Liventa Bioscience

Viscosupplementation for Knee Osteoarthritis

MONOGRAPH

Amnio-Viscosupplementation:
Review of the Safety and Efficacy of Amniotic Fluid in the Management of Joint Pain in Osteoarthritis

Background:

Osteoarthritis (degenerative joint disease – DJD) of the knee is a condition characterized by the progressive destruction of the cartilage that lines the knee joint and in the more severe cases results in bone-on-bone friction and accompanying pain, immobility and a deterioration of the activities of daily living.

In 2012 the estimated prevalence of osteoarthritis among adults in the United States, the number of individuals who had ever been told by a doctor that they had the condition was approximately 52.5 million cases (source: Centers for Disease Control and Prevention; National Statistics: National Health Interview Survey [NHIS] Arthritis Surveillance). Prevalence rates vary by the joint involved and the method of diagnosis (clinical vs. radiographic). Symptomatically, the knee is the most frequently affected joint. The prevalence of osteoarthritis of the knee is increasing rapidly because of shifting population demographics. The primary risk factors for osteoarthritis of the knee are aging, obesity, prior injury, repetitive use and female gender.

The prevalence of symptomatic knee osteoarthritis may reach 50% by the age of 75. From 2002 to 2012 the number of individuals in the US with a total knee replacement doubled from some 2 million to approximately 4 million. (Source: *Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease of the Knee*; Agency for Healthcare Research and Quality [AHRQ] Department of Health and Human Services; U.S. Government).

Osteoarthritis of the knee is usually diagnosed clinically based on pain. Radiographic evidence of osteoarthritis may precede symptomatic osteoarthritis but it correlates weakly with symptom severity.

The goals of treatment for osteoarthritis of the knee include pain relief, reduced inflammation, slowing the progression of the disease and improved mobility and function as well as health-related quality of life.

Treatment options for osteoarthritis of the knee include oral or topical analgesics, injected corticosteroids, physical therapy and exercise, weight loss, viscosupplementation using natural joint lubricants (most commonly hyaluronic acid [HA]), and partial or total arthroplasty.

Viscosupplementation, which was first used as a therapy in 1970s (trade name of Healon®) for ophthalmic use and veterinary use (Hylartil-Vet®), has become a standard of care within the continuum of care for symptomatic osteoarthritic knees.

The purpose of viscosupplements is to replenish the naturally occurring synovial fluid with a substance as close to normal, healthy synovial fluid as possible. Healthy synovial fluid, in addition to providing nourishment to the cartilage cells, also lubricates the articulating boney structures of the joint during low impact movement and shock absorption during high impact activities.

Many studies have shown that the early onset of osteoarthritis causes a deterioration of synovial fluid's properties -- specifically elasticity and viscosity. There are various disease processes at work in an

arthritic knee including production of certain enzymes and "toxic" precursors. The result is a diseased synovial fluid which cannot perform the functions of lubrication or shock-absorption.

At every stage of the osteoarthritic disease process, the deteriorating ability of the synovial fluid can be experienced by the patient as pain, stiffness and reduced function of the joint.

The principal of viscosupplementation is to break the cycle of synovial fluid deterioration. In fact, HA viscosupplement products are not registered as drugs but rather as medical devices, like liquid bio-prosthesis.

Viscosupplementation helps an OA joint by forming a protective layer around the inflamed articulating structures, covering micro-fractures and defects, and helping to restore the lubrication and protection that healthy synovial fluid offers.

Until very recently, all viscosupplementation products were derived from either rooster combs or from bacterial fermentation processes.

This paper reviews the interim data from a new source of HA – human amniotic fluid. Human amniotic fluid has been used as a viscosupplement for ophthalmic use (*Use of topical human amniotic fluid in the treatment of acute ocular alkali injuries in mice*; Am. J. Ophthalmol. 2006 Aug;142(2):271-8 S.Herretes, et al).

Ocular fluid, synovial fluid and amniotic fluid are highly similar materials with equally similar biologic functions. All three fluids are designed to provide lubrication, cushioning and shock absorption within an enclosed tissue structure like the synovium or placenta. All three contain significant levels of hyaluronan as well as phosolipids, cholesterol and such inorganic compounds as sodium, potassium and magnesium.

The hypothesis is that a human derived viscosupplement with largely the same components as healthy synovial fluid would be a safe and effective viscosupplement for the management of joint pain in the osteoarthritic patient.

Objectives:

The purpose of this single arm, registry study is to assess the efficacy and safety of amnio-viscosupplementation in the management of joint pain in the osteoarthritic knee.

Methods:

In a protocol driven, single arm post-marketing Registry approved by the Western Institutional Review Board (Olympia, WA) patients with Kellgren Lawrence Grade 1-3 OA via radiologic examination were treated with a single injection of processed donated human amniotic fluid. Excluded patients were < 35 years, had BMI > 45 or had received Hyaluronic Acid injections in the previous six months, or steroid or PRP injection in the last three months. There were no threshold pain inclusion or exclusion criteria. Eligible patients were injected with 4cc of minimally processed amniotic fluid (AmnioVisc; *Liventa Bioscience, West Conshohocken, PA)* into the affected knee.

Primary efficacy endpoints are VAS scores and WOMAC overall and Pain, Stiffness and Difficulty (function) sub-score scales, measured during office visits at baseline and at 30, 90 and 180 days. Enrollees also filled out weekly Pain Diaries to report WOMAC Pain sub-score (5 questions) at weeks 1-4 post-treatment.

Interim Results:

To date 275 patients have completed their enrollment and had their clinical results reported. The total number of patients for whom data is available is 275 (241 with 30 day follow up data, 162 with 90 day follow-up data and 63 with 180 day follow-up data). All data was collected and analyzed by OMEGA Statistics, Murieta, CA.

The patients reported statistically significant decreases in mean (average) pain, stiffness or difficulty scores from baseline to 30-day, 90-day and 180-day follow-up for all VAS and WOMAC scores.

At 30 day follow up 84.65% of the patients reported 40% or greater improvement based on the Total WOMAC score. More than 78% of the patients reported 40% or greater improvement based on the VAS pain score. The mean (average) percentage of improvement was 61.7% for total WOMAC, 61.45% for WOMAC difficulty, 61.92% for WOMAC stiffness, 62.50% for WOMAC pain and 58.78% for VAS Pain. (Table 1 below)

TABLE 1	**Baseline**	**30 day (t_{30})**				
	Baseline (t_0) Avg	**30 day (t_{30}) Avg**	**30 day (t_{30}) Avg improved from t_0**	**30 day (t_{30}) Avg % improved from t_0**	**30 day (t_{30}) % over 40% improved from t_0**	**30 day (t_{30}) % over 75% improved from t_0**
WOMAC /2400	1057.69 ± 555.75 1047 (53 – 2400)	405.02 ± 447.75 246 (0 – 2179)	-652.67 ± 519.85 -578 (-1966 – 971)	61.71%	84.65%	52.28%
WOMAC DIFFICULTY /1700	747.57 ± 409.05 730 (29 – 1700)	288.16 ± 324.63 168 (0 – 1563)	-459.41 ± 377.25 -394 (-1436 – 652)	61.45	80.01	48.13
WOMAC STIFFNESS /200	97.63 ± 53.29 97 (1 – 200)	37.18 ± 42.56 22 (0 – 185)	-60.45 ± 53.22 -56 (-175 – 81)	61.92	75.10	46.89
WOMAC PAIN /500	212.49 ± 116.76 205 (8 – 500)	79.68 ± 93.09 48 (0 – 458)	-132.80 ± 116.03 -112 (-451 – 251)	62.50	74.69	52.70
VAS	55.04 ± 23.69 558 (2 – 100)	22.69 ± 23.13 15 (0 – 98)	-32.35 ± 26.60 -32 (-99 – 37)	58.78	78.84	52.70

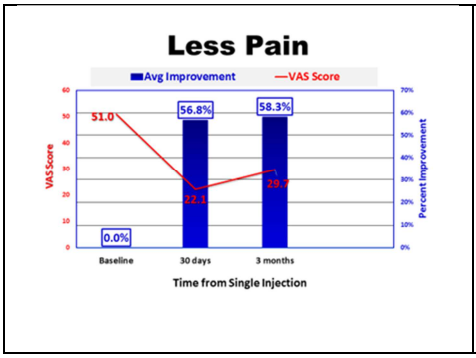
Statistical and Analysis of Variance tests (ANOVA) were conducted (OMEGA Statistics, Murieta, CA) for all endpoint measures to explore the impact of treatment at t=0, 30, 90 and 180 days. Tests of within-subjects effects for all endpoints across the three time periods of the study indicated that there was a significant within-subjects effect (p value < .0005) for the mean scores, from t=0 to t=30 to t=90 and to t=180 for all five endpoints.

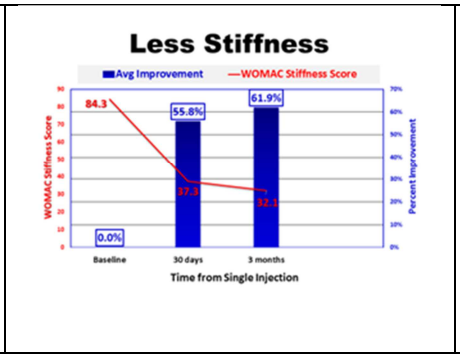
All rates of improvement over baseline at 30 days were statistically significant.

TABLE 2	**90 day (t_{90})**				
	90 day (t_{90}) Avg	**90 day (t_{90}) Avg improved from t_0**	**90 day (t_{90}) Avg % improved from t_0**	**90 day (t_{90}) % over 40% improved from t_0**	**90 day (t_{90}) % over 75 % improved from t_0**
WOMAC /2400	366.17 ±473.43 153 (0 – 2246)	-686.91 ± 501.75 -590.5 (-2122 – 445)	65.23%	82.10%	54.94%
WOMAC DIFFICULTY /1700	256.05 ± 336.30 99.5 (0 – 1616)	-486.29 ± 367.62 -435.5 (-1533 – 305)	65.51	81.48	55.56
WOMAC STIFFNESS /200	34.64 ±46.48 14 (0 – 197)	-64.02 ± 54.05 -67 (-181 – 106)	64.90	79.63	61.11
WOMAC PAIN /500	75.48 ± 98.76 34.5 (0 – 433)	-136.60 ± 111.00 -109 (-459 – 119)	64.41	77.78	54.94
VAS	20.33 ± 24.16 10.5 (0 – 100)	-34.89 ± 27.39 -36 (-100 – 36)	63.18	75.93	54.32

At 90 day follow up 82.10% of the patients reported 40% or greater improvement based on the Total WOMAC score. More than 75% of the patients reported 40% or greater improvement based on the VAS pain score. The mean (average) percentage of improvement was 65.23% for WOMAC/2400, 65.51% for WOMAC difficulty, 64.90% for WOMAC stiffness, 64.41% for WOMAC pain and 63.18% for VAS Pain. (Table 2 above)

All rates of improvement over baseline at 90 days were statistically significant.





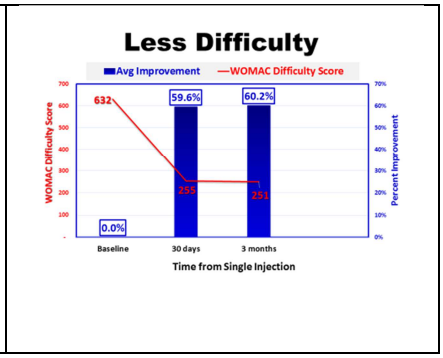
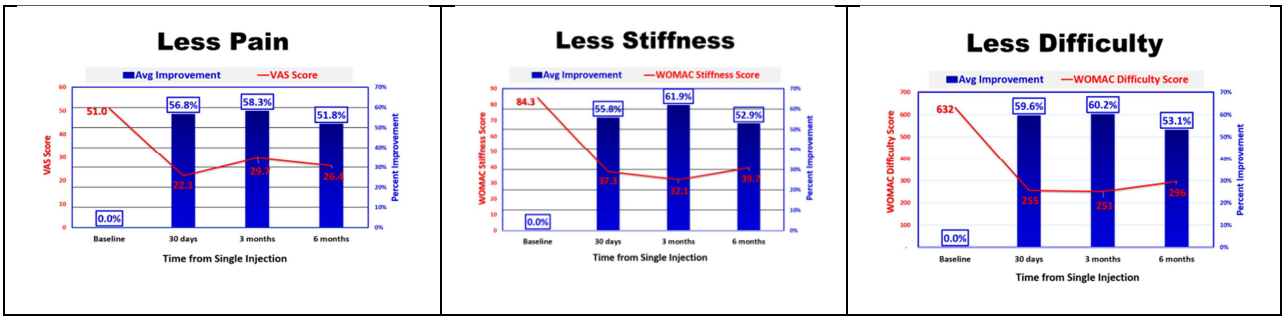


TABLE 3	180 day (t_{180})				
	180 day (t_{180}) Avg	**180 day (t_{180}) Avg improved from t_0**	**180 day (t_{180}) Avg % improved from t_0**	**180 day (t_{180}) % over 40% improved from t_0**	**180 day (t_{180}) % over 75 % improved from t_0**
WOMAC /2400	423.76 ± 582.65 150 (0 – 2265)	-483.48 ± 624.42 -342 (-1814 – 1098)	53.29%	66.67%	50.79%
WOMAC DIFFICULTY /1700	296.13 ± 417.78 99 (0 – 1627)	-335.48 ± 452.39 -227 (-1263 – 835)	53.12	69.84	52.38
WOMAC STIFFNESS /200	39.71 ± 53.77 15 (0 – 200)	-44.60 ± 58.01 -34 (-168 – 80)	52.89	71.43	47.62
WOMAC PAIN /500	87.92 ± 118.16 31 (0 – 470)	-103.40 ± 130.91 -84 (-413 – 249)	54.05	66.67	52.38
VAS	24.56 ± 29.74 9 (0 – 100)	-26.44 ± 30.88 -23 (-89 – 41)	51.84	65.08	55.56

At 180 day follow up 66.67% of the patients reported 40% or greater improvement based on the Total WOMAC score. More than 65% of the patients reported 40% or greater improvement based on the VAS pain score. The mean (average) percentage of improvement was 53.29% for WOMAC/2400, 53.12% for WOMAC difficulty, 52.89% for WOMAC stiffness, 54.05% for WOMAC pain and 51.84% for VAS Pain. (Table 3 above)

All rates of improvement over baseline at 180 days were statistically significant. The increase in pain, stiffness and difficulty WOMAC and VAS scores between 90 and 180 days was <u>not</u> deemed to be statistically significant.



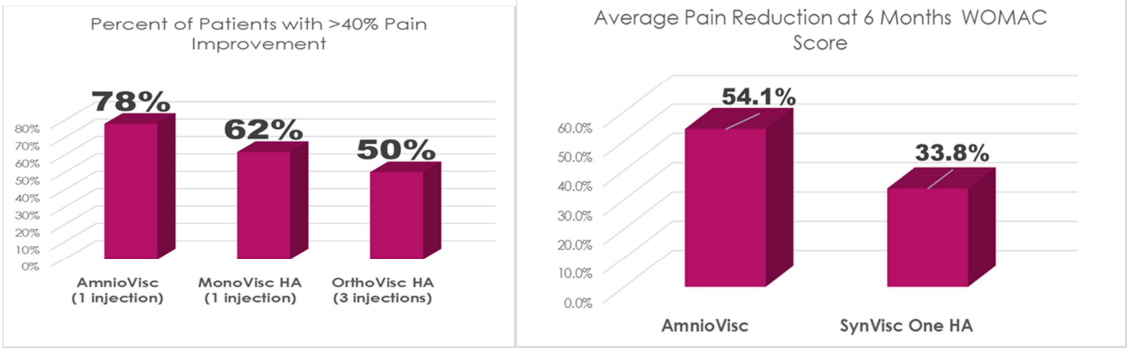
Adverse Events:
Seven treatment-related adverse events were reported among 275 patients (2.5%) returning for 30 day visits. Transient pain/tenderness resolved in days with no treatment in all cases.

Discussion:
Human amniotic fluid as a new source of viscosupplementation was shown in this protocol-driven, WIRB controlled Registry to reduce pain, stiffness and difficulty at statistically significant levels for patients with knee osteoarthritis.

At 30 days, 84.65% of the patients reported pain relief greater than 40% based on the total WOMAC score. Impressively, the percentage of patients reporting greater than 40% relief remained over 80% at 90 days and at the 180 (six month) mark, two thirds of the patients (66.67%) were still reporting greater than 40% pain relief based on the total WOMAC score.

These improvements from baseline are superior to those reported in the literature for more traditional forms of HA based viscosupplementation.

The single-injection Monovisc pivotal clinical trial (Anika Therapeutics and DePuy Synthes), reported that 61.8% of its patients achieved a 40% or greater level of pain relief at 7-22 weeks. The 3-injection OrthoVisc pivotal clinical trial reported that 50.2% of its patients achieved a 40% or greater rate of pain relief at 7-22 weeks. (source: http://www.accessdata.fda.gov/cdrh_docs/pdf9/P090031c.pdf)



The Synvisc One pivotal trial reported that the average rate of pain relief at 180 days was 33.8% over baseline using the WOMAC scale. By contrast, patients treated with human amniotic fluid reported an average 54.1% rate of pain reduction over baseline using the WOMAC scale at six months.

Traditional sources of HA viscosupplementation, rooster combs and fermentation technologies, have proven to be somewhat effective but remain controversial.

In a recent review of the literature in the journal *Clinical Evidence* (Scott and Kowalczyk, 2006), the authors found that intra-articular hyaluronan and hyaluronan derivatives may improve knee pain and function compared with placebo at up to 13 weeks after injection, but may have no longer-term benefits. The authors went on to say that hyaluronan may be more effective than intra-articular

corticosteroids at reducing pain at 5 to 13 weeks, although they may be as effective as each other in the shorter term. According to the review, this conclusion is based upon very low-quality evidence.

Recent guidance from the National Institute for Health and Clinical Excellence (2008) concluded that the hyaluronan viscosupplementation reduced pain up to 3 months after a series of 3 to 5 injections, although the effect size is generally small. "Given this, and the cost of the therapies together with increased clinician visits required for injections, there appears to be a poor rationale for routine clinical use."

More recently, the American Academy of Orthopedic Surgeons (2013) concluded that they "cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee." This conclusion was a strong recommendation and was based on a metaanalysis of studies that failed to show a clinically significant benefit from viscosupplementation.

By contrast, amniotic fluid derived viscosupplementation appears to offer patients higher and more durable rates of pain, stiffness and difficulty relief based on the 275 patients documented so far in this protocol-driven study.

There may be three reasons why amniotic fluid is a more effective viscosupplement than either rooster comb derived HA or HA produced by fermentation technique. Those reasons are;

1. It is human HA. Amniotic fluid has human hyaluronan and is known to be immune privileged since it lacks MHC antigens.
2. Human amniotic fluid is a homolog for human synovial fluid. The components of amniotic fluid are very similar to healthy, native synovial fluid. Both amniotic fluid and synovial fluid are ultrafiltrates from blood plasma and contain not only hyaluronan but also phospholipids, cholesterol, growth factor proteins, cytokines and nearly the same inorganic compounds.
3. Restores the correct pH levels. Human amniotic fluid has a pH level of about 7.0 which is the same as health synovial fluid. The disease of osteoarthritis tends to create an acidic and toxic environment in the knee and pH levels fall, typically, to about 3.5. Human amniotic viscosupplementation restores health pH levels which, in turn, create the conditions for the synovium to recover and potentially to slow down or even stop the disease progression.

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