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Experience of Anti-VEGF Treatment and Clinical Levels of Depression and Anxiety in Patients with Wet Age-Related Macular Degeneration

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Abstract

Purpose: To investigate detailed patient experiences specific to receiving vascular endothelial growth factor inhibitors (anti-VEGF) for wet Age-Related Macular Degeneration (wAMD), and to acquire a snapshot of the frequency of clinically significant levels of depression, anxiety and post-traumatic stress among patients and levels of burden in patients' carers.

Design: Observational cross-sectional mixed-methods study

Methods: 300 patients with wAMD receiving anti-VEGF treatment and 100 patient carers were recruited. Qualitative data on patients' experience of treatment were collected using a structured survey. Standardised validated questionnaires were used to quantify clinically significant levels of anxiety, depression, post-traumatic stress, as well as cognitive function and carers' burden.

Results: Qualitative data showed that 56% of patients (n =132) reported anxiety related to anti-VEGF treatment. The main sources of anxiety were fear of going blind due to intravitreal injections, and concerns about treatment effectiveness rather than around pain. From validated questionnaires, 17% of patients (n=52) showed clinical levels of anxiety, and 12% (n=36) showed clinical levels of depression. Depression levels, but not anxiety, were significantly higher in patients who received up to 3 injections compared to patients who received from 4 to 12 injections (ANOVA P=.027) and compared to patients who received more than 12 injections (ANOVA P=.001).

Conclusions: Anti-VEGF treatment is often experienced with some anxiety related to treatment regardless of the number of injections received. Clinical levels of depression seem to be more frequent in patients at early stages of anti-VEGF treatment. Strategies to improve patient experience of treatment and minimise morbidity are suggested.

Key Words: Wet Age-Related Macular Degeneration; Anti-VEGF; Depression; Anxiety; Experience.

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Short Title: Patient Experience of Anti-VEGF treatment for Wet AMD

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of vision loss and blindness in people aged 50 years and older, particularly in the developed world (1,2). Currently, wet AMD (wAMD) is the only form of AMD that is treatable, usually involving the use of vascular endothelial growth factor inhibitors (anti-VEGF) such as bevacizumab, ranibizumab, or aflibercept (3,4). Anti-VEGF treatments are regarded as a generational breakthrough in the treatment of macular diseases such as wAMD (5). Recent studies have shown that anti-VEGF treatment can significantly reduce patients' risk of severe visual impairment as it has great potential for halting disease progression (3-5). However, this treatment is administered by invasive intravitreal injections, often at the conclusion of lengthy, frequent and repeated visits after transport to a suitably equipped hospital.

The specific act of these intraocular anti-VEGF injections can be experienced by patients as a stressful event, with anticipatory anxiety and expectations of pain and discomfort (6-8). Evidence on this topic is still limited due the lack of studies exploring the complexity and diversity of patient experiences of anti-VEGF treatment for wAMD (9). A recent review of the literature (9) only found 3 studies exploring in-depth patients' experiences of receiving anti-VEGF treatments using qualitative designs (8,10,11). The remaining studies addressing the experience of receiving anti-VEGF treatment were mainly focused on medical aspects such as the anaesthetic's effectiveness to prevent pain when receiving an intravitreal injection (12-17). The studies suggest that anticipatory anxiety associated with anti-VEGF treatment tends to be circumscribed to the first injections, i.e. at early stages of treatment (17,18). The aspects of anti-VEGF treatment in which patients have reported more discomfort and anxiety are (6-8,10,18): needle entry; application of drops; insertion of speculum; waiting for injection; experiences of pain, fear of losing sight, fear for the unknown and side effects. One qualitative study (11) also stressed the potential importance of other variables for the way patients experience anti-VEGF treatment and cope with anxiety and the fear for the "unknown". These variables are: communication between healthcare professionals and patients, especially about treatment procedures; and the way service is delivered, with a special attention for anticipatory anxiety induced by waiting times before the injection. In another qualitative study on patient experience of anti-VEGF treatment (8), cautious optimism regarding treatment success and disease stabilization was found as a frequent and valid response to treatment from wet AMD patients. There is, overall, a need for more research exploring the complexity of patient experience of anti-VEGF treatment to clarify reasons underlying patients' anxieties when receiving regular intravitreal injections (9).

The relationship between AMD and depression and anxiety has been well documented in literature (19-24). Research shows a wide prevalence range from 15.7% to 44% for depressive symptoms and 9.6% to 30.1% for anxiety symptoms among AMD patients (19). Previous studies have suggested that vision-related disability (caused by visual impairment) (25-28), visual acuity (29,30), and social support (31,32) can play an important role in the link between visual impairment and depression. Other studies have highlighted the link between ageing and depression (33) which might also play a role in the relationship between AMD and depression. However, most studies on depression associated with AMD were conducted prior to the implementation of anti-VEGF treatments or were conducted on general AMD patients (dry and wet) (22,34). This might be explained by the fact of anti-VEGF treatment is relatively recent and previous research on AMD and depression was conducted before the dissemination of anti-VEGF as the first line treatment for wAMD (34).

Considering the positive effects of anti-VEGF to prevent further vision loss in wAMD patients, the question has been raised as to whether patients receiving anti-VEGF treatment might present a different prevalence of depression and anxiety (34,35). Existing studies in this field are still limited in generating evidence and often with low numbers (9,34). A recent

review on this topic (9) found four studies where the prevalence of depression was examined in patients receiving anti-VEGF treatments (22-24,36). Findings were preliminary but suggested that the wAMD patient group receiving anti-VEGF treatment still present higher rates of depression and anxiety in comparison with general population. Finally, previous research has also shown that despite depression and anxiety being common among adults with vision loss, they tend to not be tackled by health services and therefore remain untreated (36-39).

The primary purpose of this study is to investigate the patient experience of receiving anti-VEGF treatment for wAMD, with a particular focus on patient sources of anxiety related to anti-VEGF treatment. The secondary aim of this study is to achieve a snapshot of the frequency of clinical levels of anxiety, depression, and post-traumatic stress (PTS), among patients attending for treatment of wet AMD, and to explore levels of burden among patient carers. To the best of our knowledge there is no literature supporting the existence of any link between AMD or anti-VEGF and PTS, but we included the assessment of PTS as exploratory of any serious unmet mental health needs that could influence patients' experience of treatment. Additionally, we want to explore clinical levels of depression and anxiety between patients with different number of injections received and between patients with different visual acuity. Mental health problems in our patient group could be related to their AMD, the injection treatments, ageing, personal history, burden of travel or other internal and external factors and we do not attempt to prove any specific link between anti-VEGF and psychological symptoms. Instead we aimed to explore any existent mental health needs in our patient group, exploring clinical levels of depression and anxiety across different patient sub-groups to derive a general picture of patients' mental health and whether these needs are being met by health services. With regard to patient carers, we also wanted to achieve a snapshot of the burden experienced by carers of a patient who regularly receives anti-VEGF treatment. Our study aims were built upon two premises: the fact our patient group is receiving regular invasive treatment that has been described as potential stressful; and the fact of AMD patients are generally considered at risk of having comorbid mental health problems that tend to not be addressed by health services. Our ultimate hope is that information from this study can be used to help managing the psychological as well as ophthalmic needs of our patients in AMD clinics.

Literature on depression and anxiety among wAMD patients receiving anti-VEGF treatment is still very limited and scarce, which necessitates a more exploratory scope for our study. However, we hypothesise that patient anxiety related to anti-VEGF is more frequent among patients at early stages of treatment, i.e., in patients who have received up to 3 injections than in patients who are receiving treatment for longer, in light of what was suggested in previous studies (17,18). Additionally, we hypothesise that clinical levels of depression and anxiety are significantly more frequent in patients who are at early stages of treatment (who have received up to 3 injections) than in patients receiving treatment for longer, i.e., the higher the number of anti-VEGF injections received, the less frequent anxiety and depression are seen. Finally we also hypothesise that the frequency of clinical levels of depression and anxiety are negatively correlated with visual acuity, as previous studies suggested that depression is associated with poorer visual acuity in patients with vision disorders (29,30).

Methods

Ethics

North West Research Ethics Committee (NHS, UK) approved study procedures (reference 15/NW/0288). The study adheres to the tenets of the declaration of Helsinki. We offered all participants a participant information sheet, and obtained informed consent prior to recruitment.

Study Design

We carried out an observational cross-sectional mixed-methods study. The qualitative strand used a structured survey to explore patient experience of receiving anti-VEGF treatment and sources of anxiety associated with this treatment. The quantitative strand of this study used standardised psychological instruments to investigate depression and anxiety, and post-traumatic stress in our sample of patients and levels of burden among patients' carers. This mixed-methods design allows us to combine the measurement of psychological health in patients undergoing treatment for wAMD (depression, anxiety and post-traumatic stress) with in-depth data (qualitative strand) that explores experience of treatment and sources of anxiety associated with treatment.

Participants

We invited consecutive patients with formal diagnoses of wAMD attending the macular treatment centre at Manchester Royal Eye Hospital to take part in the study. Patients and carers were recruited from May 2015 to November 2015. Inclusion criteria for patients were: to have a confirmed diagnosis of wAMD, to have received at least one anti-VEGF injection prior to the interview for this study, and to be followed-up in the macular treatment centre of the corresponding hospital. We included in our study patients who were receiving and who were not receiving psychological and psychiatric treatment. We excluded patients whose first anti-VEGF injection was on the day of interview and patients who were not able to communicate effectively. For carers the inclusion criteria was only to be carer of a patient currently receiving anti-VEGF treatment for wAMD. In our study, all researchers were blinded to carer-patient relationship, i.e., we interviewed carers without knowing who was the corresponding patient of each carer, in order to allow carers to be as open and honest as possible.

Procedures

Participants were approached by an experienced clinical psychologist (HS) on the same day they were scheduled to have the medical appointment and receive treatment. All patients were invited to participate in an individual interview before receiving the injection, in a private room where all study instruments were administered. Participants were issued with a patient information sheet, and given the opportunity to ask questions about their participation. They provided written informed consent if they agreed to participate. Questionnaires and forms were read to patients who were unable to read as a result of their vision loss or having received topical eye medication. Carers of patients were approached by another researcher (NM) on the same day, following the same procedures.

M**easures for Qualitative Strand**

For the qualitative strand of this study, we were keen to acquire a broad range of information specific to AMD. A structured survey was developed from input provided by a patient and public involvement (PPI) group, previous literature on the topic, and considering our prior experience of dealing with AMD patients. The PPI event consisted of an informative meeting with wAMD patients, researchers and healthcare professionals who worked with these patients on a daily basis. The PPI group helped to identify key issues of patients' perceptions and concerns about anti-VEGF treatment and the way it has been delivered, which shaped the development of the survey. The PPI meeting lasted 2 hours and was audio-recorded and transcribed to identify the main and key concerns raised by participants about the treatment for wet AMD and the way the treatment is being delivered by our service. Although our survey was built upon the main topics raised by PPI participants, we have also included

questions addressing topics that have been highlighted in previous literature on patient experience of anti-VEGF treatment (9), such as sources of anxiety related to anti-VEGF treatment, and experiences of pain when receiving an injection. The final version of our survey comprised of 17 closed-ended questions addressing patients' demographics, clinical data and experience and perception of anti-VEGF treatment, and one open-ended question addressing patient concerns and anxieties on the anti-VEGF treatment (for more details on the survey please see appendix A). Topics covered by the survey included anxieties and concerns about anti-VEGF treatment, treatment preferences and options, doctor/patient relationship, pain experienced when receiving treatment and perception of carer's burden.

Measures for Quantitative Strand

We defined patients' visual acuity (VA) as the best-corrected VA of the eye with better vision. Best-corrected VA was converted into the logarithm of the minimum angle of resolution during analysis. We divided patients into 3 groups, based on the World Health Organization (WHO) classification of visual impairment (40): no visual impairment or mild visual impairment (VA≥6/18), moderate impairment (6/60 < VA<6/18) and severe impairment (VA<6/60).

Depression and anxiety were assessed by the Hospital Anxiety and Depression Scale (HADS) (41). HADS is a 14-item self-report scale, comprising two subscales evaluating levels of anxiety (HADS-Anxiety) and levels of depression (HADS-Depression). The HADS has been used extensively in the hospital setting as a standardised psychological screening tool for emotional disorders (41). Each subscale includes 7 items, generating possible scores of 0 to 21 for anxiety (Cronbach's $\alpha = 0.89$) and depression (Cronbach's $\alpha = 0.91$). A score of 8 and above is widely used to indicate the presence of clinical levels of anxiety or depression that may warrant further psychological investigation (41,42).

Post-traumatic stress (PTS) symptoms related to receiving an intravitreal injection was assessed by the Impact of Events Scale-Revised (IES-R) (43). IES-R is a validated measure of self-reported posttraumatic stress symptoms experienced in the past seven days in relation to a specific stressor (40). IES-R consists of 22 items, each ranging from 0 ("Not at all") to 4 ("Extremely"), with the total score ranging from 0 to 88. Three symptom clusters associated with post-traumatic stress are assessed with the IES-R, including intrusion, avoidance and hyperarousal. Intrusion relates to intrusive thoughts, nightmares and imagery associated with the traumatic event (8 items; Cronbach's $\alpha = 0.90$), avoidance relates to avoidance of any feelings or situations (8 items; Cronbach's $\alpha = 0.95$) and hyper-arousal is an inability to concentrate, anger, irritability and hypervigilance (6 items; Cronbach's $\alpha = 0.96$). Higher scores indicate more symptoms of posttraumatic stress, with scores above 24 indicating the potential need for clinical assessment and care (43).

The Mini-Mental State Examination (MMSE) (44) was used to assess patients' cognitive status. MMSE consists of two sections: the first section requires oral responses regarding temporal and spatial orientation, memory and attention; the second section requires the subject to name simple objects, follow verbal written commands, write a sentence spontaneously, and copy two intersecting pentagons, in order to assess language and visuo-spatial functions. MMSE final score ranges from 0 to 30 (the maximum score). MMSE scores from 25 to 30 suggest a questionably significant degree of cognitive impairment. Scores from 21 to 24 indicate mild cognitive impairment. Scores from 10 to 20 suggest moderate cognitive impairment, and scores below 10 suggest severe cognitive impairment. We adjusted some vision-related tasks to make them suitable for patients with vision impairment: for the task "writing a sentence" we helped the patient to find the paper and writing space; for the task "reading a sentence" we provided larger letters printed in bold; and for "identifying a pen and a watch" we adjusted the distance of those objects to the patients'

eyes. We only excluded the last MMSE task which consists of asking the patient to copy a pair of intersecting pentagons, as this task involves more complex visuospatial planning and executive skills. We anticipated that some patients would perform inaccurately in this task due to reduced visual acuity which would compromise the reliability of results. Final scores were adjusted from 0 (minimum) to 29 (maximum) because one point refers to the last test task involving the copy of a pair of pentagons. Cut-off scores were also adjusted, i.e., we used the original test cut-off scores minus 1 point. The internal consistency of the MMSE obtained Cronbach's alphas of 0.82 in elderly patients admitted to a medical service and 0.84 in elderly nursing home residents (44,45).

The Burden Assessment Scale (BAS) (46) was used to assess burden in patients' carers. BAS is a 19-item measure that evaluates burden in an objective way, that is, the amendment of caring for someone with limitations imposed on the level of activities and resources of the caregiver. BAS employs a 4-point scale (1–4), with higher scores indicating greater levels of caregiving burden. Cronbach's alphas for the subscales and total scale were as follows: a = 0.82 for limitation in activity, a = 0.64 for feelings of worry and guilt, a = 0.71 for social burden, and a = 0.81 for total scale.

Data Analysis

Results are presented mainly with descriptive statistics using SPSS software. We had no prior sample to perform power calculations. As part of pilot analyses, Chi-square test was used to investigate whether or not anxiety related to treatment is more frequent in patients who have received up to 3 injections than in patients who have received more injections, i.e., patients receiving treatment for longer. The basic assumptions for this statistical test were satisfied in that there were distinct categories and all expected frequencies were greater than 5. We created three sub-groups of patients who received up to 3 injections, i.e. patients who are at early stages of treatment (Group 1, n=21); patients who received 4 to 12 injections, i.e., patients who are not at early stages of treatment but are more experienced with treatment and are not yet regarded as chronically treated (Group 2, n= 119); and patients who have received more than 12 injections and therefore are more likely to be chronically treated with anti-VEGF (Group 3, n=160). The choice of sub-groups was based upon patient and public involvement meetings and upon timeframes cited in previous literature indicating patient anxiety associated with earlier stages of treatment (17,18). Univariate ANOVA was used to investigate differences in HADS scores for depression and anxiety between all sub-groups of patients (G1, G2 and G3). Chi-square test was used to investigate differences in the frequency of patients with HADS scores indicating clinical levels of depression between all sub-groups of patients (G1, G2 and G3). Chi-square post-hoc analysis was performed using adjusted residuals (47) to investigate which sub-groups of patients present significant differences in number of cases of clinical levels of depression. The samples were from a number of independent groups and the variables were normally distributed with similar variance in each group. Pearson correlation was used to investigate associations between HADS scores and visual acuity (LogMAR), and between HADS scores and number of injections received. Data from the survey was analysed in terms of frequency of responses for each closed-ended question. The final open-ended question of the survey was analysed for the frequency of each source/type of anxiety related to anti-VEGF treatment that patients reported.

Results

Patient Characteristics

We invited 345 patients and 100 carers to participate in our study. Of 345 patients 41 refused to participate and 4 were not eligible because they were not able to communicate effectively with the interviewer. A total of 300 wAMD patients and 100 carers gave their consent and

agreed to participate in this study. Patients' demographic and clinical data are presented in Table 1. Our sample of patients had a higher percentage of women (59.7%), and patients who were receiving treatment for more than 1 year (72%). The great majority of patients (85%) had good visual acuity or mild visual impairment. More than 95% of our patients were not receiving any psychological or psychiatric support at the time of the interview.

Please insert Table 1 here

Qualitative Strand – Broad Experience of Receiving Anti-VEGF Treatment from Survey

Patients' experience of receiving anti-VEGF treatment is presented in table 2 and table 3. Generally patients reported a positive feedback on doctor/patient relationship and the quality of care received. Most patients were satisfied with the support received from the hospital and also satisfied with the information received about the condition and treatment. Most patients also preferred to rely on the doctors to make treatment decisions. With regard to patients' treatment concerns and anxiety, we found that 132 patients (56%) reported some type of anxiety related to anti-VEGF treatment. Further analysis showed that the patients' main concerns and sources of anxiety related to anti-VEGF treatment were: fear of going blind due to intravitreal injections / fear of the needle causing damage in the eye (n=118; 39.3%); hope the treatment works properly / fear of getting worse because the treatment didn't work (n=111; 37%); waiting in the patient waiting room / anticipatory anxiety (n=104; 34.6%); and fear of the unknown in relation to treatment outcomes and disease progression (n=91; 30%). In contrast, anxiety around injection pain (n=10; 3.3%) were relatively infrequently raised. 127 patients (42.3%) did report experiences of pain when receiving an intravitreal injection, but the level of pain was relatively minor with mean score of 2.4 (±3.17) on a scale from 0 to 10 with 67% of patients experiencing a level of pain equal or below to 3 (scale 0 to 10). Among those patients who reported pain when receiving an injection, 42 patients (33%) experienced pain only during the initial treatment injection(s), 55 patients (43.3%) experienced pain half way through their treatment, and 30 patients (23.6%) experienced pain only during the last few injections received. More than half of patients (53.7%) reported to have expected more pain than they really experienced when receiving an intravitreal injection.

Please insert Table 2 and Table 3 here

Anxiety related to Anti-VEGF treatment and Number of Injections Received

Frequency of anxiety related to treatment in each patient sub-group for the number of injections received is presented in Table 4. Chi-Square showed no significant differences ($P>.05$) in the frequency of anxiety related to anti-VEGF treatment between patients who have received different number of injections, i.e., between all patient sub-groups (G1, G2 and G3).

Please insert Table 4 here

Quantitative Strand – Clinical Levels of Depression, Anxiety, Post-traumatic stress and Carers Burden

Results from the standardized measures on depression, anxiety, post-traumatic stress, cognitive function and burden are presented in Table 1. HADS-Anxiety scores indicated that 17% (n=52) of all wAMD patients had clinical levels of anxiety, 10.6% (n=5) of which were receiving psychological or psychiatric treatment at the time of interview. HADS-Depression scores indicated that 12% (n=36) of all wAMD patients had clinical levels of depression, 9%

(n=3) of which were receiving psychological or psychiatric treatment for depression. Therefore 89% (n=47) of patients who showed anxiety, and 91% (n=33) of patients who showed depression were not receiving appropriate psychological and psychiatric treatment for their condition. 1 % (n=3) of patients showed symptoms of post-traumatic stress disorder according to the IES-R. Most patients (90.3%; n=271) did not exhibit impaired cognition according to MMSE. All patients were able to perform the administrated MMSE vision-related tasks successfully. Finally, according to BAS scores, 73% (n=73) of carers reported little or no burden, 19% (n=19) reported mild to moderate burden, and 8% (n=8) reported moderate to severe burden. No carers reported severe burden.

Please insert Table 5 here

Depression and Anxiety Investigated for Number of Anti-VEGF Injections Received and Visual Acuity

Table 5 displays HADS scores in different sub-groups of patients regarding the number of anti-VEGF injections received. HADS-Depression scores were significantly higher in patients who had received up to 3 injections (Group 1) in comparison with patients who had received from 4 to 12 injections (Group 2) (ANOVA P=.027), and in comparison with patients who had received more than 12 injections (Group 3) (ANOVA P=.001). No significant differences were found in HADS-Anxiety scores between the three sub-groups of patients for the number of injections received (ANOVA P=.22).

Table 6 displays the frequency of patients with a HADS-Depression score indicating clinical levels of depression in the three sub-groups of patients (HADS-Depression≥8). Chi-square test showed significant differences between groups (P=.003*).* Chi-square post-hoc analysis indicated that the number of patients with clinical levels of depression were significantly higher in Group 1 (patients who had received up to 3 injections) (P=.002), considering the adjusted Bonferroni corrected P-value of .008.

HADS-Depression scores were significantly but weakly correlated with number of anti-VEGF injections received (R=-.126; P=.03). HADS-Anxiety scores were not significantly correlated with number of injections (P=.325). Both HADS-Anxiety (P=.536) and HADS-Depression scores (P=.635) were not significantly correlated with VA (LogMAR).

Please insert Table 6 here

Discussion

The qualitative findings of the study demonstrated that patients generally reported to have a good understanding of anti-VEGF treatment, and a good relationship with healthcare professionals. Additionally, they acknowledged the need for receiving treatment and its potential benefits for their eye health. However, despite presenting positive feedback on anti-VEGF treatment, more than half of the patients reported anxiety associated with receiving anti-VEGF treatment. In addition, our findings suggest that the frequency of anxiety related to treatment is similar between patients who are at early stages of treatment, i.e., patients who had received up to 3 injections, and patients who are receiving treatment for longer. This finding rejects our hypothesis that patients anxiety related to treatment is higher in patients who have received up to 3 injections and suggests that the anxiety related to anti-VEGF might persist throughout the treatment, which is not consistent with some previous literature (17,18). A possible explanation for this finding is the fact of patients' three most frequent sources of anxiety related to treatment in our study were related to fear of going blind due to injections, concerns about vision getting worse from treatment failure and waiting in the waiting room. These sources of anxiety are known to be frequent in this patient group

(8,10,11) and are triggered by treatment preconceptions, and anticipatory anxiety induced by regular waiting times in the waiting area before receiving treatment (11). Further cohort studies will better clarify patient anxiety related to anti-VEGF treatment, in terms of variance throughout the treatment and identifying potential anxiety triggers.

Previous literature has suggested that the main sources of patient discomfort and anxiety are related to the injection procedure and the fear of a needle causing damage in the eye (6,8,10,11). Our survey acknowledges this but suggests greater patient fears of going blind either as the final route of wAMD and / or as a consequence of an unexpected adverse event occurred during the injection, which is very unlikely to occur. These fears occurred despite patients having received routine information from the medical staff about the potential benefits of anti-VEGF treatment and the safety of treatment procedures. The findings from the survey suggest patients may benefit from additional and very specific information before they start the treatment with regard to the success rates of anti-VEGF treatment in halting disease progression, the disease process and how treatment can reduce the risk of becoming blind in the future. Additionally, it would be useful for patients to be informed that the needle in the eye will not be applied in the central area of the ocular globe, i.e., the patient will not see the needle coming into the eye. Finally patients need to be better informed about low likelihood of serious problems following the treatment, and that most adverse effects can be easily manageable after the treatment. Further patient resources and/or communication skills training for health professionals would help to better inform patients.

The quantitative finding of the study illustrated a considerable frequency of patients with clinical levels of depression and anxiety, and low percentage of patients with symptoms of post-traumatic stress. According to epidemiologic studies on depression and anxiety (48,49), the frequency of clinical levels of anxiety and depression we found in our patient group is higher than general population, and within the range of what has been found in studies on general AMD patients (dry and wet AMD) (19). However, it is also noticeable that the frequency of patients with clinical levels of anxiety that we found in our validated questionnaires (17%) is clearly lower than the frequency of patients reporting anxiety related to treatment in our survey (56%). This difference is explained by the concept that patient anxiety related to treatment does not necessarily have clinical value or entail clinical levels of anxiety, i.e., a patient can have concerns and anxiety about the treatment but not being clinically anxious.

Another important issue was that most of our patients were not receiving any psychiatric or psychological treatment at the time of interview. These findings draw attention to the need of tackling mental health needs among adults with vision loss, especially in health services dedicated to provide care for ophthalmologic diseases. Previous research has highlighted the tendency for these needs to remain unaddressed (36-39), which might have a negative impact on patient healthy life-style, and eventually compromise medical treatment outcomes.

The study results partially reject our previous hypothesis that the frequency of clinical levels of depression and anxiety is higher at early stages of anti-VEGF treatment. We only confirmed the hypothesis that the frequency of clinical levels of depression is higher in patients who were at early stages of treatment (had received up to 3 intravitreal injections), compared to patients who had received more than 3 injections, i.e., patients who were at later stages of treatment. This hypothesis is also supported by the correlation we found between the number of injections received and HADS-Depression scores. However, this finding should be confirmed in further studies conducted on a larger sample size, as our group 1 sample was small and the correlation coefficient we found was significant but weak. Previous literature on this topic is very limited and inconclusive about the frequency of depression in patients at different anti-VEGF treatment stages (9,22,28,34). One possible hypothesis to explain why depression is higher in patients at early stages of treatment is the fact of AMD is

often seen as a threatening condition that entails further blindness (50). Patients recently diagnosed with wAMD can therefore have that expectation of going blind. Previous qualitative and mixed-methods studies on adults with serious vision disorders suggested that the fear of further vision loss and blindness can be an important source of emotional distress (32,51,52), which can ultimately lead to depression (32). In light of this, patients at early stages of anti-VEGF treatment might be at higher risk of having depression due to their fear of going blind because of wAMD. However, as anti-VEGF treatment proceeds, patients can become more optimistic about treatment success and disease stabilization (8).

Patients in this study were on anti-VEGF therapy and the great majority of them had good visual acuity and did not have visual impairment according to the WHO's criteria (40). We still found that a percentage of wAMD patients are clinically depressed and anxious within the same prevalence range found in previous studies conducted with adults with visual impairment (53-55). Additionally, we rejected our hypothesis that depression and anxiety are negatively correlated with visual acuity, which is not consistent with some previous literature suggesting that patients with lower visual acuity are more likely to suffer from depression than patients with better visual acuity (29,30). However this is possibly explained by the fact of the great majority of our patients did not have visual impairment and therefore they were not likely to suffer from vision-related disability which my triggers depression (25-28).

Social support has been described as playing an important role in patient experience of illness and depression (31,32). Most of patient carers them did not report experience of burden while being carers of someone with wAMD. This finding is consistent with the fact that most of our patients didn't perceive themselves as a source of burden for carers which might suggest that the majority of our patients had no issues with social support.

Our study highlights common sources of anxiety related to the process of treatment for wet macular degeneration and an awareness of these would be useful for any clinician to improve the patient experience with wAMD. It is suggested that some patient anxiety such as the fear of going blind due to injections, fear for the unknown and fear of getting worse, might be attenuated with effective communication from healthcare professionals and some counselling if needed. To ask patients about their preconceptions and expectations of treatment and prepare them for initiating anti-VEGF treatment, explaining how injections are administrated and how unlikely it is to go blind because of injections, might help patients to cope with treatment. Physicians should also be aware of the prevalence of undiagnosed anxiety and depression in their AMD patients and be alert to the opportunity to manage this. Inclusion of standardized tools to screen wAMD patients for symptoms of anxiety and depression in the clinical routine of a macular treatment unit could help to better identify such patients. This should be applied irrespective of how long patients have been having injections.

In the current study, some limitations need to be acknowledged. This is a cross-sectional study and therefore it is more limited in providing insights into dynamic changes in clinical levels of depression and anxiety over time which would be valuable to understand these symptoms in our sample. In our study there was potential for selective bias in data collection because we were not able to identify patients who discontinued treatment after initial injection and patients with very good response (no recurrence after the first loading phase of 3 injections) or very poor response to treatment (vision drop below 6/60 despite treatment), because these patients' follow-up is usually carried out outside the hospital. One of the researchers who collected data for this study (HS) also contributed to the study design and data analysis which may have entailed some bias to the results of study. Furthermore some of the researchers involved in the study have had prior clinical experience with wAMD patients, and therefore may hold preconceptions about patients' coping behaviours with treatment, which may also contribute as a source of bias. In our study the researcher were blinded to the patient-carer relationship, and did not link carers to the corresponding patients to ensure they

would provide a more authentic input of their experiences and perceptions of being a carer. However, a limitation of this was that we were not able to know about the potential importance of patients' social support for their experience of treatment and for the occurrence of clinical levels of depression. Finally, the authors were not able to have data on the clinical characteristics of the 41 patients who refused to participate and therefore didn't provide informed consent, and the 4 patients who were excluded because they were unable to communicate effectively with the interviewer.

In conclusion, this study represents one of the largest and most detailed examinations of patients undergoing anti-VEGF therapy to date. We found that although anti-VEGF treatments themselves are generally well-accepted, particular causes of anxiety exist which could potentially be reduced by improved education and minor alterations in practice. Our additional study using validated objective questionnaires demonstrated that in our examined population, a substantial percentage of patients with wAMD receiving anti-VEGF treatment had undiagnosed clinical levels of anxiety and depression, despite the good visual acuity and the promising outcomes offered by anti-VEGF treatment in preventing further visual impairment. Doctors should be vigilant to this finding that might impair patients' quality of life and consider measures to detect and address this. Further longitudinal studies and controlled trials are needed to provide a more in-depth understanding about depression and anxiety in wAMD patients and to aid development of new intervention tools, at both the patient and clinical level, aiming to reduce these symptoms and to improve the well-being of patients receiving anti-VEGF treatment.

Abbreviations and Acronyms:

wAMD: Wet Age-Related Macular Degeneration; **Anti-VEGF**: Vascular endothelial growth factor inhibitors; **HADS:** Hospital Anxiety and Depression Scale; **IES-R:** Impact of Events Scale Revised; **MME:** Mini-Mental State Examination; **VA:** Visual Acuity; **BAS:** Burden Assessment Scale

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Table 1 – Demographical and Clinical Data

Variable		**No. (%)**	**Range**	**Mean ± SD**
Age			56-95	80±7.4
Gender	Female	179 (59.7%)		
	Male	121 (40.3%)		
Years of education	<10	193 (64.3%)	4-21	10.8±2.5
	≥10	107 (35.7%)		
Relationship status	Single	22 (7.3%)		
	Married	122 (40.7%)		
	Widowed	123 (41%)		
	Cohabited	7 (2.3%)		
	Divorced	36 (8.7%)		
Visual acuity (LogMAR)	Good VA / Mild visual impairment (≥6/18)	255 (85%)	0.02-1.0	0.6±0.26
	Moderate VA (6.60≤VA<6/18)	42 (14%)		
	Poor VA (<6/60)	3 (1%)		
Type of anti-VEGF treatment	Ranibizumab	120 (40%)		
	Aflibercept	175 (58.3%)		
	Bevacizumab	5 (1.6%)		
Elapsed time since the first anti-VEGF injection (Treatment Duration)	≤ 1 Year	84 (28%)	0-96	30.9±24
	> 1 Year	216 (72%)		
Number of injections received to date			1-66	16.6±11.6
Receiving any type of psychiatric or psychological treatment	Yes	13 (4,3%)		
	No	287 (95,7%)		
Symptoms of Clinical Depression (HADS-D)	No symptoms of depression	264 (88%)		
	Symptoms of depression	36 (12%)		
Symptoms of Clinical Anxiety (HADS-A)	No symptoms of anxiety	248 (82.7%)		
	Symptoms of anxiety	52 (17.3%)		
Symptoms of PTS (IES-R)	No symptoms of PTS	297 (99%)		
	Symptoms of PTS	3 (1%)		
Cognitive Impairment	No cognitive impairment	271 (90.3%)		

(MMES)	Mild cognitive impairment	25 (8.3%)		
	Moderate to severe cognitive impairment	4 (1.3%)		
Carers' Perception of Burden (BAS)	Little or no burden (0-20)	73 (73%)	0-55	14.4±13.07
	Mild to moderate burden (21-40)	19 (19%)		
	Moderate to severe burden (41-60)	8 (8%)		
	Severe burden (61-88)	0		

Table 2 Results from Survey about Patient Experiences of Anti-VEGF treatment

Survey Topic	**Sub-Topics**		**No.(%)**
Anxiety related to anti-VEGF Treatment		Anxiety / concerns related to treatment not reported	132 (44%)
		Anxiety / concerns related to treatment reported	168 (56%)
Preferences about the treatment	Hospital Visits	Prefer having fewer hospital visits	163 (54.3%)
		Don't mind about the number of hospital visits	137 (45.7%)
	Frequency of Intravitreal Injections	Prefer receiving less frequent injections	174 (58%)
		Don't mind about the frequency of injections	126 (42%)
Expectation of Pain before start the Treatment		No pain expected	128 (42.7%)
		Pain expected	161 (53.7%)
Experience of Pain When Receiving an Intravitreal Injection		No painful experience	162 (54%)
		One or more painful experiences	127 (42.3%)
Doctor/patient relationship	Understanding of Treatment Options	Good understanding of the different treatment options	192 (64%)
		Poor understanding of the different treatment options	21 (7%)
		Have only been told about one treatment option	87 (29%)
	Making Decisions on the Eye Treatment	Prefer just rely on the doctors for making decisions on the AMD treatment	197 (65.7%)
		Prefer to be more in charge for making decisions on the AMD treatment	8 (2.7%)
		Both (to rely on the doctors and to be in charge for making decisions)	38 (31.7%)
	Contradictory	Have received contradictory	22 (7.3%)

	Information about the Condition and Treatment	information about the diagnosis and treatment	
		Did not have received contradictory information about the diagnosis and treatment	277 (92.3%)
	Satisfaction with the support received from the hospital	Some disappointment	38 (12.7%)
		Not disappointed	262 (87.3%)
	Explanation about treatments and exams	Insufficient	35 (11.7%)
		Good	265 (88.3%)
Perception of carer's burden	The carer has been burdened with hospital visits		44 (14.6%)
	The carer has not been burdened with hospital visits		130 (43.3%)
	Not applicable / no carer		126 (42%)

Table 3 Results from Survey about Patient Concerns and Sources of Anxiety Related to Anti-VEGF Treatment

Concerns / Anxieties Associated with anti-VEGF Treatment	**No.(% of total sample)**
Fear of going bling due to injections / fear of the needle in the eye	118 (39.3%)
Hope the treatment works properly / Fear of getting worse because the treatment didn't work (treatment effectiveness)	111 (37%)
Waiting in the waiting room / Anticipatory anxiety	104 (34.7%)
Fear of the unknown in relation to treatment outcomes and disease progression	91 (30%)
Anxiety caused by being in the eye hospital for a medical appointment, exam or eye-treatment	52 (17.3%)
Fear of pain when receiving an injection	10 (3.3%)
Fear of side effects	8 (2.6%)

Table 4 – Frequency of Anxiety related to Anti-VEGF Treatment between Sub-Groups of Patients

	G1: Up to 3 injections received (N=21)	G2: From 4 to 12 injections received (N=119)	G3: More than 12 injections received (N=160)	*P*-value*
Patients who reported anxiety related to treatment (N=168)	14 (66,7%)	64 (53,8%)	90 (56,3%)	.546
Patients who did not report anxiety related to treatment (N=132)	7 (33,3%)	55 (46,2%)	70 (43,8%)	

G: Sub-Group of Patients; *Chi-Square test

Table 5 – HADS scores in Sub-Groups of Patients

	G1: Up to 3 injections received (N=21)	G2: From 4 to 12 injections received (N=119)	G3: More than 12 injections received (N=160)	*P*-value* between G1-G2	*P*-value* between G1-G3	*P*-value* between G2-G3
HADS-Anxiety (±SD)	5.1±3.9	3.8±4.1	3.56±3.51	.34	.19	.83
HADS-Depression (±SD)	5.8±4.5	3.7±3.8	2.9±2.9	.027**	.001**	.11

G: Sub-Group of Patients; VA: Visual Acuity; VI: Visual Impairment

* Univariate ANOVA; ***P*<0.05

Table 6 – Frequency of Clinical Levels of Depression between Sub-Groups of Patients

	G1: Up to 3 injections received (N=21)	G2: From 4 to 12 injections received (N=119)	G3: More than 12 injections received (N=160)	*P* Value*
Patients with Clinical Levels of Depression (HADS-D≥8)	7 (33,3%) *P=.001***	16 (13,4%) *P=.54***	13 (8,1%) *P*=.03**	.003

* Chi-Square Test before Post-Hoc analysis; ** Chi-Square Post-Hoc Analysis (Adjusted Bonferroni Corrected *P*-value=.008)