CASE REPORT

Incomplete Retinal Vascularization After Ranibizumab Treatment of Retinopathy of Prematurity

Shelley Day, MD; Annis M. Rainey, MD; Clio A. Harper III, MD

Ophthalmic Surgery, Lasers and Imaging Retina
January 2017 - Volume 48 · Issue 1: 75-78
Posted January 10, 2017
DOI: 10.3928/23258160-20161219-11

Abstract

A former 24-week-old premature infant was treated with intravitreal ranibizumab (Lucentis; Genentech, South San Francisco, CA) in one eye and conventional laser in the other eye for aggressive posterior retinopathy of prematurity in both eyes. Fluorescein angiography performed at 149 weeks of age showed persistent avascularity of the temporal peripheral retina in the ranibizumab-treated eye. This case report confirms the need for long-term follow-up of patients treated with ranibizumab monotherapy.


Introduction

After early reports of the efficacy of anti-vascular endothelial growth factor (VEGF) treatment for retinopathy of prematurity (ROP), the use of anti-VEGF treatment has become increasingly common either as an adjuvant to conventional laser therapy or as monotherapy.1–3 Recent studies have reported that although bevacizumab (Avastin; Genentech, South San Francisco, CA) treatment in ROP can be effective for posterior disease and allowing some growth of peripheral retinal vessels, many patients can continue to have peripheral vascular abnormalities such as avascular areas, abnormal branching, shunt vessels, and leakage.4–7 These changes can persist up to 259 weeks of age.5 Although bevacizumab is more commonly used for treatment of ROP, we have chosen to use ranibizumab (Lucentis; Genetech, South San Francisco, CA) for its smaller molecule size resulting in decreased systemic absorption and less suppression of systemic VEGF, ease of preparation without the need for a compounding pharmacy and accompanying safety issues, and ready availability in certain countries such as China, where bevacizumab is prohibited.8 Though the efficacy of ranibizumab versus bevacizumab has been studied with some case series suggesting that the
rate of ROP recurrence is similar and others suggesting that ranibizumab may have higher or earlier reactivation rates, the long-term vascular effects of ranibizumab have not been as thoroughly explored.9–10

**Case Report**

A former 24-week-old premature female infant (birth weight 454 grams) with aggressive posterior ROP in zone I of both eyes was treated with laser in the right eye and intravitreal ranibizumab injection in the left eye at 31 weeks postmenstrual age (Figure 1). After treatment, the plus disease resolved and peripheral neovascularization regressed in both eyes. Fluorescein angiography (FA) performed at 149 weeks postmenstrual age (118 weeks after treatment) showed further development of the retinal vessels but persistent avascularity of the temporal peripheral retina in the ranibizumab-treated eye (Figures 2 and 3). The laser-treated eye had peripheral chorioretinal scarring without vascular abnormalities (Figures 4 and 5). Cycloplegic refraction showed that the patient was 3 diopters (D) more myopic in the ranibizumab-treated eye.

![Figure 1. Color fundus photo taken at 31 weeks of age prior to treatment with ranibizumab.](http://www.healio.com/ophthalmology/journals/osli/2017-1-48-1/%7Bc14d60fc-abdd-4696-8aa9-c763f0b0988%7D/incomplete-retinal-vascularization-atfe...
Incomplete Retinal Vascularization After Ranibizumab Treatment of Retinopathy of Prematurity

Figure 2.
Fluorescein angiography performed at 149 weeks of age showing further growth of retinal vessels but persistent temporal retinal avascularity in the ranibizumab-treated eye.

Figure 3.
Color fundus photo taken at 149 weeks of age of ranibizumab-treated eye.
Discussion

To our knowledge, this is the first report of FA findings more than 2 years after treatment of ROP with ranibizumab. This case report confirms the findings in the long-term bevacizumab treatment trials, which suggest that continued follow-up is crucial in patients who have only received anti-VEGF monotherapy. Although the initial regression of plus disease and neovascularization after anti-VEGF treatment is dramatic, peripheral vascular anomalies can persist years after anti-VEGF treatment. Although this particular patient did not demonstrate reactivation of ROP, it is unknown what the impact of these vascular abnormalities may be in the future. There have been case reports of late recurrences of ROP after bevacizumab
monotherapy resulting in retinal detachment as far out as 2.5 years of age.\textsuperscript{11} It may be advisable to consider laser treatment to the areas of avascular retina to prevent late reactivation of ROP. In addition, Tasman has observed that in long-term follow-up of patients with untreated ROP, there was a high rate of lattice degeneration and retinal pigmentation.\textsuperscript{12} These abnormal peripheral watershed areas may predispose to retinal thinning and formation of lattice degeneration, which may be an additional rationale for laser treatment.

It is also somewhat surprising that the ranibizumab-treated eye was 3 D more myopic than the laser-treated eye, since previous studies have shown that more very high myopia was found in eyes that underwent conventional laser treatment than bevacizumab injection.\textsuperscript{13} It is unclear whether this may be normal variation, or if the myopia may be related to use of ranibizumab instead of bevacizumab, although there has been one study that suggests that high myopia was more prevalent in bevacizumab compared to ranibizumab-treated eyes.\textsuperscript{9}

References


Authors

From Austin Retina Associates, Austin, TX (SD, CH); and Dell Children's Medical Center of Central Texas, Austin, TX (AR).

The authors report no relevant financial disclosures.

Address correspondence to Shelley Day, MD, Austin Retina Associates, 801 West 38th St., Suite 200, Austin TX, 78705; email: sday@austinretina.com.

Copyright 2017, SLACK Incorporated

Received: April 26, 2016
Accepted: November 02, 2016
10.3928/23258160-20161219-11

A former 24-week-old premature infant was treated with intravitreal ranibizumab (Lucentis; Genentech, South San Francisco, CA) in one eye and conventional laser in the other eye for aggressive posterior retinopathy of prematurity in both eyes. Fluorescein angiography performed at 149 weeks of age showed persistent avascularity of the temporal peripheral retina in the ranibizumab-treated eye. This case report confirms the need for long-term follow-up of patients treated with ranibizumab monotherapy.

*[Ophthalmic Surg Lasers Imaging Retina. 2017;48:75–78.]*

From Austin Retina Associates, Austin, TX (SD, CH); and Dell Children's Medical Center of Central Texas, Austin, TX (AR).
The authors report no relevant financial disclosures.

Address correspondence to Shelley Day, MD, Austin Retina Associates, 801 West 38th St., Suite 200, Austin TX, 78705; email: sday@austinretina.com.

Copyright 2017, SLACK Incorporated

Received: April 26, 2016
Accepted: November 02, 2016

Introduction

After early reports of the efficacy of anti-vascular endothelial growth factor (VEGF) treatment for retinopathy of prematurity (ROP), the use of anti-VEGF treatment has become increasingly common either as an adjuvant to conventional laser therapy or as monotherapy.\(^1\)\(^-\)\(^3\) Recent studies have reported that although bevacizumab (Avastin; Genentech, South San Francisco, CA) treatment in ROP can be effective for posterior disease and allowing some growth of peripheral retinal vessels, many patients can continue to have peripheral vascular abnormalities such as avascular areas, abnormal branching, shunt vessels, and leakage.\(^4\)\(^-\)\(^7\) These changes can persist up to 259 weeks of age.\(^5\) Although bevacizumab is more commonly used for treatment of ROP, we have chosen to use ranibizumab (Lucentis; Genetech, South San Francisco, CA) for its smaller molecule size resulting in decreased systemic absorption and less suppression of systemic VEGF, ease of preparation without the need for a compounding pharmacy and accompanying safety issues, and ready availability in certain countries such as China, where bevacizumab is prohibited.\(^8\) Though the efficacy of ranibizumab versus bevacizumab has been studied with some case series suggesting that the rate of ROP recurrence is similar and others suggesting that ranibizumab may have higher or earlier reactivation rates, the long-term vascular effects of ranibizumab have not been as thoroughly explored.\(^9\)\(^-\)\(^10\)

Case Report

A former 24-week-old premature female infant (birth weight 454 grams) with aggressive posterior ROP in zone I of both eyes was treated with laser in the right eye and intravitreal ranibizumab injection in the left eye at 31 weeks postmenstrual age (Figure 1). After treatment, the plus disease resolved and peripheral neovascularization regressed in both eyes. Fluorescein angiography (FA) performed at 149 weeks postmenstrual age (118 weeks after treatment) showed further development of the retinal vessels but persistent avascularity of the temporal peripheral retina in the ranibizumab-treated eye
Incomplete Retinal Vascularization After Ranibizumab Treatment of Retinopathy of Prematurity

(Figures 2 and 3). The laser-treated eye had peripheral chorioretinal scarring without vascular abnormalities (Figures 4 and 5). Cycloplegic refraction showed that the patient was 3 diopters (D) more myopic in the ranibizumab-treated eye.

Figure 1.
Color fundus photo taken at 31 weeks of age prior to treatment with ranibizumab.

Figure 2.
Fluorescein angiography performed at 149 weeks of age showing further growth of retinal vessels but persistent temporal retinal avascularity in the ranibizumab-treated eye.
Incomplete Retinal Vascularization After Ranibizumab Treatment of Retinopathy of Prematurity

Figure 3.
Color fundus photo taken at 149 weeks of age of ranibizumab-treated eye.

Figure 4.
Color fundus photo taken at 149 weeks of age of laser-treated eye.
Discussion

To our knowledge, this is the first report of FA findings more than 2 years after treatment of ROP with ranibizumab. This case report confirms the findings in the long-term bevacizumab treatment trials, which suggest that continued follow-up is crucial in patients who have only received anti-VEGF monotherapy. Although the initial regression of plus disease and neovascularization after anti-VEGF treatment is dramatic, peripheral vascular anomalies can persist years after anti-VEGF treatment. Although this particular patient did not demonstrate reactivation of ROP, it is unknown what the impact of these vascular abnormalities may be in the future. There have been case reports of late recurrences of ROP after bevacizumab monotherapy resulting in retinal detachment as far out as 2.5 years of age.\textsuperscript{11} It may be advisable to consider laser treatment to the areas of avascular retina to prevent late reactivation of ROP. In addition, Tasman has observed that in long-term follow-up of patients with untreated ROP, there was a high rate of lattice degeneration and retinal pigmentation.\textsuperscript{12} These abnormal peripheral watershed areas may predispose to retinal thinning and formation of lattice degeneration, which may be an additional rationale for laser treatment.

It is also somewhat surprising that the ranibizumab-treated eye was 3 D more myopic than the laser-treated eye, since previous studies have shown that more very high myopia was found in eyes that underwent conventional laser treatment than bevacizumab injection.\textsuperscript{13} It is unclear whether this may be normal variation, or if the myopia may be related to use of ranibizumab instead of bevacizumab, although there has been one study that suggests that high myopia was more prevalent in bevacizumab compared to ranibizumab-treated eyes.\textsuperscript{9}

References

http://www.healio.com/ophthalmology/journals/osli/2017-1-48-1/%7Bc14d60fc-abdd-4696-8aa9-c7f63fab099b%7D/incomplete-retinal-vascularization-aft...


From Austin Retina Associates, Austin, TX (SD, CH); and Dell Children's Medical Center of Central Texas, Austin, TX (AR).

The authors report no relevant financial disclosures.

Address correspondence to Shelley Day, MD, Austin Retina Associates, 801 West 38th St., Suite 200, Austin TX, 78705; email: sday@austinretina.com.

Copyright 2017, SLACK Incorporated

Received: April 26, 2016
Accepted: November 02, 2016