Use of the Port Delivery System in AMD

Anti-VEGF therapy has revolutionized the management of neovascular age-related macular degeneration (AMD) by offering the potential for patients to maintain functional vision for their lifetimes. Nevertheless, there are unmet needs in the management of neovascular AMD. The heavy treatment burden associated with frequent intravitreal injections has created unintended consequences for patients, providers, and the health care system. For many patients, intravitreal injections are required as frequently as every month. Even when patients do not need to be treated monthly, continuous and frequent follow-up is needed for surveillance, which carries both direct and indirect costs for patients and providers.

Furthermore, real-world data show that patients tend to gain less VA with anti-VEGF treatments than has been reported in clinical trial outcomes. This is thought to be due, at least in part, to relative undertreatment.\(^1\)\(^4\) In clinical practice, long-term frequent follow-up visits and treatments may be difficult, and patients may be lost to follow-up for a variety of reasons.\(^5\)

A POTENTIAL SOLUTION

Multiple attempts to develop extended drug delivery systems for anti-VEGF agents have been proposed. The Port Delivery System (PDS; Genentech), which dispenses ranibizumab (Lucentis, Genentech), may be the first to receive approval from the US FDA. The PDS is a novel device that may offer a solution to relieve the burden of repeated intravitreal injections and frequent monitoring visits.

The PDS is designed to be a permanent, reusable drug reservoir. It is initially surgically placed in the OR, and subsequent refills are performed in

AT A GLANCE

- Despite the success of anti-VEGF therapy in the treatment of neovascular AMD, a heavy treatment burden on patients, physicians, and the health care system remains.
- The Port Delivery System is a durable drug reservoir designed to dispense ranibizumab over time after surgical implantation, with refills performed in the office.
- In the phase 2 LADDER clinical trial, in patients receiving the highest concentration ranibizumab, roughly 80% were able to go at least 6 months before needing the first refill of medication. A phase 3 trial has finished enrollment.
the office (Figure 1). The device is made of polysulfone, and it includes a silicone septum that can be entered with a special needle to refill the device. During a refill, the needle flushes out the device while at the same time refilling it with fresh ranibizumab (Figure 2). At the distal end of the septum, there is a semipermeable titanium membrane that permits continuous passive diffusion of the drug from the higher concentration in the reservoir into the vitreous.

THE LADDER TRIAL

The phase 2 multicenter, randomized, interventional, active-treatment–controlled LADDER study evaluated the durability and safety of the PDS in patients with neovascular AMD. The trial compared the PDS, using three concentrations of ranibizumab (10 mg/mL, 40 mg/mL, and 100 mg/mL), with a control group receiving the gold standard of monthly 0.5 mg ranibizumab intravitreal injections.

Patients included in the study had a diagnosis of neovascular AMD within the previous 9 months with a VA between 20/20 and 20/200, had received previous treatment with at least two or more anti-VEGF injections prior to screening, and had demonstrated anatomic or visual response to intravitreal anti-VEGF therapy. The purpose of these inclusion criteria was to capture patients who were responsive to anti-VEGF therapy and who had relatively new choroidal neovascular lesions.

Patients were excluded if they had received anti-VEGF agents other than ranibizumab within 1 month prior to randomization or if they had a history of vitrectomy surgery, glaucoma-filtering surgery, tube shunt implantation, or microinvasive glaucoma surgery in the study eye.

The primary endpoint of the trial was the time to first refill of the PDS. The need for refill was determined based on specific visual and anatomic criteria. Secondary endpoints included visual and anatomic outcomes and safety.

RESULTS

The LADDER study included 220 patients, and the treatment groups were well balanced at baseline, with average baseline BCVA of 20/40. Most of the patients had been diagnosed with neovascular AMD in the preceding 4 months (range, 3.2-3.9 months) and had on average three previous injections.

For the primary endpoint of time to first required PDS refill, a dose response was observed among the three PDS treatment arms: The median time to first refill in the 10 mg/mL arm was 8.7 months; in the 40 mg/mL arm, 13.0 months; and in the 100 mg/mL arm, 15.0 months (Figure 3). Of those receiving the 100 mg/mL dose, roughly 80% were able to go at least 6 months before needing their first refill of medication.

It was also crucial in this trial to ensure that visual and anatomic outcomes in patients with the PDS were similar to those in patients receiving monthly intravitreal ranibizumab 0.5 mg injections. Indeed, at month 9, gains in VA and reductions in measurements of central retinal thickness were comparable between the PDS 100 mg/mL group and the monthly intravitreal injection group.

COMPLICATIONS

As with any novel surgical device, it was important to implement the PDS only after proper surgical training. Investigators went through extensive training and had access to supplemental educational materials, including step-by-step videos and a practice mannequin. Furthermore, surgical liaisons were available for consultation during the procedures and refills. The initial surgical procedure involved a simple one-pass stab incision with a 3.2 mm blade and no choroidal cautery. However, this technique resulted in a 50% rate of vitreous hemorrhage following the procedure early in the phase 2 study.

After reevaluation of the technique, a modification to the procedure was developed. The revised technique required scleral dissection to the pars plana followed by careful cautery.
The need for frequent intravitreal injections has been a major concern since the beginning of the anti-VEGF era. It is likely that the burden of therapy leads to undertreatment in real-world patient populations, and undertreatment has been associated with inferior VA outcomes over time. A device for sustained release that is effective and safe may represent a step forward toward a more practical solution for all stakeholders and overall better outcomes.

### ADDITIONAL CONSIDERATIONS

A possible downside to use of the PDS is that an initial procedure in the OR is required, with the related risks of intraocular surgery and additional upfront costs. Although the costs for the surgical procedure, the device, and the concentrated drug are unknown, there is a potential for cost savings to the patient and the health care system when compared with the direct and indirect costs of the current treatment paradigm, which requires repeated injections, testing, and trips to the provider.

The ARCHWAY trial will also include intensive surgical education for the investigators. Extra attention has been directed toward meticulous surgical technique, including conjunctival and Tenon capsule dissections and maintenance of hemostasis to minimize postoperative complications.