HTA 16.09.10 Systematic review of treatment of dry age-related macular degeneration and Stargardt disease.

Supplementary file 3. Cell therapies

Schwartz et al

See Appendix 2 (Stargardt's disease)

Song et al

Study details	**Participant details**
Song WK, Park KM, Kim HJ, Lee JH, Choi J, Chong SY, et al. Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients. Stem Cell Reports 2015;4:860-72 *Country:* Korea *Design:* Case series *Number of centres:* one *Funding:* commercial and non-commercial *Trial ID:* none	*Number of Participants*: 4 (2 dry AMD; 2 Stargardt's macular dystrophy). *Number of eyes* 4 *Sample attrition/dropout*: not applicable *Sample crossovers:* not applicable *Inclusion criteria:* none reported. *Exclusion criteria:* none reported

Intervention details	**Outcomes**
Intervention *1.* subretinal transplantation of human embryonic-stem-cell (hESC)-derived retinal pigment epithelium *Dose details:* details of the derivation of the RPE cells from the hESCs reported, not extracted. *Dose modifications:* not applicable *Concurrent treatment:* immunosuppression (no further details) *Duration of treatment:* 12 months	*Outcomes (state if primary)* BCVA Adverse events *Length of follow-up:* 12 months

Participant characteristics, %			
	hESC transplantation in dry AMD, n=2	**hESC transplantation in Stargard'ts, n=2**	**P value**
Age, years range	65-79 years	40-45	
Sex, % male	100	100	
Ethnic origin *% White*	0	0	
Classification			
Smoking history			
visual acuity, BCVA (ETDRS letters)	Pt 1: study eye CF4ft (1 letter), fellow eye 20/25 (80 letters) Pt 2: study eye 20/320 (25 letters), fellow eye 20/85 (55 letters)	Pt 1: study eye CF2ft (1 letter); fellow eye 20/800 (4 letters) Pt 2: study eye 20/640 (13 letters); fellow eye 20/250 (32 letters)	

Comments: CF4ft, counting fingers at 4 feet; CF2ft, counting fingers at 2 feet.			
Results			
	hESC transplantation in dry AMD, n=2	**hESC transplantation in Stargardt's, n=2**	**P Value**
BCVA (ETDRS letters) at 1 year	Pt 1: study eye CF4ft (2 letters, fellow eye 20/32 (75 letters) Pt 2: study eye 20/200 (34 letters), fellow eye 20/200 (35 letters).	Pt 1: study eye 20/640 (13 letters); fellow eye 20/500 (13 letters) Pt 2: study eye 20/250 (32 letters); 20/160 (41 letters)	
Adverse events			
Ocular or systemic serious adverse events	0	0	
Pt one (dry AMD): coryza, senile purpura, gynecomastia, constipation, and allergic conjunctivitis Pt 2 (dry AMD): laryngopharyngeal reflux, upper respiratory infection with rhinorrhea, potassium level elevation, diarrhoea, indigestion, tinnitus, arm tremor (all unrelated to treatment and resolved). Pneumonia possibly related to immunosuppression. Pt 3 (Stargardt's) Skin bullae at the left forearm, a contusion of the right hand, external otitis, rhinorrhea, sneezing, fatigue, headache, upper respiratory infection, and chronic gingivitis were mild and unrelated adverse events. Herpetic vesicles developed on right arm possibly related to immunosuppressive. Pt 4 (Stargardt's) Upper respiratory infection, aggravation of reflux esophagitis, and loss of a dental implant were mild and unrelated adverse events			

Case series studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Was the study population clearly and fully described, including a case definition?		x	
3. Were the cases consecutive?			CD
4. Were the subjects comparable?		x	
5. Was the intervention clearly described?	x		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
7. Was the length of follow-up adequate?	x		
8. Were the statistical methods well-described?			NA
9. Were the results well-described?	x		

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Ho et al 2017

Study details	Participant details
Ho AC, Chang TS, Samuel M, Williamson P, Willenbucher RF, Malone T.Experience With a Subretinal Cell-based Therapy in Patients With Geographic Atrophy Secondary to Age-related Macular Degeneration. 2017. Am J Ophthalmol;179:67-80 *Country:* USA *Design:* cohort study, two phases 1) dose escalating, 2) 1 of 2 doses 'randomised'. Data for the two cohorts was combined. *Number of centres:* multicentre (number not stated) *Funding:* Commercial *Trial ID:* NCT01226628	*Number of Participants*: total 35 enrolled; 33 treated: phase 1 29; phase 2 4 *Number of eyes* total 35 *Sample attrition/dropout*: 2 (in phase 1) underwent a partial surgical procedure but did not receive the cell implant because of retinal perforations; 3 (from phase 1) discontinued prior to 12 month follow-up. *Sample crossovers:* not applicable *Inclusion criteria:* ≥50 years of age with a confirmed diagnosis of bilateral GA caused by AMD (confirmed within 21 days prior to administration of the intervention); ≥1 GA lesion involving the centre of the macula, diameter of 360 µm, BCVA ≤20/200 in phase 1 and ≤20/80 in phase 2. The study eye was the eye with the worst visual acuity or selected by the investigator phase 1, and the worst eye in phase 2. *Exclusion criteria:* exudative AMD in either eye; evidence of other significant ophthalmic disease; any ophthalmic condition that reduced the clarity of the media (further details reported in the publication)

Intervention details	Outcomes
Intervention *1.* subretinal administration of palucorcel (cell-based therapy) *2.* fellow eye control *Dose details:* human umbilical tissue–derived cells in a proprietary cryopreserved formulation. In phase 1 a single dose of palucorcel (ranging from 6.0 X 10^4 to 5.6 X 10^5 viable cells [12 received 6.0 X 10^4, 3 received 1.2 X 10^5, 15 received 3.0 X 10^5, 3 received 5.6 X 10^5 cells) In phase 2, single dose of 1 of the 2 doses of palucorcel (6.0 X 10^4 or 3 X 10^5 viable cells) *Dose modifications:* not applicable *Concurrent treatment:* standard postoperative care without systemic immunosuppression. *Duration of treatment:* not applicable	*Outcomes* Adverse events (safety and tolerability primary outcome) BCVA (ETDRS/logMAR/Snellen). Contrast Sensitivity Reading speed (not reported) Reading acuity Changes to area of GA Quality of life (NEI VFQ-25) (states reported elsewhere, reference not provided) Immune response (not extracted) Low luminance BCVA and Low Luminance Deficit (not extracted) *Length of follow-up:* 4 years (ongoing), study endpoints 12 months Enrolment into phase 2 was suspended after 4 patients (for development of a more refined surgical technique for cell delivery).

Participant characteristics, %			
	Surgical procedure, n=35		
Age, years median (range)	82.0 (66-94)		
Sex, % male	45.7		
Ethnic origin *% White*	100		
	Cell implant, n=33 eyes	**Fellow eyes, n=33**	

Median (range): *BCVA, logMAR*[a] *BCVA letters* *BCVA Snellen equivalent*	 1.10 (0.7 – 1.6) 26.0 (2-50) 20/250 (20/100 – 20/800)	 0.60 (0.2–1.5) 56.0 (10–77) 20/80 (20/30 to 20/600)	
Total area of GA, median (range) mm[b]	14.26 (5.7–35.9)	11.05 (3.1–33.6)	
[a]Following protocol amendment in June 2012, baseline BCVA was defined as the median visual acuity when 3 assessments were performed or as the assessment showing better visual acuity when only 2 assessments were performed. [b]measure obtained from 2 or 3 readers interpreting the same image			
Results			
	Cell implant, n=33 eyes	**Fellow eyes, n=33**	**P Value**
BCVA letters, median (range) change at 12 months	4.5 (-41 to 32)	-0.5 (-30 to 15)	
BCVA ≥10 letter gains at 12 months, %	34.5 (n=29)	3.3 (n=30)	
BCVA ≥15 letter gains at 12 months, %	24.1 (n=29)	3.3 (n=30)	
Comments: states that the primary objective of this study was to evaluate the safety and tolerability of palucorcel delivered subretinally and that the sample size of the study was small, statistical testing of any hypotheses was not considered appropriate.			
BCVA Snellen equivalent, median (range) at 12 months	20/250	20/100	
Comments: states the percentage of subjects with a gain of >10 letters in BCVA was >30% at months 3, 6, and 12 in the intervention eye and peaked at approximately 13% at month 3 in the fellow eye			
BCVA logMAR, median (range) change at 12 months	NR	NR	
Comments:			
Contrast sensitivity	NR	NR	
Comments: states there was considerable variability with low reliability in measures of contrast sensitivity and reading acuity. Visual field assessments showed relatively small changes in the mean deviation and pattern standard deviation in the treated eye during the first 12 months. Visual field reliability was also poor for many with impaired visual functioning owing to GA.			
Area of GA median (range) change at 12 months, mm^2	2.86 (1.0-8.1)	2.37 (0.6 – 8.9)	
Comments			
Adverse events (AE)	**Cell implant, n=33**		
≥ 1 SAE, %	39.4		
Serious ocular AE[c]	15.2		
[c]retinal detachment (15.2%); proliferative retinopathy (6.1%)			
Severe AE, %	51.5		
Severe ocular AE[d], %	12.1		
[d]retinal detachment (9.1%), retinal perforation (6.1%), periorbital oedema (3.0%), reduced visual acuity (3.0%)			
≥ 1 AE, %	97.0		
Eye disorder AE[e], %	78.8		
[e]The most common ocular AEs were retinal perforation (36.4%), conjunctival haemorrhage (30.3%), retinal detachment (15.2%), retinal haemorrhage (15.2%), eye pain (12.1%), and reduced visual acuity (12.1%). Data for eye adverse events in the surgically treated group also presented but not extracted. Study states approximately 76% who received palucorcel experienced >1 AE related to eye surgery, the surgical delivery system, and/or palucorcel and approximately 58% experienced an AE considered to be reasonably related to the surgical delivery system, most notably retinal tears. Also reports rate of retinal detachment after a protocol change to introduce ophthalmic endoscopy during surgery, not extracted.			
Death in phase 1, n	3		
No deaths were considered related to study treatments or procedures			
Subgroups			

NIH Risk of bias for observational studies

1. Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	Not met
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		x	
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	Overall no
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Fair

*CD, cannot determine; NA, not applicable; NR, not reported