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Early Response to Ranibizumab Is Predictive of Treatment Demand after a Therapeutic Switch to Aflibercept

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Objective: In many case series, anatomical but not functional improvements have been documented after a switch in therapy from ranibizumab to aflibercept. We wished to compare the outcomes of eyes that had undergone a switch in therapy from ranibizumab to aflibercept because of a high treatment demand or for other reasons.

Design: Retrospective comparative case series.

Participants: Patients (≥50 years of age) undergoing treatment for neovascular age-related macular degeneration in a routine clinical setting.

Methods: Eyes monitored for ≥10 months after switch in intravitreal therapy from ranibizumab to aflibercept were allocated to one of 2 groups: eyes with high treatment demand because of insufficient response to ranibizumab (persisting intraretinal fluid or injection frequency of ≤6 weeks [group 1, $n = 34$]) and eyes in which the switch had been instigated for other reasons ($n = 94$).

Main Outcome Measures: Annual number of injections before and after the switch in therapy.

Results: Patients were of comparable ages at the time of diagnosis. The follow-up time before switching, but not thereafter, was shorter in group 1 than in group 2 ($P = 0.001$). Visual acuity and central retinal thickness did not change appreciably during the follow-up period. The annual number of injections was higher under ranibizumab than under aflibercept in group 1 (9.1±2.2 injections vs. 5.7±2.2 injections; $P = 0.0005$) but not in group 2 (4.9±2.0 injections vs. 4.6±1.8 injections; $P = 0.24$). After the switch from ranibizumab to aflibercept, the eyes in group 1 required more injections than did those in group 2 ($P = 0.007$). The time that elapsed to a reinjection differed between the 2 groups under treatment with ranibizumab ($P = 0.0005$) as well as under that with aflibercept ($P = 0.007$).

Conclusion: After the switch in therapy from ranibizumab to aflibercept, visual acuity remained stable for >12 months in both groups. Nevertheless, eyes that required frequent reinjections under ranibizumab also had a higher treatment demand under aflibercept. *Ophthalmology Retina 2017;1:210-216 © 2016 by the American Academy of Ophthalmology*

In large randomized clinical trials involving patients with wet age-related macular degeneration (AMD), treatment failures during the first year have been reported in 10% to 15% of cases. Moreover, although an inactive state with good results and no need for continuous injections is achieved in 20% of patients, 20% to 30% respond poorly to the therapy. Irrespective of the response, most of the patients require continuous active treatment. Although a long-term decline in visual acuity may thus reflect the natural progression of the atrophic disease, an insufficient response to treatment or undertreatment cannot be ruled out. Hence, there is a potential for further improvement.[1] Even after monthly injections, 9% to 10% of eyes lose 3 or more lines of vision, due, in most cases, to submacular fibrosis; in 38%, gains of 3 or more lines of vision are achieved.[2] Predictors of a poor outcome include advanced age, a delay in the onset of treatment, the presence of a classical choroidal neovascularization, a high initial visual acuity, and a large lesion but not the formation of a new scar or atrophy.[2,3]

Two anti−vascular endothelial growth factor (anti-VEGF) therapies are now approved for the treatment of wet AMD: ranibizumab (since 2007) and aflibercept (since 2011 to 2012).[4,5] Hence, in the event of irresponsiveness to one, an alternative is available. Data on long-term outcomes of ≤72 months are forthcoming for ranibizumab but not for aflibercept. Hence, we are currently not in a position to compare the responsiveness of eyes to the 2 medications. Several reports that have been published during the past few years document good anatomical outcomes in the absence of a functional improvement after a switch from ranibizumab to aflibercept due to an insufficient response to the former.[6−11] The common limitations of the published studies are the heterogeneity of the reasons for the therapeutic switch in the pooled retrospective series and the usually short follow-up time of 6 to 12 months thereafter. Although strategies have been developed to improve the outcomes in eyes that respond unsatisfactorily to anti-VEGF medications,[12] the pathophysiological basis for the resistance to these agents is

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not understood. We wished to gain an insight into the factors that underlie an insufficient response to ranibizumab, which includes the persistence of fluid and the need for frequent reinjections, as well as those that contribute to the possible absence of a net functional improvement after switching to aflibercept. With these aims in view, we reassessed the records of patients with wet AMD who had undergone therapy with aflibercept between December 2012 and June 2014 and had been monitored for a minimum of 12 months after the switch from ranibizumab to this medication had been effected.

Methods

In this retrospective study, patients with wet AMD who had been treated in the macula clinic of the Berner Augenklinik am Lindenhofspital were included if they fulfilled the following criteria: (i) a need for intravitreal therapy due to choroidal neovascularization (CNV) activity, as indicated by the manifestation of intra- and subretinal fluid in OCT results; (ii) treatment with ≥3 intravitreal injections of ranibizumab and thereafter as needed (pro re nata [PRN]) according to spectral-domain OCT–based anatomic findings (with the aim of stabilizing the lesion at each recurrence prior to the switch to aflibercept [≥3 intravitreal injections]); and (iii) a follow-up time of ≥10 months after the onset of aflibercept therapy. Eyes that satisfied the inclusion criteria were subdivided into 2 groups: those in which the switch to aflibercept had been effected because of a high treatment demand or because of an insufficient response to ranibizumab (group 1) and those in which the switch had been made for any other reason (group 2). In group 1 eyes, lesion stability (absence of intraretinal fluid, no or a constant level of subretinal fluid, and no progression of the pigmented epithelial detachment over 3 consecutive injection intervals) had not been achieved prior to the switch in therapy. In these eyes, treatment at mean intervals of ≤6 weeks for the last 3 injections prior to the switch were necessary to maintain anatomical and functional stability (±5 letters). In the eyes of group 2, stability had been achieved prior to the switch in therapy. In these eyes, the therapeutic interval was extended to ≥8 weeks for the last 3 injections prior to the switch. In 19 eyes, treatment with a single injection of ranibizumab had been reinitiated because of a recurrence in lesion activity within 6 weeks before aflibercept had been approved for medical use in Switzerland. During the breaks in therapy, the eyes were monitored every 4 to 8 weeks. In group 2, the reasons for the switch in therapy included the hope of reducing the number of intravitreal injections and the hope of improving the persistent though stable pigmented epithelial detachment, as well as an express wish of the patient.

The study was approved by the local regulatory authorities (Institutional Ethics Committee, University of Bern, under the reference KEK 099/15), and was conducted with the informed consent of the patients to use their coded data.

Exclusion Criteria

Patients with underlying diseases that could interfere with the clinical outcome, namely, those with an active vascular affection (i.e., any stage of active diabetic retinopathy) or an inflammatory ocular disorder (uveitis), were excluded from the study; so, too, were those in whom the CNV was of another etiology. Individuals who had not attended the scheduled consultations or who had undergone pretreatment with intravitreal steroids within 6 months of the switch in therapy were likewise excluded from the study.

Definitions

A *high treatment demand* for anti-VEGF therapy at the time of the switch was defined either by the presence of persisting intraretinal fluid in the face of adequate (monthly) treatment, which was indicative of an insufficient control of the exudative lesion activity; or by the need—to maintain stability—for frequent reinjections at intervals that could not be extended beyond 6 weeks for the last 3 injections prior to the switch.

An *unsatisfactory response* to an anti-VEGF agent was defined as the absence of an improvement in vision or in OCT-assessed anatomical parameters after ≥3 monthly injections.[13]

Data Acquisition

Data appertaining to the patients were retrieved from their electronic records and from the OCT-database entries that were linked to the corresponding visits. From these data, we extracted the Snellen best-corrected visual acuities, which were converted to the corresponding Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores; the intraocular pressures; and the functionally relevant anatomical findings.

Both eyes of a patient were included if bilateral treatment had been effected. The measurement of central foveal thickness, as well as the investigator's classification of the macula as being either dry (absence of any fluid) or not dry (any fluid in the central zone with a diameter of 1 millimeter) were based on the use of a horizontal line algorithm with a length of 6 millimeters (Spectralis, Heidelberg Instruments, Heidelberg, Germany). All central foveal thickness measurements were performed by a trained independent reader (H.M.R.), who was blinded to the group affiliations. They were made on a micrometer scale from the inner retinal surface to Bruch's membrane, where this was visible, or estimated where it was obscured by the hyperreflective subretinal fibrovascular complex.

The data were collected from the time of the diagnosis until that of the final checkup before the data lock on August 1, 2015 (6 measurement points). They were recorded at the time of the diagnosis, before the onset of treatment with ranibizumab (T0), after 3 subsequent and consecutive intravitreal injections of ranibizumab (T1), prior to the third injection before the switch to aflibercept was effected (T2), at the onset of aflibercept therapy (T3), 4 to 6 weeks after the third intravitreal injection of aflibercept (T4), and prior to the final injection of aflibercept before the data lock (T5). Missing data ranged from 0% (T0, T3, T5) to 11% (T2, T4) in both groups. Ranibizumab was administered according to a PRN protocol (monthly, until dryness was achieved, and then with a break in therapy until either the reappearance of any fluid, an increase in the level of persisting subretinal fluid, or a progression of the pigmented epithelial detachment). In cases of a recurrence, the re-treatment intensity was adjusted according to the disease activity, which was usually less than that at the onset of the therapy. After the switch in therapy, the follow-up examinations included retinal biomicroscopy and OCT assessments every 4 to 8 weeks according to OCT-based disease-activity estimates. After the stabilization of the lesion activity (no intraretinal fluid, no or constant levels of subretinal fluid, and no progression of pigmented epithelial detachment), the examination and the treatment intervals were extended to ≤12 weeks.

Statistical Evaluation of the Data

On the basis of the assumptions that the 2 groups were independent and behaved differently in their temporal responses to therapy, and that the data were not normally distributed, a series of nonparametric tests was conducted. To estimate the significance of the

ETDRS change, the Wilcoxon signed rank test was performed for each group separately. Because multiple comparisons increase the risk of introducing a type I error, the significance level was adjusted using a Bonferroni correction. To ascertain whether the change in ETDRS, the yearly number of intravitreal injections, and the time to re-treatment differed between the 2 groups, the Mann−Whitney *U* test was applied.

Qualitative data appertaining to the number of patients with dry AMD in the 2 groups were analyzed by implementing separate Pearson chi-square tests for each time point. All statistical analyses were performed using the SPSS software package version 23 (SPSS, Chicago, IL), with the level of significance being set at $P < 0.05$. Unless otherwise stated, the data are represented as mean values with the standard deviation (SD).

Results

Among the 255 eyes (198 patients) that had undergone therapy with aflibercept since its introduction to the market in December 2012, a total of 128 satisfied the criteria for inclusion in the study: 34 in group 1 (insufficient response to ranibizumab; 26.6% of all patients) and 94 in group 2 (switch from ranibizumab to aflibercept effected at the time of a recurrence and when the treatment was reinitiated after a stable phase; 73.4% of patients). Of the remaining 127 eyes, 37 were treatment naïve and 90 failed to satisfy the inclusion criteria.

At the time of diagnosis, the patients in the 2 groups were of comparable age (group 1: 77.3±6.6 years [64.3−94.6 years {range}]; group 2: 78.3±7.2 years [60.0−94.9 years]; $P > 0.05$). The total follow-up time was shorter in group 1 (43.0±17.6 months [17.3−97.0 months]) than in group 2 (54.1±17.5 months [19−93.5 months]; $P = 0.001$). This finding reflects the shorter monitoring period under ranibizumab therapy in the former group than in the latter (17.3±14.5 months [3−67 months] vs. 27.9±17.1 months [5−73.5 months]; $P = 0.0005$), because after the switch to aflibercept, the follow-up times in the 2 categories were similar (group 1: 26.1±3.9 months [18−31 months]; group 2: 25.8±5.0 months [11−46 months]; $P = 0.59$). At the time of the diagnosis and prior to the onset of treatment with ranibizumab (T0), the percentage of the eyes in which no intra- or subretinal fluid was evident, either with or without an associated detachment of the pigmented epithelium involving the fovea, was 0% in group 1 and 2.1% in group 2 ($P > 0.05$; chi-square test). This difference between the 2 groups was sustained during the subsequent course of therapy [T1−T5; $P > 0.05$; Fig 1]. Following the onset of treatment with 3 loading injections of ranibizumab between T0 and T1, the visual acuity of the eyes in both groups improved. But thereafter and until the switch in therapy to aflibercept (between T1 and T3), this parameter first declined and then stabilized (Fig 2; Table 1).

In group 1, the decrease of 5.4 letters that occurred after the ranibizumab-loading phase and prior to the switch to aflibercept (71.0±9.6 letters vs. 65.6±14.8 letters; $P = 0.002$) is readily accounted for by the poor response to treatment. In group 2, the corresponding decrease of 5.8 letters (69.3±13.2 letters vs. 63.5±15.6 letters; $P < 0.0005$) reflects the circumstance that in 74 eyes (78.7%), the situation had stabilized and the therapy had been interrupted >2 months prior to the switch to aflibercept. On the basis of anatomical criteria, 50 eyes (53.2%) in group 2 (compared with 0% in group 1) had attained a state of stability that was sustained for ≥3 months without treatment; in 16 (17.0%), the

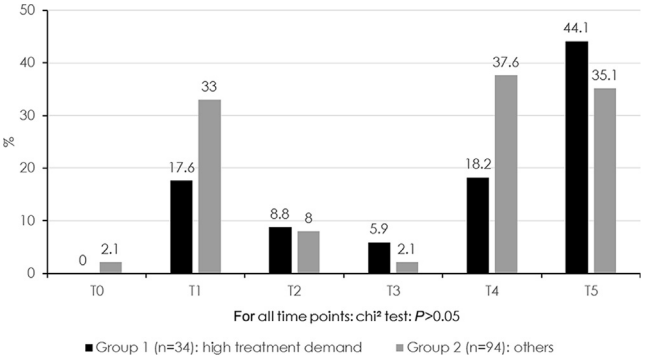

Figure 1. Percentage of the eyes in which no foveal fluid was revealed in OCT results. Mean values are represented. No significant difference between groups 1 and 2 was observed at any of the junctures (chi-square test: $P > 0.05$).

period of stability extended beyond 6 months before the resurgence of activity. The visual acuity in these eyes declined further, by 4.9 letters, after the first 3 intravitreal injections of aflibercept until the end of the observation period (from 66.2±15.7 letters to 61.3±18.6 letters; $P < 0.0005$).

The temporal decrease in central retinal thickness was similar in the 2 groups (Figure 3). The number of injections that were administered was based on OCT-guided re-treatment criteria (manifestation of new or persisting intra- or subretinal fluid). These data and the average time that elapsed to a reinjection are summarized in Tables 2 and 3. On the basis of the total number of injections that were administered with time, the annual number for each of the 2 medications differed in group 1 (9.1±2.3 injections [1−13 injections] under ranibizumab vs. 5.5±2.2 injections [1.5−10.2 injections] under aflibercept; z =−4.5, $P = 0.005$) but not in group 2. Moreover, the total number of injections that were administered was higher for both medications in group 1 than in group 2 (Table 2). Finally, the time that elapsed to a reinjection was shorter in group 1 than in group 2 ($P < 0.0005$) under both ranibizumab ($P = 0.0005$) and aflibercept ($P = 0.007$). The time that elapsed to a reinjection differed between the 2 medications in group 1 but not in group 2 (Table 3).

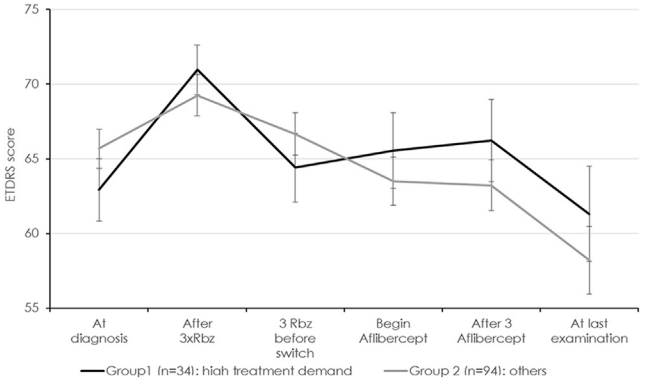

Figure 2. Temporal changes in best-corrected visual acuity. Mean values are represented with the standard deviations. No significant difference between groups 1 and 2 was observed at any of the junctures ($P > 0.05$). Rbz = Ranibizumab.

Table 1. Temporal Changes in Visual Acuity Under Therapy (ETDRS Letter Scores)

	T0–T1		T1–T3		T3–T4		T4–T5	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Group 1	+8.0 ($P = 0.005$)	9.5	−5.4 ($P = 0.002$)	11.4	+0.5 ($P = 0.33$)	7.0	−4.9 ($P = 0.046$)	11.4
Group 2	+3.7 ($P = 0.005$)	10	−5.8 ($P = 0.005$)	14.1	−0.3 ($P = 0.38$)	11.2	−5.0 ($P = 0.002$)	13.3
Mann–Whitney *U* test, group 1 vs. group 2	$P = 0.09$		$P = 0.81$		$P = 0.74$		$P = 0.90$	

SD = standard deviation.

After annualizing the number of injections for the 12 months prior to and after the switch in therapy, differences between the 2 groups were observed at each juncture (before the switch: 9.9±1.7 injections [6.5–13.1 injections] in group 1 vs. 4.6±2.2 injections [0–8.7 injections] in group 2; $P < 0.00001$; after the switch: 6.4±1.9 injections [6.5–12.7 injections] in group 1 vs. 4.7±1.7 injections [1–9 injections] in group 2; $P < 0.00001$). In group 1, the annualized number of injections of ranibizumab that were administered prior to the switch to aflibercept was higher (9.9±1.7 injections [1–13 injections]) than that of injections of the latter medication that were delivered thereafter (4.7±1.7 injections [1–9 injections]; $P < 0.00001$). In group 2, the corresponding annual numbers of injections of ranibizumab (4.6±2.2 injections [0–8.7 injections]) and aflibercept (4.7±1.7 injections [1–9 injections]) did not differ ($P = 0.6$). Interestingly, the treatment-naïve eyes in group 1 received more injections of ranibizumab than did the pretreated ones (10.7±1.5 injections [8.5–13.1 injections] vs. 9.3±1.6 injections [6.5–12.7 injections]; $P = 0.012$), whereas the number of injections of aflibercept that were administered after the switch in therapy did not differ ($P = 0.62$). Similar findings were observed in group 2 (before the switch: 6.4±1.5 injections of ranibizumab in treatment-naïve eyes vs. 4.0±2.0; $P < 0.00001$; after the switch: 5.4±1.8 injections of aflibercept in treatment-naïve eyes vs. 4.5±1.6 in pretreated ones; $P = 0.043$). These observations partially reflect the initial loading of treatment-naïve eyes with 3 injections of ranibizumab, which was not the case in instances of recurrence.

Discussion

Eyes that had undergone a switch in intravitreal therapy from ranibizumab to aflibercept because of a high treatment demand under the former regimen, as determined by the time that elapsed to a reinjection before the switch was effected (group 1), differed basically in their therapeutic requirements from those in which the switch was instigated for other reasons (group 2). This circumstance is evidenced by 3 observations: (i) the shorter period of treatment prior to the switch to aflibercept, (ii) the shorter time that elapsed to a reinjection, and (iii) the higher annual number of injections that were required under treatment with both ranibizumab and aflibercept. The study design and our outcomes are well in line with a study published by Yonekawa and coworkers.[11] In contrast, the decline in visual acuity that was observed over a mean follow-up time of 26 months under aflibercept in group 2 eyes has to be seen as an independent finding that is probably associated with the increase in the size of the fibrovascular lesion that occurred before the reinitiation of treatment with aflibercept. In accordance with this tenet, the proportion of eyes in which no intra- or subretinal fluid was observed in OCT results increased from 18% to 44% in group 1 but mildly decreased from 38% to 35% in group 2. Whether this is representative of the progressive nature of this disease (persistent disease activity has been demonstrated in 55% using OCT and in 25% angiographically despite monthly ranibizumab injections in the CATT study[14]) or whether this is indicative of undertreatment remains open to speculation. Surely, the retrospective nature and the lack of a prespecified end point of the study may also partially account for these findings. Because virtually all of the eyes were still in need of treatment at the end of the observation period (T5), this juncture does not serve as a clinically valid reference point.[15] On the other hand, the circumstance that the proportion of the eyes in which no intraretinal fluid was observed was higher under aflibercept than under ranibizumab therapy and the finding that the CRT decreased further after the switch from ranibizumab to aflibercept suggest that the latter medication may be the more efficacious of the 2 in effecting fluid reversion, which accords with existing data.[6,16] Although our assessment is retrospective in nature, several factors, including the higher number of injections that were required after the switch in therapy, support the assumption that the maculopathy in group 1 eyes was less responsive to treatment.[17]

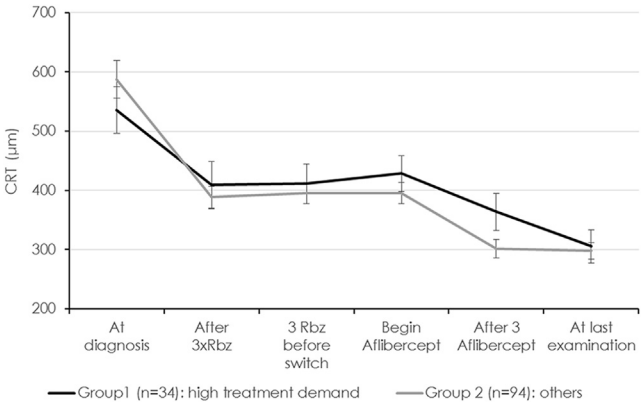

Figure 3. Temporal changes in central retinal thickness. Mean values are represented with the standard deviations. No significant difference between groups 1 and 2 was observed at any of the time junctures ($P > 0.05$). Rzb=ranibizumab.

Table 2. Annual Number of Intravitreal Injections

Injections Per Year (n)	Total		Ranibizumab		Aflibercept		Wilcoxon Signed-Rank Test
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Group 1	6.6	1.8	9.1	2.3	5.7	2.2	$z = -4.5$, $P = 0.0005$
Group 2	4.6	1.5	4.9	2.0	4.6	1.8	$z = -1.9$, $P = 0.24$
Mann–Whitney *U* test, group 1 vs. group 22	$U = 627.5$, $z = -5.2$, $P = 0.0005$		$U = 288$, $z = -7.1$, $P = 0.0005$		$U = 1097$, $z = -2.7$, $P = 0.007$		

SD = standard deviation.

This view is supported by the findings of a recent study: a switch back from aflibercept to ranibizumab after a poor response to the former met with success.[18] Moreover, in a small prospective study, no difference between the effects of ranibizumab and aflibercept was observed in eyes with high treatment demands.[19] Data appertaining to temporal changes in the size of the fibrovascular lesion would be of help in interpreting our data. But, unfortunately, this information is not available.

We attempted to normalize the number of injections that were administered during the year prior to and after the switch in therapy. However, in doing so, we encountered several obstacles that stemmed from the retrospective nature of the analysis: the annual number of injections that were administered in the patients who had primarily responded well to treatment, and in whom the therapy had been interrupted for several months prior to a recurrence of CNV activity, was appreciably lower than was the real demand after treatment reinitiation due to the reactivation of their lesion. Correspondingly, the annualized number of injections that were administered in the eyes with recurrent activity and in treatment-naïve ones differed significantly in both groups. Moreover, the need for an intensified treatment or a new loading phase after switching in insufficiently responsive eyes is not comparable to the needs of a stable eye switched for other reasons. By calculating the annual number of injections that were administered over the entire observation period, this unsharpness may be averaged in either direction. This problem could be circumvented by excluding the injections of the loading phase, whereby the patients with the poorest responses, namely those in whom the switch was effected directly after the loading phase, would be likewise excluded. An implicit unsharpness would remain in cases of a recurrence, in which no standard loading therapy is usually initiated. The comparison of averaged and normalized numbers of injections, nevertheless, did not change the readout of our data. According to a recent consensus paper, primary nonresponse to anti-VEGF agents should be proven not with the total treatment needs but with the absence of a functional or anatomic improvement at the end of the loading phase with 3 monthly injections.[13] As outlined above, we did not tailor the groups according to the primary response; instead, we looked at secondary responsiveness. On the basis of our data, we still believe that an averaging of the last 3 injection intervals prior to the switch in therapy is more representative of the treatment demand at the time of the switch than is the normalized annual number of injections. At the end of the day, the clinical decision to switch is based on the response to treatment and the treatment demand during the period prior to the switch.

Because significant differences were observed between treatment-naïve eyes and those needing re-treatment after a stable phase of inactivity, which did not depend on the manner in which the annual number of injections was calculated, a differentiation between newly diagnosed and recurrent cases may be of more relevance in understanding the data appertaining to the treatment demand before and after the switch.

Our study design did not permit a direct assessment of the response to treatment with time and the possibility of tachyphylaxis.[15] Nevertheless, indirect arguments support the contention that the primary treatment demand is higher in some eyes. To distinguish primary from secondary unresponsiveness on the basis of the development of resistance to treatment or of tachyphylaxis, a poor reaction to anti-VEGF agents should not be argued on the grounds of the total treatment requirements.[13]

As previously reported by others, we observed no improvement in visual acuity after the switch in therapy.[16] This finding may in part be related to the fact that patients did not receive a new loading therapy with 3 monthly injections.[20] Likewise, in accordance with existing data, a temporal

Table 3. Time That Elapsed to a Re-injection

Time That Elapsed to a Re-injection (Wks)	Total		Ranibizumab		Aflibercept		Wilcoxon Signed-Rank Test
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Group 1	8.5	2.6	6.2	1.9	11.6	7.4	$z = 4.2$, $P = 0.0005$
Group 2	12.8	4.8	13.8	10.2	13.7	7.1	$z = 0.7$, $P = 0.48$
Mann–Whitney *U* test, group 1 vs. group 2	$U = 2568$, $z = 5.2$, $P = 0.0005$		$U = 2908$, $z = 7.1$, $P = 0.0005$		$U = 2099$, $z = 2.7$, $P = 0.007$		

SD = standard deviation.

decline in this parameter was observed after the switch to aflibercept, which, bearing in mind the number of eyes in which residual fluid was evident, may be partially accounted for by the adherence to the treatment and the number of injections that were administered in the real-life setting. A similar tendency was recently reported in 85 eyes that had been monitored for 12 months after a switch from ranibizumab to aflibercept had been effected because of either poor responsiveness or a reactivation of the disease.[21] Although the number of injections that were administered lay well below the number that is reported in the fixed treatment arm in the treatment-naïve eyes of the VIEW studies,[22] our data fit the outcome of the post hoc analysis of the PRN arm in the same investigations.[23] At this juncture, it may be worth mentioning that our patients had undergone, on average, >4 years of treatment at the end of the observation period.

In eyes that had undergone a switch in therapy after recurrence, but in which there was no evidence of an insufficient response to treatment, the annual number of injections that were required during the year before and that after the switch in therapy were reported as similar,[7,24] which accords with our data. In eyes that react insufficiently to ranibizumab, the treatment demand may be higher than in responsive ones. In our study, the treatment demand for aflibercept was lower than that for ranibizumab, which was reflected also in the time that elapsed to a reinjection. If these data were prospective and thus more robust, one might conclude that insufficient response after the loading phase should already trigger a switch of treatment,[20] affecting roughly every fourth patient (26.6% in our series). In a noncomparative series of cases involving only unresponsive eyes, the functional and the anatomical effects of switching were comparable to those that were observed in our study. However, the number of injections—3.5 during the first 12 months—was, according to our experience, surprisingly low.[24]

One mechanism that could contribute to the incomplete response according to our definition may be the duration of the treatment effect. Two weeks after the injection of 0.5 mg of ranibizumab into eyes that were deemed to be refractory to this treatment, a significant reduction in the level of fluid was observed in 75% of the cases. Most of the eyes were completely dry, and reversion of the fluid was observed until week 4 to week 6.[25]

In conclusion, whereas the treatment demand was similar for both anti-VEGF medications in the majority (73.4%) of well-responding eyes, eyes that responded insufficiently to the first 3 injections of ranibizumab had a higher treatment demand not only for this medication but also for aflibercept after the switch in therapy. Hence, we believe that lesion-specific characteristics may account for the early and the long-term response to anti-VEGF agents over a period of up to 2 years or more after the switch.

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Footnotes and Financial Disclosures

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Data collection: Russ, Pfister

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **anti-VEGF** = anti–vascular endothelial growth factor; **CNV** = choroidal neovascularization; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **PRN** = Pro re nata; **SD** = standard deviation.

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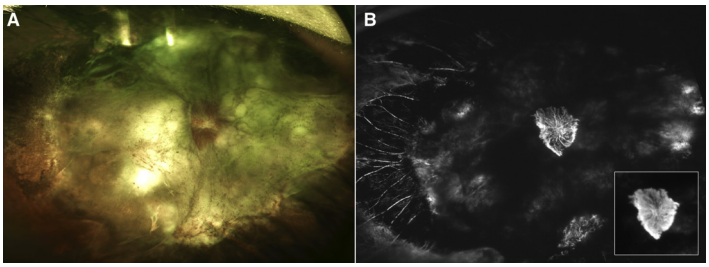
Pictures & Perspectives



Tractional Retinal Detachment Secondary to Central Retinal Artery Occlusion after Dermal Filler Injection

A 26-year-old woman presented for a second opinion. She lost vision 8 minutes after a facial dermal filler injection 3 months ago and subsequently underwent hyperbaric oxygen treatment without any visual improvement. On our examination, her vision was no light perception. Fundoscopy revealed florid neovascularization of the optic disc and an extensive tractional retinal detachment (Fig 1**A**; 200Tx, Optos, Marlborough, MA). Widefield fluorescein angiography (Fig 1**B**) showed leakage from the optic disc neovascularization (Figure 1**B, inset**) and nonperfusion of the retinal vasculature. The patient developed an unusual tractional retinal detachment secondary to a central retinal artery occlusion from a dermal filler injection.

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