

Anti-VEGF Intravitreal Injections for ROP: Risk Management Analysis and Recommendations

OMIC ROP Task Force

OMIC has devoted considerable time and effort to improve the safety of premature infants and reduce the liability of the care that ophthalmologists provide to these patients. We are grateful to the ophthalmologists on our Board and Committees for their expertise. This specific document reflects the input of the following Board, Committee, and staff members: Anne M. Menke, RN, PhD; Denise Chamblee, MD; Robert Gold, MD; Betsy Kelley; Pauline Merrill, MD, Trexler M. Topping, MD; Robert Wiggins, MD; and George Williams, MD.

RISK MANAGEMENT RECOMMENDATIONS AND UNDERWRITING REQUIREMENTS

OMIC regularly analyzes its claims experience to determine loss prevention measures that our insured ophthalmologists can take to reduce the likelihood of professional liability lawsuits. OMIC policyholders are generally not required to implement risk management recommendations. Rather, physicians use their professional judgment in determining the applicability of a given recommendation to their particular patient and practice situation. **Some of the risk management recommendations about ROP, however, have become underwriting requirements;** these are detailed in the ROP Questionnaire that OMIC policyholders who provide ROP care are asked to complete. Please contact your underwriting representative for more information.

These loss prevention documents may refer to clinical care guidelines such as the American Academy of Ophthalmology's *Preferred Practice Patterns*, peer-reviewed articles, or to federal or state laws and regulations. However, our risk management recommendations and underwriting requirements do not constitute the standard of care nor do they provide legal advice. If legal advice is desired or needed, an attorney should be consulted. Information contained here is not intended to be a modification of the terms and conditions of the OMIC professional and limited office premises liability insurance policy. Please refer to the OMIC policy for these terms and conditions.

Revised 4/4/16 to address research on neurodevelopment delays

OMIC ROP resources

OMIC is committed to helping ophthalmologists provide safe care for infants at risk for retinopathy of prematurity (ROP). To that end, we have published online our analysis of ROP malpractice claims, as well as toolkits for both hospital- and office-based care. Please see "Retinopathy of Prematurity: Creating a Safety Net (2nd edition)", "Retinopathy of Prematurity: Materials for Creating a Hospital ROP Safety Net," and "Retinopathy of Prematurity: Materials

for Creating an Office ROP Safety Net,” all available at <http://www.omic.com/rop-resources/>. Our sample consent form for laser treatment of ROP is included in the hospital toolkit.

To further reduce the risk and severity of ROP malpractice claims, OMIC conducts an underwriting review on an annual basis of all insured physicians who provide ROP care, and has mandated certain loss prevention actions. If you have any concerns about the requirements or any other aspect of ROP care, please contact OMIC Risk Manager Anne Menke by calling toll free at 800-562-6642, extension 651, directly at 415-202-4651, or via email at amenke@omic.com. The assistance is confidential.

Treatment of ROP

The current standard treatment for ROP is laser surgery. Some babies are too sick to tolerate the anesthesia needed during the surgery. In others, the abnormal vessels are in an area that the laser cannot safely reach, or the view is obstructed by blood or a persistent tunica vasculosa lenticis. Some infants have disease that persists despite laser. Other means of arresting ROP are thus needed.

Adult patients with retinal conditions due at least in part to VEGF have been successfully treated for many years now with intravitreal injections of anti-VEGF agents such as Avastin™ (bevacizumab), Macugen™ (pegaptanib), Lucentis™ (ranibizumab), and Eylea™ (aflibercept); intravitreal injection of anti-VEGF agents is hereafter referred to as **IVAV**. ROP is similar to certain retinal conditions in adults, prompting clinical trials on the use of IVAV in neonatal populations. Published reports of IVAV from both clinical trials and off-label use suggest that it can be effective. **The efficacy, safety, and long-term consequences have are not yet known.**

Concerns about IVAV both as primary or salvage therapy have been addressed in the literature and at eye society meetings. In addition, many questions are currently being studied and debated, such as agent, dosage amount, volume, timing of injections, length of follow-up, and contraindications. Two recent studies have analyzed the effect of Avastin on the infant's neurodevelopment. *Pediatrics* published a report¹ showing that the odds of severe neurodevelopmental disabilities was 3.1 times higher in infants treated with Avastin than those treated with laser. Another article² showed increased odds only in infants treated with both Avastin and laser. Research is ongoing to determine if Avastin and other anti-VEGF drugs are safe.

Despite these uncertainties, when faced with aggressive or refractive ROP, ophthalmologists at times feel there is no other prudent choice but to treat ROP with IVAV. Given the extremely high indemnity payments required to settle ROP malpractice claims, ophthalmologists are understandably concerned: they feel they are caught between the need to administer vision-preserving care and the risk of litigation—even decades later—for doing so. This document will address those concerns, and

¹ Warren J, Luu TM, Superstein R, et al. Neurodevelopmental Outcomes Following Bevacizumab Injections for Retinopathy of Prematurity. *Pediatrics*. 2016; 137 (4): e20153218.

<http://pediatrics.aappublications.org/content/early/2016/03/16/peds.2015-3218>

² Lien R, Yu M-H, Hsu K-H, Liao P-J, Chen Y-P, Lai C-C, et al. (2016) Neurodevelopmental Outcomes in Infants with Retinopathy of Prematurity and Bevacizumab Treatment. *PLoS ONE* 11(1): e0148019.

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0148019>

provide risk management recommendations specific to the off-label use of anti-VEGF agents to treat ROP.

Obtaining informed consent for IVAV treatment of ROP

Even though research is ongoing to determine if Avastin and other anti-VEGF drugs are safe, ophthalmologists have to explain what they do know about these drugs to parents or legal guardians (whom we call “caretakers”). Neonatologists are a vital partner in the decision to use IVAV. Discuss the decision to use IVAV with the infant’s neonatologist to help determine the risk/benefit ratio in the particular child. Document the discussion, and relate it to the caretakers. Consider asking the neonatologist to be present during the informed consent discussion.

Informed consent discussions are often difficult, but rarely more so than in situations like this. Ophthalmologist who screen infants for ROP may not meet the parents during the screening process, and may thus be talking to the caretakers for the first time when they need to obtain consent. Once the need for treatment is identified, the eye surgeon needs to provide it within 72 hours to prevent progression to a retinal detachment; this timeline may make caretakers uncomfortable about making an informed choice. Premature infants run the risk of serious cardiac and respiratory complications with invasive treatment. In addition, the VEGF that causes ROP is vital for the development of the infant’s brain, lungs, and kidneys. When the treatment being proposed is relatively new and has unknown long-term risks, it is even more difficult for physicians to discuss, and for parents and caretakers to consent. OMIC has resources to help with this discussion.

- “Dear caregiver letter” in the ROP Hospital and Office Toolkits: OMIC requires insured physicians to provide caretakers with a brief explanation of ROP as of the very first examination and prior to discharge from the hospital. This educational effort helps prevent allegations made by plaintiffs in ROP malpractice lawsuits that they did not know that the infant was at risk for ROP.
 - Our sample ROP protocols recommend that neonatologist and neonatal nurses help educate parents and caregivers about ROP.
- Sample consent form for IVAV for ROP, available at <http://www.omic.com/rop-anti-vegf-injection/>. As always, our sample forms need to be reviewed and may need to be revised. The hospital may need to have the form reviewed by its Forms Committee. As a general rule, our sample consent forms indicate that the patient does not have to consent to treatment. This is the case only for adult patients with decision-making capacity. While the consent of the caretaker is legally required, lack of consent may constitute child neglect if the proposed care is needed to prevent significant harm to the minor. Indeed, physicians must take action if there is a reasonable belief that there is child neglect or abuse. The consent form includes a paragraph that states that the surgeon “must discuss the refusal with other physicians and Child Protective Services.”

Off-label use of anti-VEGF drugs

The federal Food and Drug Administration (FDA) approves and regulates the production, sale, and clinical research of medical drugs and devices. No drugs are currently approved to treat ROP. Any use of anti-VEGF drugs to treat ROP outside of clinical trials is off-label. The sample consent form addresses off-label use.

The FDA does not directly regulate the practice of medicine. Rather this oversight is provided by state legislatures, which pass medical practice acts generally granting the physician the right to use any and all means to diagnose and treat disease. Medical practice is further regulated by state medical boards, which issue licenses to practice medicine, and set conditions for license maintenance and renewal.

As part of the practice of medicine, physicians regularly use FDA-approved medications both for the stated purpose and for many other conditions for which approval may never be sought. The FDA has explicitly addressed off-label use in an Information Sheet.³ The Sheet starts by declaring “Good medical practice and the best interests of the patient **require** that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment (emphasis added).” The FDA advises physicians who use approved products off-label to “be well-informed about the product, base its use on firm scientific method and sound medical evidence, and maintain records of its use and effects.”

OMIC has analyzed the FDA guidance and its 29 years of ophthalmic claims, and concurs that it is not only legal but necessary for ophthalmologists to administer medications off-label when treating their patients. Moreover, OMIC feels that the ophthalmologist is in the best position to determine how to treat an individual patient. Accordingly, our professional liability policy provides coverage for such use. In the event of a lawsuit related to off-label use, ophthalmologists who are challenged will rely upon the expert witness testimony of ophthalmologists, peer-reviewed literature, and their well-documented efforts to provide quality care.

Caretakers who insist on IVAV treatment

While IVAV has an imprecise safety profile, it does spare the peripheral retina and may allow for better overall vision. Some caretakers prefer this treatment option. OMIC’s Risk Management Department has already fielded calls from ophthalmologists who are uncomfortable with demands made by caretakers to use IVAV when laser surgery is, in the physician’s judgment, the best treatment. As in any case where the patient, or the patient’s legal representative, wants to engage upon a different course of treatment, clarify the reasons for the preference. Explain your reservations. Enlist the assistance of other members of the patient’s healthcare team. Document all discussions. If after careful discussion and consideration you feel you cannot provide the treatment that is requested, arrange for an ophthalmologist with current competency in ROP to assume care of the infant and provide treatment in the appropriate time interval before withdrawing from care. Send a letter confirming the end of the physician-patient relationship. OMIC has sample termination of care letters at www.omic.com.

Prolonged follow up after IVAV

Studies and presentations have indicated that IVAV changes the natural history of ROP. Significantly, recurrence may occur months after it is expected. As a result, infants who receive IVAV need to be

³ Food and Drug Administration. Regulatory Information: “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet”. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>. Accessed 8/15/12.

examined for longer periods. The need for longer and additional follow-up may increase the risk for noncompliance with some caretakers. Consider whether IVAV or IVAV alone is the best choice in the setting of unreliable caretakers. Carefully monitor appointments and promptly involve Child Protective Services if needed. The office toolkit includes recommendations for tracking of appointments, and sample letters to caretakers that warn of the possible need to contact the authorities.

Keep current and keep a file on ROP

Screening and treatment of ROP is a rapidly evolving discipline. Keep current by reviewing pertinent journals and attending talks. Keep a file containing such articles or notes from talks. Consider taking a course that provides advanced training in the diagnosis and treatment of ROP. OMIC has identified such a course, and will pay enrollment fees for insured physicians who provide ROP care. If you are interested, please contact Risk Management Coordinator Linda Nakamura at lnakamura@omic.com or by calling 800-562-6642, extension 652, or directly at 415-202-4652..

Confidential risk management assistance

If you have any questions or concerns about our forms, recommendations, or any aspect of ROP care, please contact OMIC Risk Manager Anne Menke by calling toll-free at 800-562-6642, extension 651, directly at 415-202-4651, or via email at amenke@omic.com.