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Association of Systemic or Intravitreal Antivascular Endothelial Growth Factor (Anti-VEGF) and Impaired Wound Healing in Pediatric Patients

Collagen to the Rescue

Vita Boyar

ABSTRACT

BACKGROUND: Bevacizumab is a humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that has been used as a systemic chemotherapy treatment of various malignancies in adults since 2000. It has been used for pediatric patients over the last decade. In addition, bevacizumab is used for neonatal intravitreal administration for retinopathy of prematurity, a major complication of preterm birth, characterized by incomplete and abnormal vascularization of the retina that can lead to retinal detachment and blindness without treatment.

CASES: The objective of this multiple case series is to report impaired wound healing seen in 3 adolescents and 1 premature neonate receiving bevacizumab and to propose collagen-based dermal template as a choice for the management of such wounds. The 3 adolescents were undergoing treatment of malignancies and developed wound healing complication within weeks of receiving anti-VEGF. The premature neonate experienced an extravasation and had a slow wound healing trajectory after receiving intravitreal administration of bevacizumab for retinopathy of prematurity. All wounds achieved closure following topical treatment with a collagen dermal template.

CONCLUSION: Use of bevacizumab is increasing in the pediatric population. Clinicians should be aware of compromised wound healing and higher likelihood of wound dehiscence after bevacizumab administration. We recommend waiting for at least 4 to 6 weeks between anti-VEGF administration (either systemic or vitreous) and elective surgical procedures, consistent with adult literature recommendations. If patient has an existing wound, we assert that bevacizumab should not be administered until that wound is healed. If wound healing is stalled, we recommend dermal template as a safe and effective accelerator of wound healing.

KEYWORDS: Antivascular endothelial growth factor (anti-VEGF), Collagen dermal template, Impaired wound healing, Pediatrics.

INTRODUCTION

Bevacizumab (Avastin, Genentech, San Francisco, California) is a humanized monoclonal antibody to vascular endothelial growth factor (VEGF), a systemic chemotherapy agent indicated for use in metastatic colon cancer, breast cancer, and glioblastoma multiforme. In addition, it is used for non–small cell lung cancer, and it is being investigated for possible use in endometrial, cervical, ovarian, gastric, and renal cell cancers.[1]

Vascular endothelial growth factor is a family of glycoproteins that stimulates angiogenesis; anti-VEGF agents work by inhibiting new vessel growth, leading to regression of angioneogenesis within a malignancy and tumor growth suppression.[2] It was expanded to intravitreal administration in adults for macular degeneration and diabetic retinopathy and in 2005 to neonates for retinopathy of prematurity (ROP).[3-5] Retinopathy of prematurity is a major complication of preterm birth and oxygen administration for underdeveloped lungs with the secondary changes in preterm retina. It is characterized by incomplete and abnormal vascularization of the retina that can lead to retinal detachment and blindness without treatment.[3] Prevention is the mainstay of ROP management. Treatments have evolved from cryotherapy to diode laser photocoagulation to anti-VEGF injections (bevacizumab) to vitreoretinal surgery. Anti-VEGF is used to halt the progression of abnormal retinal vascularization, based on the findings from BEAT-ROP trial (Bevacizumab Eliminates the Threat of Retinopathy of Prematurity).[3] Multiple systemic effects of bevacizumab, including arterial thrombosis, bowel perforation, hypertension, and delay in wound healing or surgical wound dehiscence, have been reported in studies conducted in adult patients.[1,6,7] Studies in pediatric patients are scarce; nevertheless, bevacizumab use is becoming more widespread in the neonatal population suffering from ROP and in adolescents with metastatic or terminal cancers.

Wounds heal in an organized way and follow 4 stages: hemostasis, inflammation, proliferation, and maturation. During hemostasis, platelets aggregate and degranulate, leading to fibrin plug formation to contain blood loss.[8] Hypoxia and vascular constriction induce vasoactive mediators, such

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as platelets, which release growth factors and cytokine that support wound healing evolution to the next stage, inflammation. Neutrophils and lymphocytes induce chemotaxis and recruit more cells, including monocytes that transform into macrophages, paramount in wound debridement and damaged cells apoptosis. During proliferation, multiple cytokines and chemokines induce vascular growth factors and fibroblast growth factors to initiate angiogenesis, fibroplasia, extracellular matrix (ECM) deposition, and wound contraction. Eventually, remodeling ensures, with ECM degradation, capillary regression, scar revision, and increased tensile strength.

Bevacizumab selectively binds VEGF-A receptor and inhibits its signaling pathways in endothelial cells, inducing endothelial cell apoptosis and blocking angiogenesis.[9] Its half-life is approximately 20 hours. Activated platelets during hemostasis release VEGF, which helps recruit macrophages, fibroblasts, and endothelial cells; monocytes also release VEGF, which stimulates other monocytes to remodel clots. Vascular endothelial growth factor increases microvascular permeability, allowing neutrophils to clear bacteria and macrophages to phagocytose wound debris. Vascular endothelial growth factor is also released by fibroblasts that deposit types I and III collagen to form new ECM. Findings from studies in adults demonstrated that anti-VEGF disrupts wound healing by disrupting vasodilation, vascular permeability, and angiogenesis.[10] This multiple case series reports impaired wound healing in children receiving bevacizumab; we also describe our experience using a collagen-based dermal template to manage these wounds.

CASES

All wounds were assessed based on initial consultation. Systemic conditions and comorbidities were managed by the medical team as deemed appropriate. Management for each of the 4 cases described in this article was individualized as indicated.

Case 1

A was a 15-year-old adolescent boy with a history of colon cancer who had undergone partial tumor resection and had been receiving multiple cycles of chemotherapy that involved bevacizumab as part of his protocol. His most recent complications involved an infected mediport that required removal. His latest dose of anti-VEGF was administered 3 weeks ago. I met A 7 days post mediport removal, at which point he had a stagnant, open, nongranulating wound. The wound was gently debrided with microfiber debrider pad (Debrisoft, Lohmann & Rauscher, Rengsdorf, Germany). A dermal template collagen dressing (Endoform, Aroa Biosurgery Limited, Auckland, New Zealand) was packed into the wound, covered by portable single-use negative pressure wound therapy—sNPWT (PICO, Smith & Nephew, London, United Kingdom). His wound was evaluated after 5 days; at this point in his care, he was finishing systemic antibiotics and remained in hospital. The collagen dressing was completely incorporated into the wound bed, new growth was visible, but slough was also appreciated (Figure 1). His wound was debrided in the same manner, packed with new collagen template, and covered with sNPWT (Figure 2). A was sent home with an outpatient follow-up and he returned to clinic 6 days later. Assessment revealed a clean wound bed that was granulating and slowly contracting in size (Figure 3). The same dressing protocol was applied. When Patient A returned 6 days later with the wound completely filled in and 90% smaller in size (Figure 4). He was transitioned into topical medical honey (Medihoney gel, Derma Sciences, Inc, Auckland, New Zealand) and atraumatic silicon dressing (designed to adhere to dry skin but not to a moist wound bed).

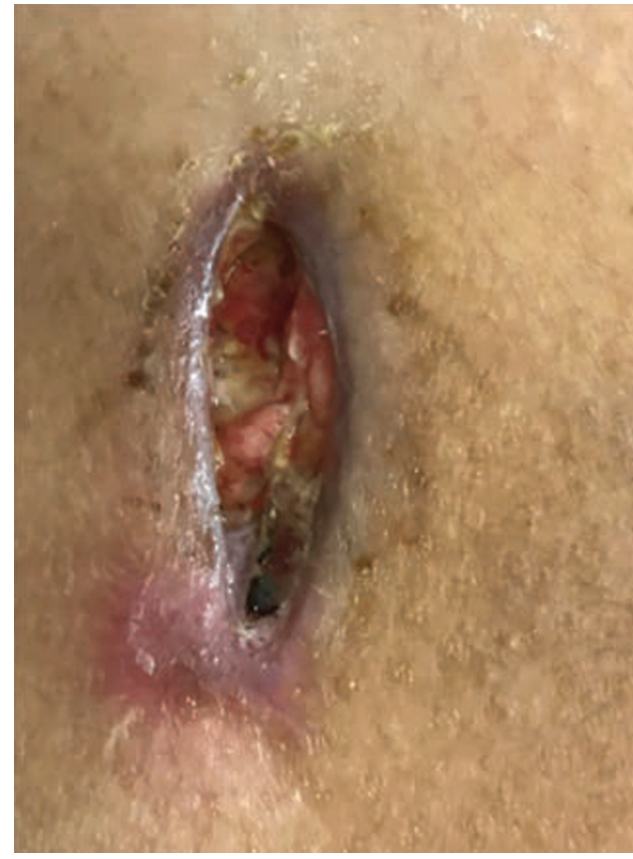

Figure 1. Case 1: Appearance of wound after 5 days of collagen dressing. New growth and slough are visible.

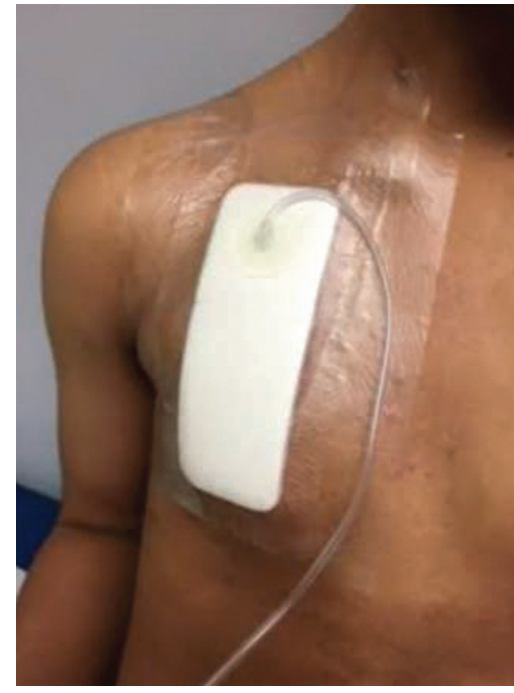

Figure 2. Case 1: Single-use negative pressure wound healing is used as an outer dressing.

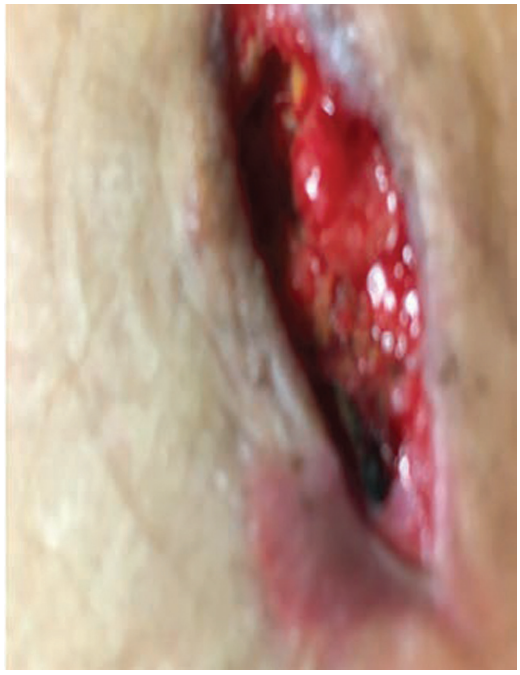

Figure 3. Case 1: Appearance of wound 2 weeks since treatment started. The wound is clean, granulating, and slowly contracting in size.

Case 2

D was a 16-year-old adolescent girl with colon cancer who sustained a hand/forearm extravasation from an antibiotic vesicant. A partial thickness wound developed after extravasation with slough. The slough was managed with a collagenase-based enzymatic debriding agent (Endo Pharmaceuticals, Chesterbrook, Pennsylvania), followed by sharp debridement and topical medical honey. After 2 weeks, D's wound had made only minimal progress toward healing. She underwent treatment with bevacizumab 4 weeks prior for colon cancer. A dermal template collagen dressing was applied, covered by a nonadherent, perforated polyamide net coated with silicone dressing (Mepitel Contact Layer, Molnycke, Norcross, Georgia) and a border foam dressing (Mepilex Border, Molnycke). The collagen dressing was completely incorporated into the wound by 4 days and a second dermal template was placed on day 7. After 2 weeks, the wound showed improvement, with granulation and 40% contraction. Wound care was transitioned to topical honey and D was discharged home.

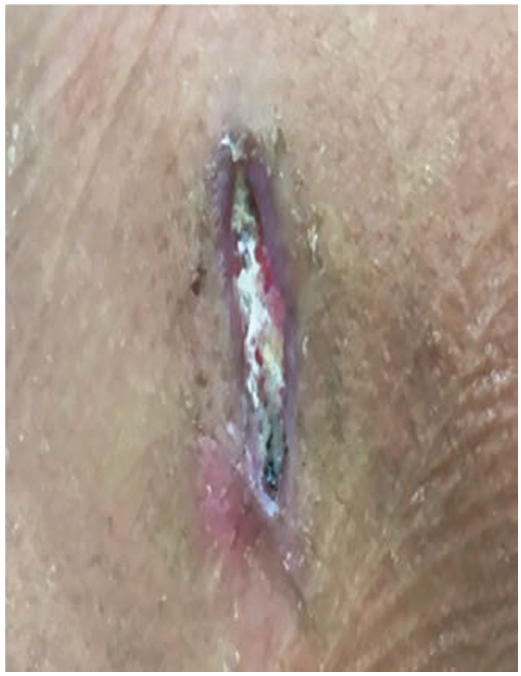

Figure 4. Case 1: Appearance of wound 1 week after third dermal template and single-use negative pressure wound healing application.

Case 3

T was a 17-year-old adolescent boy with metastatic cancer receiving palliative care who was admitted to hospital for cellulitis of his upper chest in the area of his central port. Despite aggressive systemic therapy, the port required removal. The pocket was packed with antimicrobial packing tape and his wound infection but did not respond to treatment despite ongoing packing. He had undergone administration of bevacizumab 4 weeks prior to hospital admission. A dermal template collagen dressing was packed into the wound along with appropriate outer dressing. After 12 days and 2 dermal dressing changes, an improvement was noted with internal tissue growth and internal closure. T was discharged from hospital to inpatient palliative care.

Case 4

M was a 110-day-old premature male infant delivered at 24 weeks who developed an extravasation of an intravenous line placed in the foot for delivery of antibiotics used to manage late-onset sepsis. M had many comorbid conditions associated with prematurity, including chronic lung disease, ventilator dependency, pulmonary hypertension, feeding intolerance, hydrocephalus secondary to high-grade intraventricular hemorrhage, and ROP. He underwent ostomy surgery due to sequelae of necrotizing enterocolitis. Two weeks prior to extravasation, M received unilateral intravitreous bevacizumab injection for ROP that was well tolerated.

His extravasation was treated according to our protocol. M was initially treated with hyaluronic acid, but the extravasation site evolved into a partial thickness wound with slough requiring debridement with collagenase and topical medical honey (Figure 5). I noticed a lower healing trajectory than we normally anticipate with our extravasations. I concluded that intravitreous bevacizumab administration contributed to his delayed wound healing. With that in mind, a dermal template collagen dressing was applied to the wound. The dressing was moistened with a few drops of normal saline, covered by a nonadherent, perforated polyamide net coated with silicone dressing. This topical treatment was repeated in 5 days. After the first treatment 40% of the wound was covered with granulation tissue; repeat assessment revealed a wound bed comprising 90% granulation tissue with contraction following the second treatment (Figure 6). Following these initial gains, M was switched to treatment with topical medical honey and his wound closed without complications.

DISCUSSION

Bevacizumab is a humanized monoclonal antibody that binds the VEGF-A receptor and inhibits signaling pathways in endothelial cells, blocking tumor growth by preventing preexisting vessel outgrowth, normalizing tumor vasculature, inducing endothelial-cell apoptosis, and enhancing chemotherapy

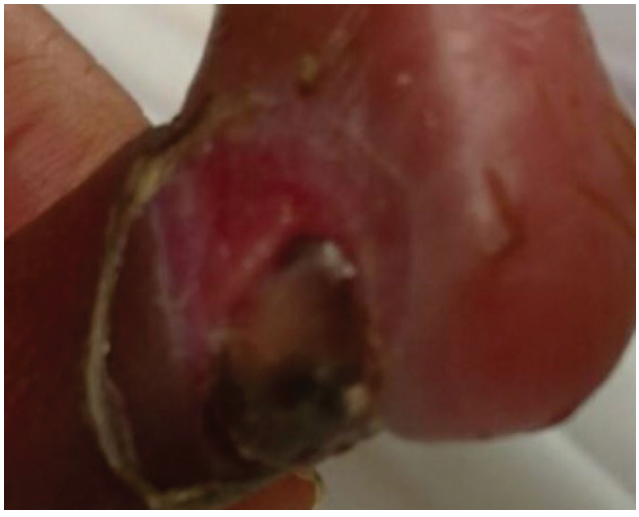

Figure 5. Case 4: Appearance of partial thickness wound after 2 days of collagenase and first debridement. A significant amount of adherent slough layer is visible.

cytotoxicity.[9,10] Inhibition of VEGF disrupts every stage of wound healing, beginning with poor recruitment of macrophages, neutrophils, and fibroblasts; slow clearing of wound debris due to inadequate vascular permeability; inadequate collagen production/deposition; and lack of ECM production. While its half-life has been shown to be 20 days on average, bevacizumab can be detected in the plasma up to 6 to 8 weeks after administration and its effects are lingering, producing undesirable wound healing complications.[4,5] Studies in adult colorectal patients have shown 13% occurrence of wound healing complications when bevacizumab given 0 to 60 days before surgery. In contrast, the wound healing complication rate was 1.3% when bevacizumab was administered 28 to 60 days after surgery.[11] Similarly, a National Surgical Adjuvant Breast and Bowel Project randomized controlled trial found a 1.7% wound complication rate when bevacizumab was administered along with a chemotherapy regimen versus a 0.3%

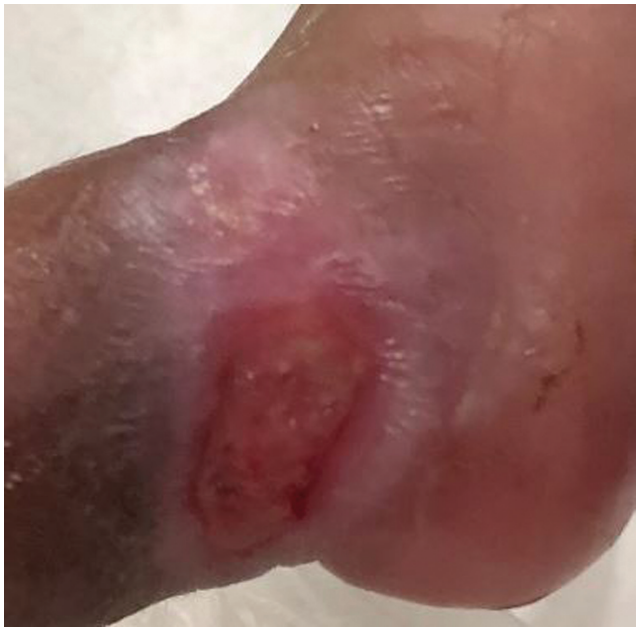

Figure 6. Case 4: Appearance of wound 5 days after first dermal template application.

complication rate with chemotherapy alone.[12] An observational cohort study of patients with colon cancer found a 4.4% incidence of surgical-site complications when the procedure was performed within 90 days of neoadjuvant bevacizumab; complications were especially common when completed less than 2 weeks after the last bevacizumab dose.[13]

Clark and colleagues[14] reported a retrospective study of repeat craniotomy for recurrent glioblastoma in 209 patients who received bevacizumab. They found a significantly higher incidence of wound healing complications in patients receiving preoperative bevacizumab than in patients managed without this agent (35% vs 10%). They further noted that administration of bevacizumab less than 4 weeks postoperatively produced the greatest likelihood of wound healing complications.[14] In breast cancer trials, administration of bevacizumab resulted in 16% rate of wound breakdown when administered within 3 weeks of surgery and a 50% incidence of reconstruction loss compared to 0% of these complications in patients managed without bevacizumab.[15] Neoadjuvant bevacizumab given 4 weeks before nephrectomy resulted in 20.9% complications rate (delayed wound healing and/or fascial dehiscence); this incidence was significantly higher than the 2% rate from a matched historical cohort receiving chemotherapy alone.[16]

I searched the literature but found no studies in neonates of children that evaluated wound healing complications yet in patients receiving bevacizumab. Instead, research in these populations has focused on the efficacy of bevacizumab in ROP and its role in the involution of retinal vessels. There are 2 stages of retinal vascular development: during early development, the retina is characterized by a relatively hyperoxic, vasoobliterative state, followed by a later stage characterized by a hypoxic, neovascularization period that occurs around 32 weeks of gestation.[3] Vascular endothelial growth factor is the main cytokine secreted by immature avascular retina, and oxygen is the main regulator of VEGF production. Specifically, hypoxia induces VEGF production and hyperoxia inhibits it. Retinopathy or prematurity is divided into 3 zones and 5 stages according to International Classification of ROP. Bevacizumab is used off-label for the treatment of zone 1, stage 3 ROP to halt the progression of abnormal retinal vascularization; its use is based on findings from the BEAT-ROP trial and guidelines from the American Academy of Pediatrics section on Ophthalmology.[3] Bevacizumab is an important treatment option for ROP. The main alternative treatment, conventional laser therapy, leads to permanent destruction of the peripheral retina. While the BEAT-ROP trial provided evidence of efficacy, the sample was too small to provide a robust assessment of adverse side effects.

Research demonstrates that VEGF is present on many essential cells/tissues including the vascular system and bones, leading to concerns regarding the possibility of diminished angiogenesis and poor organ development when an anti-VEGF agent is administered.[17] Neonatal studies on serum bevacizumab levels show detection up to 60 days after intravitreal administration and suppression of serum VEGF levels up to 8 weeks via systemic leakage.[3-5,18,19] These levels are sufficient to suppress angiogenesis and slow down vessels/ECM growth. Few case reports have also noted systemic hypertension after neonatal intravitreal administration,[20] reported previously in up to 35% of adult patients.

Both animal and human studies have supported the histopathology of delayed wound healing by noticing diminished numbers of endothelial cells, vascular thrombosis, and dermal

and subdermal infraction.[20–22] Another study supported disrupted angiogenesis, lack of dermal matrix regeneration, and lack of fibrosis, supported by histologic lack of basal keratinocytes and reduced keratinocyte growth factor in patients who have received bevacizumab.[6]

Assuming that lack of effective dermal matrix regeneration and poor angiogenesis are at the core of slow healing or dehiscence, we treated our patients with natural dermal template (Endoform, Aroa Biosurgery Limited, New Zealand), an ovine-, forestomach-derived porous ECM. Collagen plays a key role in each phase of wound healing. As a major ECM protein, collagen is the most abundant protein in humans, contributing 25% of total protein mass and approximately 80% of the skin's dry weight.[23,24] Collagen acts as structural scaffold in tissues due to its stiff, triple-stranded helical structure. Collagen types 1, 2, and 3 are the main types found in connective tissue. Structurally, collagen is a natural substrate for cellular attachment, proliferation, and differentiation. Functionally, it is chemotactic and modulates cellular responses.[25] Endoform dermal template contains 85% collagen types 1and 4, as well as secondary molecules, including hyaluronic acid, glycosaminoglycan, heparin sulfate, fibronectin, and laminin.[24] These molecules facilitate cell infiltration, bind water to keep the matrix hydrated, regulate remodeling, adhere to epithelial cells, connect scaffold proteins, and guide epithelial migration. All wounds responded well to treatment with closure.

Bevacizumab has gained prominence in neonatal population afflicted with ROP and adolescents with certain cancers. It seems to be effective and overall has an acceptable side effect profile (considering it is an adjuvant chemotherapeutic agent) as long as wound complications are taken into account. In general, more robust studies are needed as most are small retrospective reviews, case reports, and very few are from pediatric patients. We found compromised wound healing and higher likelihood of wound dehiscence after bevacizumab administration in pediatric patients. I recommend a prolonged interval of at least 4 to 6 weeks between systemic and vitreous administration of anti-VEGF agents such as bevacizumab and elective surgical procedures, consistent with adult literature recommedations.[1] If the patient has an existing wound, bevacizumab should not be administered until that wound is healed. If wound healing is stalled, I have found dermal template to be a safe and effective accelerator of such wounds in pediatric population.

KEY POINTS

- Anti-VEGF agents such as bevacizumab inhibiting new vessel growth are used for the treatment of angioneogenesis seen in selected malignancies and retinopathy of prematurity.
- Bevacizumab selectively binds VEGF-A receptor and inhibits signaling pathways in endothelial cells, inducing endothelial cell apoptosis and blocking angiogenesis; these effects have the potential to impair wound healing.
- I recommend a prolonged interval of at least 4 to 6 weeks between systemic and vitreous administration of and elective surgery in pediatric patients and delaying administration of bevacizumab in children with open wounds.
- If wound healing is stalled following administration of bevacizumab, I have found dermal template to be a safe and effective accelerator of healing in the pediatric population.

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