Journal of Stem Cell Research

Genesis-JSCR-2(2)-21
Volume 2 | Issue 2
Open Access

Pilot Safety Study of an Extracellular Vesicle Isolate Product for Treatment of Osteoarthritis in Combat-Related Injuries: One Year Follow Up

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Citation: East J, Dordevic M. (2021) Pilot Safety Study of an Extracellular Vesicle Isolate Product for Treatment of Osteoarthritis in Combat-Related Injuries: One Year Follow Up. J Stem Cell Res. 2(2):1-10.

Received: June 29, 2021 | **Published:** July 15, 2021

Abstract

Objective: This is the first report on the safety and clinical efficacy of a bone marrow mesenchymal cell extracellular vesicle isolate product (XoFlo™) to treat osteoarthritis (OA).

Design, Setting, and Methods: Thirty-three Navy SEAL veterans were treated with XoFlo for OA of the knee (n=58), shoulder (n=32), elbow (n=16), hip (n=12), ankle (n=8) or wrist (n=6). Four Pain and Motion Indexes were used to evaluate patients' OA.

Results: At 1-year follow-up, the average patient improved 82% in BPI, 77% in ODI, 67% in LEFS, 50% in UEFS, and 77% in QD. All improvements were statistically significant with values of $p<0.001$. Ninety-five percent of the improvement occurred within the first six weeks following the injection and continued through the 1-year follow-up. There were no complications or adverse events, minor or major. No patient was observed to have accelerated OA progression or made clinically worse from the XoFlo injection.

Conclusions: At 1-year follow-up, a 2cc injection per joint of XoFlo appears to be safe and clinically efficacious for the treatment of patients with at least Grade 2 changes of OA utilizing the Kellgren-Lawrence scale. These patients will continue to be followed for at least two years.

Keywords

Extracellular vesicles; Osteoarthritis; Bone marrow; Mesenchymal stem cells

Introduction

What causes the pain in osteoarthritis (OA)? The correlation between the imaging studies and reported pain is low. Articular cartilage has no direct nerve or blood supply. Without direct innervation, articular cartilage itself is not capable of directly generating pain [1]. The synovium and joint capsule are richly innervated and likely the primary source of pain in patients with OA [2]. The synovial reaction in OA includes synovial hyperplasia, fibrosis, thickening of the synovial capsule, activated synoviocytes (primarily mesenchymal stem cells), and lymphocytic T and B-cell infiltrates [3-7]. The synovium is of obvious relevance as the most densely innervated structure in the joint. Irritation of sensory nerve endings within the synovium is due to the release of prostaglandins, leukotrienes, proteinases, neuropeptides, and cytokines. Pro-inflammatory cytokines including IL1-β, IL6, and IL8, along with tumor necrosis factor, are known mediators of chronic inflammation and associated pain in OA [8]. A semi-quantitative measure of infrapatellar fat pad synovitis is associated with pain severity. Any decrease in synovitis is associated with a decrease in osteoarthritis pain severity [9].

OA is the most common chronic disease in the United States of America. In both cadaveric and radiographic studies, osteoarthritis has been demonstrated to affect up to 55 million patients greater than 60 years old [10]. It is projected that over the next decade, approximately 5,000 people every day will turn 65 in the United States, increasing the current population of this age group by 18 million people [11]. Patients with OA in the lower extremities have pain, crepitus, loss of motion, and decreased ability to weight bear or ambulate. In the upper extremities, symptoms are similar. For example, the patient experiences difficulty placing their hand in a desired position in space. Limiting the ability to move the upper extremity can severely impair certain activities of daily living.

Current options for the treatment of OA are limited. The nonsurgical treatments for OA, according to the American Academy of Orthopedic Surgeons (AAOS), include weight loss, gentle exercise, and the use of non-steroidal anti-inflammatory medications. The surgical treatment for OA is total joint arthroplasty (TJA) [12]. The AAOS does not recommend arthroscopy or the use of hyaluronic acid injections for the treatment of OA [13-17]. There is a huge void between non-operative and operative options for patients suffering pain and impairments from OA. A systematic review of 14 studies that reported pain results following total knee arthroplasty (TKA) demonstrated that between 10% to 34% of patients report chronic pain despite getting their knee replaced [18]. Another large study looked at 1217 consecutive patients who had TKA between 2006 and 2008 and filled out validated quality of life and functional questionnaires. The authors found that 1 in 5 people was dissatisfied with their knee replacement results [19]. A recent study that analyzed government-collected data from TKA patients found that the current overall practice of TKA is not cost-effective. The use of TKA in younger people results in higher

rates of patients who are dissatisfied with the results. When used in older patients with lower expectations, TKA has higher patient satisfaction. Hence, the move towards replacing younger knees has made TKA overall not cost-effective [20].

Currently, the field of regenerative medicine is utilizing first-generation cellular therapies to treat OA [21]. While living mesenchymal stem cells have been shown to alleviate inflammation and pain in OA preclinical models, these autologous cell-based treatments rely upon obtaining relatively rare and highly variable concentrations of stem and progenitor cells from bone marrow or adipose tissues [22]. Stem cell concentrations in these tissues have been reported to decrease with age. Unfortunately, most patients seeking OA treatment are older, and age-related comorbidities and the relatively high cost of these first-generation therapeutics further confound justification of their use. Second-generation regenerative therapeutics have now been developed to address prior generation deficiencies. It is now generally accepted that the majority of the therapeutic benefit of mesenchymal stem/stromal (MSC) cell therapies lies within the protein and vesicle populations secreted by these cells [23,24]. Use of these cell "secretome" based therapies enables the efficacy of cell therapies to be delivered without worrying about cell survival or safety issues associated with their delivery. Here, we describe the use of one such second-generation therapeutic, referred to as an extracellular vesicle isolate product (EVIP). The cells used in its generation were derived from bone marrow stromal cells of a young, healthy, adult female donor tested to be free of any adventitious agents. The donor's MSC cells used to produce the EVIP were fully characterized to meet ISSCR definitions for mesenchymal stem cells and have a master record filed with the FDA. The EVIP was manufactured using cGMP methods which ensure its quality and safety. The growth factors and extracellular vesicles, including exosomes in the EVIP, are created with a proprietary method to maximize the concentration of these materials. EVIP concentration and GF biomolecule content are evaluated for each production batch to verify that the vials meet product specifications [25].

This physician-initiated IRB-approved study's primary objective was to determine safety, followed by the clinical efficacy of intra-articular injection of the EVIP (XoFlo) to treat combat-related OA in Navy SEAL veterans.

Materials and Methods

Study design

This study was a prospective, open-label, non-randomized IRB-approved pilot safety study of a single 2mL XoFlo injection for the treatment of OA in up to 4 joints. Total number of different joints injected at each location was as follows: knee (n=58), shoulder (n=32), elbow (n=16), hip (n=12), ankle (n=8), or wrist (n=6). The treatment was offered free to study participants. The study protocol for the treatment was approved by an IRB (Institute of Regenerative and Cellular Medicine, Protocol number: APRM-OA-001, IRB approval number: IRCM-2019-226). All patients were counseled and consented as per established IRB requirements. The study was performed at a single center.

All patients were Navy SEAL veterans (n=33) with a primary complaint consistent with combat-related

injuries resulting in moderate to severe knee, shoulder, elbow, hip, ankle, or wrist OA. Inclusion criteria required patients to have at least grade-2 changes utilizing the Kellgren-Lawrence scale for OA [26]. Every patient had four joints injected (n=132). Patients underwent a pre-injection medical history and physical examination of all their OA joints. Every Navy SEAL was also evaluated with a Brief Pain Inventory (BPI), Oswestry Disability Index (ODI), Lower Extremity Functional Scale (LEFS), Upper Extremity Functional Scale (UEFS), and a QuickDash Scale (QD). Follow-up evaluations were obtained at 12 hours, 24 hours, 48 hours, 2 weeks, 6 weeks, 3 months, and 6 months and 1 year. Two-year follow-ups are planned.

OA was defined by pain and stiffness in the joint, worsened by exercise, and decreased range of motion. Patients treated for OA had radiographs of the joint to rate them 2, 3, or 4 on the Kellgren-Lawrence scale (K-L scale) [26].

Therapeutic Description

XoFlo (Direct Biologics LLC, Austin, TX) is composed of secreted proteins and extracellular vesicles, primarily exosomes which are obtained from bone marrow mesenchymal stem/stromal cells. A CLIA licensed laboratory performed the donor bone marrow screening and testing for the presence of any virus or infective agents. The BM-MSCs have been fully characterized as CD90+, CD166+, CD45- MSCs, and have a master file recorded with the FDA. XoFlo contains hundreds of different molecular communication molecules (proteins and RNA) within the more than 30 billion extracellular vesicles per milliliter. XoFlo sterilization is achieved through 0.2µm ultrafiltration, not radiation, using cGMP manufacturing methods to ensure the highest possible safety profile. The product is stored frozen (≤0°C) to ensure bioactivity is maintained. It is thawed to room temperature prior to use. As part of the lot release specifications, XoFlo is evaluated for the presence of specific growth factors, extracellular vesicle size and concentration, sterility, and particle size distribution to verify that every lot meets product release specifications.

Patient Demographics

The number of patients undergoing treatment for knee, shoulder, elbow, hip, ankle, and wrist, along with average BMI and average age, is shown in (Table 1).

	Average	**Range**
Body Mass Index	28.5	23-35
Age	48.8 years	36-70 years
Population size = 33	31 Males	2 Females

Table 1: Description of study patient demographics.

Radiographic Analysis

Every patient underwent a standing AP and lateral radiograph of all OA lower extremity joints and a non-weight bearing AP and lateral radiograph of all OA upper extremity joints just prior to the treatment. Treatment site distribution is described in (Table 2).

	K-L 2	K-L 3	K-L 4	Total Injected
Knee	44	12	2	58
Shoulder	29	3	0	32
Elbow	14	2	0	16
Hip	9	3	0	12
Ankle	5	3	0	8

Table 2: Kellgren-Lawrence (K-L) description and total number of each joint injected.

Injection Technique

All joint injections were performed by the principal investigator utilizing an aseptic technique with betadine skin prep. Under fluoroscopic guidance, a 22-gauge needle was placed into the arthritic joint, and the needle position was verified. Needle placement was verified under fluoroscopic control as 2 mL of thawed XoFlo was placed into the joint. The entire procedure of injecting a maximum of four joints per patient required 30 minutes on average. Patients were not prescribed any pain medications. They were placed on restricted physical activity for 2 weeks following the procedure, which included an immediate passive, low-resistance range of motion was encouraged immediately. After two weeks, patients were allowed to return to full activity.

Statistical Tests

Univariable data comparisons were analyzed by a two-tailed Student's t-test with a 95% confidence interval (α=0.05. Microsoft Excel).

Results

Every patient was evaluated immediately after the injection and then contacted for follow-up 12 hours, 24 hours, 48 hours, and at 2 weeks, 6 weeks, 3 months, 6 months, and 1 year to survey for and discuss any possible adverse side effects from the XoFlo injection and to obtain clinical evaluation data. One-year follow-up data was obtained from all but one Navy Seal (97% follow-up). Reported adverse events included increased backache for 24 hours in one patient, increased joint pain in the injected joint for 24 hours in four patients, a change in bowel habits in one patient for 24 hours, and disturbed sleep for two nights in one patient. No patient was determined to have become clinically worse from the injections. One year after the XoFlo administration, the average patient experienced statistically improved outcome measures, as shown in (x 1).

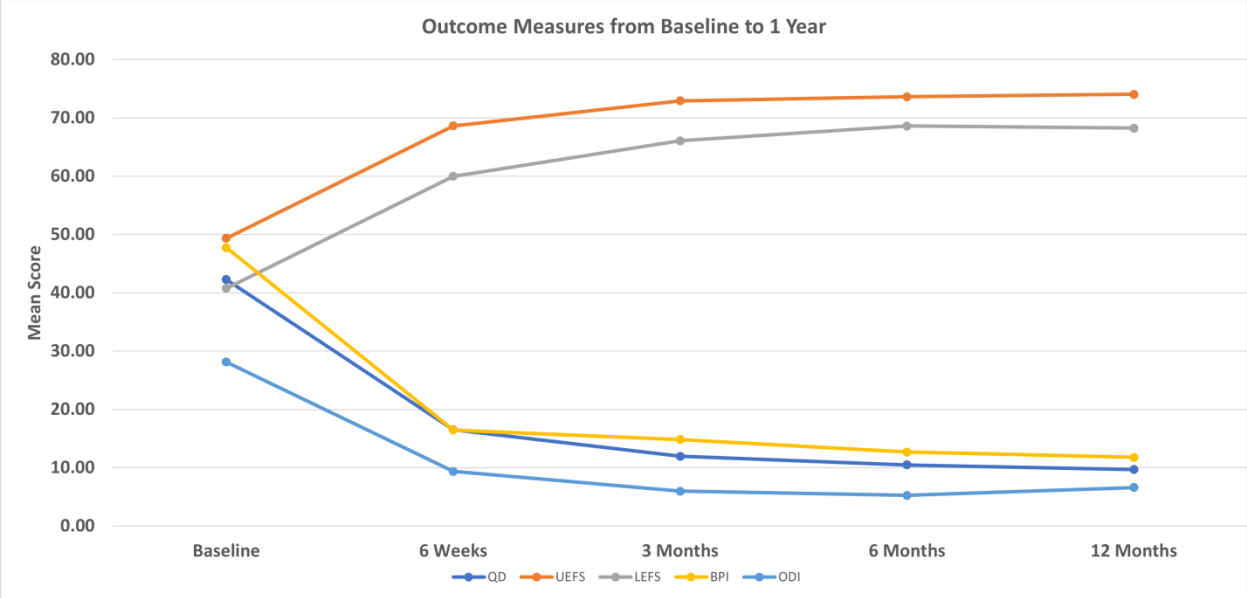

Figure 1: Patient progress versus time after EVIP injection into the Knee, Shoulder, Elbow, Hip, Ankle, Wrist (n=132) QD = QuickDASH, a measure of function with lower scores being ideal, UEFS= higher number indicates better function, LEFS= Higher scores indicate better function, Brief Pain Inventory (BPI) = higher scores indicate higher pain, ODI =Lower score indicates higher function. All p values were <0.001 for all timepoints versus baseline measurement comparisons.

The average clinical improvement for each pain and functionality test at each time interval is described in (Table 3).

	6 Weeks	3 Month	6 Month	1 year
BPI	65.52%	68.97%	73.48%	81.82%
ODI	66.77%	78.77%	81.36%	76.55%
UEFS	39.02%	47.76%	49.11%	49.97%
LEFS	47.21%	62.08%	68.33%	67.45%
QD	60.89%	71.76%	75.20%	77.11%

Table 3: Percentage improvement from baseline at each follow-up period.

The actual score for each of the five tests at 6 weeks, 3 months, 6 months, and 1-year intervals is presented in (Table 4). A patient self-perception assessment was performed. The overall amount of clinical improvement each patient opined when asked, "How much better does each of your specific joints that were injected feel after 6 weeks and1 Year" is detailed in (Table 5).

	Baseline	6 Weeks	3 Month	6 Month	1 year
BPI	47.76	16.47	14.82	12.67	11.78
ODI	28.12	9.34	5.97	5.24	6.59
UEFS	49.36	68.63	72.94	73.61	74.03
LEFS	40.76	60.00	66.06	68.61	68.25
QD	42.27	16.53	11.94	10.48	9.68

Table 4: Percentage Improvement from Baseline at Each Follow-up Period. Mean value at each timepoint for each test versus baseline yielded p-value <0.001 by paired t test analysis.

	LT. KNEE	RT. Knee	LT. Shld	RT. Shld	LT. Hip	RT. Hip	LT. Ankle	RT. Ankle	LT. Elbow	RT. Elbow	LT. Wrist	RT. Wrist	RT. Thumb
6 Weeks	38%	38%	51%	42%	42%	32%	50%	70%	41%	20%	0%	20%	0.43%
1 YEAR	59%	60%	65%	64%	50%	38%	10%	70%	64%	52%	0%	40%	0.75%

Table 5: Self-reported average improvement of each joint in terms of pain and function six weeks and 1 Year after a single injection of 2cc of XoFlo.

There is a slight difference in the 6-month results reported in this paper versus the 6-month results reported in our previous paper [34]. This is due to a reanalysis of the raw data and noting slight errors with how the data in the 6-month paper was calculated. None of this discrepancy changed any of the statistical analysis or overall results.

Discussion

This preliminary investigator-led IRB study of the second generation regenerative therapeutic EVIP product (XoFlo) to treat OS successfully demonstrates safety and secondarily provides evidence of clinical efficacy for treatment of OA in the knee, shoulder, elbow, hip, ankle, or wrist with a single 2cc injection. One-year post-XoFlo injection, the average patient improved 82% in BPI, 77% in ODI, 67% in LEFS, 50% in UEFS, and 77% in QD. All improvements were to a value of $p<0.001$. Most of the improvement (95%) occurred within the first 6 weeks post-treatment, indicating rapid and sustained resolution of OA-associated pain. There were no complications or serious adverse events, minor or major, and no patient was made worse from the therapeutic injection. Four patients reported no significant improvement from the injection. One patient developed cervical radiculopathy, and one developed lumbar radiculopathy that over-shadowed their OA symptoms in filling out the follow-up

forms. Two patients did not improve clinically after the injection for unknown reasons. The 100% safety profile of XoFlo (no product-associated adverse events) seen in this study is consistent with another recently reported clinical trial of its use to treat severe COVID-ARDS.[27] Given the obvious advantage of delivering the smaller-sized EVs (approximately 1000 times smaller than MSCs themselves), the efficacy of MSC therapy is now able to be administered without the whole cell-associated safety risks, in particular, further exacerbation of the ongoing chronic inflammation within the OA joints.

The injected diarthrodial joints all have a synovial lining and a joint capsule. The synovial capsule contains numerous synovial MSCs (more abundant per unit volume than bone marrow or adipose). During the development of OA, pro-inflammatory and catabolic factors are produced by these synovial MSCs. This creates a chronically inflamed, painful, and degenerative joint environment. Delivering the MSCs themselves risks the cells being reprogrammed by these surrounding synovial MSC cells and causing them to, in turn, also produce inflammatory signals. Delivering the extracellular vesicles from MSCs optimized to generate a healing response alleviates this potential safety issue since the content of the EV therapeutic is static and not reprogrammable by the host cells.

The observed efficacy of XoFlo to resolve OA symptoms of the patients in this study is consistent with both preclinical and emerging clinical evidence of extracellular vesicles from bone marrow MSCs to contain numerous paracrine immunomodulatory molecules. Exosome growth factors and RNA content have been shown *in vitro* to alter immune cell proliferation, cytokine expression, and chemotaxis [23,24]. Additionally, the small size and large number of EVs (at least 30 billion exosomes per cc) within XoFlo enables delivery of a more efficacious dose compared to BMC and PRP into the OA joint without the potential of inflammation due to cell death and clearance observed in the first-generation cell therapeutics.

The multi-faceted capacity of EV-based therapeutics such as XoFlo provides a clear therapeutic advantage. XoFlo's complex biochemistry provides a multi-targeted approach to treat OA. XoFlo's anti-inflammatory protein factors can immediately interact with leukocytes and synoviocytes to decrease their pro-inflammatory activity within the OA joint. Concurrently, the XoFlo's EVs deliver their mRNA and miRNA content into the recipient cells, which are then translated or used to inhibit pro-inflammatory protein production. This provides a power trifecta of ways by which the inflammation can be resolved and by which pain is reduced.

It should be noted that while this study provides compelling evidence of EV-based second-generation regenerative medicine to address osteoarthritis, the limitations of the study should be considered. The study's limitations include the small number of patients and the relatively short 1-year follow-up. The study was not randomized or double-blinded with a control group. Additionally, this population of retired Navy SEALS are conditioned soldiers that may have a higher tolerance to pain than the general population, which could skew the subjective pain reduction results. Nevertheless, the results of this study indicate it may be reasonable to consider an injection of acellular allogeneic bone marrow derived XoFlo into any joint with OA prior to a patient undergoing joint arthroplasty.

Acknowledgments

The authors would like to acknowledge the Navy SEAL veterans for their keen interest in exosome-based therapy for the treatment of their combat-related joint injuries.

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