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Review Article

Retinal prostheses in degenerative retinal diseases

Tai-Chi Lin [a,b], Hua-Ming Chang [c,d], Chih-Chien Hsu [a,b], Kuo-Hsuan Hung [b,e], Yan-Ting Chen [b,f,g], Szu-Yu Chen [c], Shih-Jen Chen [a,*]

[a] *Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[c] *Department of Optics and Photonics, National Central University, Taoyuan, Taiwan, ROC*
[d] *Bade Veterans Home, Taoyuan, Taiwan, ROC*
[e] *Department of Ophthalmology, National Yang-Ming University Hospital, Yilan, Taiwan, ROC*
[f] *Department of Ophthalmology, Changhua Christian Hospital, Changhua, Taiwan, ROC*
[g] *Department of Optometry, Central Taiwan University of Science and Technology, Taichung, Taiwan, ROC*

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Abstract

Degenerative retinal diseases may lead to significant loss of vision. Age-related macular degeneration (AMD) and retinitis pigmentosa (RP), which eventually affect the photoreceptors, are the two most common retinal degenerative diseases. Once the photoreceptorcells are lost, there are no known effective therapies for AMD or RP. The concept of retinal prosthesis is to elicit neural activity in the remaining retinal neurons by detecting light and converting it into electrical stimuli using artificial devices. Subretinal, epiretinal, and other retinal prostheses implants are currently designed to restore functional vision in retinal degenerative diseases. In this review, we have summarized different types of retinal prostheses, implant locations, and visual outcomes. Our discussions will further elucidate the results from clinical trials, and the challenges that will need to be overcome to more efficaciously assist patients with AMD and RP in the future.

Keywords: age-related macular degeneration; epiretinal implants; retinal prosthesis; retinitis pigmentosa; subretinal implants

1. Introduction

Retinal prostheses are being developed to replace the photoreceptor of the eye in cases with severe retinal degeneration.[1] The mechanism of prosthesis as it relates to photoreceptors of the eye is to utilize an artificial device to detect and transform light energy into an electrical signal, conveying the electrical signal to the unaffected areas of the inner retinal neurons to evoke downstream visual pathway.[2] In other words, through electrical stimulation of the inner retinal layers, degenerative diseases of the outer retina are bypassed and substituted (Fig. 1).[3,4]

In patients with age-related macular degeneration (AMD), < 20% of the rod and cone cells are preserved.[5,6] Although large amounts of outer retinal cells may be destroyed as retinal diseases become further exacerbated, the inner retinal neurons appear intact. The cell density of the inner retina juxtaposed to the normal retinal pigment epithelium (RPE) is comparable to that between AMD patients and the normal control group.[7] As much as 70% and 25–40% of ganglion cells are preserved in the inner retinal region in patients with AMD and retinitis pigmentosa (RP), respectively. By contrast, morphologic studies in RP patients with variable severity have shown a greater preservation of the inner nuclear layer than the ganglion cell layer and the outer nuclear layer.[6,8] Despite the

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* Corresponding author. Dr. Shih-Jen Chen, Department of Ophthalmology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: sjchen@vghtpe.gov.tw (S.-J. Chen).

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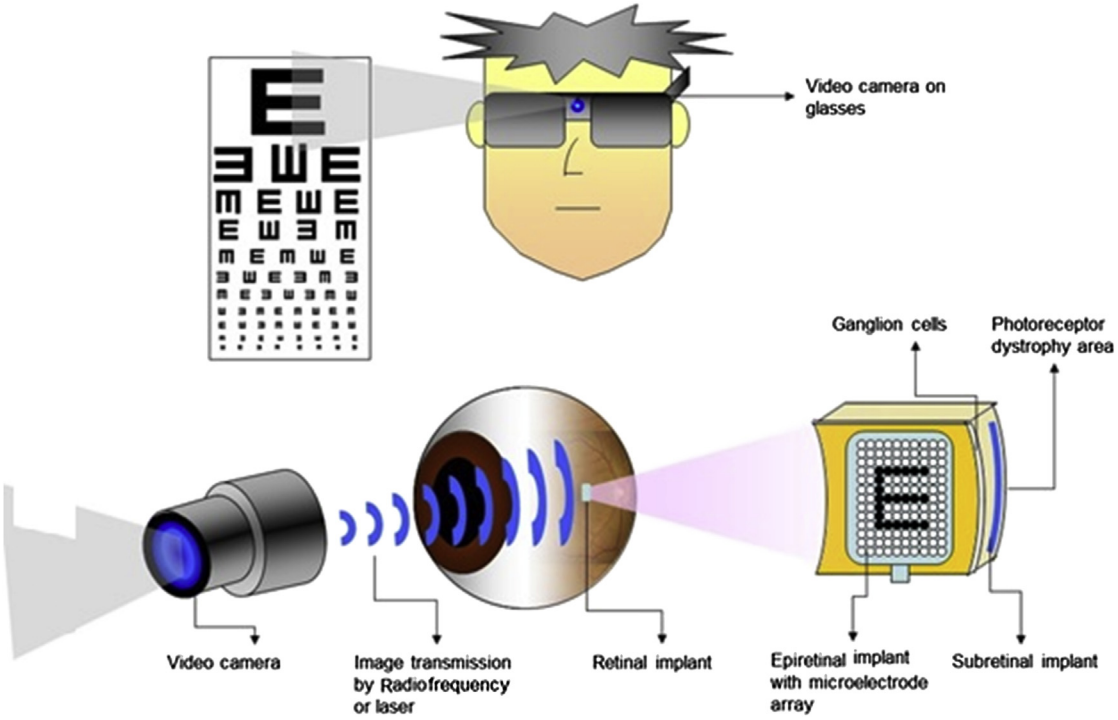

Fig. 1. Concept of the retinal prosthesis: light energy is converted into electrical signal from either an external camera or an implanted imaging component in different systems. For external cameras, data are transmitted wirelessly to the implant. The implant generates a stimulation pattern based on the light pattern on the camera and delivers this stimulation pattern to the multielectrode array.

preservation of the inner retinal cells after photoreceptor degeneration in RP cases, significant changes occur in the retinal structure and in the connections between neurons.[9] Rod cells can exhibit neurite sprouting extending into the ganglion cell layer even in areas where retinal photoreceptor loss has occurred.[10] Available evidence suggests extensive neurite sprouting in horizontal and amacrine cells, a phenomenon that was not present in the age-matched control patients. Furthermore, the inner retina exhibits remodeling and reconnection during the progression of degeneration. Retinal cells that survive will integrate into other residual retinal layers in later stages.[5] However, non-neuronal cells also participate in retinal degeneration. For example, Müller cells, as a constructive pillar of retinal structure, are involved in the formation of a barrier between RPE and the remaining retinal neurons.[11] However, whether the ongoing function of the remaining disorganized retinal neurons can respond to electrical stimulation from artificial devices as a case of normal ocular physiology needs additional clarification. Thus, despite the fact that retinal prostheses have both existed and been studied for > 50 years, numerous obstacles remain to be solved.

Recently, clinical trials have shown that electrical stimulation to a specific area of the retina will generate stable visual perceptions that spatially correspond to the stimulated region with promising and reproducible results.[1,2,12] In this paper, we reviewed different types of retinal prostheses, visual outcomes, and current progression from clinical trials, providing useful information for future investigation.

2. Retinal prostheses

Electronic retinal prostheses are neither able to restore full visual acuity nor all visual functions because the high density of photoreceptors in the fovea cannot be completely replaced by current microelectronic devices. These devices are intended to only improve visual acuity from blindness into low vision. Although there are several different types of retinal implants, all of them contain an image capture unit with either a microphoto diode array or an external camera plus an array of electrodes for stimulation of the inner retinal neurons to mediate the luminance and spatial information of images. The most commonly used classification of retinal implants is based on their localization: epiretinal, subretinal, or suprachoroidal types and even inside the optic nerve head.[1,2] In this review, we focus on the subretinal and epiretinal types of prostheses. We will also discuss four representative retinal prostheses, namely, Argus II, EPI-RET 3, Intelligent Medical Implants (IMIs), and Alpha-Institute for Microelectronics Stuttgart (Alpha-IMS), along with the results of clinical trials that have been conducted to date (Table 1).

2.1. Subretinal prostheses

Subretinal prostheses are implanted in that common location where photoreceptors are typically found. These prostheses can be divided into passive and active systems. The active system is driven by the surrounding light of the image

Table 1
Summary of currently available retinal prostheses.

Prostheses type	Argus II	EPI-RET 3	Intelligent Medical Implants	Alpha-Institute for Microelectronics Stuttgart
Image capture	External camera	External camera	External camera	Multi-photodiode array
Location	Epiretinal	Epiretinal	Epiretinal	Subretinal
Clinical trial	Food & Drug Administration, Europe	Europe	Europe	Europe & Hong Kong

itself and contains an external power supply. In most of these prostheses, the photoreceptor component and the electrode array are combined into one subretinal chip; the number of independently working pixels among the devices varies between 200, 512, 1500, and 5000.[13] Because the incident light contains only limited energy, which is insufficient for the luminance–current conversion in a single pixel, passive implants were unable to mediate a meaningful perception. Therefore, no passive visual system is in use at present. In active subretinal chips, the incident luminance is converted into a graded electrical current via amplifiers in each pixel, thus creating an electronic image, which is transmitted pixel-by-pixel to the bipolar cells. The image is perceived as shades of gray. With subretinal photodiode systems, however, no light adaptation, similar to natural vision, is possible.

One of the main advantages of subretinal prosthesis is the relatively natural feeling of perception. This is due to the fact that the remaining visual pathway from the bipolar cells onward is used and the information processing in the inner retina can be maintained and utilized. In addition, with the photoreceptive array being put inside the eye, natural eye movements are used. Natural eye movement is very important for a normal perception of vision, which is in contrast to those systems with cameras attached to spectacle frames, where head movements are necessary to find the object of interest. In addition, ocular microsaccades allow for constant refreshing of the retinal images. Furthermore, the number of pixels creating the electronic image in subretinal implants is the highest of all visual implant devices developed thus far. The subretinal implants allow for a higher resolution of vision and more potential for the visual function. However, subretinal device implant surgery is complicated by the requirement of a large transchoroidal incision, followed by the introduction of a cable into the subretinal space without direct visualization, which demands special attention during implantation. In addition, the active device surgical procedure includes a silicone oil tamponade as a guard against the propagation of retinal detachment. Finally, regardless of whether the implant is epiretinal or subretinal, as long as there is a transscleral cable, long-term secured wound closure around the cable will need to be addressed to prevent hypotony.[2] To date, the Alpha-IMS (Retina Implant AG, Reutlingen, Germany) is the only subretinal prosthetic device that has been applied in a human clinical trial.[13,14]

2.2. Epiretinal prostheses

The epiretinal prosthesis is implanted on top of the ganglion cell layer with the electrode array fixed to the retina with retinal tacks. Thus, the ganglion cells are stimulated directly without mediation of the inner nuclear layer, whereas the image information comes from an external camera mounted on glasses and is mediated wirelessly through an inductive coil to the intraocular electrode array. Bypassing the bipolar cells requires transformation electronics to generate signal for direct ganglion cell stimulation. All epiretinal visual implants are provided with an external battery system for power supply.[15–18] The external camera captures the image and allows for magnification and zoom of the target, which enables an optimization of the functional artificial vision despite a relatively low number of pixels in the electrode array.[19] The external camera, however, eliminates natural eye movements from the vision process, which may result in perception fading due to missing microsaccades refreshing the retinal image. We further elucidate upon the present types of epiretinal retinal prostheses, namely, Argus II, EPI-RET 3, and IMIs, and the results of their clinical trials.

2.2.1. Argus II

Argus II is the first approved device in clinical trials in both the USA (Food and Drug Administration Phase 4 postmarket surveillance) and Europe (Phase IV, European CE marking).[2,20] Argus II consists of a 60-electrode array and has been implanted in 30 patients for up to 38.3 months with 94.4% of electrodes retaining functionality throughout the study period.[15] Argus II is designed with transscleral cables, and the image capturing process of Argus II involves acquisition of image from external camera, transferring the signal to a processor/transmitter coil, and then a wireless transmission to an electronics case. The electronics case is connected by a transscleral cable to the epiretinal implant, which is held in place with retinal tacks.[15]

Twenty-nine patients continued home use of the device.[21] Among the 29 patients, the highest score and highest achieved visual acuity (ranging from logMAR 1.6 to logMAR 2.9) was with a letter reading measured at 20/1262. Furthermore, with the aid of tracing paths on touch screens and auditory feedback, this device had a higher accuracy, but longer times with the implant on promotes the potential learning and reactivating of the visual pathway.[20] However, although external electronic devices allow a simpler surgical technique for implant setting, long-term risk of infection may be elevated with transscleral cables. Complications including conjunctival erosion, endophthalmitis, and ocular hypotony have been reported in follow-up.[15,21]

2.2.2. EPI-RET 3

Recently, the EPI-RET 3 has been used in clinical trials in Europe in which the device was implanted in six patients for

28 days.[22] Electronic stimulation produced visual perceptions in patients, who were encouraged to describe the experiences and identify unknown objects.[14] Future developments in this area encompass glasses with an external camera for wireless data and power transfer to a receiver module. Moreover, visual testing and higher resolution should be confirmed before implantation success is determined.[22]

With no transscleral cable, the long-term risks of complication may be reduced with the use of EPI-RET 3. However, when the device was explanted, some tacks were found to be loose, and growth of epiretinal membranes was observed.[22] During the 2-year follow-up, gliosis also appeared near the tacked sites, but no change in the quality of life was noted.[17]

2.2.3. Intelligent Medical Implants

IMI retinal prosthesis is in clinical trials in Europe. A recent study reported the results of temporary implantation in 20 patients for 45 minutes. During that period, patients were able to identify and describe phosphenes, or light perception from electronic stimulation.[23] IMI uses an external camera for image capture with wireless data and power transfer. Receiver electronics connect via a scleral tunnel to this epiretinal implant. The IMI device includes a retina encoder that allows individual calibration attained through a series of repetitive adjustments to the implanted device to optimize each patient's visual perception. This may help overcome neural remodeling after decades of disuse, as visual perceptions can be shaped to match physical reality. In this trial, only one case of retinal detachment has been reported.[24]

2.2.4. Alpha-IMS

Alpha-IMS has been involved in clinical trials in Europe and Hong Kong.[14] Unlike all other discussed devices, Alpha-IMS does not depend on an external camera. Instead, the subretinal implant is a 1500-pixel multi-photodiode array. Each of the 1500 pixels consists of a light-sensing photodiode that responds to ambient light entering the eye. Signals are amplified and transferred to local electrodes, stimulating the geographic region corresponding to phosphene detection.[25] While image acquisition is solely intraocular, a cable connecting the implant to a subdermal power control unit, which charges wirelessly through a handheld control unit, enables light-sensitivity adjustment.[26,27] Early models with a transdermal power supply limited the study to 126 days. However, wireless power supply has eliminated the time limitation in later trials.[28] In the most updated trial 19 patients were implanted, and visual testing was performed on eight recipients over 3−9 months.[29] The highest achieved visual acuity was logMAR 1.43 with Snellen 20/546 as measured using the Landolt C chart. As image acquisition is achieved intraocularly, the working frequency of the implant, ranging from 5 Hz to 7 Hz, was individually optimized to avoid object fading in visual perception. Microaneurysm is known to occur on the surface of the active chip, possibly as an adaptation mechanism for the regained inner neuronal activity and metabolism or a relative ischemia sign.[30] Corrosion of the seal on the device and one case of subretinal bleeding causing increased intraocular pressure were reported in recent trials.[27]

3. Discussion

Among the many therapeutic devices available for degenerative retinal diseases, retinal prostheses have achieved major milestones in recent years. Continued improvement in visual acuity has been achieved by increasing the number and density of electrodes. The retinal prostheses demonstrate therapeutic potential for restoration of vision. In this review, we assessed and summarized clinical results of four major retinal prostheses. The efficacy of these devices was verified in clinical trials, which demonstrated the ability of these devices to provide basic functional vision to enrolled patients and restore their independence in daily life.

Some of the best visual acuity has been obtained through human testing of the Alpha-IMS6 and Argus II devices, which have promised patients the capacity to identify household objects, detect personal mobility, and to read letters. For patients who have experienced loss of visual function for years to decades, this is a significant step to restore independence in daily activities. However, these clinical trials constitute only a minute proportion of patients with degenerative retinal diseases. Furthermore, preliminary results of electrical stimulation studies in the remaining retinal neurons cannot be predictably correlated with clinical change in visual acuity, leaving a potential gap between presumed clinical relevance and actual research results.[14]

Furthermore, larger devices generate more heat and may require more difficult surgical insertion with potential complication, presenting a biological limit on electrode number. In addition, an increased pixel number also requires a more advanced engineering design.

In conclusion, despite the current achievements in retinal prostheses development, we still need to devote more time not only to clinical and biological testing, but also to enhance product engineering and technical improvements in these devices. The future primary goal of these retinal prostheses is to have a majority of recipients experience the benefit to their everyday living activities.

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