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Antidepressant medication and ocular factors in association with the need for anti-VEGF retreatment in neovascular age-related macular degeneration

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ABSTRACT

Background/Aims Vascular endothelial growth factor (VEGF) is a key player in the pathogenesis of neovascular age-related macular degeneration (nAMD) and is also involved in the final common pathway of antidepressant medication. This study investigated the relationship between the need for anti-VEGF retreatment in patients with nAMD and antidepressant medication, and the potential impact of ocular structural factors.

Methods Data from two identical prospective 2-year treatment protocols using ranibizumab or aflibercept in a variable-dosing regimen ('Observe-and-Plan') were analysed. Retreatment requirement was compared with antidepressant medication intake (primary outcome) and a variety of ocular factors from baseline and from month 3 response (secondary outcomes), using univariate and multivariate analyses.

Results Of the 206 included patients (227 eyes), 19 were on antidepressant medication. Their nAMD eyes significantly more often had pigment epithelium detachment (PED, p=0.04). Multivariate analysis revealed a significant association between anti-VEGF retreatment requirement and antidepressant medication use (p=0.027), as well as thicker central retinal thickness at month 3 (p<0.0001) and month 3 PED height (p=0.001).

Conclusion This study provides evidence that treatment with antidepressant medication increases the anti-VEGF retreatment requirement in patients with nAMD, possibly through the interplay of antidepressant medication, depression status and VEGF levels.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in people >50 years old due to neovascular AMD (nAMD) and geographic atrophy (GA). nAMD is typically treated with repeated intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF), which improve visual outcomes, irrespective of using ranibizumab,[1] aflibercept[2] or bevacizumab.[3] Anti-VEGF treatment has profoundly changed the visual prognosis of patients with nAMD. However, frequent or chronic reinjections are often needed. This retreatment need varies widely between patients,[4] for unclear reasons, from patients who are refractory to the maximal monthly treatments due to persistent or recurrent exudative fluid,[5] to those responding to a regimen with 3-monthly or fewer injections, without recurrent exudation.[4 6]

The factors associated with anti-VEGF refractoriness and the number of anti-VEGF retreatments required are poorly understood. Vitreomacular adhesion and traction,[7] polypoidal choroidal vasculopathy, older age and male sex,[8] and untreated obstructive sleep apnoea[9] may increase recurrence risk. The role of genetic polymorphisms[8] and beta blocker medication[10] remains controversial.

Depressive symptoms are present in 20%–24% of patients with AMD, particularly early during the anti-VEGF treatment.[11] Patients with AMD might be at risk of developing depression due to fear or actual vision loss. On the other hand, depression and antidepressant medication could influence AMD course since there is a strong link among depression, its treatment and VEGF levels. Indeed, VEGF polymorphisms are risk factors for major depressive disorder.[12] Furthermore, VEGF and VEGF receptor 2 gene expression and VEGF serum levels are sometimes reported increased in major depressive disorder.[13–15] Most crucially, antidepressant response is related to increased VEGF serum levels,[16 17] and preclinical studies formally demonstrated the need of a hippocampal VEGF receptor activation.[18 19] To the best of our knowledge, there is no evidence in epidemiological studies for depression as a risk factor to develop nAMD. As the VEGF pathway can be clearly linked to the effect of antidepressant medication, but only relatively uncertain to the depressive disorder itself, we focused here on the use of antidepressant medication.

Thus, we investigated the relationship between antidepressant medication and retreatment need in an interval-based individualised retreatment regimen for nAMD. Second, we investigated various ocular and systemic factors that might impact retreatment need.

METHODS

Data from two consecutive prospective interventional 2-year studies were used in this post-hoc analysis. Both protocols were originally designed to investigate the usefulness of the Observe-and-Plan regimen, an individually planned, interval-based, variable-dosing regimen, using ranibizumab[4] or aflibercept[20] as the anti-VEGF drug for treating naïve nAMD. The first study, using ranibizumab,[4] was performed in 2011–2013, and the second study, using aflibercept,[20] was performed in 2013–2015, due to the later availability of the drug. The Observe-and-Plan regimen (see online supplementary material) was identical, safe and efficient in

both studies. Only eyes that had completed the 2-year study protocol were included in the present study.

Data collection and image analysis

The following baseline data were collected: age, sex, weight, height, history of arterial hypertension, cardiovascular disorders, smoking, medication, in particular antidepressant medication, and the best corrected visual acuity (BCVA) on the ETDRS chart. Information about the depression status was not available.

Imaging data were collected from the baseline multimodal imaging, including colour fundus photography (Topcon TRC-50IX, Tokyo, Japan), fundus autofluorescence, fluorescein angiography and indocyanine green angiography using a Topcon TRC-50IX or the Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany), and spectral domain optical coherence tomography (SD-OCT). The SD-OCT parameters included automatic measurements of the central retinal thickness (CRT), the presence/absence of intraretinal cysts, the presence/absence of subretinal fluid, the presence and thickness of the subretinal tissue complex, the presence and height of pigment epithelium detachment (PED; measured vertical to the Bruch membrane, 1:1 µm mode), the subfoveal choroidal thickness, the presence of an epiretinal membrane, and the presence of vitreomacular adhesion (or traction). Multimodal imaging parameters included choroidal neovascular membrane (CNV) type and size (measured in disc areas), the presence of soft drusen (determined from colour photography), the presence of reticular pseudodrusen (determined by infrared and autofluorescence) and the presence of GA (defined as a dark zone on fundus autofluorescence, increased visibility of the choroidal vessels on fluorescein angiography or colour photography, a sharply demarcated area with higher reflectivity of the choroid on SD-OCT, and an absent retinal pigment epithelium line). The minimum diameter of the GA was 250 µm.

The anti-VEGF drug administered and the number of injections given according to the Observe-and-Plan regimen over the 2-year period were recorded. The 3-month follow-up parameters were collected and included CRT on SD-OCT, the presence/absence of intraretinal cysts, the presence/absence of subretinal fluid, and the PED height on SD-OCT.

The study-specific characteristics were grouped together, as they were invariably linked. The first study used ranibizumab for the Observe-and-Plan regimen, the Cirrus SD-OCT (512x126; Carl Zeiss Meditec, Oberkochen, Germany) with investigator team 1, while the second study used aflibercept for the Observe-and-Plan regimen, the Heidelberg Spectralis SD-OCT (6 mm, 49 lines; Heidelberg Engineering, Germany) with investigator team 2. The same SD-OCT machine was used for each eye throughout the respective studies. Therefore, the 'study' parameter included the drug used, the decision-making team and the SD-OCT machine employed.

The primary outcome measure was the influence of antidepressant medication on the CNV and the need for retreatment with anti-VEGF. The secondary outcome measures were various potential factors associated with the retreatment need (number of injections), according to univariate and multivariate analyses.

Statistical analysis

Descriptive statistics were performed, and univariate and multivariate analyses were used to identify risk factors associated with the number of anti-VEGF injections required over the 2-year treatment protocol. Univariate analyses involved Pearson's correlation and analysis of variance for continuous and categorical variables, respectively. Stepwise multivariate linear regression analysis was performed with the number of anti-VEGF injections as the dependent variable and factors with a p value <0.2 in the univariate analysis. The presence of intraretinal or subretinal fluid at month 3 was excluded from multivariate analysis, as these directly influence the number of the injections, by definition.

For data analysis, a Microsoft Excel V.2010 spreadsheet and JMP software for Windows (V.8.0.1, SAS Institute, Cary, North Carolina, USA) were used. A two-tailed p value of ≤0.05 was considered to indicate statistically significant differences.

RESULTS

One hundred and eighty-six patients (205 eyes) completed the 2 years of the two prospective Observe-and-Plan trials and were included in this post-hoc analysis. The mean age of these patients was 79.6 (±7.1) years and 68.1% were female. Visual acuity improved from 60.6 (±16.6) ETDRS letters, at baseline, by 8.8 (±10.3), 9.3 (±11.9) and 7.7 (±14.6) letters by months 3, 12 and 24, respectively. A mean of 14.1 (±5.9) injections of either ranibizumab (105 eyes, 51.2%) or aflibercept (100 eyes, 48.8%) was used.

Nineteen patients (19 eyes, 9.3%) used antidepressant medication. The type of antidepressant was a selective serotonine reuptake inhibitor in 14 cases, and a norepinephrine/serotonine reuptake inhibitor in 5 cases. Patients with antidepressant medication showed a statistically significantly higher proportion of PED ≥200 µm (p=0.01), were more often smokers (p=0.006) and less often had the right eye affected (p=0.04). They also required non-significantly more retreatment (mean number of injections: 16.0 (±6.06)) than patients without antidepressant medication (mean number of injections: 13.8 (±5.8)) (p=0.12). The baseline and treatment characteristics of the antidepressant medication group are summarised in online supplementary table 1.

The need for retreatment (number of injections over the 2-year study period) was analysed for various potential ocular and systemic factors. Univariate analysis showed significant association between the need for injections and increased PED height (p=0.0001) and CRT (p=0.02, corrected for the OCT machine used) at baseline. Furthermore, injection need was associated with the presence of subretinal (p<0.0001) or intraretinal fluid (p=0.001), the PED height (p<0.0001), the CRT (p<0.0001, corrected for OCT machine) at month 3, and the study type (drug, OCT machine and investigation team; p=0.01). These baseline and month 3 parameters were included in multivariate analysis (except for the presence of month 3 subretinal/intraretinal fluid, as described earlier). Additionally, the amount of subretinal fluid at baseline (p=0.10), the presence of depigmentation at baseline (p=0.06), body mass index (p=0.12) and the use of antidepressant medication (p=0.12) were included.

A summary is given in table 1. The full version of the univariate analysis is available as online supplementary table 2, also including the results with p value >0.2 for the following parameters: age, sex, eye, BCVA, the angiographic CNV type, the CNV size, intraretinal cysts, subretinal tissue complex, choroidal thickness, reticular pseudodrusen, soft drusen, hyperpigmentation, GA, epiretinal membrane and vitreomacular adhesion at baseline, BCVA and BCVA change at month 3, CRT change at month 3, arterial hypertension, cardiovascular discorders, and smoking history.

The multivariate analysis with the above-mentioned parameters led to a final significant model (R^2=0.22, p=0.001)

Table 1 Summary of the most significant results in univariate analysis of the association of ocular and systemic factors with the number of anti-VEGF injections required over 2 years of Observe-and-Plan, an interval-based variable-dosing regimen for neovascular age-related macular degeneration

Factors	n	Mean number of anti-VEGF injections Mean±SD	P values
Overall	205	14.1±5.9	
Quartiles	205	10/14/18	
Ocular baseline characteristics			
RPE detachment baseline			
Present ≥200 µm height	57	15.4±0.8	0.054
Absent or <200 µm height	148	13.6±0.5	
Per 10 µm thickness increase	205	0.09±0.00 (r=0.27)	0.0001*
CRT baseline			
Per 10 µm thickness (corrected for study/SD-OCT machine)	205	0.10±0.003 (r=0.22)	0.002* (0.02*)
Subretinal fluid			
Present	18	14.5±0.46	0.17
Absent	46	13.1±0.86	
Missing data	1		
Per 10 µm thickness increase	204	0.07±0.004 (r=0.12)	0.10
Depigmentation			
Present	109	13.3±0.56	0.06
Absent	89	14.9±0.62	
Ocular follow-up characteristics			
Study			
Aflibercept/OCT Spectralis /team 2	100	15.2±0.58	0.01*
Ranibizumab/OCT Cirrus/team 1	105	13.1±0.56	
Type of fluid at month 3			
Subretinal+intraretinal fluid	25	19.5±1.04	
Subretinal fluid only	25	16.9±1.04	
Intraretinal fluid only	91	14.1±0.55	<0.0001*
No subretinal or intraretinal fluid	64	11.0±0.65	
Subretinal fluid at month 3			
Present	50	18.2±0.76	<0.0001*
Absent	155	12.8±0.43	
Intraretinal fluid at month 3			
Present	116	15.3±0.53	
Absent	89	12.6±0.61	0.001*
RPE detachment at month 3			
Per 10 µm thickness	205	0.12±0.003 (r=0.27)	<0.0001*
CRT at month 3			
Per 10 µm thickness (corrected for study/OCT machine)	205	0.36±0.006 (r=0.38)	<0.0001* (<0.0001*)
Systemic characteristics			
BMI (kg/m^2)			
Per unit	189	−0.13±0.09 (r=−0.11)	0.12
Antidepressant medication			
Yes	19	13.8±0.43	
No	184	16.0±1.33	0.12
Missing data	2		

*P<0.05.
Anti-VEGF, antivascular endothelial growth factor; BMI, body mass index; CRT, central retinal thickness; RPE, retinal pigment epithelium; SD-OCT, spectral domain optical coherence tomography.

Table 2 Multivariate regression analysis to identify factors associated with the number of injections needed during 2 years of anti-VEGF treatment for neovascular age-related macular degeneration

Characteristics	Unstandardised coefficient (SE)	P values
CRT at month 3	0.03 (0.007)	<0.0001*
PED at month 3	0.009 (0.003)	0.0014*
Antidepressant medication	1.50 (0.67)	0.027*
BMI	−0.13 (0.08)	0.11
Study/drug type/OCT machine	0.45 (0.40)	0.26

Anti-VEGF, antivascular endothelial growth factor; BMI, body mass index; CRT, central retinal thickness; PED, pigment epithelium detachment; OCT, optical coherence tomography.

that included month 3 CRT (corrected for the OCT machine/study, p<0.0001), month 3 PED height (p=0.0014) and the intake of antidepressant medication (p=0.027) (table 2).

DISCUSSION

We here investigated systemic and ocular anatomical factors associated with the variable need for anti-VEGF retreatment. Multivariate analysis showed a significant association of the anti-VEGF retreatment need with antidepressant medication, month 3 CRT and month 3 PED height. The role of antidepressant medication was not significant in the univariate analysis, probably because of major differences in the groups (online supplementary table 1).

Previous reports have described a strong relationship between antidepressant response and VEGF, and its receptor activation in the hippocampus.[16–18] Patients with major depressive disorder, presumably on antidepressant treatment, show higher serum VEGF levels.[21 22] Since choroidal neovessels are directly in contact with the serum and since the retina is part of the central nervous system, we hypothesised that a depression and/or antidepressant-related VEGF increase might influence exudative activity in nAMD and increase the anti-VEGF treatment need. A higher anti-VEGF treatment need was associated with antidepressant medication use, despite the few patients on antidepressant medication (n=19, 9.3% of eyes) in our multivariate analysis (p=0.027).

This finding is new, but is consistent with those of previous reports. VEGF serum levels and gene expression are implicated in major depressive disorder.[13–15] Preclinical research has conclusively demonstrated the pivotal role of VEGF in antidepressant treatment. VEGF expression is induced by numerous classes of antidepressants,[16] and VEGF signalling through the Flk-1 receptor is required for both antidepressant-induced cell proliferation and for an antidepressant behavioural response.[16] Greene *et al*[18] confirmed that the antidepressant effect of fluoxetine in rats could be blocked by pharmacological inhibition of VEGF receptor signalling. Furthermore, chronic fluoxetine administration increased VEGF expression in both hippocampal neurons and endothelial cells.[18] Lee *et al*[19] also showed that specific knockdown of VEGF in hippocampal dentate gyrus cells inhibited antidepressant-like behaviour in mice. The antidepressant effect of regular exercise in chronically stressed mice is also VEGF-mediated and could be abrogated by an inhibitor of the VEGF receptor Flk-1.[17]

Moreover, a clinical pilot study by Ibrahim *et al*[21] reported that the antidepressant effect of sleep deprivation in patients with major depressive disorder correlated with increasing VEGF

levels. In a prospective controlled trial using duloxetine as antidepressant medication, circulating VEGF levels increased in the early responder group, but decreased in the early non-responder group.[22] The antidepressant effect appears to be mediated by hippocampal VEGF receptors.[16–18]

In nAMD, local VEGF production induces choroidal neovascular growth and exudation. Exudative signs are used as the retreatment criterion. The critical VEGF concentration might be reached earlier by increased circulating VEGF or locally produced VEGF due to antidepressant exposure. This might lead to a greater number of injections per time period.

However, in terms of visual function, there was no difference between patients on antidepressant medication or not (online supplementary table 1). Apparently, the influence of antidepressant medication on the VEGF pathway can be effectively compensated by the eye-specific adjustment of the retreatment frequency according to the exudative signs.

Additionally, our results implicated the CRT and the PED height at month 3. A thicker retina is usually associated with the presence of fluid and a greater retreatment need, although not directly linked to the retreatment protocol. PED is found in a high percentage of refractory nAMD.[23]

The factors identified in this study explain only some of the treatment need variability. Our multifactorial model, although statistically significant, remains incomplete (R^2=0.22), implicating other as yet unidentified factors.

Previously described factors, such as vitreomacular adhesion and traction,[7] older age, and male sex,[8] were not confirmed in our study. Polypoidal choroidal vasculopathy, reported to increase the need for retreatment,[8] was not included in our study. Additionally, we did not include sufficient information on obstructive sleep apnoea[9] or genetic polymorphisms for analysis.[8]

Recently, we found that macular atrophy was more frequent in patients needing fewer injections.[24] This suggests a change during the treatment course, from the pure neovascular form to some atrophic changes, occurring with reduced VEGF production and a lower retreatment need. However, the presence of GA at baseline was not associated with the treatment requirement.

Interestingly, the anti-VEGF drug (aflibercept or ranibizumab) did not influence the number of treatment sessions. However, this parameter was invariably linked to the study, the team and the OCT machine used, and these grouped parameters were associated with an increased treatment need in the study using aflibercept and the Spectralis SD-OCT, perhaps due to the high sensitivity of the Heidelberg Spectralis. The parameter per se lost significance in the multivariate model.

The study was limited in that it was not prospectively designed. We compensated for using different OCT machines by using the study team/anti-VEGF drug/OCT machine parameter for analysis correction. Few patients were on antidepressant medication, and current psychiatric diagnosis and depression intensity were unknown.

In conclusion, this study provided evidence that antidepressant medication influences anti-VEGF treatment requirement in patients with nAMD, possibly via the pro-VEGF effect of the medication, and/or depression status. Because AMD is frequently associated with depressive symptoms and thus potentially with antidepressant therapy,[11] further studies are needed to confirm the role of antidepressants in the management of patients with nAMD. Furthermore, we described the presence and height of PED and a thicker CRT as factors predicting higher anti-VEGF treatment requirements in nAMD. Additional factors, both systemic and ocular, that may explain the major differences in anti-VEGF treatment requirement between individuals/eyes with nAMD should be identified.

Contributors All authors have significantly contributed to the study and the manuscript. IM: study concept, data acquisition, statistical analysis, manuscript writing. MZ: data acquisition and manuscript writing. OM: pharmacological expertise, manuscript review. RG: study concept, psychiatric expertise, manuscript review. FB-C: study concept, manuscript review.

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Patient consent Obtained.

Ethics approval The study was approved by the local ethics committee (Ethics Committee Vaud, Switzerland) and was performed according to the ethical standards set by the Declaration of Helsinki.

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