Journal of Experimental and Basic Medical Sciences 2021;2(3):326-335

Review

Systematic Review of Novel Advances in Epiretinal and Subretinal Prosthesis

Alper Kurt[1], Recep Tayyip Özbek[1], Oytun Erbaş[1]

ABSTRACT

Nowadays, millions of people experience vision loss due to diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). These diseases can be treated with methods such as gene exchange therapy when diagnosed early. However, retinal implants come into play as a solution for many patients. In this review, retinal implants were examined in two main groups, as Epiretinal implants and Subretinal implants. While Argus II, intelligent medical implants (IMI), EPI-RET3 retinal prosthesis implants were reviewed under the epiretinal title, Alpha IMS and AMS, PRIMA retinal implant, and Boston retinal implant were reviewed in detail under the Subretinal title. In addition, the benefits and disadvantages of retinal implants, as well as the components they include and the studies that have been conducted with these implants, are discussed in this article. Even though retinal implants have been studied for many years, they still have serious shortcomings and negative effects. Many patients with vision loss will have great hope in the near future if these flaws and negative effects are solved.

Keywords: Age-related macular degeneration, Argus II, microelectrode, retinal implant, retinal prosthesis, retinitis pigmentosa

Retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are diseases that majorly affect photoreceptors of the retina and cause progressive vision loss.[1] While RP mainly affects 1.5 million people worldwide which are children and young adults, AMD affects 30-50 million people which are mainly the elder population of the society.[2-4] In the last decades, new approaches have emerged for the treatment of individuals affected by these diseases. Generally, gene replacement therapy can be applied to those suitable for early stages of degeneration where photoreceptor recovery is possible. On the other hand, electronic retinal implants are the only solution for patients in advanced stages where most of the photoreceptors are lost.[5,6]

The fundamentals of the retinal implant idea were first put forward in 1752 by Benjamin Franklin's theory that loss of vision and hearing can be recovered by using electricity.[7] In 1955, French scientist Charles Leroy, who was thought to be influenced by Benjamin Franklin's theory, began research for the blind to recover their vision. In a study conducted for this research, Leroy showed how visual disturbances were stimulated by wrapping a wire conducting current through the head of a volunteer.[8] Thus, it has formed the basis for artificial retinal implants to be made.

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey

Correspondence: Alper Kurt. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye.

E-mail: :alper.kurt@ozu.edu.tr

Cite this article as: Kurt A,Özbek RT, Erbaş O. Systematic Review of Novel Advances in Epiretinal and Subretinal Prosthesis. JEB Med Sci 2021;2(3):326-335.

doi: 10.5606/jebms.2021.75674

Received : March 19, 2021
Accepted : April 3, 2021
Published online : March 8, 2022

In 1929, Foerster discovered that it was possible to create an artificial vision by delivering a stimulus from the outside to the brain. He named this vision phosphene. In 1952, Hodgkin and Huxley explained the nature of the idea of artificial vision that Foerster talked about by showing how electrical signals are transmitted in nerves.[9] In 1968, Brindley and Lewin developed a prototype from a radio receiver array connected to electrodes placed on the right occipital lobe of a man who had never seen anything before, allowing them to create models by adjusting various parameters. As a result of these experiments, phosphenes formed in the blind man's left visual field. Brindley and Lewin stated in their own words that, with this study, a device that can provide a useful view for a blind person can be developed as follows: "Our findings strongly suggest that it will be

possible by improving our prototype to make a useful prosthesis."[10]

At the end of the 20th century, the knowledge about RP and AMD diseases has increased thanks to the advances in imaging technologies. With this increasing knowledge, researchers' studies focused on the retinal approach instead of the cortical approach.[11]

In this article, retinal implants have been classified into two types, subretinal and epiretinal. Under the Epiretinal heading: Argus II, Intelligent medical implants (IMI), Intelligent retinal implant system II (IRIS II), EPI-RET3 implants, and under the Subretinal heading: Boston retinal implant project, Alpha IMS and AMS, PRIMA implants have been examined in detail.

EPIRETINAL PROSTHESES

Epiretinal implants are placed on the upper surface of the retina and stimulate ganglion cells by bypassing Cone and Rod photoreceptor cells, Horizontal cells, bipolar cells, and amacrine cells. The microelectrodes used for this stimulation are fixed to the retinal surface with a tack. Surgeons are more prone to implants made with the epiretinal approach because of its similarity with routine vitreoretinal surgery. In addition, it is relatively easy to place an implant and perform an explanation as needed. In these systems, it bypasses intraretinal processing as the stimulation is delivered directly to the retinal ganglion cells (RGCs). Therefore, the ability to recreate the physiological retinal topographic organization is limited, and instead of neural network processing complex image processing techniques are required.[12]

ARGUS II RETINAL PROSTHESIS SYSTEM

The Argus II retinal prosthesis system received CE (Conformitè Europëenne) mark and FDA (Food and Drug Administration) approval in 2011 and 2013 respectively. Argus II retinal prosthesis is one of the most implanted retinal prostheses. There are more than 100 individuals worldwide who have been implanted with Argus II.[4]

Argus II has been formed with external components which are a camera attached to the glasses, a video processing unit (VPU), radio frequency (RF) Telemetry transmitter coil, and internal components which are RF Telemetry receiver coil, application-specific integrated circuit (ASIC), 60 (6X10) microelectrode array. Visual information of the environment is taken from a camera mounted on glasses. Then, this image is transmitted to the VPU by cable. The image information received in the VPU is transformed into a real-time brightness map. The brightness map is sent to the receiver coil with an RF telemetry coil. The data and power that are needed for ASIC are sent wirelessly. While high frequency is required for data, lower frequencies are required to transmit power. The data from the receiver coil is processed in ASIC and converted into electrical impulses to be sent to the microelectrodes. These pulses stimulate the ganglion cells in the retina through electrodes, creating artificial vision phosphenes.[2,4]

In an experiment involving 21 subjects implanted with Argus II, the letters were divided into three different groups according to their topographic complexity. Since it consists of vertical and horizontal lines, the easiest group to read is the A group, which contains the letters E, F, H, I, J, L, T, U. The B group, which consists of oblique and circular letters (A, C, D, M, N, O, Q, V, W, Z), is more complex than the A group. The most complex group is group C, which consists of curved (B, G, K, P, R, S, X, Y) letters whose length is half the length of the letter. Group A was shown to all of 21 patients, group B to 19 of 21 patients, and group C to 20 of 21 patients. In all three different groups, an improvement was observed in the active state of the implant compared to the inactive state. The results of the experiment are as follows: Mean percentage of correct identification is 72.3% with 24.6% standard deviation, 55.0% with 27.4% standard deviation, 51.7% with 28.9% standard deviation for group A letters, group B letters, and group C letters respectively when the implant is switched on. The mean percentage of correct identification is 17.7% with 12.9% standard deviation, 11.8% with 10.7% standard deviation, 15.3% with 7.4% standard deviation for group A letters, group B letters, and group C letters respectively when the implant is switched off.[13]

In another experiment with seven patients, the subjects were shown eight objects that are frequently encountered in everyday life. These eight objects, either white or metal, were displayed on a black background in room light and the subjects were asked to recognize the object within 30 seconds. The percentage of the participants correctly identifying the objects is 12.5% when the device is turned off and 35.7% when it is turned on.[14]

In an experiment involving 28 people implanted with Argus II, the motion perception of the patients was tested. 15 of these 28 subjects detected a high-constricted (white) bar moving on the black

screen more accurately than their natural vision while the implant was active.[15]

Argus II has improved vision for people with reduced vision or who are completely blind. Since it is the most implanted retinal implant so far, its compatibility in the eye and its effects on patients are known. However, the shortcomings of the Argus II implant have also been recognized. A person needs 600 pixels to perform daily tasks such as reading and navigation.[16] However, Argus II with its 6 X 10 electrode, i.e. 60-pixel, falls short of this basic requirement.

While the retinal ganglion cells bodies are 15 µm in diameter, the diameter of each electrode of the Argus II is 200 µm, which causes each electrode of the array to stimulate more than one RGC.[17] This situation negatively affects the image quality. To overcome this issue, the number of electrodes should be increased, and the diameter of the electrode should be decreased. Thus, the ganglion cell stimulated per electrode will decrease, and the image quality will increase. In other words, it is necessary to produce small and large numbers of phosphenes.[18] However, when the diameter of the electrode becomes smaller, the current density and charge density on the electrode will increase, which might harm the cells in the retina. To prevent damage to the degenerated retina during electrical stimulation, minimizing and appropriately dissipating the heat generated by the array is an important issue. The patient can localize objects within a 20° area using the camera mounted to the glasses. To increase the field of view (FOV), the patient must scan the environment with head movements instead of eye movements. Therefore, patients must be trained after surgery.[17]

In a study of 30 patients using the Argus II implant for five years, 18 of the 30 patients had no serious adverse events (SAEs). A total of 24 SAEs were observed in the remaining 12 patients. Four of these patients had conjunctival erosion. Four of these patients had hypotony, three of them had conjunctival dehiscence. Three of these patients were suspected of having endophthalmitis. Three of these patients had endophthalmitis presumably. Two of these patients had retack. Two of these patients had Rhegmatogenous. There was serious in one of these patients. One of these patients had a retinal tear another had uveitis.[19]

Scientists have developed some methods to overcome the problems observed in Argus II and to eliminate some deficiencies. For example, as the current density increases with the decrease in electrode diameter and retinal cells are damaged due to the heat generated, "current focusing" and "current steering/virtual electrode" stimulation strategies have been developed for Argus II to obtain higher resolution images with fewer electrodes.[17]

Another study showed that the use of a thermal camera in addition to a normal camera used in the Argus II is easier for patients to distinguish living things and objects that radiate heat in daily life. While the phosphenes formed by a normal camera do not reflect the distinction between the background and the human in detail, the human body emitting heat on a cold background becomes much more selectable than the background thanks to the thermal camera. The same study showed that there is a trade-off between FOV and resolution. As the FOV increases, the quality of the resulting image decreases. This situation forces patients to scan the environment with head movement to obtain better quality vision with less FOV. Therefore, patients are trained for this behavior.[20]

A new image processing feature has been developed using signal coding for face or obstacle recognition. In this method, the camera automatically recognizes a face or obstacle that separates it from the background and shows the patient only the separated face or obstacle. Thus, the patient becomes able to easily select the face of a person and see the obstacles in his daily life.[21]

In summary, scientists, who saw the shortcomings of Argus II and the features to be improved, developed different methods for Argus II. One of the most important criteria for retinal implants is the number of electrodes. Argus II is not able to fulfill this criterion with 60 electrodes. To remedy this deficiency, Argus II developers are working on a new generation implant with 240 electrodes.[22]

INTELLIGENT MEDICAL IMPLANTS (IMI, IRIS II)

Intelligent medical implants work began with the establishment of intelligent implants GmbH in 1998, and the goal of this company was to develop a new implant by gathering the knowledge available to help visually impaired individuals. The epiretinal implant, developed with a different perspective, was named as Learning Retinal Implant System (IMI Intelligent Medical Implants AG, Zug, Switzerland). This system basically consists of a digital camera, glasses (visual interface), software as well as a processor with a

power supply and a microelectrode array connected to the retina, also known as this microelectrode array retinal stimulator.[23]

Intelligent medical implants consist of 49 platinum electrodes which are 250 micrometers in diameter and 120 micrometers wide and are implanted in an area of 2.4mm^2 of the macular region of the retina. IMI retinal prosthesis is in clinical trials in Europe. In one study, 20 patients were temporarily implanted for 45 minutes, and it was concluded that the phosphors or light perception of the patients as a result of electronic stimulation was identified.[24]

Intelligent medical implants are very similar to Argus II in terms of working principle and number of electrodes, but unlike the IMI, Argus II has a learning algorithm in the processing center.[25] Thanks to this learning algorithm, in a clinical trial conducted in 2005, a 49-electrode implant was applied to four patients and it was stated that they could learn simple lines, points, and horizontal movement.[26]

In 2007, a multicenter clinical trial was initiated in which a prototype with 61 electrodes was implanted into RP patients. These patients were followed for four months and were published at the 2009 European Association for Vision and Eye Research Conference, in which patients reported reliable visual perceptions.[27,28]

While a single transceiver RF coil is used in Argus II, RF transmission is used for power transmission and an infrared (IR) optical link is used for data transmission in IMI. A high data rate is achieved thanks to optical connections. In another experiment, IMI was tested on four subjects for nine months. The results positively showed that the implant did not cause any problems such as tissue damage or cell growth in the eye. Device performance over nine months is unknown.[29]

Although intelligent medical implants have increased the data transmission rate and facilitated the implant, the number of electrodes was insufficient as Argus II and could not provide sufficient resolution. Recognizing this, Pixium Vision bought IMI in 2016 and set out to develop it and firstly increased the number of electrodes to 150. He named this new implant IRIS II. A clinical trial has been initiated to explain the data of the designed implant.[30]

Several distinctive features have been mentioned, although not yet disclosed. These features include having more electrodes than epiretinal systems, a camera capable of capturing changes, and a special design that allows easy removal of the electrode system.[31]

Despite receiving clinical approval of the European approval (CE mark) in 2016 for safety and performance, Pixium Vision ceased the work of IRIS II and focused on PRIMA, a retinal prosthesis based on photovoltaic silicone materials.[32]

EPI-RET3 RETINAL PROSTHESIS

The EPI-RET3 retinal prosthesis consists of extraocular and intraocular components. Extraocular components are a portable computer system determining the stimulation patterns, a transmitter module, and a transmitter coil for data and power transfer. The intraocular component is a system that combined the receiver coil within an intraocular lens together with two microchips (receiver and stimulation) which are responsible for generating the stimulation pulses.[33] In other words, internal components of EPI-RET3 are entirely intraocular, which is the main difference from the Argus II and IRIS implants.[34]

Enough energy to drive the implant is provided by the inductive link between the transmitter and receiver. The data will be used for pulse pattern is realized by amplitude shift keying (ASK).[34] Generated pulses are transmitted to the electrodes to stimulate the RGCs. There are 25 microelectrodes are linked with a flexible micro cable to chip, which are 100 µm in diameter and 25 µm in height.[33] The core material of the EPI-RET3 implant is polyimide and electrodes are made with gold-covered by plasma-activated iridium oxide.[34]

Several experiments were done to identify the features of EPI-RET3 for fabrication. Biocompatibility and feasibility of the implant were studied in the first phase of the development.[35,36] EPI-RET3 is demonstrated in rabbits and pigs that the materials are well tolerated within the eye. Also, functional tests were performed demonstrating evoked electrical potentials in rabbits in the second phase.[37]

In the first clinical trial, a basic 25-electrode system was implanted into six subjects for four weeks in 2006. The implant can be activated just in the clinic. There was no available system for home use. Patients were evaluated on days seven, 14, and 27 during the four weeks. There was no serious complication, except for one case of sterile hypopyon, which was treated. The implant was removed at four weeks as planned. A giant retinal tear was developed during removal which requires further surgery.[38-40] Phosphenes

generated by the electrodes stimulating the retina were reported by all six patients. Characteristics of the phosphenes are greatly varied between patients.[41]

The development of very large electrode arrays for epiretinal stimulation (VLARS) which will be cover 37° of the field of vision has been focused on EPI-RET3.[42] However, the group that developed EPI-RET3 did not publish any results for VLARS so far.

SUBRETINAL IMPLANTS

The main principle in the positioning of subretinal implants is to take advantage of the own signal processing capabilities of retinal interneurons in inner layers by placing the implant in the layer where the degenerated RP is, thus creating a more physiological visual process by using less complex image processing methods. Since the device is closer to the targeted retinal layer, it can perform its function with lower stimulation intensities thanks to natural signal amplification. Some reports state that the placement of subretinal implants is surgically complex and this approach is less familiar to surgeons.[43]

ALPHA IMS AND AMS

The Alpha IMS (Retina Implant AG, Reutlingen, Germany) received a CE mark in 2013 which makes Alpha IMS the first subretinal implant which received this marking. Alpha IMS is a 3-mm^2 microchip system consisting of 1500 independent photodiode-amplifier-electrode units forming the multiphotodiode array (MPDA). In other words, each photodiode is connected to an amplifier which amplifies the signal coming from the photodiode generated by luminance. This amplifier is connected to a titanium nitride electrode. Each unit transforms the signal which is obtained from the luminance coming from the environment to an electrical signal. The device is designed to be placed subretinal and needs an external energy source to operate and amplify the signal. Power is supplied via a silicone supply cable passing under the temporal muscle to a subdermal coil, which is placed to the postauricular cranial bone. Power is transmitted wirelessly with a coil attached from the outside directly opposite the subdermal coil, and this coil also gives the possibility to control brightness and contrast sensitivity with the received information from a handheld unit.[44]

After Alpha IMS, Alpha AMS consisting of 1600 MPDA was developed. The Alpha AMS has been used in clinical trials in Europe since February 2014. Implant received the CE mark in March 2016 and is currently in the market as a product.[45]

In an experiment with nine Alpha IMS implanted patients, ages 35 to 62, standardized screen tasks, table tasks of activities of daily living, and letter recognition tests were performed in order to measure the efficacy of the implant. Experiments were carried out while the implant was switched on and switched off in order to observe the improvement in vision. One of the subjects was removed from the experiments because the implant lost its functionality, and thus 8 subjects participated in the experiment. In standardized screen tasks, light perception threshold in full-field illumination, light source localization, and motion detection with a moving random dot pattern were tested. The results showed that when the implant was activated, light perception developed in all subjects compared to the inactive state. Moreover, seven patients were able to localize a light wedge on the screen, and five subjects were able to detect the motion of dot patterns on the screen. In table tasks of activities of daily living, four of six geometrical objects (square, circle, triangle, rectangle, ring, or crescent) were placed on a black background. The patients were asked to report the number of observed objects, to locate them, and to name them in order to test the identification, localization, and discrimination ability of the patients. The experiment showed that there is a noticeable increase in identification, localization, and discrimination ability when the implant is switched on compared to the situation in which the implant is switched off. In the letter recognition test, white letters were shown on the black screen to the subjects. All the letters were visible within the visual field of the Alpha IMS. Several letters (e.g. T, V, L, I, O) were read by three subjects spontaneously.[46]

A total of 75 adverse events occurred in the experiment involving nine subjects. It was revealed that 31 of these events were definitely related to the implant and 19 of them had a possible relation to the implant. While 31 adverse events were resolved without sequelae, two resolved with sequelae. Eleven adverse events remained unresolved. The implant has not caused any non-ocular SAEs.[47]

Due to the intra-ocular placement of the multiphotodiode array (MPDA) and the extra-orbital placement of the induction coil, different surgical specialist teams are required to perform different surgeries. This situation prolongs and complicates the operation time.[48]

Alpha AMS increased the number of electrodes from 1500 to 1600. studies showed that very different

results were not obtained from Alpha AMS in terms of image enhancement capacity and SAEs that were seen in the patients. Overall, the two implants showed similar results. However, Alpha AMS has been reported to have much longer functional longevity than Alpha IMS.[49]

PRIMA RETINAL IMPLANT

PRIMA retinal implant, owned by Pixium Vision, is the development of the subretinal wireless implant available at Stanford University. The PRIMA implant used a wireless photovoltaic microchip array, eliminating the cable used for data transfer.[50] Photovoltaic arrays allow wireless operation of the implantation and simplify the implant operating procedure.[51]

The photovoltaic retinal implant transforms the signals into biphasic currents and stimulates bipolar neurons by transferring the data from the camera in the glasses that the patient is wearing, to the digital mirror projector and then to the photovoltaic microchip array.[52-54] Another feature that distinguishes the prima retinal implant from other implants is that it enables natural eye movements due to its wireless operation and the light coming directly into the eye instead of the head-mounted camera.[55]

The PRIMA retinal implant is placed subretinally as a 30-micrometer thick, 1mm wide, 142-pixel hexagonal cell array. However, different research groups have developed and tested PRIMA implants of different widths and pixel counts. The infrared ray sent to the microchip inside the eye was specially selected at 880nm wavelength.[50] The reason for this is to prevent the photophobic and phototoxic effects of bright lighting and to prevent interference with the residual vision that AMD patients have in their peripheral FOV.

Another distinctive feature of this implant is that each pixel consists of two photodiodes connected in series, and thanks to these photodiodes, the incoming near-infrared light is converted into electrical current and stimulates bipolar nerve cells.[52] The prima retinal implant restored the visual perception of rats blinded and made their visual perception sharper in one study.[50]

In 2018, Ho et al.[56] were able to stimulate blind Royal College of Surgeon rats by sending near-infrared light with 1mm and 2mm photovoltaic implants.

The prima retinal implant with 1.5mm and 2mm implants was tested in cats and near-human primates in 2015. These normal, domestic, male, and cats between 11-16 months of age were followed up for 43 to 106 days with 1.5 mm implants. As a primate, the cynomolgus monkey was used as male and female. Some of these monkeys had 2mm implants and some 1.5mm implants. Implants are made in only one eye. No intraoperative complications were seen with a total of 11 implants to the cats during the 43 - 106 days follow-up period. Eleven implants that size 1.5mm to the primates did not show any adverse events during the six weeks to 12 months follow-up period, but four primates with 2mm implants were euthanized after the intervention.[57]

PRIMA retinal implant is a study open to various studies to achieve better pixels. In different experiments, both the number of electrodes and the gaps between electrodes was changed to reach various pixel numbers. It has been limited to clinical studies yet. It is not available as a product on the market. Studies have estimated that the lifespan in the body is over 27 years.[58]

BOSTON RETINAL IMPLANT

The Boston Retinal Implant Project (BRIP) pioneered the earliest acute trials in human subjects, making it one of the first of its kind.[59] BRIP is similar to Argus II in terms of design, but they eliminated the need to fix the device by using the subretinal approach and eliminated the use of tacks.[60]

Almost all of the device is outside of the eye in order to minimize the biocompatibility problems caused by the components to be placed inside the eye. The fact that the stimulation chip is outside of the eye has allowed the use of a non-biocompatible titanium coating to be used in the packaging of the chip. The electrode that enters the eye is made of polyimide, a flexible material of 10um thickness, to prevent damage to retinal cells. These electrodes are manufactured using microfabrication technology.[61]

The system includes an external computer where users can set the parameters that will control the stimulation. Parameters set by users are translated into digital control data that will modulate a power transmitter. Data and power are transferred wirelessly to the implant. The transmitted power and data are received by the integrated circuit and converted into stimulation information. In future studies, a camera that will take the image and a portable processor that will process this image will be added to the system.[62]

The Massachusetts Institute of Technology (MIT)-Harvard group started to work on the device

with 256 electrodes after placing the 15-channel prototype in the mini-pig and observing that it has been functional for one year. The group decided to develop an implant that would create a working vision before adopting an institutional strategy for the development of the existing retinal implant.[62]

Nowadays, retinitis pigmentosa and age-related macular degeneration, which are common eye disorders, negatively affect the quality of life and vision of patients. Furthermore, it creates labor and financial losses for countries. While gene therapy is an option in early diagnosis for these diseases, retinal implants are used as the most effective method in the later stages. Retinal implants that can be purchased on the market today are Argus II and Alpha IMS.

Argus II, the most implanted worldwide, has played a pioneering role for retinal implants, both accustoming patients to the retinal implant idea and providing surgeons with experience in this field. Despite being implanted in a large number of patients, Argus II still has some deficiencies and problems. For example, the Tack used to attach the Argus II implant to the retina caused inflammation in the eye. Moreover, in some cases, it was detached from the patient's retina and rendered the chip dysfunctional. In addition, since the artificial image created with Argus II shows a very narrow area, patients have to scan the environment with head movements in order to see their surroundings. For this movement, they receive special training after surgery. Different SAEs originating from Argus II has been reported. These problems have been noticed, at least in clinical settings, and treatment methods have been applied for most of them. However, the advantages and disadvantages of other implants have not yet been fully defined, as they have not yet progressed in clinical studies and have not applied implants to a sufficient number of patients.

Intelligent medical implants and EPI-RET3 take the operating principle of Argus II as their basic operating principle. These retinal implants have brought innovations by developing the Argus II. For example, IMI has tried to obtain a higher resolution image by developing different artificial intelligence-based algorithms and increasing the number of electrodes in the retinal implant. However, they abandoned their work and began to develop the PRIMA retinal implant, which adopted the subretinal approach.

Unlike Argus II, EPI-RET3 designed a more compact system by producing the receiver coil, receiver chip, and stimulator chip under a single package. However, the studies conducted are only clinical and are only about forming phosphene, not image in patients. They did not design a system that can be used in daily life. The group has started working on a system that also has a higher number of electrodes and external components such as a camera but has not yet submitted any reports on implant development.

Argus II, IMI, and EPI-RET3 have adopted the epiretinal approach. This approach has advantages as well as disadvantages. In the epiretinal approach, the electrodes bypass the natural imaging process because they directly contact the ganglion cells. Therefore, more complex image processing algorithms are needed to create an image. The subretinal approach has come to the fore with the advancing technology to eliminate these complex processes and to get rid of the Tack used to attach electrodes to the retina.

In the subretinal approach, there is a possibility of retinal damage as the chip is placed in the lower layer of the retina, and this type of operation is not an operation that surgeons are familiar with. However, since the excitation by the electrode starts from the layer where the photoreceptors are located, transmission is done by all the remaining cells. As a result, the complexity of the required image processing algorithms is reduced because the natural image processing process takes place. The oldest implant which adopted this approach is the Boston Retinal implant and pioneered subretinal implants. The current implants in this approach are Alpa IMS and PRIMA. Alpha IMS has been tested more on humans than PRIMA. It was commercially marketed and appeared on the market as an additional option to the Argus II.

Compared to other implants, the number of Alpha IMS electrodes stands out. For this reason, the image that will be formed will be much higher resolution than other implants. Also, Alpha IMS doesn't need an external camera. It receives visible light with the help of 1500 Microphotodiode inside and sends it to its electrodes by magnifying it. For this reason, while head movements are used for visual processing in Argus II, eye movements have become possible in Alpha IMS. Finally, the team developed Alpha AMS with 1600 electrodes and conducted clinical studies.

PRIMA retinal implant, which has the most up-to-date studies today, is a more flexible study compared to other retinal implants. Different study groups achieve varied results by making differences in the number of electrodes of the PRIMA retinal

implant and even the alloys from which the electrode is made. This implant has not yet been tested on humans at the clinical stage. However, the results have been analyzed by testing rats, cats, and near-human primates, and the shortcomings are being studied. PRIMA retinal implant is promising for people in terms of comfort as it only works with a pair of glasses.

The images created with retinal implants are very low resolution compared to those of a healthy person, but these images mean a lot for people who have lost their visual ability for many years. Argus II is quite inadequate in terms of resolution and surgery compared to other implants. While Argus II offers 60-pixel images to people as a resolution, implants such as Alpha IMS and PRIMA, which are being studied today, are aimed to increase the number of pixels to more than 1000 pixels. Some studies have suggested that 600 pixels are sufficient for patients to perform functions such as reading, walking, and writing in their daily lives. Also, the tack used in the Argus II will not be a problem for humans. However, no implant that is currently being worked on and currently on the market cannot provide a colorful image to patients. One of the biggest developments in retinal implants will be to perceive colors in patients.

In conclusion, in the light of the information obtained from all implants studied so far, the most important points to be considered in a developed implant are to use the number of electrodes and algorithms that provide a resolution that can do the daily work of the patients, to be implanted without being surgically invasive and to adapt to the body after implantation and to use materials that will maintain its function for a long time. Retinal implants, which are currently being studied and available on the market, are a great source of hope for RP and AMD patients. The development of these implants will contribute to both the social life and the workforce by reintegrating the young and old population who have moved away from society due to vision loss and whose quality of life has decreased considerably.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Congdon N, O'Colmain B, Klaver CC, Klein R, Muñoz B, Friedman DS, et al. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol. 2004 Apr;122:477-85.
2. Yue L, Weiland JD, Roska B, Humayun MS. Retinal stimulation strategies to restore vision: Fundamentals and systems. Prog Retin Eye Res. 2016 Jul;53:21-47.
3. Rizzo S, Barale PO, Ayello-Scheer S, Devenyi RG, Delyfer MN, Korobelnik JF, et al. ADVERSE EVENTS OF THE ARGUS II RETINAL PROSTHESIS: Incidence, Causes, and Best Practices for Managing and Preventing Conjunctival Erosion. Retina. 2020 Feb;40:303-311.
4. Luo YH, da Cruz L. The Argus(®) II Retinal Prosthesis System. Prog Retin Eye Res. 2016 Jan;50:89-107.
5. Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, et al. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. Vision Res. 2003 Nov;43:2573-81.
6. Veraart C, Wanet-Defalque MC, Gérard B, Vanlierde A, Delbeke J. Pattern recognition with the optic nerve visual prosthesis. Artif Organs. 2003 Nov;27:996-1004.
7. Franklin B, Watson W. An Account of Mr. Benjamin Franklin's Treatise, Lately Published, Intituled, Experiments, and Observations on Electricity, Made at Philadelphia in America. Philos Trans (1683-1775). 1951;47:202-211
8. Ghezzi D. Translation of a photovoltaic retinal prosthesis. Nat Biomed Eng. 2020 Feb;4:137-138
9. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol. 1952 Aug;117:500-44.
10. Brindley GS, Lewin WS. The sensations produced by electrical stimulation of the visual cortex. J Physiol. 1968 May;196:479-93.
11. Normann RA, Warren DJ, Ammermuller J, Fernandez E, Guillory S. High-resolution spatio-temporal mapping of visual pathways using multi-electrode arrays. Vision Res. 2001;41:1261-75.
12. Marc R, Pfeiffer R, Jones B. Retinal prosthetics, optogenetics, and chemical photoswitches. ACS Chem Neurosci. 2014 Oct 15;5:895-901.
13. da Cruz L, Coley BF, Dorn J, Merlini F, Filley E, Christopher P, et al. Argus II Study Group. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. Br J Ophthalmol. 2013 May;97:632-6.
14. Luo YHL, Zhong J, Merlini F, Anaflous F, Arsiero M, Stanga PE. The use of Argus® II retinal prosthesis to identify common objects in blind subjects with outer retinal dystrophies. Invest Ophthalmol Vis Sci. 2014 Apr;55:1834.
15. Ahuja AK, Yeoh J, Dorn JD, Caspi A, Wuyyuru V, McMahon MJ, et al. Factors Affecting Perceptual Threshold in Argus II Retinal Prosthesis Subjects. Transl Vis Sci Technol. 2013 Apr;2:1.
16. Weiland JD, Faraji B, Greenberg RJ, Humayun MS, Shellock

FG. Assessment of MRI issues for the Argus II retinal prosthesis. Magn Reson Imaging. 2012 Apr;30:382-9.
17. Özmert E, Arslan U. Retinal Prostheses and Artificial Vision. Turk J Ophthalmol. 2019 Sep 3;49:213-219.
18. Rachitskaya AV, Yuan A, Marino MJ, Reese J, Ehlers JP. Intraoperative OCT Imaging of the Argus II Retinal Prosthesis System. Ophthalmic Surg Lasers Imaging Retina. 2016 Nov 1;47:999-1003.
19. da Cruz L, Dorn JD, Humayun MS, Dagnelie G, Handa J, Barale PO, et al. Argus II Study Group. Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial. Ophthalmology. 2016 Oct;123:2248-54.
20. He Y, Huang NT, Caspi A, Roy A, Montezuma SR. Trade-Off Between Field-of-View and Resolution in the Thermal-Integrated Argus II System. Transl Vis Sci Technol. 2019 Aug 19;8:29.
21. Stanga P, Sahel J, Mohand-Said S, Caspi A, Merlini F, Greenberg R. Face detection using the Argus® II retinal prosthesis system. Invest Ophthalmol Vis Sci. 2013 Jun;54:1766.
22. Duncan JL, Richards TP, Arditi A, da Cruz L, Dagnelie G, Dorn JD, et al. Improvements in vision-related quality of life in blind patients implanted with the Argus II Epiretinal Prosthesis. Clin Exp Optom. 2017 Mar;100:144-150.
23. Hornig R, Zehnder T, Velikay-Parel M, Laube T, Feucht M, Richard G. The IMI retinal implant system. In: Humayun MS, Weiland JD, Chader G, Greenbaum E, editors. Artificial sight. 1sted. Springer, New York, NY; 2007. v24. Keserü M, Feucht M, Bornfeld N, Laube T, Walter P, Rössler G, et al. Acute electrical stimulation of the human retina with an epiretinal electrode array. Acta Ophthalmol. 2012 Feb;90:e1-8.
25. Eckmiller R, Neumann D, Baruth O. Tunable retina encoders for retina implants: why and how. J Neural Eng. 2005 Mar;2:S91-S104.
26. Richard G, Keserue M, Feucht M, Post N, Hornig R. Visual Perception After Long-Term Implantation of a Retinal Implant. Invest Ophthalmol Vis Sci. 2008;49:1786.
27. Velikay-Parel M, Ivastinovic D, Langmann G, Hornig R, Georgi T, Wedrich A. First experience with The IRIS retinal implant system. Acta Ophthalmol. 2009 Sep;87:0
28. Luo YH, da Cruz L. A review and update on the current status of retinal prostheses (bionic eye). Br Med Bull. 2014;109:31-44.
29. Richard G, Hornig R, Keserü M, Feucht M. Chronic epiretinal chip implant in blind patients with retinitis pigmentosa: long-term clinical results. Invest Ophthalmol Vis Sci. 2007 May;48, 666.
30. Nowik K, Langwińska-Wośko E, Skopiński P, Nowik KE, Szaflik JP. Bionic eye review - An update. J Clin Neurosci. 2020 Aug;78:8-19.
31. Lorach H, Benosman R, Marre O, Ieng SH, Sahel JA, Picaud S. Artificial retina: the multichannel processing of the mammalian retina achieved with a neuromorphic asynchronous light acquisition device. J Neural Eng. 2012 Dec;9:066004.
32. Shim S, Eom K, Jeong J, Kim SJ. Retinal Prosthetic Approaches to Enhance Visual Perception for Blind Patients. Micromachines (Basel). 2020 May 24;11:535.
33. Menzel-Severing J, Laube T, Brockmann C, Bornfeld N, Mokwa W, Mazinani B, et al. Implantation and explantation of an active epiretinal visual prosthesis: 2-year follow-up data from the EPIRET3 prospective clinical trial. Eye (Lond). 2012 Apr;26:501-9.
34. Walter P. A fully intraocular approach for a bi-directional retinal prosthesis. In: Gabel PV, editors. Artificial Vision. 1sted. Springer, Charm; 2017. p. 151-161
35. Walter P, Szurman P, Vobig M, Berk H, Lüdtke-Handjery HC, Richter H, et al. Successful long-term implantation of electrically inactive epiretinal microelectrode arrays in rabbits. Retina. 1999;19:546-52.
36. Menzel-Severing J, Sellhaus B, Laube T, Brockmann C, Bornfeld N, Walter P, et al. Surgical Results and Microscopic Analysis of the Tissue Reaction following Implantation and Explantation of an Intraocular Implant for Epiretinal Stimulation in Minipigs. Ophthalmic Res. 2011 Oct;46:192-8.
37. Walter P, Heimann K. Evoked cortical potentials after electrical stimulation of the inner retina in rabbits. Graefes Arch Clin Exp Ophthalmol. 2000 Apr;238:315-8.
38. Roessler G, Laube T, Brockmann C, Kirschkamp T, Mazinani B, Goertz M, et al. Implantation and explantation of a wireless epiretinal retina implant device: observations during the EPIRET3 prospective clinical trial. Invest Ophthalmol Vis Sci. 2009 Jun;50:3003-8.
39. Koch C, Mokwa W, Goertz M, Walter P. First results of a study on a completely implanted retinal prosthesis in blind humans. In: SENSORS; 2008 Oct; Lecce, Italy; 2008. p. 1237-1240
40. Menzel-Severing J, Laube T, Brockmann C, Bornfeld N, Mokwa W, Mazinani B, et al. Implantation and explantation of an active epiretinal visual prosthesis: 2-year follow-up data from the EPIRET3 prospective clinical trial. Eye (Lond). 2012 Apr;26(4):501-9.
41. Klauke S, Goertz M, Rein S, Hoehl D, Thomas U, Eckhorn R, et al. Stimulation with a wireless intraocular epiretinal implant elicits visual percepts in blind humans. Invest Ophthalmol Vis Sci. 2011 Jan 21;52:449-55.
42. Waschkowski F, Hesse S, Rieck AC, Lohmann T, Brockmann C, Laube T, et al. Development of very large electrode arrays for epiretinal stimulation (VLARS). Biomed Eng Online. 2014 Feb 6;13:11.
43. Bloch E, Luo Y, da Cruz L. Advances in retinal prosthesis systems. Ther Adv Ophthalmol. 2019 Jan 17;11:2515841418817501.
44. Zrenner E, Bartz-Schmidt KU, Benav H, Besch D, Bruckmann A, Gabel VP, et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. Proc Biol Sci. 2011 May 22;278:1489-97.
45. Daschner R, Rothermel A, Rudorf R, Rudorf S, Stett A. Functionality and performance of the subretinal implant chip Alpha AMS. Sens Mater. 2018 Nov; 30:179-192
46. Bach M, Wilke M, Wilhelm B, Zrenner E, Wilke R. Basic quantitative assessment of visual performance in patients with very low vision. Invest Ophthalmol Vis Sci.

2010 Feb;51:1255-60.

47. Kitiratschky VB, Stingl K, Wilhelm B, Peters T, Besch D, Sachs H, et al. Safety evaluation of "retina implant alpha IMS"--a prospective clinical trial. Graefes Arch Clin Exp Ophthalmol. 2015 Mar;253:381-7.
48. Zrenner E, Bartz-Schmidt KU, Besch D, Gekeler F, Koitschev A, Sachs HG, et al. The subretinal implant ALPHA: implantation and functional results. In: Gabel PV, editors. Artificial Vision. 1sted. Springer, Charm; 2017. p. 65-83
49. Stingl K, Schippert R, Bartz-Schmidt KU, Besch D, Cottriall CL, Edwards TL, et al. Interim Results of a Multicenter Trial with the New Electronic Subretinal Implant Alpha AMS in 15 Patients Blind from Inherited Retinal Degenerations. Front Neurosci. 2017 Aug 23;11:445.
50. Lorach H, Goetz G, Smith R, Lei X, Mandel Y, Kamins T, et al. Photovoltaic restoration of sight with high visual acuity. Nat Med. 2015 May;21:476-82.
51. Palanker D, Vankov A, Huie P, Baccus S. Design of a high-resolution optoelectronic retinal prosthesis. J Neural Eng. 2005 Mar;2:S105-20.
52. Mathieson K, Loudin J, Goetz G, Huie P, Wang L, Kamins TI, et al. Photovoltaic Retinal Prosthesis with High Pixel Density. Nat Photonics. 2012 Jun 1;6(6):391-397.
53. Loudin JD, Simanovskii DM, Vijayraghavan K, Sramek CK, Butterwick AF, Huie P, et al. Optoelectronic retinal prosthesis: system design and performance. J Neural Eng. 2007 Mar;4:S72-84.
54. Lorach H, Goetz G, Smith R, Lei X, Mandel Y, Kamins T, et al. Photovoltaic restoration of sight with high visual acuity. Nat Med. 2015 May;21:476-82.
55. Cheng DL, Greenberg PB, Borton DA. Advances in Retinal Prosthetic Research: A Systematic Review of Engineering and Clinical Characteristics of Current Prosthetic Initiatives. Curr Eye Res. 2017 Mar;42:334-347
56. Ho E, Lorach H, Goetz G, Laszlo F, Lei X, Kamins T, et al. Temporal structure in spiking patterns of ganglion cells defines perceptual thresholds in rodents with subretinal prosthesis. Sci Rep. 2018 Feb 16;8:3145.
57. Muqit MMK, Hubschman JP, Picaud S, McCreery DB, van Meurs JC, Hornig R, et al. PRIMA subretinal wireless photovoltaic microchip implantation in non-human primate and feline models. PLoS One. 2020 Apr 8;15:e0230713.
58. Lemoine D, Simon E, Buc G, Deterre M. In vitro reliability testing and in vivo lifespan estimation of wireless Pixium Vision PRIMA photovoltaic subretinal prostheses suggest prolonged durability and functionality in clinical practice. J Neural Eng. 2020 Jun 12;17:035005.
59. Rizzo JF 3rd, Wyatt J, Loewenstein J, Kelly S, Shire D. Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays. Invest Ophthalmol Vis Sci. 2003 Dec;44:5355-61.
60. Rizzo JF 3rd, Shire DB, Kelly SK, Troyk P, Gingerich M, McKee B, et al. Development of the boston retinal prosthesis. Annu Int Conf IEEE Eng Med Biol Soc. 2011;2011:3135-8.
61. Rizzo JF 3rd. Update on retinal prosthetic research: the Boston Retinal Implant Project. J Neuroophthalmol. 2011 Jun;31:160-8.
62. Kelly SK, Shire DB, Chen J, Gingerich MD, Cogan SF, Drohan WA, et al. Developments on the Boston 256-channel retinal implant. In: ICMEW IEEE International Conference on Multimedia and Expo Workshops; 2013 Jul 15-19; San Jose, CA, USA; 2013. p. 1-6.