How Does the Standard of Care Evolve? Anti–Vascular Endothelial Growth Factor Agents in Retinopathy of Prematurity Treatment as an Example

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As an ophthalmologist whose career involves both clinical practice and research in retinopathy of prematurity (ROP), I am sometimes asked whether I believe practice and research in retinopathy of prematurity (ROP), I

As an academician, I am sometimes asked by residents, “Why do I need to perform and learn about research if I ‘only’ want to take care of patients during my career?” These questions have made me think about how and why the standard of care in clinical medicine evolves.

On the very first day of medical school, entering students are frequently told, “During your career, you’ll find that half of what you learn over the next 4 years will turn out to be obsolete or incorrect. Unfortunately, we don’t know which half it will be.” As an incoming medical student 25 years ago, I didn’t believe this could be correct. But in my career, I’ve seen that this in fact has been true: the standard of ophthalmic practice changes rapidly because of a sequence in which gaps in clinical care motivate basic, translational, and clinical research. This is followed by early adoption of new treatment methods and by subsequent policy making, all of which can affect mainstream clinical practice patterns gradually.

An example is intravitreal injections of anti-VEGF agents for neovascular retinal disease. As a resident, I learned about age-related macular degeneration (AMD) management using laser photocoagulation, based on findings from the Macular Photocoagulation Study trials. Since that time, anti-VEGF therapy has become the standard of care for neovascular AMD treatment. Now, only 15 years after finishing my residency training, I find some residents I teach are surprised that laser photocoagulation was once the first-line treatment for neovascular AMD. Meanwhile, the same trends may be occurring in ROP.

What are the gaps in ROP care? When I began practicing, laser photocoagulation was the standard of care for treatment-requiring ROP based on criteria and protocols developed in the multicenter Cryotherapy for ROP and Early Treatment for ROP trials. Laser treatment generally is effective and predictable for ROP, but it is time-consuming, is technically difficult to learn and perform appropriately, results in permanent ablation of the peripheral avascular retina, subjects fragile premature infants to the risks of sedation or general anesthesia, and requires significant infrastructure and scheduling. In my experience, laser treatment failures often are related to inadequate treatment (so-called skip areas) and are more common in zone I and aggressive posterior ROP, even with appropriate laser treatment. These gaps in care stimulated the earliest efforts to use intravitreal anti-VEGF agents for ROP treatment.

What was the basic science research? As a medical student, I learned about the pioneering research of Folkman regarding the proangiogenic and antiangiogenic factors in tumor pathogenesis. This took place over several decades and included in vitro laboratory studies and animal models of disease performed together by researchers in fields such as clinical medicine, biochemistry, cell and vascular biology, and bioengineering. Although this work initially was applied to oncology, it was hypothesized that the pathogenesis of other diseases was based on angiogenic factors. While in school, I read textbooks describing a theoretical factor X and still remember reading the original articles identifying VEGF as such a factor associated with iris neovascularization in primate disease models and with diabetic retinopathy in humans.

How did this lead to translational and clinical research in ophthalmology? Several years later, in 2006, intravitreal injection of ranibizumab (Lucentis; Genentech, South San Francisco, CA) was shown to improve mean visual acuity in eyes with minimally classic or occult neovascular AMD. Ranibizumab has been approved by the Food and Drug Administration for treatment of neovascular AMD, and the use of other intravitreal anti-VEGF agents such as bevacizumab (Avastin; Genentech) and aflibercept (EYLEA, Regeneron, Tarrytown, NY) has become widespread. Since that time, intravitreal injection has become among the most commonly performed procedures in the United States within any field of medicine. Because of the gaps in care described previously, because laser treatment often was impractical in the developing world, and because limited time often was available for ophthalmologists to devote to ROP care, anti-VEGF agents were applied for ROP treatment with excellent initial results.

What is the evidence base for anti-VEGF agents in ROP treatment? Overall, a 2016 American Academy of Ophthalmology technology assessment involving anti-VEGF agents as primary therapy for ROP found no level I evidence, 6 level II prospective randomized controlled trials, and 7 level III retrospective studies. For example, the multicenter prospective randomized Bevacizumab Eliminates the Angiogenic Threat of ROP trial found that treatment of severe ROP with intravitreal anti-VEGF injections is
associated with fewer treatment-requiring recurrences than laser.\textsuperscript{13} Because extensive ablation of peripheral avascular retina is not required, there are potential benefits with regard to visual field, particularly in infants with posterior disease. Several articles, including a follow-up study involving the Bevacizumab Eliminates the Angiogenic Threat of ROP cohort, have reported that infants treated with bevacizumab had significantly lower incidence of myopia than those receiving laser therapy.\textsuperscript{14–16}

What are the potential risks? The risks of physical intravitreal injection include bleeding, retinal detachment, infection, cataract, increased intraocular pressure, and loss of vision. Beyond that, ROP frequently recurs after intravitreal anti-VEGF injection, necessitating extensive follow-up examinations that often are logistically difficult for families and technically difficult for ophthalmologists.\textsuperscript{17,18} Aggressive recurrent disease has been reported to cause blindness and visual loss. Because of concerns such as possible late disease recurrence and the need for frequent follow-up examinations, managing ophthalmologists often perform laser photocoagulation for recurrent ROP that fails to regress or for persistent avascular retina.\textsuperscript{19} Although intravitreal anti-VEGF agents only rarely are associated with systemic side effects in adults, bevacizumab levels are detectable in serum for several months after injection, which raises concerns about long-term systemic effects in rapidly developing premature infants.\textsuperscript{20}

One nonrandomized retrospective study suggests that anti-VEGF agents are associated with higher incidence of neurodevelopmental disability compared with infants treated with laser, but other studies do not identify clear differences in neurodevelopmental outcomes between infants treated with laser photocoagulation versus those treated with anti-VEGF agents.\textsuperscript{21–23}

What key questions remain unanswered? Several anti-VEGF agents have been used for ROP, particularly bevacizumab and ranibizumab, and the optimal agent and dosage are not known.\textsuperscript{24} Although most work to date has involved bevacizumab, multicenter clinical trials involving ranibizumab are in progress. As described previously, the long-term systemic and ocular impact of anti-VEGF therapy is not known, nor is the optimal ophthalmic follow-up regimen and indications for treatment of recurrent ROP with laser photocoagulation.

What is the current standard of care for ROP treatment? Surveys of retinal specialists and pediatric ophthalmologists in the United States, Canada, and United Kingdom suggest that some ophthalmologists exclusively use laser photocoagulation or exclusively use anti-VEGF therapy as first-line ROP treatment, whereas most seem to use either method depending on the specific clinical scenario.\textsuperscript{25–28} Anti-VEGF agents are not currently approved by the Food and Drug Administration for treatment of ROP, and current consensus ROP screening guidelines published jointly in 2013 by the American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology & Strabismus, and American Association of Certified Orthoptists state that bevacizumab may be used for treatment of severe ROP after careful informed consent.\textsuperscript{29}

What are the general lessons from this story? Overall, anti-VEGF agents have revolutionized management of retinal neovascular diseases and have had a significant impact on treatment strategies for ROP. Larger randomized trials involving anti-VEGF agents are ongoing, and others may be warranted in the future. In answer to the first question about my personal first-line method for ROP therapy, I’d say I continue to use laser photocoagulation in most cases, but I use anti-VEGF agents when I am most concerned about poor outcomes from laser, generally in zone I or posterior zone II disease and in other aggressive disease. In my assessment, a number of babies whom I have managed using anti-VEGF agents likely would have lost vision if treated only with laser photocoagulation. And in answer to the second question about why residents should perform and understand research, I’d say it is because what they were taught on the first day of medical school was completely correct: advances in basic and clinical research lead to evolution in the standard of care, and ophthalmologists need to understand the process of knowledge discovery, study design, and data analysis to determine which of those advances to incorporate into their practices.

References


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