A Phase 1 Open-Label Investigator Initiated Trial of Allogeneic Gene-Modified Human Umbilical Vein Endothelial Cells as an Adjunct Cell Therapy for Arthroscopic Rotator Cuff Repair

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INTRODUCTION:

A full-thickness rotator cuff tear presents a significant clinical challenge. These injuries are often accompanied by incomplete or failed healing following surgical repair as well as a slow rate of complete functional recovery, both of which negatively impact patients qualify of life post-surgery. The frequency of a failure to heal with a recurrent defect following repair may occur in 20-40% of patients over the age of 60 due to age-related, intrinsic degenerative changes involving the muscle, tendon, and/or enthesis [1,2]. Injection of gene-modified endothelial cells have been shown to aid in tissue repair making them a promising therapeutic intervention [3-5]. Accordingly, we have conducted an FDA-cleared Phase 1 open-label, single-center investigator-initiated trial of allogeneic gene-modified human umbilical vein endothelial cells ($E4^+$ HUVECs) as an adjunct cell therapy with standard arthroscopic rotator cuff repair (RCR).

METHODS:

After IRB approval, 20 subjects between ages 45 to 70 with a full-thickness supraspinatus tear and no prior history of cuff repair were enrolled and treated. After arthroscopic RCR was completed, allogeneic $E4^+$ HUVECs were injected under direct arthroscopic visualization into the supraspinatus muscle belly (~10 million cells/10cc) and the tendon-bone attachment site (~5 million cells/5cc). Each cell preparation was assessed for cell viability, sterility, and endotoxin. Subjects were followed for a 1-year period (10 visits) and assessed for local and systemic safety and toxicity, patient-reported outcomes (PROs), range of motion (ROM), isokinetic strength, MRI assessment of muscle and tendon, and ultrasound shear wave elastography. Adverse events (AEs) were described using descriptive analysis and cumulative incidence was generated using the Kaplan-Meier analysis. Differences in continuous measures over time were analyzed using a one-way ANOVA with a Tukey's multiple comparison post-hoc test. Prism version 9 was used for all analyses and statistical significance was defined as $p \leq 0.05$.

RESULTS:

$E4^+$ HUVECs were delivered at a mean cell concentration of 2.75E6 ± 0.35E6/mL of viable cells with mean post-thaw viability of 89% ± 3%. There were no serious adverse events (SAEs) related to the intervention. Overall, our study population had a cumulative probability of AEs of 45%, the majority of which were minor and were not judged to be directly related to the injected cells (**Fig. 1**). There was significant improvement in PROs using the PROMIS-10, ASES, and Penn Pain Score forms from baseline to postop day 360 with a mean increase of 8.27 ($p = 0.0016$; 95% C.I. [3.50 13.04]), 17.95 ($p = 0.0032$; 95% C.I. [6.54, 29.37]), 12.24 ($p = 0.0032$; 95% C.I. [6.54, 17.93]), respectively. At postop day 360, mean ASES functional subscore of the subject's surgical arm significantly improved to levels comparable to their control nonsurgical arm (45.15 and 49.24, $p = 0.23$;). Ultrasound (US) grade for degree of tendinopathy on a scale from 0-3 decreased from preop baseline to all postop timepoints, with a significant difference of 1.40 ± 0.35 ($p = 0.027$) from baseline to postop day 360 (**Fig 2**). At postop days 90 and 180 glenohumeral synovitis and subacromial bursitis was frequently seen on MRI. However, at day 360, no patients had synovitis and mild bursitis was seen in 22.2% (**Fig 2)**. MRI identified a partial or focal full-thickness defect in 55.5% of the cases at postop day 360 (**Fig 2**); however, all patients had improvement in rotator cuff function compared to baseline.

DISCUSSION AND CONCLUSION:

This study demonstrates the initial safety and feasibility of allogeneic $E4^+$ HUVEC cell therapy concurrent with standard arthroscopic RCR. No clinically meaningful adverse events directly attributable to $E4^+$ HUVECs were observed. Clinical improvement occurred in all subjects completing the postop day 360 visit accompanied by statistically significant decrease in US-graded tendinopathy, although a relatively high rate of recurrent tendon defects was seen on the MRI. Further analysis of this data is planned to correlate the clinical and imaging outcomes. Inherent limitations of the small sample sizes in Phase 1 clinical trials limit the ability to draw conclusions about efficacy. As the initial safety appears promising, further assessment with a randomized clinical trial evaluating a larger study population would be warranted.

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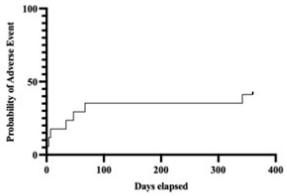
A

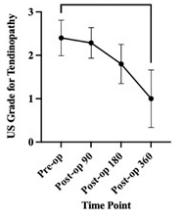


B

Adverse event type/Description of the adverse event	Time after surgery(days)	Adverse Event Frequency n (%)
Bacterial growth in cell preparation broth	0	3 (15)
Urinary retention and dysuria	1	1 (5)
Portal erythema	4	1 (5)
Sling Rash	7	1 (5)
Complex regional pain syndrome	34	1 (5)
New tendon defect in the infraspinatus	47	1 (5)
Rotator cuff repair of infraspinatus tendon following a traumatic incident/fall	147	1 (5)
Contracted COVID-19	342	1 (5)

Figure 1
Cumulative Incidence curve (Kaplan-Meier) by adverse events occurrence for study participants (**A**); Distribution of adverse events types in patient population (**B**)

A



B

Visit	Full Thickness Partial Width (%)	Partial Thickness (%)
Post-op 90	11.8	11.8
Post-op 180	37.5	37.5
Post-op 360	33.3	22.2

C

Visit	Synovitis (%)	Bursitis (%)
Post-op 90	11.8	94.1
Post-op 180	12.5	68.8
Post-op 360	0.0	22.2

Figure 2
US grade for the degree of tendinopathy over time with 95% confidence interval (**A**); Rates of supraspinatus defect on post-operative MRI (**B**); Rates of glenohumeral synovitis and subacromial bursitis on MRI (**C**)