

Intravitreal Injections

Policy

Patients undergoing intravitreal injections require the care and judgment of an ophthalmologist experienced in diagnosing and treating retinal diseases as well as potential complications that may necessitate surgical intervention. The Academy strongly supports the position that all intravitreal injections should be performed only by ophthalmologists, which are licensed doctors of medicine or osteopathy.

Background

Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments.¹ Since that time, intravitreal injections have been used to treat a variety of conditions, including endophthalmitis, intraocular lymphoma, cytomegalovirus (CMV) retinitis, submacular hemorrhage, vitreous hemorrhage, retinal vascular occlusive disease, diabetic retinopathy, and neovascular age-related macular degeneration (AMD). The primary benefit of intravitreal injection is the targeting of the therapeutic agent in the eye while minimizing systemic absorption. In 1998, the United States Food and Drug Administration (FDA) approved the use of the first agent for intravitreal injections, fomivirsen sodium (Vitravene®, Isis Pharmaceuticals, Carlsbad, CA), an antiviral used in the treatment of CMV retinitis.

Anti-VEGF Agents

The frequency of intravitreal injections significantly increased with the introduction of anti-vascular endothelial growth factor (anti-VEGF) medications. In the early 2000s, the use of intravitreal injections accelerated fueled by clinical trials and technology assessments that demonstrated the safety and effectiveness of VEGF inhibitors for the treatment of neovascular AMD.^{2,3} Anti-VEGF agents have become the first-line of therapy for treating and stabilizing most cases of neovascular AMD.^{2,4} FDA-approved intravitreal injection agents for neovascular AMD treatment include: pegaptanib sodium (Macugen®, Eyetech, Inc., Cedar Knolls, NJ), ranibizumab (Lucentis®, Genentech/Roche, Inc., South San Francisco, CA), aflibercept (Eylea®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY), and dexamethasone, an intravitreal implant (Ozurdex®, Allergan, Inc., Irvine, CA). Intravitreal bevacizumab (Avastin®, Genentech/Roche, Inc., South San Francisco, CA) is also used widely in an off-label application to treat choroidal neovascularization.

Intravitreal agents are used for treatment of many other retinal diseases -- macular edema, retinal vein occlusion, and vitreous hemorrhage. Multiple well-designed studies have demonstrated that intravitreal anti-VEGF agents provide a more effective treatment for center-involving CSME than monotherapy with laser surgery;^{9,10,11,12,13,14,15-21} making anti-VEGF agents the initial treatment choice for center-involving CSME.⁹ FDA-approved intravitreal injection agents for diabetic macular edema and macular edema associated with retinal vein occlusion treatment include: ranibizumab (Lucentis), aflibercept (Eylea), and dexamethasone intravitreal

implant (Ozurdex).

Recommendations for Patient Care

It is important to master the techniques of effective injections for patient safety, and guidelines for intravitreal injections have been developed.^{22,23} Performing intravitreal injections involves the following steps:

1. Establishing an accurate diagnosis and developing a treatment plan; including obtaining informed patient consent.²⁴
2. Assessing a patient pre-procedure for any condition that could increase complications from intravitreal injections (pre-existing glaucoma or porphyria, active infection, allergies to povidone-iodine or verteporfin (Visudyne)).
3. Preparing the eye before administering the intravitreal injection (anesthetics; antiseptics, povidone iodine or betadine applied to the ocular surface;²⁵ mydriatics; antibiotics are not routinely indicated²⁶).
4. Performing the injection.
5. Assessing a patient post-procedure; examining for retinal tears/detachment, retinal artery perfusion, lens trauma, etc.
6. Informing the patient of symptoms and signs of postoperative complications.
7. Determining the need for subsequent therapy. This can include evaluation of visual function, response to initial therapy, status of the fellow eye, and results of ocular imaging studies.

Injection Risks

For the injection, in-depth knowledge of the surgical anatomy of the eye is essential to avoid complications. The needle should be inserted perpendicularly through the sclera with the tip aimed toward the center of the globe to avoid the posterior lens.² Injections are generally performed inferotemporally or superotemporally to optimize exposure and to avoid damage to the retina and other eye structures. Possible iatrogenic injuries include lens injury, corneal abrasion, intraocular hemorrhage, and retinal tears.^{22,28} For example, the lens capsule can become damaged during the injection and a traumatic cataract can result, requiring subsequent cataract surgery.^{1,6} The retina may also be damaged, resulting in tears or even a detachment that requires surgical repair.^{21,28,29}

During the injection procedure, IOP can increase transiently and the ophthalmologist may need to reduce IOP.³⁰ If the central retinal artery is not perfused after the injection, the ophthalmologist may need to perform an anterior chamber tap.²⁹ In which case, the surgeon must insert a needle into the anterior chamber (or rarely posterior segment) of the eye to remove fluid and reduce the pressure. This procedure carries many of the same risks of the first injection (cataract, endophthalmitis, etc.).

Post-Injection Risks

Intravitreal injections of various agents have been studied extensively and the overall risk of complications is low in the hands of experienced ophthalmologists.^{1,31} However, known risks of intravitreal injections can be vision-threatening and require prompt diagnosis and treatment, possibly surgical intervention. The most serious, but rarely occurring injection-related complications, include: acute-onset endophthalmitis,³² pseudo-endophthalmitis, cataract development/progression, retinal detachment, and hemorrhage.¹ Additional infrequent complications include: hypotony, sustained increase in IOP after injection with triamcinolone acetonide and anti-VEGF agents, angle closure, hemiretinal vein occlusion, retinal pigment epithelial tears, iritis/uveitis, optic disc atrophy, corneal epitheliopathy, maculopathy, and anaphylactic reaction to the injected agent in the vitreous.^{1,28,33}

After injections of bevacizumab (Avastin), ranibizumab (Lucentis), or aflibercept (Eylea), patients must be instructed to promptly report any symptoms of pain, worsening redness, reduced vision, increased sensitivity to light, or increased floaters, which may indicate endophthalmitis.^{2,21}

A meta-analysis of the literature between January 2005 and May 2012 found that the rate of endophthalmitis was (0.056%) based on 197 of 350,535 intravitreal anti-VEGF injections. The most common organisms isolated were coagulase-negative Staphylococcus (38.24%) and Streptococcus species (29.41%).³⁴ Another meta-analysis of the literature from 2005 to March 2010 found a rate of 0.049% (52/105,536 injections). The organisms identified in culture positive cases were Staphylococcus in 65.4% and Streptococcus species in 30.8% of the time.³⁵ Unless treated effectively in a timely fashion, endophthalmitis can result in severe vision loss or blindness. Treatment includes appropriate antibiotic therapy and possible surgical procedures, such as a pars plana vitrectomy. In a case series and case control study of 27,736 injections performed between 2009–2010, no modifiable risk factors to prevent endophthalmitis were identified.³⁶

A multicenter case series found the incidence rate of rhegmatogenous retinal detachment to be 0.013% (5/35,942) per injection.³⁷ Other studies have identified sustained intraocular pressure as a complication to be monitored after injections.³⁸⁻⁴⁰ Hemorrhages, including subconjunctival, choroidal and subretinal hemorrhages, have been reported in a systematic review of the literature from 2005 to 2012.⁴¹

Complications

In addition certain agents, such as anti-VEGF agents and corticosteroids, when given systemically have significant and potentially life-threatening complications. The potential systemic side effects of anti-VEGF agents include thromboembolic events, such as stroke, myocardial infarction, and angina,⁴² and other complications, such as gastrointestinal perforation, hemorrhage, hypertensive crisis, congestive heart failure, and neutropenic sepsis.⁴³ Although all anti-VEGF treatments may carry theoretical risks for systemic arterial thromboembolic events and increased intraocular pressure, the results of clinical trials studying these risks remain inconclusive.⁴⁴⁻⁴⁷ Physicians need to monitor the possibility of long-term systemic

side effects.

Summary

Ophthalmologists have been the pioneers and innovators in the field of intravitreal injections. Eye MDs train under faculty supervision to perform intravitreal injections during their residency and fellowship programs. The optimal outcome for a patient after intravitreal injections depends on the physician making an accurate diagnosis, screening patients for any reasons to delay treatment, considering alternative methods, and using prescription drugs pre- and post-procedure, if appropriate. Patient outcome is also affected by the technical skills in placement of the needle to avoid damage to adjacent structures. Optimization of the patient outcome depends on the prompt and accurate recognition, management of vision-threatening complications, the use and timing of subsequent injections, and adjunctive or alternative treatments.

The associated risks of complications with intravitreal injections, requiring medical and/or surgical intervention, justify adherence by regulatory authorities that all intravitreal injections are performed only by licensed ophthalmologists.

References

1. Jager RD, Aiello LP, Patel SC, Cunningham ET: Risks of intravitreal injection: a comprehensive review. *Retina* 2004; 24:676-698.
2. American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2015. Available at: www.aao.org/ppp. Accessed January 15, 2015.
3. Ip, MS, Scott, IU, Brown GC, et al: Anti-vascular endothelial growth factor pharmacotherapy for age-related macular degeneration: a report by the American Academy of Ophthalmology. *Ophthalmology* 2008; 115(10):1837-46.
4. Vedula S, Krzystolik M. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2008, Issue 2. Art. No.: CD005139. DOI: 10.1002/14651858.CD005139.pub2.
5. Patel JJ, Mendes MA, Bounthavong M, et al. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. *J Eval Clin Pract* 2012;18:247-55.
6. Chapman JA, Beckey C. Pegaptanib: a novel approach to ocular neovascularization. *Ann Pharmacother* 2006;40:1322-6.
7. Web JA. Genentech decision expands access to bevacizumab. *Ophthalmol Times*. January 15, 2008.
8. Martin DF, Maguire MG, Ying GS, et al. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364:1897-908.
9. American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2015. Available at: www.aao.org/ppp. Accessed January 15, 2015.

10. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796-806.
11. Elman MJ, Qin H, Aiello LP, et al. Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmol 2012;119:2312-8.
12. Do DV, Nguyen QD, Khwaja AA, et al. READ-2 Study Group. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. JAMA Ophthalmol 2013;131:139-45.
13. Early Treatment Diabetic Retinopathy Study Research Group. Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report number 19. Arch Ophthalmol 1995;113:1144-55.
14. Elman MJ, Bressler NM, Qin H, et al. Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmol 2011;118:609-14.
15. Diabetic Retinopathy Clinical Research Network, Googe J, Brucker AJ, Bressler NM, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. Retina 2011;31:1009-27.
16. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmol 2010;117:1064-77.
17. Ho AC, Scott IU, Kim SJ, et al. Anti-vascular endothelial growth factor pharmacotherapy for diabetic macular edema: a report by the American Academy of Ophthalmology. Ophthalmol 2012;119:2179-88.
18. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. RESTORE Study Group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmol 2011;118:615-25.
19. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmol 2012;119:789-801.
20. Thomas BJ, Shienbaum G, Boyer DS, Flynn HW, Jr. Evolving strategies in the management of diabetic macular edema: clinical trials and current management. Can J Ophthalmol 2013;48:22-30.
21. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Lucentis (ranibizumab injection). BLA 25156. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2006/125156lbl.pdf. Accessed December 11, 2014.
22. Avery RL, Bakri SJ, Blumenkranz MS, et al. Intravitreal injection technique and monitoring: updated guidelines of an expert panel. Retina 2014; 34(12):S1-S18.
23. The Royal College of Ophthalmologists. Guidelines for intravitreal injections procedure 2009. Available at: www.rcophth.ac.uk/page.asp?section=451. Accessed September 4, 2014.

24. Ophthalmic Mutual Insurance Company. Consent Forms. Avastin Intravitreal Injection Consent. Available at: www.omic.com/avastin-intravitreal-injection-consent/ Accessed September 9, 2014.
25. Wykoff CC, Flynn HW, Jr. Endophthalmitis after intravitreal injection: prevention and management. *Retina* 2011;31:633-5.
26. Cheung CS, Wong AW, Lui A, et al. Incidence of endophthalmitis and use of antibiotic prophylaxis after intravitreal injections. *Ophthalmol* 2012;119:1609-14.
27. Wen JC, McCannel CA, Mochon AB, Garner OB. Bacterial dispersal associated with speech in the setting of intravitreal injections. *Arch Ophthalmol* 2011;129:1551-4.
28. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the Internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;90:1344-9.
29. Brucker AJ, Hopkins TB. Retinal detachment surgery: the latest in current management. *Retina* 2006;26:S28-33.
30. Hollands H, Wong J, Bruen R, et al. Short-term intraocular pressure changes after intravitreal injection of bevacizumab. *Can J Ophthalmol* 2007;42:807-11.
31. Jonas JB, Spandau UH, Schlichtenbrede F. Short-term complications of intravitreal injections of triamcinolone and bevacizumab. *Eye (Lond)* 2008;22:590-1.
32. Ta CN. Minimizing the risk of endophthalmitis following intravitreal injections. *Retina* 2004;24:699-705.
33. Jonas JB, Kreissig I, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetonide. *Br J Ophthalmol* 2003; 87(1):24-27.
34. Fileta, JB, Scott, IU, Flynn, HW. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmic Surg Lasers Imaging Retina* 2014; 45(2):143-9.
35. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. *Retina* 2011;31:654-61.
36. Shah CP, Garg SJ, Vander JF, et al. Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmology* 2011;118:2028-34.
37. Meyer, CH, Michels, S, Rodrigues, EB, Hager, A, Mennel, S, Schmidt, JC, Helb, HM, Farah, ME. Incidence of rhegmatogenous retinal detachments after intravitreal antivascular endothelial factor injections. *Acta Ophthalmol* 2011; 89(1):70-5.
38. Hoang QV, Tsuang AJ, Gelman R, et al. Clinical predictors of sustained intraocular pressure elevation due to intravitreal anti-vascular endothelial growth factor therapy. *Retina* 2013;33:179-87.
39. Hoang QV, Mendonca LS, Della Torre KE, et al. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. *Ophthalmol* 2012;119(2):321-26.
40. Choi DY, Ortube MC, McCannel CA, et al. Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina* 2011;31:1028-35.

41. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)* 2013;27:787-94.
42. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007;99:1232-9.
43. National Cancer Institute. Drug Information FDA approval for Bevacizumab. Available at: www.cancer.gov/cancertopics/druginfo/fda-bevacizumab. Accessed December 11, 2014.
44. Toalster N, Russell M, Ng P. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. *Retina* 2013;33:1351-8.
45. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. *Arch Ophthalmol* 1999;117:1329-45.
46. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization--verteporfin in photodynamic therapy report 2. *Am J Ophthalmol* 2001;131:541-60.
47. Barbazetto I, Burdan A, Bressler NM, et al. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment--TAP and VIP report number 2. *Arch Ophthalmol* 2003;121:1253-68.

Approvals

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