Extrapolating Adult Pharmacotherapy Data to Treat Retinal Diseases in Children

Drugs present possibilities and pitfalls for pediatric indications.

WITH PHILIP J. FERRONE, MD

Retina Today spoke to Philip J. Ferrone, MD, about pharmacotherapy for retinal diseases in the pediatric population—the drugs currently in use in children and the promises and pitfalls of extrapolating data from adult pharmacotherapy for use in the much smaller pediatric eye.

***Retina Today*:** What classes of drugs are currently being used to treat pediatric retinal diseases?

Dr. Ferrone: Pharmacotherapy for retinal diseases in children typically involves either of 2 classes of drugs that are commonly used in the adult population: corticosteroids and anti-VEGF agents.

Steroids can be used in pediatric patients as a periocular injection such as posterior sub-Tenon injection. The periocular route is useful in lower-than-adult doses for severe postoperative inflammation or to help control uveitis, specifically intermediate uveitis or severe posterior uveitis, as a temporary treatment until immunomodulatory therapy begins to have an effect, which usually takes about 6 weeks.

In adults, steroids can cause an intraocular pressure (IOP) elevation and cataract. If they are used in children, even at lower doses than in adults, this can also occur. Cataract formation does not seem to be as common, but they can develop, particularly when steroids are given repeatedly. Most importantly, however, the younger the child, the more likely they are to get an IOP rise from steroids.

Therefore, steroids are used in a limited fashion in children, whereas in adults they are used commonly for diabetic macular edema, postoperative macular edema, postoperative inflammation control, and also for intermediate uveitis or severe posterior uveitis.

Outside of the realm of injections, children may receive immunomodulatory therapies orally or intravenously for uveitis. As in an adult, treatment can progress from lesser powerful drugs to more potent drugs until the inflammation is controlled. If oral methotrexate does not control the disease, the next step might be mycophenolate mofetil (Cellcept, Genentech), and then possibly infliximab or another immunomodulatory drug. Most ophthalmologists consult with rheumatologists to manage these types of treatments.

The other class of drugs currently being used with some frequency in the pediatric population is anti-VEGF agents. They are used right now principally for treatment of retinopathy of prematurity (ROP). There is currently considerable debate about safety: Which of the available anti-VEGF drugs should be used, what is the threshold for using them, and what is the appropriate dose?

Bevacizumab (Avastin, Genentech) may be the agent most widely studied at present, but ranibizumab (Lucentis, Genentech) may be theoretically safer for the pediatric population because it clears from the serum more quickly.

***RT*:** Please discuss this safety issue further. Bevacizumab has been used in a number of published clinical studies, including BEAT-ROP.[1]

Dr. Ferrone: BEAT-ROP was a prospective randomized trial to assess bevacizumab monotherapy for zone 1 and zone 2 posterior stage 3 ROP with plus disease. The dose given was 0.625 mg in 0.025 mL solution—half the adult dose. Compared with conventional laser, bevacizumab monotherapy showed a benefit in zone 1 but not zone 2 disease.

There were a number of problems with the design of BEAT-ROP. I discussed these in a presentation at the Aspen Retinal Detachment Society meeting last year.[2]

First, the trial was not fully powered to detect issues regarding drug safety. The time to recurrence was significantly different between the 2 treatment groups. With the trial design used, some eyes in the bevacizumab group may have experienced recurrence after the primary endpoint exam. Specifically, 48% of potential recurrences in the bevacizumab group could have come after the primary endpoint; this was not the case for the laser group. The primary trial endpoint was changed midway through the trial. Injections were done relatively posterior: 2.5 mm posterior to the limbus. The mortality was higher in the bevacizumab group—4 deaths, vs 1 in the laser group. And the primary laser failure rate was very high: 42%, compared with 9% in ETROP.[3] If the laser failure rate were more like what was reported in ETROP, there would have been no statistical difference between the drug and laser in BEAT-ROP.

Also, as I said earlier, bevacizumab may be not be the optimal drug in this population. Sato and colleagues[4] showed that intravitreally administered bevacizumab escapes from the eye into the systemic circulation and reduces the serum level of VEGF in infants with ROP. In developing neonates, this is may not be optimal. A smaller anti-VEGF molecule, such as ranibizumab (molecular weight 50 kD, compared with 150 kD for bevacizumab), might be more appropriate for use in children. Reviewing published safety data for intravitreal anti-VEGF therapies, Tolentino[5] found that ranibizumab has a longer half-life in the vitreous, a shorter systemic half-life, and lower peak serum concentration.

Also, the dose of bevacizumab used in BEAT-ROP and other studies, half the adult dose, may be too high. There is a limit to how much volume an infant eye can accommodate. The full adult dose, with a volume of 0.5 mL, would send a premature infant's IOP very high. The half dose, in 0.25 mL volume, is better, but is probably still a bit high for a neonate. Considering the ratios of eye volume, body weight, body mass, and body surface area to the drug, it is a high dose. And the blood-ocular barrier in ROP neonates is not as good as in an adult, allowing entry of drug into the bloodstream.

The current thinking is that with a smaller drug (anti-body fragment, without the Fc portion), such as ranibizumab at less than half the adult dose, the safety profile should be better. That should still be enough drug to treat the disease. Recurrence of ROP can occur after anti-VEGF treatment,[6] but at least the patients' blood vessels grow out further in their eyes, and the retinal vessels develop more normally.

> "In general, whether periocular steroids, or intraocular anti-VEGF agents, half the adult dose can sometimes be too much, especially in smaller children."

***RT*:** What are other indications for anti-VEGF use in pediatric patients?

Dr. Ferrone: There are a number of unusual indications for which anti-VEGF therapy is useful in children, such as an idiopathic subretinal neovascular membrane. These are rarely seen, but they can occur. I have given anti-VEGF injections for those membranes, and they work very well. Similarly, if choroidal neovascularization develops off the nerve, due to an optic nerve abnormality such as an optic nerve head pit or coloboma, an injection of anti-VEGF can help those patients.

Use of anti-VEGF agents in Coats disease is controversial. I do not think it is of particular help. In familial exudative vitreoretinopathy (FEVR), a particularly exudative type of FEVR, anti-VEGF therapy probably helps, but one has to be careful, because the patients can develop organization of the vitreous around those abnormal blood vessels. It does not happen commonly, but it can, just as it can in adult diabetics. I have never seen anti-VEGF agents used in incontinentia pigmenti, but they could be, in addition to laser. For sickle-cell disease, laser is still the treatment of choice.

There are a number of very unusual conditions for which anti-VEGF drugs can be used in children, and it can be a great choice that can really benefit the patients, especially with a lower drug dose, even less than half the adult dose, and in my opinion, ideally ranibizumab.

***RT*:** Can any general statements be made about the use of pharmacotherapy in the pediatric population?

Dr. Ferrone: In general, whether periocular steroids, or intraocular anti-VEGF agents, half the adult dose can

sometimes be too much, especially in smaller children. You could make the same statement for antibiotics, if a child developed an intraocular infection. An infant's eye is probably 60% of the size of an adult eye. A smaller dose is needed because of the differences between the adult and child—differences in eye size, and the risk of IOP rise in an eye with 40% less volume than an adult eye.

Currently, the main indication for anti-VEGF therapy in children is ROP. Many in the pediatric retina community have mixed feelings about the reflexive use of anti-VEGF therapy in ROP as opposed to laser. Some people are looking for a therapy that is 1 and done, but anti-VEGF is not necessarily 1 and done. In very posterior disease, ROP can recur 3 or 4 months later, and severe retinal detachments can result. As mentioned above the drug has been seen in the serum, with a reduction of serum VEGF levels, after injection of intraocular anti-VEGF.

Now, can an anti-VEGF drug, specifically very low-dose ranibizumab, help these kids with very severe disease? I'd say yes, absolutely, I think it does. Is there probably some systemic risk that has not been fully characterized? Yes, probably. But looking at the benefits and risks, if you use a drug like ranibizumab at a very low dose in very severe ROP, do the benefits outweigh the risks? Yes, I think they do. But you have to follow these patients, and apply laser if they need it subsequently.

I have seen eyes of micro-preemies that were injected with bevacizumab at the lower dose (0.5 mg), and they looked great. At 8 months or 1 year later, their blood vessels developed in a near-normal way. So, in my opinion, there is promise with these drugs, but we must be careful with their use and follow these children closely. ■

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