ADIPOSE-DERIVED CELL THERAPY FOR HAND DYSFUNCTION IN PATIENTS WITH SYSTEMIC SCLEROSIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Background

Hand dysfunction is almost universal in systemic sclerosis (SSc). There is no approved treatment for this indication. Adipose-Derived Regenerative Cells (ADRCs) are a population of cells isolated from a patient's adipose tissue. Preclinical studies and a 12-patient, open-label pilot clinical trial have suggested that ADRCs have the capacity to reduce inflammation, improve vascularity, and thereby, improve hand function. The STAR Trial was a 88-patient, 19-center prospective, double-blind, randomized, controlled trial to to test this hypothesis.

Primary End Point

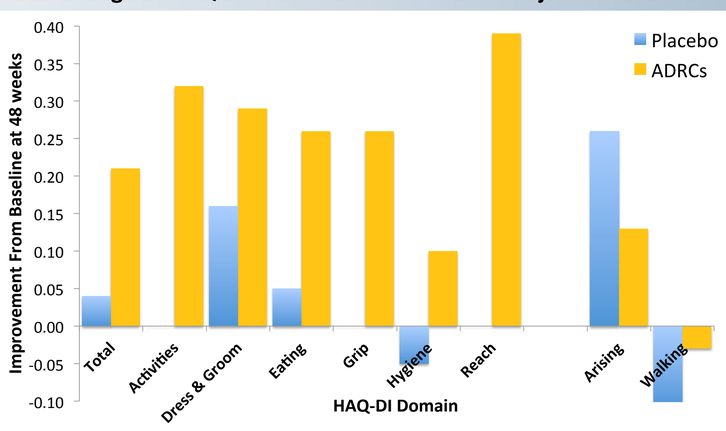
Cochin Hand Function Scale (CHFS):
The primary endpoint was change in the CHFS at 24 and 48 weeks after treatment. Data for subjects with diffuse SSc indicate an early and sustained improvement in CHFS for subjects treated with ADRCs that was greater than that for subjects in the placebo group (Figure 1). This difference approached statistical significance at 48 weeks (p=0.0689).

Key Secondary End Points

Raynaud's Condition Score (RCS):
Improvement from baseline in Raynaud's Condition Score at 12 weeks for the ADRC-treated subjects was greater than that for the placebo group for all subjects, and for subjects with diffuse and limited SSc (nominal p-values 0.009, 0.09, and 0.022 respectively). The same trends were apparent at 48 weeks (all subjects: ADRCs 27% improvement, Placebo 14%; diffuse SSc ADRCs 21%, Placebo 8%; limited SSc ADRCs 33% Placebo 21%), however, these differences were not associated with nominal p-values of less than 0.05.

Scleroderma Health Assessment Questionnaire (SHAQ)
The main component of the SHAQ is the validated HAQ-DI; the mean improvement in the HAQ-DI at 48 weeks for subjects treated with ADRCs was greater than that for the placebo arm for all groups. Subjects with diffuse SSc in the treated arm improved by an average of 0.21 at 48 weeks compared with a mean of 0.04 in the placebo arm (between-group difference =0.17 points; nominal p=0.044). These differences were most evident in HAQ-DI domains associated with hand use (Figure 2).

Figure 2: Change in HAQ-DI Subscores at 48 weeks: Subjects with Diffuse SSc



Exploratory End Points

Improvement from baseline at 48 weeks that was greater for the ADRC-treated arm than for the placebo arm was also evident in other endpoints. For EQ-5D and Patient Global Score these changes were associated with a nominal p-value of less than 0.05. No changes favoring the placebo arm approached or achieved nominal p-values of less than 0.05 (Table 2).

Table 2: Improvement from Baseline for Other Endpoints at 48 weeks in Subjects with Diffuse SSc

Parameter	Placebo	ADRCs	Group Favored	Nominal p-value
EQ-5D 3L	-0.09 ± 0.02	0.04 ± 0.12	ADRCs	0.0112
Patient Global SSc Activity Score	-0.16 ± 1.8	1.03 + 2.81	ADRCs	0.0152
Physician Global SSc Activity Score	-0.05 ± 1.75	0.61 ± 1.54	ADRCs	0.169
1st Corner Distance (mm)	1.0 ± 14.2	4.4 ± 18.3	ADRCs	0.484
2nd-4th Corner Distance (mm)	-2.0 ± 12.0	9.2 ± 28.2	ADRCs	0.107
Grip Strength (right hand; kg)	2.1 ± 11.9	0.5 ± 12.5	Placebo	0.679
Pinch Strength (right hand; kg)	-0.22 ± 2.63	0.16 ± 3.28	ADRCs	0.673
MRSS (hand only)	-1.5 ± 4.2	-0.7 + 2.3	Placebo	0.506

References:
1. *STAR data set for subjects with diffuse SSc*
2. *Khanna et al (2005) Ann Rheum Dis 2006;65:1325–1329*

Methods

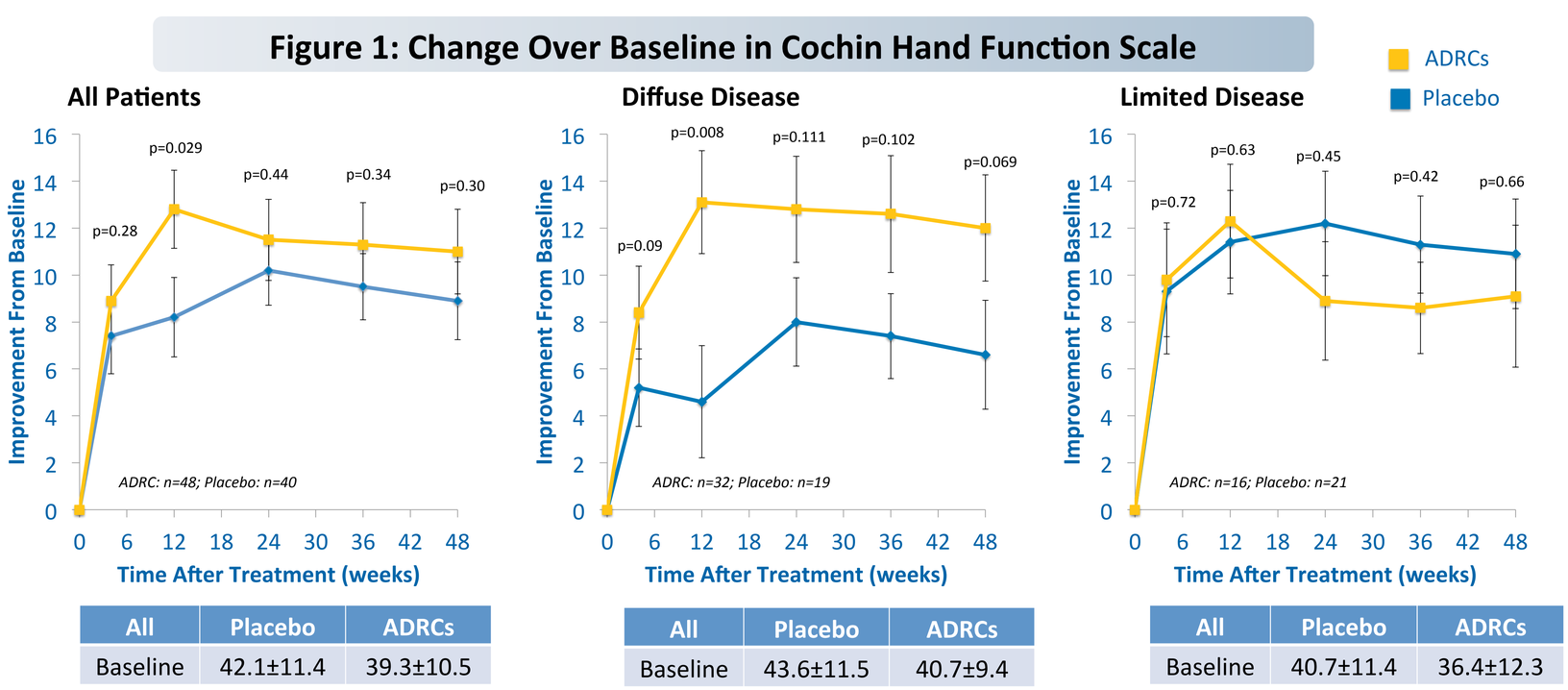
Adipose tissue collected by a small volume liposuction was processed with the Celution® System (Cytori Therapeutics Inc.) to prepare ADRCs for immediate subcutaneous administration under local anesthesia. Subjects with significant impairment of hand function (baseline Cochin Hand Function Scale [CHFS] >20 points; scale 0-90) were randomized (1:1) to receive ADRCs ($4x10^6$ per finger) or a visually-matched placebo into all fingers of each hand. Safety was assessed throughout the trial. Efficacy was evaluated at multiple time points over 48 weeks using the CHFS, SHAQ, and other patient-reported and quantitative assessments of hand function.

Demographics

Table 1: Demographics of Subjects Enrolled in the STAR Trial

Variable	ADRC	Placebo
Number of Subjects	48	40
Gender (% female)	85% (40/48)	88% (35/40)
Age (years)	54±9	52±12
Disease Duration (SSc diagnosis) (years)	12.7 ±7.9 y	13.3 ± 8.9 y
Duration Since Raynaud's Onset (years)	14.7 ± 9.5 y	15.4 ± 10.5 y
Diffuse SSc Subtype (%)	67% (32/48)	48% (19/40)
Subjects with Digital Ulcers at Baseline	35%	33%

Figure 1: Change Over Baseline in Cochin Hand Function Scale



All	Placebo	ADRCs
Baseline	42.1±11.4	39.3±10.5

All	Placebo	ADRCs
Baseline	43.6±11.5	40.7±9.4

All	Placebo	ADRCs
Baseline	40.7±11.4	36.4±12.3

Responder Analysis: Subjects with Diffuse SSc

Responder rates based on assumed thresholds of change >9.5 for the CHFS[1] and change ≥0.125 (more than slight improvement) and change >0.25 (more than mild improvement) for the HAQ-DI[1,2] showed that only 16% (3/19) of subjects with diffuse SSc in the placebo arm responded in both the CHFS and HAQ-DI compared with 52% (16/31) of subjects in the treated arm (nominal p=0.0163; Figures 3 and 4).

Figure 3: Improvement in CHFS and HAQ-DI at 48 weeks

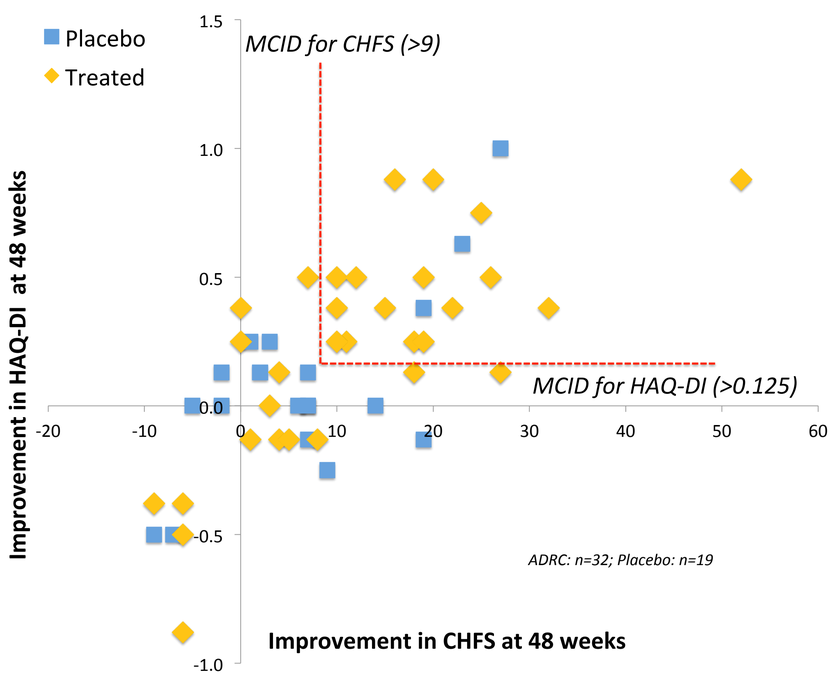
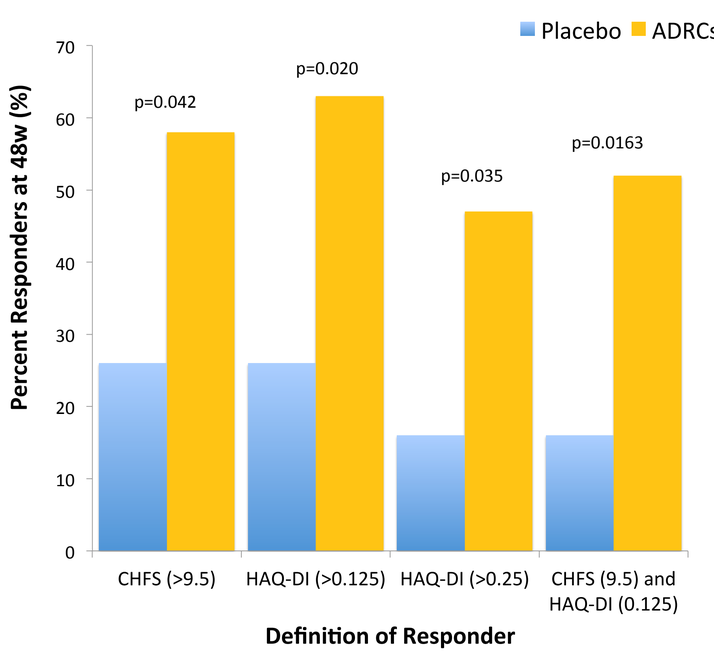


Figure 4: Percent Responders in ADRC and Placebo Groups



Safety

The procedure was well-tolerated; 6 subjects reported serious adverse events [1 ADRC (2.1%); 5 placebo (12.5%)] with no SAEs in the hand and no deaths. Adverse events affecting at least 5% of subjects in either the ADRC or placebo group are shown in Table 3. The overall rate of adverse events was very similar for both groups. Notable differences were observed between treatment groups in the percentage of subjects who experienced peripheral vascular related events and those with calcinosis. Peripheral vascular events (e.g., hypertension, hypotension, digital infarction, and worsening of Raynaud's phenomenon) were observed in 6 of the 40 placebo treated subjects (15.0%), compared with none of the 48 ADRC-treated subjects. Similarly, calcinosis was observed in 5 of 40 (12.5% of subjects in the placebo group compared with 1 of 48 (2.1%) in the ADRC group.

Table 3: Summary of Most Common Adverse Events Reported

Preferred Term	Placebo (%)	ADRCs (%)
Any Adverse Event	81.3	82.5
Localized infection	15.0	6.3
Skin ulcer	15.0	8.3
Upper respiratory tract infection	15.0	20.8
Calcinosis	12.5	2.1
Diarrhea	10.0	6.3
Rash	7.5	0.0
Limb injury	7.5	0.0
Anemia	7.5	0.0
Nausea	7.5	4.2
Arthralgia	5.0	6.3
Cellulitis	5.0	8.3
Pain in extremity	2.5	6.3
Hypoesthesia	0.0	8.3

ITT Data Set; all subjects irrespective of SSc subtype
Events occurring in at least 5% of either ADRC or placebo group
Preferred Terms are listed in decreasing order of frequency based on the placebo group

Conclusions

Treatment with ADRCs was safe. While not meeting the primary endpoint for all SSc patients, the STAR trial revealed strong signals of efficacy. In particular, improvement over baseline at 3 months was greater for the ADRC treatment group than for placebo for the CHFS, RCS, and HAQ-DI scores for the entire ITT group. For subjects with diffuse SSc, improvements from baseline at 48 weeks in the ADRC group that were greater than those in the placebo group and associated with nominal p-values of less than 0.05 were evident for several key parameters including CHFS, HAQ-DI, EQ-5D, and Patient Global Assessment of SSc activity.