LONG-TERM EFFICACY AND SAFETY OF A COMBINED HYALURONIC ACID IN OSTEOARTHRITIS OF THE KNEE

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Abstract

OBJECTIVES
To evaluate the long term efficacy and safety of a combined HA of low and high molecular weight and different concentrations (DMW) in comparison to low molecular weight (LMW 500-730 KDa) or high molecular weight (HMW 6000 KDa) HA products in reducing pain at rest and pain at walking associated with knee osteoarthritis, as compared to placebo.

DESIGN
A randomized, double-blind, placebo-controlled study of two hyaluronic acids with different characteristics for the long-term treatment of knee osteoarthritis.

PATIENTS
Two hundred eligible consented patients were randomized into four cohorts - Active treatment 1 (DMW), Active treatment 2 (LMW), Active treatment 3 (HMW), and Placebo (saline).
Patients received intra-articular injection once weekly for three weeks and were followed up at week 16, 52 and 104.

OUTCOME MEASURES
Assessments were done at baseline, weeks 2, 3, 16, 52 and 104. Efficacy measures included patient's visual analogue scale (VAS) of pain when seated (0-100 mm) and VAS of self-paced 40m walking pain. Other efficacy measures include the use of concomitant medications between groups, the review of adverse events, patient global satisfaction of knee osteoarthritis.
At week 52, repeat intra articular injections were given to patients with walking VAS pain >45 mm.

RESULTS
Performance
At 16, 52 and 104 weeks respectively, walking VAS pain was significantly improved in all treatment groups vs. placebo:
- DMW (89.3%, p<0.001; 87.4%, p<0.001; 88.1%, p<0.001);
- LMW (81.3%, p<0.001; 78.2%, p<0.001; 77.0%, p<0.001) and;
- HMW (78.1%, p<0.001; 81.1%, p<0.001; 79.4%, p<0.001).

At 52 weeks, 8 patients in DMW group had resting VAS <45mm. No patient in the LMW or HMW groups had VAS<45mm.
DMW had lower (62mm, p<0.001) compared to LMW (76mm) and HMW (88mm) VAS at rest. Similar differences were observed for walking VAS (77mm vs 89mm vs 91mm respectively).
39, 41 and 43 (DMW, LMW, HMW) received repeat injections.
At 104 weeks, these differences were similar.
DMW and LMW had no reported adverse events; HMW had 2 local reactions at 52 weeks and 1 at 104 weeks.

Safety
There were no serious adverse events. Non- serious adverse events included pain and local swelling at the injection site (21%), erythema at the injection site (12%) and stiffness in the index knee (7%).

CONCLUSION
Intra-articular hyaluronic acid injections using any of low, high or combined MW were highly effective in improving resting and more so, walking pain in patients with osteoarthritis of the knee. Greater improvement in both rest and activity outcomes in patients who received the DMW product, with concomitantly greater patient satisfaction and fewer use of concomitant therapeutic modalities at 16, 52 and 104 weeks suggest that combining a range of MW hyaluronic acid may be advantageous long term, particularly among active osteoarthritis patients.

Introduction

Several HA compounds are currently utilized world-wide by clinicians which differ in concentration and molecular weight composition, dosing regimens and claims of efficacy. Specifically, it is unclear whether differences in efficacy are found among products, while patients receive specific products without any objective criteria for a given choice.

The differences in HA molecular weight and concentrations in the synovial fluid occur among adults with a shift in the elastic-viscous ratio in osteoarthritis that is consistent with the degree of severity and character of symptoms. The knee in dynamic motion requires elastic composition at optimal molecular weight (MW) in balance with viscous needs. For example, high frequency loading through synovial fluid is dissipated through a dynamic change in Sodium Hyaluronate toward more elastic modulus compared to more viscous properties when the load to Sodium Hyaluronate is of low frequency.

Introduction

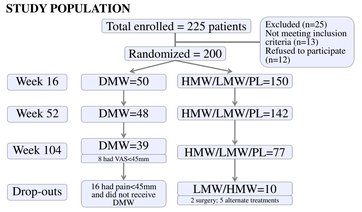
While a given HA product has a limited range of molecular weight typically low, medium or high, no product has been designed to provide a complement of composition that mimics the needs of the active osteoarthritic knee joint. These attributes may promote a more beneficial rheological environment in the osteoarthritic joint . Indeed, in an earlier study we described the efficacy and safety of DMW vs LMW and HMW over 16 weeks.

The purpose of this study was to evaluate the long-term clinical outcomes of pain at rest and following walking activity as well as adverse events, the use of concomitant therapeutic modalities and patient satisfaction following randomization to one of intra-articular viscosupplementation with a lower (500-730 kDa), higher (6 million Da) or combined lower and higher MW (DMW) Sodium Hyaluronate in osteoarthritis of the knee.

Methods

STUDY DESIGN
A single-center, randomized, double-blind, placebo-controlled study.

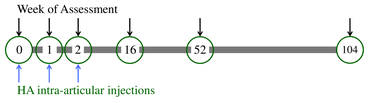
STUDY POPULATION



ASSESSMENT

	Visit 1	Visit 2	Visit 3	Visit 4 (w16), 5(w52), 6(w104) (Follow-up assessment)
Vital Signs	X	X	X	X
Brief history & physical review	X	X	X	X
Check for AEs	X			
IA knee injection	X	X	X	
Knee X-ray (if necessary)	X			
Self-paced 40mm pain (VAS)	X	X	X	X
Seated rest pain (VAS)	X	X	X	X
Patient global satisfaction of knee OA	X	X	X	X
Pill count / Rescue medication (dispensed)	X		X	
Concomitant medications	X	X	X	X
Review of AEs	X	X	X	X
Pain < 45mm prior to injection				X

Intervention



Statistical Power and Sample Size
Analysis of variance with repeated measures and χ^2 tests were used to test for differences from baseline characteristics of the group among the primary and secondary outcomes at each injection series interval. Analysis was conducted using sigma stat (SPSS Inc., Chicago, Illinois) and Microsoft Excel (Microsoft Corp, Redmond, Washington). Significance was established at $p< 0.05$.
The sample size was determined to allow the detection of a 20-mm difference in weight-bearing VAS at W16 assuming a standard deviation 10 mm of the mean distribution, an α of 5%, and a β level of 10%, giving a statistical power of 90%. With a potential dropout rate of 20%, we estimated a sample size of 225 patients.

Results

BASELINE COMPARABILITY

Baseline Characteristics of experimental group and all other referrals during 3-month recruitment period

Variable	Placebo N = 50	DMW N = 50	LMW N = 50	HMW N = 50
Age (years)	71±8	68±6	69±5	71±9
Gender				
(Female, *n*)	30	28	27	29
(Male, *n*)	20	22	23	21
BMI (Kg/m^2)	27.2±2.1	26.9±3.0	27.3±2.1	26.7±2.6
Years of OA symptoms	7.4±4.1	6.9±5.0	8.1±6.0	9.1±6.7
Grade knee OA (1 or 2, *n*)	39	41	41	38
Use of concomitant OA therapies (*n*)	3±1	2±1	3±2	2±1
Prior use of HA product (*n*)	10	7	9	7
Values mean ± SD				

EFFICACY
At 16, 52 and 104 weeks respectively, the change in walking VAS pain significantly improved from baseline in all three active treatment groups:
- DMW (89.3%, p<0.001; 87.4%, p<0.001; 88.1%, p<0.001);
- LMW (81.3%, p<0.001; 78.2%, p<0.001; 77.0%, p<0.001) and,
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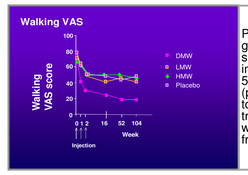
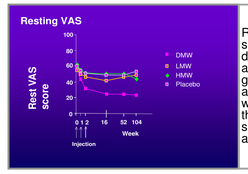
Similar differences were observed for walking VAS. 39, 41 and 43 (DMW, LMW, HMW) received repeat injections. At 104 weeks, these differences were similar.

Patients in the DMW group had significantly greater improvement at 16, 52 and 104 weeks (p<0.001) compared to the other active treatment groups which did not differ from each other.

Rest VAS pain was significantly decreased in all 3 active treatment groups from baseline at 16, 52 and 104 weeks, however, there was no significant difference among groups



Patients in the DMW group had significantly greater improvement at 16, 52 and 104 weeks (p<0.001) compared to the other active treatment groups which did not differ from each other.



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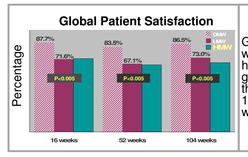

Global satisfaction was significantly higher for the DMW group compared to the other groups at 16, 52 and 104 weeks (p<0.005).

Concomitant Medications
There were no differences among the active treatments for concomitant osteoarthritis medications. There was no significant change in concomitant medications at any of the study timepoints.

Conclusions

Greater improvement in patients who received the DMW product was achieved by the second injection persistent to 104 weeks. Combination of Sodium Hyaluronate of lower and higher ranges of molecular weight with low and high concentrations, may provide patients with a more physiologically dynamic HA viscosupplementation and hence a more responsive synovial rheology that improves pain and function in their osteoarthritic knee.

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