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Transcorneal Electrical Stimulation Therapy

Application, effect, and patient's benefit of OkuStim® therapy in the treatment of retinitis pigmentosa

The hereditary retinal disease retinitis pigmentosa (RP) leads to a slow progressive loss of vision and eventually to blindness. There is no cure for this disease. OkuStim® therapy is an evidence-based and clinically available method for preserving vision. It activates neuroprotective signaling pathways in the retina through transcorneal electrical stimulation (TES), slowing the loss of photoreceptor function and progressive narrowing of the visual field. OkuStim therapy is used at home and in an outpatient setting. The safety of TES therapy with the OkuStim system has been demonstrated in in several clinical trials with over 400 treated patients and no serious adverse events.

Retinitis pigmentosa

Retinitis pigmentosa (or retinopathia pigmentosa, RP) is the most common inherited retinal dystrophy. It comprises a heterogeneous group of retinal diseases leading to night blindness and progressive vision loss. The prevalence is approximately one case per 4,000 people.[1] The most common form of RP begins with the degeneration of rods in the peripheral retina, involves the loss of cones, and progresses towards the center. Typical is tunnel vision with long lasting good visual acuity, but progressive loss of the peripheral and eventually also the central visual field irrevocably leads to serious visual impairment up to blindness. The loss of visual field area follows an exponentially decreasing course with an annual decrease between 5% and 17%.[2]

A multitude of genes is associated with RP, and accordingly the individual clinical pictures and time courses of the gene-specific subtypes of RP are heterogeneous.[1] Common to all is the mutation of one or more genes and resulting structural defects of retinal proteins of the photoreceptors or the pigment epithelium. This disturbance of the integrity of the photoreceptors and their metabolism leads to the demise of the rods and subsequently of the cones.

There is yet no causal treatment for all forms of RP. It severely limits the activities of daily living[3] and seriously impacts the quality of life of RP patients.[4] Seventy-five percent of patients with RP become symptomatic by the age of 30,[5] 50% are legally blind by the age of 55.[2]

To preserve or restore vision, various approaches are being pursued. For early stages of the disease, when photoreceptor cells are still intact, gene therapies are being developed, clinically tested, and implemented.[6] Stem cell therapy, optogenetic therapy, and electronic retinal implants are other approaches to restore vision in later stages of retinal degeneration.[7] Transcorneal electrical stimulation (TES, also referred to as TcES , Fig. 1) is used as a neuroprotective therapy.[8, 9] It aims to activate neuroprotective signaling pathways in the retina,[10] slow down disease progression, and prevent or postpone later stages of RP.

TES is considered a promising strategy and noninvasive treatment option for retinal dystrophies in scientific medical reviews.[1, 10-15]

Clinical results of TES treatment

Clinical studies show that TES triggers physiological processes both in the healthy retina of normal-sighted people and in the diseased retina of RP patients. The application directly causes a significant increase in blood flow to the central retina[16, 17] and increased oxygen consumption by retinal cells, suggesting an increased metabolism induced by TES.[18] Randomized controlled trials and observational studies with weekly application showed significant improvement in visual acuity,[16] slowing of visual field loss,[16, 19, 20] improved b-wave amplitudes in the dark-adapted[19] and light-adapted ERG,[9] and shortening of the latency of the P1 wave in the central rings of the multifocal ERG.[21] The effect of TES appears to be transient, suggesting regular and sustained use.[21]

Although the clinical data from the various studies do not yet provide a consistent picture of the long-term effects, they do indicate significant positive effects of TES on photoreceptor function and on the visual field. Acknowledging this, the German Institute for Quality and Efficiency in Health Care (IQWiG) has confirmed that TES therapy with the OkuStim system has the potential for patient-relevant benefit.[22] The German Federal Joint Committee (G-BA) has subsequently issued a guideline for the testing of TES[23] and commissioned a prospective trial.[24]

Fig. 1. | *OkuStim therapy for slowing of progressive loss of visual field in retinitis pigmentosa. Transcorneal electrical stimulation is administered via a thin electrode filament contacting the ocular surface.*

Recently, the German Ophthalmological Society (DOG) updated its guideline recommending electrical stimulation as a therapy for RP.[25]

In most of the studies performed so far, only patients with a diagnosed rod-cone dystrophy were admitted, including those with Usher syndrom. Therefore, clinical data on other forms of retinal dystrophies are scarce. Due to the very rare occurrence of cone-rod dystrophy, choroideremia and others, isolated clinical data to unequivocally demonstrate the clinical performance of TES in these retinal dystrophies has so far been very difficult to obtain in clinical trials and are limited to case reports.[26]

Mechanism of action

TES therapy addresses the final stage of the pathophysiological mechanisms involved in the different gene-specific subtypes of RP. It aims at protecting the photoreceptors and inner retinal cells and preventing or delaying late stages of the disease with complete photoreceptor demise. The effects of electrical stimulation are primarily mediated by the effect of the local electrical field induced by the stimulation current on voltage-sensitive proteins in retinal cells and secondarily by the subcellular pathways modulated by it. The therapeutic effects of TES are associated with anti-apoptotic, neurotrophic, vasodilative, anti-inflammatory, and anti-glutamate mechanisms. Multiple TES-induced protective mechanisms may also act simultaneously and together promote retinal cell survival.[10, 12]

In TES with the OkuStim system, the ocular surface below the cornea is stimulated with a thin electrode filament (Fig. 1). Return electrodes are located on the forehead. The stimulation current is in the range of 100 to 950 µA. Current enters the eye, spreads intraocularly and polarizes retinal cells,[27] triggering cellular activity in all layers of the retina.[28, 29] Both normal-sighted people and people with degenerative retinal diseases perceive this activation as flickers of light (so-called phosphenes[30]) when stimulation is sufficiently strong.

Polarization of cell membranes leads to a modulation of the conductivity of voltage-gated ion channels and the intracellular homeostatis. Especially the triggering of Ca2+ channels and an increased intracellular Ca2+ concentration is linked with the activation of subcellular biochemical cascades related to neuroprotective pathways in the retina.[31] Preclinical studies have demonstrated that ocular electrical stimulation modifies retinal gene expression profiles,[29, 32, 33] activates anti-apoptotic and neuroprotective signaling pathways and suppresses inflammatory signaling pathways, thereby producing a cell-preserving effect in the retina (see reviews[14, 34, 35]).

In animal models for RP it has been demonstrated that TES decelerates degenerative processes in the retina markedly and increases the survival of photoreceptors.[36, 37] An important role is attributed to the protective and repair function of Müller cells, the glial cells of the retina.[31, 38] Electrical stimulation enhances their proliferation and expression of photoreceptor progenitor cell markers via voltage-gated calcium channels. The activation of the cell-preserving mechanisms and subsequently the degree of protection depended on the waveform, strength, and frequency of the current.[36, 37, 39]

In summary, the studies collectively suggest that TES activates subcellular pathways in a dose-dependent manner which leads to cellular and thus potentially clinically relevant protective effects in the retina.[10]

Although not explicitly supported by clinical data, it can be assumed that the current delivered into the

eye by TES has a delaying effect on the course of the final stages of photoreceptor degeneration regardless of the form of generalized retinal dystrophy. Thus, not only for people with primary RP, but also for people with the much rarer forms such as cone-rod dystrophy, Usher syndrome, and choroideremia, there is a chance that the progression of visual field loss will be slowed by TES therapy.

Safe therapy for RP

Electrostimulation of the eye for the treatment of vision loss is generally considered to be safe.[15] The Working Group Clinical Issues (AKF) of the Scientific Medical Advisory Board of PRO RETINA Deutschland e. V. evaluated the use of TES with the OkuStim device in retinal dystrophies as safe and has no objections to its controlled use in patients with RP and other generalized hereditary retinal dystrophies such as cone and rod dystrophies, choroideremia and Usher syndrome.[40]

All clinical studies conducted to date with the OkuStim system uniformly demonstrate the safety of using TES therapy in outpatient settings and in the delivery of therapy at home. Almost 500 patients participated in the studies (Fig. 2) and collectively stimulated their eyes for a total of more than 100 years, including more than 60 years of home use. With a total of almost 3,000 documented hours of stimulation, no serious adverse event related to the device or therapy occurred. The most common side effects during treatment were dry eye symptoms, which were reported by 72% of patients treated with TES in the EST2 clinical trial.[20] It has since been recommended to use artificial tears immediately before and during TES treatment to reduce the occurrence of dry eye symptoms. Pain and visual discomfort were reported by 6% of treated patients. In general, the side effects were mild and transient.

Clinical trials with OkuStim®

Safety and efficacy of OkuStim therapy for RP have been investigated in several clinical trials (Fig. 2).

Pilot study EST 1

In the randomized controlled pilot study, 16 RP patients were treated with TES for 6 weeks (EST 1 trial, clinicaltrials.gov: NCT00804102). Patients were randomly assigned to treatment with 0.0 mA (placebo), 66% or 150% of their individual threshold for electrically evoked phosphenes. The most stimulated group showed a 17% increase in visual field area ($p<0.001$) and a 13% increase in b-wave in the dark-adapted (scotopic) ERG ($p<0.027$) compared to the untreated control group. *Publication: Schatz et al., 2011* [19]

Follow-up study EST 2

In the randomized controlled follow-up trial (EST 2 trial, clinicaltrials.gov: NCT01837901), 63 RP patients were treated with the OkuStim system in one eye weekly over one year; 52 patients completed the study per-protocol. Patients were randomly assigned to treatment with 0.0 mA (placebo), 150% or 200% of their individual threshold for electrically evoked phosphenes. A significant improvement ($p<0.0001$) of the b-wave was measured in the light-adapted (photopic) ERG.[9] However, the results of the pilot study regarding the visual field could not be reproduced. There was only a tendency to improve the visual field area for the 200%-stimulated group.

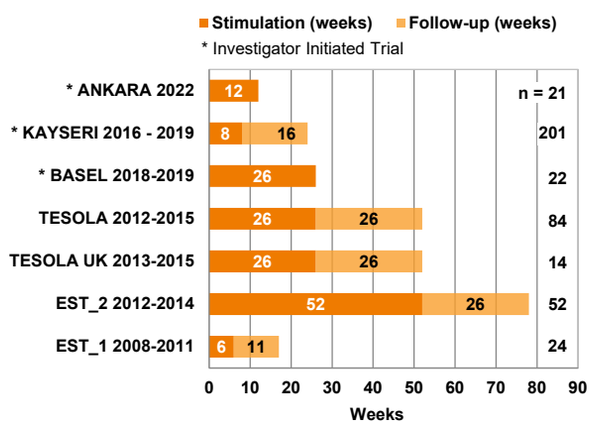

Fig. 2. | *Clinical trials on the application of TES with the OkuStim system in retinitis pigmentosa. Left axis: name and duration of the trials, lower axis: duration of the trials (stimulation and unstimulated follow-up period); right axis: number of participating patients.*

An a posteriori analysis of the data revealed that the TES effect correlates with the current strength and not with the phosphene threshold.[20] Following the exploratory reanalysis, the mean loss in visual field area in all stimulated eyes was shown to be 64% less than in untreated fellow eyes ($p = 0.013$) and 72% less than in placebo-treated eyes ($p = 0.103$). The slowing effect correlated with current amplitude ($p = 0.043$, Fig. 3A) and the visual field was stable and better preserved in patients who received 0.8 – 1.0 mA than with placebo stimulation ($p = 0.036$, Fig. 3B).

Publications: Schatz et al., 2017 [9]*; Stett et al., 2023* [20]

Interventional safety trials TESOLA + TESOLA UK

In two multicenter interventional safety trials (clinicaltrials.gov: NCT01835002, NCT01847365)

conducted in 11 European clinics, the safety of the use of the OkuStim system was clearly demonstrated. In the prospective, open-label studies, RP patients underwent weekly stimulation with the OkuStim system at home (32 patients) or in the clinic (73 patients) for 6 months and were then followed up for an additional 6 months without stimulation. No serious adverse events (SAEs) related to the device and therapy occurred throughout the study. A common adverse event was transient dry eyes, which was easily treatable with eye drops.

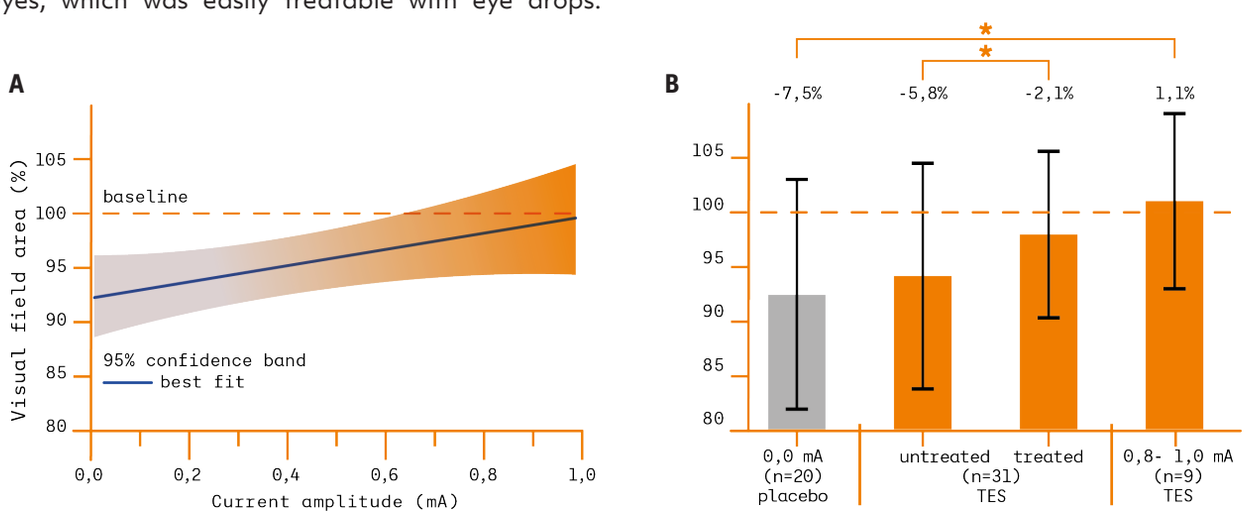

Fig. 3 | *Visual field area (VFA) after one year of TES treatment.* **A)** *In the EST2 study, the decline in VFA depended on the average stimulation intensity. The higher the current intensity, the better the VFA was preserved.* **B)** *After one year of TES treatment, the average loss of VFA was 2,1% compared to 7,5% in eyes treated with placebo. In eyes stimulated with currents between 0,8 and 1,0 mA, the visual field remained stable on average. Bars: Average visual field area (V4e) relative to baseline. Error bars: Standard deviation. n is the number of patients treated. The asterisk indicates a statistically significant difference (p < 0,05, paired Wilcoxon rank sum test). The numbers inserted above indicate the mean relative change of VFA compared to baseline.*

Visual fields and visual acuities of stimulated and non-stimulated eyes remained objectively stable throughout the observation period, and most participants were very satisfied with the treatment. *Publications: Jolly et al., 2019* [41]*; Wagner et al., 2017* [42]

Observational study BASEL

In a prospective observational study of 22 RP patients, weekly 30-minute stimulation with the OkuStim system showed increased oxygen consumption with unchanged retinal vessel diameters after six months. This proves that TES triggers physiological processes in the retina of RP patients. *Publication: Della Volpe-Waizel et al., 2019* [43]

Retrospective study KAYSERI

A retrospective study with 101 treated and 100 untreated RP patients (202 treated eyes) showed a statistically significant improvement in visual field and visual acuity after 2 months of treatment with TES and a shortening of the latency of the P1 wave in the central rings of the multifocal ERG. However, the positive effects seem to be transient, as they were no longer detectable after 6 months without further treatment. This suggests a regular and permanent therapy with TES. *Publication: Sinim Kahraman et al., 2020* [21]

Retrospective study ANKARA

Twenty-one patients with early-stage RP were included in this retrospective study. They received the stimulation with 200% EPT in 12 weekly sessions under supervision in the clinic. After TES treatment, the best corrected visual acuity, color vision level and P1 amplitude in ring 1 of in mf-ERG were statistically significant increased ($p < 0.001$). Ninety-five of the patients stated that they were satisfied with the therapy. No noteworthy side effects occurred. *Publication: Demir et al., 2022* [44]

Long-term testing study TES-RP (ongoing)

In most cases, TES is not yet reimbursed by healthcare payors. It is also not yet recommended as an evidence-based treatment option for RP in national and international guidelines. Both require further proof of therapeutic benefit over a longer clinical observation period. The type of effect to be demonstrated (significant slowing of visual field loss on a multi-year time scale with large interindividual differences) requires a large patient population and a long treatment period. The German Federal Joint Committee (G-BA) has commissioned the University Hospital of Tübingen with the planning and scientific monitoring of a testing study ("Erprobungsstudie"). The aim is to determine

Indications for OkuStim® Therapy

TES therapy with OkuStim is suitable for the treatment of patients with retinitis pigmentosa (also syndromal, e.g., Usher syndrome)

Contraindications

The OkuStim therapy should not be used by patients with acute inflammation of the eye and who exhibit blood vessels with growth processes that could be accelerated by electrical stimulation (ocular neovascularization of any origin, macular edema, artery or vein occlusion, diabetic retinopathy, age-related macular degeneration).

Application of the OkuStim® Therapy

Medical prescription.

OkuStim products are only dispensed after diagnosis and determination of therapy eligibility and tolerance threshold upon a doctor's prescription to ensure regular progress control – at least once per year.

Determination of the individual stimulation intensity.

The physician determines the individual current amplitude for the electrical stimulation. The highest tolerable value should be chosen.

Therapy procedure.

Patients stimulate at home once a week for 30 minutes and regularly (every 6 - 8 months, but at least once per year) visit the clinic for check-ups.

Stimulation parameters.

Biphasic current pulses (max. 0.95 mA), pulse duration 10 ms, frequency 20 Hz.

Handling of the OkuStim 2 system.

Operation of the OkuStim 2 system is simple and tailored to the patients' needs. It offers acoustic output of system messages to be used autonomously by patients also in an advanced stages of the disease.

Availability

The OkuStim System is an active medical device with CE marking. It is available in Europe.
For clinical centers and distributors please refer to **www.okuvision.de/en.**

whether TES can influence patient-relevant endpoints (especially visual field) in such a way that a sufficient benefit is achieved compared to untreated patients. The multicenter study enrolled 134 patients with syndromal and non-syndromal RP (autosomal dominant, autosomal recessive, and X-linked) who will use TES for three years. Patient enrollment was closed in February 2023, results are expected in 2026. *Publications: IQWiG, 2014* [22]*; Kahle et al., 2021* [24]

What TES cannot do

RP does not only lead to loss of photoreceptors. It is also associated with extensive remodeling of the neuronal and vascular architecture of the retina and functional reorganization of cellular networks.45 The question of whether neurovascular changes are reversible after years of degeneration remains unanswered. A short-term study with 6 months of TES application showed no significant effect on retinal blood vessels.46 The earlier TES therapy is started, the greater the chances of avoiding or delaying losses of cells. The therapy can only protect what is still there: Perished photoreceptors cannot be restored by TES and retinal remodeling is not reversible.

Summary and conclusion

The OkuStim therapy is an evidence-based, safe and effective method that is CE marked and available for home use in Europe. The results of clinical trials show that regular electrical stimulation of the eye with weak currents can slow down the decrease of the visual field in people suffering from RP. This allows those affected to maintain vision and vision-related quality of life for longer.

OkuStim® is the only available and topically applied treatment for retinitis pigmentosa.

Okuvision products are not for sale in the USA.

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Okuvision GmbH
Gerhard-Kindler-Str. 17
72770 Reutlingen, DE
Tel: +49 7121 159 35 0
www.okuvision.de/en

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OkuStim® Therapy

Neuroprotection for RP. Now!

Transcorneal electrical stimulation (TES) with **OkuStim®** triggers neuroprotective signalling pathways in the cells of the retina. As a result, the progression of retinitis pigmentosa and other degenerative retinal diseases can be **slowed down.** Set new impulses and find out more on **okuvision.de/en.**

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