry applying the above-mentioned inclusion and exclusion criteria.

Values were recorded at baseline concerning clinical history and demographic information.

Radiological evaluations were made using the Kellgren-Lawrence hip OA scale[25] on a non-weight bearing X-ray, taken no more than 6 months before treatment, and the pain was evaluated on a 100-mm VAS scale and Lequesne Index[26].

Each patient received a single 4 ml (60 mg) intra-articular injection of HyalOne®/Hyalubrix® 60 into the affected hip every 6 months; if clinically requested, it was possible to administer up to two additional injections, with a maximum of one injection per 3-month period, in 1 year. Injections were performed every 6 months even in patients reporting an improvement in clinical parameters in order to maintain clinical benefit and to prevent flare of disease. All intra-articular injections were performed using ultrasound guidance to ensure accurate placement[21]. Patients were followed-up every 3 months, assessing pain on a 100-mm Visual Analogue Scale (VAS), Lequesne Index, throughout the whole study period (84 months), as commonly performed in routine clinical and therapeutic practice in our facility.

Radiographic evaluation was carried out every 24 months through standard x-ray.

Dropouts were comprised of patients who were lost to follow-up for non-presentation to control visits or injection sessions and of those referred to other clinical facilities. Patients who died and those who underwent THR were also included in this category.

Statistical Analysis

Descriptive statistics are reported for representation of patients (and patient groups) considered in this study, where appropriate. For continuous variables reported measures include mean, standard deviation, range and numerousness, whereas for discrete variables measures reported are count and proportions. Any changes from baseline in measures Lequesne index, pain VAS, NSAIDs intake, Global Medical Assessment (GMA) and Global Patient Assessment (GPA); were recorded at each study point. These changes were compared with baseline using Wilcoxon test for paired data, to determine statistically significant changes. Alpha value was adjusted for number of comparisons (as reported for each analysis), due to number of analysis performed on each variable. The Odds ratio and respective confidence intervals (CI) were calculated (at p-value = 0.05) and were cross-classified over patient groups. The patient population was categorized at baseline age into following classes: first group containing patients under age of 40 years, second group containing patients between ages 41 and 50 years, third groups containing patients between 51 and 60 years, fourth group containing patients between 61 and 70 years, fifth group containing patients between 71 and 80, and the last sixth groups containing patients above 80 years old. Another classification provides distribution of patients over body mass index (BMI), having groups containing; normal weight patients, overweight and obese. Yet, another classification was done to study the effects of gender. All the data provided are based on the ANTIAGE register and were obtained with the approval of the Ethical Committee of Azienda Ospedaliera San Camillo Forlanini, Rome. Following variables were used for the analysis performed:

- Age: grouped at baseline.
- Lequesne index: classified as low (index 4), moderate (in range 5 and 7), or high (index 8).
- US pattern: US performed on hip joint at baseline was used to split patients into two groups, regular *vs.* non-regular profiles.
- Kellgren-Lawrence radiological index.
- Responder patients per Lequesne index: a patient was considered responder if a reduction in Lequesne index of at least 30% was shown, when compared to baseline for at least two consecutive study points.
- Responder patients per pain VAS: a patient was considered responder if a reduction in pain VAS of at least 30% was shown, when compared to baseline for at least two consecutive study points.
- Time to response: time between baseline and first study point at which 30% reduction to baseline was shown in a responder patient.

Results

1022 patients were enrolled in this study with a mean age of 62 years. The values of the assessments were reported at baseline and every 3 months up to 7 years of follow-up, but the statistical analysis was performed only on data gathered every six months. Descriptive statistics of the study cohort is reported in Table I.

Number of dropouts by cause is detailed in Table II.

VAS of pain, the composite of Lequesne index, the consumption of NSAIDs (in days of use per month) were recorded. The GMA and the GPA were also evaluated in accordance with the OMERACT criteria.

Table I. Characteristics of sample at baseline.

Patients (n)	1022
Males	495 (48.4%)
Females	527 (51.6%)
Age (years, mean)	60 (±18.4 SD)
BMI (mean)	26.4 (±2.9 SD)
Weight (kg, mean)	74.9 (±10.9 SD)
Height (cm, mean)	168.4 (±7.8 SD)
Smokers	298 (29.4%)
Lequesne index mean	8.9 (3.9 SD)
Pain VAS mean	5.9 (1.8 SD)
NSAID intake (days/months mean)	6.4 (6.2 SD)
Concomitant knee OA	388 (38%)
Diabetes mellitus	65 (6.4%)
Age classes (years)	
Under 40	117 (11.5%)
41-50	136 (13.4%)
51-60	253 (24.8%)
61-70	260 (25.5%)
71-80	186 (18.2%)
Over 80	70 (6.6%)
Hip affected	
Right	438 (42.9%)
Left	472 (46.1%)
Bilateral	112 (11%)
Kellgren-Lawrence radiological index	
Grade I	69 (6.8%)
Grade II	405 (39.6%)
Grade III	384 (37.5%)
Grade IV	164 (16.1%)
BMI categorization	
Normal	380 (37.1%)
Overweight	470 (46%)
Obese	172 (16.9%)

Table II. Cause of dropouts.

Total of treated patients	1022
Total Dropouts	120
Surgery	57
Lost to follow-up	45
End of life	18

Results Categorized by Age (Figure 1)

Visual Analogue Scale (VAS)

In comparison with the baseline values, there is a statistically significant reduction ($p < 0.05$) over the time, shown in all the groups. In the population over 80 years the pain is reduced from (mean ± SD) 6.9 ± 2.54 to 6.01 ± 1.88 (-11.1%) at six months and to 5.38 ± 1.98 (-25.4%) after 84 months (Figure 1). Patients under 40 years report 3.19 ±1.88 at 84 months. In patients aged between 70 and 80 years, the reduction of values of pain is from baseline 6.94 ±2.16 to 4.8±1.72 (-29.3%) at six months with a further decline to 3.9±1.24 (-34.6%) at 66 months and to a final assessment 3.54±1.66 (-36.1%) at 84 months.

Lequesne INDEX

All the groups show a statistically significant reduction at all time points ($p<0.05$) compared to baseline values. Patients over 80 and between 70 and 80 years old are those who have the highest score of the Lequesne index at baseline 11.48±5.35 and 11.23±6.07, respectively, and show a significant reduction in the index as early as six months from the first injection ($p<0.05$). In patients over 80, this is maintained over time and is progressively reduced to 6.35 ± 2.04 and 6.08±3.42 (-46%) at 36 months and 84 months; in the group of patients aged between 70 and 80 years the score reduction was to 6.35±1.32 at 36 months to 6.18±2.56 (-44%) at 84 months. The other decades "40-50", "50-60", and "60-70" exhibit the following behavior: they have the lowest baseline score, respectively 8.11±4.22, 8.21 ± 3.63 and 8.33±3.71, with a statistically significant reduction at six months ($p<0.05$); their score then progressively decreases over time until 84 months with final percentage reductions of -49%, -47%, and -49.5%. The decade from 60 to 70 appears to show the greatest percentage reduction. Patients under 40 starting from a baseline value 7.3±3.45 show a significant reduction at six months ($p < 0.05$) with a score of 5.8±1.31 and is further reduced to 5.08 ± 2.31 (-34%) at 84 months.

NSAID Consumption

All the groups show a statistically significant reduction at all time points ($p<0.05$) compared to baseline values. Patients over 80 and "70-80" have the highest baseline consumption of NSAIDs over about 8.5 days per month. However, the two populations show a different behavior. The population over 80 presents a reduction to 6.28±3.12 (-24.8%) at 84 months, showing a reduction of two days per month. In patients between 70 and 80 years old, the reduction is even more drastic decreasing to 4.17±2.94 days monthly (-52.3%) at 84 months.

The three groups "40-50", "50-60", and "60-70" report the lowest baseline averages respectively 5.8 ± 3.61, 5.7 ± 3.77 and, 5.9±3.62 days per month and these mean are significantly reduced at six months ($p<0.05$) to 3.41±1.25, 3.44±1.17 and 3.61±1.25 days; they then continued at a similar level for up to 84 months where the final values were 3.5±1.36 (-32.8%), 3.25±2.14 (-31.39%) and

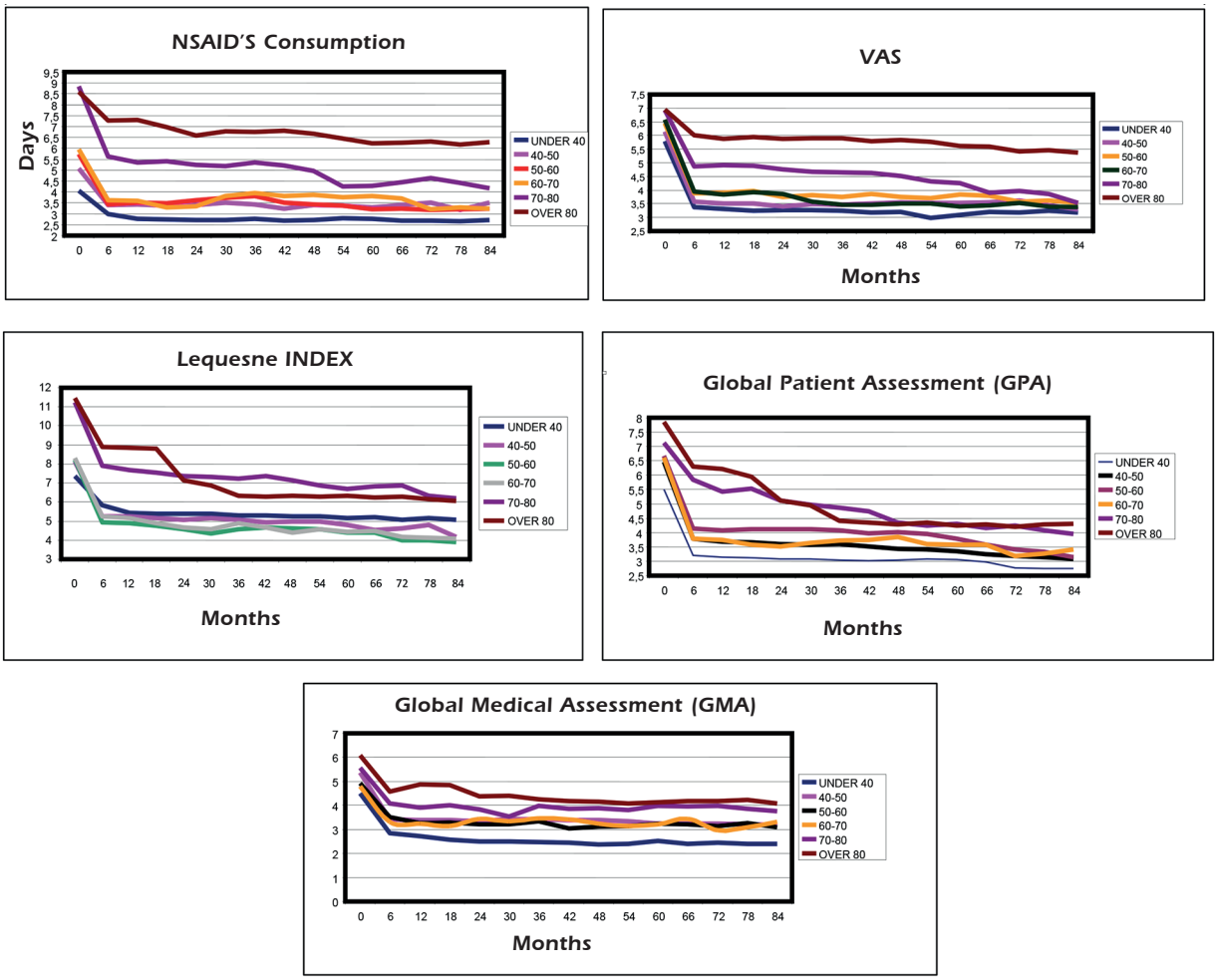

Figure 1. Results of five parameters categorized by classes of age.

3.2±1.61 (-30.7%). Patients under 40 years old reported a very low baseline consumption of NSAIDs, around 4 days, with a modest reduction of one day after six months ($p < 0.05$), and reaching a monthly consumption of 2.7±1.83 (-33.3%) days at 84 months ($p<0.05$). The group between 70 and 80 years showed the highest consumption of NSAIDs at baseline as well as the highest rate of decrease at 84 months.

Global Patient Assessment

All the groups show a statistically significant reduction at all time points ($p<0.05$) compared to baseline values. The highest baseline values are reported in the category over 80 years equal to an average value of 7.8±2.45; followed by patients aged between 70 and 80. Similar values are shown in the groups aged between 40 and 70 years (range 6.46-6.68). Patients under 40 show the lowest baseline value 5.5±2.31. Over time there is a progressive reduction of the values in the highest age group that falls gradually to 4.31±2.08 and 3.9±1.84, respectively, in patients over 80 years and "70-80". It is to be noted that the groups aged less than 70 years of age show a statistically significant reduction ($p<0.05$) greater than older groups already at 6 months, which is then maintained over time, and that gradually decreases further after 48 months until 84 months, indicating a selection of a subpopulation which progresses further.

Global Medical Assessment

All the groups show a statistically significant reduction at all time points ($p<0.05$) compared to baseline values. The GMA showed a characteristic trend, reporting higher values at baseline in a parallel manner among classes, the more aged

the higher values, with a statistically significant decreasing trend, stable and parallel over time among all examined groups.

Categorization for BMI and Gender

The study population is comprised of 380 patients normal weight (BMI 18-25), 470 overweight patients (BMI 25-30) and 172 obese patients (BMI 30-35). All the groups and both genders show a statistically significant reduction of all variables at all time points compared to baseline values ($p<0.05$).

In normal weight patients (380 patients), baseline pain values were higher in females than in males. Specifically, there are no statistically significant gender differences ($p > 0.05$) in normal weight patients. There is a statistically significant reduction ($p<0.05$) at 6 months that is prolonged to 84 months. The pain VAS values fell from 5.6±3.01 to 3.5±1.37 in males. Regarding the Lequesne index, there is no difference in trend between males and females, a rapid reduction ($p>0.05$) is already reported at six months with a further progressive reduction up to 84 months. The decline in males was from 6.98±2-71 at baseline to 4±1.37 (-36.6%) at 6 six months and to 3.6±1.45 (-48.8%) at 84 months. Females showed baseline values of 7.2±3.01 and 4.5±2.21 (-33.4%) at six months and 3.7±1.45 (-42.7%) at 84 months. Similarly, consumption of NSAIDs showed no difference between males and females ($p<0.05$) and the reduction observed at six months was maintained until 84 months. Likewise, the GPA did not show a statistically significant difference between males and females. There is, however, a slight difference ($p<0.05$) as regards the GMA which seems to be different in favor of women. This decreased in women from 4.79±1.72 to 3.09±1.82 (-33.4%) and in men from 4.15±2.45 to 3.36±1.27 (-26%). The overweight subgroup was made up of 470 patients. Clinical indices showed a rapid decrease after the first administration that extended for 84 months (Figure 2). Pain VAS decreased from 6.58±1.41 to 3.38±1.04 (-48.5%). The Lequesne index declined from 8.11± 2.16 to 4.28±1.18 (-46.62%). The monthly use of NSAIDs declined from 7.9±3.82 days/month to 3.2±2.61 (-57%).

The GPA fell from 6.6±2.21 to 3.4±1.74 (-48.7%). Instead, the GMA decreased from 4.9±1.45 to 3.1±2.08 (-37.3%) at 84 months. There was no significant difference between the genders ($p>0.05$) within the overweight group for pain VAS and even if the females showed a non-significant trend ($p>0.05$) to a smaller reduction in the Lequesne index. NSAID consumption fell from an average of 8.25±3.21 to 3.8±2.24 (-51.2%) in males; while in females, it decreased from 8.9±3.33 days to 4.6±2.83 (-48.8%). Also in this item females showed a greater use of NSAIDs. The GPA was similar between males and females at baseline ($p>0.05$); in female it decreased rapidly then remained stationary until the end of the study period, with a score of 4.45±1.46 at six months and 4.21±1.26 at 84 months. In male patients it also reduced drastically at six months after the start of treatment to 4.5±1.98, decreasing further over time to 3.82±1.43 at 84 months. Percentage reduction at six months is similar for both sexes (about 38%) while at 84 months, the male gender showed a 51.5% reduction compared to baseline ($p<0.05$), while in females the reduction was 41.3 % ($p<0.05$). GMA males appear to have a slightly higher value at baseline even if non-significant ($p>0.05$), they then showed a more rapid reduction of values compared with females which was maintained over time.

The obese population was comprised of 172 patients. Even in this population a statistically significant reduction of the values was observed at six months ($p<0.05$) and was maintained until 84 months. The pain VAS decreased from 7.5±1.96 to 4.8±2.16 (-36%) and 4.4±1.35 (-37.5%) at six months ($p<0.05$) and at 84 months. The Lequesne index decreased from 8.6±3.32 to 5.5±2.09 (-35.3%) ($p<0.05$) and 5.1±2.16 (-33.3%) at six months and 84 months. The consumption of NSAIDs declined from 8.8±4.37 days month to 5.6±3.62 (-36.3%) ($p<0.05$) and 4.8±3.26 (-55%) in the above mentioned times. The GPA declined from a baseline mean of 6.2±2.09 to 4.8±1.35 (-24.7%) at six months ($p<0.05$) before slowing to 4.1± 1.96 (-32.3%) at 84 months ($p<0.05$).

The GMA declined from a mean baseline of 5.4±1.78 to 3.9±1.25 (-28%) ($p<0.05$) and 3.5±1.31 (-34%) ($p<0.05$) respectively after 6 and 84 months.

Regarding pain VAS between males and females, there was a baseline difference: males have a lower value 7.01±1.84 compared to 7.98±1.45 in females ($p>0.05$); while in successive time points there was a similar trend. On the contrary, the Lequesne index showed baseline values almost overlapping; in contrast, over time a progressively better response of males was observed, while the response was basically stable in females. The reduction in males was from 8.48±2.76 to 4.31±2.66 (-45.4%) ($p<0.05$), while in females it was from 8.98±2.76 to 5.28±1.74 (-40.7%) ($p<0.05$). The dif-

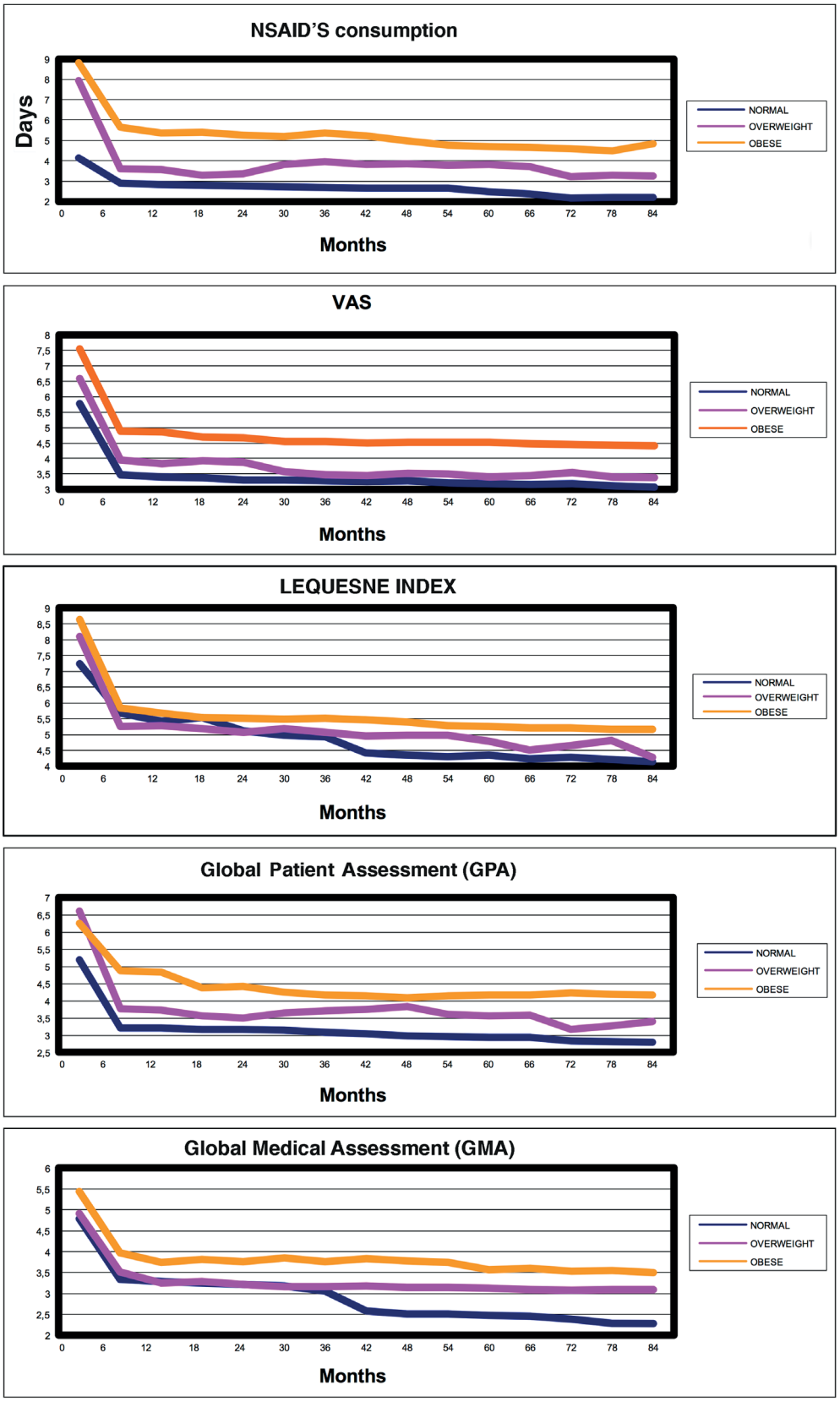

Figure 2. Results of five clinical indexes with patients categorized by BMI.

ference in the consumption of NSAIDs was more pronounced for men than women. Female patients started with 9.2±3.78 days per month NSAIDs consumption with a reduction to 6.98±3.26 (-26.6%) (p<0.05) at six months reaching 6.1±2.97 (-32.3%) at 84 months (p<0.05).

In males, there was a reduction from baseline consumption of 8.78±4.42 to 4.95±1.82 (-47.3%) (p<0.05) at six months decreasing to 4.46±1.61 (-49.15%) at 84 months. GPA in males showed slightly higher values compared to females at all time points without a statistically significant difference (p>0.05). The same can be said with regard to the evaluation of the GMA with respect to gender.

In the graph in Figure 2 we report patients in relation to normal weight, overweight and obese, all categories showed a significant reduction already at six months after treatment with HyalOne®/Hyalubrix® which was maintained in time even up to 84 months, although the obese patients showed greater values than overweight and normal-weight patients at the end of the observation period.

Safety

Systemic or severe local side effects were not reported. In some cases there was a sensation of pain lasting from several hours to a few days, confirming the data we previously published[39].

Discussion

To our knowledge, this is the first study reporting efficacy and safety data on a large cohort of patients affected by hip OA with a long follow-up of 7 years and treated with HyalOne®/Hyalubrix® 60 by US guide injection. Data reported in this observational study confirm efficacy and safety shown in the previous studies adding the value that HyalOne®/Hyalubrix® 60 does not lose efficacy over time maintaining an excellent safety profile even after repeated cycles of injections (up to 14 injections in some patients).

US guided injections of HyalOne®/Hyalubrix® 60 repeated every six months, or every three months (if the patient's symptoms demanded the anticipation of the injection) seem to be confirmed as a good dosage in order to control symptoms. The technique of US guidance plays a crucial role to achieve the efficacy of the injection, allowing the right positioning of HA and avoiding local side effects due to the extra-articular placement of the product, even if there is no control group without US guidance in this study. These data support the use of HyalOne®/Hyalubrix® 60 as background therapy in hip OA. Hip VS should be considered in the complex management of hip OA together with other interventions. This study reports data on the impact of VS in the real world showing control of symptoms and reduction of NSAID intake over time and in all classes of patients. The distribution of age groups was typical of the population suffering from osteoarthritis, with a higher peak between 50 and 70 years, although there is a considerable number of young patients (under 40) and patients between 40-50 years with an early onset of OA. About 10% of the entire population is aged between 40 and 50 years. Likewise, there are patients over 70 years old who were treated, 186 patients between 70-80 years old and 70 patients aged over 80 years, confirming the usefulness of viscosupplementation also in an elderly population.

A statistically significant reduction of all clinical outcomes versus baseline condition was reported at all time points starting soon after the first treatment. However, some differences arise in the categorization of patients by age or BMI that can help us to predict the range of efficacy in subgroups of patients. Patients aged less than 40 seem to respond better in terms of pain reduction achieving a notable decrease of 46.7%. Even if the baseline values are lower than in other classes. However, also patients aged more than 70 showed a relevant reduction of pain progressively declining to more than 25%. Functionality after treatment has been explored using the Lequesne index. The subgroup of patients over 80 years and the decade 70-80 are those who have the highest score of the Lequesne index at baseline. They showed a significant reduction as early as three months from the first injection that is maintained over time with a slight progressive reduction of about 45% at the end of the study.

Other decades also exhibit a similar trend, even if they show the lowest baseline value, they report about 50% of functional improvement at 84 months. In detail, the decade 50-60 appears to obtain the greatest amelioration. The relatively lower improvement (34%) in patients under 40 deserves further explanations. It most likely that this subgroup is nor affected by a clear OA but may be suffering from a morphological pathology (such as a femoral-acetabular impingement). Clearly, without removing the mechanical factor, functionality and pain cannot improve dramatically.

In overweight patients, even if there are no statistically significant gender differences, we observe that males achieve a lower level compared to females at 84 months in GPA outcome and females showed a higher NSAID intake at all time points.

In obese patients similarly no statistically significant gender differences are observed. However, we can make three observations: females showed higher baseline level of pain; males achieve a lower level of Lequesne index compared to female at 84 months; NSAID intake results again higher in female patients at all time points. The obese patients seem to be those who consume more pain killers.

The differences observed in the categorization of patients by age or BMI can help us to design better investigative studies to identify the best candidates for VS.

Conclusions

The data in this cohort study extended up to 7 years confirm previous data about the efficacy, safety and reproducibility in the short, medium and long term of the intra-articular treatment with HyalOne®/Hyalubrix® 60 at 4 ml dose in symptomatic hip OA. In particular, it is clear that after a statistically significant improvement achieved in the first six months of treatment, the repetition of successive injections (at least 2 times/year) keeps the level of benefit achieved without loss of efficacy. It appears to be effective in all subgroups categorized by age and BMI; although the greatest efficacy appears to occur in the age group 50-70 and in the overweight group compared to the other tested categories. There were no significant gender differences. In conclusion, the data confirm the use of US VS as background therapy in the management of hip OA. Further studies are needed to identify the predictors of response, as well as the persistence in therapy. Similarly, additional studies are required to investigate the predictors of the progression of improvement compared to the level of improvement achieved immediately after six months.

Conflict of interest

Prof Alberto Migliore received grants as consultant from PFIZER, ABBVIE, MSD, FIDIA, SANOFI, IBSA for national and international studies and courses. The other authors declare that they have no conflict of interests.

References

1) Zhang YQ, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010; 26: 355-369.
2) Roman-Blas JA, Bizzi E, Largo R, Migliore A, Herrero-Beaumont G. An update on the up and coming therapies to treat osteoarthritis, a multifaceted disease. Expert Opin Pharmacother 2016; 4: 1-12.
3) Migliore A, Bizzi E, Herrero-Beaumont J, Petrella RJ, Raman R, Chevalier X. The discrepancy between recommendations and clinical practice for viscosupplementation in osteoarthritis: mind the gap. Eur Rev Med Pharmacol Sci 2015; 19: 1124-1129.
4) Henrotin Y, Raman R, Richette P, Bard H, Jerosch J, Conrozier T, Chevalier X, Migliore A. Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis. Semin Arthritis Rheum 2015; 45: 140-149.
5) Paoloni M, Bernetti A, Belelli A, Brignoli O, Buoso S, Caputi AP, Catani F, Coclite D, Fini M, Mantovani L, Migliore A, Napoletano A, Viora U, Santilli V. Appropriateness of clinical and organizational criteria for intraarticular injection therapies in osteoarthritis. A Delphi method consensus initiative among experts in Italy. Ann Ist Super Sanita 2015; 51: 131-138.
6) HYAP15 (Hyalubrix®). Clinical investigator's brochure 2004; Padova: Fidia Farmaceutici SpA.
7) Guidolin D, Franceschi F. Viscosupplementation with high molecular weight native hyaluronan. Focus on a 1500-2000 KDa fraction (Hyalubrix®). Eur Rev Med Pharmacol Sci 2014; 18: 3326-3338.
8) Schieb F. Intraartikulär injizierte Hyaluronsäure bei Arthropathien. Arthritis Rheum 2003; 23: 338-340.
9) Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med 2011; 47: 407-415.
10) Priano F, Guelfi M. Efficacy of intra-articular hyaluronic acid (Hyalubrix) in arthroscopy. Artroscopia 2017; VIII: 3-12.
11) Smiderle C, Scapin M, Ronconi L, Baldo M, Villaminar R. Gait analysis of changes in clinical and biomechanical parameters in osteoarthritis knee patients after intra-articular infiltration with hyaluronic acid. m.w. Eur Med Phys 2007; 43(Suppl 1-3): 5-17.
12) Vad VB, Sakalkale D, Sculco TP, Wickiewicz TL. Role of hylan G-F 20 in treatment of osteoarthritis of the hip joint. Arch Phys Med Rehabil 2003; 84: 1224-1226.
13) Caglar-Yagci H, Unsal S, Yagci I, Dulgeroglu D, Ozel S. Safety and efficacy of ultrasound-guided intra-articular hylan G-F 20 injection in osteoarthritis of the hip: a pilot study. Rheumatol Int 2005; 25: 341-344.

14) Migliore A, Tormenta S, Martin Martin LS, Valente C, Massafra U, Granata M, Alimonti A. Open pilot study of ultrasound-guided intra-articular injection of hylan G-F 20 (Synvisc) in the treatment of symptomatic hip osteoarthritis. Clin Rheumatol 2005; 24: 285-289.

15) Migliore A, Tormenta S, Martin Martin LS, Iannessi F, Massafra U, Carloni E, Monno D, Alimonti A, Granata M. The symptomatic effects of intra-articular administration of hylan G-F 20 on osteoarthritis of the hip: clinical data of 6 months followup. Clin Rheumatol 2006; 25: 389-393.

16) Migliore A, Massafra U, Iannessi F, Capuano A, Diaco ML, Mascheroni E, Alimonti A, Granata G, Padalino C, Tormenta S. Efficacy and safety of hyalubrix® administration in hip osteoarthritis: prospective cohort study. Ann Rheum Dis 2006; 65 (Suppl II): 399.

17) Migliore A, Bizzi E, Massafra U, Alimonti A, Martin-Martin S, Tormenta S. Articular administration of hyalubrix® in 344 patients with symptomatic osteoarthritis of the hip. Osteoarthr Cartil 2008; 16: 118-119.

18) Qvistgaard E, Kristoffersen H, Terslev L, Danneskiold-Samsøe B, Torp-Pedersen S, Bliddal H. Guidance by ultrasound of intra-articular injections in the knee and hip joints. Osteoarthr Cartil 2001; 9: 512-517.

19) Migliore A, Martin LS, Alimonti A, Valente C, Tormenta S. Efficacy and safety of viscosupplementation by ultrasound-guided intraarticular injection in osteoarthritis of the hip. Osteoarthr Cartil 2003; 11: 305-306.

20) Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, Alimonti A, Tormenta S. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther 2009; 11: R183.

21) Migliore A, Massafra U, Bizzi E, Lagana B, Germano V, Piscitelli P, Granata M, Tormenta S. Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa; HyalOne®) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg 2011; 131: 1677-1685.

22) Migliore A, Bella A, Bisignani M, Calderaro M, De Amicis D, Logroscino G, Mariottini F, Moreschini O, Massafra U, Bizzi E, Laganà B, Piscitelli P, Tormenta S. Total hip replacement rate in a cohort of patients affected by symptomatic hip osteoarthritis following intra-articular sodium hyaluronate (MW 1,500-2,000 kDa) ORTOBRIX study. Clin Rheumatol 2012; 31: 1187-1196.

23) Migliore A, Tormenta S, Laganà B, Piscitelli P, Granata M, Bizzi E, Massafra U, Giovannangeli F, Maggi C, De Chiara R, Iannessi F, Sanfilippo A, Camminiti M, Pagano MG, Bagnato G, Iolascon G. Safety of intraarticular hip injection of hyaluronic acid products by ultrasound guidance: an open study from ANTIAGE register. Eur Rev Med Pharmacol Sci 2013; 17: 1752-1759.

24) Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, Brown C, Cooke TD, Daniel W, Feldman D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.

25) Kellgren JK, Lawrence JS. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957; 15: 494-501.

26) Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. J Rheumatology 1997; 24: 779-781