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Port Delivery System With Ranibizumab: As Always – Risks Versus Benefits for the Recipients

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Since anti-vascular endothelial growth factor (anti-VEGF) therapies were first administered intravitreally for neovascular age-related macular degeneration (nAMD), they have revolutionized treatment paradigms for nAMD and have become the standard of care for different retinal vascular diseases such as diabetic retinopathy and retinal vein occlusion. However, they constitute a significant treatment burden for patients and ophthalmologists alike due to repeated injections and frequent visits. Vision gain has been repeatedly shown to be associated with higher injection frequency. Nonadherence can lead to fluctuations in drug concentrations inside the vitreous with subsequent reduced vision outcomes.[1] Various approaches have been evaluated to decrease treatment burden and maintain sustained intravitreal drug delivery.

The Port Delivery System (PDS) with ranibizumab (RBZ) is a novel drug delivery method that aims at reducing patient visits, treatment burden and drug level fluctuation by providing a long-term sustained drug delivery. PDS with RBZ is a refillable, nonbiodegradable, surgically placed implant that acts as a reservoir which dispenses RBZ directly into the vitreous over extended periods of time. Ranibizumab formulation is customized and is different from the commercially available for intravitreal injection (IVI). The customized preparation is stable under body temperature for long time leading to maintained drug delivery. PDS has been recently approved by the United States Food and Drug Administration for the treatment of nAMD following the LADDER phase 2 and ARCHWAY phase 3 clinical trials.[2,3]

The implantation procedure for PDS, as described in the phase 2 and 3 clinical trials, is performed in the operation room under sterile conditions. The technique has been adjusted and evolved along with the progression of the clinical trials.[4] Proper surgical technique is essential to decrease the incidence of serious postoperative complications. Meticulous dissection and handling of the conjunctiva and Tenon's capsule is paramount to facilitate their proper closure. Careful scleral dissection followed by laser ablation of the pars plana prior to globe penetration has been shown to decrease postoperative vitreous hemorrhage from 50% to nearly 5% in the phase 2 study. The scleral wound should be aimed to be 3.5 mm in length and if longer, it should be sutured to avoid postoperative hypotony and implant dislocation during refill procedures. Cautious Tenon's capsule and conjunctival

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closure is a cardinal safety step to avoid conjunctival erosion. The conjunctiva should be left slightly overhanging over the limbus to avoid retraction. Conjunctival handling is probably the most important factor in the prevention of endophthalmitis associated with PDS. Refilling procedure is, on the other hand, an office-based procedure but also requires special preparation different from standard IVI including unique needles and the requirement of supplemental task lightening and magnification.[2–5]

The phase 2 clinical trial included four groups: three groups with different ranibizumab concentrations (10 mg/ml, 40 mg/ml and 100 mg/ml) and one group with monthly ranibizumab IVI. It showed that about 80% and 60% of the high concentration ranibizumab group (100 mg/ml) did not require refilling at 6 and 12 months, respectively, according to predetermined criteria including changes in best corrected visual acuity (BCVA) and central foveal thickness (CFT). No statistically significant difference in ETDRS letter gain was observed between the high concentration group and the monthly ranibizumab group at 9 months. The phase 3 clinical trial compared fixed 24-week PDS refill with monthly injections. The PDS Q24W was found to be both noninferior and equivalent to the monthly ranibizumab IVI in terms of change of BCVA over the average of 36–40 weeks. Change in central macular point thickness (CPT) at 36 weeks was also comparable between the 2 groups. Nearly all (98.4%) patients in the Q24W group did not require supplemental ranibizumab IVI before the refill procedure at 24 weeks.[2,3]

The results from both phase 2 and 3 clinical trials are promising. PDS was able to maintain BCVA for 24 weeks in 98.4% of patients without supplemental IVI injections. The technology significantly decreases the treatment burden on both patients and caregivers. The finding also demonstrates that PDS has the potential to decrease fluctuations in the drug concentrations, hence leading to better real-life outcomes, as suggested by the noninferiority and equivalency to monthly injections.[2,3]

The main limitation of the PDS with RBZ is its safety profile—clearly with the surgical procedures and not with the anti-VEGF pharmacologic agent itself. As expected from a surgical procedure, in both phase 2 and 3 trials, the PDS group had more adverse events when compared with the ranibizumab group. The most concerning event was endophthalmitis, which occurred at the rates of 1.8% and 1.6% in the phases 2 and 3 trials, respectively, which is a significantly higher rate compared to incidence of endophthalmitis associated with intravitreal injections of anti-VEGF therapy. While in the phase 2 trial, one endophthalmitis case occurred in the immediate postoperative period, in the phase 3 trial, all endophthalmitis cases occurred more than 1 month post implantation, the latest being at 282 days. Overall, the majority of the endophthalmitis cases were associated with conjunctival retraction. Such outcome highlights the extreme importance of proper conjunctival handling during device implantation.[3,5] Additionally, in the phase 3 trial, rhegmatogenous retinal detachment occurred at the rate of 0.8% in the PDS group and none occurred in the IVI group. Overall, 5.6% of patients in the PDS group experienced serious ocular adverse events including endophthalmitis, retinal detachment, retinal tear, choroidal detachment, and transient postoperative vision loss.[3]

In summary, PDS is a promising therapeutic option for nAMD that has the potential to significantly decrease treatment burden and mitigate noncompliance in patients. However, the safety profile needs to be discussed thoroughly with potential recipients. Proper surgical technique and patient selection are crucial to maximize patient visual outcomes and minimize adverse events.

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