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Brief communication

Long-term follow-up after autologous adipose-derived stromal vascular fraction injection into fingers in systemic sclerosis patients

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ABSTRACT

Introduction. – Hand involvement confers a substantial handicap in work and daily activities in patients with Systemic sclerosis (SSc). Autologous adipose-derived stromal vascular fraction is as an easily accessible source of cells with regenerative effects. We previously performed a phase I open-label clinical trial (NTC01813279) assessing the safety of subcutaneous injection of autologous adipose-derived stromal vascular fraction. Six and 12-month data have been reported. As patients were followed in our medical centre, we report their longer-term outcome beyond the end of the trial.
Patients and method. – Twelve females, mean age 54.5 ± 10.3 years, initially enrolled in the clinical trial were assessed during a scheduled medical care, which took place between 22 and 30 months after treatment.
Results. – Multiple patient-reported outcomes showed sustained improvement, in comparison with the assessment performed just before surgery: 62.5% in the Cochin Hand Function Scale, 51.1% in the Scleroderma Health Assessment Questionnaire, 33.1% in hand pain, and 88.3% in the Raynaud Condition Score. A decrease in the number of digital ulcers number was noted. Mobility, strength and fibrosis of the hand also showed improvement. None of the 8 patients who had previously received iloprost infusion required new infusion.
Conclusion. – Despite the limits of an open label study, the data are in favour of the long-term safety of the adipose-derived stromal vascular fraction injection. Two randomized double blind, placebo-controlled trials of this therapeutic agent are ongoing in the USA (NCT02396238) and in France (NCT02558543) and will help determine the place of this innovative therapy for SSc patients.

1. Introduction

Hand involvement is frequent in systemic Sclerosis (SSc) and confers a substantial handicap in work and daily activities [1]. To date, clinical care for the hand relies on vasodilators, cold and trauma protection, and regular physiotherapy. No antifibrotic therapy has proven effective.

The regenerative properties of cells derived from adipose tissue have been explored for over a decade. In 2002, Zuk identified and described a putative population of multipotent stem and progenitor cells within the stromal vascular fraction (SVF) cell population derived by enzymatic digestion of adipose tissue [2]. The SVF is composed of blood cells, fibroblasts, endothelial cells and their progenitors, pericytes, adipose stromal/stem cells (ASC) and preadipocytes. This population has been reported to possess multiple angiogenic, anti-inflammatory, immunomodulatory and regenerative properties [3].

We previously performed a phase I open-label single center clinical trial, called SCLERADEC (NCT01813279) assessing the safety and efficacy of adipose-derived stromal vascular fraction (ADSVF) in 12 SSc patients followed for 6 months [4], and later reported their extending outcome at 12 months [5]. We took advantage of routine medical follow-up of these patients to assess their longer-term outcome.

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Table 1
Outcome of assessed parameters from baseline to last complete evaluation.

	Mean ± SD Median [min-max]			Least square mean difference [adjusted 95% CI]	Test of LSM difference at M24	
	Baseline	6 months	22–30 months		Raw *P*-value	*P*-value Tukey adjustment
SHAQ Score/3	1.4 ± 0.3 1.4 [0.8–2.1]	0.8 ± 0.4 0.8 [0.0–1.5]	0.7 ± 0.5 0.7 [0.0–1.9]	−0.6 [−1.1; −0.1]	0.0006	0.0051
CHFS total/90	48.5 ± 10.8 48.5 [30.0–69.0]	21.2 ± 15.4 20.0 [0.0–48.0]	18.6 ± 13.8 13.0 [0.0–45.0]	−28.6 [−43.0; −14.2]	< 0.0001	< 0.0001
RCS/10	7.2 ± 0.9 7.5 [6.5–8.0]	2.9 ± 1.4 3.0 [2.5–3.0]	0.8 ± 0.9 0.5 [0.0–2.5]	−6.3 [−7.7; −5.0]	< 0.0001	<0.0001
Hand pain VAS/100	59.4 ± 17.2 58.5 [50.0–72.5]	17.8 ± 15.3 13.6 [9.0–26.0]	29.5 ± 25.2 32.5 [0.0–72.0]	−26.6 [−50.1; −3.0]	0.0025	0.02
Jamar score (kg) Dominant hand	16.0 ± 5.8 15.0 [9.0–26.5]	19.4 ± 7.4 20.0 [5.0–30.0]	19.0 ± 6.1 19.0 [8.0–29.0]	3.2 [−3.5; 10.0]	0.1793	0.6512
Jamar score (kg) Non-dominant hand	14.9 ± 6.1 14.0 [8.0–30.0]	17.6 ± 8.0 20.0 [3.5–29.0]	18.6 ± 6.3 18.0 [6.0–30.0]	4.3 [−1.6; 10.2]	0.0421	0.2398
Pinch score (kg) Dominant hand	1.3 ± 1.1 0.9 [0.2–4.1]	2.3 ± 1.3 2.0 [0.9–5.4]	5.7 ± 1.8 5.0 [3.5–9.0]	4.2 [2.7; 5.8]	< 0.0001	< 0.0001
Pinch score (kg) Non-dominant hand	1.3 ± 0.9 0.9 [0.2–3.2]	2.1 ± 1.0 2.0 [0.7–3.6]	5.5 ± 1.5 5.0 [4.5–6.0]	3.9 [2.6; 5.2]	< 0.0001	< 0.0001
mRSS applied to hand/18	10.9 ± 4.9 11.5 [3.0–18.0]	9.9 ± 6.0 12.0 [1.0–18.0]	8.8 ± 5.9 9.5 [0.0–16.0]	−1.5 [−4.7; 1.7]	0.1828	0.6587
1st corner distance (mm) Dominant hand	105.6 ± 24.7 112.0 [57–142]	112.9 ± 29.2 118.5 [57–154]	121.4 ± 27.9 126.0 [56–155]	15.2 [−4.7; 35.2]	0.0353	0.2084
1st corner distance (mm) Non-dominant hand	115.8 ± 24.5 118.5 [65–152]	122.3 ± 20.9 121.5 [88–155]	128.7 ± 23.4 130.5 [90–174]	13.4 [−6.0; 32.7]	0.0554	0.2974
Sum of corners distances (mm) Dominant hand	133.9 ± 18.5 130.5 [110–168]	131.2 ± 20.7 131.0 [94–169]	130.4 ± 30.4 134.0 [80–1179]	2.7 [−17.8; 23.3]	0.7057	0.9953
Sum of corners distances (mm) Non-dominant hand	132.1 ± 24.6 139.0 [73–158]	133.7 ± 29.4 139.5 [64–166]	135.0 ± 24.2 138.0 [100–186]	5.7 [−10.2; 21.5]	0.3136	0.8442
Sum of Pad/DPL distance (mm) Dominant hand	52.0 ± 46.5 49.5 [0–160]	47.3 ± 43.8 46.0 [0–115]	25.9 ± 45.0 0.0 [0–110]	−29.8 [−62.3; 2.7]	0.0124	0.0858
Sum of Pad/DPL distance (mm) Non-dominant hand	48.1 ± 54.5 32.0 [0–144]	46.8 ± 52.0 38.5 [0–160]	30.2 ± 57.0 0.0 [0–165]	−22.7 [−57.7; 12.4]	0.0719	0.3612
Kapandji score/10 Dominant hand	8.0 (± 1.4) 8.0 [7.0–9.0]	8.4 ± 1.7 9.3 [5.0–10.0]	8.5 (± 1.6) 9.0 [7.5–10.0]	0.6 [−0.6; 1.7]	0.1574	0.6050
Kapandji score/10 Non-dominant hand	8.5 (± 1.2) 9.0 [8.0–9.5]	8.8 ± 1.3 9.0 [6.0–10.0]	8.8 (± 1.3) 9.0 [8.0–10.0]	0.4 [−0.7; 1.5]	0.3068	0.8371

SD: Standard Deviation; SHAQ: Scleroderma Health Assessment Questionnaire, score ranged from 0 = no disability, to 3 = severe disability; CHFS: Cochin Hand Function Scale, 0 = performed without difficulty, to 5 = impossible to do. Disability was recorded as the total score (range 0–90); VAS: Visual Analogue Scale for hand pain (0–100); RCS: Raynaud's Condition Score recording the frequency and severity of the attack on a scale from 0 to 10; grip and pinch strength was assessed using a Jamar and pinch dynamometers; mRSS: Modified Rodnan Skin Score applied to the hands assessed skin thickening on the dorsal hand and the first and second phalanges of the most affected finger, scale 0 = no skin fibrosis, to 18 = maximum fibrosis (3 tested sites for each hand); Lateral range of motion of the fingers was performed by measuring the distance between the thumb and index finger (1st corner) and the sum of the distances between the four fingers (2nd, 3rd, and 4th corners) upon maximum stretch; Finger pad to distal palmar line (DPL) assessed fingers' flexion (mm); Kapandji Score assessed opposition of the thumb, scale 0 = impossible to 10 = complete.

2. Patients and methods

2.1. Patients

Twelve SSc patients, all female, were enrolled from December 2012 through May 2013. The population was composed of 8 subjects with limited cutaneous SSc and 3 with diffuse disease. Three patients were classified as early SSc disease (< 4 years). Subjects had mean age of 54.5 ± 10.3 years and body mass index of 22.0 ± 2.1 kg/m^2. As part of the inclusion criteria, all subjects had hand disability of at least 20 points using the Cochin Hand Function Scale (CHFS).

2.2. Procedures

Adipose tissue collection, ADSVF extraction and quality controls have previously been described [4,5]. ADSVF was obtained within 2 hours after lipoaspiration using the automated processing Celution800/CRS system (Cytori Therapeutics, San Diego, USA). An average of 3.76 ± 1.85 × 10^6 cells was injected into each finger as previously described [3–5].

2.3. Outcome

After completion of the trial, patients continued their routine medical appointments. This allowed us to assess their hand function and other parameters using the same evaluators and tools as those applied within the trial [4]. This was performed during a single visit occurring within the range of 22 to 30 months from the date of the ADSVF injection.

2.4. Data analysis

Continuous data were summarized by mean ± standard deviation and median [minimum-maximum]. CHFS, Scleroderma Health Assessment Questionnaire (SHAQ), Raynaud's Condition Score (RCS) and hand pain visual analogue scale (VAS) were analyzed as co-primary outcomes. Mean changes from baseline were analyzed using mixed model with cutaneous form (diffuse or limited) as fixed effect and time (2, 6, 12 and 24 months) as repeated effect. Least square mean differences form baseline were tested with Tukey adjustment. Significance was set at $P < 0.05$ level after adjustment.

3. Results

Consistent with prior reports [4,5], no evidence of treatment-related adverse events was noted in any patient. Results of functional assessments are shown in Table 1 and Fig. 1. Results show that the benefit reported at the 6-month time point of the trial is sustained at 22–30 months. For example, the long-term follow-up data for CHFS, SHAQ, and RCS endpoints showed 62.5, 51.1 and 88.3% improvement over baseline respectively. It is worth noting that the decrease of the VAS for hand pain which had lost statistical significance at 12 months post-surgery [5] regained significance at 24 months (33.1% decrease from baseline) (Fig. 1). Improvement in objective endpoints such as Jamar grip strength