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CLINICAL TRIAL REPORT

Corneal Epithelial Stem Cell Supernatant in the Treatment of Severe Dry Eye Disease: A Pilot Study

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Purpose: To report the subjective assessment of topical self-administered, cadaver-derived corneal epithelial stem cell supernatant for treatment of severe dry eye disease (DED).

Methods: Thirty-four eyes of 17 patients with advanced DED as defined by Standardized Patient Evaluation of Eye Dryness (SPEED^{TM}) questionnaire ≥14, Ocular Surface Disease Index (OSDI©) score ≥40 and documented attempt of at least six conventional dry eye therapies were enrolled into a prospective clinical trial at a single private practice institution. Treatment consisted of patient self-administered topical instillation of the corneal epithelial stem cell-derived product four times daily in both eyes for 12 weeks. Patient-reported outcome measures (PROMs) were taken with the SPEED^{TM} questionnaire (the main outcome variable), OSDI© score and visual analog score (VAS; UNC Dry Eye Management Scale©), and objective clinical measurements were taken with best-corrected visual acuity (BCVA), corneal topographic index measurements and tear film osmolarity. These measurements were compared at baseline versus the endpoint at completion of the 12-week treatment.

Results: All 34 eyes tolerated the treatment without any adverse events or significant side effects. Compared with baseline, both the SPEED^{TM} questionnaire and the VAS significantly improved at the conclusion of the 12-week treatment ($p = 0.0054$ and $p = 0.0202$, respectively). The OSDI© improved by an average of 10.9 points after the treatment but was not statistically significant ($p = 0.1409$). There were no significant changes in any of the objective clinical measurements. None of the study subjects failed to complete the treatment course, experienced decrease in any of the PROMs or lost one or more lines of BCVA during the follow-up period.

Conclusion: Topical corneal epithelial stem cell-derived supernatant that can be self-administered by the patient shows promise at improving patient symptoms and quality of life in the setting of severe DED that is unresponsive to conventional therapies.

Keywords: dry eye disease, corneal epithelial stem cells, conjunctival goblet cells, supernatant, chronic ocular surface disease, glycocalyx, galectin-3, mucins

Introduction

The prevalence of dry eye disease (DED) has been estimated to be as high as 50% of the population.[1] Systematic literature reviews have detailed the substantial economic liability of DED including the loss in work productivity.[2,3] The overall annual burden of DED on the United States healthcare system and society at large may well be in excess of $50 billion (USD).[4] While there is a definite predilection for DED in females and in patients with autoimmune disorders, DED occurs in all ethnicities and in all population demographics as age increases.[5–8] The treatment strategy for DED may vary depending upon the underlying etiology of the dry eye (aqueous deficiency versus evaporative), clinical examination findings and the

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presence of other associated ocular surface diseases.[9] There are many conventional therapies for DED which include ocular lubricants, oral essential fatty acid supplementation, lid hygiene and warm compresses, punctal occlusion, various treatments to obstructed meibomian glands, topical antibiotics, topical corticosteroids, topical secretagogues, topical non-glucocorticoid immunomodulatory drugs and scleral contact lenses.[10,11] Even with the current multitude of therapeutic options, investigators have observed the urgent need to develop more safe and effective treatment modalities.[12] Furthermore, evaluating response to treatment for DED has always been challenging due to the fact that there is a poor correlation among the patient's symptoms and the objective clinical findings.[13,14]

Knowing that there is tremendous need for improved therapeutic options, there has been considerable effort to elucidate the underlying pathophysiological mechanisms of DED at both the cellular and molecular levels. Several recent studies have described in great detail the biologic niche for both the corneal limbal epithelial stem cells and the conjunctival goblet cells.[15,16] These ocular surface epithelial cells secrete mucins that form a hydrophilic barrier for the protection and lubrication of the eye.[17–19] This complex interaction of proteins in the extracellular matrix consists of glycosylated membrane-associated mucins that contain lattices of galectin-3 and other integrated proteins to form the glycocalyx structure.[20,21] It has been hypothesized that alteration and dysfunction in mucin-associated homeostasis is a major contributor in the pathogenesis of DED.[22–25] This knowledge has been applied to the development of more innovative treatments for ocular surface regeneration which include biologic agents such as growth factors, blood products and cell-based therapies.[26,27] For example, autologous serum eye drops, which contain biochemical components that more closely mimic natural tears, have shown superiority relative to plain lubricating eye drops in the treatment of chronic ocular surface diseases, and it is gaining more widespread acceptance and use in the treatment of more advanced cases of DED.[28] With reasonable degree of success, investigators have also tried other biologic agents that are not naturally indigenous to the ocular surfaces such as amniotic membrane grafts that are derived from a donated mother's placenta to help promote ocular surface healing.[29] The only regenerative biologic treatment that is native and specific to the eye requires staged culturing of autologous or allogenic corneal epithelial stem cells for several weeks followed by surgical transplantation of the newly created graft onto the ocular surface, a treatment that has been used primarily in the setting of limbal stem cell deficiency and not DED.[30–32]

Presently, there are no reports describing a safe and effective therapeutic biologic agent for DED that does not either require invasive surgery or require biologic material that is not specific and differentiated for the ocular surface. In this study, we investigate first-in-human use of a novel, patient-delivered topical application of a corneal epithelial stem cell-derived product for the treatment of severe DED.

Methods

Study Design

The Salus Independent Review Board (IORG0005674) approved this prospective pilot case series of severe DED patients that underwent topical, self-administered treatment with the corneal epithelial stem cell-derived product from May 2019 through December 2019 at a single private practice institution in Amarillo, TX, USA. All components of the study adhered to the tenets of the Declaration of Helsinki and were performed in accordance with human research standards and regulations. The study is registered at ClinicalTrials.gov (NCT03302273, last accessed January 1, 2020).

Participants

Consecutive patients with severe DED presenting to a single clinical practice were assessed for study eligibility. Inclusion criteria was comprised of clinical diagnosis of dry eye syndrome, severe DED (as defined by Standardized Patient Evaluation of Eye Dryness (SPEED™) questionnaire ≥14, Ocular Surface Disease Index (OSDI©) score ≥40, and documented attempt and/or current use of at least six conventional dry eye therapies),[10–11] age 25–75, and willingness and ability to participate in a research trial. Exclusion criteria consisted of inability or unwillingness to participate in an investigational study. Both eyes in all study subjects were treated simultaneously according to the protocol. All enrolled subjects were given a written informed consent.

Randomization and Masking

There was no active comparator in the study since it was a pilot series. The study participants were not aware of the study design and intent. Only the ophthalmic technicians

that collected the objective study data (see below) were masked as to which patients were enrolled into the research trial. The treating physician (SWR) was an unmasked observer.

Intervention

Enrolled study subjects that signed the written informed consent document were given instructions on the treatment plan. The treatment consisted of patient-administered topical instillation of the corneal epithelial stem cell-derived eye drop product (described below) four times daily (QID) to both eyes for a total of 12 weeks. The patient was instructed to refrigerate the stem cell-derived product which was dispensed in eye-dropper bottles in 5 mL aliquots. Patients continued treatment as usual with all prior therapies. No changes were made to any of these existing dry eye treatments during the study interval.

Harvesting and Culturing of the Corneal Epithelial Stem Cells

The corneal epithelial stem cells were derived from corneoscleral rim cadaver donors. All corneal donors were transplantable grade tissue that were received from an Eye Bank Association of America (EBAA) accredited facility and had negative serology testing. The harvesting technique was initiated under sterile environment where the anterior sections of the tissue are trimmed to contain the epithelial side of sclera, conjunctiva and cornea. This tissue was delivered to the manufacturing laboratory at the participating blood bank (see below). The tissue was transported in 10 mL of Optisol-GS corneal preservation media.

The harvested corneal epithelial stem cells were transferred to a licensed blood and tissue facility (Oklahoma Blood Institute, 901 N. Lincoln Blvd, Oklahoma City, OK 73104, USA). The facility is accredited by the American Association of Blood Banks (AABB) and compliant with all applicable registration and regulatory requirements for the handling and manufacturing of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). The cells were cultured and expanded using serum-free, antibiotic-free EpiLife media with calcium (ThermoFisher Scientific) containing Human Corneal Growth Supplement (HCGS, ThermoFisher Scientific).

The final product was prepared according to Current Good Manufacturing Practice (cGMP) requirements and with minimal manipulation and a clinical application for homologous use according to the FDA's current thinking and guidance for industry regarding tissue-based products.[33] The supernatant was collected for the culture plates and diluted with 19mL of PBS, and centrifuged to remove any cells contaminating the supernatant. The diluted acellular supernatant was transferred to six sterile eye dropper bottles, 6.0mL/bottle. A small volume of supernatant was reserved for sterility testing. The dropper bottles were sealed, labeled, and stored at −15°C to −25°C until the results of sterility testing were complete. Supernatant lots with negative 14-day sterility testing results were released for use in treatment.

Data Collection, Assessments and Outcome Measures

The demographic and baseline characteristics collected from each study participant included age, gender, ethnicity, type and number of previous and current conventional dry eye treatments used, associated autoimmune disorders, other systemic and ocular comorbidities, and lens status. Subjective patient reported outcome measures (PROMs) were taken with the SPEED^{TM} questionnaire[34,35] (the main outcome variable), OSDI© score[36] and visual analog score (VAS; UNC Dry Eye Management Scale©).[37,38] Objective measurements included best-corrected visual acuity (BCVA), tear film osmolarity and corneal topographic measurements (surface regularity index (SRI), projected visual acuity (PVA) and surface asymmetry index (SAI)) using the TMS-4 Topographer (Tomey; Phoenix, AZ, USA). The objective measurements were averages among both eyes for each study patient. All outcome variables were taken at baseline (4 weeks prior to treatment and then again immediately prior to treatment) and at 4 weeks, 8 weeks, 12 weeks after treatment initiated and then finally at 12 weeks after the treatment course was completed.

Sample Size, Power Calculation and Statistical Analysis

Standard deviation of the main outcome variable (SPEED^{TM} questionnaire) was determined to be 8 by a pre-treatment sampling of the first four enrolled patients. Using power of 90%, alpha of 0.05 and difference to detect of 8 (33% difference from the sampling mean), the sample size was calculated to be 13 patients. The JMP 11 software from the SAS Institute (Cary, NC, USA) was used to analyze distributions and calculate means with standard deviations. One-way analysis of the variance was used to compare means of the baseline measurements versus the post-treatment measurements. Visual acuity change was considered significant if there was change by logMAR 0.3 or more, whereas the other comparisons were considered statistically significant at the $p<0.05$ level.

Safety Monitoring

The enrolled study patients were assessed at 2 weeks after initiation of treatment in addition to each scheduled data collection appointment for symptoms and clinical findings of side effects or adverse events. Patients were given 24 hour emergency contact information for any concerns. Any suspected or known adverse events were immediately reported to the Salus Independent Review Board according to approved study protocol guidelines.

Results

A total of 22 consecutive patients with severe DED met eligibility criteria during the enrollment period and were presented with the opportunity to participate in the clinical trial. Five of these patients (22.7%) either declined or were unable to enroll into the study. Therefore, there were 34 eyes of 17 patients included in the analysis, all of whom completed the study (100% completion rate). A flow chart of the study enrollment data is given in Figure 1. All patients reported treatment compliance and completion of the 12-week treatment. One patient had a 3 week interruption in the treatment but still completed a 12-week course. The baseline characteristics and demographic features of the study population are summarized in Table 1. The average number of previous DED treatments that failed to achieve symptom stability for the study population was 9.1 (±2.6), but no specific algorithm had been used to determine the types, order of use, or combinations of

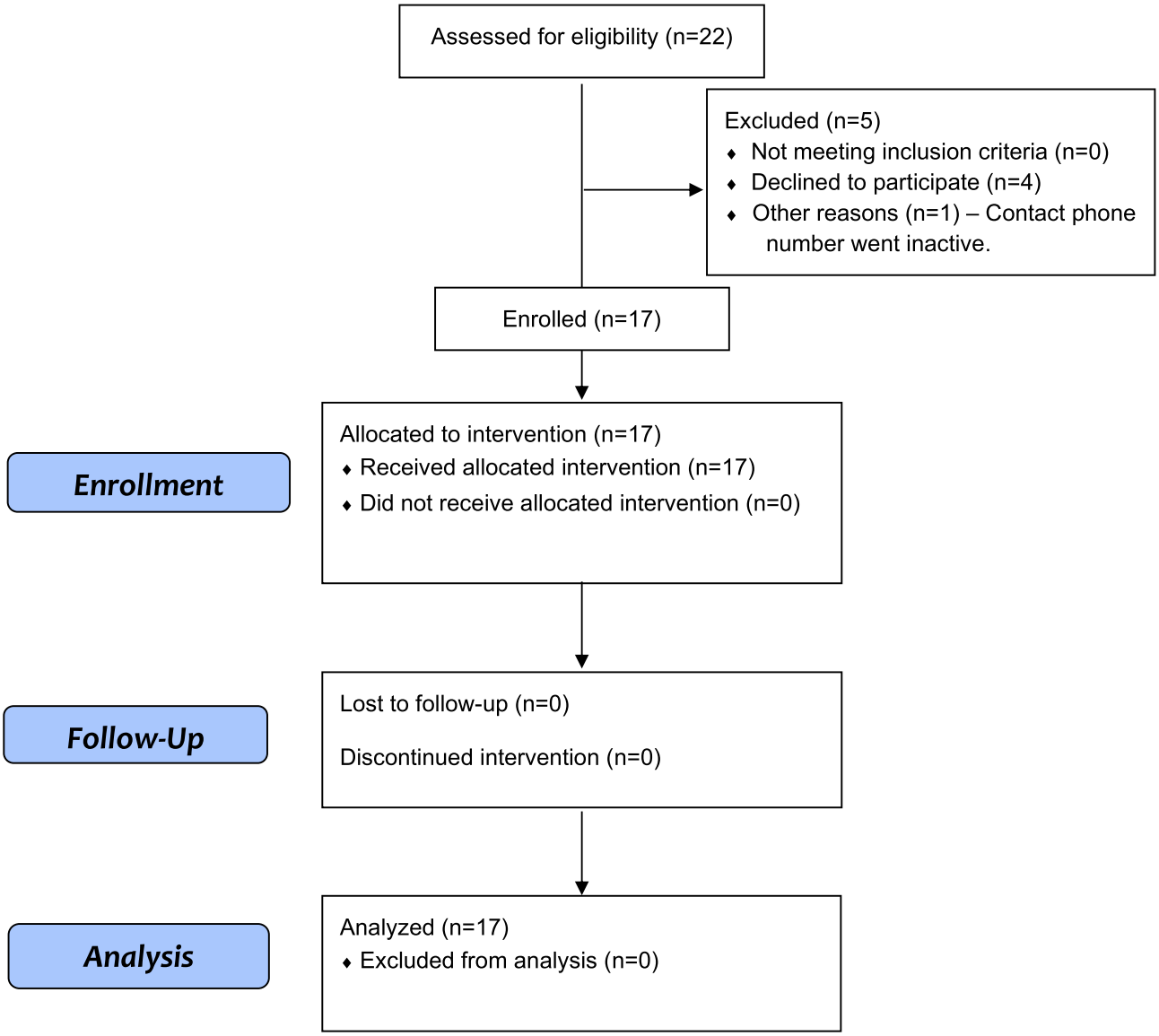

Figure 1 Corneal epithelial stem cell-derived therapy for dry eye disease. Flow chart for enrollment into the clinical trial.

Table 1 Corneal Epithelial Stem Cell-Derived Supernatant for Dry Eye Disease. Baseline Demographics and Characteristics of the Study Population

Baseline Characteristics and Demographics (n=34 Eyes of 17 Patients)	**Means with (Standard Deviations)**
Age (years)	57.9 (±13.7) Range = 27 to 75
Gender	Male = 0 (0.0%) Female = 17 (100.0%)
Ethnicity	Caucasian = 16 (94.1%) Hispanic = 1 (5.9%) Other = 0 (0.0%)
Number of Previous Dry Eye Treatments	9.1 (±2.6) Range = 6 to 14
Treatment Distributions	Artificial Tears = 17 (100.0%) Lubricating Ophthalmic Ointment = 17 (100.0%) Topical Cyclosporine = 17 (100%) Topical Corticosteroids = 16 (94.1%) Punctal Occlusion = 13 (76.5%) Oral Omega-3 Supplement = 12 (70.6%) Warm Compresses and Lid Scrubs = 10 (58.8%) Moisture Chamber Goggles, Sleep Masks or other Eyewear Products = 7 (41.2%) Topical Lifitegrast = 6 (35.3%) Autologous Serum/Blood Products = 6 (35.3%) Hydroxypropyl Cellulose Ophthalmic Inserts = 6 (35.3%) Eyelid Thermal Pulsation = 5 (29.4%) Other Anti-inflammatory Systemics = 5 (29.4%) Systemic Cholinergic Agonists = 3 (17.6%) Amniotic Membrane Grafting = 2 (11.8%) Meibomian Gland Expression = 2 (11.8%) Topical Antihistamines = 2 (11.8%) Topical Antibiotics = 2 (11.8%) Scleral Contact Lenses = 1 (5.9%) Liposome Spray = 1 (5.9%) Topical Chondroitin Sulfate = 1 (5.9%)
Previous Use of Autologous Serum or other Topical Blood-derived Product	Yes = 6 (35.3%) No = 11 (64.7%)
Autoimmune Disorder Diagnosis	Yes = 7 (41.2%)* No = 10 (58.8%) Sjogren's Syndrome = 6 Rheumatoid Arthritis = 2 Systemic Lupus Erythematosus = 2 Scleroderma = 1
Other Systemic Disorders	Yes = 6 (35.3%) No = 11 (64.7%) Thyroid Disorder = 4 Atopy = 2 Diabetes Mellitus = 1 Graft versus Host Disease (GVHD) = 1

(*Continued*)

Table 1 (Continued).

Baseline Characteristics and Demographics (n=34 Eyes of 17 Patients)	Means with (Standard Deviations)
Other Ocular Comorbidities	Yes = 3 (17.6%) No = 14 (82.4%) Herpes Zoster Ophthalmicus = 1 Floppy Eyelid Syndrome = 1 Superior Limbic Keratitis = 1 Salzmann Nodular Degeneration = 1
History of Previous Refractive Surgery	Yes = 4 (LASIK = 4, PRK = 0 and RK = 0) (23.5%) No = 13 (76.5%)
Lens Status	Phakic = 12 (70.6%) Pseudophakic = 5 (29.4%)

Note: *Some study subjects had multiple diagnoses.

treatments that were used for any particular patient. Furthermore, all of the patients had previous care delivered by multiple providers. None of the patients with history of LASIK had the surgery done within the past 3 years.

The outcome comparison among average baseline versus 12-week post-treatment outcomes is detailed in Table 2. The main outcome variable (SPEED^{TM} questionnaire) significantly improved from baseline by an average of 4.7 points (23.0%) (p=0.0054). OSDI© score improved from baseline by an average of 10.9 points (17.1%) (p=0.1409, not statistically significant) and VAS improved from baseline by an average of 1.1 points (14.1%) (p=0.0202). Figure 2 shows the trend in all three of the measured PROMs over the treatment course. No patients had worsening in any of the PROMs throughout the duration of the follow-up time interval during the treatment. BCVA and tear film osmolarity showed a trend for improvement but did not achieve statistical significance (p=0.5678 and p=0.1884, respectively). None of the other objective clinical measurements showed significant changes.

Table 2 Corneal Epithelial Stem Cell-Derived Supernatant for Dry Eye Disease. Average Baseline versus Twelve Week Post-Treatment Outcome Comparisons

Outcomes (n=34 Eyes of 17 Patients)	Average Baseline Values Means with (95% Confidence Intervals)	Post-Treatment Values Means with (95% Confidence Intervals)	p-value
Standardized Patient Evaluation of Eye Dryness (SPEED^{TM}) Questionnaire (scaled 0 to 28 with 28 being the worst)	20.4 (18.1–22.7)	15.7 (13.4–18.0)	0.0054
Ocular Surface Disease Index (OSDI©) Score (scaled 0 to 100 with 100 being the worst)	63.4 (53.2–73.6)	52.5 (42.0–63.1)	0.1409
Visual Analog Scale (VAS) (scaled 1 to 10 with 10 being the worst)	8.0 (7.3–8.6)	6.8 (6.2–7.5)	0.0202
Best Spectacle Corrected Visual Acuity (logMAR)	0.18 (0.15–0.25)	0.15 (0.07–0.22)	0.5678
Tear Film Osmolarity (mOSM/L)	318.9 (306.6–331.1)	307.3 (294.6–320.0)	0.1884
Topographic Surface Regularity Index (SRI)	0.70 (0.51–0.89)	0.75 (0.55–0.95)	0.7413
Topographic Projected Visual Acuity (PVA) (logMAR)	0.12 (0.08–0.17)	0.13 (0.08–0.18)	0.8673
Average Topographic Surface Asymmetry Index (SAI)	0.81 (0.57–1.05)	1.02 (0.77–1.26)	0.2240

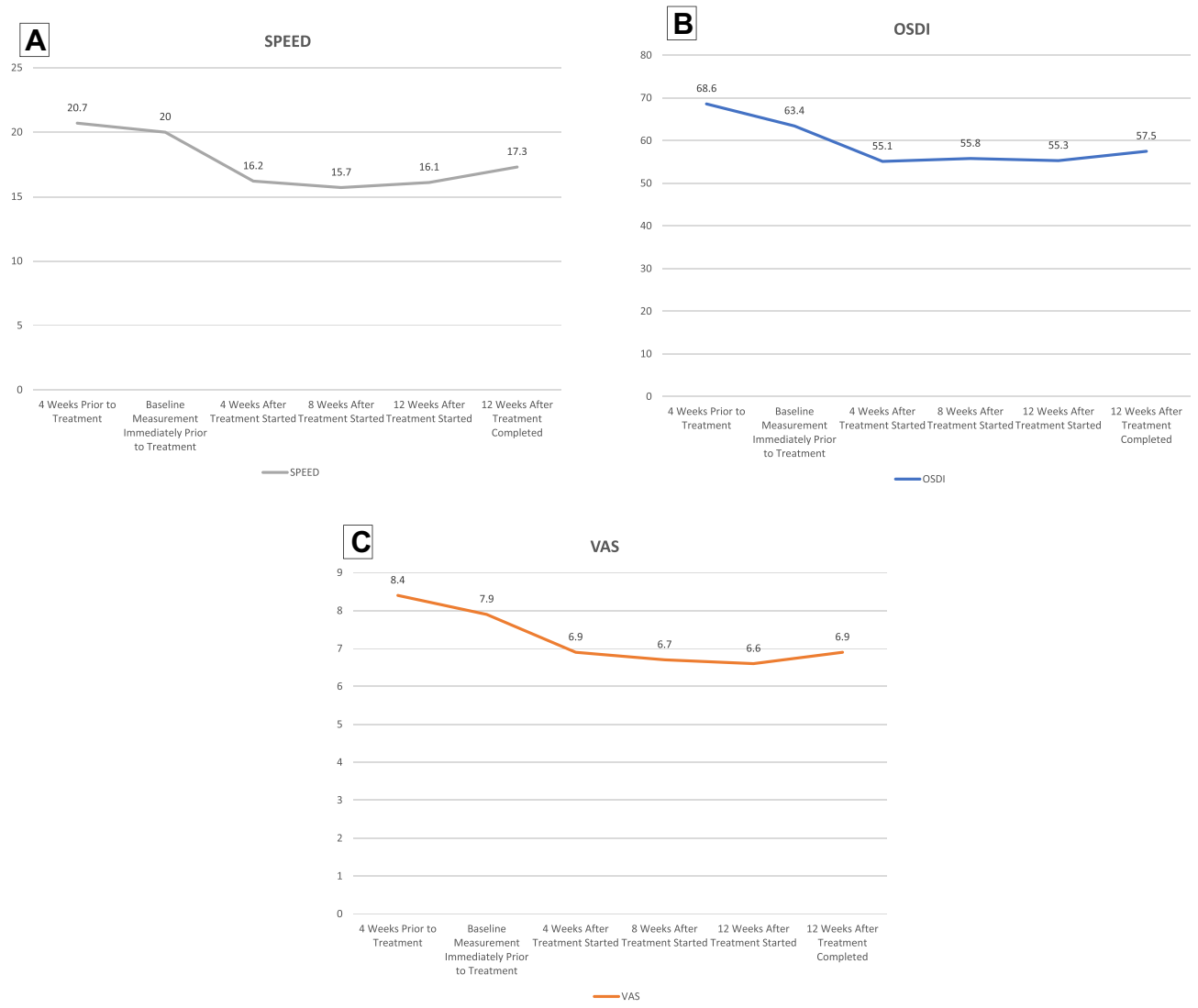

Figure 2 Corneal epithelial stem cell-derived supernatant for dry eye disease. Mean patient reported outcome measurements of over various time intervals during the 12 week treatment period for (**A**) Standardized Patient Evaluation of Eye Dryness (SPEED™) Questionnaire, (**B**) Ocular Surface Disease Index (OSDI©) Score and (**C**) Visual Analog Scale (VAS).

Change in the four-week pre-treatment baseline from immediate pre-treatment baseline PROMs was compared to change in immediate pre-treatment baseline from average post-treatment PROMs at 12 weeks. All three outcomes showed significant improvement using this comparison technique (Table 3). In addition, extended follow-up comparison was done with the time point 12 weeks after the treatment was completed (24 weeks from baseline at the time treatment was originally started) which showed a small upward trend to baseline but was not statistically significant.

Subset analysis was done to determine if there were any significant differences in response to therapy among patients that have an underlying autoimmune disorder or among patients that have previously tried autologous serum (or other topical blood-derived products). In both instances, the patients in these categories responded similarly to those in the remaining cohort without any apparent statistical trends.

Exit surveys were given to get additional patient feedback. All 17 patients stated that the study treatment was better than artificial tears and that they would want to do it again. All patients also reported decreased use of artificial tears PRN during the treatment period. Fifteen patients (88.2%) described the treatment as "soothing" when they used the eye drops. All 17 of the patients in this study were either currently using or had previously used cyclosporine ophthalmic emulsion (Restasis®), and 100% of

Table 3 Corneal Epithelial Stem Cell-Derived Supernatant for Dry Eye Disease. Patient Reported Outcome Measurement Comparisons for Change in Four Week Pre-Treatment Baseline from Immediate Pre-Treatment Baseline versus Change in Immediate Baseline from Average Post-Treatment Values

Outcomes (n=34 Eyes of 17 Patients)	Change in Four Week Pre-Treatment Baseline from Immediate Pre-Treatment Baseline Values Means with (95% Confidence Intervals)	Change in Immediate Pre-Treatment Baseline from Average Post-Treatment Values Means with (95% Confidence Intervals)	p-value
Standardized Patient Evaluation of Eye Dryness (SPEED™) Questionnaire	+0.7 (−2.1 to +3.4)	−4.4 (−6.6 to −2.1)	0.0077
Ocular Surface Disease Index (OSDI©) Score	−0.2 (−8.9 to +8.5)	−15.7 (−23.3 to −8.2)	0.0110
Visual Analog Scale (VAS)	−0.15 (−0.75 to +0.45)	−0.98 (−1.48 to −0.49)	0.0372

them stated that the treatment used in this clinical trial was preferred and even superior with regard to alleviating their dry eye symptoms over a 12-week period.

There were no identifiable trends for severe side effects or adverse events during the study period for any of the enrolled study participants. Lengthy questionnaire with ocular symptoms were administered to each patient. With regard to subjective symptoms, 2 patients noticed transient stinging/burning, 2 patients noticed mild aftertaste, 1 patient noticed itching, and 1 patient noticed mattering/crusting that correlated with instillation of the drops. As it relates to objective clinical findings, the examiner noticed subconjunctival hemorrhage in one patient over the duration of the study interval. There were no other observable examination findings the correlated with use of the therapy.

Discussion

To our knowledge, this is the first human clinical trial demonstrating effective use of a corneal epithelial stem cell-derived biologic agent in the setting of DED. Furthermore, lack of noticeable side effects and adverse events demonstrate its preliminary safety as a viable treatment for DED. There is a growing body of literature regarding biologic treatments for DED that will promote ocular surface regeneration. Compared to other experimental biologic treatments, the topical administration of this product by the patient obviates the need for surgical intervention as is the case for limbal epithelial transplants.[30–32] Another advantage of this treatment over autologous serum and other non-allogenic blood-based products is that there is no need for frequent blood draws or finger pricks. With particular regard to autologous serum eye drops, systematic reviews have shown their failure to improve PROMs in the setting of DED.[39]

Since it is well-known that treatment satisfaction in the setting of DED is underestimated and does not necessarily correlate with objective clinical outcome measures,[40] more investigators are starting to rely exclusively on the impact on quality of life and the PROMs in order to gauge the response to treatment.[41] Even with classic clinical measures such as Schirmer's testing, tear break up times and corneal staining findings along with newer diagnostic technology using measurements of tear film osmolarity, matrix metalloproteinase 9 and various ocular surface/meibomian gland imaging modalities, authors have concluded that there still exists no gold standard for the diagnosis and monitoring of DED.[42] For this reason, we believe that the future development of biologic agents in the treatment of DED must rely more upon demonstrating improvement in PROMs in order to translate into improved quality of life. Demonstrating statistically significant improvement in two of the three PROMs evaluated for a DED treatment in the biological realm is a relative strength of this study. The OSDI© score, BCVA and tear osmolarity all started to show a trend for improvement, but the study was not adequately powered to determine statistical significance.

In this study, a subset analysis of patients with previous failed use or current use of autologous serum (n=6) showed no significant difference in response to therapy as measured by change in SPEED™ questionnaire compared to those patients that have never tried autologous serum previously ($p>0.05$). Because of these findings, we hypothesize that this non-homogenous biologic product may have a different therapeutic

mechanism of action in the treatment of DED than blood-based biologic products. The composition of this eye-specific product derived from the cultured corneal epithelial stem cell supernatant is distinct from other non-homogenous blood-based biologic products in that laboratory testing has shown that it contains galectin-3 and other glycocalyx components that will serve as a protective barrier to the diseased ocular surface. Future molecular studies are necessary to determine if the supernatant has any biologic components that will integrate into galectin-3 lattice formations and other glycocalyx structures present on the ocular surface biologic niche which may be damaged in the setting of DED.

We recognize that this study included exclusively females. The gender disparity for DED has been notable in prior studies.[5] In our clinical practice it is unusual to encounter males with OSDI© score greater than 40. We suspect that a study that had recruited patients with all severity levels of DED would have equalized the gender imbalance to some degree.

It is also noteworthy that the therapeutic effects of the treatment tended to fade after discontinuation of the treatment for 12 weeks whereas the improvement seen in the PROMs trended back to baseline, but it was not statistically significant. This finding may indicate that ongoing treatment will be required to have a lasting impact on patient quality of life. Longer follow-up interval will be able to make this determination.

Weaknesses of this study include its open label and unblinded study design, the lack of a control group, the small number of cases and the relatively short follow-up interval. In summary, we have described a novel and transplantable corneal epithelial stem cell-derived product that is comprised of supernatant containing glycocalyx components that can be self-administered by the patient. We have established safety on a small cohort of severe DED patients and demonstrated promising outcomes with regard to efficacy for the improvement of PROMs specific for DED. Future investigations with a randomized, double-blinded and controlled study design with long-term data will be necessary to validate this study's findings and will need to be done on patients with all severity levels of DED. It will also be necessary to compare this treatment to other well-established DED treatments and to other newly emerging regenerative biologic agents.

Abbreviations

DED, dry eye disease; BCVA, best corrected visual acuity; LogMAR, logarithm of minimum angle of resolution; PROMs, patient reported outcome measures; SPEED^{TM}, Standardized Patient Evaluation of Eye Dryness; OSDI©, Ocular Surface Disease Index; VAS, visual analog score; HCT/Ps, Human Cells, Tissues, and Cellular and Tissue-Based Products; cGMP, Current Good Manufacturing Practice.

Declarations

The study was approved by the Salus Independent Review Board in accordance with the Ethical Standards laid down in the Declaration of Helsinki.

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable requests.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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There is no funding to report.

Disclosure

SWR and HD have proprietary interest in the biologic treatment studied. SWR and HD are managing partners of RegenKera, LLC which has an exclusive licensing agreement with Texas Tech University System for the patent-pending technology used to create the biologic product. SWR has a patent Stem cell supernatant manufacturing techniques pending to RegenKera, LLC. HD reports a patent WO 2020/018868 A1 pending. JC is affiliated with Oklahoma Blood Institute which has played a role in manufacturing the product used in this clinical trial. None of the investigators were paid to participate in the execution of the clinical study.

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