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Combination of Aflibercept and Bromfenac Therapy in Age-Related Macular Degeneration: A Pilot Study Aflibercept and Bromfenac in AMD

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Data Interpretation D
Manuscript Preparation E
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Background: Among many protocols for treatment of exudative AMD, combined therapy of anti-VEGF agents and non-steroidal anti-inflammatory drugs (NSAIDs) seems to be an ideal alternative to monotherapy based on ranibizumab or bevacizumab. The aim of this study was to evaluate the effectiveness of aflibercept and bromfenac in the treatment of exudative AMD.

Material/Methods: The study was conducted on a group of 27 patients with exudative AMD who were administered intravitreal aflibercept and topical bromfenac (study group) once a month. Additional injections were administered up to 3 months after the third administration, depending on response to treatment. The control group consisted of subjects treated with aflibercept only. Visual acuity and anatomical outcomes in optical coherence tomography (OCT) were assessed at baseline visit, 4 months after the first dose, and 6 months after the start of the treatment.

Results: Visual acuity improved over time in the study group and the differences between the groups were statistically significant. No statistically significant differences were found in OCT parameters.

Conclusions: Combined therapy of aflibercept and bromfenac in the treatment of wet AMD is more effective than single aflibercept therapy.

MeSH Keywords: Intravitreal Injections • Macular Degeneration • Tomography, Optical Coherence

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Background

Age-related macular degeneration (AMD) is a leading cause of adult blindness [1]. It has been reported that about 30–40 million people have this disease worldwide [2] and about 500 000 new cases are reported each year [3].

The exact mechanism of AMD etiology is not completely understood. Several factors affect the pathogenesis of the disease: age, female sex, smoking, atherosclerosis, hypertension, low level of physical activity, and increased exposure to UV radiation [2]. Some authors also indicate the significance of genetic factors, such as mutation Y402H in gene CFH of the H factor of the complement system [4]. Other mutations in genes (ABCA4, ELOVE4, FIBL-6, SOD-2, and APOE) might also influence the initiation of AMD, but is unlikely in single mutations [3,5,6].

It has been reported that diet rich in antioxidants, zinc, and selenium, as well as consumption of low-fat and low-carbohydrate products, might prevent the disease [2].

The symptoms of AMD include blurred vision with gradual deterioration of visual acuity, possibly causing blindness. Two types of AMD can be distinguished: exudative and dry.

Severe visual loss from AMD is caused by subfoveal geographic atrophy and choroidal neovascularization, which is a hallmark of exudative AMD. It is widely reported that vascular endothelial growth factor (VEGF) is a major pathogenic factor in exudative AMD, as it stimulates angiogenesis and increases vascular permeability [7].

The most common treatment of the disease is intravitreal injections of anti-VEGF agents, such as ranibizumab (Lucentis), bevacizumab (Avastin), or aflibercept (Eylea).

Aflibercept is a recombinant fusion protein consisting of key human VEGF extracellular domains – receptors 1 and 2 (VEGF 1 and VEGF 2) – fused to the Fc domain of human IgG1 [8]. It is a dimeric glycoprotein with a molecular weight of 115 kDa. Aflibercept has 3 theoretical advantages over other VEGF blockers. First, it has a much higher binding affinity for VEGF (~0.5 pM dissociation constant for VEGF 165 and VEGF 121) than either bevacizumab or ranibizumab. Second, it binds related growth factors, such as placental growth factors 1 and 2 (PLGF 1 and PLGF 2) and VEGF-B, which may be advantageous in certain diseases, including retinal neovascularization [9,10]. VEGF-A and PLGF are angiogenic VEGF factors; they can act as mitogenic and chemotactic factors, as well as increasing permeability of vessels of the endothelium. VEGF can bind to 2 different receptors of tyrosine receptors – VEGFR-1 and VEGFR-2 – situated on the epithelial surface. However, PLGF can bind only to VEGFR-1 receptor, which can be also found in leukocytes. Hyperactivity of the receptors by VEGF-A may lead to angiogenesis and vessel hyperpermeability. Moreover, the vitreous half-life of aflibercept (18 days) is longer than that of ranibizumab (9 days), but slightly shorter than that of bevacizumab (21 days) [11].

Third, aflibercept binds the receptor with high stability and creates a chemically neutral complex (with a 1:1 ratio). In contrast, anti-VEGF agents form multimeric immunologic complexes that are easily eliminated from the circulatory system and can accumulate in various tissues [12]. Aflibercept is produced from recombinant Chinese hamster ovary (CHO) cells.

However, several studies have shown the advantage of additional topical non-steroidal anti-inflammatory drugs (NSAIDs), such as bromfenac [13,14].

It was recently found that non-steroidal anti-inflammatory drugs can also play a major role in ophthalmology, especially in the treatment of exudative AMD [15]. The use of NSAIDs is based on their ability to suppress prostaglandin-induced inflammation, which is linked to the development and maintenance of choroidal neovascularization. Bromfenac belongs to the class of non-steroidal anti-inflammatory agents, which suppress the production of prostaglandins by inhibiting cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to cyclic endoperoxides, which are precursors of prostaglandins. Bromfenac and other non-steroidal anti-inflammatory drugs are approved for the treatment of inflammation after cataract surgery. Retinal levels have also been investigated after topical administration and were found to be within the therapeutic index. According to Jones et al., use of bromfenac and other NSAIDs for treatment and prevention of cystoid macular edema is increasing, and could have clinical utility in other diseases of vascular permeability [16].

The aim of this study was to evaluate the effectiveness of combination therapy of aflibercept and bromfenac in the treatment of exudative AMD.

Material and Methods

The study was conducted on a group of 27 patients (13 males and 14 females, mean age 72.25 years) who were administered intravitreal aflibercept (Eylea, 2 mg) and topical bromfenac (study group). The control group consisted of 27 patients (12 males, 15 females, mean age 72.77) who received aflibercept therapy only.

The research was conducted in accordance with the WMA Declaration of Helsinki and all patients signed informed consent.

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Table 1. Descriptive statistics for visual acuity (logMAR) for control group.

Visit number	N	Mean	Std. dev.	95% CI	Median	Min	Max
Visit 0	27	0.977	0.521	0.771–1.183	1.000	0.222	3.000
Visit 1	27	0.954	0.301	0.835–1.073	1.000	0.222	1.699
Visit 2	27	0.867	0.301	0.748–0.986	1.000	0.301	1.699

Table 2. Descriptive statistics for visual acuity (logMAR) for study group.

Visit number	N	Mean	Std. dev.	95% CI	Median	Min	Max
Visit 0	27	0.693	0.357	0.552–0.834	0.699	0.222	1.398
Visit 1	27	0.558	0.324	0.43–0.686	0.523	0.000	1.097
Visit 2	27	0.512	0.300	0.393–0.631	0.523	0.000	1.097

Inclusion criteria for both groups were: age above 50 years, active choroidal neovascularization (CNV) manifesting exudative AMD in fluorescein angiography, subretinal fluid detected by OCT (iVue, Optovue, USA), and typical image in fundus examination.

Exclusion criteria for the study and control group were: ocular or periocular infections, active intraocular inflammation, prior anti-VEGF therapy (ranibizumab or bevacizumab), retinal detachment, acute increases in intraocular pressure (>30 mmHg), advanced glaucoma, stroke or myocardial infarction within the previous 6 months, anticoagulation therapy with INR over 1.5, and known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

Patients in both groups were treated with 3 intravitreal injections of aflibercept administered every 4 weeks. Additional injections administered until 3 months after the third administration depended on the subretinal fluid leakage as assessed by OCT and/or deterioration of visual acuity. Each time a minimally higher or new amount of subretinal fluid was observed on OCT examination, an additional injection was administered. Intravitreal injections were performed under standard protocol with preoperative topical anaesthesia and aseptic technique (surface disinfection with 5% povidone-iodine solution). Moxifloxacin (5 mg/ml) eye drops (Vigamox) were used 3 times daily 3 days before and 3 days after each injection in order to avoid any ocular and periocular infections or active intraocular inflammation.

Patients from the study group were instructed to apply 1 drop of bromfenac to the treated eye twice daily for 3 months starting on the day after the first dose of aflibercept.

Any adverse effects were assessed at each stage of the study.

A complete ophthalmic examination, consisting of distance best-corrected visual acuity (BCVA), slit-lamp biomicroscopy (SL-3G Topcon Corporation, Tokyo, Japan), intraocular pressure with Goldmann applanation tonometry (XPERT NCT PLUS Reichert, USA), fundus examination, and OCT, was conducted at each visit. Fluorescein angiography (TRC NW8F Topcon Corporation, Tokyo, Japan) was performed at the beginning of the treatment and its result acted as an inclusion criteria.

For the purpose of the analysis, the following outcomes were measured at 3 stages of the study: on the day of first injection (baseline – visit 0), 4 months after (visit 1) the first dose, and 6 months (visit 2) after the start of the treatment:

- BCVA for distance (assessed with Snellen chart, than transformed into LogMar);
- Central retinal thickness (CRT);
- Height and length of subretinal fluid.

The results were compared at each stage of the study and the number of injections was analyzed to determine the factors correlating with injection frequency.

Statistics

Statistical analysis of the data was performed using STATISTICA software (version 10). Normality of the samples was assessed with the Kolmogorov-Smirnov test. All variables (except OCT CRT) were abnormally distributed. Therefore, in order to compare several related samples, the Friedman and Wilcoxon signed-rank tests were used.

Spearman correlation coefficients were used to assess the correlation between variables.

A 2-tailed p-value of <0.05 was used to indicate significance.

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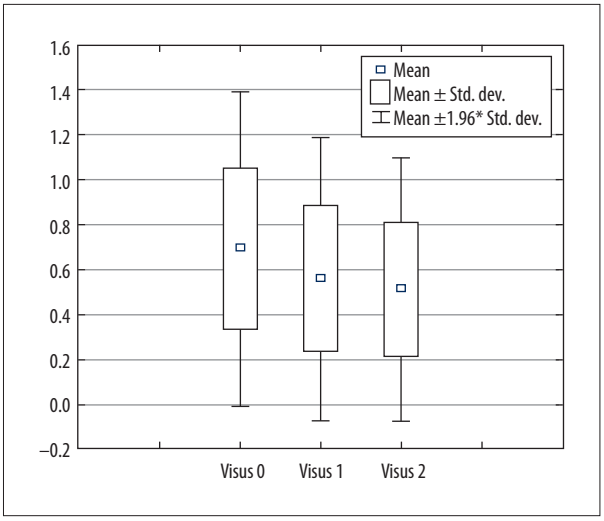

Figure 1. Visual acuity at all visits for study group.

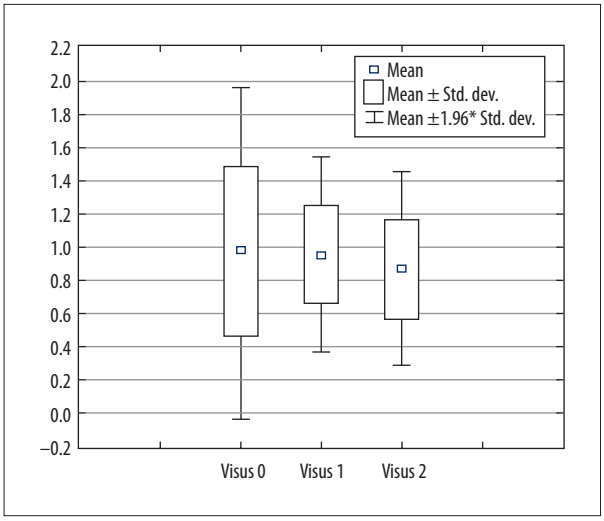

Figure 2. Visual acuity at all visits for control group.

Results

Basic descriptive statistics for visual acuity (logMAR) at visits 0, 1, and 2 for study and control groups are reported in Tables 1, 2.

The results showed that visual acuity was the worst at the baseline visit in both groups and that an improvement was observed at the last visit.

Friedmann's ANOVA for the study group revealed that the visual acuity significantly decreased over time (Figure 1), especially from visit 0 to 1 (Wilcoxon test with Bonferroni correction, p=0.001346) and from visit 0 to 2 (Wilcoxon test, p=0.000748). There were no significant differences between means of visual acuity over time in the control group (Figure 2).

Mann-Whitney test results showed a significant difference in visual acuity change for study and control groups between visit 0 and 1 and 0 and 2 (p=0.0298, p=0.01938). The Mann-Whitney test did not show any significant difference in the alterations of visual acuity for study and control groups between visit 1 and 2 (p=0.8602).

Central retinal thickness did not change significantly between visit 0 and 1 (p=0.2), visit 0 and 2 (p=0.6), and visit 1 and 2 (p=0.8) in either group (Friedmann's ANOVA test), and the differences between these parameters were not significant. The raw results of CRT are shown in Table 3.

Analysis of the mean height of the subretinal fluid in OCT showed that it decreased from 144.7 um (for study group) and 128.48 um (for control group) to 107.74 um and 117.63 um respectively. Friedmann's ANOVA and Wilcoxon singed-rank test with Bonferroni adjustment revealed a significant decrease in height of subretinal fluid over time in the study group, especially between visit 0 and 2 (p=0.000435). No statistical significance was reported when analyzing the differences between visit 0 and 1 and visit 1 and 2 (Figure 3). Similar results were obtained in the control group (Figure 4). The differences between the mean changes in height between groups was insignificant (p>0.05).

Table 3. CRT characteristics.

	Mean	SD
CRT – study group		
Visit 1	402.1481	151.6506
Visit 2	386.9630	136.9928
Visit 3	377.2222	143.4000
CRT – control group		
Visit 1	389.5185	110.2743
Visit 2	393.2222	117.8445
Visit 3	376.7037	110.6334

Although the height of subretinal fluid in the study group decreased, the mean results were statistically insignificant. According to the Mann-Whitney test, the differences were only significant between visit 0 and 1 (p=0.04).

To evaluate the correlations between the visual acuity and each parameter of the OCT in both groups separately, the Spearman rank test was used. It showed a significant positive correlation between CRT and visual acuity (VA) for all visits (0, 1, and 2), as well as VA and height of subretinal fluid for visits 1 and 2 in the study group.

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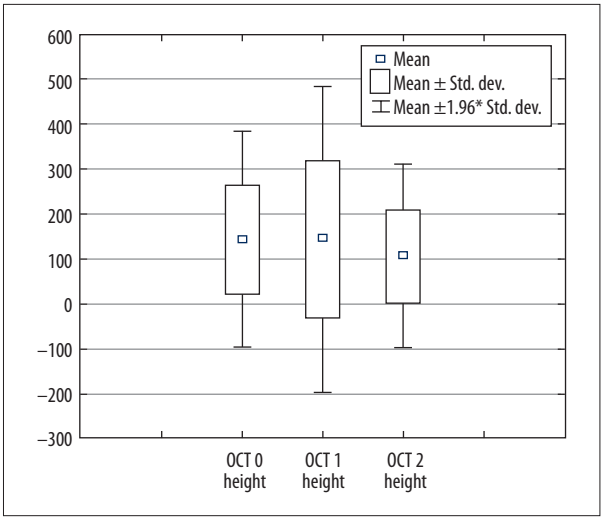

Figure 3. Mean height of subretinal fluid in study group.

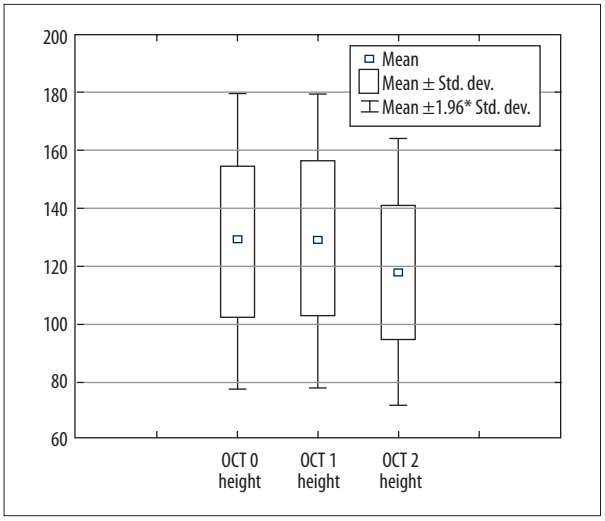

Figure 4. Mean height of subretinal fluid in control group.

In the control group positive correlations were found for VA and height of subretinal fluid at visits 1 and 3 as well as for VA and height of the fluid for all visits. CRT did not correlate positively with visual acuity in the control group.

Discussion

There are several schedules of anti-VEGF therapy; most are based on clinician experience. It is appalling that we still lack worldwide consensus on precise guidelines for the treatment of exudative AMD, especially one that would cover all available options, such as pegaptanib, bevacizumab, ranibizumab, or aflibercept with NSAIDs. A recent study of British scientists presents definitions of response to anti-VEGF therapy and recommendations on when to consider discontinuation of therapy because of treatment success or failure [17]. However, the proposal does not refer to combination therapy. On the other hand, it might be the first step in creating a worldwide position paper on exudative AMD treatment.

As far as aflibercept is concerned, many publications have focused on the superiority of aflibercept after multiple intravitreal injections of bevacizumab or ranibizumab in treatment-resistant wet AMD [18–23]. Interestingly, many authors distinguish visual and anatomical outcomes of the treatment, revealing better anatomical response over the improvement in visual acuity [22]. They favor aflibercept in cases with persistent fluid on OCT despite previous ranibizumab or bevacizumab therapy [22,24,25]. The improvements cover a decrease in CRT, subretinal fluid (CRF), and other OCT parameters [22–24]. Also, in these studies, visual acuity was found to be unaltered [22–24]. Stewart revealed that intravitreal aflibercept given monthly or every 2 months produces visual improvement and decrease in macular thickness comparable to monthly ranibizumab [26].

In our study, in order to avoid any influence of prior anti-VEGF therapy (bevacizumab or ranibizumab), only subjects without previous treatment were qualified for the study.

To the best of our knowledge, there are no previous studies on therapy with a combination of aflibercept and bromfenac. This is the first report of such protocol. Therefore, we refer to publications concerning either monotherapy with the application of aflibercept or combination therapy with NSAIDs and ranibizumab or bevacizumab.

The role and effectiveness of NSAIDs combined with anti-VEGF therapy has been reported by many clinicians [27–30]. In most studies fewer injections of anti-VEGF agent in the group treated in combination with NSAIDs were recorded [27]. This usually resulted in better quality of life and economic benefits.

As in other publications, the effectiveness of the combined therapy was assessed by 2 parameters – changes in visual acuity and anatomical changes presented in OCT.

Batioglu reported that the mean BCVA values before and after aflibercept injection were 0.83 and 0.77 LogMAR, respectively [31]. In our study, the results obtained for the control group were 09.7 and 0.86 LogMAR, respectively, and 0.69 and 0.51 LogMAR, respectively, for the study group. Moreover, visual acuity significantly decreased over time in the study group. This might prove the advantage of combined therapy over application of aflibercept alone.

Regarding central retinal thickness, Ho et al. reported that mean central foveal thickness decreased –18 µm (range, –242 to 198 µm; P=0.06), and Cho found that central subfoveal thickness improved from 295 to 272 microns (p<0.001) after 1 aflibercept injection. After an average of 4.4 aflibercept

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injections (range 3–6) over 6 months, the central subfoveal thickness remained improved (274 microns, p=0.008). Similar results were observed in our study.

Results concerning the height of subretinal fluid were comparable with ours. Komar et al. reported that maximum pigment epithelial detachment height improved significantly, from 260±162 μm (IQR 129–368 μm) to 214±142 μm (IQR 111–305 μm). Similarly, Rewal et al. showed that mean maximal height (MH) was 288.7±175.9 μm before 12-month treatment with the application of aflibercept and 248.27±146.2 μm (P=0.002) after the therapy. In our study the height decreased from 144.70 um (for the study group) and 128.48 um (for the control group) to 107.74 um and 117.63 um, respectively. Although raw results between the groups seem to differ, no statistical significance was found.

Thorel et al. reported ischemic stroke after intravitreal injection of aflibercept, but no adverse effects were observed in our patients [32].

Although our study had a small number of subjects, it yielded preliminary results that have never been published before. Our study not only confirms previous findings of the effectiveness of aflibercept in wet AMD presented by other authors, but it also shows an intensified impact in terms of combined therapy (with bromfenac). We believe that our protocol might serve as an alternative therapy for exudative AMD.

Conclusions

The study revealed that aflibercept itself is a confirmed therapy in the treatment of exudative AMD, and that combined with bromfenac gives better results in visual acuity and some OCT parameters.

Statement

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