

Standardized Follow-up of Patients with Symptomatic Knee Osteoarthritis Treated with a Single Intra-articular Injection of a Combination of Cross-Linked Hyaluronic Acid and Mannitol

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ABSTRACT

OBJECTIVES: The objective of this study is to obtain pilot data from daily practice conditions of a viscosupplement made of a cross-linked high-molecular-weight hyaluronic acid (HA) combined with mannitol in patients with knee osteoarthritis (KOA).

METHODS: The data of 40 consecutive patients, 29 women and 11 men, who were prospectively followed up for 6 months, using a standardized procedure, were retrospectively analyzed. All patients have received a single intra-articular injection of HAnox-M-XL (4.4 mL), viscosupplement made of a cross-linked HA (16 mg/mL) + mannitol (35 mg/mL), in the target knee. The primary outcome was safety. The secondary end points included 3- and 6-month change in the WOMAC pain (0–50) and WOMAC total (0–240) and patient's global assessment (PGA). Patient's self-assessment of treatment efficacy (0–3) and analgesic consumption were obtained at months 3 and 6. An intent-to-treat analysis was performed.

RESULTS: Mean (SD) age was 60.7 (13.9) years, and mean BMI was 28.6 (5.0). Kellgren–Lawrence radiological grade was I/II and III/IV in 13 and 27 of the subjects, respectively. The average WOMAC pain and WOMAC total scores at baseline were 21.5 (9.8) and 89.9 (42.8), respectively. Thirty-nine patients completed the follow-up. HAnox-M-XL was well tolerated; two patients experienced knee pain after injection, which resolved within three days. No treatment-related severe adverse event was reported. Mean (SD) variations in WOMAC pain and WOMAC total scores were –8.2 (8.9) and –38.4 (35.6), respectively, at month 6 ($P = 0.001$). PGA decreased from 5.5 (2.0) to 3.0 (2.2) ($P = 0.006$). Efficacy was rated as *good or very good* in 76.9% of the cases. Most of the regular analgesics users decreased their consumption.

CONCLUSION: Treatment with one injection of 4.4 mL HAnox-M-XL is effective to alleviate KOA symptoms over six months, without safety concern. Controlled trials are needed to confirm these pilot data.

KEYWORDS: hyaluronic acid, viscosupplementation, knee osteoarthritis, mannitol, intra-articular injection

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Introduction

Present recommendations for the treatment of knee osteoarthritis (KOA) include a combination of nonpharmacological and pharmacological modalities.^{1–4} Among the latter, intra-articular (IA) injections of hyaluronic acid (HA)⁵ – viscosupplementation – are claimed to alleviate pain and to improve joint function, likely by restoring the physiological joint homeostasis.^{5,6} *In vitro* and *in vivo* trials have also suggested that HA may have chondroprotective properties by decreasing type II collagen degradation.^{7–12} Viscosupplementation is currently recommended in patients suffering from KOA not adequately relieved with conventional therapy.^{13–15} Recent works have ranked VS as the most effective treatment for this condition,^{16–18} but other studies showed controversial results regarding

viscosupplementation efficacy.^{19,20} Usually recommended dosing regimens vary from one to five injections, at weekly intervals, depending on the HA structure. Indeed, HA intra-articular residence time ranges from few days for linear molecules²¹ to few weeks^{22,23} for the solutions of cross-linked HA. Because oxidative stress is the main way for HA depolymerization, mannitol and sorbitol, two polyols known for their properties to scavenge radical oxygen species (ROS), are claimed to increase the intra-articular residence time of HA.^{24–26} *In vitro* the ability of mannitol to protect HA against ROS-mediated degradation was clearly demonstrated,^{27,28} suggesting that the combination of mannitol with HA could improve the viscosupplement performances. Furthermore, in an animal model, mannitol has exhibited its own anti-inflammatory effect.²⁹



HAnox-M-XL (HAPpyCross®; LABRHA SAS) is a viscosupplement, which is a combination of cross-linked sodium hyaluronate and mannitol. A single injection of 2.2 mL of HAnox-M-XL has been shown to be effective and well tolerated in a large cohort of patients with hip osteoarthritis.³⁰ Furthermore, a randomized double-blinded placebo-controlled trial, in 81 patients with KOA, showed that a single IA injection of 2.2 mL of HAnox-M-XL reduced the serum levels of Coll2-1, a specific marker of cartilage degradation and was well tolerated (only two adverse effects attributable to the product were reported).³¹ Because of this good tolerability, a double dose dosing regimen is commonly used in our department of rheumatology in patients with advanced stages of KOA, in whom the chances of success are lower than in early stages.

The aim of the present work was to obtain pilot data, in daily practice conditions, on safety and efficacy of a double dose (4.4 mL) of HAnox-M-XL administered through a single injection in patients with symptomatic KOA.

Patients and Methods

Study design. In the department of rheumatology of the Nord Franche-Comté Hospital (Belfort, France), patients requiring viscosupplementation for KOA are followed up using a standardized questionnaire administered at the time of injection(s) then at three and six months postinjection(s) whatever the used viscosupplement. Before injection, patients are required to give agreement to the scientific and anonymous usage of the data collected during consultations. The protocol was approved by the Hôpital Nord Franche-Comté Scientific and Ethics Committee. All patients gave informed consent prior to being included in the study. The study was performed in accordance with the ethical standards of the Declaration of Helsinki and Good Clinical Practice.

The present study is a post hoc analysis of data obtained from patients prospectively followed up after viscosupplementation with HAnox-M-XL for KOA. Consequently, there were no inclusion/exclusion criteria in this observational retrospective study, performed in daily practice conditions. According to the French Authorities recommendations, viscosupplementation is indicated in patients suffering from KOA not sufficiently improved by the first-line treatments, including analgesics and nonpharmacological modalities. The standardized questionnaires included demographic and anthropometric data, medical history of KOA, prior and present treatments for knee OA – including surgery – were collected. The patient's global assessment (PGA) of knee pain and the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC index)³² were collected at each visit. At baseline, the radiography was performed by a single experienced observer (TC) to determine the Kellgren–Lawrence grade.³³

Viscosupplement. The treatment to be studied was HAnox-M-XL, a viscosupplement made of cross-linked sodium hyaluronate concentrated at 16 mg/mL combined with a high concentration (3.5%) of mannitol, conferring a

very high viscosity (ie, 2560 Pa s at 0.01 s⁻¹).³⁴ HAnox-M-XL was supplied in syringe containing 2.2 mL of solution. The content of two syringes (4.4 mL) was injected into the target knee through a 21-gauge needle, after careful removal of synovial fluid effusion if present, by an experienced rheumatologist. According to recent recommendations, all the injections were achieved using a lateral mid-patellar approach.³⁵

Concomitant treatments. Patients were allowed to take the following concomitant medications for knee OA: paracetamol (up to 4 g/d), weak opioids (tramadol and codein), systemic and topical nonsteroidal anti-inflammatory drugs (NSAIDs), and symptomatic slow acting drugs for OA (glucosamine, chondroitin sulfate, diacerhein, or avocado/soya unsaponifiables). Only patients who did not received intra-articular corticosteroids within two months before injection and those who did not have viscosupplementation within six months before injection were included in the analysis. Analgesic consumption was assessed at each visit by recording any change since the previous visit. The variation in analgesic consumption was also self-assessed by the patient using a four-point scale ($\leq 25\%$, 26–50%, 51–75%, and $>75\%$). All concomitant medications were also recorded at each visit.

Safety evaluation. Adverse events (AEs) were recorded at each visit with a particular care for those occurring immediately and the very next days after injection. Definition of adverse events (AEs) and serious adverse events (SAEs) were in accordance with the European standard EN ISO 14155:2011. Throughout the follow-up, investigators had to record all AEs, on the report form. Any AE had to be graded by the investigator, regarding severity, intensity into *mild*, *moderate*, or *severe*. The investigator also assessed the causal relationship as *excluded* or *not excluded* with the treatment and/or the procedure of IA injection. All AEs whose occurrence could not reasonably be attributed to causes other than the injected treatment were to be considered potential reactions to it and the relationship was assessed not excluded.

Efficacy outcome measures. The primary efficacy outcome was the change, between the date of injection and the last follow-up visit, in the WOMAC A pain subscore (0–50 points). Other efficacy outcomes were the change throughout the follow-up of the following criteria: PGA on a 11-point scale (PGA: 0–10), WOMAC function subscore (0–170), and WOMAC total score (0–240). WOMAC score and PGA were assessed at baseline and then at months 3 and 6, and their variations over time were compared to the minimal clinically important improvement (MCII) thresholds in both absolute values (–2 points) and percentage of change (20%).³⁶ At months 3 and 6, patients were also asked to self-evaluate the treatment efficacy (0 = nul, 1 = mild, 2 = good, and 3 = very good). Analgesic consumption was assessed at each visit by recording any change since the previous visit. The variation in analgesic consumption was also self-assessed by the patient using a four-point scale ($\leq 25\%$, 26–50%, 51–75%, and $>75\%$).



Study population. The intent-to-treat (ITT) population included all subjects who were treated with HAnox-M-XL for symptomatic KOA in the department of rheumatology between July 2014 and June 2015. The perprotocol (PP) population was made of the patients from the ITT population who completed the six-month follow-up.

Statistics. The XLstats software was used for carrying out the statistical analyses. Descriptive statistical analyses (means, standard deviations, medians, percentages, and confidence intervals) were used to describe the demographics, history of the disease and treatments, the clinical and radiological examinations, treatment effectiveness, and AEs. The following methods were used to assess the efficacy and safety of the treatment: the normality of variables was previously evaluated using Shapiro–Wilk test. If normality, they were evaluated by analysis of variance on repeated measures if relevant. If matched data, this analysis was complemented by an appropriate t-test. In case of non-normality, a generalized nonlinear model was performed in addition to or replacement of nonparametric tests. Descriptive analyzes of outcome measures were performed at all follow-up times.

Results

Forty patients were treated with HAnox-M-XL, using the same procedure, during the selected period. Thirty-nine patients completed the follow-up. One subject had total knee replacement at month 5. Characteristics of the patients were consistent

with those expected, namely an average age (SD) of 60.7 (13.9) years, a moderate overweight (mean BMI 28.6 ± 5.0 kg/m²), a female predominance (27 women and 13 men). Kellgren–Lawrence grade was I, II, III, and IV in 2, 11, 17, and 10 patients, respectively. The average WOMAC pain and WOMAC total scores at baseline were 21.5 (9.8) and 89.9 (42.8). The mean PGA was 5.5 (2.0). Baseline data are summarized in Table 1.

Safety evaluation. Forty subjects were analyzed. Two target knee AEs were reported (5%). Both occurred a few hours after injection of HAnox-M-XL. Adverse reactions were both transient worsening of pain in the target knee that resolved without sequel within 36 and 72 hours. Neither occurrence of effusion nor systemic AE was reported. One patients had SAE during the follow-up. She was hospitalized for total knee replacement five months after injection. At baseline, she was reporting a high level of pain (WOMAC A = 39), her BMI was 31.4 and she had a KL grade IV. This SAE was unrelated to treatment or procedure.

Efficacy secondary end points. Results are summarized in Table 2. The average WOMAC pain score at baseline was 21.5 (9.8). WOMAC total at baseline was 89.9 (42.8) and PGA was 5.5 (2.0). Mean (SD) variations in WOMAC pain score were -8.4 (10.1) and -8.2 (8.9) mm, at months 3 and 6, respectively (all $P = 0.001$). Mean (SD) changes in WOMAC total score were -29.4 (36.0) and -38.4 (35.6) mm, at months 3 and 6, respectively (all $P = 0.001$). At month 6, efficacy was rated as *good or very good* in 29 patients (76.9% of the cases). PGA decreased from 5.5 (2.0) to 3.0 (2.2) ($P = 0.006$). Efficacy was unrelated to age ($P = 0.69$), gender ($P = 0.89$), X-ray grade ($P = 0.09$), and BMI ($P = 0.11$) but inversely correlated with WOMAC scores at baseline ($P = 0.034$).

Analgesic consumption. Among the 25 patients who were regular analgesics users, 23 decreased their consumption. The reduction was over 50% in most cases and over 75% in 14 patients. Nine patients treated completely have stopped analgesics consumption.

Discussion

Assessing safety was the primary objective of the study. Indeed, this trial was the first one investigating a viscosupplement containing such a high amount of mannitol (144 mg). Our data showed that tolerability of HAnox-M-XL was absolutely

Table 1. Patients' characteristics at baseline.

ITEMS	MEAN	SD	RANGE
Age	60.7	13.9	37–79
Height cm	165.9	9.3	151–188
Weight kg	77.9	18.0	50–109
BMI cm/kg ²	28.6	5.0	19.5–38.6
Disease duration months	44.5	18.0	3–200
WOMAC pain (0–50)	21.5	9.8	9–38
WOMAC stiffness (0–20)	8.9	4.9	0–18
WOMAC Function (0–140)	58.0	31.8	21–127
PGA (0–10)	5.5	2.0	3–9

Abbreviations: BMI, body mass index; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; PGA, Patient's Global Assessment.

Table 2. Efficacy outcomes variations.

OUTCOMES	BASELINE MEAN (SD)	MONTH 3 MEAN (SD)	MONTH 6 MEAN (SD)	P-VALUE BASELINE VS. MONTH 3	P-VALUE BASELINE VS. MONTH 6
WOMAC pain (0–50)	21.5 (9.8)	12.2 (9.7)	12.4 (12.3)	0.001	0.008
WOMAC stiffness (0–20)	8.9 (4.9)	6.0 (5.8)	5.8 (6.1)	0.003	0.017
WOMAC Function (0–140)	58.0 (31.8)	39.4 (30.4)	35.9 (39.5)	0.002	0.001
PGA (0–10)	5.5 (2.0)	3.4 (1.8)	3.0 (2.2)	<0.001	<0.001

Abbreviations: WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; PGA, Patient's Global Assessment.



similar to that of regular viscosupplements not containing mannitol, demonstrating that the addition of mannitol to HA does not modify the local or general tolerability of viscosupplementation. No device-related severe adverse reaction has been reported during follow-up. The only reported AE was, not surprisingly, a transient worsening of knee pain, occurring a few hours after injection. In the two cases, the evolution was favorable in less than three days without resorting to other treatments than rest and analgesics. In our study, no case of pseudoseptic reaction occurred. Similarly, no similar case was reported in other studies with viscosupplements containing polyols, suggesting mannitol does not increase the risk of such adverse event. These results were consistent with those of previous studies showing a good tolerability of viscosupplements containing sorbitol^{24,37} and mannitol.^{30,38} However, we cannot exclude the possibility of adverse effect with low incidence in such a sample size. Nevertheless, based on the very short half-life of mannitol (four hours), it is unlikely that significant adverse reactions occur more than two days after injection.

Mannitol is a polyol known for its antioxidant properties by scavenging radical oxygen species (ROS).²⁷ The *in vitro* effectiveness of mannitol to protect HA against ROS-mediated depolymerization has been demonstrated suggesting that addition of mannitol to HA might increase the IA residence time of the latter and consequently might allow to use a single injection regimen.^{26,28} Furthermore, mannitol might have a own analgesic effect. If so, it is not clear that the shorter onset of efficacy is due to anti-inflammatory properties, as suggested by animal model of adjuvant-induced arthritis.²⁹ With regard to efficacy, a single injection of two syringes of HAnox-M-XL enabled a quick reduction in pain and disability, as evidenced by a significant decrease in WOMAC subscores at all assessment visits, greater than the MCII thresholds for pain, disability, and PGA, in both absolute values and percentage.³⁶ Our study also highlights the fact that viscosupplementation with HAnox-M-XL allows to reduce the use of analgesics in a large majority of patients. In economic terms, this is an element to take into account seeing the direct cost of painkillers, and the indirect costs related to the potential problems of intolerance, common in an elderly population.³⁹ One of the main strengths of this work is it has been achieved in daily practice conditions, without any selection of the patients. Both patients with moderate and severe KOA were analyzed. Two-thirds of the subjects had radiological grades III and IV, and one out of four had a complete joint space narrowing. The lack of significant correlation between efficacy and radiological grade is probably the consequence of a lack of power due to the small sample of patients. However, there was a trend to a lesser effectiveness in patients with severe joint space loss. It was the same regarding the relationship between BMI and efficacy, with a tendency in less good results in patients with overweight. Another important point to notice is the very low rate of patients' withdrawal, only one of them having been recourse to total knee prosthesis, albeit,

as mentioned previously, most of them were suffering from an advanced disease.

Of course, the study suffers of several limitations. In the absence of a control group, the real efficacy of the treatment cannot be proved conclusively. Furthermore, we do not have any data to determine the reason why this particular viscosupplement, rather than another, has been chosen by the rheumatologist. In France, most viscosupplements administered through a multiple injection regimen are fully reimbursed, whereas those designed for a single injection are not. So the physician proposes the two therapeutic options to the patient who chooses what he prefers. We cannot exclude this has set a selection bias, although this is unlikely, because the studied population was very similar to that of other comparable trials.^{40–42} The follow-up, not exceeding six months, is another limitation, and further studies are necessary to assess the duration of efficacy up to 12 months of HAnox-M-XL.

In summary, this observational study, designed and conducted according to validated recommendations, evidences that HAnox-M-XL is well tolerated and strongly suggests it is effective in patients with KOA. A single injection of 4.4 mL of HAnox-M-XL allows a long-lasting pain relief and a significant decrease of analgesic consumption with local and systemic safety similar to that of viscosupplement not containing mannitol, indicating that the addition of high concentrations of this antioxidant does not modify the tolerability of HA.

Author Contributions

Conceived and designed the experiments: TC, MS, ALW. Analyzed the data: TC, MS, AMB. Wrote the first draft of the manuscript: TC. Contributed to the writing of the manuscript: MB, JCB. Agree with manuscript results and conclusions: AMB, AWL, MS. Jointly developed the structure and arguments for the paper: TC, MB, JCB. Made critical revisions and approved final version: AWL, MS. All authors reviewed and approved of the final manuscript.

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