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RETINA

Retinal Prostheses: What Next After Argus Approval?

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INTERVIEWING J. FERNANDO AREVALO, MD, GRACE L. SHEN, PHD, AND JOHN T. THOMPSON, MD

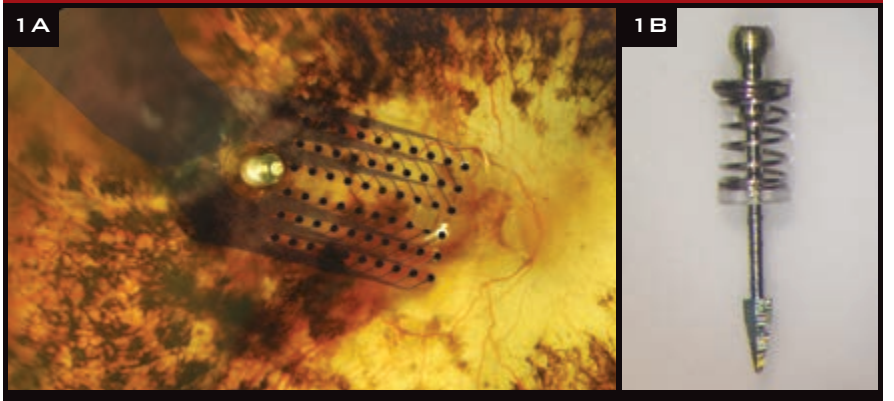
In the United States, approximately 100,000 people have retinitis pigmentosa (RP), and the number worldwide is estimated at 1.5 million.[1] This inherited, progressive retinal condition causes rod and cone photoreceptor cells to degenerate, leading to total or near-total blindness. Although a nutritional regimen has shown promise in delaying RP progression,[2] there is yet no treatment that can undo the sight-robbing damage once it has occurred.

But patients received more than a glimmer of hope with the February 2013 FDA approval of the Argus II Retinal Prosthesis System (Second Sight Medical Products) for use in advanced RP. (It received the European CE mark in 2011.)

The Argus II is an epiretinal-stimulating device designed to improve visual functioning in people who are blind—or, more accurately, to give people who are blind from severe RP the ability to perceive black and white images and motion. Although it is currently the only such device approved in the United States, others are pressing forward in development, most notably the Alpha IMS, manufactured by Retina Implant AG in Germany.

Now that this critical approval barrier has been crossed, what are the implications for RP patients and their ophthalmologists? Three retina specialists take a look at where we are now—and what impediments remain—in the development and adoption of retinal prostheses.

Epiretinal Placement



(1A) Position of the Argus II array on the retina. **(1B)** Titanium tack for affixing epiretinal implant. Notice the tacking location in 1A, represented by the large round structure at the left side of the array.

What Does This Approval Mean?

Argus II was approved as a "humanitarian use device," an FDA category for devices that treat or diagnose fewer than 4,000 people in the United States per year. This type of approval does not require proof of effectiveness; rather, Second Sight had to provide evidence to the FDA showing that the probable benefits of Argus II outweigh its risks and that no comparable device is available for treating RP.

Now, Argus II can be offered to all RP patients who meet the treatment criteria, not just those in clinical trials. According to product labeling, patients must be at least 25 years old, with a diagnosis of retinitis pigmentosa, with bare light or no light perception in both eyes, and a history of previous useful form vision. Moreover, they must be phakic or pseudophakic as well as willing and able to receive the recommended postimplant clinical follow-up, device fitting, and visual rehabilitation.

A long process of development. The hard-won FDA approval for Argus II followed more than 20 years of planning, device development, and testing by a team led by Mark Humayun, MD, PhD, of Doheny Eye Institute and Second Sight, and Robert J. Greenberg, MD, PhD, of Second Sight. "This is a clear demonstration of restoring sight in patients," said Grace L. Shen, PhD, director of the Retinal Disease Program at the National Eye Institute. NEI has spent roughly $29.7 million on the development of Argus I and II, including preliminary work.

The device consists of an eyeglass-mounted video camera for capturing images, a video processing unit (VPU)

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worn on the belt, and a microelectrode array (Fig. 1) that is surgically implanted onto the retina via a pars plana sclerotomy. The VPU transforms video images into electronic data, transmitted wirelessly to the microelectrode array, which stimulates the underlying ganglion cells to produce patterns of light. Argus I, which utilized a 16-microelectrode display, was implanted into the first of six patients in 2002 at Doheny Eye Institute in Los Angeles. The currently approved Argus II model has a 60-electrode array for improved spatial resolution.

Research Shows Gains With Argus II

Although the FDA did not require proof of effectiveness, there is some evidence of gains in visual functioning with Argus II. In the FDA hearing on Sept. 12, 2012, several patients who participated in the clinical trials gave anecdotal reports of improvement following implantation and training, such as being able to perceive motion as well as curb edges and crosswalk markings or tree limbs in their path. Another described gaining the ability to sort white, black, and gray socks.[3]

Recently published research shows that some Argus II recipients are able to read large letters and words of up to four letters on a computer screen.[4] The research included 21 patients whose duration of experience with the Argus II ranged from 8.6 months to 34.8 months (average, 19.9 months). In the first round of testing, patients were asked to identify letters of various sizes and typographic complexity; those who could identify at least 50 percent of single letters within 60 seconds per letter were further tested with smaller letters and, ultimately, short words.

Four patients "graduated" to the third trial phase, in which they were asked to read three 10-word sets (consisting of two-, three-, or four-letter words). Three of these patients succeeded in reading at least 50 percent of the words in each set, and two read all 10 words in at least one set.

The researchers noted that, among the 21 patients who participated in the first test, the time needed to identify a letter varied widely, ranging from 6 to 221 seconds; similarly, there was wide variation in the size of letter perceived.

According to the authors, it is not clear what differentiated the high-performing test subjects from the others. Identifying these factors—which could include age at diagnosis, age at implantation, or genotype—will be critical in selecting patients to receive a retinal implant.[4]

Other Devices in Development

In addition to Second Sight's postmarketing trials of Argus, three companies have devices in human studies, currently either recruiting or under way, as registered at www.ClinicalTrials.gov. These include a subretinal implant from Retina Implant AG (registry numbers NCT01024803 and NCT01497379), an epiretinal implant from Pixium Vision SA (NCT01864486), and a prototype suprachoroidal wide-view implant from Bionic Vision Australia (NCT 01603576).

Another device innovator, the Boston Retina Implant Project, has completed more than two years of testing its subretinal device in pigs and is preparing for human testing.[5]

Alpha IMS. Apart from Argus, the Alpha IMS from Retina Implant AG is the farthest along in development and is the only retinal prosthesis that has undergone long-term testing in humans. In July 2013, it received the CE mark in Europe.

Unlike Argus, it does not require an external eyeglass-mounted camera. Rather, it uses a wireless subretinal chip, which moves with the eye, containing 1,500 electrodes, which transform the incoming light to electrical signals. These signals, after passing through an amplification circuit, stimulate intact retinal cells to induce visual perceptions.

Earlier this year, clinical trial results were reported from nine blind patients who were implanted with the Alpha IMS device.[6] The researchers reported "reliable and luminance-dependent signal generation" in all nine subjects over a three- to nine-month period.

Differences in activities of daily living, recognition of letters, and safety were studied with the device on or off. Eight subjects experienced light perception; seven could localize the source of light; and five detected motion. The researchers were able to measure grating acuity in six subjects and visual acuity in two (up to 20/546 Snellen); three subjects could read letters spontaneously. Five subjects reported using their implant-dependent visual function in carrying out activities of daily life.[6]

Substantial Barriers Remain

Despite these encouraging results, researchers continue to grapple with safety and technical challenges.

Safety. Among the 30 patients in the Argus II study, 17 device- or surgery-related serious adverse events (SAEs) occurred, some of which were clustered in the same individual. The most common SAEs were endophthalmitis, hypotony, and conjunctival dehiscence (three events each). However, the researchers noted that they were able to adapt their surgical methods in the trial to reduce adverse events; for example, no cases of endophthalmitis were seen in the second 15 patients.[7]

Implantation surgery. In placing epiretinal implants, it is difficult to make them conform closely to the retinal surface, and they are most commonly tacked to the retinal surface (Fig. 1).[5] The implant may require later retacking, as occurred in two patients in the study.[7]

One of the surgical challenges for subretinal implants is that the device and cables must be placed without direct visualization. In addition, silicone oil tamponade is used to forestall retinal detachment.[8]

Predictions for Adoption

Will these devices be widely adopted by retina surgeons? "I don't see that happening yet," said John T. Thompson, MD, of Baltimore, who is president of the American Society of Retina Specialists (ASRS). "One reason is that very few of our patients with RP have visual acuity low enough to be eligible

for the visual prosthesis."

The rate of implantation could change, though, as indications for the technology expand into areas like age-related macular degeneration or other diseases primarily involving the outer retina. "For patients eligible today," added Dr. Thompson, "I would refer them to a medical center that has been offering the implant."

Approval of the Argus—and ongoing efforts with the other devices—demonstrates effective translational research that incorporates new findings in retinal cell function, neural circuitry, and disease processes. Dr. Thompson described these developments as "a scientific tour de force." He added that "ASRS is always interested in new tools to help our patients. We support the concept and hope the technology will extend to patients who are blind from retinal degenerative disease. The best hope right now is the visual prosthesis."

Dr. Shen agreed that we have come a long way in making visual prostheses available as a possible treatment, but she noted that Argus and the other retinal prostheses in development are like the first personal computers. They are the beginning. "Once you show it can work, it can move quickly." ■

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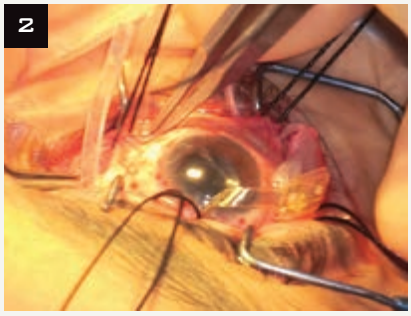
John T. Thompson, MD, *is in practice with Retina Specialists, Baltimore. Financial disclosure: Has received grant support from Genentech, Pfizer, and Regeneron.*

A Surgeon's Argus Experience in Saudi Arabia

In February 2013, J. Fernando Arevalo, MD—along with fellow vitreoretinal surgeons Stanislao Rizzo, MD, and Saba Al Rashaed, MD—implanted the first two Argus II devices in the Middle East at King Khaled Eye Specialist Hospital (KKESH) in Riyadh (Fig. 2). Dr. Arevalo leads the vitreoretinal division at KKESH as part of a research, education, and patient care collaboration between that institution and the Wilmer Eye Institute, where he is a professor.



IMPLANT SURGERY. The silicone band part of the implant is placed under the rectus muscles. The flexible cable and electrode array will be placed in the vitreous cavity after vitrectomy through a sclerotomy and fixed with a retinal tack.

Dr. Arevalo said that RP is unusually prevalent in Saudi Arabia and surrounding regions. "We've been flooded with inquiries from patients and doctors throughout the Middle East."

Patient selection and commitment. Patient selection criteria at KKESH are the same as in the FDA-approved labeling discussed above. Beyond that, Dr. Arevalo is very clear that patients must understand the procedure and the intense commitment required for rehabilitation training. For patients, the program begins with a battery of tests, followed by the surgery and 20 scheduled follow-up visits, including a rigorous rehabilitation program.

The surgical team tempers high expectations on the part of the patients and families with facts based on research findings. "We tell the patients that this is going to take time," said Dr. Arevalo. As to the outcomes for the first two KKESH patients: "After just two months of rehabilitation and training, they are already able to see doors, people passing by, and outside buildings."

Surgical training. Dr. Arevalo learned the procedure from the Second Sight training team. For a surgeon who is new to the procedure, he said, the implantation of the epiretinal array can take about four hours—but only after several days of onsite education from the manufacturer that covers patient testing, surgical procedures, use of special instrumentation, and wet labs. "I would say that anyone who's performed vitreoretinal surgery can learn to implant the array," said Dr. Arevalo. Training is also required in rehabilitation techniques to help patients make effective use of the device's input. He emphasized, however, that the commitment is not for everyone because it reaches far beyond the operating room into patient relationships, time management, and hospital issues.

As for the biggest surgical challenge, "It definitely has to be the tacking of the implant in the retina," said Dr. Arevalo. The specially designed titanium retinal tack (Fig. 1B) is passed from the stimulating array, through the retina, retinal pigment epithelium and choroid, and finally through the sclera, where it is anchored. "Today's surgeons learned vitreoretinal surgery after tacks were no longer in use," he noted. "This surgery has revived retinal tacking."

MORE ONLINE. *Watch a video of retinal implant surgery at KKESH at www.eyenet.org (available after Aug. 15).*

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