Title:

Two years functional and anatomical results after converting treatment resistant eyes with exudative age-related macular degeneration to aflibercept in accordance with a treat and extend protocol

Øystein Kalsnes Jørstad¹, Rowan Thomas Faber¹ and Morten Carstens Moe¹

¹Department of Ophthalmology, Oslo University Hospital and University of Oslo, Norway

Corresponding author:

Øystein Kalsnes Jørstad, MD

Department of Ophthalmology

Oslo University Hospital

Postboks 4950 Nydalen

0424 Oslo

Norway

Tel: +47 22 11 85 45

Email: OEYJOE@ous-hf.no

Abstract

Purpose

To study the effects of converting to aflibercept in accordance with a treat and extend (T&E) strategy in eyes with treatment resistant exudative age-related macular degeneration (AMD).

Methods

Two year prospective study of eyes with exudative AMD and persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab. Eyes were converted to 2.0 mg aflibercept in accordance with a T&E protocol.

Results

Fifty eyes from 47 patients were included. At baseline the mean central retinal thickness (CRT) was 273 μm and mean best-corrected visual acuity (BCVA) 0.25 logarithm of the minimal angle of resolution (logMAR). The mean number of aflibercept injections the first year was 9.2. After 1 year there was a reduction in mean CRT to 228 μm ($p<0.001$); 22 eyes (44%) had a dry macula and the mean BCVA was 0.24 logMAR ($p=0.531$). The mean number of aflibercept injections the second year was 8.0 ($p=0.013$ compared to first year). After 2 years 24 eyes (48%) received treatment more frequently than every eighth week. The mean CRT was 225 μm ($p<0.001$ compared to baseline); 31 eyes (62%) had a dry macula and mean BCVA was 0.32 logMAR ($p=0.005$ compared to baseline). Five eyes did not complete 2 years of aflibercept treatment after failing to improve.

Conclusion

A majority of eyes showed improved anatomic outcomes. There was a small decrease in mean BCVA after the second year of treatment. About half of the eyes required treatment more frequently than the recommended aflibercept label of an 8 week interval.

Key words

aflibercept, exudative age-related macular degeneration, AMD, treatment resistance

The efficacy of anti-vascular endothelial growth factor (anti-VEGF) therapy in exudative age-related macular degeneration (AMD) was initially demonstrated in 2 trials, ANCHOR and MARINA.(Rosenfeld et al. 2006; Brown et al. 2009) The modified antibody fragment ranibizumab prevented further vision loss and even lead to visual gain in many patients. Off-label treatment with the antibody bevacizumab, approved for the treatment of several malignancies, has also proven to be an effective therapy for exudative AMD in studies like CATT and IVAN.(Comparison of Age-related Macular Degeneration Treatments Trials Research et al. 2012; Chakravarthy et al. 2013) With individualized therapeutic strategies like treat and extend (T&E), favourable functional and anatomic outcomes can be achieved with longer injection intervals than the initially recommended monthly dosing. In other cases, however, persistent fluid is seen despite monthly treatment with ranibizumab or bevacizumab.

The recombinant fusion protein aflibercept, a VEGF-trap, represents a promising therapeutic option for eyes with persistent macular fluid. Its binding affinity for VEGF is substantially greater than that of bevacizumab or ranibizumab.(Holash et al. 2002) In the current study, we present the 2 year functional and anatomical effects of converting to aflibercept, in accordance with a T&E strategy, in eyes with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab.

Materials and Methods

When aflibercept became commercially available in Norway in May 2013 all consenting exudative AMD patients in our clinic with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab were converted to 2.0 mg aflibercept. At the same time, a prospective, single-center quality register, approved by the Oslo University Hospital, was created to study the results. We searched the electronic records of all patients treated with aflibercept the first 16 weeks after it became available. In order to be included in the present study, the patients had to be previously diagnosed with exudative AMD, with angiographic

evidence of a classic or occult membrane or a retinal angiomatous proliferation. OCT at the time of switching to aflibercept had to show sub- and/or intraretinal macular fluid. Previous treatment with ranibizumab or bevacizumab had to have lasted for at least 6 months, and at least, the 3 last injections before conversion had to have been given monthly. A deviation from the defined injection intervals of ± 1 week was allowed.

Both before and after conversion to aflibercept, patients included in the study received treatment in accordance with a T&E strategy adapted from the LUCAS study.(Berg et al. 2015) As all eyes had macular fluid on OCT at the timepoint of switching treatment no eyes were treated at extended intervals before conversion. After conversion and extension of the treatment interval to 8 weeks according to the the recommended aflibercept treatment regimen at the time, we departed from this strategy and monthly injections were given as long as residual macular fluid was present on OCT. If a dry macula was achieved the injection interval was extended by 2 weeks at a time. If examination showed a new macular haemorrhage or OCT revealed recurring macular fluid, the treatment interval was reduced by 2 week intervals until a dry macula was again achieved or the macular haemorrhage was absorbed. The injection interval was then again extended by 2 weeks at a time, but with a maximum final interval 2 weeks shorter than the interval causing recurrent disease. A change of treatment strategy with monthly observation and further injections only “as needed” was allowed if the macula stayed dry over 12 week intervals. We defined failure to improve after conversion to aflibercept as no anatomical improvement on OCT after at least 3 monthly aflibercept injections. In the clinical protocol, reintroduction of previous anti-VEGF therapy, or rescue treatment at the discretion of the investigator, was allowed if an eye met the criteria for failure to improve. Eyes that underwent cataract surgery og YAG laser capsulotomy during the 2 years of follow up were excluded from the study.

Data were collected at the time of switching to aflibercept (baseline), at the first visit after 1 year and at the first visit after 2 years of aflibercept treatment. Best-corrected visual

acuity (BCVA) was obtained from a ClearChart (Reichert Technologies, Depew, NY) digital acuity test. We used letter optotypes and logarithm of the minimal angle of resolution (logMAR) line size progression. For individual eyes we defined that a BCVA difference ≥ 0.1 logMAR, equal to 5 letters, represented a clinically important difference, while a difference < 0.1 logMAR represented a clinically stable BCVA. (Beck et al. 2007) Twelve radial spectral domain (SD)-OCT scans of the macula were performed using a RS-3000 OCT Retinascan (NIDEK CO., LTD., Gamagori, Japan). Central retinal thickness (CRT) values were only included in the study for patients where accurate measurements could be obtained from OCT scans at both baseline and the 2 following examinations. A structural evaluation of all OCT examinations for each eye was performed and compared using the follow-up function in the NAVIS-EX software (NIDEK CO., LTD.). A paired samples t-test was used for statistical analysis. Significance was defined as $p < 0.05$.

Results

A total of 141 patients (any retinal condition) were treated with aflibercept. Of these, 50 eyes from 47 patients fulfilled the inclusion criteria for the study. Accurate CRT measurements could be obtained from 44 eyes. At baseline the eyes had received a mean of 29 (6-74) prior injections. The mean treatment duration was 38 months (6-81). 43 eyes were converted from bevacizumab and 7 from ranibizumab. 31 eyes (62%) had previously been treated with both drugs. Structural evaluation of all baseline SD-OCT examinations showed that in addition to macular fluid, 47 eyes (94%) had a pigment epithelial detachment (PED). Mean CRT was 273 μm and mean BCVA was 0.25 logMAR. The main results are shown in table 1.

The mean number of aflibercept injections given the first year was 9.2. After 1 year of aflibercept treatment, structural evaluation of individual SD-OCT compared to baseline showed a dry macula in 22 eyes (44%) and less macular fluid in an additional 20 eyes (40%). Two eyes showed no change in macular fluid, while 2 eyes showed worsening. Two eyes

failed to improve after conversion to aflibercept during the first year of follow up and were converted back to the previous anti-VEGF therapy. One eye received rescue treatment with intravitreal tissue plasminogen activator and gas injection in addition to continued anti-VEGF due to a subretinal macular bleed. Of the 46 eyes with a PED, 28 (61%) had a smaller PED than at baseline. Compared to baseline there was a significant reduction in mean CRT to 228 μm ($p < 0.001$, paired t-test). Mean BCVA was 0.24 logMAR ($p = 0.531$). Regression analysis showed very weak relationships between change in CRT and BCVA, and previous treatment duration at baseline and change in BCVA; the coefficient of determination (R^2) was 0.0803 and 0.0067, respectively.

The mean number of aflibercept injections given the second year was 8.0 ($p = 0.013$ compared to the first year). The most common treatment interval after 2 years was 6 weeks. 24 eyes (48%) received treatment more frequently than every 8 weeks. The treatment intervals after 2 years are shown in figure 1. After 2 year of aflibercept treatment, structural evaluation of individual SD-OCT compared to baseline showed a dry macula in 31 eyes (62%) and less macular fluid in an additional 11 eyes (22%). One eye showed no change in macular fluid, while 2 eyes showed worsening. One eye failed to improve after conversion to aflibercept during the second year of follow up and was converted back to the previous anti-VEGF therapy. One eye received rescue treatment with photodynamic therapy plus intravitreal dexamethasone in addition to continued anti-VEGF therapy. Of the 46 eyes with a PED, 30 (65%) had a smaller PED than at baseline. Compared to baseline there was a significant reduction in mean CRT to 225 μm ($p < 0.001$). Mean BCVA was 0.32 logMAR, representing a small decrease in visual acuity equal to 3.5 letters lost compared to baseline ($p = 0.005$). After 2 years of aflibercept treatment 6 (12%) eyes had a clinically important improvement and 14 (28%) eyes had a clinically important decline in BCVA, equal to at least 5 letters. BCVA remained clinically stable for 25 (50%) eyes. Regression analysis showed very weak relationships between change in CRT and BCVA, and previous treatment duration

at baseline and change in BCVA; the R^2 was 0.0955 and 0.0428, respectively. Scatter plots of these relationships are shown in figure 2.

Discussion

The first systematic meta-analysis evaluating the visual and anatomical outcomes of patients with resistant AMD converted to aflibercept was recently published.(Seguin-Greenstein et al. 2016) The meta-analysis of four retrospective and three prospective studies provides substantial evidence that there is a significant positive anatomical effect of switching to aflibercept. The effect on visual function is far more modest. The first year results in our study are comparable to those from the meta-analysis. After 1 year we found a significant reduction in mean CRT and anatomical improvement for a majority of eyes, while mean BCVA remained unchanged. The longest follow up in the meta-analysis was 12 months, and to our knowledge the present study is the first to provide 2-year outcomes and a T&E strategy. The two year follow-up data show that the anatomical effect of switching to aflibercept persisted through the second year. Unlike the first year results where mean BCVA remained unchanged from baseline there was a small decrease in mean BCVA during the second year, with 14 (28%) eyes having a clinically important decline in BCVA equal to at least 5 letters after 2 years.

Systematic treatment in accordance with a T&E strategy makes the study particularly relevant as this regimen appears to be the most favored in clinical practice today.(Patel et al. 2015) Moreover, we have previously reported data that suggest aflibercept's superior 28-day VEGF binding activity is needed to achieve improvement in treatment resistant exudative AMD, and that even for aflibercept, declining binding activity after 2 months proves insufficient to prevent residual macular fluid.(Jorstad et al. 2015) This observation favours a T&E strategy which maintains monthly treatment if needed. In the present study, after 2 years of aflibercept treatment, many eyes required treatment more frequently than the recommended

aflibercept label of an 8 week injection interval. However, the study also found a subgroup of eyes where treatment intervals could be extended to more than 8 weeks. Theoretically aflibercept's biological activity at the end of such long intervals is no longer superior to the monthly anti-VEGF therapy eyes received before conversion.(Stewart & Rosenfeld 2008) This raises the question as to whether superior VEGF binding alone can explain the effect of switching to aflibercept for some eyes. Patients with choroidal neovascularization who develop tachyphylaxis to ranibizumab or bevacizumab may respond better when switching to the opposite drug.(Gasperini et al. 2012) One could argue that a tachyphylaxis mechanism to prior treatment might also contribute to the functional and anatomical improvement when switching to aflibercept, at least for patients in the subgroup independent of intensive aflibercept treatment.

Both the meta-analysis and our study lack strong correlation between anatomical and functional results. This could be related to permanent retinal damage due to long term active neovascular disease before converting to aflibercept. If so, we could expect a negative correlation between treatment duration at baseline and change in BCVA after converting to aflibercept. However, we found no correlation between these variables in our study. These results raise the question as to whether converting to an aflibercept T&E strategy, that aims to resolve all macular fluid, achieves the best long term functional outcomes. An ongoing study that compares functional results between a treatment strategy that tolerates small amounts of subretinal fluid, and intensive treatment with no tolerance of fluid, might provide new insights into retreatment criteria for managing exudative AMD using a T&E regimen.(Arnold et al. 2016) Furthermore, as most eyes were converted from less expensive treatment with bevacizumab, the results also question the cost-effectiveness of the investigated converting strategy.

The main limitation of our study, like the studies in the recent meta-analysis, is the lack of a control group; the functional and anatomical effects of continuing the previous

therapy for an additional 2 years are unknown. Furthermore, as in the meta-analysis, the eyes converted to aflibercept are heterogeneous in regard to both previous treatment duration and anti-VEGF therapy, reflecting the study's real-life setting.

In conclusion, a majority of eyes with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab, showed improved anatomic outcomes two years after converting to aflibercept using a T&E strategy. We found no correlation between anatomical and functional results, and a small decrease in mean BCVA, equal to 3.5 letters, after the second year of treatment. Treatment burden in terms of mean number of injections was reduced, but after 2 years about half of the eyes still required treatment more frequently than the recommended aflibercept label of an 8 week injection interval.

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Figure Legends

Figure 1: Treatment intervals at the first visit after 2 years of aflibercept treatment.

Figure 2: Scatter plots with line of best fit and coefficient of determination (R^2) show very weak relationships between change in central retinal thickness (CRT) and best-corrected visual acuity (BCVA), and previous treatment duration at baseline and change in BCVA after 2 years.

Table Legends

Table 1: Main results.