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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 2016;■:1–7 © 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 optical coherence tomography (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