Switching to aflibercept versus continuing bevacizumab for treatment-resistant neovascular age-related macular degeneration: a one-year comparative observational study

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ABSTRACT.

Purpose: To compare outcomes of a treatment algorithm that allows for switching treatment-resistant neovascular age-related macular degeneration (nAMD) eyes to aflibercept with continuing bevacizumab.

Methods: Retrospective study of nAMD patients who initiated treatment in 2012 (aflibercept unavailable) and 2018 (aflibercept available). Eyes were included in the case of residual macular fluid after a minimum of 4 monthly bevacizumab injections. Only eyes in the 2018 group could then switch to aflibercept.

Results: The study included 40 eyes from 2012 and 88 eyes from 2018. Patient characteristics were similar across the groups at baseline and 4 months. In 2018, 59 eyes (67%) were switched to aflibercept after 4 months. Mean change in BCVA from 4 months to one year was +2.8 letters in 2018 versus −1.7 letters in 2012 (p = 0.043). Mean change in BCVA from baseline to one year was +9.4 letters in 2018 (p < 0.001) and +4.4 letters in 2012 (p = 0.073). Mean change in CRT from 4 months to one year was −36 μm in 2018 versus −23 μm in 2012 (p = 0.373). Mean change in CRT from baseline to one year was −100 μm in 2018 (p < 0.001) and −75 μm in 2012 (p < 0.001). Mean number of injections given in one year was 11.8 in 2018 versus 10.4 in 2012 (p < 0.001). After one year, a majority of eyes in both groups still received treatment at 4-week intervals.

Conclusion: The study suggests that the possibility of switching eyes with treatment-resistant nAMD to aflibercept leads to a modest visual benefit compared with continuing first-line bevacizumab therapy.

Key words: neovascular age-related macular degeneration – treatment resistance – switching – anti-VEGF – aflibercept – bevacizumab

Introduction

Neovascular age-related macular degeneration (nAMD) is a common retinal disease; the prevalence in elderly Caucasians is estimated to be 2.5% (Erke et al. 2012). Vision loss from nAMD is provoked by abnormal growth of choroidal blood vessels, choroidal neovascularization (CNV), into the macula, and the natural history is devastating (De Laey 1983). Vascular endothelial growth factor (VEGF), a potent angiogenic signal protein family, is a key player in the pathophysiology of CNV, and the introduction of intravitreal anti-VEGF therapy in the mid-2000s resulted in a paradigm shift in the treatment and prognosis of nAMD (Rosenfeld et al. 2006; Brown et al. 2009).

The first years of anti-VEGF therapy for nAMD were characterized by dispute over ophthalmic off-label use of bevacizumab (Avastin; Roche, Basel, Switzerland), an inexpensive alternative to approved treatment with ranibizumab (Lucentis; Novartis, Basel Switzerland), an inexpensive alternative to approved treatment with ranibizumab (Lucentis; Novartis, Basel Switzerland) (Kim & D’Amore 2012). In 2009, the Department of Ophthalmology at Oslo University Hospital (OUH) launched a Norwegian multicentre research initiative, LUCAS, to compare ranibizumab and bevacizumab for nAMD according to a treat-and-extend (T&E) protocol. This randomized controlled trial (RCT) showed that the two drugs had
equivalent functional and anatomical effects and also that the T&E algorithm was a feasible alternative to monthly dosing (Berg et al. 2015; Berg et al. 2016).

LUCAS laid a solid foundation for the nAMD treatment at OUH, and our original clinical practice guideline indeed recommended bevacizumab in accordance with a T&E algorithm. In May 2013, however, aflibercept (Eylea; Bayer, Leverkusen, Germany) was commercially introduced in Norway. As its much greater affinity for VEGF-A and ability to bind VEGF-B and placental growth factor could translate into higher efficacy, aflibercept challenged further off-label use of bevacizumab (Heier et al. 2012). At OUH, the debate on continued bevacizumab versus aflibercept treatment was settled by a compromise; since May 2013, clinicians have had the option of switching to second-line therapy with aflibercept for eyes with residual macular fluid despite monthly bevacizumab injections.

Systematic reviews and meta-analyses generally show that converting to aflibercept in treatment-resistant nAMD results in anatomical improvement, but there is doubt about the visual benefit (Seguin-Greenstein et al. 2016; Mantel et al. 2018; Pikkel & Attas 2018; Empeslidis et al. 2019). It should be emphasized that the literature generally consists of uncontrolled case series, and recurring limitations prohibit a firm conclusion about the usefulness of switching from one drug to another (Mantel et al. 2018). Eyes that meet criteria for switching may demonstrate further improvement despite continuing the original treatment, and the only RCT to this day ambiguously suggests similar outcomes with or without converting to aflibercept (Mantel et al. 2016; Ferris et al. 2017). Still, the introduction of aflibercept as second-line therapy at OUH gradually resulted in an almost one to one usage ratio between bevacizumab and aflibercept, regardless of the lack of conclusive evidence that switching leads to improved visual outcomes. The rising proportion of aflibercept at the expense of bevacizumab apparently contradicts the LUCAS initiative and challenges the cost-effectiveness of contemporary nAMD treatment (Elshout et al. 2018; Jorstad et al. 2019). Evidently, there is need for well-designed switch studies and for research that identifies nAMD patients who indisputably benefit from converting to aflibercept.

The purpose of this study was to compare outcomes of our present treatment algorithm, which allows for switching treatment-resistant nAMD eyes to aflibercept, with our pre-2013 approach to residual macular fluid, for which continuing monthly bevacizumab was the routine.

Materials and methods

This was a retrospective observational study. It took place at the Department of Ophthalmology at OUH and was approved by the institutional data protection officer. Two groups of nAMD patients were compared. The first group contained treatment-naïve nAMD patients who completed one year of anti-VEGF therapy within the last year before aflibercept was introduced in mid-2013. The second group contained treatment-naïve nAMD patients who initiated anti-VEGF therapy in 2018, thereby portraying the department’s present-day nAMD treatment. To identify these patients, we reviewed the medical records of new patients in 2012 and 2018 with the International Classification of Diseases (ICD-10) code H35.3: Degeneration of macula and posterior pole and the Nordic Medico-Statistical Committee’s Classification of Surgical Procedures (NCSP) code C00D05: Intravitreal injection of drug. The code H35.3 encompasses several macular diseases, but only eyes diagnosed with nAMD were included in this study. To avoid dependent data, one eye was randomized to enrolment if both eyes of a patient met the inclusion criteria.

Identification of treatment-resistant nAMD and time-points

In agreement with our current clinical practice guideline, treatment-resistant nAMD was defined as presence of residual macular fluid on spectral-domain optical coherence tomography (SD-OCT) after a minimum of 4 monthly bevacizumab injections. To identify eyes that fulfilled the definition of treatment resistance, we verified whether the initial bevacizumab injections had been administered monthly (deviation from a monthly interval of less than 2 weeks was accepted). For eyes that had only received monthly injections, we evaluated the SD-OCT performed at the first visit after 4 months (16 weeks) of treatment; eyes with residual macular fluid at this visit fulfilled the definition of treatment-resistant nAMD and were included. Eyes were excluded if concurrent macular disease contributed to the residual fluid, for example, vitreomacular traction. Eyes that underwent cataract surgery after initiation of anti-VEGF therapy were also excluded. Data were registered at the time anti-VEGF treatment was initiated (baseline visit), at the first visit after at least 4 monthly injections (when the definition of treatment-resistant nAMD was met) and at the first visit after 48 weeks of treatment (one-year visit). To avoid bias towards excluding cases with poor visual outcomes, we also included treatment-resistant eyes for which further injections had been discontinued between the 4-month visit and the one-year visit.

Treatment algorithms

Of particular note was the possibility for the treating physician to convert eyes in the 2018 group to aflibercept in the case of residual macular fluid after 4 monthly bevacizumab injections. Regardless of continued bevacizumab or conversion to aflibercept, further injections were administered in accordance with the same T&E algorithm; monthly intervals were maintained if residual macular fluid was present on OCT but extended by 2 weeks at a time (up to a maximum of 12 weeks) if the macular fluid resolved.

Functional and structural measurements

Best-corrected visual acuity (BCVA) was obtained from a ClearChart (Reichert Technologies, Depew, NY) digital acuity test, which displays 5 letter optotypes per line and logarithm of the minimal angle of resolution (logMAR) line size progression (i.e. each letter has a score of 0.02 logMAR).

Radial OCT images from all visits were evaluated by YSH for presence of macular fluid. In cases of doubt about OCT findings, ØKJ also evaluated the images, and agreement was reached through consensus decision-making. We also recorded the central retinal
thickness (CRT), but because our current spectral-domain OCT system (NIDEK Co., Ltd., Gamagori, Japan) replaced an older time-domain system in the beginning of 2012, we could not acquire reliable baseline CRT values for all 2012 eyes. In consequence, only a subset of the 2012 eyes was included in the analysis of change in CRT from baseline. The evaluation for treatment-resistant nAMD after 4 months was always performed on SD-OCT.

Additionally, we registered whether any other form of nAMD treatment had been given (e.g. photodynamic therapy or conversion to ranibizumab) or bevacizumab had been reinstated before the one-year visit.

Statistical analyses

Decimal BCVA values were converted to logMAR for statistical analyses. Counting fingers and hand motion were assigned logMAR 2.0 and 2.3 (Lange et al. 2009). Pearson’s chi-square or Fisher’s exact test (for small sample sizes) was used for categorical variables, and the Student’s t-test was used for continuous variables. Calculations were performed with IBM SPSS Statistics, Version 25.0 (Armonk, NY: IBM Corp.). Threshold for statistical significance was set at alpha = 0.05. Data are presented as mean (standard deviation) or proportions.

Results

Patient characteristics at baseline and after 4 months

A total of 198 nAMD eyes initiated treatment in 2012 and 340 nAMD eyes initiated treatment in 2018. Among eyes receiving monthly bevacizumab injections, 49 eyes in the 2012 group and 98 eyes in the 2018 group had residual macular fluid on OCT at the first visit after 4 months. Three eyes in 2012 group and 6 eyes in the 2018 group had concurrent macular disease contributing to the residual fluid, and 3 eyes in 2012 group underwent cataract surgery after initiating anti-VEGF therapy. For 3 patients in the 2012 group and 4 patients in the 2018 group, both eyes met the inclusion criteria, and one eye was randomized to enrollment. Ultimately, 40 of 198 eyes (20%) in the 2012 group and 88 of 340 eyes (26%) in the 2018 group were included in the study. A baseline CRT value on the basis of SD-OCT was available for 22 of 40 eyes in the 2012 group and 87 of 88 eyes in the 2018 group.

Patient characteristics were similar across the 2 groups at baseline and after 4 months (Table 1). The mean number of bevacizumab injections administered from baseline to the 4-month visit, however, was slightly higher in the 2018 group than in the 2012 group (4.9 versus 4.4 injections; p < 0.001).

Treatment from the 4-month visit in the 2012 group (aflibercept unavailable)

Seven of 40 eyes were switched from bevacizumab to ranibizumab after the 4-month visit (3 of the 7 eyes were later switched back to bevacizumab), and one eye received PDT. Furthermore, 3 eyes had the bevacizumab injection interval shortened to every 3 weeks. At the one-year visit, treatment had been discontinued for 3 eyes because of a poor visual prognosis, and one eye had been converted to a pro re nata regimen.

Treatment from the 4-month visit in the 2018 group (aflibercept available)

Fifty-nine of 88 eyes (67%) were switched from bevacizumab to aflibercept after the 4-month visit. The eyes received a mean of 6.3 (1.8) bevacizumab injections before switching. Three eyes were first switched to aflibercept but then back to bevacizumab, and one eye was first switched to aflibercept and then to ranibizumab. One eye had the aflibercept injection interval shortened to every 3 weeks. At the one-year visit, treatment had been discontinued for 5 eyes because of a poor visual prognosis, and 2 eyes had been converted to a pro re nata regimen.

Visual findings at the one-year visit

There was a significant difference between the 2 groups in terms of mean change in BCVA from the 4-month visit to the one-year visit: +2.8 (10.1) letters in the 2018 group versus −1.7 (14.0) letters in the 2012 group (p = 0.043) (Fig. 1). Mean change in BCVA was +1.6 (9.8) letters in the 2018 subgroup that was switched to aflibercept and +5.2 (10.4) letters in the 2018 subgroup that continued bevacizumab (p = 0.121). Within each group, only the 2018 group displayed a significant improvement in mean BCVA from baseline to the one-year visit: +9.4 (18.3) letters (p < 0.001) in the 2018 group versus +4.4 letters (15.1) (p = 0.073) in the 2012 group. The proportions of eyes with an increase or decrease in BCVA of at least 15 letters were similar across the 2 groups.

Structural findings at the one-year visit

There was no significant difference between the 2 groups in terms of mean change in CRT from the 4-month visit.
to the one-year visit: $-23\ (45)\ \mu m$ in the 2012 group versus $-36\ (67)\ \mu m$ in the 2018 group ($p = 0.373$). Within each group, there was a significant improvement in mean CRT from baseline to the one-year visit: $-75\ (56)\ \mu m$ ($p < 0.001$) in the 2012 group and $-100\ (88)\ \mu m$ ($p < 0.001$) in the 2018 group.

Six of 40 eyes (15%) in the 2012 group and 20 of 88 eyes (23%) in the 2018 group had no macular fluid on OCT at the one-year visit; the proportions were similar across the 2 groups ($p = 0.314$). Table 2 presents an overview of the main outcomes.

**Treatment intensity at the one-year visit**

The mean number of injections given from the 4-month visit to the one-year visit was higher in the 2018 group than in the 2012 group (6.9 versus 6.0 injections; $p < 0.011$). At the one-year visit, a majority of eyes in both groups still received treatment at 4-week intervals; the proportions were similar across the 2 groups ($p = 0.297$) (Fig. 2).

**Discussion**

This one-year observational study compared 2 groups of nAMD eyes with residual macular fluid after initial treatment with monthly bevacizumab injections. Only eyes in the 2018 group then had the possibility of switching to aflibercept at the discretion of the treating physician. The anti-VEGF treatment was otherwise administered in accordance with the same T&F protocol. There was a difference in favour of the eyes that could be switched to aflibercept in terms of change in mean BCVA from the 4-month visit to one year: 2.8 letters improvement versus 1.7 letters decline.

This observation suggests that the possibility of switching eyes with treatment-resistant nAMD to aflibercept leads to a modest visual benefit.

Despite lack of high-level evidence that it improves visual outcomes, ophthalmologists commonly switch anti-VEGF agent when encountered with persisting macular fluid in nAMD (ASRS. 2019). A poorly evidenced practice of converting from bevacizumab to aflibercept is in conflict with the tremendous efforts that have been made to establish a firm scientific basis for inexpensive off-label use of bevacizumab. One limitation in particular, the general absence of a control group, makes it hard to draw firm conclusions from the literature about the value of switching. To the best of our knowledge, the only pertinent RCT to this day suggests similar outcomes with or without converting to aflibercept for nAMD eyes dependent on monthly ranibizumab treatment (Mantel et al. 2016). Principally, its randomized controlled design is superior to our observational study, but the aforementioned RCT also has important limitations: the sample size was small, long-term exudation (24 months) before switching may have restricted the potential for further visual improvement, and as approximately 30% of the eyes were included because monthly retreatment was required to maintain a dry macula and not because of persisting macular fluid, not all eyes could achieve further visual or anatomical improvement. The limitations of our observational study design notwithstanding, its findings challenge those of the RCT and argue for a

**Fig. 1.** Mean change in best-corrected visual acuity (BCVA). There was a significant difference between the two groups in terms of mean change in BCVA from the 4-month visit to the one-year visit: +2.8 letters in the 2018 group versus −1.7 letters in the 2012 group ($p = 0.043$).

**Table 2.** Main outcomes after one year

|                      | 2012 group  | 2018 group  | $p$ value |
|----------------------|-------------|-------------|-----------|
|                      | (aflibercept| (aflibercept|           |
|                      | unavailable)| available)  |           |
| BCVA (letters)       |             |             |           |
| Mean change from 4-month visit (SD) | $-1.7\ (14.0)$ | $+2.8\ (10.1)$ | 0.043     |
| Mean change from baseline (SD)    | $+4.4\ (15.1)$ | $+9.4\ (18.3)$ | 0.133     |
| Proportion with      |             |             |           |
| Increase of ≥15 letters | $7/40\ (18\%)$ | $21/88\ (24\%)$ | 0.807     |
| Decrease of ≥15 letters | $1/40\ (3\%)$ | $5/88\ (6\%)$ | 0.430     |
| CRT (µm)*            |             |             |           |
| Mean change from 4-month visit (SD) | $-23\ (45)$ | $-36\ (67)$ | 0.373     |
| Mean change from baseline (SD)    | $-75\ (56)$ | $-100\ (88)$ | 0.200     |
| Macular fluid resolved on OCT |             |             |           |
| Proportion            | $6/40\ (15\%)$ | $20/88\ (23\%)$ | 0.314     |
| Injections            |             |             |           |
| Mean no. from 4-month visit (SD) | $6.0\ (1.8)$ | $6.8\ (1.8)$ | 0.011     |
| Mean no. from baseline (SD)    | $10.4\ (1.8)$ | $11.8\ (1.5)$ | <0.001    |

BCVA = best-corrected visual acuity, CRT = central retinal thickness, SD = standard deviation, OCT = optical coherence tomography.

* A baseline CRT value on the basis of spectral-domain OCT was available for 22 of 40 eyes in the 2012 group and 87 of 88 eyes in the 2018 group.
modest visual benefit of switching to aflibercept at the discretion of the treating physician, provided that it takes place within the first year and is motivated by residual macular fluid. Undeniably, a well-designed RCT remains essential to provide conclusive evidence as to whether the common strategy of switching anti-VEGF agent in response to treatment-resistant nAMD is effective.

While functional outcomes favoured the group that could switch to aflibercept, no significant differences in structural outcomes were found. Both groups displayed improvement in CRT, and only the point estimates were slightly better for the group that could switch to aflibercept. We can only speculate on the cause of an apparent lack of correlation between functional and structural outcomes, but the standard deviation for CRT reveals high variability in both groups, and the study may be underpowered to detect a true structural difference. It should also be noted that residual macular fluid was present at one year for a majority of eyes in both groups, but mean CRT values well below 300 µm indicate that the amount of remaining fluid was sparse.

In agreement with the observational design, the patients in this study were managed according to clinical practice guidelines, not a rigorous study protocol. Tailoring nAMD treatment to individual needs is in many ways an art form on its own. Correspondingly, the contemporary option of converting eyes with persistent fluid to aflibercept was sometimes delayed beyond 4 monthly bevacizumab injections or not utilized at all. Likewise, cases of photodynamic therapy or ranibizumab injections were found in the 2012 group. It should also be emphasized that eyes in both groups met the same definition of treatment resistance, residual macular fluid after initial treatment with aflibercept was not mandatory but kept at the discretion of the treating physician. Presumably, a decision to continue bevacizumab injections was determined on an individual basis, as the treatment decision was not mandatory but kept at the discretion of the treating physician. One might argue that eyes in the 2018 group should only be included if they were in fact switched to aflibercept. However, switching to aflibercept was not mandatory but kept at the discretion of the treating physician.

In conclusion, this one-year observational study suggests the possibility of switching eyes with treatment-resistant nAMD to aflibercept leads to a modest visual benefit compared with continuing first-line therapy with bevacizumab. There is still a need for a randomized controlled trial to ascertain whether the common strategy of switching anti-VEGF agent in response to treatment-resistant nAMD truly improves outcomes.
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