VISCOSUPPLEMENTATION WITH HANOX-M-XL IS EFFECTIVE IN MODERATE HIP OSTEOARTHRITIS BUT IS NOT AN ALTERNATIVE TO HIP JOINT SURGERY IN PATIENTS WITH SEVERE DISEASE. RESULTS OF A CLINICAL SURVEY IN 191 PATIENTS TREATED IN DAILY PRACTICE

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Viscosupplementation with hyaluronic acid (HA) or its derivatives for the symptomatic relief of osteoarthritis (OA) of the hip joint have been studied in open-label and placebo-controlled trials with conflicting results. The objective of this survey was to obtain data from the daily practice on efficacy and safety of HANOX M-XL, a novel viscosupplement made of non-animal cross-linked HA and high concentration of mannitol (HappyCross®) administered through a single injection regimen in patients suffering from hip OA. Multicenter retrospective clinical survey using a standardized questionnaire in which one hundred ninety one consecutive patients treated with a single intra-articular injection of HANOX M-XL for symptomatic hip OA were included. Demographic data, imaging guidance, pain on a 10 point Likert scale (LS), patient's self-evaluation of efficacy, satisfaction with the treatment and tolerability were obtained. According to the patient's own decision, which was taken prior to the injection, patients were classified into two groups: those for which the viscosupplementation was the last resort before total hip arthroplasty (THA group) and those who would not consider surgery in the short term (Non Surgery- NS group). Tolerability was very good/good in 165 patients (86.4%), moderate in 14 (7.3%) and poor in 12 (6.3%) cases. In the total population, the percentage of patients very satisfied/satisfied and not really satisfied/not satisfied with the treatment was 24.6%, 27.7% and 22.5% and 25.1% respectively. The efficacy was considered as very good/good in 51.8%, moderate in 23.6% and poor in 24.6% of the cases respectively. Efficacy was unrelated to gender, age, and guidance but was highly correlated with pain on LS ($p<0.0001$). Efficacy was significantly different with regard to the clinical severity: 66.6% of the NS group patients were satisfied with the treatment versus only 25% of those belonging to the THA group ($p<0.0001$). In satisfied patients the decrease of analgesics/NSAIDs consumption was >75% in 60.5% of cases. These data suggest that despite HANOX M-XL is a safe and efficient intra-articular treatment of hip OA, it is not a valuable alternative to surgery in advanced disease.

Osteoarthritis (OA) is the most common musculoskeletal condition and one of the major cause of disablement in elderly. As a cause of disability affecting large joints, hip OA is second only to knee OA and its prevalence is estimated between 3 and 11 % in subjects aged over 35 years (1, 2)

Current treatment for hip OA is made of a combination of non-pharmacological and pharmacological modalities (3, 6) including viscosupplementation (VS). VS is a therapeutic

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consisting in intra-articular injections of hyaluronic acid (HA) or its derivatives (7). The aim of VS is to reduce joint pain and improve function, possibly by restoring the physiological and rheological state of arthritic joints (7). *In vitro* and *in vivo* studies have also suggested that HA could have protective effects on cartilage (8-12). VS is widely used in the symptomatic treatment of knee OA (13) and several studies have suggested it could also be useful as a safe and well tolerated adjuvant treatment in patients with symptomatic hip OA, not adequately relieved with conventional therapy (analgesics, non-steroidal anti-inflammatory drugs –NSAIDs, physiotherapy) (14, 15). However clinical trials showed controversial results regarding the effectiveness of VS in hip OA, a number of open-label trials have reported promising results (16-20), though no definitive conclusions can be drawn from these studies in the absence of a placebo group. On the opposite Qvistgaard et al (21) as well as Richette et al (22) did not show evidence of efficacy in randomised double blind, placebo-controlled trials. Nevertheless there are several possible explanations for these conflicting results. These could result from the difference of design of the studies (small samples with lack of statistical power), the choice of the regimen (single or serial injections), possible differences of efficacy between HA derivatives (linear or cross-linked, HA concentration and molecular weight) (13), and/or from the selected population (moderate to severe disease). Furthermore, if the efficacy is usefully observed in about 50% of the patients, no predictive factors of response has been clearly identified, excepted, in some studies, the Kellgren-Lawrence grade (23, 24).

HANOX-M-XL (marketed as HappyCross®, Laboratoire LABRHA, Lyon, France) is a new viscosupplement, specifically designed to treat hip OA, that combines a high molecular weight cross-linked sodium hyaluronate (15.5g/L) of non-animal origin with a high concentration (3.5%) of mannitol, a polyol known for its antioxidant properties by scavenging radical oxygen species (ROS). The in vitro effectiveness of mannitol to protect HA against ROS mediated depolymerization has been widely demonstrated (25, 26) suggesting that the addition of mannitol to HA might increase the intra-articular residence time of the latter and consequently might allow to use a single injection regimen. The aim of the survey was to assess the efficacy of a single injection of HANOX-M-XL in patients with symptomatic hip OA in daily practice, by comparing those in who viscosupplementation was the last resort before total hip replacement and those with a less severe symptomatology, irrespective to the radiological grade of the disease.

MATERIALS AND METHODS

One hundred and ninety-one patients, who have been referred to a rheumatologist for symptomatic hip OA, and who received a single injection of HANOX-M-XL into the hip joint within the 6 previous months were contacted by phone and were interviewed using a 10-item standardized questionnaire. Only 1 patient refused to answer the interview. Demographic data (gender, age), analgesic or NSAIDs consumption, imaging guidance (fluoroscopy, ultrasonography or no guidance), pain on a 10 point Likert scale (LS), patient's self-evaluation of efficacy using a 4 point LS, satisfaction with the treatment (4 pt LS) and tolerability (4 pt LS) were obtained. The goal of the study was to assess whether viscosupplementation could be a valuable alternative to hip replacement in patients who did not wish to be operated or in those who were on waiting list for surgery. Consequently patients were classified into two groups, according to the patient's answer to the question: "Before viscosupplementation, was your own decision taken, to have surgery in case of treatment failure?". The THA group consisted of patients for whom the viscosupplementation was the last resort before total hip arthroplasty; The No Surgery -NS group-consisted of those who would not consider surgery in the short term. The classification was made according to the patient and physician decision irrespective to the radiological features. The patients gave the informed consent prior being included into the survey. The survey was performed in agreement with the French Conseil National Informatique et libertés (CNIL N°1583599V0).

The patients gave informed consent prior being included into the study. The study was authorized by the local ethical committee and was performed in accordance with the Ethical standards of the 1964 Declaration of Helsinki as revised in 2000.

A descriptive analysis was performed on all the collected data. Qualitative variables were described using frequencies and percentages. Quantitative variables were describes using mean, standard deviation and some characteristics of their distribution (minimum, maximum and median). Univariate analysis was performed using chi-2 test or Fischer's exact test, or Mann-Whitney test as

appropriate. All statistical tests were carried out two tailed at the 5% level of significance. The statistical analysis was carried out using Statview software version 5.0 (SAS institute Inc).

RESULTS

Data are summarized in Table I. Among the 191 patients, 82 were men and 109 women. Patients mean age (SD) was 65.2 (12.7) and the average follow-up since the injection was 15.3 (11.7) weeks. Intra-articular injection was performed under fluoroscopic guidance in 167 cases and ultrasonography in 24 cases. Sixty-six percent of the subjects were analgesics and/or NSAIDs regular users. Patients from the THA group (N= 68) were more frequently men than women (p=0.004) and NSAIDs consumers (75% versus 60.9%, p=0.002) but did not differ significantly regarding age (p=0.25) compared with those of the NS group (N= 123).

In the total population, the percentage of patients very satisfied/satisfied/not really satisfied/not satisfied at all with the treatment was 24.6%, 27.7%, 22.5% and 25.1% respectively. The efficacy was considered as very good/good in 51.8%, moderate in 23.6% and poor in 24.6% of the cases respectively.

Efficacy was unrelated to sex (p=0.29), age (p=0.53), and guidance (p=0.20). Efficacy was highly correlated with pain on LS (p<0.0001) at the time of interview. In satisfied patients the average pain on LS (SD) was 3.0 (2.3) while it was 7.6 (1.9) in not satisfied subjects. In satisfied patients the patients self-assessed decrease of analgesics/NSAIDs consumption was >50% in 79% and >75% in 60.5% of the cases. When patients were stratified according the surgical decision, 66.6% of the NS group patients were satisfied with the treatment versus only 25% of those belonging to the THA group (p<0.0001).

Tolerability was very good/good in 165 patients (86.4%), moderate in 14 (7.3%) and poor in 12 (6.3%) cases, without any difference between THA and NS groups (p=0.95). The only reported side-effect was a transient increase of hip pain, that lasted from 1 to 7 days after the injection, unrelated to the imaging guidance (p=0.39).

DISCUSSION

Despite its limitations, which will be discussed below, this retrospective survey provides interesting data. Indeed, they come from real life but not from a particular recruitment and effectiveness as tolerance are evaluated by patients themselves. The average age was consistent with that of usual clinical trials (19, 20, 22) and the patients self-reported success rate, self- about 50% - was similar to that obtained

Table I. *Characteristics of 191 patients with hip osteoarthritis treated with a single injection of HANOX-M-XL.*

Population	All patients N=191	No Surgery N=123	THR N=68	p NS vsTHR
Age (SD)	65.2 (12.7)	65.7 (13.4)	64.5 (9.9)	0.25
Gender (M/F)	82/109	48/75	34/34	0.004
VAS pain mm (SD)	5.3 (3.0)	4.4 (3.02)	6.8 (2.4)	<0.0001
Time since injection (weeks)	15.3 (11.7)	15.2 (12.8)	15.5 (8.9)	0.64
Guidance (Fluo/US)	167/24	106/17	61/7	0.94
Satisfied (Yes/No)	100/91	82/41	18/50	<0.0001
Efficacy (Yes/No)	99/92	82/41	17/51	<0.0001
NSAIDs/ analgesics baseline (Yes/No)	126/65	51/45	51/17	0.002
Tolerability (good/moderate/poor)	165/14/12	107/10/6	58/4/6	0.95

THR: total hip replacement; VAS: Visual analogue scale; Fluo: fluoroscopy; US: Ultra-sound; NSAIDs: Non steroidal anti inflammatory drugs.

in an open-label study with hylan GF-20, in which the percentage of responders according to the OMERACT-OARSI response criteria was 53.6% (24). The main lesson to be drawn from this survey is the very low rate of satisfaction with the treatments in the group of patients in whom viscosupplementation was considered as the last resort before total hip replacement. Only 1 out of 4 patients waiting for surgery was satisfied with viscosupplementation. In contrast, those who do not consider surgery in the short term had a high satisfaction rate, similar to that of patients fulfilling the Minimal Clinically Important Improvement (27) in an uncontrolled trial, performed in patients with mild to moderate hip OA (20). On the other hand, in patients with less severe disease, the results of viscosupplementation were satisfactory in two third of the patients. Furthermore those who were regularly taking NSAIDs and who were satisfied with the treatment, have dramatically reduced their NSAIDs consumption in more than 3/4 of cases. The main limitations of the present study is the lack of radiographic data and the fact to classify patients according to the future decision to have surgery or not. However, radiographic examination, although essential for the surgeon for the pre-operative planning and for the choice of the type of prosthesis, often does not provide essential information in the surgical decision since it has been demonstrated that the radiological severity is not related to the functional impairment (28). Patient's willingness to undergo surgery is, of course, mainly due to pain and functional impairment but other parameters are to be taken in consideration such as their socio-economic status, their age, geographical variation in access to joint replacement, the patient lifestyle, and chiefly the advice of their doctor (28-30). If age is considered as a complex factor in predicting whether patients will undergo arthroplasty and previous studies have found that subjects older than 65 to be less willing to operate (30), we did not find any difference regarding age in patients waiting or not for surgery. In our population, men were more likely than women to say they want to have surgery. This is consistent with data of the literature showing that women older than 54 had lower rates of surgery than men of the same age and similar self-reported co-morbidities, and are less likely to have discussed the option of arthroplasty with a primary care doctor (30, 31). The failure of treatment in advanced forms of arthritis can be easily explained although the mechanisms by which viscosupplementation reduces pain are still imperfectly known. Its seems that hyaluronic acid is acting by reducing the cartilage matrix degradation (32-37) and prostaglandin E2 (38, 39) and bradikinin production (39) and consequently by decreasing the reactional synovitis, Now osteoarthritic pain is not only related to inflammatory processes and there is evidence for the sensitization of pain pathways, involving changes in both joint nociceptors and nociceptive processing in the spinal cord, brainstem, and thalamocortical system (40), particularly at late stages of the disease. Herein, HA does not seem to be able to act on these components. In summary, the present survey showed that three months after a single injection of HANOX M-XL in the target hip of patients with hip OA, more than 1 patient out of 2 was satisfied with the treatment, with no particular or unexpected safety concern. The proportion of satisfied patients reached 66% in subjects with moderate disease, while it was only of 15.5% in those waiting for hip replacement. These data suggest that HANOX M-XL is a safe and efficient intra-articular treatment of hip OA but must not to be considered as an alternative to surgery in advanced disease. A large scale prospective trial with MRI and radiological assessment is already in progress to determine with certainty the predictive factors of response to HA injection in patients with hip OA.

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All the other authors declare no conflict of interest

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