An Evidence-Based Review of Vascular Endothelial Growth Factor Inhibition in Pediatric Retinal Diseases: Part 2. Coats’ Disease, Best Disease, and Uveitis With Childhood Neovascularization

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ABSTRACT
Vascular endothelial growth factor (VEGF) is an important factor in the pathogenesis of multiple retinal neovascular disorders. This report focuses on the quality and depth of new evidence for the use of VEGF inhibitors in selected pediatric ocular diseases, including Coats’ disease, Best disease, and childhood uveitis. Because much of the literature comprises case reports and retrospective case series, the level of evidence supporting its use as a primary treatment option, or even as adjuvant therapy, is low. The standard of care is treatment of the underlying disorder to prevent neovascularization (retinal or subretinal), vitreous hemorrhage, or subsequent retinal detachment. However, these complications may not present until late in the disease course. It may then be useful to treat with these agents. Prospective studies are warranted to further elucidate the role of anti-VEGF therapy in these diseases. [J Pediatr Ophthalmol Strabismus 2013;50:11-19.]

INTRODUCTION
During embryonic development, the growth of retinal blood vessels is a well-regulated and sensitive process. As the primary vitreous regresses, the retinal vessels, which originate from the central retinal artery, begin to develop. Vascularization of the temporal retina is usually complete at 36 weeks of gestation and the temporal retina at 40 weeks.1

Angiogenesis occurs as a tightly modulated process during fetal ocular development, allowing for the orderly growth of normal retinal blood vessels. Levels of vascular endothelial growth factor (VEGF) are regulated by sophisticated intermolecular interactions (Wnt-Flt1 pathway). This regulation is critical to the suppression of aberrant branching while still allowing for normal retinal vascular development.2 VEGF has also been found to be an important mediator of ocular neovascularization and a powerful agent of vascular permeability.3-6 Areas of retinal non-perfusion (seen in Coats’ disease and diabetic and sickle cell retinopathies) are associated with increased VEGF levels, which may then lead to neovascularization.7-10 Vascular endothelial growth factor is also involved in the inflammatory process as it has been linked to cytokines associated with the inflammatory cascade.11-13 Thus, VEGF plays an important role in the complications associated with persistent uveitis.

PHARMACOLOGY AND USE OF ANTI-VEGF AGENTS
The use of anti-vascular endothelial growth factor (anti-VEGF) pharmaceutical agents has revolu-
tionized the field of ophthalmology. Three agents that are currently in clinical use are bevacizumab (Avastin; Genentech Inc., South San Francisco, CA), pegaptanib (Macugen; OSI/Eyetech, New York, NY), and ranibizumab (Lucentis; Genentech Inc.).

These agents have become first-line treatments for neovascular age-related macular degeneration and have shown efficacy in the treatment of other retinal vascular diseases, including proliferative diabetic retinopathy, diabetic clinically significant macular edema, central and branch retinal vein occlusion, neovascular glaucoma, and retinopathy of prematurity.3,9,10,14-18 Ranibizumab, a monoclonal antibody that targets VEGF, was approved by the U.S. Food and Drug Administration for the treatment of age-related macular degeneration after several randomized controlled clinical trials reported it could prevent visual loss and may improve visual acuity.14-16,19,20 Bevacizumab, also a monoclonal antibody targeting VEGF, differs from ranibizumab by having two antigen-binding domains instead of one, and has also been used extensively to treat neovascular vessels in the eye.9,10 The Comparison of Age-related Macular Degeneration Treatments Trials study has shown bevacizumab's efficacy in the treatment of choroidal neovascularization associated with age-related macular degeneration to be equal to that of ranibizumab.1 Other studies that advocate the use of anti-VEGF agents in wet age-related macular degeneration include the ANCHOR and MARINA studies, which compare the use of these agents versus photodynamic therapy and sham treatments, respectively.21,22

However, there are other potentially important differences between the two agents. Avery reported that the pharmacokinetics differ significantly between the two.23 The serum elimination half life has been reported to be approximately 20 days for bevacizumab and approximately 2 hours for ranibizumab. Bevacizumab is a full-length antibody, with its Fc domain binding specifically to the Fc portion on endothelial cells, which may result in the increased systemic clearance time seen. Ranibizumab is a smaller molecule, allowing for its relatively rapid clearance. Several articles have reported a reduction in systemic VEGF levels in adults from 1 week to 2 months following intravitreal anti-VEGF injections.23-27 No decrease in systemic VEGF was found in patients treated with ranibizumab compared to bevacizumab where a decrease in systemic VEGF is reported (190 to 110 pg/mL). Although these data specifically concern adults, it may be possible to extrapolate this concept to children. There have been a few reports of decreases in systemic VEGF levels in children with ROP after intravitreal injection of bevacizumab. Sato et al. reported a significant decrease of systemic VEGF from 1,628 to 269 pg/mL up to 2 weeks following intravitreal injection.28 They also noted an increase in serum bevacizumab levels over the same time. Lee et al. report a continued weekly decrease to 50 pg/mL at 7 weeks.29

Pegaptanib is an RNA oligonucleotide ligand that binds human VEGF165 with high specificity and affinity. It binds near the heparin-binding domain of VEGF, preventing VEGF165 and larger isoforms from attaching to their respective receptors.17 Pegaptanib has been used in the treatment of choroidal neovascularization associated with age-related macular degeneration and polypoidal choroidal vasculopathy with studies documenting its safety and efficacy.30 However, pegaptanib has been reported to be inferior to other anti-VEGF medications currently available. Pegaptanib has a slower mode of action when compared to other unselective anti-VEGF agents. At least three intravitreal injections may be required to be efficacious.31 It may be possible that its specificity for VEGF165 is the source of its moderate effectiveness.32

Because the above-mentioned studies were conducted in the adult population, much of these data have been extrapolated as to its use in childhood retinal diseases. The current article will review the literature, specifically focusing on the use of bevacizumab, ranibizumab, and pegaptanib in the treatment of the following retinal diseases in the pediatric population: Coats’ disease, Best disease, and childhood uveitis.

GRADE SYSTEM

The three main scientific databases of Ovid, PubMed, and Cochrane were searched for articles published between January 1, 2009, and October 1, 2011, using the following terms: Coats’ disease, Best disease, childhood neovascularization, childhood uveitis, bevacizumab, Avastin, ranibizumab, Lucentis, anti-VEGF, angiogenesis inhibitors, pediatric neovascularization, pediatric uveitis, Macugen, and pegaptanib. Each term was used first as medical subject heading, and then as title/abstract keyword.
The relevant searches were then corroborated using the AND/OR option to obtain the final list. Search results were reviewed independently by two reviewers (KMC and RML) and were further examined and included in the study if they investigated the use of bevacizumab or ranibizumab for Coats’ disease, Best disease, and childhood neovascularization due to uveitis in a case report, case series, or randomized control trials. A search was also conducted for sickle retinopathy, but all reports included only adults, with the youngest patient being 18 years old. All molecular studies, animal studies, conference proceedings not published in peer-reviewed journals, and foreign language articles were excluded from this review.

The evidence from the studies reviewed was rated using the GRADE method, developed by the Grades of Recommendation, Assessment, Development, and Evaluation Working Group and adopted by the Cochrane Collaboration for reviews (Table 1). This method uses several factors including methodology, dose-response gradient, likelihood of bias, and limitations, imprecision, and consistency of design for evaluation and subsequent rating. This allows an objective measure of the quality of the scientific evidence offered by the respective study, with the goal of aiding the readers in their evidence-based clinical decision-making process.

**SELECTED PEDIATRIC RETINAL DISEASES**

**Coats’ Disease**

*Pathogenesis.* Coats’ disease (Fig. 1A) is an uncommon ophthalmic disease in which retinal telangiectatic vessels cause intraretinal and subretinal exudation without concurrent vitreoretinal traction. This disease primarily affects males within the first decade of life and is usually unilateral. Patients may present with leukocoria, strabismus, or decrease in vision. Peripheral areas of nonperfusion may develop (Fig. 1B), resulting in upregulation in VEGF. Untreated, this may lead to increasing vascular incompetence, fluid exudation,
and eventual retinal detachment, neovascular glaucoma, phthisis, and enucleation.34-37 The Shields’ staging system is the standard modality used for describing the severity of Coats’ disease in affected patients (Table 2).

Investigators have demonstrated an increased level of VEGF in eyes with Coats’ disease and a significant decrease in VEGF after injection of intravitreal VEGF inhibitors.7,8 He et al.8 reported a series in which four patients were diagnosed as having stage 2 or 3 Coats’ disease and five eyes had rhegmatogenous retinal detachments. The mean VEGF level in these patients with Coats’ disease was 2,394.5 pg/mL compared to 15.3 pg/mL in the control group. This led the authors to postulate that VEGF may play a major role in the pathogenesis of Coats’ disease. They proposed that the ischemic drive in Coats’ disease leads to high VEGF levels and hypoxia-inducible factor-1 alpha, which may also play a role in disease progression. They stated VEGF may also contribute to the increased permeability of the telangiectatic blood vessels leading to lipoprotein leakage into the retina and subretinal space and subsequent edema or exudative retinal detachment.7,40

**Literature Review.** Currently, there are a total of 12 reports in the literature concerning the treatment of Coats’ disease with anti-VEGF agents. Of these, nine are case series or reports involving four or fewer patients (five report a single patient). One report consists of a limited prospective case series involving post-treatment questionnaires. Another study retrospectively examined 35 pediatric eyes that underwent from one to several intravitreal anti-VEGF injections. The final report is a retrospective case series of eight patients with Coats’ disease treated with laser photocoagulation and/or cryotherapy plus additional bevacizumab.

Ramasubramanian and Shields described eight patients with Coats’ disease (stage 2 to 3b) who were treated with cryotherapy (n = 8), laser photocoagulation (n = 4), and bevacizumab (n = 8). Six patients received cryotherapy and bevacizumab in the same setting. After a mean follow-up of 8.5 months, all eight patients had resolution of retinopathy, with eight patients demonstrating resolution of subretinal fluid and six showing resolution of exudates. However, atypical vitreous fibrosis was seen in four patients. This led to subsequent tractional retinal detachment and was attributed to the use of intravitreal bevacizumab. Simultaneous use of cryotherapy with injection did not correlate with vitreoretinal fibrosis. The study concluded caution is advised in the use of bevacizumab for patients with Coats’ disease.41

The case reports had an age range of 2 to 17 years, with a 4:1 male-to-female ratio. Three of these used a single intravitreal injection of VEGF inhibitor (bevacizumab or pegaptanib), with follow-up ranging from 6 to 12 months. Although some cases reported significant improvement in best-corrected visual acuity, most patients maintained their original acuity with or without mild improvement of exudates.3,8,40,42-48 The retrospective case series by Sisk et al. included 6 eyes, with some receiving a single injection and others receiving multiple injections (two to five) of both bevacizumab and triamcinolone.49 Follow-up ranged from 1 to 6 months, with a mean change in central macular thickness from 415.6 to 369.6 microns.

A population-based study from physicians in the United Kingdom was conducted by comparing different treatment regimens and outcomes.34 Using the Shields’ staging system of Coats’ disease, Mulvihill et al. used a baseline questionnaire and a 6-month follow-up questionnaire to determine the outcomes of patients with Coats’ disease after certain treatment regimens.34 The study reported treatment in 52 eyes with follow-up in 42 patients. The mainstay of treatment was laser (argon laser being the most common) with multiple adjunctive therapies including diode laser, Fd:YAG laser, cryotherapy, and an anti-VEGF (intravitreal bevacizumab) agent. The patients who

### TABLE 2

**Coats’ Disease Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Retinal telangiectasias</td>
</tr>
<tr>
<td>2</td>
<td>Telangiectasias and exudation</td>
</tr>
<tr>
<td>2A</td>
<td>Extrafoveal exudation</td>
</tr>
<tr>
<td>2B</td>
<td>Foveal exudation</td>
</tr>
<tr>
<td>3</td>
<td>Exudative retinal detachment</td>
</tr>
<tr>
<td>3A</td>
<td>Subtotal retinal detachment</td>
</tr>
<tr>
<td>3A.1</td>
<td>Extrafoveal retinal detachment</td>
</tr>
<tr>
<td>3A.2</td>
<td>Foveal retinal detachment</td>
</tr>
<tr>
<td>3B</td>
<td>Total retinal detachment</td>
</tr>
<tr>
<td>4</td>
<td>Total retinal detachment and glaucoma</td>
</tr>
<tr>
<td>5</td>
<td>Advanced end stage disease</td>
</tr>
</tbody>
</table>

Data from Sola-Villa D et al.11
received anti-VEGF agents had more advanced disease and intravitreal injections were used only as adjunctive treatment in combination with laser.

**Grade Criteria Quality Report and Analysis.** Using the GRADE 33 system outlined earlier, these reports all have a quality rating of low because most are case series or reports with a few retrospective studies. Given the multiple confounding factors in the included studies (VEGF agents being used as adjunct vs primary therapy, single vs multiple injections, and differing time points in the disease process for its administration), there is no strong evidence that supports the primary use of VEGF inhibitors in Coats’ disease at this time.

These few limited case series and reports appear to advocate the use of VEGF inhibitors in the treatment of Coats’ disease, although laser photocoagulation and cryotherapy remain the gold standard of treatment. However, it is noteworthy that in patients receiving laser as their primary treatment for Coats’ disease, 93% of patients had no active exudation.41 In patients who have developed exudative detachments, laser and cryotherapy are not always successful34 and we may need to look for more aggressive options in these patients. Other treatment modalities include drainage of subretinal fluid, which then facilitates the use of laser photocoagulation and cryotherapy. If successful, this would obviate the need for intravitreal anti-VEGF agents.32,50 However, drainage of subretinal fluid is not without risks, including choroidal detachment or hemorrhage, retinal detachment, vitreous hemorrhage, and the risk of anesthesia.51 The risks of intravitreal injection of anti-VEGF agents are also real, including infection, inflammation, cataract, and possible systemic absorption. Although there is no clear-cut evidence in the literature to support anti-VEGF use as a primary modality in Coats’ disease at this time, it may still be useful as an adjuvant therapy in advanced cases.

**Best Disease**

**Pathogenesis.** Best disease, also known as Best vitelliform dystrophy, is an autosomal dominant macular disease caused by mutations in the *VMD2* gene on chromosome 11, which encodes the bestrophin protein. The protein functions as a transmembrane chloride channel on the basolateral plasma membrane of the retinal pigment epithelium. A defect in this protein leads to the accumulation of lipofuscin secondary to abnormal ion exchange. Although results of electroretinography are normal, those of electro-oculography are always abnormal in Best disease and serve as a specific marker in symptomatic patients with normal fundi. Early in the disease process, a yellow, yolk-like (vitelliform) lesion in the macula may be seen in children. Patients usually have only moderate vision loss at this time. The lesion eventually breaks down, leaving an atrophic appearance, and visual acuity may deteriorate to 20/200. Although it has been reported that up to 20% of patients may develop a choroidal neovascular membrane in one eye,52-54 the development of choroidal neovascularization in children with Best disease is considered rare.55

**Literature Review.** A few select case reports have been published discussing positive results using intravitreal anti-VEGF agents in the treatment of choroidal neovascularization secondary to Best disease in children. We found five reports, four of which are case reports and one a retrospective case series. The case reports had an age range of 5 to 13 years, with a 3:1 male-to-female ratio. Three of the case reports used a single intravitreal injection, with follow-up ranging from 1 to 6 months.55-57 In the fourth report, the patient received a series of bilateral injections of bevacizumab and maintained a visual acuity of 20/25 over a 27-month time frame.58 All of these cases reported a favorable result with either maintenance or improvement of vision. The retrospective case series by Sisk et al. included 4 patients, some receiving a single injection and another receiving multiple injections of both bevacizumab and triamcinolone.49 Follow-up ranged from 3 to 6 months, with a mean change in central macular thickness from 274.5 to 232 microns. Laser therapy was not used in any of the mentioned reports.

**Grade Criteria Quality Report and Analysis.** Using the objective criteria suggested by the GRADE system, the quality of these reports would be rated low because most are single interventional case reports, there is poor follow-up, and there is no standardization of visual acuity (using Early Treatment of Diabetic Retinopathy Study criteria) or comparison with other treatments. Because these were all case reports, a statistical analysis was not done. Therefore, there is no strong evidence supporting the use of anti-VEGF agents in children with choroidal neovascularization associated with Best disease at this time. However, because these agents are effective against choroidal
neovascularization in adults, their success in children is not inconceivable and a randomized, prospective study would be useful.

**Pediatric Uveitis**

**Pathogenesis.** VEGF is integral to the inflammatory process because it is linked to cytokines involved in the inflammatory cascade, such as nuclear factor-kB. This factor induces the expression of VEGF. Other cytokines include interleukin-1β, tumor necrosis factor-alpha, interleukin-6, interleukin-8, and tumor growth factor-β2, which can also upregulate VEGF production.\(^\text{11-13,20,59,60}\) However, there is no definitive evidence to suggest that anti-VEGF agents would be an appropriate treatment for ocular inflammation.

Uveitis is an umbrella term referring to intraocular inflammation of both infectious and noninfectious etiologies. Children account for 2.2% to 13.8% of patients in uveitis clinics, and most published series of pediatric uveitis are limited to a small number of patients. One of the more common etiologies of childhood uveitis is juvenile rheumatoid arthritis, accounting for 21% in all cases of childhood uveitis. Other causes include idiopathic, pars planitis, toxoplasmal, and other infectious etiologies.\(^\text{61}\) Most children are diagnosed between the ages of 6 and 10 years.\(^\text{61-64}\) The treatment of choice is local or systemic corticosteroids, immunosuppressive agents, or the appropriate anti-infective agent. Long-term inflammation may lead to complications such as cystoid macular edema in up to 24% of patients.\(^\text{61}\) Anti-VEGF therapy has been considered when uveitic complications such as cystoid macular edema, choroidal neovascularization, or retinal neovascularization occur.\(^\text{20}\)

**Literature Review.** Studies have been done to interpret the efficacy of VEGF inhibitors in uveitis, but their use has not been specifically studied in children. However, there is literature describing its use with children who are included as single cases within larger cohorts.

A total of 5 studies, all of which were case reports, were found that included intervention with anti-VEGF agents in children with uveitis complicated by choroidal neovascularization, retinal neovascularization, or cystoid macular edema. A total of 11 children with an age range of 9 to 17 years were included, with a male-to-female ratio of near 1:1. Six children received one injection and five children received between two and five injections with a follow-up of 6 to 14 months.\(^\text{65-69}\) All of these case reports showed favorable results with either maintenance or improvement of vision. Uveitic pathologies included Behçet disease, multifocal posterior placoid pigment epitheliopathy, multifocal choroiditis with panuveitis, and idiopathic uveitis. The complications treated include choroidal neovascularization, cystoid macular edema, and retinal neovascularization. Other pathologies reported include choroidal neovascularization secondary to choroidal rupture, toxoplasmosis, and combined hamartomas.\(^\text{61}\) No significant complications were reported in any of the studies. Anti-VEGF treatments may play a role in the management of uveitic cystoid macular edema, choroidal neovascularization, and retinal neovascularization in cases with inactive uveitis.\(^\text{70}\)

Although intravitreal anti-VEGF therapy may serve as a useful adjunctive treatment, attention should not be drawn away from treating the underlying inflammatory disease. Given the mechanism of complications from uveitis, these data may be extrapolated to pediatric patients secondary to their underlying disease.\(^\text{61}\)

**Grade Criteria Quality Report and Analysis.**

Using the objective criteria suggested by the GRADE system, the quality of these reports would be rated as low because all are case reports, included primarily adults, had poor follow-up for children, included a range of uveitic etiologies, and were confounded by extensive medical histories in the adults. If appropriate treatment of the underlying disease according to published guidelines is followed, the risk of developing choroidal neovascularization, cystoid macular edema, or retinal neovascularization is reduced. However, if these complications do occur, treatment with an anti-VEGF agent may be warranted.\(^\text{71}\)

**CONCLUSION**

The use of anti-VEGF agents has revolutionized the treatment of several adult retinal diseases and now is also beginning to be used in the pediatric population. These agents have been used to treat the complications associated with retinopathy of prematurity. Coats’ disease, Best disease, and childhood uveitis as both primary and adjuvant therapies. Although the quality of evidence is poor for the currently published reports, there have been some positive results and they should be further evaluated. As in adults, these pharmacologic agents may
represent the next best intervention for pediatric retinal disease involving neovascular and exudative elements. Current studies are underway to determine what factors in addition to VEGF influence retinal neovascularization. Other treatment modalities such as photodynamic therapy have been studied for the treatment of neovascularization in the pediatric population. However, given the recent surge in anti-VEGF agents and positive outcomes, this drug class has become the main focus of many studies. A better understanding of the systemic and ocular effects of anti-VEGF agents would be needed to adequately compare this class with other interventions.

Risks

Although the pharmacokinetics of anti-VEGF agents have been studied in the adult population, not as much is known in the pediatric population. These medications can inhibit normal retinal vasculogenesis, revascularization, and organogenesis. These are important considerations when treating children. We must consider both the local and systemic risks and benefits of any treatment prior to its use.

It has been reported in recent literature that intravitreal anti-VEGF agents may cause adverse systemic effects. VEGF has been implicated in alveolar development and lung maturation. Studies report that systemic VEGF levels can be suppressed for weeks (possibly months) following intraocular injection. It may be difficult to tease out the true effect of these agents on pulmonary development because it is probably multifactorial, but it certainly needs to be considered.

In addition, there are other potential systemic complications that have been noted in adults. These include hypertension, myocardial infarction, stroke, venous thrombotic event, transient ischemic attack, and death from any cause. These data were collected from adult patients, and it may not be correct to extrapolate to the pediatric population. However, it is prudent to consider it in context. It remains to be seen whether pediatric patients are at increased risk from the antivasculogenic potential of these medications.

Local complications of intravitreal injection include subconjunctival hemorrhage, corneal abrasion, chemosis, increased intraocular pressure, cataract, intraocular inflammation, endophthalmitis, increased traction on neovascular vessels with subsequent retinal detachment, vitreous hemorrhage, and retinal pigment epithelial tear. These risks exist in both the adult and pediatric populations. However, the risk of direct trauma to the eye is potentially increased in the pediatric population, in which there may be less control of patient movement, relative to that in an adult. If anesthesia is given, all of the attendant risks of its administration must also be considered. In addition, there is the rarely discussed but extremely important issue of psychological trauma in a pediatric patient. Many of the patients in the above-referenced case reports and studies were certainly old enough, not only to be cognizant of the procedure, but also to remember it.

Limitations

Although this new treatment modality is promising, its evaluation is limited by the nature of the reports. Whether these agents should be considered for primary or adjuvant uses are two different questions, the evidence of which must be evaluated separately. Many of these reports and series dealt with use of these agents as adjuvant therapy. The question as to whether this led to an improvement in visual acuity, quality of life, or its potentiating the robustness of the standard of care also has not been answered. However, these questions do deserve consideration and are promising avenues of investigation. With this in mind, decisions as to the inclusion of anti-VEGF therapies in the treatment and care of a specific patient cannot be made based on any clear-cut evidence, but instead must be made on an individual basis. However, more extensive and controlled studies would certainly contribute to our understanding of how we can optimally use these agents in pediatric retinal disease.

REFERENCES


