Retinal PHYSICIAN
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Prefilled Syringe Delivery of Intravitreal Anti-VEGF Medications

Advantages for patients and physicians.

By MICHAEL COLUCCIELLO, MD March 1, 2019

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Ocular Inflammation After Intravitreal Injections

The most common exudative retinal diseases — neovascular age-related macular degeneration (nAMD), diabetic retinopathy-associated macular edema (DME), and macular edema associated with retinal venous occlusive disease — are usually treated with serial intravitreal injection of soluble anti-vascular endothelial growth factor (anti-VEGF) pharmacologic agents. Since their inception in 2005, the number of anti-VEGF injections in the United States has increased 10% to 20% annually.[1] Currently, we often rely on filling syringes in the office via vials; in the near future, we will have prefilled syringes available for delivery of these important agents to our patients — and many benefits will be realized.

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RATIONALE FOR FREQUENT, SERIAL, CHRONIC INTRAVITREAL INJECTIONS

Patients with these diseases benefit by having available a critical level of anti-VEGF agent in the vitreous during a period of active disease; at this time, we are limited to frequent serial repeated delivery of the anti-VEGF agent via intravitreal injection. Therefore, an important consideration is the intravitreal half-life of the various anti-VEGF agents. Positron emission tomography–computed tomography (PET/CT) imaging of I-124-labeled bevacizumab (Avastin; Genentech), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea; Regeneron) in a nonhuman primate (owl monkey) model disclosed intravitreal half-lives of 3.60 days for I-124 bevacizumab, 2.73 days for I-124 ranibizumab, and 2.44 days for I-124 aflibercept.[2] In a rabbit model, the vitreous half-life of bevacizumab is 6.99 days, aflibercept is 3.92 days, and ranibizumab is 2.51 days.[3] The liquefied nature of the vitreous found in

adult owl monkey eyes yields shorter half-life time periods in the primate model; similarly, significantly faster clearances are found in postvitrectomized eyes in a rabbit model using similar PET methodology. In the primate model, clearance patterns for each agent fit a 2-phase curve: an initial rapid distribution phase until day 4 was followed by a slower elimination phase from day 8 onward. Bevacizumab was detected in the vitreous cavity until day 30; aflibercept and ranibizumab were detectable until day 21.[2]

Consistent with the current limitations of anti-VEGF levels after intravitreal injection and the need for critical therapeutic levels to treat active disease, it has been shown that more frequent injections (to maintain vitreous anti-VEGF levels) provide better results than less frequent treatment. For instance, in the treatment of nAMD, the PIER study protocol of monthly ranibizumab intravitreal injections for 3 months followed by quarterly dosing and SAILOR study protocol (3 monthly loading doses followed by PRN dosing based on a quarterly monitoring schedule) both yielded inferior visual acuity results compared to consistent monthly dosing in the ANCHOR and MARINA studies.[4-7]

Regarding diabetic retinopathy, in the Ranibizumab for Edema of the mAcula in Diabetes follow-up study (READ-2), more frequent ranibizumab injections resulted in a significant gain of best-corrected visual acuity (BCVA) of 3.1 letters and a reduction in foveal thickness of 70 µm. The authors concluded that more aggressive therapy (monthly injections) may be necessary in many patients to optimally control edema and maximize vision.[8] Regarding the treatment of macular edema associated with retinal venous occlusive disease, in both the CRUISE and BRAVO studies, monthly ranibizumab dosing versus sham for 6 months showed clear improvement with ranibizumab over sham. Then, during the second 6 months, sham group patient vision improved because they were able to receive ranibizumab, but at month 12 their vision was not as good as that in patients in the ranibizumab groups, because they had received far fewer doses by month 12.[9,10]

IMPLICATIONS FOR CHRONIC INTRAVITREAL ADMINISTRATION AND ADVANTAGES OF PREFILLED SYRINGE DELIVERY

The need for chronic, serial dosing in these common retinal diseases has made the intravitreal injection procedure the most common procedure performed in ophthalmology. It is estimated that more than 6 million injections were performed in the United States in 2016 alone.[11]

Chronic, serial intravitreal injections are most efficiently performed with prefilled syringes. The anti-VEGF agents bevacizumab and ranibizumab **(Figure 1)** are currently available in prefilled syringes. It is anticipated that the other major VEGF blocker, aflibercept, will soon be available in a prefilled syringe. Prefilled syringes are a boon to patients requiring this treatment (generally our largest patient group) and retinal physicians because of the decreased endophthalmitis risk, dose accuracy, and improved clinic efficiency they can provide.

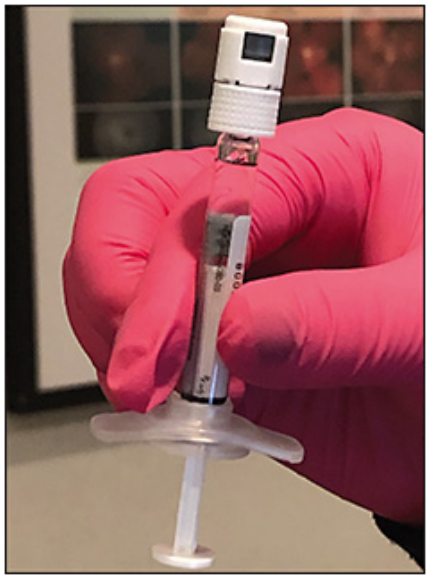

Figure 1. Prefilled syringe loaded with anti-VEGF agent.

ENDOPHTHALMITIS RISK

Repetitive administration of these agents can be challenging for patients, not only from a frequency perspective, but also because of the risk involved for endophthalmitis with repeated injections. Postinjection endophthalmitis is one of the most serious complications that can occur. If prefilled syringes are not utilized, transfer from vials to syringes and filtered-injection needle exchanges increase chances of contamination and subsequently patient risk for endophthalmitis. The risk of endophthalmitis with an intravitreal injection has been studied extensively. Large studies have reported postinjection rates of endophthalmitis at 0.02% to 0.05%.[12-14] A meta-analysis found the rate of endophthalmitis following intravitreal injections in a clinical setting to be 0.049%.[12]

Recently, a retrospective cohort study was done to determine whether sterile preloading of anti-VEGF agents reduces the risk of postintravitreal injection endophthalmitis.[15] Using 2005-2016 medical claims data from a large, national US insurer, 706,725 bevacizumab (in a prefilled syringe), 210,849 ranibizumab (from vials until late 2016), and 177,731 aflibercept (from vials) injections given to 130,327 patients were evaluated for endophthalmitis incidence. Based on the odds risk reduction of 1.29, the authors calculated that 1 case of endophthalmitis for every 8,847 injections performed could be prevented using prefilled syringes (any changes in the calculus from prefilled syringes available for ranibizumab in late 2016 would favor prefilled syringes even more). Since, in their study, 1 case of endophthalmitis occurred every 2,857 injections, this translates into the potential of avoidance of 1 out of every 3 cases of endophthalmitis — a highly significant result.

DOSE ACCURACY

Therapeutic doses of intravitreal anti-VEGF drugs (1.25 mg bevacizumab, 0.5 or 0.3 mg ranibizumab, and 2.0 mg aflibercept) are achieved by injecting a volume of 0.05 mL (50 mL) into the vitreous cavity. Studies have shown that the accuracy and reproducibility achieved with the typical syringes used for intravitreal injections can be highly variable.[16-19]

A recent “real-world” study evaluated the accuracy and precision of anti-VEGF volume delivery in the real-world setting demonstrated that the use of a prefilled syringe was associated with improved anti-VEGF dosing accuracy. Overdelivery was more common than underdelivery (16.3%), but overall precision was enhanced with the use of

prefilled syringe delivery of medication.[20]

CLINIC FLOW

Prepackaged syringes have demonstrated a 40% reduction in office preparation time, offering clinical efficiency.[21,22] Improved efficiency allows for an improved patient experience and allows the physician to treat more patients per session.

FUTURE CONSIDERATIONS: NO NEED FOR INTRAVITREAL INJECTION?

In the perhaps not too distant future, repeated intravitreal delivery of medication via needles on syringes will be less of a consideration, due to the possibilities of a port delivery (reservoir) system and gene therapy. Implanted reservoir delivery of medication has shown promise in early trials. The ranibizumab port delivery system (PDS; Genentech), in particular, has shown promise. Once implanted, the reservoir may be refilled periodically. In the phase II LADDER study, the top-line results showed that 80% of patients could go 6 months before requiring a refill of the PDS implant. The phase 2 LADDER study included 220 patients randomized to either 1 of 3 concentrations of ranibizumab (10 mg/mL, 40 mg/mL, or 100 mg/mL) in a reservoir surgically implanted in the vitreous cavity or a monthly injection of ranibizumab (.5 mg). Outcomes included the time until a patient needed a refill of the implanted ranibizumab delivery system and the effectiveness of each concentration compared to monthly injections. Patients treated with the highest ranibizumab concentration were able to go a median of 15 months before needing a refill of the reservoir in the office. Investigators found that the port delivery treatment was also as effective as monthly injections. Currently, a phase 3 study (ARCHWAY) is under way.[23]

Also, gene therapy delivery brings the hope of allowing for very long-term therapeutic levels of medication through cellular nucleus incorporation of the genetic material that may lead to the manufacture of anti-VEGF medication for the patient. Adverum Biotechnologies product ADVM-022 uses a proprietary adeno-associated virus vector that carries an aflibercept coding sequence. A primate study using one intravitreal injection showed that a single injection of ADVM-022 administered intravitreally can generate stable levels of aflibercept found to be within the therapeutic window of the standard-of-care recombinant protein for 16 months.[24] Another gene therapy product, RGX-314 (Regenxbio), utilizes a novel recombinant adeno-associated virus vector of an anti-VEGF gene delivered in a subretinal fashion to allow for potential long-term host manufacture of the anti-VEGF therapy.[25] This is currently undergoing a 24-week phase 1 trial.

CONCLUSION

At least for the near term, frequent intravitreal injections of anti-VEGF agents will be important for managing several of the most common retinal diseases. Using syringes prefilled with the soluble anti-VEGF agents will protect patients from the disastrous consequences of endophthalmitis, assure the most efficient manner of precise dosing, and assist with patient flow in growing, busy clinics. **RP**

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