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Safety of Intravitreal Anti-VEGF Agents

After nearly a decade of use, what the data says about the ocular and systemic safety of these increasingly used drugs.

Retinal specialists have been delivering intravitreal injections of vascular endothelial growth factor inhibitors for nearly a decade in their clinical practices. While neovascular age-related macular degeneration was the first, and is still the most common, indication for intravitreal anti-VEGF injections, additional approved indications include central and branch retinal vein occlusion-related macular edema as well diabetic macular edema. These agents are also used in an off-label fashion to diminish the effects of proliferative diabetic retinopathy, vitreous hemorrhage, neovascular glaucoma, retinopathy of prematurity and many other retinovascular diseases.

Pegaptanib, a selective inhibitor of the VEGF165 isoform, was the first anti-VEGF agent approved for an ocular indication in 2004,¹ followed by non-selective VEGF inhibitors with a more robust efficacy profile: ranibizumab in 2006² and aflibercept in 2011.³ Off-label intravitreal bevacizumab, also a non-selective VEGF inhibitor, has been in robust use since 2005⁴ and retains predominant market share due to having similar efficacy to ranibizumab combined with a distinct pricing advantage.

The popularity of non-selective anti-VEGF agents has largely been driven by their apparent efficacy that is measurable both functionally and anatomically. Patients, too, appreciate the merits of these anti-VEGF agents for various indications, and they do so despite knowing the burden of needing intravitreal injections every one to three months in order to realize these anatomic and functional benefits over the long term.

A lot has been said about the ocular and systemic safety of anti-VEGF agents over the last 10 years. From the beginning of the anti-VEGF era in ophthalmology in 2004, retina specialists and clinical trialists were appropriately concerned about the potential ocular and systemic side effects of constitutively inhibiting VEGF, albeit in minute anti-VEGF doses delivered into the relatively isolated intraocular environment.

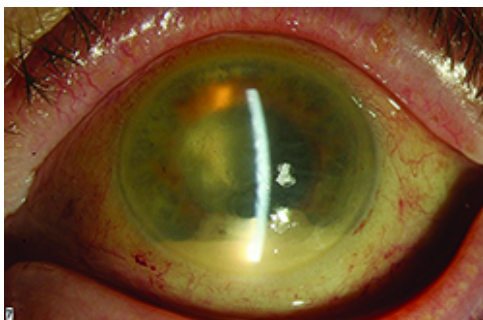


Figure 1. Slit-lamp photograph of a patient one day following intravitreal ranibizumab injection for neovascular age-related macular degeneration. The patient developed endophthalmitis due to *Streptococcus intermedius* infection.

The original salient concern for ocular complications following intravitreal anti-VEGF injections was for endophthalmitis (*See Figure 1*),⁵ followed by raised awareness of non-infectious inflammation to the biologic anti-VEGF agents (*See Figure 2*); retinal tears; retinal detachment; tears of the retinal pigment epithelium; elevated intraocular pressure; and cataract.

Our views on the systemic safety profile of these agents have likely been significantly prejudiced by the mechanism of action of these agents vis-à-vis what is known about the systemic side effects of similar drugs delivered intravenously in manifold higher doses for systemic management of disease.⁶ These concerns have perhaps been mitigated by empiric data from clinical trials for ocular indications as well as from our own clinical experience with these agents. As we will see, however, subgroup analyses of the existing data can lead to persistently unanswered questions regarding the relative systemic safety of each of these agents. Additional concerns have been raised by recent pharmacokinetic studies for each of these agents.

Ocular Safety

It is clear from our clinical trial and everyday clinical experience that the aging eye tolerates multiple intravitreal injections of anti-VEGF agents very well. The most concerning risk is the development of endophthalmitis, which multiple large retrospective studies have demonstrated occurs roughly once out of every 5,000 injections (endophthalmitis rate equal to 0.02%).⁷ Not all post-injection cases of endophthalmitis due to a bacterial source are irreversibly blinding, however, there is a relatively high proportion of culture-positive cases that have the virulent *Streptococcal* species as the causative organism. Many of these *Streptococcal* cases have dismal functional results, with visual acuity often dropping to hand motions or worse level and many cases leading to evisceration or enucleation.

While the exact source of the infectious nidus remains unknown, some evidence suggests it may be due to respiratory flora from the patient, the medical assistant or the injecting physician.^{8,9} Therefore, most practitioners have a no-talking policy during the injection process. While some have advocated the use of face masks, this is not the prevailing standard of care.¹⁰

Severe eye pain, with or without decreased vision, in the first two days following the antecedent intravitreal anti-VEGF is the most common symptom.⁷ Hypopyon, anterior chamber fibrin, cell and flare, along with vitritis are the most common ocular signs. Because patients can have variably significant ocular irritation for the first 48 hours after a routine injection due to the povidone iodine 5% sterilizing solution applied to the ocular surface, it is important to emphasize that this pain tends to lessen over time while severe and deep eye pain that worsens over time is the most concerning sign for infectious cause of their symptoms. While the “per-injection” risk of endophthalmitis is quite low, clinical trial data has revealed the “per-patient” risk of endophthalmitis is closer to 1 percent.³

Initially it was felt to be important to provide pre- or post-injection antibiotic prophylaxis to reduce the risk of endophthalmitis.⁵ We later learned that this practice not only did nothing to reduce the risk of infection, it also created more antibiotic-resistant bacteria for those cases that did develop despite the use of antibiotics.^{11,12} As a result, the use of pre- or post-injection prophylactic antibiotics is not advocated.

Insofar as off-label intravitreal bevacizumab is only available through compounding pharmacies, there is a potential risk for contamination of bevacizumab during the aliquoting process, during transportation from the pharmacy to the physician's office or during storage of the drug.¹³ It is important for physicians to become aware of their supplying pharmacy's procedures for the above and check in with them regularly to ensure appropriate compliance. Unfortunately, outbreaks of blinding cases of endophthalmitis have occurred when

deviation from established protocols has led to widespread contamination of bevacizumab lots.¹⁴

While retinal tears, retinal detachment, vitreous hemorrhage and traumatic iatrogenic cataract are reported risks following retinal intravitreal anti-VEGF agents, these are not only quite uncommon,⁵ but are also less permanently visually debilitating in general than endophthalmitis is.

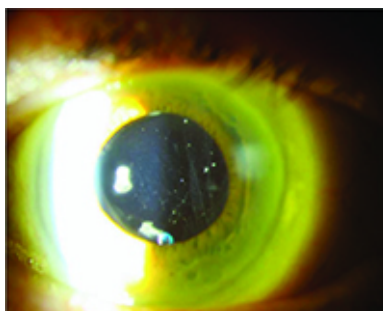


Figure 2. Slit-lamp photograph of a patient several days following his third injection of intravitreal aflibercept. Large vitreous aggregates were observed following the presentation of mild pain and decreased vision. These resolved after several weeks of topical anti-inflammatory therapy alone.

Tears of the retinal pigment epithelium have been observed in cases of neovascular AMD without treatment, with thermal laser treatment, with photodynamic therapy and with each of the anti-VEGF agents (*See Figure 3*).¹⁵ While RPE tears can occur with natural history alone, the risk of RPE tears with anti-VEGF treatment can be higher in patients with unusually large (i.e., tall) pigment epithelial detachments, according to a poster presentation this August at the American Society of Retina Specialists Annual Meeting, San Diego, Calif. (*Carle MV, et al. Tears of the retinal pigment epithelium during aflibercept therapy: PED and treatment characteristics.*) Visual loss typically occurs when the atrophic aspect of the tear is subfoveal in location. Not infrequently, massive submacular hemorrhages are found to be associated with a new tear of the RPE. RPE tears tend to do well with subsequent anti-VEGF injections.

Geographic atrophy is a well-known consequence of AMD progression, but was also observed as the number one cause of decreased vision in patients undergoing ranibizumab therapy in the MARINA trial.¹⁶

It is well-known that ocular hypertension can occur transiently immediately following the bolus injection of 50 to 100 microliters of an anti-VEGF drug. What is more concerning is the potential for significant and sustained elevations in intraocular pressure elevation. This appears to occur in 3.5 percent to 11 percent of patients receiving chronic anti-VEGF agents.¹⁷⁻¹⁹ It is unclear whether the etiology of this is mediated by the drugs' mechanisms of action on the trabecular meshwork, hydrostatic damage to the trabecular meshwork, outflow impairment, a combination of these, or due to some other unidentified mechanism. The key point here is to recognize the possibility of the risk (especially in patients with pre-existing risk factors for glaucoma), to monitor the IOP and optic nerve and to make the appropriate adjustments to the injection protocol when delivering subsequent anti-VEGF injections (e.g., lowering the volume of drug injection, using a larger-bore needle or increasing the injection interval).

Systemic Safety

VEGF is a potent promoter of vascular hyperpermeability. Anti-VEGF agents significantly reduce vascular hyperpermeability, and when delivered systemically, can also raise systemic arterial blood pressure.^{20,21} Systemic arterial hypertension is the single greatest risk factor the development of cerebrovascular accidents. Systemically delivered anti-VEGF agents are also widely known to promote the development of other thromboembolic events.^{20,21} Arterial thrombotic events, or ATEs, are defined as nonfatal stroke, nonfatal

myocardial infarction or vascular death (including deaths of unknown cause). However, these systemic events have been observed following systemic administration of anti-VEGF agents in much larger doses than what are being injected intravitreally. Do these same risks occur with such small doses that we inject into the eye routinely?

The short answer is that we do not definitively know yet. There have been no statistically significant signals derived from Level I evidence that directly point to a greater risk for the development of ATEs for patients in the anti-VEGF cohorts compared with those in the control groups in these studies. It must be understood, however, that these rigorous clinical trials were not statistically powered to answer this specific question. Additionally, it is unlikely that clinical trials designed to answer this question will be carried out, insofar as each arm of such a study would have to include more than 10,000 patients in order to be sufficiently powered to detect a meaningful difference for these rare events. That said, there is compelling clinical trial subgroup analysis and pharmacokinetic data pointing to the possibility of a risk of ATEs from intravitreal anti-VEGF drugs.

The CATT trial, for example, revealed that there was a greater risk for serious adverse events associated with bevacizumab compared with ranibizumab even though there was no significant difference between the two drugs with respect to the risk for ATEs.²² Similarly, the IVAN study demonstrated that circulating serum VEGF levels were more significantly diminished in the bevacizumab group as compared with the ranibizumab group.²³

Ranibizumab was approved for the treatment of diabetic macular edema after regulators evaluated data from the ranibizumab 0.5-mg and 0.3-mg cohorts as compared with a control group. Although each ranibizumab group had very similar efficacy data, there was an indication that the 0.5-mg group may have had a more concerning safety profile. In the pooled analysis of the RISE and RIDE ranibizumab for DME studies at three years, the ATE rate was 10.4 percent (26 of 249) with 0.5 mg ranibizumab and 10.8 percent (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8 percent (12 of 249) with 0.5 mg ranibizumab and 2.0 percent (five of 250) with 0.3 mg ranibizumab.²⁴ Additionally, over three years, fatalities occurred in 6.4 percent (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4 percent (11 of 250) of patients treated with 0.3 mg ranibizumab.²⁴ Although not statistically significant, these numerical differences were enough of a dose-dependent concern for both the sponsor and the regulator to agree to a 0.3-mg approved indication instead of the 0.5-mg dose that was previously approved for AMD and retinal vein occlusion.

The European Medicines Agency recently provided a Public Assessment Report (EPAR) on the use of aflibercept for neovascular AMD.²⁵ In its analysis of the available pooled data, the agency observed that the number of cerebrovascular accidents was higher in the aflibercept group (n=35, 1.9 percent) compared with the ranibizumab group (n=2, 0.3 percent) and that the magnitude of this difference was especially noticeable when analyzing the oldest pool of patients. For those 85 years of age and older, the number of cerebrovascular accidents after one year of therapy was 20 (7.1 percent) in the aflibercept arm versus just one (1.1 percent) in the ranibizumab arm. After two years of therapy, the difference was 27 cases (9.5 percent) in the aflibercept arm compared with three cases (3.4 percent) in the ranibizumab arm.²⁵

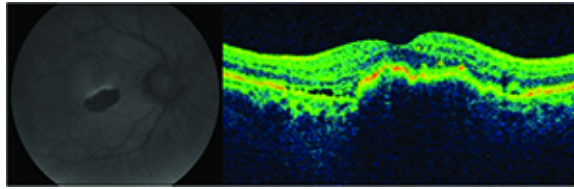


Figure 3. Fundus autofluorescence photograph of a neovascular AMD patient prior to initiation of anti-VEGF therapy. Depicted is a retinal pigment epithelial tear and corresponding vertical optical coherence tomography raster line scan through the tear.

One significant structural difference between ranibizumab²⁶ and both aflibercept²⁷ and bevacizumab²⁰ is that ranibizumab is an antibody fragment that lacks the Fc domain. Not only does ranibizumab have a much smaller molecular size than the other two, but it also exhibits lower systemic exposure following intravitreal injection by virtue of lacking the Fc domain. Robert Avery, MD, and colleagues recently demonstrated this in their pharmacokinetic study of ranibizumab, bevacizumab and aflibercept.²⁸ They observed that systemic exposure to aflibercept was five-, 37-, and ninefold higher than ranibizumab, whereas, bevacizumab was nine-, 310-, and 35-fold higher than ranibizumab. After three doses of each drug, both bevacizumab and aflibercept demonstrated systemic accumulation, while ranibizumab did not.²⁸ Furthermore, aflibercept substantially suppressed circulating plasma-free VEGF, with mean levels below the lower limit of quantitation as early as three hours after administration and lasting until $\geq$ seven days. Mean free VEGF levels with ranibizumab were largely unchanged. These data tend to support the notion that there may be pharmacokinetic variations amongst the non-specific VEGF inhibitors that could represent clinically meaningful differences in the context of the risk of ATEs.²⁸

Barry Kuppermann, MD, nicely characterized the anti-VEGF patient populations at the highest risk for ATEs in an August 2014 interview. He enumerated four high-risk groups based upon available clinical trial data, clinical experience and theoretical factors. They are: diabetics; patients 85 years and older; patients with prior strokes; and premature infants. With respect to retinopathy of prematurity, although we have limited Level 1 data, there is considerable theoretical justification for concern for the use of anti-VEGF drugs in this very vulnerable patient population.^{29,30}

Anti-VEGF agents for retinal disease are ubiquitous and very well-tolerated from an ocular perspective. While irreversible loss of vision following intravitreal anti-VEGF agents due to endophthalmitis is rare, it is a continuing risk that requires constant vigilance and attention to detail by the treating physician.

The superior efficacy of these agents over those treatments previously available is readily apparent, but clearly they remain suboptimal treatments. They are lacking not just in the fact that such frequent administration is required to achieve visual acuity and anatomic improvements, but also by their very mechanism of action that makes them so efficacious. Inhibiting systemic VEGF at such low levels opens the door to the potential for the development of ATEs. While clinical trial data have not definitively demonstrated that this risk is real, the data we do have is sufficiently concerning to warrant continued investigation and monitoring of this potential problem to determine if there are drug-specific safety characteristics that would favor one over the other.

REVIEW

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