A Single Injection of Amniotic Suspension Allograft Is Safe and Effective for Treatment of Mild to Moderate Hip Osteoarthritis: A Prospective Study

Molly C. Meadows, M.D., Katia Elisman, M.S., Shane J. Nho, M.D., Katie Mowry, Ph.D., and Marc R. Safran, M.D.

Purpose: The purpose of our study was to examine the effects of a commercially available amniotic suspension allograft (ASA) (ReNu, Organogenesis, Canton, MA) in a patient population with moderate osteoarthritis of the hip. **Methods:** Ten patients with symptomatic hip osteoarthritis, defined as Tonnis grade 1 or 2 on radiographic examination, were prospectively enrolled. Each patient received a single image-guided injection of ASA into the hip joint. Patient-reported outcomes measures, including the 12-item International Hip Outcome Tool, Modified Harris Hip Score, and Single Assessment Numeric Evaluation scores were recorded at baseline, 6 months, and 12 months postinjection. A linear regression model was performed to detect differences in outcome scores from baseline. **Results:** Nine patients had complete 12-month data available for analysis. One patient failed treatment and underwent arthroplasty at 2 months postinjection. The cohort includes 5 males and 4 females, aged 47-67. International Hip Outcome Tool scores demonstrated a significant improvement between baseline and 12 months ($P = .02$). Single Assessment Numeric Evaluation scores demonstrated a significant difference between baseline and 6 months ($P < .01$), as well as between baseline and 12 months ($P < .01$). Modified Harris Hip Scores demonstrated a significant difference between baseline and 6 months ($P = .02$) and between baseline and 12 months ($P = .01$). There were no major adverse events in the course of the study period. **Conclusion:** This study demonstrates promising results for relief of pain and improvement in patient-reported outcomes with intra-articular ASA in patients with moderate osteoarthritis of the hip for up to one year, although the exact mechanism of action remains unknown. **Level of Evidence:** IV, case series.

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Introduction

There is an increasing interest in the use of orthobiologics in the treatment of muscle, tendon, and joint pathology in orthopedics. Orthobiologic products are derived from human tissue and may contain any combination of cells, stem cells, or growth factors. These products are designed to alter the cellular and cytokine environment of the joint, thereby altering joint inflammation and preventing fibrosis.[1,2] Amniotic membrane- and fluid-derived products express anti-inflammatory proteins, including IL-1Ra and IL-10.[3] Additionally, these products have been shown to downregulate proinflammatory cytokines to divert macrophages from a proinflammatory phenotype to an anti-inflammatory phenotype.[4,5] Furthermore, amniotic membrane tissue contains a high concentration of hyaluronic acid,[6,7] and amniotic fluid-derived cells have the capacity to differentiate into chondrocytes.[8] Amniotic tissue was initially described for clinical use as a biologic dressing for skin defects.[9] Uses of amniotic membrane tissue have evolved to include treatment for ophthalmologic conditions, complex wounds, and more recently for orthopedic conditions, such as tendinopathy and osteoarthritis.[10–12]

Osteoarthritis (OA) is the leading cause of chronic disability in the United States.[13] Indeed, it is estimated

From the Stanford University Department of Orthopaedic Surgery, Redwood City, California, U.S.A. (M.C.M., K.E., M.R.S.); Midwest Orthopedics at Rush, Chicago, Illinois, U.S.A. (S.J.N.); and Organogenesis, Birmingham, Alabama, U.S.A. (K.M.).

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Address correspondence to Molly C. Meadows, M.D., Stanford University Department of Orthopaedic Surgery, 450 Broadway St. M/C, 6342, Redwood City, California U.S.A. E-mail: molly.meadows@gmail.com

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that in 2030, there will be 4.1 million Americans affected by hip OA.[14] The pathophysiology of OA is multifactorial; biomechanics, genetics, and injury contribute to cartilage degeneration, which leads to release of proinflammatory cytokines and expression of catabolic enzymes.[15] Furthermore, the concentration of the synovial fluid cytokines IL-1α, IL-1β, IL6, IL-18, and TNF-α are associated with severity of OA.[16–18] Corticosteroid, platelet rich plasma, and hyaluronic acid intra-articular injections have been used to treat symptomatic hip osteoarthritis with limited success.[19–23] Amniotic membrane and fluid-derived products represent a promising treatment option for patients with OA,[11,12] particularly those with moderate disease who are less likely to benefit from hip arthroscopy, yet are not indicated for arthroplasty due to age or severity of disease. The purpose of our study was to examine the effects of a commercially available amniotic suspension allograft (ASA) (ReNu, Organogenesis, Canton, MA) in a patient population with moderate osteoarthritis of the hip. Our hypothesis was that clinical results, as measured by patient-reported outcome (PRO) tools, would demonstrate significant sustained improvement at 12 months postinjection.

Materials and Methods

This was a multicenter open-label pilot study of cryogenically preserved ASA delivered as a single intra-articular injection for treatment of moderate OA of the hip. This study was performed at two institutions under a protocol approved by the Institutional Review Board (IRB) at both centers. Each patient who participated signed an IRB-approved informed consent form prior to enrollment. The study was funded by Organogenesis.

Patient Selection

Ten patients who met inclusion and exclusion criteria, five from each institution, gave written informed consent and enrolled in the study. Inclusion criteria included age between 18 and 70, with clinical and radiographic evidence of hip osteoarthritis. Radiographic assessment of moderate osteoarthritis was defined as Tonnis grade 1 or 2 changes on anteroposterior radiographs of the pelvis. For the purposes of this study, Tonnis grade 1 OA was defined as mild joint space narrowing, with increased subchondral sclerosis without significant loss of head sphericity. Tonnis grade 2 OA was defined as moderate joint space narrowing with mild cyst formation and moderate loss of head sphericity. Other inclusion criteria included a minimum score of 2 on the Tegner activity scale, a seven-day average pain score of 4 or greater for the involved hip, and body mass index (BMI) less than 40. Female participants were required to be actively practicing contraception, abstinence, or have a history of surgical sterilization or menopause. Patients with bilateral symptoms underwent intervention for their more symptomatic hip, and those with equivalent symptoms chose which hip to inject. The contralateral hip was allowed treatment with standard nonsurgical measures such as steroid injection. Exclusion criteria included a history of diabetes mellitus, rheumatoid arthritis or other autoimmune disorders, nonbasal cell malignancy within 5 years, morbid obesity (BMI >40), pain medication, or NSAID within 15 days prior to injection, use of pain medication other than acetaminophen for conditions unrelated to hip OA, anticoagulant use, use of immunosuppressive medication, corticosteroid or viscosupplement injection within 6 months, infection requiring antibiotic treatment within 3 months, hip dysplasia (center edge angle less than 25 degrees and/or Tonnis angle of more than 10 degrees) and surgery of either hip within 6 months.

Study Treatment

Patients received a commercially available single intra-articular injection of ASA, a cryogenically preserved suspension that contains micronized human amniotic membrane and cells derived from the amniotic fluid from the same donor. The ASA was processed in accordance with the standards of the Food and Drug Administration and the American Association of Tissue Banks. Amniotic tissue components were obtained during elective cesarean section from consenting donors. For treatment, 2 mL of ASA was thawed and combined with 0.9% saline to a total volume of 4 mL and injected into the hip joint under ultrasound guidance. If a hip joint effusion was present, the effusion was aspirated at the time of injection to avoid dilution of the product. Patients were assessed at baseline and at 1 week, 2 months, 3 months, 6 months, and 12 months post-treatment.

Safety

Assessment of safety was performed at each follow up visit, including vital signs, routine laboratory data, and a standard physical examination of the hip joint. Laboratory studies obtained at baseline and follow-up included a complete blood count with differential, basic metabolic profile, creatinine, and high-sensitivity C-reactive protein (CRP). Laboratory assessment was performed at the time of injection and at the 2 month, 6 month, and 12 month visits. Additionally, patients underwent a visit 1 week postinjection to assess any adverse reactions, such as fever, rash, infection, or bleeding.

Patient-Reported Outcomes

Patient-reported outcomes (PROs) were recorded at baseline and at subsequent follow-up visits. Hip pain and function were assessed using the Modified Harris Hip Score (mHHS), 12-item International Hip Outcome Tool (iHOT-12), SF-12, visual analog scale (VAS) pain score, and Single Assessment Numerical Evaluation (SANE)

score at baseline and at 1 week, 1 month, 2 months, 3 months, 6 months, and 12 months postinjection.

Imaging

Patients underwent an AP pelvis and lateral hip radiograph at baseline and at 12 months postinjection. Radiographic parameters, including joint space narrowing, presence of osteophytes, cyst formation, and subchondral sclerosis were measured on both the AP and lateral views at baseline and 12 months postinjection.

Statistical Methods

RStudio[1] (RStudio, PBC, Boston, Massachusetts) was used for all statistical analyses. Wilcoxon signed rank test was used to assess significant differences between PRO values at baseline, 6 months, and 12 months. The patient who underwent a total hip arthroplasty at 2 months postinjection was excluded from statistical analysis.

Results

Baseline Patient Data and Radiographic Assessment

Ten patients with Tonnis grade 1-2 hip OA were recruited from two study sites for a single injection of ASA. Each study site recruited 5 patients; however, one patient failed treatment and elected to undergo a total hip arthroplasty at two months postinjection and, thus, did not complete the study protocol. The nine patients without treatment failure included 5 male and 4 female patients, aged 48-65. The average age and BMI were 54.2±6.0 and 27.6±5.4, respectively. Age, gender, and baseline Tonnis grade scores are provided in Table 1. There was no significant difference in joint space narrowing from baseline to 12 months on the AP ($P = .36$) or cross-table lateral ($P = .94$) views.

Adverse Events

There were no immediate complications postinjection. Two patients had a transient increased in CRP to above the treating institution's normal threshold of 5 mg/L; however, this did not correlate to clinical symptoms, and the values normalized by the 6-month visit. None of the nine patients developed infection, effusion, or increased stiffness in the injected hip. None of the nine patients developed any new medical diagnoses during the 12-month follow-up period.

Patient Reported Outcomes

All nine included patients were assessed at baseline, 1 week, 1 month, 2 months, 3 months, 6 months, and 12 months postinjection using patient-reported outcomes scores, including pain and functional measures. These included the pain and function subscales of the mHHS, SF-12, iHOT, SANE, and VAS pain scores. We found significant differences in iHOT score between baseline and 1, 2, 3, 6, and 12 months postinjection ($P = .004$, .004, .004, .008, .020). The mean change from baseline to 12 months for iHOT was 31.29, which exceeds the reported Minimal clinically important difference (MCID) of 6.1.[24] SANE and mHHS scores were also significantly different between baseline and 1, 2, 3, 6, and 12-month time points (SANE: $P = .014$, .027, .020, .009, .004; mHHS: $P = .009$, .004, .009, .015, .013). Furthermore, the mean change from baseline to 12 months for mHHS was 21.50, which exceeds the reported MCID for hip osteoarthritis of 4-8 points.[25] Figure 1 represents average iHOT and mHHS scores over time. There were no significant differences in the SF-12 mental health score from baseline to any follow-up time point. The VAS pain score for average hip pain over the 3 days leading up to the appointment (VAS Question 1) demonstrated a significant difference between baseline and 6 months ($P = .027$); however, significance was not maintained at 12 months. The VAS Score for maximal pain in the prior 3 days (VAS Question 2) had significant differences between baseline and 1, 2, 3, 6, and 12-month time points ($P = .027$, .012, .027, .033, .008). Figure 2 represents the mean scores for VAS questions 1 and 2 across all time points. VAS Question 3 measured how well the injection procedure met the patients' expectations, with a 0 score defined as "did not at all" and 100 defined as "met my expectations". The average satisfaction scores peaked at 88.67 at 2 months postinjection, with an average score 75.44 at 12 months. Average PRO data at each time point are reported in Table 2, and reference data, including all individual PRO data for each time point across all patients, are reported in the appendix.

Table 1. Baseline Patient Characteristics

Identifier	Grade of OA (Tonnis)	Which Hip (L/R)	Age (Years at Injection)	Sex	Height (inches)	Weight (lbs)	BMI
Patient 1	2	R	48	Male	73	171.96	22.8
Patient 2	2	R	48	Male	72	207	28.1
Patient 3	2	R	50	Male	69	165	24.4
Patient 4	1	L	52	Female	66	131.4	20.2
Patient 5	2	R	52	Female	61	148.7	30
Patient 6	1	R	57	Female	61	167.1	31.3
Patient 7	2	R	62	Female	67	139	21.2
Patient 8	2	L	65	Male	68	196.8	30.7
Patient 9	1	L	50	Male	68	250	37.8

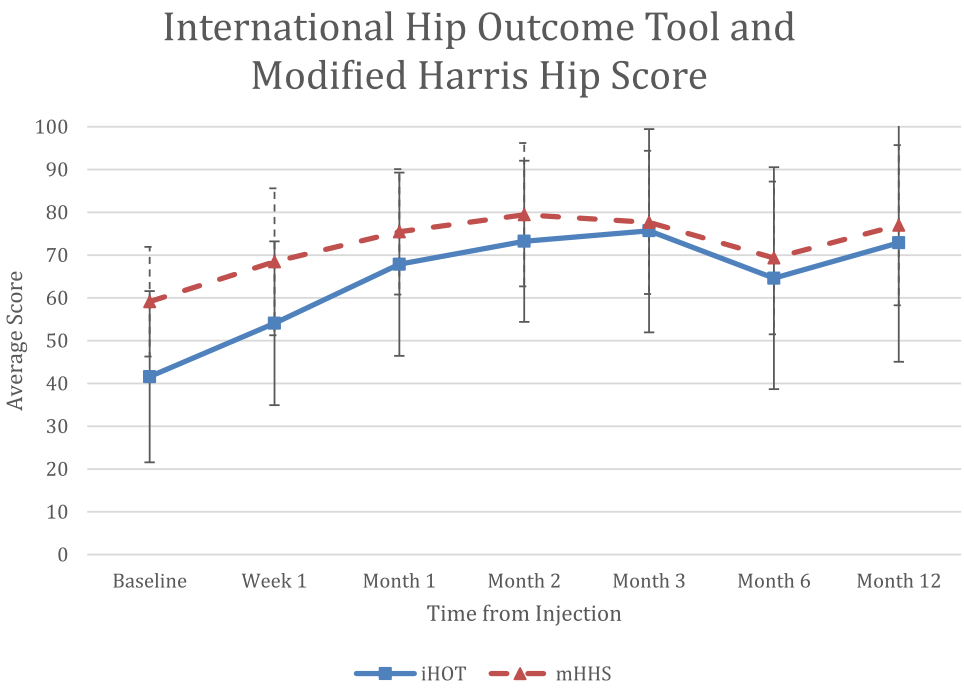

Fig. 1. Mean International Hip Outcome Tool and Modified Harris Hip Scores over all time points.

Discussion

Our study demonstrated a significant improvement in pain and function, as measured by patient-reported outcomes scores, by one-month postinjection using a commercially available ASA. This improvement was maintained at 1 year following injection, and no evidence of worsening joint space narrowing was noted. Furthermore, the mean improvement in PRO scores exceeded MCID for multiple included scores, suggesting a significant clinical improvement. There were no immediate or longer-term adverse effects during the study period. This is consistent with prior pilot studies of ASA injections, which also demonstrated no adverse effects by clinical examination or laboratory evaluation.[11] One patient did withdraw from the study and elect to undergo arthroplasty at two months postinjection. This patient had traveled to our institution to enroll in the study; however, he was dissatisfied with the injection process at the time of treatment. He returned home and saw an arthroplasty surgeon, and subsequently underwent a total hip arthroplasty at two months postinjection. Thus, while this patient does represent a treatment failure, it is important to note that his decision to withdraw from the study was related to a lack of confidence in the treatment and not in worsening pain or other symptoms.

The current AAOS Clinical Practice Guidelines (CPG) support a conservative approach to moderate hip

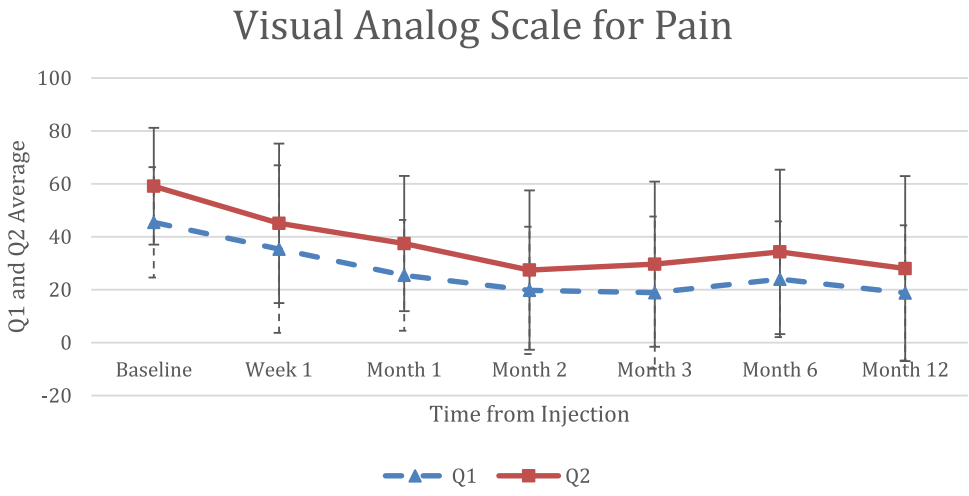

Fig. 2. Mean visual analog scale (VAS) pain scores for Question 1 (average hip pain over the 3 days leading up to the appointment) and Question 2 (maximal pain in the prior 3 days) over all time points.

Table 2. Mean Patient-Reported Outcomes Scores at all Time Points

Time	SANE	iHOT	mHHS	SF-12 M	SF-12 P	VAS Q1	VAS Q2	VAS Q3
Baseline	40.111	41.591	59.111	57.271	40.411	45.459	59.119	
Week 1	58.556	54.071	68.444	58.589	39.935	35.333	45.111	79.889
Month 1	74.111	67.872	75.444	56.91	47.624	25.444	37.444	84.444
Month 2	77.444	73.237	79.444	58.125	49.369	19.778	27.444	88.667
Month 3	77.778	75.699	77.667	59.594	47.674	18.889	29.667	87.333
Month 6	81.111	64.605	69.333	58.843	44.577	23.971	34.308	74.538
Month 12	79.667	72.883	77	56.851	48.471	18.778	28	75.444

iHOT, International Hip Outcome Tool; mHHS, Modified Harris Hip Score; SF-12 M, 12-item Short Form Health Survey (Mental Component); SF-12-P, 12-item Short Form Health Survey (Physical Component); SANE, Single Assessment Numeric Evaluation; VAS, visual analog scale.

osteoarthritis that includes NSAIDs, physical therapy, and intra-articular corticosteroid injections.[26]. However, a recent review of the literature suggests only short-term improvements in symptoms following intra-articular corticosteroid injections to the hip.[19] HA injections may improve pain in patients with OA, but the evidence to support its use in the hip joint is weak.[21] Given the paucity of effective treatments for moderate hip OA, there is interest in orthobiologic solutions, including platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), adipose-derived stem cells, and placental-derived products. However, the literature examining the efficacy of biologic treatments in the hip joint is limited,[20,22,23,27–30] and high-level studies are lacking.

There are multiple prior studies describing the use of amniotic tissue in treatment of osteoarthritis. To date, five preclinical studies have examined the effects of amniotic tissue on a rat model of osteoarthritis. Willet et al used a Lewis rat OA model with medial meniscus transection (MMT) and randomized treatment groups to receive either saline or micronized dehydrated human amniotic / chorionic membrane (μ-dHACM) injections. Additionally, a group of rats that did not undergo MMT received similar injections of saline or μ-dHACM. The authors found that the surgically treated rats that received μ-dHACM had a significant reduction in cartilage damage, including fewer focal defects and less attenuation, as compared to controls.[31] Raines et al. used a similar Lewis rat OA model with MMT and administered injections of saline or human cryopreserved particulate amniotic membrane / umbilical cord (AM/UC) at 50 μg/mL or 100 μg/mL doses. The authors found that at 1 week postinjection, both AM/UC groups had a significant reduction in lesion area compared the control group. Furthermore, the rats that received the high-dose AM/UC injection demonstrated increased cartilage thickness and volume at 1 week, as well as a significant reduction in lesion size at 4 weeks compared with the low-dose AM/UC and saline groups. Finally, rats that received AM/UC injections had significantly higher Osteoarthritis Research Society International (OARSI) histologic joint scores than controls.[32] Marino-Martinez et al induced OA in bilateral knees in a rabbit model and injected human lyophilized AM in one knee and saline into the contralateral knee. They found decreased cartilage damage at 3 and 6 weeks postinjection in the treatment knees as compared to the control knees.[33] Reece et al. administered μ-dHACM injections consisting of two different particle sizes, along with saline injections as a control, to a group of rats following MMT. The authors found that standard μ-dHACM resulted in decreased cartilage degeneration; however, reduced particle size μ-dHACM resulted in increased roughness of cartilage[34]. Finally, Kimmerling et al. created a chemically induced OA model in rat knees and treated with saline, triamcinolone, or ASA in 25 μL or 50 μL doses. On behavioral assays, they noted significant improvements in pain threshold with decreased weight-bearing aversion and swelling in the ASA-treated rats; however, there were no differences in histological grading scores.[35]

To date, there are four published clinical studies describing the use of amniotic products in knee OA, including one randomized controlled trial. The first study, performed by Vines et al., was an open-label pilot study designed to establish safety of intra-articular ASA in human subjects. Six patients received intra-articular injections of 2 mL of ASA, and patients were closely monitored with laboratory studies that included an immunologic panel. The authors noted no clinically significant changes in lab values and reported improved Knee injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee, and KOOS scores at 12 months postinjection.[11] Alden et al. reported a retrospective case series of 100 knees in 82 patients that were treated with μ-dHACM for symptomatic knee osteoarthritis. They noted improved KOOS scores at 6 weeks, 3 months, and 6 months posttreatment, without any severe adverse events during the study period.[36] Castellanos et al. administered AM/UC particulate injections to 20 patients with knee osteoarthritis, and those who did not have a >30% reduction in pain at 6 weeks posttreatment received a second AM/UC injection. They reported a significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index pain and physical function scores at 6, 12, and 24 weeks post-treatment, with improvements exceeding the MCID for the Western Ontario and McMaster Universities

Osteoarthritis Index. Eleven of 20 patients required a second injection, which was correlated with a body mass index of >30kg/m^2. They also reviewed knee MRIs pre- and post-treatment and noted a decrease in severity of bone marrow lesions in 7/19 (37%) of patients at 24 weeks.[37]

In the highest-quality study to date, Farr et al. conducted a multicenter randomized controlled trial of ASA injections for knee OA. They randomized 200 patients to receive ASA, hyaluronic acid (HA), or saline injections, with the subjects blinded to their treatment allocation. Patients completed follow-up visits at 1 week, 6 weeks, 3 months, and 6 months postinjection, with PROs at the 3- and 6-month visits. If patients reported unacceptable pain at the 3-month visit, they were considered treatment failures and withdrawn from the study. They found significant improvements in the EQ-5D-5L pain and anxiety subsets, the KOOS pain, symptoms, and ADL subsets, and the VAS pain scores in the ASA group, compared with the HA group at 3 months. Additionally, the ASA group demonstrated improved KOOS symptoms scores, as compared to the saline group at 3 months. At 6 months posttreatment, the ASA group had significantly greater improvement from baseline in multiple PRO subsets as compared with the HA and saline groups, with a significantly greater responder rate (69.1%) in the ASA group. They concluded that ASA injections produce a clinically meaningful improvement in symptoms of knee OA as compared to HA and saline injections.[12]

Limitations

Our study has several limitations. It is a pilot study with a small sample size and no control group. Furthermore, the study inclusion and exclusion criteria are fairly stringent and may not represent the full cohort of patients eligible for ASA injection treatment for hip OA.

Conclusions

This study demonstrates promising results for relief of pain and improvement in patient-reported outcomes with intra-articular ASA in patients with mild to moderate osteoarthritis of the hip for up to one year, although the exact mechanism of action remains unknown.

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