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Safety and efficacy of human amniotic epithelial stem cell eye drops in ocular chronic graft-*versus*-host disease

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Contributions

X.C., W.F., and R.H. contributed equally to this work. X.C., W.F., and R.H. performed the research and prepared the manuscript. Y.Z. and H.T. performed the ophthalmic index analysis. S.H. collected and analyzed the data. G.Z.prepared the hAESC eye drops. X.Z. and R.Y., and X.W. contributed equally to this work. X.Z. and R.Y. provided advice on the study design and critical review and editing of the manuscript. X.W. is the Ph.D. advisor for X.C. and W.F. and helped with selecting

the research project, designing and supervising the study and editing the manuscript. All authors had access to the data and were involved in the interpretation of data, contributed to the manuscript review and revisions, and approved the final version for submission.

Data-sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author Xiaoqi Wang xiaoqiwang27@gmail.com.

Declaration of interests

The authors declare no conflicts of interest.

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Clinical trial information

Title: Amniotic epithelial stem cell eye drops for ocular cGVHD : a single arm, open clinical study

Registration number: ChiCTR2200057857

https://www.chictr.org.cn/showproj.html?proj=135963

LETTER TO THE EDITOR

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for certain hematologic diseases. Chronic graft-versus-host disease (cGVHD) is the most common complication after allo-HSCT, occurring in 30% to 70% of patients[1]. The eye is one of the major target organs affected by cGVHD, with ocGVHD present in more than 50% of patients with cGVHD[2]. The common symptoms of ocGVHD are dryness, ocular pain, and even visual impairment, which severely decrease the patient's quality of life[3]. Nevertheless, the current clinical therapies for ocGVHD, including artificial tears, glucocorticoids, cyclosporine and tacrolimus, usually provide limited benefits[4]. Thus, novel therapeutic strategies are urgently needed.

Previously, we discovered that amniotic membrane transplantation can significantly alleviate ocular symptoms in ocGVHD patients[5]. Human amniotic epithelial stem cells (hAESC), a stem cell population isolated from the epithelium of the human amnion membrane, present unique characteristics, including pluripotency, low immunogenicity, and nontumorigenicity, which suggests that they can be used as a safe cell therapy[6]. Moreover, hAESC also could inhibit the activation and proliferation of T lymphocytes by initiating their programmed death and produce a variety of immunoregulatory factors that suppress the functions of inflammatory cells and promote tissue repair and downregulate the expression of extracellular matrix deposition-related cytokines to decrease fibrosis[7]. OcGVHD is predominantly characterized by T-cell-mediated inflammatory damage, which leads to ocular tissue damage and progressive fibrosis[8,9]. Hence, we postulate that the application of hAESC could improve ocular symptoms in ocGVHD patients and investigate the safety and efficacy of hAESC for treating ocGVHD in the clinical study.

This was designed as a single-center, prospective study for patients following HSCT. The study was reviewed and approved by the Army Medical University Xinqiao

Hospital Medical Science Research Ethics Committee and performed in accordance with the tenets of the Declaration of Helsinki. The study was registered at the Chinese Clinical Trials Registry (ChiCTR2200057857). OcGVHD patients were diagnosed in accordance with the National Institutes of Health (NIH) consensus, and the inclusion criteria were set as ocular GVHD patients between the ages of 18 and 60 who were willing to participate in the study. Eligible patients also had to present with controlled and stable systematic GVHD signs in other organs but show poor responses to the available ocular treatments, including artificial tears, glucocorticoids, immunosuppressors such as topical cyclosporine and tacrolimus, or punctual occlusion, thus resulting in a diagnosis of refractory ocGVHD. The exclusion criteria included ocular surgery within the preceding 6 months, ocular injury, other ocular diseases (such as infection, allergy, glaucoma, retinopathy, and autoimmune disease), pregnancy, long-term use of any topical ocular medications, and uncooperative patients. At the time of recruitment, clinical data, including demographic information, diagnosis, source of transplant, type of transplant, occurrence of systemic acute/chronic GVHD, and manifestations of cGVHD, were collected (Online Supplementary Figure 1). Then, the patients were advised to apply 2 drops 4 times daily per eye for 6 weeks. The hAESC eye drops were obtained from iCell Biological Technology Co., Ltd. (Online Supplementary table 1). The hAESC eye drops will be stored at -4 □ for 12 hours. The patients were further advised to report any adverse event immediately either by phone or through scheduling an immediate appointment. A team of hematologists and ophthalmologists diagnosed and graded the severity of ocGVHD in the patients based on the consensus of the NIH cGVHD score criteria. Visual acuity, ocular pressure, slit-lamp biomicroscopy, OSDI, Schirmer's test without anesthesia, CFS score, FTBUT and in vivo confocal microscopy (IVCM) results were all evaluated for all participants by the same ophthalmologist. Finally, the sum of the score in each quadrant was the final result for each eye.Patients were

followed at 2 weeks, 4 weeks, 6 weeks, 3 months and 6 months after using hAESC eye drops and whenever clinically indicated. A complete ophthalmologic examination was conducted at each visit to the extent tolerated by the patient. The differences in ocular examination results between baseline and after treatment were analyzed using the paired Student's t test. GraphPad Prism 10.0 for Windows was used to conduct statistical analysis and image graphing (GraphPad Software, Inc., San Diego, CA, USA). Adobe Illustrator 2020 was used for drawing. $P<0.05$ was considered to indicate statistical significance.

In total, 26 patients were included in the study. However, 6 patients did not complete the 2-week treatment and second ophthalmic examination and were excluded. Consequently, the population considered for analysis consisted of 20 patients, whose characteristics are summarized in Online Supplementary Table 2. More male than female patients were recruited (5 females, 15 males, range 21 to 56 years). The average time of ocGVHD onset following allo-HSCT was 9 months. The ocGVHD patients had cGVHD involvement in other organ systems, including the skin, liver, gastrointestinal system, oral mucosa, and lungs.

No serious adverse events were reported (Table 1). A total of 4 AEs, including hypersensitivity, application site pain, ocular itching, and increased intraocular pressure (IOP), were evaluated during this study. During treatment with the hAESC eye drops, 1 patient developed ocular itching rated 1 (mild) on a 1 to 5 scale, which did not stop immediately after discontinuation of the study medication for 1 day. Hence, it was considered unlikely to be related to the study medication, and the patient resumed hAESC eye drop therapy. After two weeks of treatment (n=20), patients demonstrated a significant reduction in OSDI from 47.40±24.73 at baseline to 35.64±24.89 (P=0.0003). After 4 weeks (n=15) and 6 weeks (n=12) of treatment, the mean OSDI decreased from 51.81±24.52 to 30.56±24.30 at baseline(P=0.0002) and from 48.49±25.38 to 23.67±22.60 at baseline(P=0.0001) (Figure 1A). After treatment

with hAESC eye drops, most patients also exhibited increased tear secretions (D0 versus 2 weeks: 2.48±3.30 versus 4.25±5.60, *P*=0.0237; D0 versus 4 weeks: 2.67±3.57 versus 5.89 ±8.09, *P*=0.0216) and (Figure 1B). Most importantly, we also observed a marked reduction in corneal epithelial damage and improvement in epithelial recovery as detected by fluorescein staining after use of hAESC eye drops (D0 versus 2 weeks: 9.23±5.83 versus 7.00±6.06, *P*<0.0001; D0 versus 4 weeks: 8.93 ±5.70 versus 6.27 ±5.44, *P*=0.0003; D0 versus 6 weeks: 7.96 ± 6.04 versus 6.87±5.72, *P*=0.0393) (Figure 2A and 2B). Interestingly, we found that corneal subbasal nerve density was significantly increased after hAESC treatment (D0 versus 2 weeks: 9.84±5.23 versus 12.53±5.83, *P*=0.006; D0 versus 4 weeks: 10.44±5.47 versus 12.85±5.18, *P*=0.0221) (Figure 2C and 2D). This result indicated that hAESC eye drops might enhance corneal sensitivity in ocGVHD patients.

OcGVHD is devastating because of limited therapeutic options, as patients usually fail to respond to current drugs, causing them to suffer from unbearable pain and apparent visual impairment, severely affecting their quality of life[10]. In the current trial, all enrolled patients had used long-term artificial tears without relief of dry eye symptoms. Artificial tears are usually administered to complement the insufficiency of tears but are unable to prevent the progression of dry eye disease[11]. Moreover, steroids and immunosuppressants are nonspecific and do not restore immune homeostasis on the ocular surface well. Meanwhile, long-term steroids are always avoided in clinical practice because of an increased risk of side effects, including infection, glaucoma, and cataracts[12].Stem cell therapy is considered an ideal option because of its ability to induce long-term recovery for injuries. In a prospective clinical trial, 14 ocGVHD patients exhibited substantial relief after MSC-exo treatment, showing reduced fluorescein scores and lower OSDI scores[13]. However, the flexible immune response and controversial tumorigenicity under pathological environments restrict their use for autoimmune disease patients. Moreover,

autologous MSC therapy requires invasive extraction for harvesting in most cases. In contrast, hAESC, deriving from the placenta, can be noninvasively harvested without ethical concerns and have no tumorigenicity due to the lack of telomerase[14]. Importantly, hAESC have demonstrated immunomodulatory properties in inhibiting the activity of immune cells and efficaciousness and have regenerative repair and antifibrotic properties[15]. The relative stability of hAESC when administered noninvasively has led to the application of cell eye drops rather than injections as a therapeutic approach for ocGVHD.

Our clinical trial showed that the application of hAESC eye drops four times daily improved the clinical signs and symptoms of ocGVHD within 2 weeks. The hAESC caused no irritation to the eyes, resulting in excellent compliance. According to our results, the mean reductions in the total OSDI was more apparent as the duration of treatment increased. All changes were greater than 10 points, which is generally considered to indicate a significant change in this group of severely affected patients. The eye symptoms in ocGVHD patients, including stinging, burning sensations, crust, or redness, were relieved after hAESC eye drop treatment. In our study, the treatment also showed an increase in tear production in Schirmer's test. We showed that in addition to prominent symptomatic improvement, the CFS was significantly improved, indicating healing of the epitheliopathy. Corneal innervation is one of the most important aspects indicating the state of the ocular surface. As evidenced by previous studies using IVCM, the density of subbasal nerves in ocGVHD was lower than that in normal eyes. A review revealed that the density of the subbasal corneal nerve is thought to be positively correlated with corneal sensitivity. Our study showed that the density of subbasal nerves improved after using hAESC eye drops. The online supplementary table 1 provides a description of the growth factors found in hAESC eye drops, such as transforming growth factor-β1 (TGF-β1), angiogenin (AGN), insulin-like growth factor (IGF) and so on. These growth factors play a crucial role in

the recovery of the corneal epithelium and nerves for ocGVHD patients. Further research is necessary to ascertain the exact mechanisms by which growth factors repair corneal epithelial cells and nerves.

In conclusion, hAESC eye drops are a safe, noninvasive, and efficient therapy for ocGVHD patients. Consistent with a safety study, sample sizes were relatively small in the study population. Further trials using hAESC eye drops in larger groups are planned to validate these findings. Furthermore, it would be appropriate for us to conduct relevant animal research in the future to explain the mechanism by which hAESC treat ocGVHD.

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Table 1. Overall Summary of Adverse Events in the hAESC Eye Drops Trial

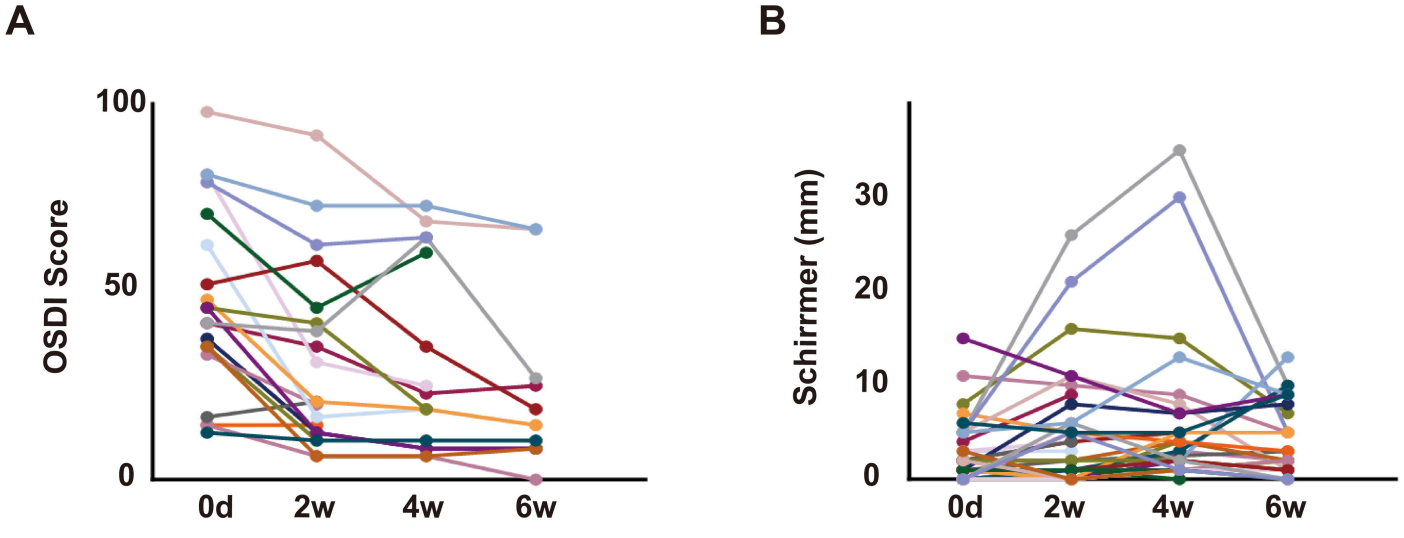
Adverse Events	Exist/Severity (n, %)	Relationship	Action taken
Hypersensitivity	0(0%)	N/A	N/A
Application site	0(0%)	N/A	N/A
Ocular itching	1(5%)	N/A	Discontinuation hAESC for 1 day and continue
IOP	0(0%)	N/A	N/A

IOP=increased intraocular pressure

Figure Legends

Figure 1. **hAESC eye drops ameliorated ocular symptoms in ocGVHD patients**. (A) After 2 weeks treatment of hAESC eye drops, Most of patients ameliorated ocular symptoms and improved their quality of life, as reflected by decreased OSDI scores. Each line represents a patient(n=20). (B) After 2 weeks treatment of hAESC eye drops, patients presented with increased tear volume by Schirmer's test. Each line represents one eye(n=40). hAESC=human Amniotic Epithelial Stem Cell.

Figure 2. **Changes in Corneal Fluorescein Staining and corneal subbasal nerve density.** (A,B) Representative images of the ocular anterior segment under slit-lamp microscopy and fluorescein examination before and 2 weeks after hAESC treatment. After hAESC eye drops usage, the cornea was more transparent, with fewer punctate areas of erosion. Fluorescein scores of individual eyes before and 6 weeks after treatment with hAESC eye drop showed that the fluorescein score tended to decrease in most eyes. (C,D) In vivo confocal microscopy images of corneal subbasal nerve density in patients before and after treatment, showing an increased corneal nerve density after using hAESC eye drops. (A to D) Each line represents one eye(n=40). hAESC=human Amniotic Epithelial Stem Cell.


A
100
50
0
OSDI Score
0d
2w
4w
6w
B
30
20
10
0
Schirrmer (mm)
0d
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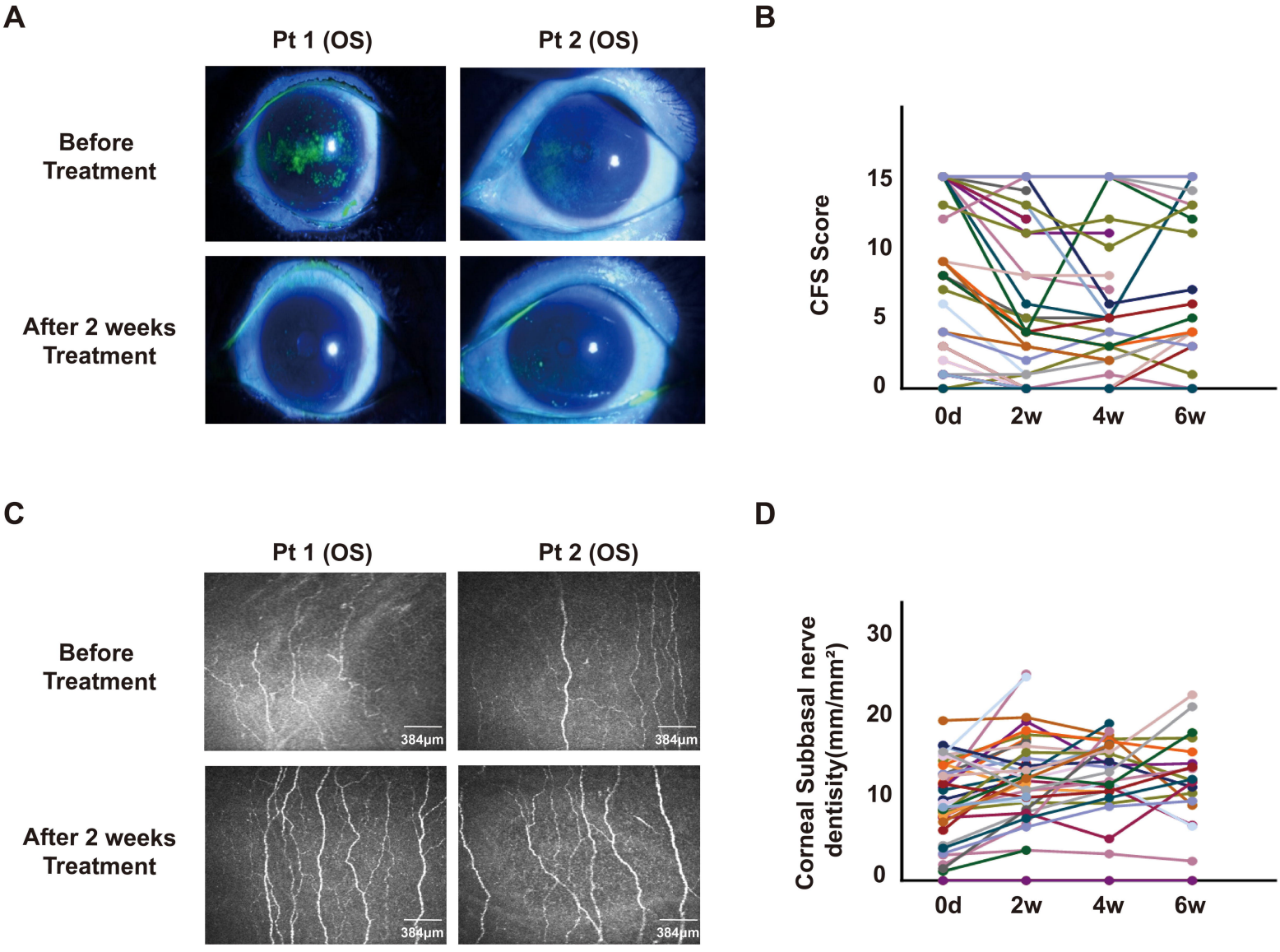
4w
6w


A
Pt 1 (OS)
Pt 2 (OS)
Before Treatment
After 2 weeks Treatment
B
CFS Score
15
10
5
0
0d
2w
4w
6w
C
Pt 1 (OS)
Pt 2 (OS)
Before Treatment
After 2 weeks Treatment
384μm
384μm
384μm
384μm
D
Corneal Subbasal nerve dentisity(mm/mm²)
30
20
10
0
0d
2w
4w
6w

Safety and Efficacy of Human Amniotic Epithelial Stem Cell Eye Drops in Ocular Chronic Graft-versus-host Disease

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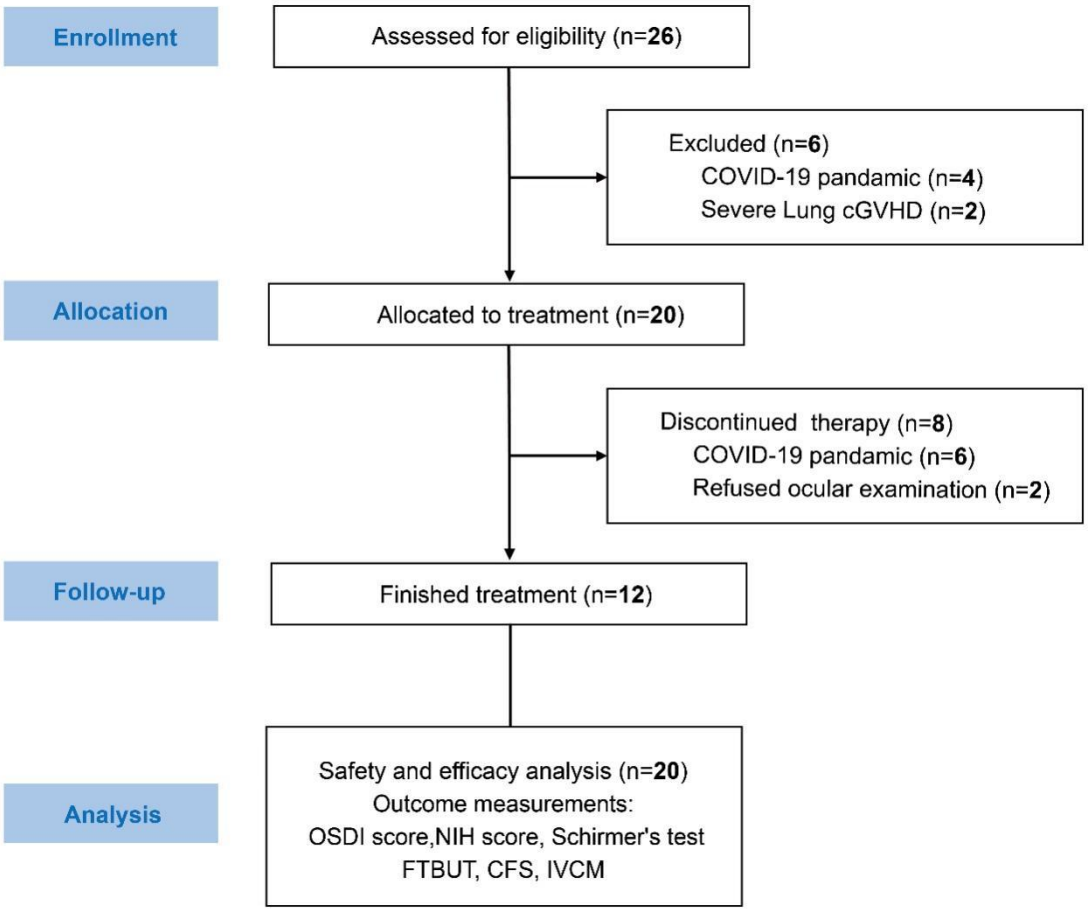
Online Supplementary Figure 1



Consolidated Standards of Reporting Trials (CONSORT) diagram of the hAESC eye drops trial. OSDI=ocular surface disease index; FTBUT=fluorescein tear break-up time; CFS=corneal fluorescein staining; IVCM=in vivo confocal microscopy.

Online Supplementary table 1 Manufacturing details of the hAESC eye drop products

The amniotic membrane was peeled from the placental chorion and washed in Hank's balanced salt solution (HBSS) to remove blood cells. The amniotic membrane was digested with 0.25% trypsin (EDTA) for 30 min at 37 °C in a water bath. Culture medium (F12/DMEM, 10% KSR (Knock Out Serum Replacement), 2 mmol/L L-glutamine, 1% nonessential amino acid, 55 μmol/L 2-mer-captoethanol, 1 mmol/L sodium pyruvate, 1% antibiotic-antimycotic (all from Gibco) and 10 ng/mL EGF (Peprotech) was added to the trypsin digestion medium, and the sample was centrifuged for 10 min at 300×g. The cell pellet was suspended in complete culture medium for subsequent cell culture. The cultured hAESC were frozen in CELLBANKER (ZENOAQ, Fukushima, Japan) at a concentration of 5×10^6/mL and stored at -80 °C overnight. Then, frozen vials were transferred into liquid nitrogen for long-term preservation. The hAESC were thawed by gently agitating the vial in a 37 °C water bath. Then, the hAESC eye drops were made at a concentration of 1×10^6/mL. In addition, 12 growth factors were identified in the suspension of hAESC using enzyme-linked immunosorbent assay research.

Items	Results
Appearance	Colorless translucent cell suspension, no foreign matter or granular material
Cell Viability	≥90%
Cell Phenotypic CD324	≥90%
Cell Phenotypic CD146	≤5%
HLA-DR	≤2%
Bacteria	Negative
Fungi	Negative
Mycoplasma	Negative
Endotoxin	≤2.5EU/ml
TGF-β2	Negative
TGF-β3	Negative
bFGF	Negative
EGF	Negative
HGF	Negative
TGF-β1	7.4 ng/ml

AGN	35.5 pg/ml
IGF	5.1 ng/ml
KGF	210.3 pg/ml
NGF	3.0 ng/ml
NT-3	7.5 pg/ml
VEGF	438.0 pg/ml

TGF-β2=Transforming growth factor-β2; basic fibroblast growth factor=bFGF; epidermal growth factor=EGF; Hepatocyte growth factor=HGF; AGN=angiogenin; IGF=insulin-like growth factor; KGF=keratinocyte growth factors; NGF=nerve growth factor; NT-3=neurotrophin-3; VEGF=vascular endothelial growth factor

Online Supplementary table 2. Characteristics of patients with ocular chronic graft-versus-host disease

Pts	Sex	Age	Diag-nosis	Type of Transplant	Baseline Time after HSCT (months)	Systemic cGVHD	Overall NIH Score	Topical treatment before hAESC treatment	Baseline ophthalmic characteristics				
									OSDI score	Schirmer (mm) (OD,OS)	FTBUT (s) (OD,OS)	CFS score (OD,OS)	Eye NIH score
1	M	56	AML	UD-HSCT	66	Oral, Eye	2	AT, PSL	12.5	5, 6	5, 3	1, 0	1
2	M	49	AML	Sib-HSCT	90	Eye	3	AT, PSL, CSA, ASD, Punctal plug	81.25	0, 0	1, 1	15, 15	3
3	M	38	AML	Sib-HSCT	60	Oral, Eye	4	AT, PSL	79.17	2, 3	3, 4	9, 9	3
4	F	29	MDS	Sib-HSCT	43	Skin, Oral, Joint, Eye	6	AT, PSL, CSA, FK506	41.67	1, 1	1, 1	8, 8	3
5	M	33	TCL	UD-HSCT	5	Skin, Liver, Eye	4	AT, PSL	35.42	2, 15	3, 5	15, 1	2
6	M	30	MDS	Sib-HSCT	40	Oral, Liver, Eye	5	AT, PSL, CSA, FK506	97.92	1, 0	0, 0	0, 0	3
7	M	51	MDS	haplo-HSCT	16	Liver, Eye	4	AT, CSA, FK506	70.83	0, 0	3, 3	15, 15	3
8	M	24	AML	UD-HSCT	32	Lung, Eye	3	AT, PSL, CSA, FK506	52.08	1, 0	3, 4	13, 12	2
9	F	51	AML	UD-HSCT	24	Lung, Eye	3	AT, PSL, CSA, FK506, Punctal plug	45.83	0, 2	0, 0	15, 15	2
10	M	21	ALL	Sib-HSCT	10	Skin, Oral, Eye	5	AT, PSL, CSA	45.83	0, 1	6, 7	9, 15	3
11	M	35	AMOL	haplo-HSCT	19	Skin, Liver, Lung, Joint, Eye	7	AT, PSL, CSA, FK506	81.25	0, 0	0, 0	15, 15	3
12	M	33	AML	haplo-HSCT	21.5	Eye	1	AT, PSL, FK506	47.92	5, 5	4, 2	1, 4	1
13	F	37	ALL	Sib-HSCT	50	Eye	2	AT, CSA	62.5	5, 2	8, 5	3, 4	2
14	F	52	AML	Sib-HSCT	30	Liver, Eye	3	AT, PSL	41.67	2, 0	5, 3	3, 15	2
15	F	30	MDS	Sib-HSCT	4	Liver, Lung, Joint, Eye	5	AT, PSL, CSA, FK506	33.33	2, 0	4, 2	7, 15	2

16	M	48	ALL	Sib-HSCT	40.5	Oral, Liver, Eye	4	AT, PSL	35.42	7，3	3，1	2，2	2
17	M	43	AML	Sib-HSCT	58	Oral, Eye	3	AT, PSL, CSA, FK506	16.67	4，3	8，3	1，6	2
18	M	40	ALL	UD-HSCT	14	Liver, Eye	4	AT, PSL, CSA, FK506	14.58	8，11	10，1	0，3	2
19	M	26	ALL	UD-HSCT	34.5	Skin, Eye	4	AT, CSA, FK506	37.5	1，1	3，3	15，15	3
20	M	53	AML	Sib-HSCT	50	Oral, Liver, Eye	4	AT, CSA	14.58	0，0	1，2	15，15，	2

ALL=acute lymphoblastic leukemia; AML=acute myelogenous leukemia; CML=chronic myelogenous leukemia; AMOL =acute monocytic leukemia; BMs =bone marrow stem cells; PBSCs =peripheral blood stem cells; TCL= T-cell lymphoma; UD-HSCT= unrelated donor hematopoietic stem cell transplantation; Sib-HSCT= sibling donor hematopoietic stem cell transplantation; haplo-HSCT=haploidentical hematopoietic stem cell transplantation; AT=artificial tear; PSL=prednisolone; CSA=cyclosporin; FK506=tacrolimus; ASD=autologous serum eye drops; OS=oculus sinister; OD=oculus dexter