



Department of Veterans Affairs Office of Inspector General

Healthcare Inspection

Oversight Review of Ophthalmology Adverse Drug Events VA Greater Los Angeles Healthcare System Los Angeles, California

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Executive Summary

The VA Office of Inspector General Office of Healthcare Inspections conducted an oversight review to assess actions taken by VA Greater Los Angeles Healthcare System (the facility) leadership in addressing intravitreal injections (treatment to deliver medication into the eye between the lens and the retina) that led to blindness in the treated eyes of five patients. This review describes actions taken by Veterans Integrated Service Network (VISN) 22 and the facility to address and respond to the adverse drug events and includes findings and makes a recommendation relative to these actions.

We determined that appropriate actions were taken, including: (1) conducting initial institutional disclosures with the five affected patients; (2) halting the administration of Avastin® intravitreal injections; and (3) reporting the adverse drug events to the VISN, the U.S. Food and Drug Administration (FDA), and the VA National Center for Patient Safety, which led to multiple external site visits that resulted in findings and recommendations. The facility has initiated corrective actions and implemented new procedures related to ordering, compounding, staffing, and staffing competencies.

We determined that VISN and facility managers complied with Veterans Health Administration (VHA) policy in taking immediate action as described in this oversight review. They appropriately notified the patients and contacted FDA and VHA leaders while ascertaining the cause of the adverse drug events. The facility's follow-up disclosure to the patients that a medication error occurred is consistent with VA's commitment to transparency. We noted that the facility Director convened an administrative board of inquiry (ABI) on February 23, 2012, to address additional administrative and patient safety issues.

We recommended that the Facility Director ensure that recommendations from the local and external reviews are implemented and monitored, that the ABI is completed in a timely manner, and that corrective actions in response to the ABI are taken if indicated.

The VISN and Facility Directors concurred with our findings and recommendation and provided an acceptable action plan. We will follow up on the planned actions until they are completed.



DEPARTMENT OF VETERANS AFFAIRS
Office of Inspector General
Washington, DC 20420

TO: Director, Desert Pacific Healthcare Network (10N22)

SUBJECT: Healthcare Inspection – Oversight Review of Ophthalmology Adverse Drug Events, VA Greater Los Angeles Healthcare System, Los Angeles, California.

Purpose

The VA Office of Inspector General (OIG) Office of Healthcare Inspections conducted an oversight review to assess actions taken by VA Greater Los Angeles Healthcare System (the facility) leadership in addressing intravitreal injections¹ that led to blindness in the treated eyes of five patients.

This review describes actions taken by Veterans Integrated Service Network (VISN) 22 and the facility to address and respond to the adverse drug events and includes findings and makes a recommendation relative to these actions.

Background

The facility, which is part of the Pacific Desert Healthcare Network (VISN 22), is one of the largest integrated health care organizations in VA and offers a full range of inpatient and outpatient services, including ophthalmology care at the Sepulveda Ambulatory Care Center (SACC), a satellite location.

Age-related macular degeneration (AMD) is an eye disease that damages the retina and is the leading cause of blindness. There are two forms of AMD—dry and wet. Dry AMD is less severe, and vision loss is usually gradual. Wet AMD is more severe and occurs when abnormal blood vessels grow under the macula (part of the retina in the back of the central region of the eye). These new blood vessels tend to be fragile and often leak blood and fluid, which raises the macula from its normal location in the back of the eye.

¹ Treatment to deliver medication into the eye between the lens and the retina where the vitreous humor (a gel-like substance) is found.

Abnormally high levels of a specific growth factor (vascular endothelial growth factor (VEGF) A) occur in eyes with wet AMD and promote the growth of abnormal new blood vessels.²

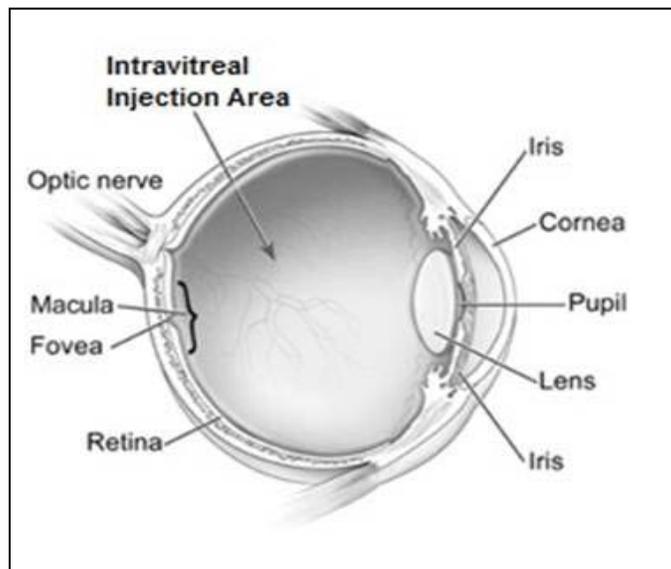


Figure 1. Cross-sectional diagram of eye and intravitreal injection area.

Avastin® (bevacizumab), a drug commonly used to treat various metastatic (spreading) cancers, blocks the growth of new blood vessels by inhibiting VEGF.³ Intravitreal injections of Avastin® in smaller doses than those used in cancer patients have been used to slow the progression of AMD even though it is not currently approved by the U.S. Food and Drug Administration (FDA) for such use (known as off-label use). Avastin® is supplied in a vial and is prepared in smaller doses by pharmacy staff before ocular use.

Lucentis® (ranibizumab) is another drug used to slow the progression of AMD and is FDA-approved for such use. It is also injected intravitreally but does not require compounding (mixing). Clinical trials by the National Eye Institute comparing Avastin® and Lucentis® for treating AMD concluded that the two drugs are about equal in their effectiveness but that safety measurements and long-term effects will require further study. However, in terms of cost, an ocular dose of Lucentis® is about 10 times the cost of an ocular dose of Avastin®.⁴

Since 2005, the off-label ocular use of Avastin® has been widely accepted. VA supports the use of this drug for intravitreal injections in VA facilities, and for the past 7 years, the facility has been providing 30–40 intravitreal injections per week.

² National Eye Institute (NEI), *Facts about Age-Related Macular Degeneration*. Retrieved February 15, 2012, from http://www.nei.nih.gov/health/maculardegen/armd_facts.asp.

³ How Avastin Is Designed to Work. Retrieved February 15, 2012, from <http://www.avastin.com/patient/crc/about/index.html>.

⁴ Marilyn Haddrill, *Lucentis vs Avastin: A Macular Degeneration Treatment Controversy*, May 2011. Retrieved February 15, 2012, from <http://www.allaboutvision.com/conditions/lucentis-vs-avastin.htm>.

In August, 2011, six doses of Avastin® were prepared in single-dose syringes at the facility's pharmacy and then packaged and transported to the SACC for the following day's clinic. Six patients were scheduled for Avastin® intravitreal injections at the SACC. However, only five patients arrived for the injections. The five patients each had a single eye treated by a senior resident under the supervision of an attending physician. The sixth syringe was returned to the facility unused and was eventually sent to an FDA-approved forensic laboratory for analysis.

Within 24–48 hours of the injections, three of the five patients reported to the facility's emergency department complaining of severe eye pain. Within 5 days of the injections, all five patients had developed complete blindness in the treated eye. Within 7 days of the injections, all affected patients were notified of the adverse events even though the cause of their blindness was not known at the time.

VA and Facility Actions. On August 31, 2011, the FDA issued an alert following reports that 16 people in two states had developed severe ocular infections.⁵ On September 6, VA issued a system-wide moratorium, through the National Pharmacy Benefits Management Services (PBM) Bulletin, on the use of Avastin® for ophthalmic indications. During this time, providers were directed to use Lucentis® until an evaluation of VA practices associated with the preparation and administration of the Avastin® was performed. On October 18, it was determined that the adverse events reported in the FDA alert were not related to the drug itself,⁶ and the PBM issued updated interim guidance on the use of intravitreal Avastin®.⁷ On October 28, VA allowed ophthalmologists to resume use of Avastin® in their eye clinics, subject to the additional provisions stated in the interim guidance. Final PBM guidance on the use of Avastin® for ophthalmology indications is pending.

On January 27, 2012, the FDA informed facility leadership that the facility's adverse events were not related to infections and that the wrong drug appeared to have been injected into the patients. The forensic laboratory found traces of Velcade® (bortezomib), another medication that kills cancer cells, in the sixth syringe. Velcade® is not intended for intraocular injection. On February 27, the facility contacted all affected patients, disclosed that a medication error had occurred, and apologized. The follow-up institutional disclosures are documented in the patients' electronic medical records.

Timeline of Events. On August 15, 2011, upon learning of the five adverse reactions to intravitreal injections of Avastin®, the facility halted all intraocular Avastin® injections. The facility notified VA and VISN officials as well as the FDA. In addition to local investigations by ophthalmology and pharmacy managers, the VA National Center for

⁵ FDA, *FDA Alerts Healthcare Professionals of Infection Risk from Repackaged Avastin Intravitreal Injections*, August 30, 2011. Retrieved March 1, 2012, from <http://www.fda.gov/Drugs/DrugSafety/ucm215175.htm>.

⁶ VA Memorandum, *Updated Guidance on the Use of Intravitreal Bevacizumab (Avastin)*, October 28, 2011.

⁷ National PBM Bulletin, *Intravitreal Bevacizumab (Avastin) Therapy Update to Interim Guidance*, October 18, 2011.

Patient Safety (NCPS) and VISN staff performed their own investigations. Facility actions are noted in Table 1 below.

Date	Event/Actions
August 15, 2011	All Avastin® intravitreal injections halted at the facility; Avastin® vial lot sequestered.
August 16	Facility review of senior resident cases; facility pharmacy preliminary investigation results presented.
August 17	Institutional disclosures initiated; sixth Avastin® syringe sent to external forensic laboratory for testing; issue brief submitted.
August 18	Report submitted to the FDA and the VA NCPS.
August 19	Institutional disclosures completed for all five patients (cause of their blindness unknown at the time).
August 30–31	VA NCPS site visit.
September 6	First FDA site visit; National PBM Bulletin issued immediately halting all use of Avastin® for ophthalmic indications.
October 6	VISN 22 site visit.
October 12	Second FDA site visit; submission of Avastin® vials/samples to FDA.
October 18	National PBM Bulletin issued providing interim guidance and reinstating the use of Avastin® in ophthalmology clinics.
December 21	Third FDA site visit; submission of Velcade® vials/samples to FDA.
January 27, 2012	FDA report to facility regarding forensic testing results of sixth syringe; VA OIG Office of Criminal Investigations contacted.
February 27	Follow-up institutional disclosures completed and documented in the patients' electronic medical records.

Table 1: Timeline of events.

Current Status. Several recommendations resulted from the local and external reviews. The facility has initiated corrective actions and implemented new procedures related to ordering, compounding, staffing, and staffing competencies. Additionally, although VA has resumed the off-label use of Avastin®, the facility decided to continue AMD treatment with Lucentis®. On February 27, 2012, facility leadership contacted all affected patients and appropriately communicated the medication errors and documented the discussion in the patients' electronic health records.

Scope and Methodology

This review comments on events subsequent to the case referral to the Office of Healthcare Inspections for oversight. We examined VHA policies, patients' electronic health records, and pertinent facility documents, including the FDA, NCPS, and VISN reports. We reviewed facility action plans, the progress that has been made in response to the adverse events, and the deficiencies identified in the NCPS and VISN reports.

We conducted the inspection in accordance with *Quality Standards for Inspection and Evaluation* published by the Council of the Inspectors General on Integrity and Efficiency.

Review Results

Issue 1: Adverse Event Disclosure

VHA policy states that facilities and individual providers have an ethical and legal obligation to disclose to patients adverse events that have been sustained in the course of their care.⁸ We acknowledge the facility's timely efforts to notify patients of the adverse events in August 2011 even though the cause of their blindness was not known at the time.

During the course of our review, we learned that on February 27, 2012, facility leadership and clinicians contacted all affected patients and informed them that a medication error occurred. Patients were informed that Velcade®, another cancer treatment drug, was administered in error. Facility leadership expressed regret and apologized for this error. These institutional disclosures are appropriately documented in the patients' electronic health records. The facility's disclosure of adverse events is consistent with VA's commitment to transparency. Therefore, we did not make a recommendation.

Issue 2: Competencies and Due Diligence

It is a community standard and a facility practice for pharmacy technicians to review assigned medication orders, prepare the medications, and label them accordingly. A licensed pharmacist then checks to ensure accuracy by reviewing the medication orders and examining the original medication packaging and the drug preparation itself prior to release for transport to the SACC.

Based on the FDA confirmation that Velcade® and not Avastin® was found in the syringes, multiple safety steps during medication preparation were missed. Facility managers reported that they have implemented new procedures related to ordering, compounding, staffing, and staffing competencies. Pharmacy staff training and competency assessment have been completed. In addition, on February 23, 2012, the

⁸ VHA Directive 2008-002, *Disclosure of Adverse Events to Patients*, January 18, 2008.

facility Director convened an Administrative Board of Inquiry (ABI)⁹ to address additional administrative and patient safety issues.

Conclusions

We determined that VISN and facility managers complied with VHA policy in taking immediate action as described in this oversight review. They appropriately notified the patients and contacted the FDA and VHA leaders while ascertaining the cause of the adverse drug events. The facility's action of disclosing to the patients that a medication error occurred is consistent with VA's commitment to transparency. In addition, the ABI that is underway to address additional administrative and patient safety issues is reasonable.

Recommendation

We recommended that the Facility Director ensure that the recommendations from the local and external reviews are implemented and monitored, that the ABI is completed in a timely manner, and that corrective actions in response to the ABI are taken if indicated.

Comments

The VISN and Facility Directors concurred with our recommendations and provided an acceptable action plan. (See Appendixes A and B, pages 7–9, for the Directors' comments.) We will follow up on the planned actions until they are completed.



JOHN D. DAIGH, JR., M.D.
Assistant Inspector General for
Healthcare Inspections

⁹ VA Handbook 0700, *Administrative Investigations*, July 31, 2002, and VA Directive 0700, *Administrative Investigations*, March 25, 2002.

VISN Director Comments

**Department of
Veterans Affairs**

Memorandum

Date: March 23, 2012

From: Director, Desert Pacific Healthcare Network (10N22)

Subject: **Healthcare Inspection – Oversight Review of Ophthalmology Adverse Drug Events, VA Greater Los Angeles Healthcare System, Los Angeles, CA**

To: Director, Los Angeles Office of Healthcare Inspections (54LA)

Thru: Director, VHA Management Review Service (10A4A4)

1. I concur with the findings and recommendations in the Draft Report OIG Healthcare Inspection - Ophthalmology ADEs (2012-0698) of the VA Greater Los Angeles Healthcare System, Los Angeles, CA.
2. If you have any questions regarding our responses and actions to the recommendations in the draft report, please contact me at (562) 826-5963.

(original signed by:)

Stan Johnson, MHA, FACHE
Director, Desert Pacific Network (10N22)

Facility Director Comments

**Department of
Veterans Affairs**

Memorandum

Date: March 23, 2012

From: Director, VA Greater Los Angeles Healthcare System
(691/00)

**Subject: Healthcare Inspection – Oversight Review of Ophthalmology
Adverse Drug Events, VA Greater Los Angeles Healthcare
System, Los Angeles, CA**

To: Director, Desert Pacific Healthcare Network (10N22)

1. Attached is the response to the Draft Report OIG Healthcare Inspection – Ophthalmology ADEs, VA Greater Los Angeles Healthcare System.
2. If you have any questions or require additional information, please contact Joan Lopes, Chief, Quality Management, at (310) 478-3711, extension 83585 or Karen Stewart-Dorsaint, Administrative Officer to the Chief of Quality Management , at (310) 478-3711, extension 84240.

(original signed by:)

Donna M. Beiter, R.N., M.S.N.

Director, VA Greater Los Angeles Healthcare System (691/00)

Director's Comments to Office of Inspector General's Report

The following Director's comments are submitted in response to the recommendation in the Office of Inspector General's report:

OIG Recommendation

Recommendation. We recommended that the facility Director ensure that the recommendations from the local and external reviews are implemented and monitored, that the ABI is completed in a timely manner, and that corrective actions in response to the ABI are taken if indicated.

Concur

Target Completion Date: 4/20/2012

Facility's Response:

The Administrative Board Investigation (ABI) team is slated to arrive on March 26, 2012, and the Board of Investigation (BOI) will start on March 27, 2012. GLA anticipates completion on April 20, 2012. It takes at least one (1) week for the transcripts to return to Quality Management (QM). Any recommendations from local and external reviews have been addressed and appropriate corrective actions have been implemented.

Status: Open

OIG Contact and Staff Acknowledgments

OIG Contact	For more information about this report, please contact the Office of Inspector General at (202) 461-4720.
Acknowledgments	Daisy Arugay, MT Mary Toy, RN

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