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Pilot Study

Safety and Efficacy of Intravenous ExoFlo in the Treatment of Complex Regional Pain Syndrome

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Conflict of interest: Dr. Paicius is a consultant to Abbott, Mesoblast, Direct Biologics, Vertos, and Spinal Simplicity; Dr. Lee is a consultant to Abbott, Medtronic, Mainstay Medical, and Petal Surgical; Dr. White is director of Clinical Research at SC Spine & Sport; Ms. Smith is coordinator of Clinical Research at SC Spine & Sport; Mrs. Sasha Speare is a Nurse Practitioner at SC Spine & Sport. Dr. Lightner is the Chief Medical Officer at Direct Biologics, Dr. Ransom is Senior Medical Writer at Direct Biologics.

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Background: Complex regional pain syndrome (CRPS) is an extremely painful disorder driven primarily by inflammation.

Objectives: We hypothesized that the immunomodulatory biologic, ExoFlo™, composed of bone marrow mesenchymal stem cell-derived extracellular vesicles, could be safely administered to CRPS patients and alleviate symptoms.

Study Design: Ten patients received 2 intravenous (IV) infusions, each containing 15 mL ExoFlo, on day one and day 4. A series of tests were performed at baseline (day 0, prior to infusion), week one, and months one, 3, and 6 after the second infusion.

Setting: All patients were treated in one of 2 outpatient pain management clinics in Orange County, CA.

Methods: Testing for clinical improvement included: visual analog scale of pain, brief pain inventory, 36-item short-form questionnaire, range of motion analysis, and jamar dynamometer testing.

Results: No serious adverse events related to ExoFlo treatment occurred. Statistically significant improvements in pain and motion assessments occurred across the patient pool.

Limitations: This study was limited by its patient number enrolled (10), it lacked a control arm, and one patient who dropped out of the study.

Conclusions: IV delivery of ExoFlo appears safe in patients with CRPS. In addition, ExoFlo exhibited efficacy in addressing CRPS symptoms. Given the lack of effective and safe treatments available to CRPS patients, these results suggest that further studies are warranted to explore and validate this potential treatment for CRPS.

Key words: Complex regional pain syndrome (CRPS), mesenchymal stem cell, extracellular vesicle, ExoFlo

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Complex regional pain syndrome (CRPS) is a painful and disabling disorder that can occur in an extremity after a major trauma or surgery, or may develop spontaneously (1,2). CRPS is a multisystem disease that incorporates different elements from the autonomic nervous system; however, the largest driver of symptomatology is inflammation. Currently, there is no single proven effective treatment modality for patients suffering from CRPS identified from clinical trials.

ExoFloTM has been used to treat multiple inflammatory disorders, including osteoarthritis, androgenic alopecia (male pattern baldness), evidence of solid abdominal organ rejection (Lightner, submitted), and chronic obstructive pulmonary disease across several investigator-initiated studies and patient series. In addition, phase 2 randomized control data found ExoFlo significantly reduced the morbidity and mortality associated with COVID-19-induced acute respiratory distress syndrome (3-9).

ExoFlo is a human bone marrow mesenchymal stem (bmMSC) cell-derived extracellular vesicle (EV) isolate product. Its therapeutic mechanism of action involves normal cell-to-cell communication functions as the EVs contain over 1,000 growth factors, cytokines, chemokines, messenger RNAs, and microRNAs that are secreted from MSCs, all of which regulate cellular activation and gene regulation. The ExoFlo EVs are therefore harvested paracrine mediators of tissue inflammation, regeneration, and repair, and may have the capability to reduce the proinflammatory cell signals in patients with CRPS.

When delivered intravenously, ExoFlo successfully reduced the severity of a multitude of autoimmune and inflammatory diseases. This prospective pilot study sought to analyze the safety of IV ExoFlo in patients with CRPS, and secondarily, assess patient improvement in pain levels, functionality, and emotional and behavioral health.

Methods

Study Design

Between October 8, 2021 and June 21, 2022, 10 patients with CRPS, who met all inclusion and exclusion criteria, received 15 mL of bmMSC EVs via an IV route over 30 minutes on day one and day 4 (2 doses). ExoFlo (15 mL) was mixed with 85 mL of normal saline and the total 100 mL mixture was a IV dministered. This dosing protocol was selected as it was shown to be safe and effective in a previous study (8). Measurements were taken at baseline prior to any dose, one week after the second dose, and one month, 3 months, and 6 months after the second dose. During the trial, one patient was lost to follow-up and their information was excluded from the study results and analyses.

Measurements and Statistical Analysis

Assessments performed included the visual analog scale (VAS) of pain, the brief pain inventory (BPI), the 36-item short-form (SF-36) questionnaire, the range of motion (ROM) analysis, and the Jamar dynamometer test (10-13). All results were subjected to one-way analysis of variance, using the Geisser-Greenhouse correction, followed by the Dunnett multiple comparison test using GraphPad Prism 9.5.1.

Enrollment

Patients were recruited from the primary investigator's practice and affiliated medical groups. As CRPS affects more women than men (ratio range of 2.3-4:1), women were well represented (Table 1) (1,2,14). In this pilot study, diversity was not addressed.

Inclusion Criteria

Enrolled patients had to have primary complaints of chronic intractable pain of the upper or lower extremity secondary to CRPS. Other possible etiologies of pain had to be ruled out first prior to being enrolled in the study. Patients had to have a minimum VAS score > 6 in the greatest area of pain and failed to achieve adequate pain relief from at least 2 prior pharmacologic or interventional treatments. Patient age > 22 years old. The patients had stable neurologic function in the past 30 days. In the investigator's opinion, the patient had to be psychologically appropriate. Patients were able to provide written and informed consent and were agreeable to the follow-up schedule and protocol. Worker's compensation enrollees had to be of permanent and stationary status.

Exclusion Criteria

The patient has exhibited escalating or changing pain conditions in the past 30 days. Patients currently involved in medical litigation were excluded. Patients having had corticosteroid therapy in the past 30 days. Patient's pain medication dosage is not stable for 30 days. Patients with cognitive, physical, or sensory impairment that in the opinion of the investigator may limit their reporting capabilities. Patients that had an

active systemic infection. The patient had significant medical comorbidity, in the opinion of the investigator. The patient participated in another clinical investigation in the past 30 days. Diagnosed with cancer in the past 2 years. The patient was pregnant, nursing, or plans to become pregnant. Worker's Compensation patients who have not reached maximum medical benefit were excluded from the study.

Results

Patient Demographics

Seven of the 10 patients were women, consistent with the 3-fold higher incidence in women compared to men (Table 1) (15). The age range of patients was 22-72 years old. The average age was 55.8 years, also consistent with the prevalence of CRPS in older individuals (15). One patient was lost to follow-up.

Table 1. *Gender and age demographics of patients. *Patient lost to follow-up.*

Patient Identifier	Age	Gender
SCSS-CRPS-001*	80	M
SCSS-CRPS-002	47	W
SCSS-CRPS-003	42	W
SCSS-CRPS-004	56	W
SCSS-CRPS-005	61	M
SCSS-CRPS-006	71	W
SCSS-CRPS-007	63	W
SCSS-CRPS-008	48	W
SCSS-CRPS-009	40	M
SCSS-CRPS-010	50	W

Primary Endpoints

Of the 10 patients enrolled in the study, none reported any serious adverse events (SAEs) related to treatment or investigational product. Two patients contracted COVID-19 during the study, but remained enrolled and fully participated. One patient developed congestive heart failure, although this was ascribed to preexisting comorbidities rather than the treatment protocol or investigational product.

Secondary Endpoints

At baseline, the average VAS score in the 9 patients analyzed was 7.78 (Fig. 1). The average VAS was 5.56, 5.5, and 4.89 at one, 3, and 6 months, respectively. As a group, statistically significant improvements were observed at all follow-up time points. At the onemonth follow-up, one patient reported ≥ 50% VAS reduction. At the 3-month follow-up, 3 patients reported ≥ 50% VAS reduction. Amongst the 5 patients remaining, 4 patients reported ≥ 50% VAS reduction at the 6-month mark. The remaining patient reported improvements in VAS to a lesser degree.

BPI pain scores were separated into Pain Interference and Pain Severity scores (Fig. 2). Trends toward improvement were observed during the study, but statistical significance was only apparent for Pain Interference at the 3-month point. Average baseline values for both were 6.99 and 7.61 for severity and interference, respectively. There were further reductions to 5.55 and 5.66, 4.90 and 4.59, and 4.94 and 5.16 at one, 3, and 6 months, respectively, when compared to baseline.

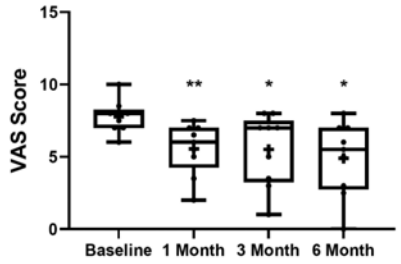

Fig. 1. *Box and whisker plot of mean VAS pain assessment results over the 6-month study period. The box identifies the 25th and 75th percentiles with the interior line identifying the median value and the '+' identifying the mean value. Upper and lower whisker lines denote maximal and minimal data values, respectively. Individual data points are displayed as single dots (·). (*P < 0.05; **P < 0.01); VAS, Visual Analog Scale.*

There was a decrease of 29.23% and 32.22% in pain with respect to severity and interference at 6 months.

When calculating SF-36 scores, significant improvements were observed at the 3- and 6-month follow-ups for pain, energy/fatigue, and social functioning metrics (Fig. 3). Significant improvements were apparent at the 3-month point for physical functioning and limitations physical categories. Trends for improvement were seen for limitations in emotional and emotional well-being during the study, but these did not reach significance. Little change was observed for the general health category.

ROM evaluation was dependent on the anatomic location of the affected joint. Data points were collected at baseline, the 3- and 6-month marks (Fig. 4). Values were recorded in degrees and then compared to normal rotational degrees of a normal joint. Of the 9 patients in the population, 7 had impaired ROM in their CRPS-affected limb when compared to normal.

On average, patients had an 83.37% increase in their ROM of their affected limb, and had 82% of their normal ROM at the end of the study (Table 2).

Of the 9 patients in the study, only 3 had grip strength affected in the upper extremity (Jamar test). Overall, grip strength improved with respect to the

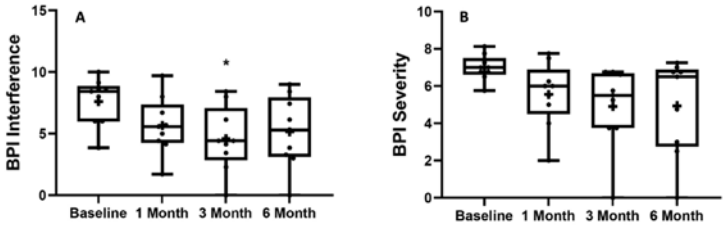

Fig. 2. *BPI (A, pain interference and B, pain severity) assessment results over the 6-month study period. Plots and P value markers are as in Fig. 1. BPI, Brief Pain Index.*

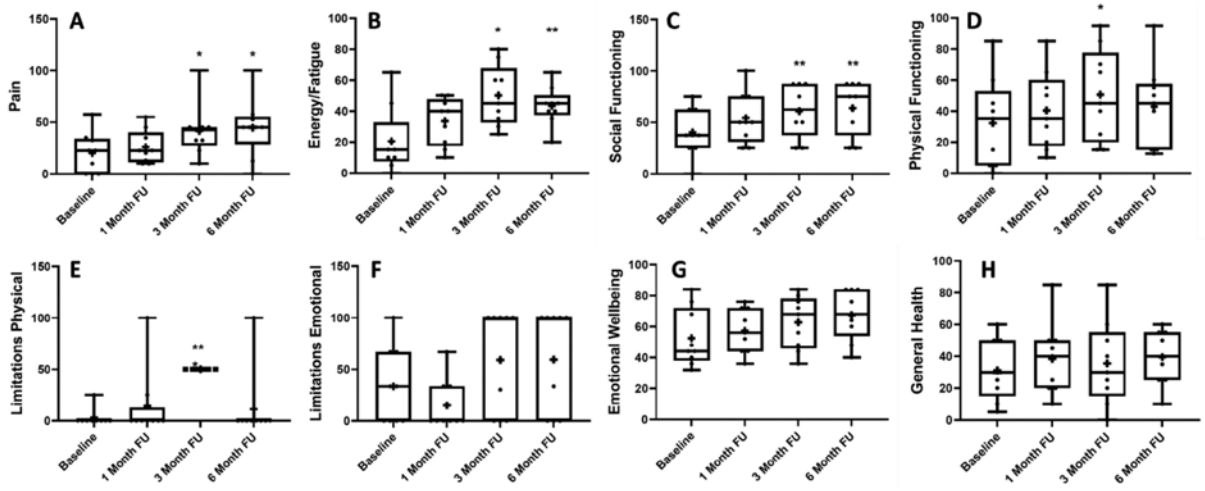

Fig. 3. *SF-36 assessment results, by category, over the 6-month study period. Categories are A) pain, B) energy/fatigue, C) social functioning, D) physical functioning, E) limitations physical, F) limitations emotional, G) emotional well-being, and H) general health. Plots and P value markers are as in Fig. 1. SF-36, 36-Item Short-Form.*

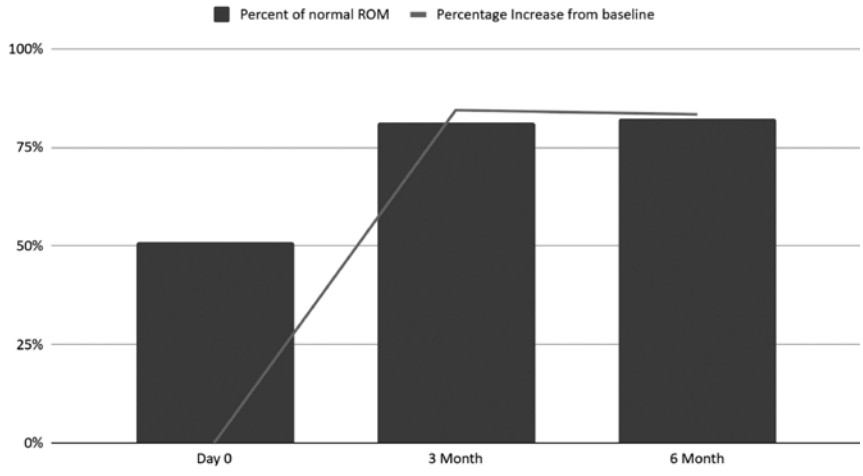

Fig. 4. *ROM assessment results over the 6-month study period. ROM, range of motion.*

CRPS-affected side, as well as their unaffected control side (Fig. 5). All patients evaluated had equalization of grip strength after 6 months (Table 3).

Discussion

This pilot study sought to assess the safety of ExoFlo in CRPS patients as a primary endpoint, and, as a secondary goal, to explore its potential for fostering improvements in symptoms associated with CRPS. The primary endpoint was met with no reported SAEs throughout the entire 6-month follow-up period. During this study, 2 patients contracted COVID-19 and reported adverse complications regarding their CRPS diagnosis. One patient contracted COVID-19 between the 3- and 6-month marks, and had extremity pain, color change, and swelling return to baseline. Another patient contracted COVID-19 between the one- and 3-month marks, and stated their neurogenic pain flare-ups had resumed, but overall had a decrease in swelling, and burning sensations as well as increased energy levels. At the 6-month mark, the same patient reported that the burning pain was completely gone. One of the patients who contracted COVID-19 during the study reported no change in pain interference or pain severity on the BPI scale. This brings into question whether or not COVID-19 had an interference with the therapeutic effects of this patient's ExoFlo therapy. Between the one- and 3-month marks, one patient was diagnosed with congestive heart failure, although, it is believed this patient did not develop congestive heart failure as a result of the ExoFlo treatment, rather their prior comorbidities and lifestyle habits. The same patient reported a 50% decrease in pain, and overall had an increase in ROM.

Functional assessments uniformly showed positive patient responses to the treatment. Comparison of VAS scores from baseline to 6 months showed, on average, all patients had an improvement in pain. Overall, there was almost a 50% decrease in pain by the end of the study. One patient reported no pain at the end of the study, when at baseline their pain was rated at a 7/10. One patient reported no change in pain at baseline to 6 months, but had a decrease in pain at the one-month and 3-month follow-ups.

When evaluating BPI scores, on average, all patients had a decrease in pain severity and pain interference. The greatest improvement was seen with regard to pain interference in daily life, with an overall 32% decrease in pain interference by the end of the study. One patient reported no pain interference or severity at 3 months and at the end of the 6-month trial. All but 2 patients reported a decrease in pain severity throughout the trial, and the remaining 2 patients reported no change. All but one patient reported a decrease in pain interference at the end of the trial, and their pain levels did not increase, but remained the same. The same patient reported no change in pain severity or pain interference when compared to baseline. This same patient contracted COVID-19 during the one- and 3-month marks of the study. Overall, most of the observed benefit was reported by the 3-month mark, with a slight rebound in pain interference at the conclusion of the 6-month trial.

Evaluation of SF-36 scores showed all patients showed improvement at the end of the 6-month clinical trial when compared to original baseline scores. The most significant improvements were seen in pain, energy levels, social functioning, and physical functioning, with a positive trend in emotional well-being, and the least significant improvements were seen in general health. Out of the 9 patients in this study, 5 reported zero emotional limitations by the end of the 6-month study. One patient reported zero physical limitations and zero limitations with regard to pain by the 6-month mark, as well.

Table 2. *ROM assessment results over the 6-month study period.*

ROM Average	Day 0	3 Mo	6 Mo
Percent of Normal ROM	51%	81%	82%
Percentage Increase from Baseline	0%	84.41%	83.37%

Abbreviation: ROM, range of motion.

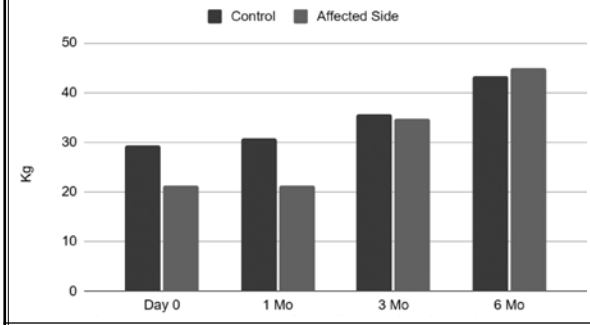

Fig. 5. *Jamar dynamometer test assessment results over the 6-month study period.*

Table 3. *Jamar dynamometer test assessment results over the 6-month study period.*

Average (kg)	Day 0	1 Mo	3 Mo	6 Mo
Control	29.33	30.67	35.67	43.33
Affected Side	21.33	21.33	34.67	45

On average, the percent of normal ROM in the affected CRPS joint was 51% when compared to the normal anatomical degrees of rotation of an unafflicted limb. By the 3-month mark, the percent of normal ROM was 81%, with an increase from baseline of 84.41%. At the 6-month mark, the percent of normal ROM increased to 82%, with a total increase of 83.37% from baseline (Table 2). Two patients had complete restoration of normal ROM in their CRPS-affected joint at the 6-month mark. Most of the observed benefit in ROM was observed by the 3-month mark. On average, all patients had an increase in ROM at 6 months when compared to baseline. There was one patient who received no benefit from therapy with regards to ROM in one movement, extension of their shoulder, but had an increase in ROM of flexion, as well as abduction with pronation of the same joint. No patients reported a decrease in ROM throughout the study.

At baseline, the average grip strength of the unaffected control limb was measured at 29.33 kg, while the CRPS-affected limb was 21.33 kg. At the one-month mark, there was an increase to 30.66 kg and 21.33 kg with respect to the control and CRPS-afflicted side. At the 3-month mark, there was an increase to 35.67 kg and 34.67 kg, respectively. At the 6-month mark, there was an increase to 43.33 kg and 45 kg, respectively. Overall, grip strength increased by 147.73% of the control limb, and increased 210.94% of the affected CRPS limb. All patients had an increase in grip strength on their control side, as well as their CRPS-affected side. One patient had their CRPS-affected side become stronger than their control side at 6 months. These subjective and objective findings were consistent with reported improvements in limb and joint ROM, and decreased sudomotor changes, edema, allodynia, and hyperesthesia.

Two patients reported little to no hair growth on their CRPS-affected limb prior to the study. Both patients had an increase in hair growth during the study. One patient reported that by the end of the study, hair growth on the affected limb had returned to normal when compared to the unaffected limb. Of the 2 patients with reported hair growth deficits, one also had involvement of their nails. At the 6-month mark, they reported an overall increase in nail growth rate when compared to before the study began.

Additionally, one patient had their CRPS symptoms and pain completely resolved. They reported normalization of ROM, complete resolution of pain, no pain interference in daily life, and no pain interference with physical functioning, physical limitations, emotional limitations, decrease in energy, emotional well-being, social functioning, and general health.

The results of this preliminary study are limited by the small patient number enrolled, the lack of a control arm, and the one patient who dropped out of the study.

Conclusions

ExoFlo appeared safe and well tolerated in patients with CRPS. On average, all patients made improvements following the delivery of ExFlo. It is our belief that a study with a larger patient population, as well as different parameters for administration of Exoflo, should be conducted especially as this is a disease that has few successful treatment options.

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