

Ten-year outcome of anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration

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Purpose: The aim of this study was to report the 10-year visual outcome in eyes treated with anti-vascular endothelial growth factor (anti-VEGF) agents for neovascular age-related macular degeneration (nAMD) and to assess the impact of switching treatment as part of routine clinical care. **Methods:** Electronic records of treatment-naïve eyes initiated on intravitreal ranibizumab between January and December 2009 were accessed. The primary outcome measured was the change in visual acuity (VA) in Early Treatment of Diabetic Retinopathy Study letters. The frequency and reasons for treatment discontinuation during each year of follow-up and the impact of switching from ranibizumab to aflibercept were some of the secondary outcomes. **Results:** Of the 223 eyes (203 patients), 60 eyes completed 10 years of continuous follow-up. After a mean follow-up of 121.4 months, VA declined by 5.6 letters (95% confidence interval [CI] -0.25 to -11.1, $P = 0.04$). Final VA of ≥ 70 letters was seen in 20% of eyes and 35% had VA ≤ 35 letters. VA gain of ≥ 10 letters was seen in 23% and loss of ≥ 10 letters was seen in 40% of the eyes. Twenty-nine eyes remained on ranibizumab monotherapy and 31 switched to aflibercept. Switched eyes showed a visual decline of 7.1 letters (5.5 letters in monotherapy eyes, $P = 0.32$) and received a significantly higher number of injections (39.6 ± 9.9 vs. 24.4 ± 13.1 , $P < 0.0001$). Patients discontinuing treatment were older and had lower baseline vision compared to completers. **Conclusion:** VA declined below the baseline after 10 years of follow-up and switching did not have any effect on the final visual outcome.

Key words: 10-year results, anti-VEGF, nAMD, switching

Neovascular age-related macular degeneration (nAMD) is the most common cause of visual impairment in people above the age of 55 years. Untreated disease progresses and causes irreversible central visual loss and blindness in nearly 76% of patients within 3 years.^[1] The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has revolutionized the treatment of nAMD, decreasing the rate of legal blindness in more than 50% of patients.^[2,3] Despite the initial visual acuity (VA) gain, up to 10% of eyes lose 15 letters of vision within 2 years, as seen in various pivotal studies using ranibizumab and aflibercept.^[4-6] Visual decline, with mean loss of 8.6 letters (SEVEN-UP, Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials)^[7] and 14 letters (IVAN study, Inhibition of VEGF in age-related choroidal neovascularization),^[8] has been reported on exit from clinical trial. Eight-year follow-up of 40 Norwegian patients reported a visual change of 2.1 letters below the baseline vision.^[9]

The literature on 10-year outcomes of eyes treated with anti-VEGF for nAMD is sparse, with only three publications to date.^[10-12] These retrospective studies too show a similar trend of initial visual gain which is not maintained with the final VA either remaining stable or decreasing below the baseline. None of these studies have compared the visual outcome in eyes continuing on ranibizumab monotherapy, over the full course of 10 years, against eyes switching to aflibercept.

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This retrospective review reports 10-year outcome of eyes treated for nAMD with anti-VEGF at a single center in the United Kingdom (UK), where the cost of treatment is not a consideration. The primary outcome assessed was the change in VA and number of eyes gaining or losing ≥ 10 letters. The secondary outcomes measured were the impact of switching agents on the final visual results, the frequency and reasons for treatment discontinuation during each year of follow-up.

Methods

Data were extracted retrospectively from the electronic records (Medisoft®) of treatment-naïve eyes commenced on intravitreal anti-VEGF for nAMD between January and December 2009. The study adhered to the tenets of Declaration of Helsinki and was registered as a clinical audit with the hospital quality improvement project team.

Information collected included patient demographics, VA (number of Early Treatment of Diabetes Retinopathy Study [ETDRS] letters read on a logarithm of the minimum angle of resolution logMAR chart) at various time intervals (0, 4, 12, 36, 60, 90, and 120 months), anti-VEGF agent used, and the number of injections. Baseline color fundus photos (CFP) and fluorescein angiography (FA) were re-reviewed to classify lesion subtype,

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look for macular atrophy (MA) and macular fibrosis. On CFP, MA was defined as a discrete area of hypopigmentation or depigmentation of retinal pigment epithelium (RPE) within the vascular arcade, causing increased visibility of choroidal vessels. Presence of a well-defined elevated mound of yellowish-white tissue was recorded as macular fibrosis. Optical coherence tomography (OCT) findings recorded were central foveal thickness (CFT), subretinal (SRF), and intraretinal fluid (IRF) at baseline, 4 months, and final follow-up. In addition, OCT image from the last follow-up was evaluated to look for presence of macular fibrosis (presence of hyperreflective sheet-like material, either above or below RPE) and MA (zone of choroidal hypertransmission with the absence of RPE homogenous band).

The number of clinic visits per year and delay in clinic appointment were retrieved for every year of follow-up. Baseline age and VA, final VA, time, and reasons for dropout were recorded in eyes that discontinued treatment.

Treatment protocol

All eyes were initiated on three loading injections of intravitreal ranibizumab (0.5 mg/0.05 mL) followed by pro-re-nata (PRN) regimen. Patients switched to aflibercept (2 mg/0.05 mL) also received three loading injections followed by fixed bimonthly dosing for the first year of switch. Eyes that needed frequent injections, with lack of sustained response to ranibizumab, possibly related to tachyphylaxis, were switched to intravitreal aflibercept.

Outcome measures

In eyes that completed the 10 years of follow-up, the main outcome measures were change in VA, proportion of eyes with final VA of ≥ 70 letters (20/40 Snellen equivalent) and ≤ 35 letters (20/200), proportion of eyes remaining stable (VA change ± 5 letters from baseline), gaining ≥ 10 letters and losing ≥ 10 letters. Eyes that continued on ranibizumab through the whole follow-up were compared to the eyes that switched to aflibercept to assess the impact on VA and CFT. Infrequent monitoring was correlated with visual decline over the course of follow-up.

Statistical analysis

The collected data were entered into an Excel sheet and analyzed using GraphPad Prism 6.0. The data were not found to be normally distributed (D'Agostino and Pearson omnibus test). Descriptive data included mean, standard deviation,

standard error, median, range and percentages. Mann-Whitney test was used to compare the mean parameters of monotherapy and switched eyes. Time to study dropout based on baseline vision and age was analyzed using Kaplan-Meier survival and curves were compared using the Mantel-Cox test. A value of $P < 0.05$ was considered statistically significant.

Results

Of the 223 eyes in 203 patients, there were 153 women and 50 men. The mean age was 75.9 ± 7.1 years and 163 eyes dropped out at various time intervals during the 10 years. The number of eyes completing the first, third, and fifth years of follow-up were 208, 143, and 110, respectively. The mean duration of follow-up in 60 eyes (27%) that completed the full 10-year follow-up was 121.4 months (range 120–139).

Completers (60 eyes)

Baseline measures

The mean VA at baseline was 51.0 ± 16.1 letters and the mean CFT was $339.1 \pm 125.5 \mu\text{m}$. Baseline FA was available in all eyes and the lesions were categorized as occult (70%), classic (16.9%), retinal angiomatous proliferation (8.3%), and minimally classic (4.8%). Baseline OCT revealed the presence of SRF and IRF combined in 27 eyes, SRF alone in 21 eyes, and IRF alone in 10 eyes. Two eyes showed macular hemorrhage with no fluid at the baseline visit, CFP revealed MA in 13 (12 extrafoveal and 1 subfoveal), and macular fibrosis in five eyes at the first visit.

Thirty-one eyes switched to aflibercept after a mean of 60.6 ± 14.1 months, whereas 29 eyes remained on ranibizumab for the full 10 years. There was no switch back to ranibizumab and no other intravitreal agent was given during the follow-up.

Visual acuity outcome

Fig.1 shows the VA outcome of all eyes and those that switched or continued on monotherapy. The mean VA improved by 5.2 letters (95% confidence interval [CI] 2.5–7.9) at 4 months and by 5.9 letters at 12 months (95% CI, 3–8.7). This initial gain was maintained till the 36th month of follow-up. From 36 months onwards, the VA declined and the final mean VA at 120 months was 45.3 ± 22.0 letters (mean change -5.6 letters, 95% CI, $-11.1, -0.25, P = 0.04$).

Eyes receiving ranibizumab monotherapy (mean baseline VA 48.2 ± 15.2) improved by 6.5 letters at 4 months (95% CI, 2.8–

Table 1: Visual and morphological outcomes in ranibizumab monotherapy and aflibercept switch group

Mean	Monotherapy eyes	Switched eyes	P
Age (SD)	77.5 (6.5)	74.5 (7.3)	0.10
Baseline VA (SD)	48.2 (15.2)	53.7 (16.5)	0.15
Final VA (SD)	42.7 (23.2)	47.3 (21.1)	0.32
Baseline CFT (SD)	320.1 (108.6)	357 (138.9)	0.39
Final CFT (SD)	340.8 (153)	278.1 (85.9)	0.24
SRF baseline/final (%)	79.3/24.1	80.6/25.8	
IRF baseline/final (%)	65.5/27.6	54.8/35.5	
Number of injections (SD)	24.4 (13.2)	39.7 (10)	<0.0001
VA ≥ 70 letters, baseline/final (%)	3/17	19/22	
VA ≤ 35 letters, baseline/final (%)	27/44.8	16/25	
VA final change (0 ± 5) letters, number (%)	5 (17)	7 (22)	
≥ 10 letter gain, number (%)	8 (27)	6 (19)	
≥ 10 letter loss, number (%)	14 (48)	10 (32)	

VA: Visual acuity in ETDRS letters; CFT: Central foveal thickness in microns; SRF: Subretinal fluid; IRF: Intraretinal fluid; SD: Standard deviation

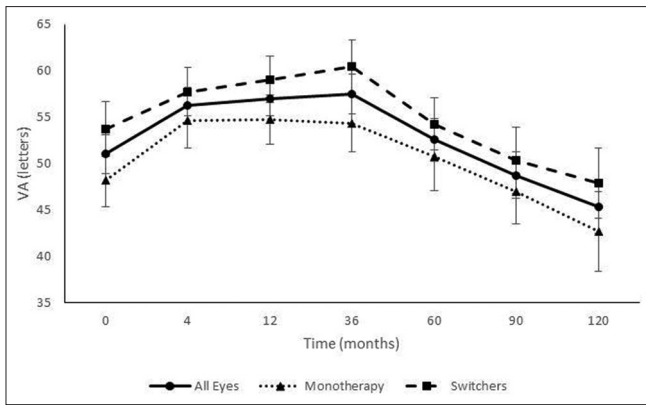


Figure 1: Graph showing visual acuity outcome in all 60 eyes completing 10 years of follow-up (error bars indicate ± 1 SE)

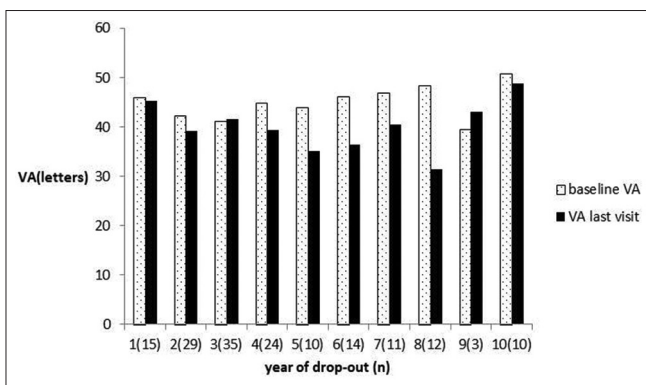


Figure 2: Bar graph showing mean baseline visual acuity (VA) and final VA at last visit in eyes of patients who dropped-out at various time-interval, year (numbers)

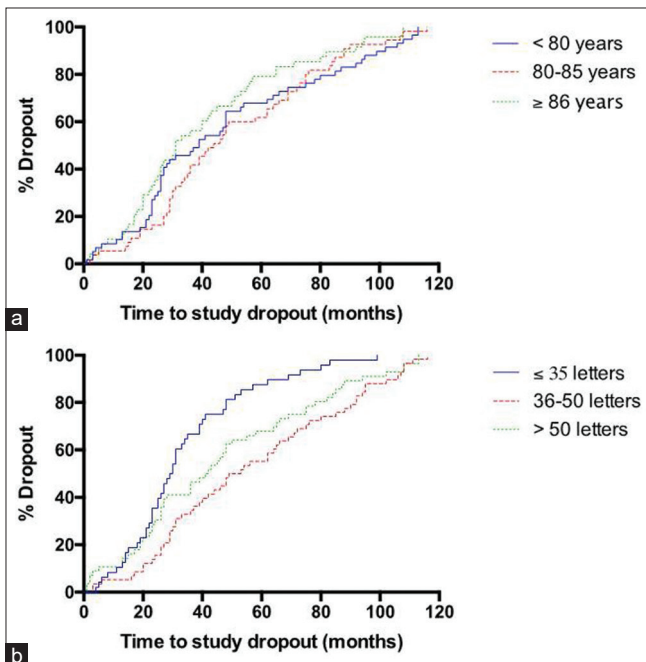


Figure 3: Kaplan–Meier plot for time to dropout according to age (a) and baseline visual acuity (b)

10.1) and by 2.6 letters at 60 months (95% CI, $-2, 8.1$). Between 60 and 120 months, the VA declined by 8.3 letters and the final VA was 42.7 ± 23.2 letters ($P = 0.18$). Switched eyes (mean baseline VA 53.7 ± 16.5 letters) showed an initial visual gain of four letters at 4 months (95% CI, $1-7.7$) and 0.5 letters at 60 months (95% CI, $-4.4, 5.5$). At switch, the VA had already declined by 1.6 letters from baseline and a further decline of 4.1 letters was seen by the final visit (final VA $47.3 \pm 21.2, P = 0.06$).

Final VA ≥ 70 letters was seen in 20% of eyes and 35% had VA ≤ 35 letters. VA gain of ≥ 10 letters was seen in 14 eyes (23.3%) and VA loss of ≥ 10 letters was seen in 24 eyes (40%) [Table 1]. Visual loss, stratified according to baseline VA, showed VA decline in all eyes except in those with baseline VA ≤ 35 letters.

Injections details

The median (first quartile–third quartile) number of injections in the first year was 6 (4–7) for all eyes) and the cumulative median was 25 (19–29) for ranibizumab monotherapy eyes and 39.5 (34.2–48) for the switched eyes. Monotherapy eyes received a median of 1 (0–4) injection in the 10th year as compared to 3 (1–5.5) in the switched eyes. Seven eyes needed more than 50 injections. The mean visual decline, at 10 years, in eyes that received ≥ 40 injections (baseline VA 51.7 ± 16.1 letters, VA decline, 3.2 ± 15.8 letters, baseline CFT $416.3 \pm 72.7\mu$) was significantly less than the eyes that received < 40 injections (baseline VA 50.7 ± 17 letters, VA decline, 6.8 ± 24.6 letters, baseline CFT $301.4 \pm 73.6 \mu; P = 0.01$).

Timing of switch

A subgroup analysis of eyes switching to aflibercept at 50 months and at 70 months showed that the 50-months switchers had declined 0.7 letters prior to switch and lost another 0.9 letters by the last follow-up. In comparison, 70-months switchers lost 2.9 letters prior to switch, and another 4.4 letters by the last follow-up ($P = 0.29$).

Anatomical outcome

The mean baseline CFT was $339.2 \pm 126 \mu\text{m}$ and the final CFT was $308.4 \pm 126 \mu\text{m}$ ($P = 0.18$). Eyes that switched at 50 months had baseline CFT of $368.7 \pm 147.8 \mu\text{m}$ (CFT at switch $358.5 \pm 126.2 \mu\text{m}$, final CFT $268.8 \pm 75 \mu\text{m}, P = 0.01$) and the eyes switching at 70 months had a baseline CFT of $340.7 \pm 139.8 \mu\text{m}$ (CFT at switch $399.6 \pm 148 \mu\text{m}$, final CFT $291 \pm 90.3 \mu\text{m}, P = 0.06$). Nearly 60% of the eyes had IRF at the last follow-up [Table 1]. The presence of combined SRF and IRF at baseline (27 eyes) was associated with significantly higher visual loss (VA decline -11 ± 23 letters) than in eyes that had SRF alone (21 eyes, VA decline 5.3 ± 22 letters) or IRF alone (10 eyes, VA decline 1.6 ± 22.5 letters).

Of the eyes losing ≥ 10 letters, baseline MA was seen in six eyes and subfoveal fibrosis in five eyes. Though CFP was not available at the final visit, evaluation of OCT scans at the last follow-up, among completers, revealed the presence of MA in 21 eyes and macular fibrosis in 22 eyes. A higher visual decline (12.5 ± 20.8 letters) was seen in eyes that developed macular fibrosis than in eyes those that developed MA (mean visual decline 7.3 ± 19.4 letters). There was no difference in the rate of development in eyes that remained on ranibizumab monotherapy or those that switched. Absence of MA or fibrosis (17 eyes) at the last follow-up was associated with visual improvement (mean gain 5 ± 21.4 letters).

Monitoring visits and clinic delays

The number of monitoring visits reduced significantly after the third year of follow-up. The mean visits were 10 in the

Table 2: Ten-year treatment outcome comparison from various studies

	Wolff <i>et al.</i> ^[11]	Gillies <i>et al.</i> ^[10]		Chandra <i>et al.</i> ^[12]	Our study
		ANZ	Swiss		
Number of eyes	116 (including 55 pre-treated eyes)	132	37	149	60
Median injections year 1	5	7	6	NA	6
Total injections	27.5 (median)	53 (median)	42 (median)	52.2 (mean)	32 (median)
Baseline VA in Letters (SD)	57.5 (median)	60.7 (17) (mean)	61.6 (14) (mean)	59.5 (13.1) (mean)	51.0 (16.1) (mean)
Final VA in Letters (SD)	39.9 (median)	60.1 (20.7) (mean)	46.8 (28.8) (mean)	57.4 (17.8) (mean)	45.3 (22) (mean)
≥ 10 Letters gain (%)	9.5	34	19	24.8	23.3
≥ 10 Letters loss (%)	63.8	27	49	27.5	40
Final VA ≥ 70 Letters (%)	16.4	42	35	33.5	15.7
Final VA ≤ 35 Letters (%)	47.4	14	38	14	35
Overall drop-out rate (including deceased) (%)	NA	61.4	86.9	75.6	73.1
Drop-out rate due to treatment failure (%)	NA	20.4	19.7	NA	21.5

first two years, 8 in the third year and 4 between the fourth and sixth years. The number of visits increased to 7 in the last 3 years as switched eyes had more frequent monitoring with treat and extend becoming the preferred monitoring regimen. An increase in waiting time for a monitoring visit correlated with the VA decline noted after 36 months.

Noncompleters (223 eyes)

Of the 223 eyes, 163 eyes (73%) failed to complete 10 years of follow-up. Fig. 2 shows the number of patients dropping out of treatment, and their baseline and final VA. Patients that dropped out were older than completers (80.9 ± 8.2 years vs. 75.9 ± 7.1 years, $P < 0.0001$) and had lower mean baseline vision (44.5 ± 15.2 letters vs. 51.0 ± 16.1 letters, $P = 0.007$). In addition, in noncompleters, VA at the last visit was worse than their baseline vision and nearly one-third of these eyes lost ≥ 15 letters of vision. The reasons documented for discontinuation were as follows: death (47.2%), permanent foveal damage (21.5%), discharged as clinically stable (12.9%), and patient refusal to attend or care being transferred to a different hospital (8.0%). No reason was recorded in 10.4% of eyes. A survival analysis curve showed that there was significantly increased likelihood of discontinuing treatment in eyes with baseline VA of ≤ 35 letters compared to eyes with better vision ($P = 0.0002$). However, age was not a significant determinant of time to dropout [Fig. 3a and b].

Discussion

This study provides an insight into the long-term results of patients receiving anti-VEGF for nAMD, providing real-world data for this complex disease. The results show visual loss commencing after 3 years of treatment initiation with an overall decline of 5.6 letters over 10 years. To the best of our knowledge, this is the first study reporting the impact of switching anti-VEGF agents in eyes initiated on intravitreal ranibizumab 10 years ago and showed that there was no additional benefit obtained by switching treatment to aflibercept.

Patients recruited in various clinical trials have shown significant visual gain in the short-term, when they are being closely monitored and receive up to 24 injections in the first 2 years. However, on exit from trials, with less intense monitoring and treatment, vision declines.^[7,8,13]

Other 10-year studies have reported suboptimal visual outcomes, as seen here. A study of French patients^[11] showed a mean loss of 18 letters and a subgroup of Swiss subjects,^[10] managed on PRN basis, reported an overall loss of 3 lines in vision [Table 2]. In our study, the initial visual gain was maintained until the third year; however, with the expansion of our service, the monitoring interval increased, thereby leading to final visual loss. Nonclinical factors for less frequent treatment have been reported previously from various countries.^[14-16]

The increase in number of monitoring visits after the seventh year was due to switching of treatment and use of treat and extend (TAE) regimen. The visual decline in our cohort is not as significant as that in the other two reported studies,^[10,11] as half of the eyes switched to aflibercept and had more frequent injections and monitoring. It is also plausible that only eyes with stable or improved vision remained in the follow-up.

The mean baseline VA in our cohort was much lower than in other 10-year studies, with 21% of eyes having baseline VA $< 20/200$. We believe that most of our eyes had permanent structural damage with no scope for further improvement. Also, eyes with better baseline VA were switched to preserve the vision, thereby receiving more intensive treatment. Though switching didn't have any effect on final VA, it helped to reduce the proportion of eyes with final VA $< 20/200$ (9% in switched vs. 17.8% in the monotherapy eyes).

A previous study^[17] has shown a direct association between the number of injections and final VA, with a higher number of injections resulting in better vision. The cumulative number of injections over the 10-year period in our cohort was less than in other studies [Table 2]. Better visual outcomes in the ANZ cohort of a recent study^[10] were due to higher rate of injection during the maintenance phase (injections at 80% of the visits using TAE regimen) compared to the Swiss cohort receiving injection at 60% of visits (treated on PRN basis). Fewer injections in our study could be the result of only stable eyes, requiring lesser injections, continuing in the follow-up.

Eyes that needed frequent injections were switched to intravitreal aflibercept and this provided an opportunity to compare these eyes with ranibizumab monotherapy eyes. The switched eyes possibly had permanent morphological damage and more aggressive disease at switch, thus limiting

the possibility of any further visual improvement. Eyes switching at 50 months were -0.9 letters from baseline, whereas the eyes switching at 70 months had already lost 2.9 letters by the time of switch. None of the eyes were switched before 50 months, making it difficult to conclude whether an earlier switch would have altered the final outcome. Published data on switching early or late in the course of follow-up has shown that VA gained after the switch is not sustained.^[18] There was no difference in the rate of MA and macular fibrosis in eyes that continued to receive ranibizumab through the whole of 10 years or those that switched to aflibercept. The number of eyes developing MA (35%) and macular fibrosis (36%) is comparable to previously published study.^[12]

Of the 163 eyes that did not complete the 10 years, 9% dropped out within the first year of follow-up. With the baseline age of noncompleters being significantly higher than completers, patient death was the most common cause of discontinuation in the first and last 3 years. Presence of co-morbidities in this group of older patients may have been another reason for noncompletion.^[19] Lower baseline VA in the noncompleters, which continued to decline, suggests that only eyes with better vision remained under active care (eyes with baseline VA ≥ 70 letters were more likely to complete 10 years).

The results of the study should be taken in the context of the time, when PRN monitoring was the preferred regimen and these were the first set of eyes initiated on anti-VEGF therapy. The final visual loss of 5.6 letters is in agreement with other publications; however, it is of limited value in advising patients who are currently being treated with TAE regimen.

This study has several limitations inherent to any retrospective review, including that only eyes with better outcomes continued the study, VA was recorded in a clinical setting, treatment decisions were based on clinicians' experience (and not protocol-driven) and eyes with better VA were switched. In addition, it was not possible to discern the macular morphology due to the absence of CFP at the final visit.

Conclusion

In conclusion, this study suggests that 10 years after treatment initiation with anti-VEGF, less than one-third of patients remain in follow-up and treatment helps to stabilize or improve vision in 40% of these eyes. Switching from ranibizumab to aflibercept doesn't alter the final visual outcome and lower baseline VA is an important factor in patients discontinuing treatment. Real-world evidence from various countries reflects the various practices adopted and is helpful in providing better understanding in managing this complex condition. The information provided here will aid clinicians in designing treatment regimens to improve visual outcomes.

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Conflicts of interest

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