Transcorneal electrical stimulation for the treatment of retinitis pigmentosa – a multicenter safety study of the OkuStim® System (TESOLA-study)

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1. Abstract

Background
Transcorneal electrical stimulation (TES) has been suggested as a possible treatment for retinitis pigmentosa (RP).

Objective
To expand the safety assessment of repeated applications of an electrical current from a DTL-like electrode in patients with RP.

Method
This single-arm open label interventional safety trial included a total of 105 RP patients from 11 European centers, who received weekly TES for six months on one eye followed by observation for another six months without stimulation. The primary outcome measure was safety, indicated by the frequency and severity of adverse events. Secondary measures included intraocular pressure and central retinal thickness. Visual field and visual acuity were examined using the methods available at each site.

Results
Dry eye sensation was the most common adverse event recorded (37.5%). Serious adverse events secondary to TES were not observed. Most adverse events were mild and all resolved without sequelae. The secondary outcome measures revealed no significant or clinically relevant changes.

Conclusion
The present results confirm the excellent safety profile of TES. Transient dry eye symptoms were the most common adverse event.

2. Introduction

Retinitis pigmentosa (RP) is an inherited retinal degeneration characterized by rod-cone degeneration, which can be caused by defects in about 90 known genes (OMIM #268000; https://www.omim.org/entry/268000). Typical non-syndromic RP has a reported prevalence of 1 in 4000 [1]. At present, there are no established treatments for inherited retinal degenerations with medical management focussing on associated problems, such as cataracts, and referral to the low vision clinic for rehabilitation.

Transcorneal electrical stimulation (TES) has been reported in the literature as a potential therapy for RP since the nineteenth century [2]. A pilot study in 2011 conducted in 24 RP patients demonstrated the safety of TES and suggested positive effects on functional tests [3]. Animal studies suggest that these positive effects may be mediated by an alteration in neurotrophic factors conferring a protective effect on photoreceptors and neural cells [4, 5]. Patients with subretinal implants have shown functional improvement in retinal areas distant from the implant, possibly indicating a global trophic effect from electrical stimulation [6, 7].

More recently, a randomized sham-controlled trial investigating TES in 52 patients with RP following weekly administration for one year yielded significant improvement in the secondary endpoint of photopic b-wave amplitude although the primary endpoint of visual field area were not reached, showing only positive trends [8].

The primary objective of the TES open label (TESOLA) study presented here was to evaluate the long term safety of TES in patients with RP. More than one hundred patients in eleven European centers were treated with the commercially available OkuStim® system for six months and followed-up for a further six months observation period.

3. Materials and Methods

Study design

The study was a multinational prospective open-label trial with the primary outcome being a measure of the safety of TES with the OkuStim® system. Eleven ophthalmology centers across Europe (Germany, UK, Netherlands, Italy, Denmark and Norway) recruited 105 participants between the ages of 18 and 80 years (Table 1). Diagnosis of RP was ascertained through history, examination and in some cases electroretinography. Patients were observed for a total time of 12 months (six months TES treatment and six months observation).

Exclusion criteria were concomitant eye disease (with potential effect on the outcome measures), previous eye surgery, pregnancy and mental illness. All patients had a visual acuity of greater than 0.02 Snellen decimal in both eyes and had sufficient dexterity to handle the device in cases where home stimulation was applied (about one third of the patients). Only one eye was treated. In the majority of cases, the worse eye was assigned as the treated eye unless the worse eye had an insufficient level of vision to complete all assessments of visual function. In this case, the better eye was treated. Worse eye was chosen primarily from visual acuity. If visual acuity was symmetrical, the eye with the smaller visual field was

chosen. The choice of eye was discussed with the patient and confirmation sought that the patient was happy to proceed on this basis. The other eye acted as a control. Patients attended the sites for assessments every 3 months.

Transcorneal stimulation and ophthalmological procedures

TES was administered using the Okustim® device on a weekly basis for the first six months. This consisted of a single- or double-wire sterile single-use DTL-like electrode (Okuel®) mounted onto a metallic spectacle-like frame (Okuspex®**,** Figure 1**)**. A skin reference electrode was placed over the *fossa temporalis.* Individual phosphene thresholds were established using the Okustim® software (version 1.4.4.0) in the eye to be treated only. Stimulation parameters included pulses of 5 ms positive deflection and 5 ms negative deflection with a frequency of 20 Hz. The current delivered was increased slowly from 0.02 mA, in increments of 0.01 - 0.05 mA to a maximum current of 1.0 mA until participants perceived phosphenes. The threshold procedure was carried out three times and an average was calculated. Each participant was allocated a unique Universal Serial Bus (USB) stick upon which the threshold was stored using the OkuStim® software. For the administration of TES, the participant's USB stick was inserted into the device to deliver the appropriate current (Fig 1A). The current of TES delivered was 150% of the individual phosphene threshold, as a previous pilot study demonstrated this to be both safe and confer improvements in psychophysical and electrophysiological outcome measures [3]. This was amended after three months. If phosphenes could not be elicited during threshold determination or the participant's phosphene threshold exceeded 0.66 mA, a current of 1.0 mA was applied. The study received ethical approval in each country with original approval granted by the Ethics Committee of the Medical Faculty at the University of Tübingen (442/2011MPG23). The study was registered at clinicaltrials.gov (NCT01835002).

Participants underwent weekly TES for a period of 30 minutes for six months. The course of TES was considered complete if less than 20% of stimulation sessions were missed (per protocol population). Thirty-two patients performed home-stimulation after a four-week training phase in the hospital, while 73 were treated in the hospitals. Ophthalmic examinations were conducted at baseline, 3 months, 6 months, 9 months, and 12 months. These included visual acuity, optical coherence tomography (OCT), and visual field analysis using locally available equipment. A questionnaire consisting of six questions regarding the subjectively perceived treatment-related changes in object localization, object recognition, letter and number recognition, person recognition, orientation and mobility, and overall satisfaction with the treatment was designed for the present study. The scale included the following options: sometimes worse (-1), unchanged (0), sometimes better (1), often better (2), usually better (3), almost always better (4), and don't know/ not sure. The questionnaire was not standardized and had a skewed scale and thus was only analysed in a qualitative manner as the unevenness of the scale prevented adequate statistical analyses.

Adverse events were reported, characterized and graded according to severity, relation to treatment, outcome and frequency by the respective principal investigator and study team.

Statistical analysis

This clinical trial was a safety study and not designed to assess efficacy. Visual function and other ocular parameters were analysed to elaborate on safety, as a sharp decrease in the visual function would indicate a toxic effect of the therapy. The primary outcome measure was safety and as such analyses were conducted with the *intention- to-treat* (ITT) population. Descriptive analysis included mean, standard deviation, minimum, and maximum. Confirmatory analyses were done using Generalized Estimating Equations (GEE) with Independence Correlation Structure (IEE). In these analyses, standard errors are estimated taking into account the dependency of measurements from the same subject. This approach was chosen as it is very robust for this kind of trial [9]. Study visit was coded in three ways, as a linear covariate, as a binary factor (baseline vs each other visit), and as a full factor (five levels, dummy coding with reference = baseline). Visual acuity was converted to decimal notation to allow comparisons to be made between the different modalities of assessment used in the centres [10]. Visual field characteristics were assessed either by means of static (mean deviation) or kinetic (visual field area – isopter III4e) strategies using different automated perimeters (Humphrey or Goldmann/Octopus respectively). Due to different measurement devices, visual field data could only be analyzed qualitatively on an ordinal scale (improvement, stable, worsening). To analyze the visual field changes across patients, intervals defined by two cut-off values were used to determine whether the individuals' visual fields improved, worsened or remained unchanged as compared to baseline. Separate ranges for mean deviation (static) and visual field area (kinetic- III4e) were computed based on a test-retest variability analysis informed by a previous pilot study [3]. The range for the cut-off values corresponded to the mean of the absolute percentage test-retest difference [11]. The resulting mean absolute percent change for static perimetry (mean deviation) was 3.1%; whereas for kinetic perimetry (III4e) was 20.8%. Separate analyses for the stimulated eye, control eye, and stimulated vs. control eye were conducted and taking into account eyes improving vs. eyes worsening (excluding eye remaining unchanged from analyses). Significance testing was done using the binomial test (separately for each visit) and a logistic regression analysis with primary test for intercept = 0 using a GEE / IEE estimator. In this analysis, a marginal model for the outcome is estimated ignoring the dependency structure, however, estimation of standard errors, and thus p-values and confidence limits take into account the observed dependency structure [9].

4. Results

A total of 105 patients were recruited into the study (ITT), out of which 98 completed the stimulation period as per protocol. A further two participants completed all the visits but missed more than 20% of the treatments with TES. Six participants did not complete the follow-up examinations in the stimulation free period (Figure 2). The statistical analysis was conducted with the ITT group of patients.

Out of the total participants, 64 were male (61%) and 41 were female (39%). Mean age ± SD for the participants was 45 ± 15 years (range 18 - 78 years). Forty-four patients were stimulated on the right eye, 61 on the left eye.

Safety Results

The primary outcome measure was the safety profile following 6 months of weekly treatment. No serious adverse events (SAEs) relating to the device were reported throughout the study. Three SAEs were recorded; injuries secondary to a traffic accident, obstructive sleep apnoea, and meatal stenosis. After medical review, these were not considered to be related to the device.

The majority of adverse events (37.5%) were dry eye symptoms, which settled within 24 hours after the treatment session and were treated with ocular lubrication. Other adverse events related or possibly related to the treatment were unilateral cataract (one case), muscle twitching (reported once), sensation of flashing lights (reported once), subconjunctival foreign bodies (one case), vomiting following stimulation (reported twice in one patient) and a tingling sensation on the side of the head (one case). All these were reported as resolved, mostly without treatment. Adverse events associated to the electrodes were categorized as "technical problems". These adverse events were solved during the course of the study as the electrode design was optimized (single-wire to double-wire). At the beginning of the study, single-wire electrodes were used by all sites. Patients reported these to be uncomfortable. After 3 months of the start of the study, the electrode was switched to double-wire electrodes. The changeover occurred at different rates across individual sites so the precise breakdown of AEs related to each electrode type was not possible. We can report that the before the change 14 AEs occurred in 3 months (averaging 4.6 AEs per month). After that, there were 52 AEs in 34 months (averaging 1.5 AEs per month). There was no correlation between the type of the electrode and the nature and frequency of AE, except for the reduction in the technical problems reported after the change. Please note, the silver thread used was identical in all cases. No adverse events related to the therapy were reported during the observation period. A comprehensive overview of all adverse events and their relation to the device, as well as an overview with respect to their intensity, outcome, and frequency is shown in Figure 3.

No significant change in IOP ($p = 0.93$ in the stimulated eye and $p = 0.16$ in the control eye, (Figure 4a) was observed during the observation period. Central retinal thickness measured with OCT ($p = 0.43$ in the stimulated eye and $P = 0.49$ in the control eye) was stable over the study period (Figure 4b). While no episodes of cystoid macular edema were reported in the stimulated eye, there was one case of macula edema in a control eye. This was not considered to be related to the device.

Visual function results

Visual acuity was converted to decimal notation to allow comparisons to be made between the different modalities of assessment used in the centres although this might not be a recommended approach [10]. Decimal notation was used to allow results from Snellen and logMAR charts to be combined. Both stimulated and control eyes showed no change in visual acuity outside of clinically established retest variability (less than 0.1 decimal visual acuity) (Figure 5). Visual field did not reveal significant changes over time when comparing simulated vs control eyes ($p = 0.581$). There were no significant differences in either the

stimulated ($p = 0.648$) or control eyes ($p = 0.593$, Figure 5). The different perimetry methods yielded comparable results.

A comprehensive overview of all quantitative data can be found on Table 2.

In regards to the questionnaire, most participants reported stable vision on all categories across visits, and were very satisfied with the treatment.

5. Discussion

This prospective single-arm observational safety study of repeated delivery of transcorneal electrical stimulation for RP demonstrated a good safety profile of the OkuStim® system. No serious adverse events related (SAEs) to the device were reported over the 12 month period. The most common adverse event was transient dry eye syndrome, which was addressed with ocular lubricants. There were no cases of cystoid macular edema secondary to the treatment throughout the study.

While the present study focused on the safety of TES, visual function was assessed using different methods at each site to monitor for marked changes in ocular pathology status as a measure of safety. The results yielded no changes in visual field parameters (kinetic or static) and the mean difference in visual acuity of approximately 0.03 Snellen decimal, equating to one ETDRS letter. The functional results must be interpreted with caution for several reasons. Different methods of assessment for visual acuity (e.g. Snellen fraction, LogMar, ETDRS letters) were utilized by the centres. This aggregation of results limits the power of the current study. The baseline characteristics between eyes were not balanced due to the use of the worse eye for treatment, which may result in a regression to the mean effect, greater variance in visual acuity measurements and possibly a differing rate of disease progression. Finally, it has to be considered that the study was not powered for changes in visual acuity, as it was designed to assess safety. The visual and ocular parameters were also used as safety markers by monitoring for unexpected decline.

Cell biology studies of TES have found alterations in the expression of a wide variety of retinal genes and altogether there is no indication of a single dominant target. Genes covering cell regulation, immunity, cell communication and cell differentiation have been implicated [12, 13]. The patients in the present study were not routinely tested for the causative genetic mutation nor selected for any specific genotype, but this may be a significant factor in predicting the success of the therapy.

Animal studies have shown that TES alters the concentration of several neurotrophic factors and other growth factors [14, 15]. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is thought to have a critical neuroprotective role in retinal disease as well as other central nervous system conditions such as Parkinson’s disease [16] and deserves further attention. BDNF is involved in the survival of retinal pigment epithelium cells [16] and has been shown to alter following TES [5, 13, 17]. BDNF is able to cross the blood-retinal barrier, which may limit the usefulness of using the contralateral eye as control eye. Although animal studies have not shown altered regulation of BDNF in the contralateral eye [13], they performed their assays after very short term stimulation so cumulative effects of multiple treatments were not assessed.

Retinal ganglion cells have been shown to have increased survival rates following TES [18, 19]. Retinal changes in multiple cell types and layers have been reported in contralateral eyes of unilateral optic nerve damage through a possible inflammatory mechanism [20]. Additionally electrical stimulation of the retina evokes electrical activity in the brain with

associated blood flow changes [21, 22]. Cortical response strength and the area of response related to the frequency of administered TES, TES length, and current intensity [21]. This indicates that the control eye may additionally benefit from contralateral TES through secondary stimulation thereby possibly washing out the treatment effect in a non-sham controlled study. Schatz et al attempted to address the problem of cross talk with the contralateral eye using a sham controlled approach [8]. Although visual acuity did not improve, they did detect an increase in the photopic electroretinogram, whilst scotopic function remained unchanged. Further laboratory studies in understanding the differential effects of the altered neurotropic factors in different light levels may be helpful in understanding this finding. Stimulus parameters for the clinical trials have been chosen based on previous animal work [5] and early clinical work. Various previous clinical studies referenced earlier have set the TES parameters at different levels and applied it for different lengths of time. However, further investigation into the stimulus parameters may be beneficial for maximal therapeutic effect [21]. The TES level is currently set based on each individual's phosphene threshold but it is not known whether this is the best approach to follow or whether a pre-defined and/or higher threshold would be beneficial.

In conclusion, TES using the OkuStim® system has been shown to be safe. TES has possible advantages over other treatments as it has a relatively low cost, can be used at all disease stages, and presents a low risk probability of serious side-effects. Patients can be taught to self-administer offering great flexibility over the treatment regime for both patients and healthcare providers, freeing up valuable clinical space and clinician time to allow a greater throughput of patients without increasing costs.

6. Appendix

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7. Supplementary Material

All data relevant to presented results and conclusions are included in the manuscript. There is no supplementary material available.

8. Statements

8.1. Acknowledgements

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8.2. Statement of Ethics

The clinical study adheres to the tenets of the Declaration of Helsinki and all subjects have given their written informed consent. The study protocol received ethical approval in each country with original approval granted by the Ethics Committee of the Medical Faculty at the University of Tübingen (442/2011MPG23). The study was registered at clinicaltrials.gov (NCT01835002).

8.3. Disclosure Statement

IZ was employed at Okuvision GmbH. FG and EZ are shareholders and consultants of Retina Implant AG of which Okuvision GmbH was a subsidiary. The STZ eyetrial (BW) was subcontracted by Okuvision GmbH and received payments for CRO services. These conflicts of interest did not influence the validity of the clinical research and the publication of this paper. All other authors declare that there is no conflict of interest.

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10.Figure Legends

Figure 1: (a) OkuStim® system consisting of stimulator device (1) – OkuStim®, electrode frame (2) – OkuSpex®, and OkuEl® electrodes (3, arrow). (b) OkuEl® electrode in its current model.

Figure 2: CONSORT diagram displaying the patient flow.

Figure 3: Description of adverse events (AEs) and serious adverse events (SAEs) seen during the trial. (a) Describes the type of AEs / SAEs seen. No serious adverse events relating to the device were reported. The SAEs were injuries secondary to a traffic accident, obstructive sleep apnoea, and meatal stenosis. (b) Describes the relationship of the AEs to the device. (c) Describes the intensity (mild, moderate, severe), the outcome (unresolved, revolved with sequelae, resolved without sequelae), and the frequency (isolated, intermittent, continuous) of the AEs related to the Okustim®.

Figure 4: Visual function: (a) Change in visual acuity over time using visual acuity converted into decimal notation. However, different tests were used across centres so this should be accounted for when interpreting the results. Visual field changes in stimulated eye (b) and control eye (c). Data from kinetic and static visual fields categorized as improved, worsened or unchanged as compared to baseline.

Figure 5: (a) Intraocular pressure: No significant differences were found between stimulated and control eyes. Most eyes remained within the normal range. (b) Central retinal thickness: no differences were found between stimulated and controls eyes.

11.Tables

Distribution of participants across sites	
Site	**Number of patients**
Tübingen	24
Bonn	10
Siegburg	10
Regensburg	8
Berlin	7
Copenhagen	10
Oslo	10
London	6
Oxford	8
Rotterdam	5
Florence	7

Table 1: Distribution of participants across sites

Data overview of Intention-to-treat (ITT) patient group																
		Baseline			**V2**			**V3**			**V4**			**V5**		
Examination [unit]	**Eye**	Mean (SD)	min	max	Mean (SD)	min	max	Mean (SD)	min	max	Mean (SD)	min	max	Mean (SD)	min	max
VA [decimal]	stimulated	0.48 (0.32)	0.01	1.2	0.52 (0.33)	0.02	1.25	0.52 (0.35)	0.02	1.25	0.52 (0,35)	0.02	1.25	0.53 (0.36)	0.01	1.25
	control	0.56 (0.35)	0.01	1.6	0.56 (0.35)	0.01	1.25	0.57 (0.34)	0.01	1.25	0.57 (0.35)	0.01	1.25	0.58 (0.35)	0.01	1.25
VF Static MD [dB] (n = 47)	stimulated	24.58 (5.65)	9.91	32.73	24.43 (5.71)	10.41	32.99	24.56 (5.99)	9.51	32.74	24.67 (5.93)	10.39	32.79	24.62 (5.91)	9.67	32.90
	control	24.14 (5.83)	9.13	32, .70	24.38 (5.71)	8.70	32.99	24.47 (6.01)	9.04	33.32	24.38 (6.04)	9.88	33.24	24.66 (6.12)	9.37	33.15
VF kinetic area [deg²] (n = 51)	stimulated	3834.27 (4227.45)	11.40	13756.10	4049.52 (4529.38)	13.00	15056.40	4155.38 (4501.25)	7.90	15017.50	4261.83 (4514.94)	9.50	14803.50	4541.37 (4648.03)	2.00	14774.20
	control	4655.39 (4429.19)	36.20	14111.20	4404.91 (4496.68)	38.50	14156.40	4703.58 (4567.33)	31.10	14490.00	4717.12 (4566.61)	28.00	14655.90	4549.39 (4467.22)	8.00	14454.80
IOP [mmHg]	stimulated	14.25 (2.32)	10	21	14.092 (3.02)	9	26	14.160 (3.389)	9	34	13.882 (2.58)	10	20	14.337 (3.06)	9	21
	control	14.184 (2.43)	10	20	13.592 (2.67)	8	21	13.9 (2.732)	9	21	13.839 (2.559)	9	19	14.63 (3.705)	9	35
OCT retinal thickness [µm]	stimulated	235.84 (65.25)	78	425	231.911 (62.118)	66	440	235.250 (64.128)	84	426	236.167 (64.1219)	92	394	237.719 (65.9073)	81	462
	control	241.59 (65.01)	74	397	239.120 (60.71)	48	396	241.866 (63.71)	55	408	241.147 (66.89)	67	463	244.1961 (64.534)	59	423

Table 2: Data overview. Table including mean (SD), minimal and maximal values across ITT patient group for all visits. Examinations included visual acuity (VA), visual field (VF) kinetic or static, intraocular pressure (IOP) and retinal thickness as measured with optical coherence tomography (OCT).