OMIC
OPHTHALMIC MUTUAL INSURANCE COMPANY
A Risk Retention Group

Risk Management Recommendations

Sponsored by the American Academy of Ophthalmology

ROP Safety Net: Anti-VEGF for ROP

OMIC policyholders who provide care must comply with the ROP Safety Net.

OMIC's ROP Safety Net is based on our claims experience. It is designed to address the causes of ROP lawsuits in order to protect the infant and the ophthalmologist. The ROP Safety Net Toolkit contains sample protocols, which may need to be customized, and refers to ROP clinical care guidelines. These protocols and guidelines are recommendations and do not constitute the standard of care. Ophthalmologists should use their professional judgment in determining the applicability of a given recommendation to their particular patients and practice situation.

The Toolkit does not provide legal advice. Consult an attorney if legal advice is desired or needed. 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.

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OMIC is committed to helping ophthalmologists provide safe care for infants at risk for retinopathy of prematurity (ROP). To that end, we have developed and published our ROP Safety Net, which includes an analysis of ROP malpractice claims, toolkits for both hospital- and office-based care, and sample consent forms for laser and anti-VEGF injection. To further reduce the risk and severity of ROP malpractice claims, OMIC conducts an underwriting review on a regular basis of all insured physicians who provide ROP care, and has mandated certain loss prevention actions that are summarized in "ROP conditions of coverage" (all documents available at http://www.omic.com/rop-safety-net/).

Treatment of ROP

Ophthalmologists have been treating ROP with laser surgery for many years. 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 lentis. 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 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**. The similarity between ROP and adult retinal conditions prompted clinical trials on the use of IVAV in neonatal populations. Published reports from both clinical trials and "off-label" use of

IVAV for ROP suggest that it can be effective and does not—so far—appear to produce many serious short or long-term side effects. **The efficacy, safety, and long-term consequences have not yet been proven.**

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. The 2018 ROP Screening Policy Statement (PS)[1] addresses these issues. The PS recommends that infants treated with IVAV be followed closely until at least 65 weeks postmenstrual age (PMA).

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 often required to settle ROP malpractice claims, physicians 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 provide risk management recommendations specific to the use of anti-VEGF agents "off-label" for the treatment of ROP.

"Off-label" use of medications

The Food and Drug Administration (FDA) approves and regulates the production, sale, and clinical research of medical drugs and devices. As a condition of approval, the manufacturer produces a "label" that summarizes the results of the research upon which the approval is based, as well as the indications, contraindications, known complications, and special warnings.

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.

The FDA has explicitly addressed "off-label" use in an Information Sheet.[2] 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 our claims history, 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.

Anti-VEGF Biosimilar Drugs

Biosimilar drugs are medications chemically changed to closely resemble an original drug. FDA-approved biosimilars are available for bevacizumab, ranibizumab, and aflibercept for a variety of diseases. Data on their use in ROP are very limited or absent with respect to plasma levels of drug at multiple time points, alteration of disease course, visual outcomes, and neurodevelopmental status. Until such data become available, biosimilar drugs should NOT be used to treat ROP.

Obtaining informed consent for IVAV for ROP

Intravitreal administration of anti-VEGF agents requires the informed consent of the infant's parents or legal guardians. Informed consent discussions are often difficult, but rarely more so than in situations like this. Ophthalmologists who screen infants for ROP may not meet the parents during the screening process, and may thus be talking to the parents 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 parents 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 parents to consent.

OMIC has resources to help prepare parents for this discussion. In response to allegations made by plaintiffs in ROP malpractice lawsuits that they did not know that the infant was at risk for ROP, OMIC requires that insured physicians provide parents with a brief explanation of ROP prior to discharge from the hospital and at the first outpatient visit (the letters are in both toolkits).

Our sample protocols also advise educational efforts by the neonatologist and neonatal nurses. 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 relay it to the parents. Consider asking the neonatologist to be present during the informed consent discussion.

OMIC has also developed a sample consent form in English (on website) and Spanish (in development) for IVAV for ROP, which is in the hospital toolkit, and at the end of this document. As always, our sample forms need to be reviewed and may need to be revised to meet current PS standards. The hospital may need to have the form approved by its Forms Committee.

While the consent of the parent or legal guardian is legally required to treat a child, lack of consent may constitute child neglect if the proposed care is needed to prevent significant harm to the minor.

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 the surgeon must discuss the refusal with other physicians and Child Protective Services.

Managing parents who insist on IVAV

While IVAV has an imprecise safety profile, it does not ablate the peripheral retina and may allow for better overall vision. Some parents prefer this treatment option. OMIC's Risk Management Department has fielded calls from ophthalmologists who are uncomfortable with demands made by parents to use IVAV when laser surgery is, in the physician's judgment, the best treatment. As in any case where the patient or legal guardian wants 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, and 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. Conduct and document the transfer of care, and send the parent a letter confirming the end of the physician-patient relationship. OMIC has sample termination of care letters at www.omic.com.

Follow up

Some studies and presentations have indicated that IVAV changes the natural history of ROP. Significantly, the disease may reoccur months later than expected. As a result, infants who receive IVAV need to be examined for longer periods. The need for longer and additional follow-up may increase the risk for noncompliance with some parents. Consider whether IVAV with laser or IVAV alone is the best choice in the setting of unreliable parents. Carefully monitor appointments and promptly involve Child Protective Services if needed. The office toolkit includes recommendations for tracking appointments, and sample letters to parents that warn of the possible need to contact the authorities.

OMIC policyholders have specific obligations if an infant is treated with IVAV:

- Follow infants closely until at least 65 weeks PMA.
- At 65 weeks PMA, may end screening if either of these endpoints has been reached:
    - Full vascularization in close proximity to the ora serrata for 360° **OR**
    - The avascular retina has been successfully treated with laser (e.g., no skip areas).
- Use professional judgment on continued monitoring in the following circumstances if no treatment endpoint has been reached at 65 weeks PMA:
    - Low-grade disease that is clearly and slowly improving
    - Stage 1 disease that is unchanged for 2 months
    - No disease, no ROP, but incomplete vascularization
    - Infant has a DNR order

Keep current and keep a file of resources

Screening and treatment of ROP is a rapidly evolving discipline. Keep current by reviewing pertinent journals and attending lectures. Keep a file containing such articles or notes from talks given at eye society meetings. 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 Linda Nakamura at lnakamura@omic.com, or at 800.562-6642, extension 652.

If you have any concerns about the underwriting requirements for ROP, please contact your Underwriting representative. For questions about any other aspect of ROP care, please contact our Risk Management Hotline by calling 800.562-6642, option 4, or via email at riskmanagement@omic.com; the assistance is confidential.

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[1] Fierson WM, American Academy of Pediatrics (AAP) Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening Examination of Premature Infants for Retinopathy of Prematurity. [Policy Statement.] *Pediatrics*. 2018;142(6):e20183061. Available at: http://pediatrics.aappublications.org/content/142/6/e20183061 (Accessed: 3/16/22).

[2]Food and Drug Administration. Regulatory Information: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet," available at https://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm. Accessed 8/17/18..