

ALLERGIC REACTION UPON INTRAVITREAL ADMINISTRATION OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

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Purpose: To describe the patient's allergic response to anti-vascular endothelial growth factor drugs after receiving intravitreal bevacizumab for choroidal neovascularization.

Methods: Clinical case report.

Results: Formal allergy evaluation revealed hypersensitivity to bevacizumab and ranibizumab, but not to pegaptanib or aflibercept.

Conclusion: Bevacizumab and ranibizumab are derivatives of murine monoclonal antibodies, whereas pegaptanib is an aptamer and aflibercept is a fusion protein of human origin. These chemical origins may allow patients to receive pegaptanib or aflibercept despite having allergy to bevacizumab or ranibizumab.

RETINAL CASES & BRIEF REPORTS 0:1–3, 2017

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Allergic events in response to anti-vascular endothelial growth factor (VEGF) agents are rare.¹ There have been reports of systemic reactions upon intravenous administration of bevacizumab (Genentech, South San Francisco, CA), but the dose used in intravenous administration is much higher than that used in intravitreal injections.^{2,3} To our knowledge, this case represents the first report of a patient with documented anti-VEGF allergy upon intravitreal injection of anti-VEGF medications.

Case Report

A 62-year-old woman with a history of presumed ocular histoplasmosis syndrome was referred to the retina clinic for a macular hemorrhage and decreased vision for 2 days in the right eye (OD). On examination, visual acuity was 20/80 OD and counting fingers at 3 feet in the left eye, and the anterior segments

appeared normal. Fundoscopy revealed mild fibrosis with sub-retinal fluid (SRF) OD and moderate fibrosis and atrophy in the left eye. Ocular coherence tomography testing confirmed SRF OD. Fluorescein angiography demonstrated late leakage as a result of choroidal neovascularization. Off-label intravitreal bevacizumab was recommended for the right eye. She reported allergies to sulfonamide antibiotics, gluten, and iodine.

The patient received an intravitreal injection of 1.25 mg of bevacizumab OD under topical anesthesia with lidocaine 2% gel (Akom, Inc., Lake Forest, IL) and povidone-iodine 5% (Alcon Laboratories, Inc., Fort Worth, TX) drops immediately before injection. The procedure was tolerated well in the office, but the patient experienced dyspnea 5 minutes after injection, which she did not report. Four weeks later, during her scheduled follow-up examination, the patient noted a small improvement in her vision, and upon testing, her acuity had improved from 20/80 OD to 20/50 OD with the resolution of SRF. A second bevacizumab injection was given.

Thinking that she might have had an allergic reaction related to her first injection, the patient chose to premedicate herself with cetirizine and diphenhydramine before the second injection, which again she did not report. During this rechallenge, she experienced less dyspnea after the second bevacizumab administration. The next morning, she reported dysphasia and throat swelling. This resolved without further treatment.

During the subsequent visit, she mentioned the symptoms suggesting an allergic reaction. Thinking the allergic symptoms might have been triggered by injection-related medications, we placed a small amount of lidocaine gel and povidone-iodine on her forearm to test for an allergic reaction, and there was none. We recommended the patient to undergo a formal allergy evaluation by a specialist. During that evaluation, a full-strength skin prick test with bevacizumab was administered. That test was negative with

None of the authors has any financial/conflicting interests to disclose.

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a positive histamine control. Upon intradermal administration of 0.01 mL of a 1:10 dilution of the drug, she quickly developed postnasal drainage, coughing, and shortness of breath. There was no sign of a local reaction. She was given 0.3 mL of epinephrine subcutaneously to combat these symptoms and advised to avoid bevacizumab in the future.

A few months later, she returned to the retina clinic, and SRF was again discovered in her right eye. It was recommended that the patient receive a ranibizumab (Genentech) injection instead of bevacizumab, but only after allergic testing for ranibizumab. A graduated challenge to ranibizumab produced an adverse reaction consisting of throat tightness and coughing at a dose of 0.01 mL of the full-strength concentration. This reaction was less severe and was successfully treated with diphenhydramine alone.

Because of the uncertainty regarding the use of anti-VEGF agents, it was decided to treat her with verteporfin (Bausch and Lomb, Rochester, NY) photodynamic therapy. She tolerated the therapy well, and the SRF resolved on subsequent visits. Because of the possibility of needing anti-VEGF injections in the future, the patient underwent allergic testing and challenge to aflibercept (Regeneron, Tarrytown, NY) and pegaptanib (Bausch and Lomb) for future reference. Interestingly, the patient subsequently tolerated a graded challenge with aflibercept and pegaptanib at a therapeutic dose without any allergic reaction despite being allergic to the other anti-VEGF agents drugs.

Discussion

Hypersensitivity to two different anti-VEGF agents without being allergic to two others has not been previously reported to our knowledge. The chemical origins of each of these drugs may elucidate the mechanism behind this finding.

Bevacizumab is a recombinant, humanized, monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human VEGF in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF.⁴ The bevacizumab product insert does not report allergic or anaphylactic reactions as potential side effects.⁴

Ranibizumab injection is a recombinant humanized IgG1-kappa isotype monoclonal antibody fragment designed for intraocular use.⁵ Ranibizumab binds to and inhibits the biologic activity of VEGF-A. Similarly, the ranibizumab product insert does not report allergic or anaphylactic reactions as potential side effects, although the US package insert does include “hypersensitivity.”⁵ Both bevacizumab and ranibizumab are recombinant, humanized, monoclonal antibodies of murine origin.^{4,5}

Pegaptanib sodium is an aptamer consisting of a covalent conjugate of an oligonucleotide of 28 nucleotides in length.⁶ Anaphylaxis/anaphylactoid reactions, including angioedema, have been identified during postapproval use but without any reliable estimate to their frequency or relationship to drug exposure.⁶

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2

extracellular domains fused to the Fc portion of human IgG1.⁷ Allergic or anaphylactic reactions were not reported in the US package insert, although “hypersensitivity” is listed.⁷

Neither pegaptanib nor aflibercept is a “humanized” murine-derived product. Instead, pegaptanib is an aptamer, and aflibercept is a “human” fusion protein.^{6,7} This murine origin may explain the patient’s comparable allergic responses to the two former drugs, but none to the latter two.

The patient had no cutaneous reaction to bevacizumab upon intradermal testing, so it is presumed that this is not an IgE-mediated response. Interestingly, skin prick tests and/or *in vitro* immunoassays may predict allergic outcomes in patients receiving infusions of murine monoclonal antibodies better than intradermal skin testing.⁸ The longer-term question is whether other murine-derived antibodies would be contraindicated if this patient were to require them for other conditions, such as cancer, rheumatoid arthritis, or other inflammatory disorders.

This case illustrates an important concept that could result in improved clinical decision making. Intravitreal administration of these drugs is a valuable tool for the ophthalmologist treating macular degeneration, diabetic retinopathy, retinal vein occlusion, or other exudative macular diseases. If a patient needs an intravitreal injection but has a known allergy to either bevacizumab or ranibizumab, based on this case, it is definitely possible that they can still receive other anti-VEGF agents. Aflibercept and pegaptanib may be good options because they are not humanized, murine, monoclonal antibodies or antibody fragments.

In conclusion, this case demonstrates that allergy to one drug in the anti-VEGF class does not necessarily mean allergy to all drugs. This case emphasizes the notion that treatment with another anti-VEGF agent is still a possibility for patients with allergies to other therapies in that class. Furthermore, this conclusion might in theory be applicable to other classes of drugs and therapeutics, depending on the antibody origin. Finally, this case suggests that design and manufacturing choices for antibodies can, in rare circumstances, have clinical ramifications.

Key words: aflibercept, allergy, bevacizumab, pegaptanib, ranibizumab.

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