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Brolucizumab-Associated Intraocular Inflammation in Eyes Without Retinal Vasculitis

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Abstract

Purpose: This work analyzes a series of eyes with brolucizumab-associated intraocular inflammation (IOI) without retinal vasculitis reported to the American Society of Retina Specialists. **Methods:** The American Society of Retina Specialists Research and Safety in Therapeutics Committee analyzed clinical characteristics from submitted reports of IOI after brolucizumab. Eyes with retinal vasculitis or that received intraocular antibiotics were excluded. **Results:** Forty-nine eyes of 45 patients were collected. Mean visual acuity (VA) at baseline was 20/49 (range, 20/20-5/200). Patients presented with IOI a mean of 24 days (range, 3-63 days) after their most recent brolucizumab injection; 61% presented for an unscheduled visit while 39% presented at routine follow-up. Mean VA at IOI presentation was 20/67 (range, 20/20-3/200). The most common symptoms were floaters (78%) and blurry vision (76%). Pain (20%) and redness (16%) were less common; 3 (6%) eyes were asymptomatic. IOI was anterior only in 18%, posterior only in 31%, and both anterior and posterior in 51% of eyes. Treatment included topical steroids alone in 67% of eyes, whereas 10% of eyes received no treatment. Mean VA at last follow-up was 20/56 (range, 20/20-1/200). Three (6%) eyes lost 3 or more lines and 1 (2%) eye lost 6 or more lines. **Conclusions:** Brolucizumab-associated IOI without retinal vasculitis typically presented with a delayed onset of a few weeks. Often, VA decline was relatively mild. Most symptoms resolved and nearly all had a return-to-baseline VA, but a small percentage of patients had a significant decrease in VA at last follow-up.

Keywords
anti-VEGF agents, inflammatory and infectious diseases, wet AMD (neovascular)

Introduction

On October 7, 2019, brolucizumab 6 mg (Beovu; Novartis International AG) was approved by the US Food and Drug Administration (FDA) for treatment of neovascular age-related macular degeneration (NVAMD) with the hope of reducing treatment burden compared with other antivascular endothelial growth factor (anti-VEGF) agents. Brolucizumab is a single-chain antibody fragment that blocks all forms of VEGF-A, and it can be concentrated to give higher molar equivalent doses than other anti-VEGF drugs because of its highly soluble nature and small molecular weight. The phase 3 HAWK and HARRIER studies demonstrated that brolucizumab had a greater drying effect on the retina than aflibercept.[1] Approximately 50% of patients could be maintained on an

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every-12-weeks brolucizumab dosing regimen with noninferior visual acuity (VA) outcomes compared with every-8-weeks aflibercept.[1]

Shortly following the FDA approval of brolucizumab, the American Society of Retina Specialists (ASRS) began receiving reports of inflammation following intravitreal brolucizumab administration for NVAMD. Some of these cases were associated with retinal vasculitis that frequently resulted in vascular occlusion and significant vision loss. Reports of retinal vasculitis associated with intraocular brolucizumab reported to the ASRS have been summarized in a previous report.[2] However, other eyes had intraocular inflammation (IOI) without retinal vasculitis and were not included in that article. The purpose of the present study is to analyze the characteristics of cases of IOI without retinal vasculitis that occurred after FDA approval of brolucizumab and were voluntarily reported to the ASRS as of June 1, 2020.

Methods

The ASRS Research and Safety in Therapeutics (ReST) Committee collected and analyzed clinical data from submitted reports of IOI without retinal vasculitis that occurred after intravitreal brolucizumab and were reported to the ASRS as of June 1, 2020. Cases with no follow-up data, that were treated with intraocular antibiotics, or that had retinal vasculitis were excluded from the study. Data were tabulated with Microsoft Excel. Snellen VA was converted to logarithm of the minimum angle of resolution equivalents for the purpose of analysis. All patient information was deidentified.

Initial reports were submitted by treating physicians to the ASRS ReST Committee through the ASRS website (https://www.asrs.org/forms/4/asrs-adverse-event-report-form). The ReST Committee followed up by sending a uniform questionnaire to reporting physicians to collect a standardized data set including geographic location, patient sex, age, left or right eye, race, medical history (including autoimmune disease), allergy history, ocular history, date of NVAMD diagnosis, previous number and type of anti-VEGF therapy (including most recent therapy preceding brolucizumab), history of anti-VEGF–associated inflammation, reason for switching to brolucizumab, number and dates of brolucizumab injection(s), lot number of the causative brolucizumab injection, dates of presentation with an adverse event (AE) and all dates of subsequent follow-up, symptoms at AE's presentation, presence or absence and location of IOI, grade of IOI (anterior chamber and vitreous cells), location of inflammation (anterior, posterior, or both), treatment modalities, final follow-up date, presence or absence of inflammation at final follow-up (and time to resolution if applicable), residual examination's findings, residual symptoms, date and type of anti-VEGF reinjection if available (including dates and whether there was recurrent inflammation), and anti-VEGF plan moving forward. VA and intraocular pressure (IOP) were recorded from each visit.

Table 1. Demographic Data.

No. of patients	49 eyes of 45 patients (1 bilateral case)
Sex	29 female (64%), 16 male (36%)
Age, y	Mean 76 (range, 56-90)
Eye	23 right, 23 left, 3 unlisted
Race	All White
Location	All in the United States: 15 Northeast, 9 West, 14 South, 7 Midwest
Autoimmune history	7 hypothyroid
11 (24%) total	1 uveitis in fellow eye
4 (13%) excluding hypothyroid	1 MS
	1 Crohn disease
	1 inflammatory liver disease
Drug allergies	No pattern (49% had no allergies)
Lens	20 phakic (41%)
	29 pseudophakic (59%)
Length of NVAMD diagnosis prior to brolucizumab, mo	4 treatment naive (8%)
	Mean 34 (range, 0-92)
No. of prior anti-VEGF (before brolucizumab)	Mean 26.4 injections (range, 0-62 injections)
	Total 1265 injections
Type of injections prior to brolucizumab (in total)	344 (27%) ranibizumab
	195 (15%) bevacizumab
	726 (57%) aflibercept
Most recent injection prior to brolucizumab	10 ranibizumab (20%)
	5 bevacizumab (10%)
	29 aflibercept (59%)
Reason to switch to brolucizumab	Extend treatment interval: 32 eyes (65%)
	Improve efficacy: 29 eyes (59%)
	Treatment naive: 4 eyes (8%)

Abbreviations: MS, multiple sclerosis; NVAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

Results

Demographics

In total, there were 39 reporting providers with 62 patients with brolucizumab-associated IOI initially reported to the ASRS. In 8 eyes, no follow-up data were provided, and they were therefore excluded from analysis. There were another 5 eyes that received intravitreal antibiotics and were therefore excluded. Another 4 eyes were excluded because of IOI with concurrent retinal vasculitis. In the end, data from 49 eyes of 45 patients with IOI without retinal vasculitis after brolucizumab were included in the study; data regarding these cases were submitted by 32 providers. Patient demographics are summarized in Table 1. Twenty-nine (64%) of reported cases occurred in women. Mean age was 76 years, and all were White, consistent with the US NVAMD population. Reported cases were seen throughout the United States. There was no identifiable pattern for medical history, ocular history, or drug allergies. Eleven (24%) patients had a known history of inflammatory or presumed inflammatory disease: 7 with hypothyroidism, 1 with uveitis in the fellow eye, 1 with multiple sclerosis (and

Table 2. Visual Acuity Data.

All eyes (49 eyes of 45 patients)	Mean logMAR VA	Mean Snellen VA	Median Snellen VA	Range
VA at most recent brolucizumab injection	0.3926	20/49	20/40	20/20-5/200
VA at AE onset	0.5258	20/67	20/50	20/25-3/200
Worst VA	0.6144	20/82	20/60	20/25-1/200
VA at most recent follow-up[a]	0.4457	20/56	20/40	20/20-1/200
3 eyes (6%) with $\geq$ 3-line VA loss at last follow-up, 1 eye (2%) with $\geq$ 6-line VA loss at last follow-up				
Eyes with > 30 days' follow-up since AE presentation (32 eyes of 30 patients)				
VA at most recent brolucizumab injection	0.4485	20/56	20/40	20/20-5/200
VA at AE onset	0.5813	20/76	20/60	20/20-5/200
Worst VA	0.6864	20/97	20/75	20/25-5/200
VA at most recent follow-up[b]	0.4739	20/60	20/45	20/20-5/200
2 eyes (6%) with $\geq$ 3-line VA loss at last follow-up, 1 eye (3%) with $\geq$ 6-line VA loss at last follow-up				

Abbreviations: AE, adverse event; VA, visual acuity.
[a]Mean 74 days since last brolucizumab injection.
[b]Mean 92 days since last brolucizumab injection.

hypothyroidism), 1 with Crohn disease, and 1 with a history of inflammatory liver disease.

Forty-five eyes (92%) had received previous treatment with other anti-VEGF agents, whereas 4 eyes (8%) were treatment naive. The mean number of prior anti-VEGF injections was 26.4 (range, 0-62 injections). The most recent anti-VEGF injection prior to brolucizumab was aflibercept in 29 eyes (59%), bevacizumab in 5 eyes (10%), and ranibizumab in 10 eyes (20%). In all eyes, there was a history of 1265 total prior anti-VEGF injections, of which 57% were aflibercept, 27% were ranibizumab, and 15% were bevacizumab. Two eyes had a history of aflibercept-associated inflammation. Five patients had same-day bilateral injections of brolucizumab, and all 5 had bilateral IOI (one of these patients developed a central retinal artery occlusion in 1 eye, and because that eye was presumed to have retinal vasculitis it was excluded from this analysis).

All AEs arose after 1 (23 eyes, 47%), 2 (20 eyes, 41%), or 3 (6 eyes, 12%) brolucizumab injections in the 8 months since FDA approval (October 7, 2019 to June 1, 2020) and 5 months since a permanent J-code had been established (January 1, 2020). The last brolucizumab injection reported in this series was on March 27, 2020. There was no identifiable association with lot number (there were 10 different lot numbers provided from 38 injecting physicians). No brolucizumab injections were given in the presence of concurrent IOI as noted by the reporting physician.

IOI Presentation

Mean time to presentation of IOI was 24 days (median, 26 days; range, 3-63 days) from the most recent brolucizumab injection. The mean time between symptom onset and presentation of IOI was 14 days (median, 7 days; range, 0-53 days). Thirty eyes (61%) presented as an unscheduled visit, whereas 39% presented with IOI for the first time at a routine follow-up visit.

Symptoms at AE onset included floaters (78%), blurry vision (76%), pain (20%), redness (16%), photophobia (4%), and nausea (1%); 3 eyes (6%) were asymptomatic at IOI presentation and throughout follow-up. Mean VA was 20/49 (median, 20/40; range, 20/20-5/200) at baseline (at the time of the causative brolucizumab injection). Mean VA decreased to 20/67 (median, 20/50; range, 20/25-3/200) at AE presentation (see Table 2 for summary of VA data). The location of IOI was anterior only in 9 (18%) eyes, posterior only in 15 (31%) eyes, and both anterior and posterior in 25 (51%) eyes. Mean grade of anterior chamber cells was 1.1+ cells (range, 0.5-2+ cells), whereas mean grade of vitreous cells was 1.2+ cells (range, 0.5-3+ cells) as graded by the reporting physician. Other examination findings at AE presentation included conjunctival injection in 10 (20%) eyes, keratic precipitates in 12 (24%) eyes, and vitreous debris in 21 (41%) eyes. No eyes had corneal edema, anterior chamber fibrin, or hypopyon. Mean IOP was 14.4 mm Hg (range, 5-21 mm Hg) at the time of most recent brolucizumab injection and 15.8 mm Hg (range, 6-33 mm Hg) at AE presentation.

Outcomes

The most recent follow-up visit occurred at a mean of 51 days following AE onset (median 49 days; range, 0-128 days) and 74 days following the last brolucizumab injection (median, 76 days; range, 5-141 days). At the most recent follow-up, mean VA was 20/56 (median, 20/40; range, 20/20-1/200). Compared with the VA at the time of the causative brolucizumab injection, 3 (6%) eyes had a greater than 3-line decrease in VA at final follow-up, and 1 (2%) eye had a greater than 6-line decrease in VA at final follow-up. There were 10 (20%) eyes that had further worsening of VA after IOI presentation. The mean worst VA in the AE course was 20/82 (median, 20/60; range, 20/25-1/200). A sensitivity analysis excluding eyes with

less than 30 days' follow-up since AE presentation revealed similar VA trends (see Table 2).

In total, 15 (31%) eyes had residual symptoms at last reported follow-up; symptoms included floaters in 12 (24%) eyes and blurry vision in 6 (12%) eyes. Mean final IOP was 16 mm Hg (range, 8-28 mm Hg) at most recent follow-up. In terms of inflammation, 32 (65%) eyes had resolution of inflammation over a mean of 26 days (median, 14 days; range, 6-80 days). In the subgroup of eyes with greater than 30 days' follow-up since AE presentation (32 eyes of 30 patients), 75% had resolution of inflammation at the last follow-up visit, and 34% had residual symptoms (floaters and/or blurry vision).

Treatment involved topical corticosteroids alone in 33 (67%) eyes, whereas 5 (10%) eyes received no treatment. The remainder were treated with topical and periocular or intraocular steroids in 5 (10%) eyes and topical and systemic steroids in 5 (10%) eyes. No eyes had a pars plana vitrectomy and, per exclusion criteria, eyes treated with intravitreal antibiotics were omitted. Of note, 1 patient died of a cardiac event deemed unrelated to brolucizumab 8 weeks after the brolucizumab injection associated with IOI.

Anti-VEGF Reinjection

Thirty-four (69%) eyes were re-treated with a different anti-VEGF agent after diagnosis of IOI related to brolucizumab. The mean number of rechallenge anti-VEGF injections after IOI presentation was 1.8 (range, 1-8 injections) at the time of data collection. Twenty-one (43%) eyes received aflibercept, 8 (16%) eyes received ranibizumab, 2 (4%) eyes received bevacizumab, and 3 (6%) eyes received a second brolucizumab injection. Of the 3 eyes that received a brolucizumab rechallenge injection, 2 were in the same patient and both of those eyes received a sub-Tenon injection of triamcinolone at the same time as the brolucizumab injection. There were no cases of recurrence or worsening of inflammation after anti-VEGF rechallenge.

Conclusions

As of June 1, 2020 (8 months after FDA approval), the ASRS collected and analyzed data from 49 eyes of 45 patients with IOI without retinal vasculitis occurring after intravitreal brolucizumab for NVAMD. Most patients (92%) had prior anti-VEGF treatment, whereas 4 (8%) were treatment naive. Most patients (61%) came in for an unscheduled visit at the initial IOI presentation; however, 39% were diagnosed with IOI only at a routine follow-up examination. The most common symptoms were floaters (78%) and blurry vision (76%); pain was less common (20%). Most eyes had only a mild decrease in VA and regained their baseline VA at last follow-up, although 3 eyes (6%) had 3-line or greater vision loss and 1 eye (2%) had 6-line or greater vision loss at the most recent follow-up. Many eyes (65%) at most recent follow-up had resolution of inflammation, and most (69%) had resolution of symptoms. Most eyes (69%) were rechallenged with another anti-VEGF, and there were no reports of recurrent inflammation in those eyes, including the 3 eyes that were rechallenged with brolucizumab.

IOI has been associated with bevacizumab (Genentech, Inc), ranibizumab (Genentech, Inc), and aflibercept (Regeneron Pharmaceuticals, Inc) at rates between 0.033% and 2.9% per injection.[3] Many cases can be treated successfully with topical or local corticosteroids, although more severe cases are often presumed infectious and treated as such.[3,4] There seems to be an underlying rate of IOI with all anti-VEGF drugs, and clusters of higher rates of inflammation may also occur.[5-11] The mechanism of IOI after anti-VEGF remains unknown; suggested mechanisms have included immune response to the drug itself, other protein byproducts within the medication, or differences in pH, while mechanisms of inflammation clusters have been attributed to silicone oil residues, silicone/protein aggregates, or endotoxins.[5-11]

In this series, IOI after brolucizumab affected women (64%) more than men, although the disparity was not as great as in our recent series of occlusive retinal vasculitis after brolucizumab (of which 88% of 25 reported patients were women).[2] This more modest sex disparity, as well as the presenting age and race of the patients affected, is consistent with the general NVAMD population in the United States.[12] There was no identifiable association with any ocular disorders, autoimmune diseases, drug allergies, or other medical disorders.

In phase 3 clinical trials and according to the FDA label, the rate of IOI with brolucizumab was higher (> 4%) than with its comparator, aflibercept (< 1%). The reason for this higher rate of inflammation is currently unknown. The high rates of anti-brolucizumab antibodies noted during HAWK and HARRIER could be an indicator as to the etiology of brolucizumab-associated IOI (and vasculitis). Even before drug initiation, 36% to 52% of patients had antibrolucizumab antibodies. After initiation of dosing, antibrolucizumab antibodies were detected in 53% to 67% of patients treated with brolucizumab, and by week 88, 23% to 25% of eyes had induced or boosted levels of antibrolucizumab antibodies.[13,14]

It was also noted that there was a higher percentage (6%) of patients with IOI among those who tested positive for antibrolucizumab antibodies compared with patients without these antibodies (2%). In comparison with brolucizumab, clinical trials with ranibizumab and aflibercept have shown 0% to 3% of patients with antidrug antibodies before treatment initiation and 1% to 9% of patients with antidrug antibodies after a 2-year treatment course.[15,16] It is possible that the higher rates of preexisting and treatment-emergent antibrolucizumab antibodies may help explain the higher rates of inflammation in relation to this drug. Conversely, neither preexisting nor treatment-emergent antibrolucizumab antibodies seemed to affect the efficacy of the drug, and the clinical significance of these antibodies remains unclear. Another possibility for the difference in inflammation rates could be differences in the manufacturing and purification processes. These differences will be important for Novartis and other drug companies to look at when trying to further elucidate the etiology of anti-VEGF–associated IOI.

In the present series, the time course and presentation of inflammation in most eyes suggest a delayed immune reaction to the drug or some component of the delivery system. The delay in presentation and clinical findings is not typical for postinjection endophthalmitis, which most commonly appears within the first week after an injection and is associated with pain, conjunctival injection, hypopyon, and dense vitritis with a minimal view to the retina.[17] An individual's predisposition to brolucizumab-associated IOI may also be suggested by the bilateral onset of IOI in all 5 patients who received bilateral brolucizumab injections (in one of these patients, 1 eye was excluded from this analysis because that eye also developed retinal vasculitis). Conversely, it is possible that the inflammatory reaction was not related to the drug or the delivery system at all, but rather some part of the injection technique or protocol that was office- or doctor-specific.

One important observation was that 3 eyes in this series had a history of aflibercept-associated IOI. If not coincidental, these patients may have either been prone to an inflammatory reaction from anti-VEGF agents in general, or they may have had an immune response to an adjuvant or contaminant present in both drugs (eg, silicone oil residues or silicone/protein aggregates). Conversely, many eyes (69%) were rechallenged with anti-VEGF medications, including 6% with brolucizumab and 43% with aflibercept, and no eyes had a recurrence of inflammation, at least on limited follow-up, suggesting that these may be idiosyncratic reactions. The fact that the 3 eyes that were rechallenged with brolucizumab did not have another inflammatory reaction suggests that the reaction may not have been to the drug itself, but rather to another component such as a contaminant in the formulation that may vary from vial to vial. If the reaction were an immune reaction to the drug specifically, we would expect a worsening inflammatory response with each injection of the same drug.

Comparison of brolucizumab-associated IOI in this series to anti-VEGF–associated IOI in other published case series should be performed with caution. However, there do appear to be some differences in the presentation and timing of onset of brolucizumab-associated IOI compared with IOI related to other anti-VEGF drugs. In reports of aflibercept-associated IOI, patients presented earlier ($\sim$2-4 days after injection on average) with worse vision, and more commonly with pain ($\sim$45%), anterior chamber reaction (75%-90%), and corneal edema (13%-21%).[7,8] Conversely, in this series of brolucizumab-associated IOI, patients commonly presented in a more delayed fashion (mean 24 days after injection), and IOI often presented only on routine follow-up (39% of eyes). Compared with aflibercept-associated IOI, patients with brolucizumab-associated IOI (without vasculitis) had better vision, less commonly presented with pain (20%), had no reports of corneal edema, had anterior chamber reaction in only 67% of eyes, and more commonly presented with floaters and vitritis (84%). The reason for differences in presentation between aflibercept-associated IOI and brolucizumab-associated IOI remains unclear but suggests there may be a different underlying pathogenesis for inflammation associated with each drug. It is also important to note that our series excluded cases of IOI with retinal vasculitis and may have also excluded more severe cases that were treated with intraocular antibiotics because of suspicion of infectious endophthalmitis.

Without long-term follow-up and with a limited number of cases with a range of severity and treatment approaches, this study was unable to determine optimal treatment modalities. However, 77% of eyes received topical treatment alone or no treatment, and most eyes recovered from preinflammation symptoms, suggesting that topical steroids alone may be sufficient in many cases.

The information in this report is limited to data that were voluntarily submitted to the ASRS ReST Committee by the reporting physicians. Voluntary reporting of safety events is always limited by inevitable underreporting, and this study was unable to assess the incidence of IOI in a real-world setting. Re-review of HAWK/HARRIER data by a Novartis-commissioned scientific review committee identified an IOI rate of 4.6% (including all cases of IOI, both with and without vasculitis) over the course of the 2-year trials; IOI without vasculitis in the trial setting occurred at a rate of 1.3%.[18]

Follow-up in this study was limited to the termination date of data collection. Similar outcomes results were found when eyes with fewer than 30 days of follow-up were excluded. However, some patients had ongoing inflammation and loss of vision at last follow-up that may improve with longer follow-up. Similarly, although we identified a small number of patients who had 3 lines or greater and 6 lines or greater vision loss at last follow-up, there were no cases of 3 lines or greater (or $\geq$ 6-line) vision loss associated with IOI in the absence of vasculitis over 2 years in HAWK/HARRIER.[18]

This study may underestimate the severity of some cases of IOI because we excluded patients who were treated with intraocular antibiotics to remove potentially confounding cases of infectious endophthalmitis. In addition, this study excluded eyes with retinal vasculitis, a recently described complication of brolucizumab that is also associated with IOI and with worse visual outcomes.[2,19]

The information gathered in this study does not indicate a clear etiology of the inflammation. The delayed onset and resolution with topical corticosteroids may suggest an immune reaction to the drug or some component of the drug, but it is unclear what the inciting factor is. Because intraocular cultures and/or polymerase chain reaction testing was not performed, the possibility of indolent infectious causes cannot be ruled out. Future studies of patients with inflammation after intravitreal injections may benefit from the inclusion of this type of testing.

In addition, at the time of this analysis, brolucizumab had been on the market for less than 8 months. In this series, all cases of brolucizumab-associated IOI arose after 1, 2, or 3 brolucizumab injections, but it is unlikely that patients were treated with many more than 3 injections in that time frame. In HAWK/HARRIER, the Novartis Safety Review Committee identified that 74% of cases of IOI (including with and without vasculitis) occurred within the first 6 months of treatment initiation, with the remainder of cases arising between 6 and 18 months; no

cases arose between 18 and 24 months in this 2-year trial.[18] Longer-term real-world experience with this drug will be important to understand whether the postapproval experience will be similar to that in the phase 3 trials.

Although the exact mechanism of these findings remains unclear, the ReST Committee recommends a careful evaluation of the anterior and posterior segment for any signs of active inflammation prior to and after any brolucizumab injection, particularly given the indolent nature of IOI presentation in some eyes. Appropriate informed consent should be obtained, and patients should be advised to return for prompt evaluation if changes in vision occur. Because all 5 patients who received bilateral same-day brolucizumab injections subsequently developed bilateral IOI, we suggest particular caution when administering this medication (or any newly approved medication) the same day bilaterally. Any inflammation following brolucizumab should be followed closely because occlusive vasculitis has been noted to develop in a delayed fashion in some eyes with IOI. Along the same lines, any consideration of infectious endophthalmitis should be managed accordingly.

In the absence of vasculitis or endophthalmitis, most patients with IOI alone in this series appeared to return close to their baseline vision with topical steroids, although a small number of eyes in this series did not recover vision. An optimal approach toward reinitiating anti-VEGF therapy is unclear but should ideally be deferred until inflammation has resolved. In this series with limited follow-up, recurrent inflammation was not reported when eyes were rechallenged with anti-VEGF. Future analyses of these cases will be important to understand long-term outcomes and management strategies. Analysis of postmarketing data is important with any drug and particularly with newly approved drugs. The ReST Committee continues to encourage physicians to report any adverse outcomes to ASRS as well as to the drug company.

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Ethical Approval

This study was deemed exempt from institutional review board oversight based on personal communication with the Human Research Protection Program at Allina Health System of Minneapolis, Minnesota.

Statement of Informed Consent

Because this study did not involve human participants but rather deidentified patient information submitted to the ASRS ReST Committee, informed consent was not obtained.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.H.: Genentech (consultant, lecture fees) and Allergan (consultant); J.F.A.: Springer Science and Business Media LLC (patents/royalties), Dutch Ophthalmic Research Center International BV (consultant, lecture fees), Allergan Inc (consultant, lecture fees), Bayer (consultant, lecture fees), Mallinckrodt (consultant), and Topcon (grant support); K.J.B.: Bausch + Lomb (consultant, lecture fees), Allergan (consultant, lecture fees), Regeneron (consultant, lecture fees), Novartis (consultant, lecture fees), and Genentech (consultant); N.C.: Allergan (consultant), Bayer (consultant), and Novartis (consultant); G.G.E.: Novartis (stock) and Regeneron (stock); R.A.G.: Genentech (research, speaker, advisory), Regeneron (advisory), Novartis (research, speaker, advisory), Allergan (research, speaker, advisory), Aerie (research), Santen (research), Graybug (research), and Novo Nordisk (research); H.T.: Alimera (stock); and R.W.W.: Novartis (research).

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