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Quality of Life in Macular Degeneration Between Photodynamic Therapy and Pegaptanib Treatment Groups

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QUALITY OF LIFE IN MACULAR DEGENERATION BETWEEN PHOTODYNAMIC THERAPY AND PEGAPTANIB TREATMENT GROUPS

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ABSTRACT

A STUDY OF QUALITY OF LIFE IN AGE-RELATED MACULAR DEGENERATION COMPARING PHOTODYNAMIC THERAPY AND PEGAPTANIB SODIUM TREATMENT GROUPS.

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The purpose of this study was to examine quality of life (QOL) in age-related macular degeneration (AMD), particularly across photodynamic therapy (PDT) and pegaptanib sodium injection treatment groups.

Patients with AMD were either mailed or were administered in person a modified version of the Visual Function Questionnaire (VFQ-25). Subgroup analysis of the VFQ-25 was performed per NEI prescribed algorithms and additional analyses regarding questions on treatment side effects were also performed. A two-tailed student t-test and mean were calculated for each treatment group and correlations between visual acuity and subgroup outcomes were calculated. Correlations between the subgroup and treatment-related subgroup outcomes were also calculated to determine which QOL deficits might occur together. Multiple linear regression models were used to estimate the association between the overall QOL score and scaled visual acuity, age, gender, and treatment history.

30 patients were interviewed in person and an additional 41 patients returned the questionnaire by mail. Of these, 37 had been treated with PDT (ten had also received intravitreal triamcinolone acetate (IVTA) injections); 16 had been treated with pegaptanib; seven had been treated with both pegaptanib and PDT (two had also received IVTA); and 25 had not been treated with any of these treatments. The mean age was 79 years. Patients' lowest subgroup scores were in perception of general vision (43.2) and in driving (50.8). The ocular pain subgroup yielded a mean score of 82.9 for the PDT group and 87.5 for the pegaptanib group ($p = 0.59$). The average vision worsening score for the first two weeks following treatment was 87.5 for the PDT group and 77.8 for the pegaptanib group ($p = 0.29$). The average mental health score for concerns related to treatments was 78.2 for the PDT group and 73.6 for the pegaptanib group ($p = 0.61$), while the average independence score related to treatment appointments was 86.1 for the PDT group and 87.5 for the pegaptanib group ($p = 0.92$). Strong positive correlations (> 0.45) were seen between general health and ocular pain; between treatment-related mental health and both overall QOL score and treatment-related vision worsening; and between numerous measures of visual function. The best predictor of overall QOL score was the near activities score. Age was moderately or weakly negatively correlated with multiple measures. Stepwise multiple linear regression analysis demonstrated that the square of SVA provided the most explanatory power for the overall QOL score, implying a non-linear relationship between visual acuity and QOL. None of the treatment modalities added explanatory power to the model when added to the square of SVA.

In conclusion, QOL, stress regarding treatment, and ocular pain did not differ between PDT and pegaptanib treatment groups. Decreasing visual acuity was associated most strongly with decreases in ability to perform near and distance activities, overall QOL, driving, and independence. Scales denoting worry and frustration about treatment did not demonstrate a strong relationship to visual function, implying patient concern about treatment across the visual acuity spectrum. A nonlinear relationship was seen between QOL and visual acuity.

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INTRODUCTION

Clinical Overview

Age related macular degeneration (AMD) is the leading cause of blindness among the elderly in the U.S. (1). There are two types of AMD: the "dry" or nonexudative type, which leads to macular pathology such as retinal pigment epithelial changes, drusen, and geographic atrophy, and the "wet" or exudative type which results from choroidal neovascularization (CNV) (2). The new vessels formed in wet AMD can leak blood and fluid that damages the macula, leading to scar tissue. Both types of AMD can result in severe vision loss; however, exudative AMD accounts for approximately 80% to 90% of AMD-related blindness (2). Treatment options have proliferated in the past 15 years, with recent products representing the most promise (2). Treatment options include laser photocoagulation, photodynamic therapy, and most recently, antiangiogenic drugs (2). Preventive efforts include oral supplementation with high doses of antioxidants and zinc in patients with intermediate AMD (3). The visual challenges presented by AMD can significantly impair a patient's ability to function independently and adversely affect health-related quality of life.

Tools for Measuring QOL

Researchers have attempted to quantify the effects on health-related QOL using a variety of tools. Tools such as the time trade-off and the standard gamble methods (4, 5) have been used to evaluate AMD patient utility values, which were found to be highly dependent on the degree of visual loss in the better-seeing eye. Other scales such as the Activities of Daily Vision Scale (6), the Quality of Well-being Scale, the Instrumental Activities of Daily Living index, self-rated general health status, and the Profile of Mood

States (7), have demonstrated emotional distress, profoundly reduced quality of life, and the need for help with key daily activities among AMD patients. While an individualized measure of QOL in AMD has been developed (the "MacDQoL") (8), measures such as these do not provide comparison across visual diseases.

Given the broad range of tools being used by researchers, in 2000 the National Eye Institute created a 25-question Visual Function Questionnaire (VFQ-25) that could be used across various chronic eye diseases to measure self-reported vision-targeted health status. The VFQ-25 has been shown to be valid and reliable in measuring vision-related quality of life for AMD patients (9). It has shown to be responsive to progression to advanced AMD and loss of VA (10).

Bilateral vs.Unilateral AMD and Severity of AMD

Bilateral AMD leads to severe loss of central vision. This loss of vision has been shown to lead to lower quality of life than for patients with unilateral AMD (11) and has been shown to result in disutility equivalent to that experienced by patients with severe medical conditions such as coronary heart disease and stroke (12). However, there are many unresolved issues regarding effects of unilateral vs. bilateral AMD. Some researchers have found that patients with only one eye affected by severe AMD may be more at risk for depression than those with both eyes affected, possibly because patients with one eye affected face uncertainty regarding vision loss in the unaffected eye, while those with both eyes affected more often accept the condition (13). Other researchers have found that worst-eye visual acuity (VA) and best-eye visual acuity contribute independently to vision-related quality of life (QOL) (14).

Among patients at risk for advancement to neovascular AMD, with good visual

function (VA > or = 20/40 in each eye), visual function was only weakly associated with vision-related QOL (15). Based on this finding, it is clear that measuring the impact of visual loss on vision-related QOL is most useful among the cohort of patients with moderately or significantly impaired VA. However, this finding also provokes questions about vision-related QOL in patients with good visual function: how much does vision-related QOL vary among this cohort? What psychological and situational factors also contribute to perceived changes in vision-related QOL, independently of objective visual loss? Among this cohort of patients, overall vision-related QOL may still be high. However, anxiety about eventual deterioration of vision may be significant. The VFQ-25 includes questions addressing this point. Understanding the degree of psychological stress that AMD places on patients across the severity spectrum could be very useful for ophthalmologists and other healthcare practitioners seeking to not only maximize visual function, but also overall QOL.

Effects of AMD Treatment on QOL

QOL indicators, including the VFQ-25, have also been used to test changes in QOL resulting from AMD treatments and other interventions (12). Photodynamic therapy with intravenous liposomal verteporfin (PDT) has been shown to effectively prevent the loss of visual acuity in AMD patients with subfoveal choroidal neovascularisation (CNV) (16). Incremental cost per quality adjusted life year (QALY) and incremental cost per vision year gained were calculated by UK researchers for verteporfin therapy at different levels of AMD severity; results suggested that treating patients at lower levels of severity would be cost effective, when NHS treatment costs and social care costs were considered (17). More dramatic cost-effectiveness was found

when both the increasing benefit of treatment during 5 years of follow-up and the decreasing number of yearly treatments over that time were considered (18). Incremental gain in QALY as a result of PDT was also shown in a Canadian cohort of patients (19). Other researchers found that improvements in subjective QOL were correlated with patients' subjective impression of VA progression, not clinically validated results of PDT (20). Such studies demonstrate that clinical improvement may not always lead to practical QOL improvement for patients, and show the importance of looking at QOL alongside clinical endpoints.

QOL following surgical procedures for AMD has also been explored. Researchers found improved vision-related QOL following macular translocation with 360 degrees peripheral retinectomy (21). In contrast, in the SST Group B Trial no difference was found in vision-targeted quality-of-life outcomes for patients randomized to submacular surgery for removal of subfoveal choroidal neovascular lesions vs. those randomized to observation; however, there were trends in favor of surgery for certain patient subgroups (22). This study highlights the need for QOL studies to be adequately-powered to make real conclusions regarding the impact of surgical treatments or other interventions.

Self-Management and Low Vision Aids

Self-management programs and low vision aids also play an important role in AMD management, particularly for those patients with very advanced disease. Loss of independence, disability, and depression are major concerns for these patients. A self-management program consisting of health education and enhancement of problem-solving skills was shown to have sustained benefits for improving self-efficacy, reducing

patient distress, and preventing depression (23). In another study, improvement in mood and function as a result of a self-management program were more significant for patients initially depressed (24). The QOL benefit of low vision rehabilitation (LVR) models has also been examined. A research group studied the effectiveness of three models of low vision rehabilitation for AMD patients, and found no difference in vision-related QOL between the groups (25); they concluded that testing LVR model effectiveness may help prevent proliferation of models that aren't QOL-enhancing. QOL studies can also inform LVR design. For instance, one low vision service was shown to reduce anxiety about issues such as deterioration of vision and safety within the home; however, these patients still felt isolated and lonely, and weren't able to resume all their everyday activities (26). Linking to community service groups that provide social support would be especially helpful for this study's cohort; the results further emphasize the importance of family and/or social network in optimizing coping and functionality for AMD patients.

STATEMENT OF HYPOTHESIS AND PURPOSE

The primary purpose of this study was to quantify vision-related QOL for AMD patients across a treatment spectrum by administering a modified version of the VFQ-25. The recent introduction of the VEGF-inhibitor pegaptanib sodium (Macugen) offers a new tool for retinal specialists in treating subfoveal CNV (3). However, its effects on QOL have yet to demonstrated. While vision-related QOL, as described above, is primarily impacted by VA and overall visual function, other factors are also relevant to QOL. Ocular discomfort and pain, for instance, may limit the amount of time patients can perform certain tasks. Need for frequent appointments, such as for pegaptanib, can increase stress, worry, and feelings of dependence on others. However, it might be that

patients who need more frequent treatments feel more hopeful about their visual prospects and feel that more is being done to prevent progression. While there is little doubt the overall improvement in visual function is of primary importance, understanding how interventions with different treatment patterns affect QOL may inform how one approaches and treats these patients, in terms of structuring injections, clinic schedules, etc. Looking at vision-related QOL for patients treated with pegaptanib will also inform clinicians' approach to ranibizumab (Lucentis), another VEGF-inhibitor currently in clinical trials. The VFQ-25 includes questions relating to dependency, mental health, and role difficulties, all of which we felt were potentially related to a treatment regimen. As such, we used to VFQ-25 (27) to determine vision-related QOL for the following sets of patients: those who have received no interventions; those who have received only preventative oral antioxidant supplements; those who have received PDT (with or without intravitreal triamcinolone acetate (IVTA) injections); those who have received pegaptanib injections; and those who have received both PDT and pegaptanib. The null hypothesis is that vision-related QOL, as a function of VA, would not differ between these treatment groups.

We also wished to examine pain and discomfort immediately after treatment, as well as stress induced by worry about treatment. We added several questions to VF-25 related to these topics. The null hypothesis is that these measures would not differ between the PDT, pegaptanib, and PDT/ pegaptanib treatment groups.

Finally, we wanted to determine if there were any adverse effects related to preventative supplements. In 2001, the Age-Related Eye Disease Study (AREDS) reported that oral supplementation with high doses of antioxidants and zinc can delay the progression of intermediate AMD to advanced AMD (3). Patients report anecdotally

difficulty swallowing the supplements, difficulty remembering to take them daily, and some side effects such as stomach pain. We added questions to the VF-25 related to these issues. The null hypothesis is that patients on these supplements would report no adverse effects.

METHODS

Measures

A modified version of the Visual Function Questionnaire (VFQ-25) was constructed. In addition to the full VFQ-25 set of questions, it contained two questions from the near-vision subscale set. These questions can be used to develop a more complete picture of patients' ability to perform near tasks. It also contained eight questions regarding treatment: four questions relating to treatment side effects, two questions relating to the psychological impact of treatment, and two questions relating to feelings of dependency due to treatments.

Participants

A list of patients with AMD was generated based on Yale Eye Center records for the past four years. Inclusion criteria for the study included: 1) diagnosis of AMD by an ophthalmologist; and 2) age $\geq$ 50 years. Exclusion criteria for the study included: 1) diabetic retinopathy (anything greater than minimal amounts); 2) intraocular surgery or laser treatment within the previous two months; 3) scheduled intraocular surgery; and 4) optic neuropathy. Diabetic retinopathy can not only lead to significant visual loss, but treatments for diabetic retinopathy could also confound the results of this study; it is unclear that patients would be able to isolate pain or other side effects experienced after

AMD treatments from pain or side effects after other treatments. Similarly, recent laser treatment or intraocular surgery could confound side effect results, and recent or scheduled laser treatments or intraocular surgery could have mental health effects (anxiety, frustration, dependency, etc.) separate from those due to AMD. Optic neuropathy also leads to significant visual loss unrelated to AMD and thus we wanted to exclude patients with such a diagnosis.

The list of patients was divided by year of most recent visit, and charts of those patients who had visited the Yale Eye Center most recently were screened first. Of the patients who met study criteria, a subset was mailed the modified version of the VFQ-25, along with an information sheet, an introductory letter, and a self-addressed stamp letter. The information sheet included an invitation to participate and explanation of voluntary participation; a description of the project, procedures, and confidentiality; a list of risks, benefits, and economic costs; and an invitation to ask questions. The questionnaire was also administered to a subset of patients while they were at the Yale Eye Center. The information from the information sheet was either verbally explained to these patients, or they were given an information sheet to read before filling out the questionnaire. In some cases, participants recruited in the clinic filled out the questionnaire completely by themselves; in other cases, the questions were read to the participants, who responded verbally. Some participants who started filling out the questionnaire by themselves required that the remainder be read to them, after receiving dilating eye drops partway through their visit. A separate informed consent form was not deemed necessary by the Yale Human Investigation Committee. No monetary compensation was provided to participants.

The following data was collected on participants from their medical charts at the

Yale Eye Center: date of birth, Snellen chart visual acuity, AMD treatment history, and use of high-dose antioxidant supplements for prevention of AMD progression. When participants were recruited in clinic, their charts were reviewed at the end of the day to obtain this information. When participants were recruited by mail, their charts were re-reviewed upon receipt of the completed questionnaire and information from the most recent clinic visit was obtained.

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Data Analysis

Scores on the VFQ-25 were analyzed and converted to a 100-point scale as laid out in the NEI VF-25 Scoring Algorithm, with 100 representing the best possible score and 0 representing the worst. Sub-scale scores were generated in the areas of general health, general vision, ocular pain, near activities, distance activities, vision-specific mental health, vision-specific social functioning, vision-specific role difficulties, vision-specific dependency, and driving. The near vision optional items were included in the near vision subscale scoring as described by the Scoring Algorithm.

From the questions regarding treatment added to the VFQ-25, additional scores were generated in the following areas: mental health: treatment-related, vision worsening: treatment-related, back pain: treatment -related, difficulty with antioxidant supplements, and dependency: treatment / visit-related. Five answers were available for each treatment question, with a "1" corresponding to 100, and a "5" corresponding to 0, with corresponding values in between. If a respondent left the question blank or chose option 6 on a treatment-related question (meaning the question was not relevant to him or her), this was coded as a missing answer. A score between 100 and 0 was generated for each of the additional treatment-related areas by the taking the average of the scores for

all the non-missing questions relating to that area.

Analysis of the demographics of the participant population was performed on variables including gender, age, source of questionnaires (sent vs. obtained in clinic), and visual acuity in better-seeing eye. Analysis of treatment history was also performed along two dimensions: PDT (with or without IVTA) and pegaptanib injections. Major treatment categories include patients who had received both PDT (with or without IVTA) and pegaptanib, patients who had received only PDT, patients who had received only pegaptanib, and patients who had received neither PDT nor pegaptanib. Additionally, patients in each of these categories were broken into those who were taking antioxidant supplements and those who were not. A mean age and two-tailed student t-test was calculated to examine age differences between patients who had received PDT and patients who had not received PDT; patients who had received pegaptanib and patients who had not received pegaptanib; patients who had received only PDT (with or without IVTA) and patients who had received only pegaptanib; patients who were receiving antioxidant supplements and those who were not; and patients who returned the questionnaire by mail and patients who returned the questionnaire by mail. Visual acuity was also compared across treatment groups.

For each of the subgroup categories for the VFQ-25, as well as the additional treatment-related subgroup categories, a mean, standard deviation (SD), and 95% confidence interval (CI) around the mean were calculated for all participants, participants who received PDT, and participants who received pegaptanib. Comparisons between the same groups as used in the age t-tests were made examining mean scores on each of the subgroup and treatment-related subgroup categories.

Visual acuity scores were converted into a numerical proxy ("scaled visual

acuity"), with 100 signifying 20/20 vision, 99 signifying 20/25 vision, and so forth (for every increase of 5 in the denominator, an additional 1 point was subtracted). Pearson correlations between scaled visual acuity and subgroup and treatment-related subgroup outcomes, and between age and these outcomes, were then calculated. Correlations between each of the subgroup and treatment-related subgroup outcomes were also calculated to determine which QOL deficits might occur together. Stepwise linear regression was performed to identify candidate variables possibly associated with Overall QOL Scores. Multiple linear regression models were used to estimate the association between the Overall QOL Score and scaled visual acuity, age, gender, and treatment history.

Statement of Student Contribution

With the oversight of and input from my advisor, I performed an initial literature review and based on that review designed the modifications to the VFQ-25. I performed all screening of patient medical records prior to sending out surveys or interviewing them in clinic, and performed the final review of participant charts. I sent out all surveys, with the exception of brief assistance with no more than twenty surveys by a Yale undergraduate student. I informed and administered the survey to all patients who were interviewed in clinic, with the exception of no more than two patients, to whom an Eye Clinic technician handed the surveys and information sheets. With the oversight of and input from my advisor, I decided on the statistical methods to be used, I programmed the analytical code, performed the data analyses, interpreted the results, synthesized the conclusions, and prepared this written report including accompanying tables and figures.

RESULTS

Demographics of Study Population

The study population (n = 71) was 54% male and 46% female (Table 1). The mean age of the population was 79 years, with over 70% of the population between 70 and 89 years. Questionnaires returned by mail represented 58% of the total, while 42% of the total were administered or completed in clinic. The study population was divided into 4 groups according to the visual acuity (VA) in the better-seeing eye: 35% of participants were in group 1 (20/20 to 20/25), 23% of participants were in group 2 (20/30 to 20/50), 30% of participants were in group 3 (20/60 to 20/200), and 13% of participants were in group 4 (worse than 20/200).

Treatment History of Study Population

Over half of the participants (52%) had received photodynamic therapy with intravenous liposomal verteporfin (PDT); 27% of these patients (14% of all participants) had also received intravitreal triamcinolone acetate (IVTA) injections (see Table 2). In contrast, only 23% of participants had received pegaptanib sodium injections. The difference in these numbers largely reflects the length time the treatments have been available in the U.S. for AMD: the FDA approved PDT for the treatment of AMD in April 2000, while pegaptanib injections were not approved for AMD until December 2004. Of patients who received pegaptanib, 44% (or 10% of all participants) of patients had received also received PDT. 46% of participants were taking antioxidant supplements to slow AMD progression. Because the Age-Related Eye Disease Study (AREDS) reported a benefit of high-dose antioxidant supplements only for delaying the progression of intermediate AMD to advanced AMD (3), supplements may not be useful in patients with early AMD. Further, contraindications such as smoking prevent many

patients from using antioxidant supplements.

The average age of participants who had received pegaptanib was 76.9, while the average age of participants who had not received pegaptanib was 80.2 ($p = 0.31$; see Table 3). A trend of patients receiving pegaptanib being younger than those not receiving this treatment, if it exists, could be due to the relatively recent appearance of this treatment on the market. Patients who previously received PDT with favorable results might not receive a benefit from pegaptanib. Additionally, some elderly patients may have been facing more pressing health matters in the past 18 months and might have slowed their visits to the Eye Center. Thus, they may not have considered pegaptanib yet. However, if this were the case, one might expect to see a difference between the ages of patients who were interviewed in clinic and those who returned the questionnaire by mail. In fact, the average age is similar: clinic-interviewed patients had an average age of 79.2, while patients who returned the questionnaire by mail had an average age of 79.6 ($p = 0.88$). The average age of patients who had received PDT was 78.8, while the average age of patients who had not received PDT was 80.1 ($p = 0.60$). The average age of patients taking antioxidant supplements to slow AMD progression was 80.4, while the average age of patients not taking these supplements was 78.6 ($p = 0.46$). Finally, the average age of patients who received PDT (with or without IVTA) but not pegaptanib was 79.9, while the average age of those who received pegaptanib but not PDT was 78.9 ($p = 0.82$). Hence, no significant ages between different treatment groups existed.

Treatment groups showed substantial range in VA in the better-seeing eye (Figure 1). All groups (including patients who had received both PDT, with or without IVTA, and pegaptanib; patients who had received only PDT; patients who had received only pegaptanib; and patients who had received neither PDT nor pegaptanib) had between

11% and 14% of patients in the worst group (VA in the better-seeing eye of 20/200 or less). A greater range existed in the percentage of patients in the highest VA group (VA of 20/20 to 20/25): only 23% of patients who had received PDT but not pegaptanib were in this VA category, while 57% of patients who had received both PDT and pegaptanib were in this VA category. However, it is difficult to draw conclusions from this observation since some patients may have poor vision in the treated eye, but excellent vision in the other eye. Moreover, some patients may have received treatment in both eyes. Patients with late disease in one eye have a 47% likelihood of developing advanced disease in the other eye within 6 years (28).

VFQ-25 Scores

Figure 2 demonstrates the mean scores for the subgroup categories for the VFQ-25 as well as the mean Overall QOL score. The lowest average subgroup score on the VFQ-25 was for General Vision, at 43.2 (69 observations, SD 21.8, 95% CI for mean: 37.7, 48.7), followed by Driving, at 50.8 (59 observations, SD 39.3, 95% CI: 40.8, 60.8). For the important category of Driving, it is instructive to lay out the reasons it is missing as an observation for a number of participants. The 12 "missing" or "not applicable" entries for Driving were recorded, as laid out in the NEI VF-25 Scoring Algorithm, for the following reasons: 5 participants previously drove, but gave up driving for reasons other than eyesight; 3 participants never drove; 3 participants listed that they gave up driving, but skipped the question related the reason for stopping; and 1 participant previously drove, but gave up driving for "both eyesight and other reasons". General Health was also rated low by participants, with an average of 55.4 (69 observations, SD 23.2, 95% CI: 50.3, 60.6), as might be expected given the comorbidities that exist in

many patients of advanced age. Distance Activities had an average rating of 59.8 (71 observations, SD 30.6, 95% CI: 52.7, 66.9), and Mental Health had an average rating of 59.8 as well (71 observations, SD 30.6, 95% CI: 52.7, 67.0). Role Difficulties had an average rating of 60.9 (71 observations, SD 33.3, 95% CI: 53.2, 68.7). Near Activities was rated higher than Distance Activities, but still relatively low, at 62.6 (71 observations, SD 28.6, 95% CI: 56.0, 69.3). Peripheral Vision was relatively well-maintained on average, with an average rating of 72.1 (70 observations, SD 27.8, 95% CI: 65.6, 78.6); this was expected, given that AMD affects central vision, as opposed to diseases such as glaucoma, which initially are restricted to peripheral vision. Participants had relatively high average scores on the Dependency and Social Functioning subgroups, with averages of 72.3 (71 observations, SD 33.5, 95% CI: 64.5, 80.1) and 75.2 (71 observations, SD 26.3, 95% CI: 69.1, 81.3), respectively. The average rating for Color Vision was 82.0 (68 observations, SD 26.6, 95% CI: 75.7, 88.3); again, this was expected, as with AMD color discrimination remains quite good. Moreover, there was only a single question on the VFQ-25 used to generate this score: "Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?" This is a low threshold to meet. Moreover, some people may fail to notice slight deficits in color discrimination – such as inability to detect stains or slight differences in shade – particularly if they lack frequent contact with family or friends who could point out such errors. Participants also didn't report a high degree of Ocular Pain – the average score for this subgroup was 84.7, where 100 represents no pain (71 observations, SD 21.1, 95% CI: 79.8, 89.6). The average Overall QOL Rating, which is an average of the all the subgroup ratings with the exception of General Health, was 65.8 (68 observations, SD 26.6, 95% CI: 75.7, 88.3).

For the treatment-related subgroups (see Figure 3), the lowest average score was in Treatment-Related Mental Health (worry about treatments and frustration about treatment side effects), at 81.2 (63 observations, SD 22.9, 95% CI: 75.5, 56.8). Participants also reported some vision worsening in the two weeks following treatment; the average Treatment-Related Vision Worsening score was 83.5 (47 observations, SD 24.0, 95% CI: 76.6, 90.4). Patients reported little dependency as a result of treatments and appointments – the average Treatment / Visit-Related Dependency score was 90.7 (62 observations, SD 22.7, 95% CI: 85.1, 96.4). Patients also reported little Treatment-Related Back Pain, with an average score of 97.8 (46 observations, SD 11.6, 95% CI: 94.5, >100), and little Difficulty with Antioxidant Supplements (includes stomach pain after taking pills and difficulty swallowing pills), with an average score of 96.6 (40 observations, SD 10.5, 95% CI: 93.6, >100).

Comparison of VFQ-25 Scores Between Treatment Groups

While we later ran multiple linear regression models to determine the impact of association of treatment history on Overall QOL Score, while adjusting for other important variables such as visual acuity, we first wished to look simply at the differences in the VFQ-25 and treatment-related subscores in the various treatment groups.

Figures 4 and 5 show the mean scores and confidence intervals for the VFQ-25 subscores and the additional treatment-related subscores, respectively, for participants who received PDT. Figures 6 and 7 show this data for participants who received pegaptanib. As shown in Table 4, no significant difference between the group of participants who had received PDT (with or without IVTA) and the group of participants

who had not received PDT was found in any of the VFQ-25 subgroups, or the additional treatment-related subgroups. A strong trend was found in Near Activities ($p = 0.08$), with an average score of 57.0 (37 observations, SD 28.7, 95% CI for mean 47.7, 66.2) for the PDT group and an average score of 68.8 (34 observations, SD 27.6, 95% CI for mean 59.8, 78.1).

Significant differences between the group of participants who had received pegaptanib and the group of participants who had not received pegaptanib were found in two areas: Peripheral Vision ($p = 0.04$) and Treatment-Related Vision Worsening ($p = 0.04$). The pegaptanib group average score for Peripheral Vision was 82.8 (16 observations, SD 19.8, 95% CI: 73.1, 92.5) while the average score for the group who had not had pegaptanib was 69.0 (54 observations – one patient in this group skipped this question, SD 29.1, 95% CI: 61.2, 76.7). The pegaptanib group average score for Treatment-Related Vision Worsening was 71.9 (16 observations, SD 28.7, 95% CI: 57.8, 85.9) while the average score for the group who had not had pegaptanib was 89.5 (31 observations – 24 patients in this group skipped this question or answered "NA", SD 19.1, 95% CI: 82.8, 96.2). While the difference in peripheral vision could certainly be due to visual acuity, the differences in vision worsening after treatment are unlikely to be due to differences in visual acuity. This comparison is a proxy for the PDT vs. pegaptanib comparison, since those patients in the "no pegaptanib" group who answered questions about vision worsening following treatment would have been those who had received PDT. Thus, there seems to be some evidence of increased vision worsening following pegaptanib than following PDT.

Numerous significant values were found in comparing patients taking antioxidant supplements to slow AMD progression and those not taking these supplements. There

are several possible reasons for this. First, there were large numbers in both groups, contributing to the ability to generate significant results. Second, since supplements have been shown useful only for patients with intermediate AMD, it is unlikely that those with advanced AMD would be placed on these supplements. Some patients with early AMD may choose to take the supplements even though they haven't been shown to be beneficial in this population. Hence, the use of antioxidant supplements might be a rough proxy for intermediate and in some cases early AMD, while not using supplements might indicate that a patient either has advanced AMD or in some cases very early AMD. Some patients have contraindications to using antioxidant supplements, such as smoking, and thus antioxidant supplements represent only a rough proxy for early to intermediate AMD.

Supporting the idea that those on supplements have better visual acuity overall, General Vision was significantly lower in the group not on supplements (37.4) than in the group using supplements (50.3), with a p value of 0.02. Those on supplements also scored dramatically higher on Mental Health (71.5) than those not on supplements (49.7), with a p value of 0.002. The average score on Role Difficulties also differed dramatically between the two groups: those on supplements had an average score of 51.6, while those on supplements had an average score of 71.6 ($p = 0.01$). Social functioning was also significantly lower in the group not on supplements (69.4) than in the group on supplements (81.8), with a p value of 0.04. Dependency was similarly lower in the group not on supplements (64.7, vs. 81.1 for those on supplements, with $p = 0.04$), as would be expected given the close relationship between poor social functioning and feelings of dependency. In fact, the group not on supplements had a lower average score on every item of the VFQ-25, and on every additional treatment-related item with the exception of

treatment-related back pain. Accordingly, the Overall QOL Rating was on average much lower for the group not on supplements (59.6, vs. 72.9 for those on supplements, with $p = 0.02$).

The only significant difference between the group who sent the questionnaire in by mail and the group that was interviewed in clinic was in Treatment-Related Mental Health; the clinic subgroup had an average score of 87.5, while the home subgroup had an average score of 76.1 ($p = 0.04$). This subgroup area involves worry about treatment complications and frustration about treatment side effects. There is no obvious rationale for a difference between the two groups on this issue. However, it is possible that there was some bias in the clinic-interviewed group to downplay their frustration and worry due to treatment, given their proximity to the clinicians who provide that treatment.

No significant differences were seen between the PDT-only and pegaptanib-only groups. There are several possible reasons for this. First, the sample size for the pegaptanib-only group was quite small ($n = 9$). The small size of this group is due to the relatively short amount of time pegaptanib has been available, as well as the fact that many patients who have received pegaptanib previously received PDT (7 participants received both pegaptanib and PDT). Second, there is less likely to be the confounding variable of differences in severity, and thus in visual acuity, in comparing these two groups than in other comparisons, since patients would have had to exhibit exudative AMD to receive either treatment. Third, the treatments are relatively similar, both involving injections of medication into the eye. While it would seem logical that pain levels, worsening of vision following treatment, and worry / frustration involving the treatments would be similar in the two, it is important to confirm this assumption. In particular, though ophthalmologists differ in the number of pegaptanib injections they

typically use and vary treatment regimens based on individual response, a recent study utilized frequent pegaptanib injections – once every six weeks (29). Hence, if patients found pegaptanib injections to be very onerous and painful, they might not return for their remaining injections. This would certainly diminish the effectiveness of this treatment over others that require fewer repeat injections; for instance, PDT is recommended at a maximum frequency of once every 3 months, + or – 2 weeks (30).

Scaled Visual Acuity Scores

As shown in Figure 8, visual acuity scores were converted into a numerical proxy ("scaled visual acuity"), with 100 signifying 20/20 vision, 99 signifying 20/25 vision, and so forth (for every increase of 5 in the denominator, an additional 1 point was subtracted). Three patients had very poor visual acuity difficult to translate into this system: one patient's visual acuity in the better-seeing eye was listed as 24"/200 (2 feet / 200, or equivalent to 20/2000), one was listed as CF (indicating the ability to "count fingers") and one was listed as CF 1 (indicating the ability to "count fingers" at one foot away). Because of the inability to translate these visual acuities readily into the scaled visual acuity scoring system, a score of 5 was chosen for these three participants. This is significantly below the score of 24 that patients with VA of 20/400 were assigned, but still greater than 0.

Pearson Correlation Coefficients

Correlations between subgroup and treatment-related subgroup outcomes, and between these outcomes and age and scaled visual acuity are shown in Table 5. Strong positive correlations (> 0.45) were seen between General Health and Ocular Pain. One

interpretation of this finding is that a sense of optimism influences both of these scores to be higher, given that they are potentially more objective than other subgroup scores. Another interpretation is that patients with low General Health scores may have other health problems that lead to increased ocular pain (and therefore lower Ocular Pain scores). Ocular Pain also showed a strong positive correlation with Treatment-Related Mental Health, as one would expect. Participants with higher degree of ocular pain (including burning, itching, and aching) would likely be more continually mindful of their AMD and treatment for their AMD. Moreover, higher degrees of ocular pain might prime patients to feel more anxiety, frustration, and worry about their AMD treatments, regardless of whether the treatment itself is responsible for the pain.

Treatment-Related Mental Health was also strongly correlated with Overall QOL Rating (correlation coefficient = 0.45) and Treatment-Related Vision Worsening (correlation coefficient = 0.45). One would expect patients with significant worsening of vision after treatments to be more worried about and frustrated with treatment side effects. However, it is clear, given that no other subscore showed a correlation coefficient of greater than 0.49 with Treatment-Related Mental Health, that worry and frustration about treatments don't necessarily increase as visual function falls.

As expected, General Vision showed strong positive correlations with numerous other subscores, including Near Activities, Distance Activities, Color Vision, Peripheral Vision, Scaled Visual Acuity, and Overall QOL Rating, as well as with "softer" evaluations of visual QOL, including Social Functioning, Mental Health, Role Difficulties, Dependency, and Driving. Moreover, subscores for Near Activities, Distance Activities, Social Functioning, Mental Health, Role Difficulties, Dependency, Driving, Color Vision, Peripheral Vision, and Overall QOL Rating all showed strong

positive correlations with one another. The best predictor of Overall QOL Rating was the Near Activities subscore (correlation coefficient of 0.92).

Treatment-Related Vision Worsening showed strong positive correlations with Distance Activities, Mental Health, Color Vision, and Treatment-Related Mental Health. As described above, the correlation with Treatment-Related Mental Health is reasonable. The correlation with Mental Health (measuring general worry about eyesight, and frustration with eyesight) is also reasonable, particularly if the treatments are frequent.

The Supplements Difficulty score showed strong positive correlation with the following subscores: Mental Health, Dependency, and Scaled Visual Acuity. Again, none of the correlation coefficients are greater than 0.50. This could indicate that there's no great predictor for patients who might have difficulty with supplements. It is possible that those who worry more about their eyesight and also feel loss of independence are simply more likely to notice problems with supplements, such as difficulty swallowing and stomach pain afterward. Another hypothesis is that these links are simply due to a common temperament that is more likely to worry, feel dependent, and have heightened attention to side effects.

Age did not exhibit a strong correlation (absolute value of correlation coefficient > or = 0.45) with any subscore. Lack of significant dispersion in age among participants, may have been difficult to detect any age effects. Age did show a moderate negative correlation with Driving, and weak negative correlations with numerous other factors, including Near and Distance Activities, Dependency, Overall QOL Rating, and Supplemental Difficulty. Hence, a weak-to-moderate trend of decreasing vision with advanced age was seen, as would be expected given that prevalence of late AMD increases significantly with age (28).

Scaled Visual Acuity showed a strong correlation to General Vision, and accordingly, demonstrated many of the same patterns in correlation to other visual indicators listed above. Scaled Visual Acuity had only a moderate correlation to Peripheral Vision (correlation coefficient 0.44), in contrast to General Vision, which had a strong correlation to Peripheral Vision (correlation coefficient 0.61). Scaled Visual Acuity also showed a strong correlation to Supplement Difficulty (correlation coefficient 0.48), which was not seen with General Vision.

Multiple Linear Regression Models

Stepwise multiple linear regression analysis was used to evaluate the influence of treatment history on the Overall QOL score after adjusting for scaled visual acuity and other factors potentially related to VFQ-25: age, gender, and clinic vs. home survey source. Each variable was examined in a step-wise fashion; inclusion in the model required both a significant p score as well as an increased F score. As shown in Table 6, the square of Scaled Visual Acuity (SVA^2) provided the most explanatory power (greater than SVA alone or both SVA and SVA^2 together) for the Overall QOL score. While a linear regression model can be used in examining the relationship between SVA^2 and Overall QOL scores, the square factor implies a nonlinear relationship between SVA and Overall QOL scores. When SVA scores are plotted on the x axis, and Overall QOL score are plotted on the y axis, one sees the QOL score rise slowly as SVA increases from very low levels, but then rise quickly (see Figure 9 for the actual data). This implies that QOL drops quickly with initial functional limitations, such as inability to drive, difficulty reading, etc., and then flattens out as SVA drops further. However, our data did not include blind patients. One might expect that the there would be more

dramatic changes in QOL at the point of "no light perception", or blindness. The rest of the multiple regression analysis involved adding other variables to the regression along with SVA^2. Only supplement use had a significant p value. Supplement use here could be a proxy for other things – optimism (patients who feel hopeless would be less likely to use supplements), lack of cigarette use which could have an impact on QOL measures (patients who smoke cannot use supplements), or some other unknown factor. However, adding supplements to the regression does not improve the F score, which gives an indication of how much of the overall data the equation would be able to explain. Thus, more of the data can be explained by using SVA^2 alone. See also Figures 9 and 10, which show the predicted and actual relationship between SVA and Overall QOL Score – the two graphs are very similar. None of the other treatment modalities added explanatory power to the model when added to Scaled Visual Acuity^2 ($p > 0.05$, as well as decreased F score). This implies that, controlling for visual acuity, the use of PDT and / or pegaptanib does not influence QOL.

To examine the influence of treatment history on treatment-related measures, a composite treatment score was created. This score is simply the average of the treatment-related subscores. Again, similar results were obtained: Scaled Visual Acuity^2 provided the most explanatory power (see Table 7). This is more surprising than the results for Overall QOL score; it implies that SVA does impact some of the treatment-related measures. Of course, some of those measures were likely related to visual function as well – dependency related to coming for treatments, etc. None of the other variables yielded a significant p value or an increased F score. This implies that, controlling for visual acuity, the use of PDT and / or pegaptanib does not influence the treatment subscales examined. See also Figures 11 and 12, which show the predicted and actual

relationship between SVA and Overall Tx. Score – the two graphs are very similar.

TABLES AND FIGURES

Table 1: Demographics of Participant Population (n = 71).

Characteristic	Number	Percent
Gender		
Male	38	53.5
Female	33	46.5
Total	*71*	*100.0*
Age		
50-59 years	5	7.0
60-69 years	6	8.5
70-79 years	21	29.6
80-89 years	31	43.7
90+ years	8	11.3
Total	*71*	*100.0*
Mean Age in Years	*79.4*	
Maximum Age in Years	*96.3*	
Minimum Age in Years	*50.8*	
Median Age in Years	*81.6*	
Standard Deviation of Age in Years	*10.2*	
95% Confidence Interval on Mean Age	*(77.1 to 81.8)*	
Questionnaire Source		
Returned via Mail	41	57.7
Interviewed / Completed in Clinic	30	42.3
Total	*71*	*100.0*
Visual Acuity		
20/20 to 20/25	25	35.2
20/30 to 20/50	16	22.5
20/60 to 20/200	21	29.6
worse than 20/200	9	12.7
Total	*71*	*100.0*

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Table 2: Treatment History of Participant Population (n = 71).*

	Photodynamic Therapy with IVTA	Photodynamic Therapy without IVTA	No Photodynamic Therapy	TOTAL
Pegaptanib Sodium Injections	2 (2, 0)	5 (2, 3)	9 (4, 5)	16 (8, 8)
No Pegaptanib Sodium Injections	8 (4, 4)	22 (10, 12)	25 (11, 14)	55 (25, 30)
TOTAL	10 (6, 4)	27 (12, 15)	34 (15, 19)	71 (33, 38)

***First number in parentheses represents the number of participants taking antioxidant supplements to slow AMD progression; the second number in parentheses represents the number of participants not taking these supplements.*

	Photodynamic Therapy with IVTA	Photodynamic Therapy without IVTA	No Photodynamic Therapy	TOTAL
Pegaptanib Sodium Injections	2.8% (2.8%, 0.0%)	7.0% (2.8%, 4.2%)	12.7% (5.6%, 7.0%)	22.5% (11.3%, 11.3%)
No Pegaptanib Sodium Injections	11.3% (5.6%, 5.6%)	31.0% (14.1%, 16.9%)	35.2% (15.5%, 19.7%)	77.5% (35.2%, 42.3%)
TOTAL	14.1% (8.5%, 5.6%)	38.0% (16.9%, 21.1%)	47.9% (21.1%, 26.8%)	100.0% (46.5%, 53.5%)

***First number in parentheses represents the percent of participants taking antioxidant supplements to slow AMD progression; the second number in parentheses represents the percent of participants not taking these supplements.*

Table 3: Mean Age of Participant Population by Treatment History (n = 71).*

	Photodynamic Therapy with IVTA	Photodynamic Therapy without IVTA	No Photodynamic Therapy	Mean Across Entire Group
Pegaptanib Sodium Injections	81.2	71.4	78.9	76.9
No Pegaptanib Sodium Injections	77.5	80.8	80.5	80.2
Mean Across Entire Group	78.2	79.1	80.1	79.4

Table 4: Comparison of VFQ-25 Scores between Treatment Groups

	General Health	General Vision	Ocular Pain	Near Activ.	Distance Activ.	Social Funct.	Mental Health	Role Diff.	Depend.	Driving	Color Vision	Periph. Vision	OVERALL QOL RATING	Mental Health: Tx Related	Vision Worsen.: Tx Related	Back Pain: Tx Related	Suppl. ** Difficulty	Depend.: Tx / Visit Related
PDT *	58.1	41.1	85.1	57.0	56.1	70.9	56.3	60.5	69.1	49.6	80.0	69.4	63.1	80.1	81.9	99.2	95.7	89.0
No PDT *	52.3	45.6	84.2	68.8	63.8	79.8	63.7	61.4	75.7	52.0	84.1	75.0	68.8	82.3	86.1	94.6	99.1	92.7
p Value	0.28	0.43	0.85	0.08	0.29	0.15	0.32	0.91	0.41	0.81	0.53	0.41	0.31	0.71	0.55	0.41	0.20	0.53
Pegaptanib	60.9	40.0	90.6	60.6	57.8	75.0	55.5	64.1	74.0	46.5	85.9	82.8	67.1	79.7	71.9	95.0	96.4	93.3
No Pegaptanib	53.8	44.2	83.0	63.2	60.4	75.2	61.1	60.0	71.8	51.9	80.8	69.0	65.4	81.6	89.5	99.2	97.0	89.9
p Value	0.24	0.50	0.15	0.75	0.77	0.98	0.51	0.67	0.83	0.68	0.45	**0.04**	0.80	0.76	**0.04**	0.42	0.90	0.65
Suppl. **	59.7	50.3	89.8	68.7	62.4	81.8	71.5	71.6	81.1	55.2	87.1	78.8	72.9	86.2	86.9	95.5	97.4	93.8
No Suppl. **	52.0	37.4	80.3	57.3	57.6	69.4	49.7	51.6	64.7	47.0	77.1	66.2	59.6	76.8	80.8	100.0	96.1	87.9
p Value	0.14	**0.02**	0.05	0.09	0.51	**0.04**	**0.00**	**0.01**	**0.04**	0.42	0.12	0.06	**0.02**	0.10	0.39	0.21	0.73	0.31
Clinic ***	56.7	43.3	88.3	63.8	59.0	74.2	61.0	63.8	73.3	52.2	81.7	77.6	67.3	87.5	76.3	95.6	93.4	92.7
Home ***	54.5	43.1	82.0	61.8	60.4	75.9	58.9	58.8	71.5	49.9	82.2	68.3	64.7	76.1	88.4	99.1	99.5	89.0
p Value	0.69	0.97	0.20	0.78	0.86	0.78	0.78	0.54	0.83	0.83	0.93	0.16	0.64	**0.04**	0.12	0.44	0.13	0.53
PDT Only *, No Pegaptanib	55.8	40.0	82.9	55.6	54.7	69.6	55.7	58.3	66.9	48.2	78.6	64.7	61.2	78.2	87.5	99.0	96.2	86.1
Pegaptanib Only, No PDT *	55.6	35.6	87.5	58.9	54.6	73.6	52.8	59.7	70.4	39.3	86.1	77.8	63.9	73.6	77.8	90.6	100.0	87.5
p Value	0.98	0.52	0.59	0.76	0.99	0.71	0.79	0.91	0.80	0.60	0.47	0.13	0.74	0.61	0.29	0.40	0.17	0.92

Indicates significant values (at the 5% level).

** With or without IVTA.*

*** Supplements refer to antioxidant supplements taken to slow AMD progression.*

**** Clinic indicates questionnaires completed in clinic, and home indicates questionnaires completed at home.*

Table 4 shows the mean for each subscore by treatment history and method of questionnaire completion. Highlighted cells identify significant values. The only criterion which yields numerous signficant results by this method is supplement use, which as described in the Results section may simply be a proxy for visual function. Patients with very advanced AMD wouldn't benefit from supplement use, while those with intermediate AMD might benefit. Benefits of supplements to those with early AMD has not been shown, but many of these patients may choose to take supplements anyway. Another method by which we gauged the importance of treatment was with multiple linear regression analysis (see Tables 6 and 7).

Table 5: Correlations between VFQ-25 Subgroup and Treatment-Related Scores

	General Health	General Vision	Ocular Pain	Near Activ.	Distance Activ.	Social Funct.	Mental Health	Role Diff.	Depend.	Driving	Color Vision	Periph. Vision	OVERALL QOL RATING	Mental Health: Tx Related	Vision Worsen.: Tx Related	Back Pain: Tx Related	Suppl. ** Difficulty	Depend.: Tx / Visit Related	Age	Scaled Visual Acuity
General Health	1.00																			
General Vision	0.36	1.00																		
Ocular Pain	0.45	0.20	1.00																	
Near Activ.	0.22	0.79	0.13	1.00																
Distance Activ.	0.13	0.72	0.15	0.86	1.00															
Social Funct.	0.20	0.65	0.17	0.77	0.72	1.00														
Mental Health	0.19	0.78	0.23	0.84	0.76	0.70	1.00													
Role Diff.	0.28	0.64	0.27	0.77	0.66	0.76	0.74	1.00												
Depend.	0.24	0.66	0.17	0.77	0.73	0.70	0.84	0.69	1.00											
Driving	0.15	0.71	0.01	0.82	0.77	0.76	0.74	0.70	0.70	1.00										
Color Vision	0.19	0.61	0.21	0.71	0.74	0.76	0.64	0.58	0.62	0.61	1.00									
Periph. Vision	0.24	0.61	0.37	0.67	0.66	0.67	0.61	0.64	0.53	0.62	0.61	1.00								
OVERALL QOL RATING	0.28	0.82	0.30	0.92	0.88	0.87	0.90	0.85	0.85	0.86	0.80	0.78	1.00							
Mental Health: Tx Related	0.30	0.36	0.49	0.39	0.30	0.41	0.40	0.36	0.23	0.36	0.40	0.36	0.45	1.00						
Vision Worsen.: Tx Related	0.04	0.42	0.20	0.42	0.49	0.40	0.46	0.36	0.18	0.39	0.50	0.17	0.44	0.45	1.00					
Back Pain: Tx Related	0.07	0.15	-0.01	0.06	0.30	-0.11	0.08	0.01	0.18	-0.04	-0.12	-0.15	0.04	0.02	0.25	1.00				
Suppl. ** Difficulty	0.04	0.33	0.02	0.29	0.22	0.37	0.50	0.39	0.50	0.39	0.07	0.15	0.38	-0.10	0.12	-0.05	1.00			
Depend.: Tx / Visit Related	0.10	0.15	0.11	0.40	0.26	0.38	0.17	0.48	0.24	0.27	0.40	0.33	0.36	0.25	-0.16	-0.07	-0.14	1.00		
Age	0.14	-0.06	0.13	-0.22	-0.22	-0.17	-0.12	-0.21	-0.27	-0.39	-0.20	-0.16	-0.22	0.04	0.08	0.08	-0.24	-0.27	1.00	
Scaled Visual Acuity	0.11	0.51	-0.07	0.69	0.67	0.62	0.58	0.55	0.61	0.65	0.58	0.44	0.67	0.13	0.05	-0.08	0.48	0.34	-0.26	1.00

Represents strong positive correlation (= or >0.45).
Represents moderate positive correlation (between 0.30 and 0.449).
Represents weak positive correlation (less than 0.299).
Represents negative correlation.

** With or without IVTA.*
*** Supplements refer to antioxidant supplements taken to slow AMD progression.*
**** Clinic indicates questionnaires completed in clinic, and home indicates questionnaires completed at home.*

Table 5 demonstrates visually the relationships between different subgroup scores. Yellow represents the strongest positive correlation (no negative correlations of this magnitude were found). General Health has a strong correlation only with Ocular Pain, as might be expected given that visual function can vary greatly among those with a particular general health status. Ignoring Ocular Pain, the block of subscores from General Vision to Overall QOL are closely correlated. The large yellow block in this portion of the table demonstrates the close relationships between these measures of visual function or of social and mental function affected strongly by loss of visual function. Ocular Pain is less predictive of other visual function deficits in this population. Similarly, treatment-related subscores did not, in most cases, correlate closely with the core measures of visual function. This finding demonstrates the need to address concerns about treatments, treatment side effects, and the mental health consequences of a particular treatment regimen with patients at all levels of visual function. Age demonstrated many negative correlations, the strongest of which was with Driving. But age in itself never demonstrated more than a moderate negative correlation with another subscore. The multiple regression analysis (see Tables 6 and 7) demonstrates that age does not add additional information once scaled visual acuity is controlled for.

Table 6: Effects of Explanatory Variables on Overall QOL Score: Estimated Coefficients from Multiple Linear Regression (n = 71).*

	SVA^2 Coefficient	Other Variable Coefficient	Intercept	SVA^2 Coefficient p value	Other Variable Coefficient p value	Intercept p value	Model R^2	Model F score
Age Only	NA	-0.5144428	106.6392	NA	0.0637666	6.587E-06	0.048929	3.549788
Scaled Visual Acuity Only	NA	0.5898132	17.030114	NA	1.889E-10	0.0155363	0.4468624	55.742912
SVA with SVA^2	0.0114399	-0.7700221	43.097257	0.0003416	0.0399667	1.808E-05	0.5425796	40.32987
SVA^2 only	0.0052129	NA	26.442189	2.176E-12	NA	1.504E-06	0.5130766	72.706056
Gender with SVA^2	0.0052472	2.2957259	25.115668	2.703E-12	0.5686979	2.508E-05	0.5154143	36.163034
PDT with SVA^2	0.0051843	-1.4583156	27.417782	4.899E-12	0.7179829	9.437E-06	0.5140165	35.961228
IVTA with SVA^2	0.0052502	9.9349848	24.761109	1.108E-12	0.0809999	5.851E-06	0.5345511	39.047757
Pegaptanib with SVA^2	0.0052181	2.3685421	25.868904	2.857E-12	0.6207848	4.363E-06	0.514839	36.079826
Supplements with SVA^2	0.0050875	10.876504	22.333576	1.068E-12	0.0054334	2.948E-05	0.5657541	44.29666
Clinic (vs. Home) with SVA^2	0.0052802	5.4642817	23.625238	1.374E-12	0.1760242	4.264E-05	0.5261058	37.745977

Indicates statistically significant result ($p < 0.05$).
Clinic vs. home refers to whether the participant filled out the questionnaire at home or at the Yale Eye Center.
SVA = Scaled Visual Acuity (transformation of Snellen chart score to a numerical score; see Figure 8).
SVA^2 = The square of Scaled Visual Acuity.
PDT = Photodynamic therapy.
IVTA = Intravitreal triamcinolone acetate.

Table 6 demonstrates the results of a stepwise multiple linear regression analysis, which attempted to demonstrate which variables or combination of variables best explained participants' Overall QOL scores. Age was examined first. Given the p value > 0.05 (see the first row) it was rejected as an explanatory variable. Scaled Visual Acuity (SVA) was examined next and was found to have explanatory value with p << 0.01. However, the square of SVA (see row 4) was an even better explanatory variable (lower p value, higher F score). Using the two values together (see row 3) did not improve the p values or the F score. While a linear regression model can be used in examining the relationship between SVA^2 and Overall QOL scores, the square factor implies a nonlinear relationship between SVA and Overall QOL scores. If SVA scores are plotted on the x axis, and Overall QOL scores are plotted on the y axis, one would see the QOL score rise slowly as SVA increases from very low levels, but then rise quickly. This implies that QOL drops quickly with initial functional limitations, such as inability to drive, difficulty reading, etc., and then flattens out as SVA drops further. However, our data did not include blind patients. One might expect that there would be more dramatic changes in QOL at the point of "no light perception", or blindness. The rest of the analysis involved adding other variables to the regression along with SVA^2. Only supplement use had a significant p value. Supplement use here could be a proxy for other things -- optimism (patients who feel hopeless would be less likely to use supplements), lack of cigarette use which could have an impact on QOL measures (patients who smoke cannot use supplements), or some other unknown factor. However, adding supplements to the regression does not improve the F score, which gives an indication of how much of the overall data the equation would be able to explain. Thus, more of the data can be explained by using SVA^2 alone. See also Figures 9 and 10, which show the predicted and actual relationship between SVA and QOL.

Table 7: Effects of Explanatory Variables on Overall Tx Score: Estimated Coefficients from Multiple Linear Regression (n = 71).*

	SVA^2 Coefficient	Other Variable Coefficient	Intercept	SVA^2 Coefficient p value	Other Variable Coefficient p value	Intercept p value	Model R^2	Model F score
Age Only	NA	-0.2118684	99.623523	NA	0.215549	3.17E-10	0.022141	1.5623183
Scaled Visual Acuity Only	NA	0.2512954	62.02552	NA	4.359E-05	3.136E-19	0.2164145	19.056757
SVA with SVA^2	0.0052204	-0.3692404	73.920782	0.029401	0.19865	2.163E-15	0.2695915	12.549291
SVA^2 only	0.0022344	NA	65.934356	8.391E-06	NA	8.623E-27	0.2514926	23.183457
Gender with SVA^2	0.0022574	1.5348999	65.047457	8.562E-06	0.6157411	6.779E-24	0.2542806	11.593558
PDT with SVA^2	0.0022535	0.9774262	65.280471	9.565E-06	0.749833	2.775E-23	0.2526192	11.492201
IVTA with SVA^2	0.0022525	4.8191861	65.11891	7.25E-06	0.2680303	6.554E-26	0.2649732	12.256816
Pegaptanib with SVA^2	0.0022321	-1.0627714	66.19159	9.863E-06	0.7700739	6.365E-26	0.2524393	11.481255
Supplements with SVA^2	0.002171	5.5032439	63.855498	1.105E-05	0.0682176	3.184E-25	0.2874723	13.717441
Clinic (vs. Home) with SVA^2	0.0022809	3.777911	63.986764	5.815E-06	0.2183202	4.023E-24	0.2681087	12.454988

Indicates statistically significant result ($p < 0.05$).
Clinic vs. home refers to whether the participant filled out the questionnaire at home or at the Yale Eye Center.
SVA = Scaled Visual Acuity (transformation of Snellen chart score to a numerical score; see Figure 8).
SVA^2 = The square of Scaled Visual Acuity.
PDT = Photodynamic therapy.
IVTA = Intravitreal triamcinolone acetate.

Table 7 demonstrates the results of a stepwise multiple linear regression analysis, which attempted to demonstrate which variables or combination of variables best explained participants' Overall Tx. scores (an average of all the treatment subscale scores). Age was examined first. Given the p value > 0.05 (see the first row) it was rejected as an explanatory variable. Scaled Visual Acuity (SVA) was examined next and was found to be have explanatory value with p << 0.01. However, the square of SVA (see row 4) was an even better explanatory variable (lower pvalue, higher F score). Using the two values together (see row 3) did not improve the p values or the F score. While a linear regression model can be used in examining the relationship between SVA^2 and Overall QOL scores, the square factor implies a non-linear relationship between SVA and Overall Tx. scores. If SVA were plotted on the x axis, and Overall Tx. score were plotted on the y axis, one would see the Tx. score rise slowly as SVA increases from very low levels, but then rise more quickly. This is more surprising than the results for Overall QOL score; it implies that SVA does impact some of the treatment-related measures. Of course, some of those measures were likely related to visual function as well -- dependency related to coming for treatments, etc. The rest of the analysis involved adding other variables to the regression along with SVA^2. None of the other variables yielded a significant p value or an increased F score.

Figure 1: Visual Acuity in Better-Seeing Eye by Treatment History

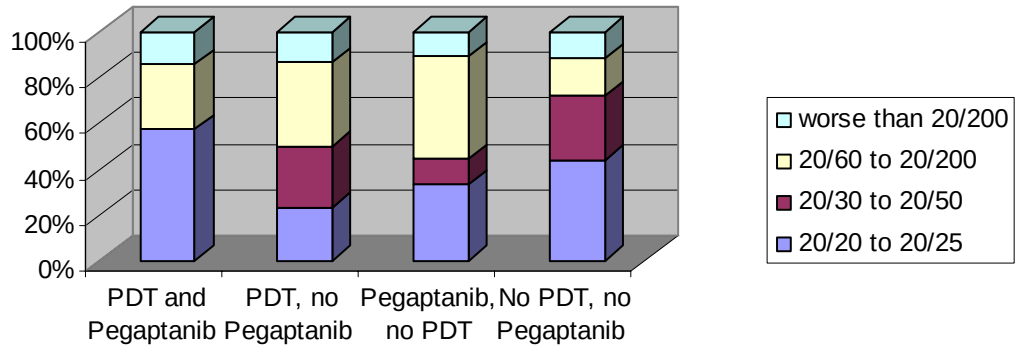


Figure 2: VFQ-25 Average Scores and 95% Confidence Intervals for All Participants

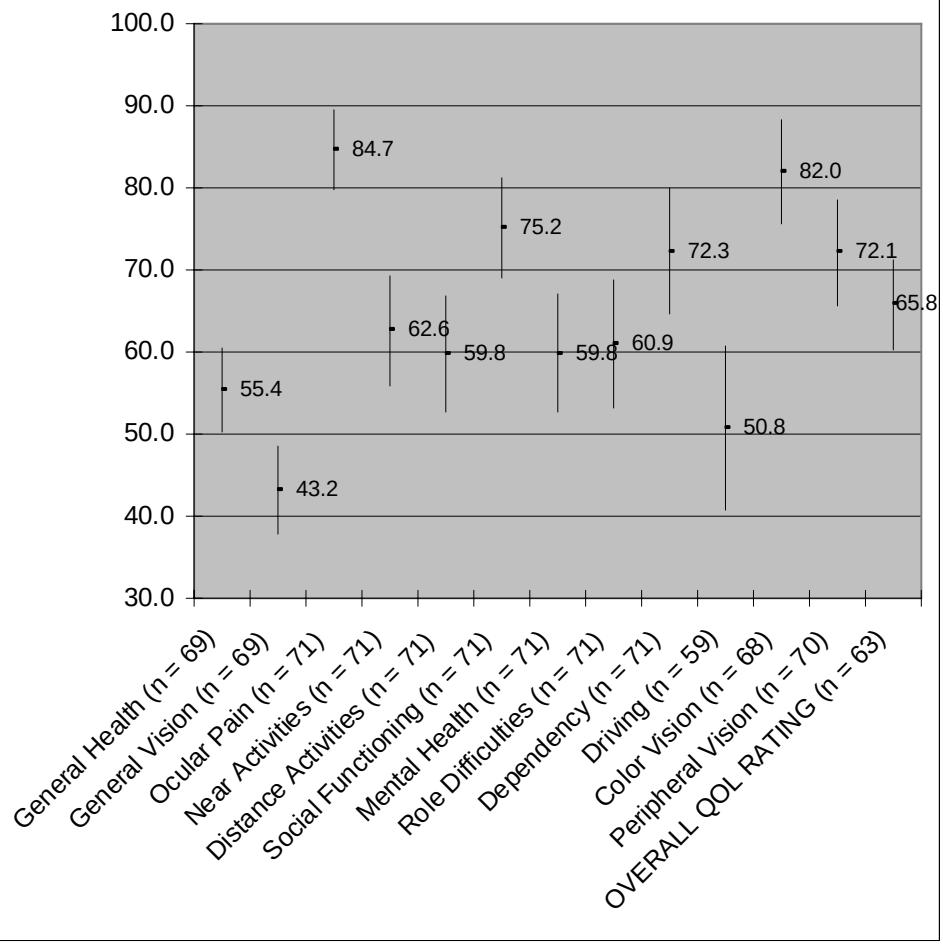


Figure 3: Additional Treatment-Related Scores and 95% Confidence Intervals for All Participants

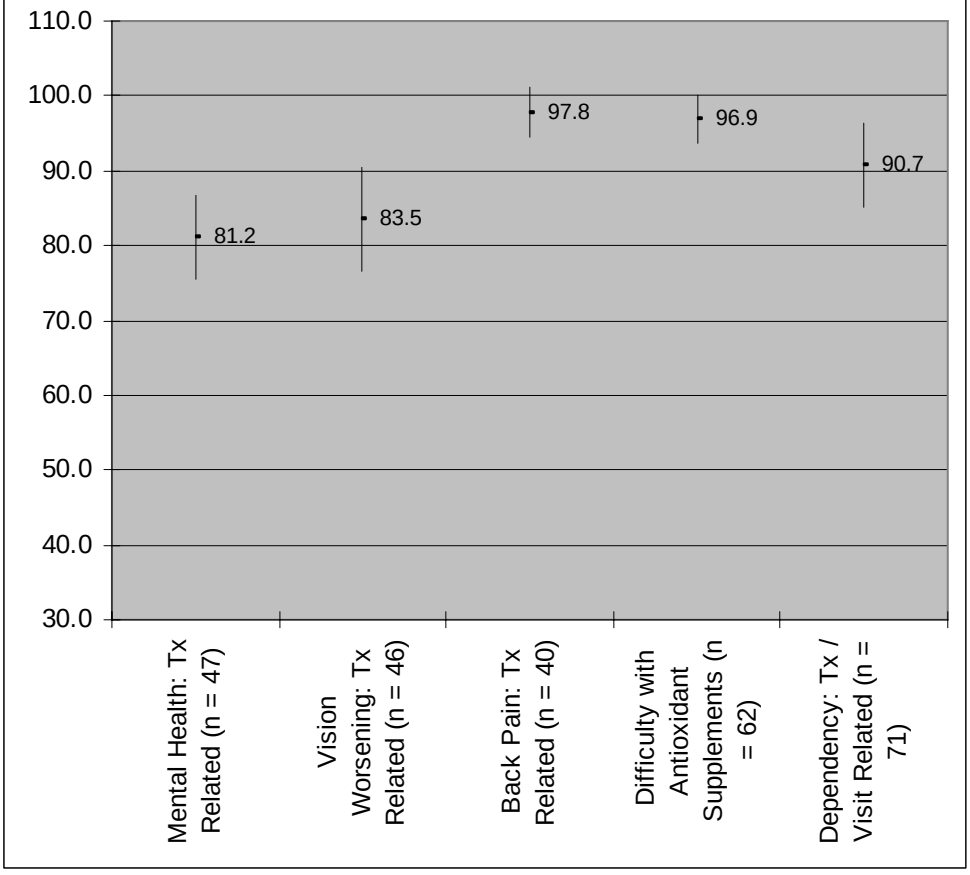


Figure 4: VFQ-25 Average Scores and 95% Confidence Intervals for Participants Who Received PDT

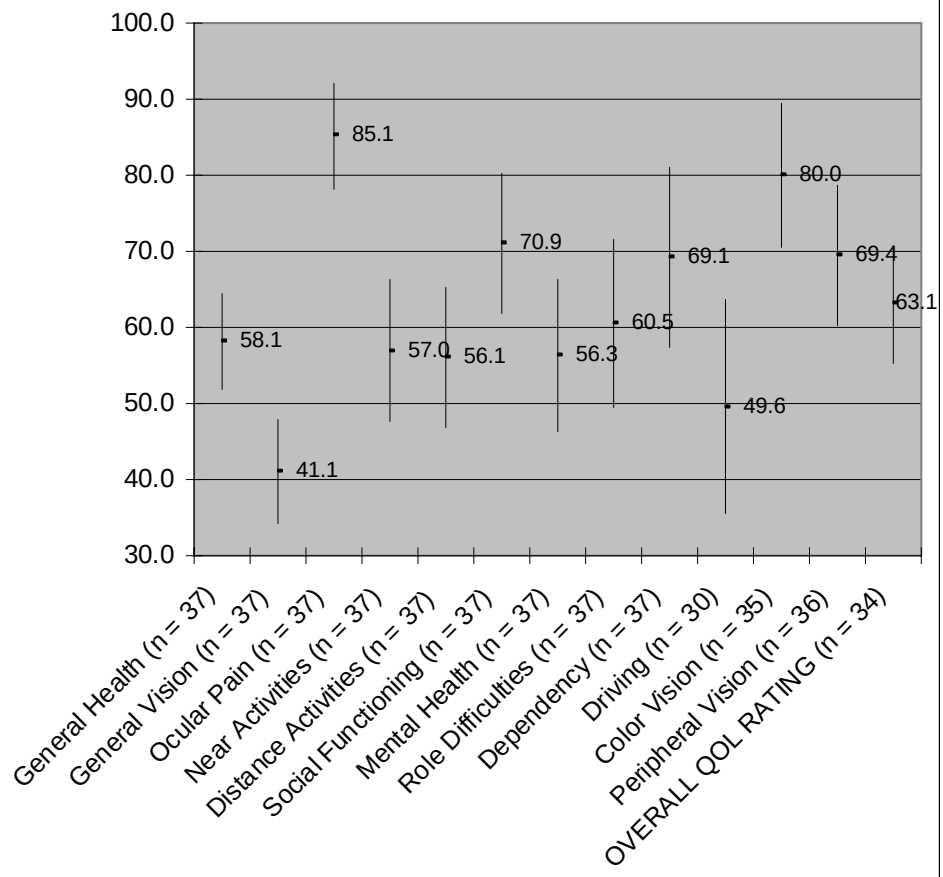


Figure 5: Additional Treatment-Related Scores and 95% Confidence Intervals for for Participants Who Received PDT

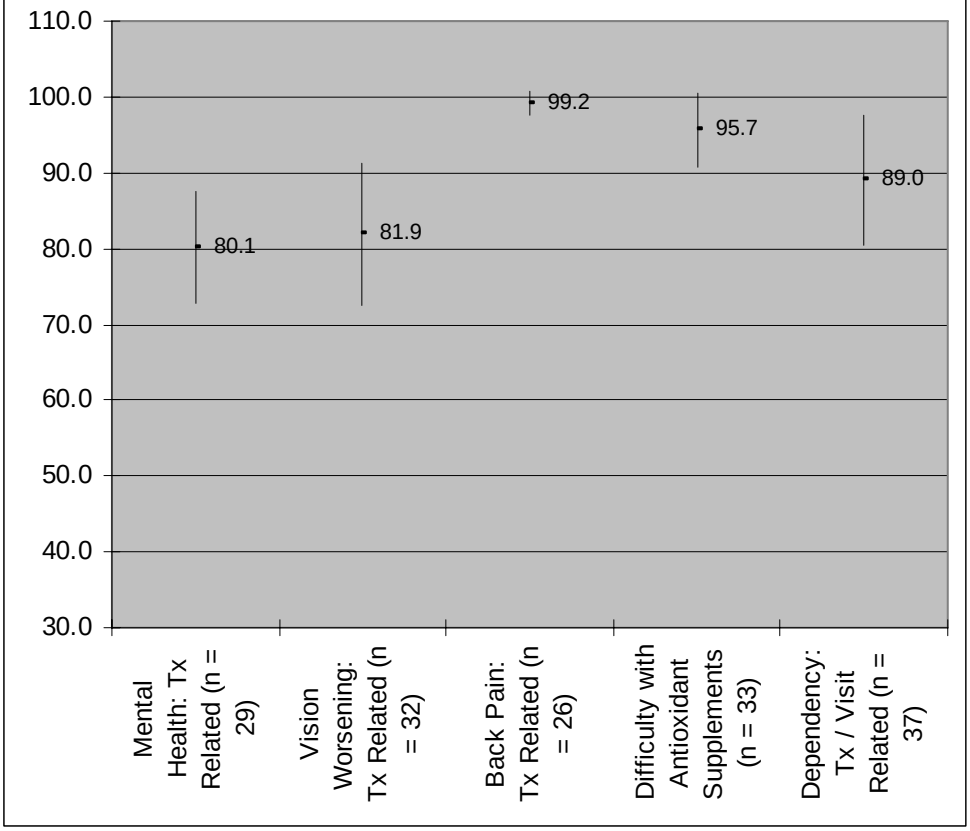


Figure 6: VFQ-25 Average Scores and 95% Confidence Intervals for Participants Who Received Pegaptanib

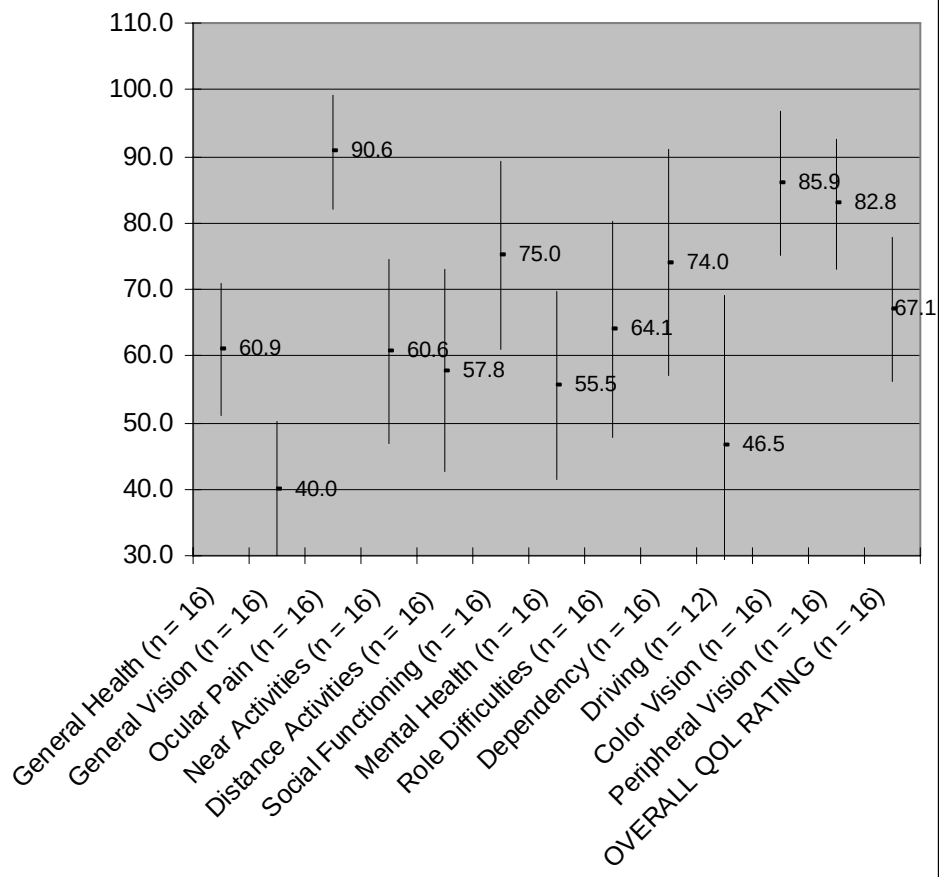


Figure 7: Additional Treatment-Related Scores and 95% Confidence Intervals for for Participants Who Received Pegaptanib

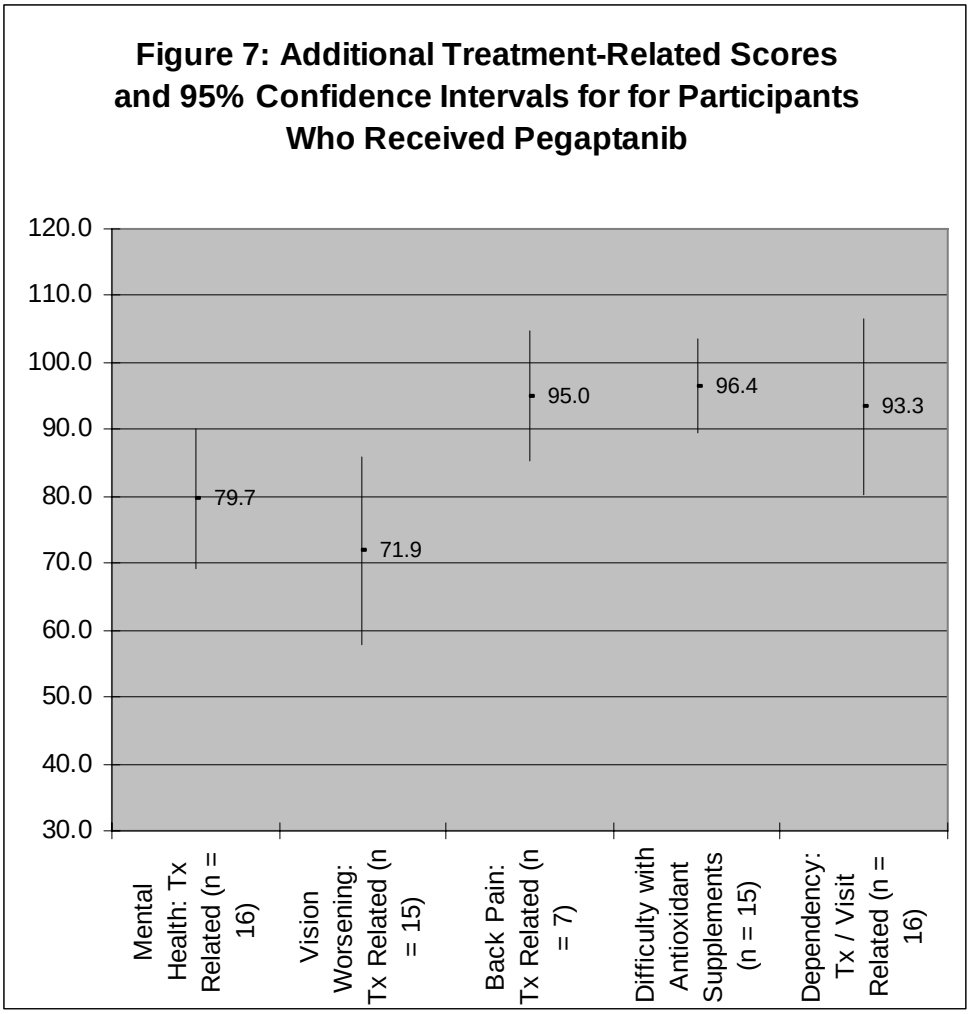


Figure 8: Scaled Visual Acuity vs. Snellen Chart Score in Better-Seeing Eye

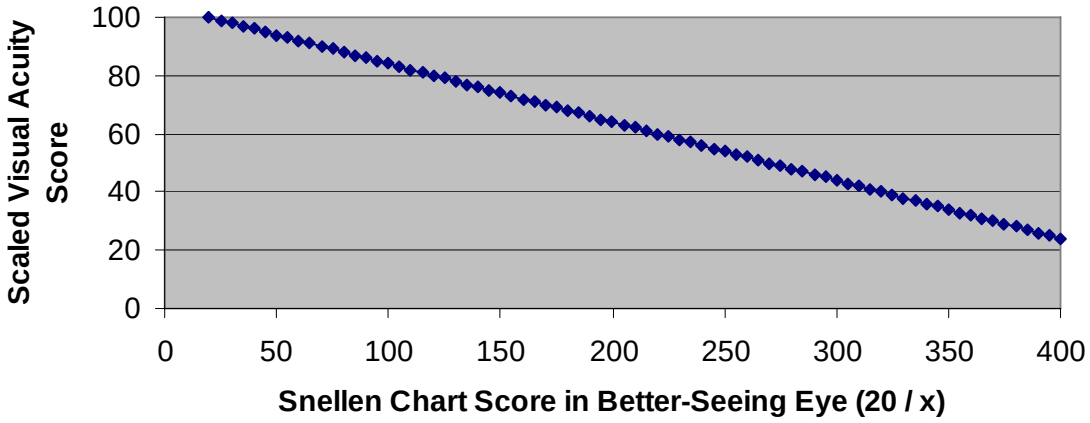


Figure 9: Actual Data for All Participants: Scaled Visual Acuity vs. Overall QOL Score (Including Excel-Generated Exponential Trendline)

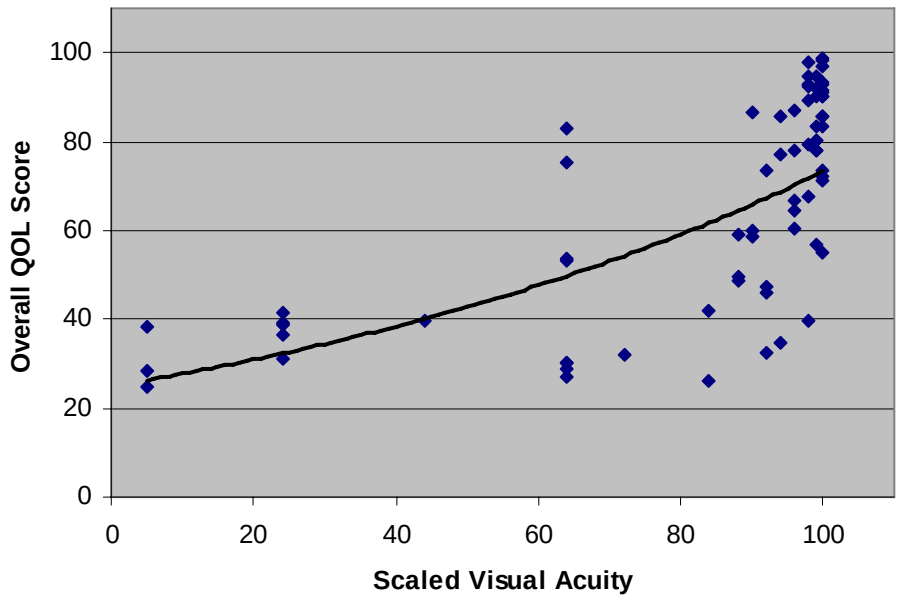


Figure 10: Predicted Data from Multiple Regression Analysis: Scaled Visual Acuity vs. Overall QOL Score

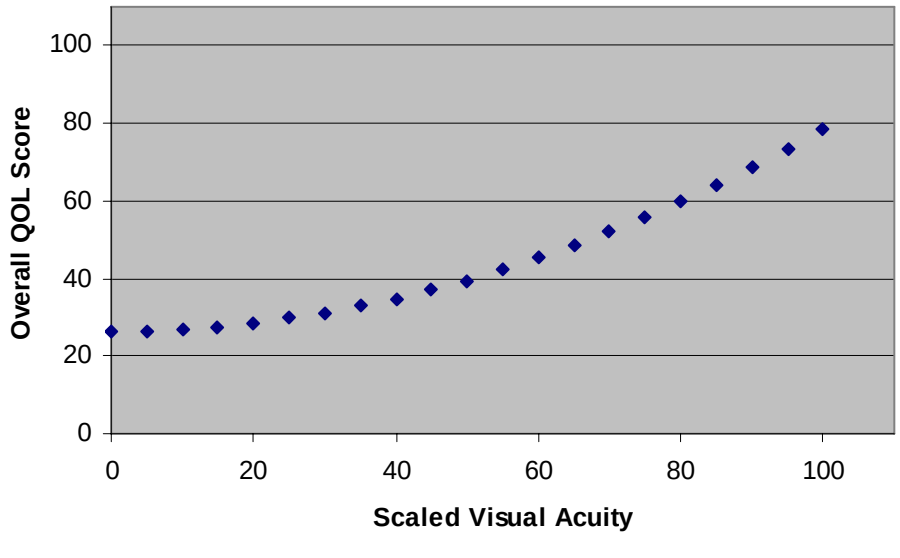


Figure 11: Actual Data for All Participants: Scaled Visual Acuity vs. Overall Tx. Score (Including Excel-Generated Exponential Trendline)

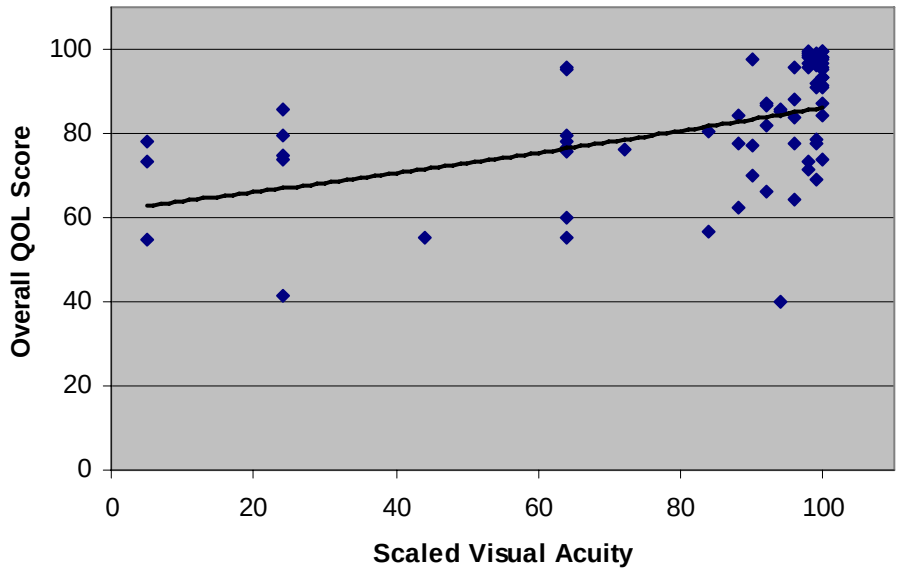
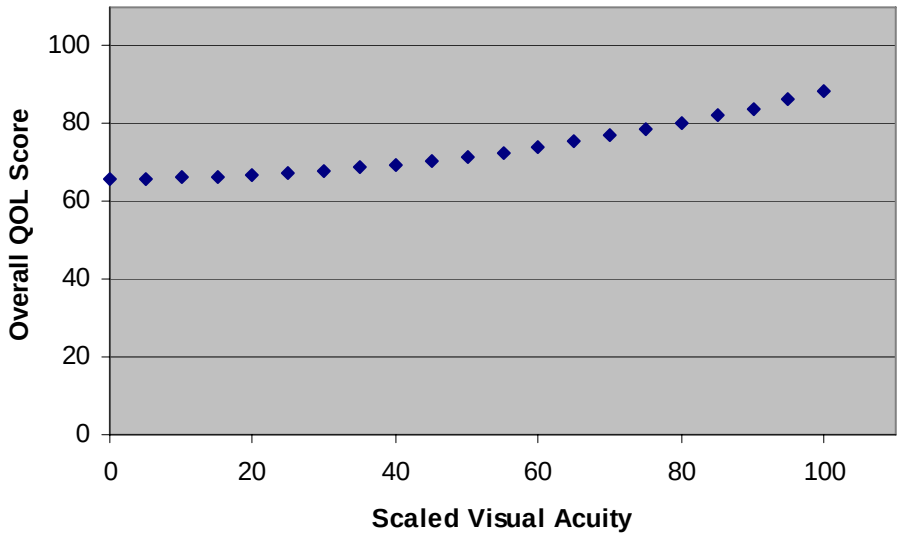


Figure 12: Predicted Data from Multiple Regression Analysis: Scaled Visual Acuity vs. Overall Tx. Score



DISCUSSION

Summary and Implications

This study had several objectives: (1) describe overall QOL in AMD patients seen at the Yale Eye Center, to add to the growing body of literature on this subject; (2) define and measure treatment-related QOL subscales in AMD patients; (3) determine which subscale scores are most likely to correlate closely; and (4) determine whether overall QOL measures or treatment-related measures differed significantly between different subsets of patients, stratified by gender, age, and treatment type.

As it has been shown that clinicians and community members may greatly underestimate the impact of AMD of all severity levels on patient QOL (31), a major goal of this and other QOL studies was to inform clinicians about the QOL deficits AMD patients face. Our cohort of patients scored lowest on General Vision, followed by Driving, General Health, Distance Activities, and Mental Health. In contrast, in a previous study using the VFQ-25 in AMD patients, the largest deficits were seen in the subscales for near and distance vision, role difficulties, dependency, social functioning, and mental health (32); hence, there is relative similarity between different studies. Slight differences between studies in the areas most strongly affected are even less important given the high correlation between these subscales.

In our study, driving in particular was mentioned by several participants as the most significant "turning point" in their disease progression, since independence is sharply restricted once the ability to drive is lost. Previous studies have shown that of AMD patients reporting to a low-vision clinic, 24% were drivers (33). Current drivers, vs. those who had stopped driving, were more likely to be younger, male, have better visual acuity, and have higher VFQ-25 scores. Over 50% of the current drivers in the

study avoided challenging driving situations. Other researchers have found that AMD patients use many strategies in driving, such as 1) using caution; (2) using memory; (3) guessing; (4) using a copilot; (5) increasing the visual field; and (6) using a visual aid (34). AMD patients may also use strategies to continue driving, including (1) self-regulating driving activities; (2) believing in driving capabilities; (3) fulfilling the desire to drive; (4) circumventing the law; (5) denying driving difficulties; and (6) using visual markers (34). These researchers found that healthcare professions may avoid discussions regarding driving and driving cessation, and that patients may use this lack of advisement as justification for continued driving. Physicians should proactively discuss driving ability with patients with moderate AMD regularly, encouraging patients to limit driving to those situations in which vision is clearest (daytime, in good weather conditions), as well as to familiar areas with the least traffic. Since some patients report problems with glare in bright light conditions, advising sunglass or solar shield use can also be helpful. Eventually, discussions regarding driving cessation may be necessary. When patients are no longer able to drive, other methods of transportation (such as public transportation) should be explored; these methods of transportation are underutilized by this population (34).

The Near Activities score was low for our cohort as well, though it was not one of the lowest subscale score reported. Reading performance, strongly reflected in the VFQ-25 in the Near Activities subscale score, has also been shown to be strongly associated with vision-related quality of life (35). Print contrast and print size have been shown to be most important in determining reading performance (35). Patients with significant problems with reading should be referred to low vision clinics, where they can be prescribed low vision aids, such as magnifying devices. Low vision aids have been

shown to be effective in helping almost nine out of 10 patients with impaired vision to read (36). Self-management programs can also help improve self-efficacy, reduce patient distress, improve mood, and prevent depression (23, 24) and patients with significant visual disability should be encouraged to consider these programs.

This cohort scored highly on the treatment-related subscales. While this is reassuring, it could be that the questions relating to treatment were not worded correctly to reveal existing deficits. From discussions with participants, questions relating to the following issues could be useful to add to future questionnaires regarding injection-based treatments:

1) How much pain is experienced at the time of treatment injection?
2) How much time in the clinic is needed at each appointment where injections are given?

Questions around supplement cost could be useful in weighing the costs and benefits in patients that may derive minimal benefit from supplements.

Correlations between different scores raised some provocative questions. Some of the correlation results were not surprising. For instance, a previous study demonstrated positive correlation between visual acuity and the following subscales: general vision, difficulty with distance tasks, difficulty with near tasks, dependency, role difficulties, mental health, and social function limitations (11). Our study showed strong positive correlations between scaled visual acuity and all these subscales, as well as driving and color vision. A previous study also demonstrated that age was not strongly correlated to any subscale other than the near tasks subscale (11). Similarly, our study did not demonstrate strong correlations between age and any particular subscale; however, the study did show weak or moderate negative correlations between age and

many subscale items.

Other studies have demonstrated limited informativeness of the Driving and Ocular Pain subscales (12). For the Driving subscale, this may be because it is not applicable to patients who have never driven, and once patients have stopped driving, no further changes in this subscale can be recorded (12). Similarly, the Ocular Pain subscale is not relevant for patients with painless AMD (12). However, we believe that driving represents an area about which patients feel strongly, as detailed above, and hence it deserves attention. Moreover, it was strongly correlated in our study to numerous other subscale scores, including General Vision and Scaled Visual Acuity. Ocular Pain, in contrast, was not strongly related to many other variables. The strong correlation between General Health and Ocular Pain implies that some patients may have eye pain related to other health problems, or that patients with more health problems may be primed to subjectively experience greater pain. This correlation suggests that ophthalmologists may want to explore the issue of ocular pain more with patients with many comorbidities.

Scores on Treatment-related Mental Health were strongly correlated to only Overall QOL Rating and Treatment-Related Vision Worsening; this implies that worry and frustration about vision don't necessarily increase as visual function falls. This conclusion is supported by the fact that some researchers have found greater depression risk among patients with only one eye affected by AMD, due to uncertainty regarding vision loss in the unaffected eye (13). Screening for depression in AMD patients then, either by ophthalmologists or by primary care providers, should not be limited to patients with severe bilateral disease.

When examining whether treatment type influences QOL, we undertook two sets

of analysis. First, we performed ttests to examine differences between treatment groups on all of the QOL subscale scores and treatment-related scores. Our results showed limited areas of significant difference between treatment groups, with most of the effect likely due to differences in visual acuity. Second, we performed multivariable regression analysis, which showed that when controlling for visual acuity (here, Scaled Visual Acuity^2 was shown to have more explanatory power than Scaled Visual Acuity alone or both Scaled Visual Acuity and Scaled Visual Acuity^2), treatment history, gender, and age provided no additional explanatory power. This finding is reassuring, as it shows that any positive impact on visual acuity due to treatment will not be consistently offset by treatment side effects, worry about treatment, or the burden of frequent appointments.

Limitations of the Study

Limitations of the study include a limited sample group, particularly in the pegaptanib subgroup. However, progress in AMD drugs has accelerated, and pegaptanib's use may decrease. Genentech's ranibizumab (Lucentis) is a humanized therapeutic antibody fragment designed to inhibit VEGF-A, which is involved in angiogenesis in the pathogenesis of wet AMD. Ranibizumab has demonstrated impressive efficacy, including an average gain of seven letters in VA, vs. an average loss of 10.5 letters for the control group (Genentech website). In February 2006, Genentech announced that the FDA had granted it a six-month Priority Review for use of ranibizumab, and that the FDA would take action on the filing by the end of June 2006. The introduction of ranibizumab and future similar VEGF inhibitors may drop market share for pegaptanib; however, it is likely that pegaptanib would continue to be used in patients who had responded well to it or for whom the side effect profile of pegaptanib is

more advantageous than that of ranibizumab. Information on the QOL impact and side effects of pegaptanib injections vs ranibizumab injections, from a subjective perspective, could inform the decision process between the two drugs in marginal cases. Similarly, PDT market share would be likely to fall in the case of ranibizumab approval.

Even more dramatic treatments are on the horizon for end-stage AMD: in 2005 a visual prosthetic device for bilateral end-stage macular degeneration, which was shown to increase QOL, was described (37). In 2005, therapeutic apheresis was shown to be effective in minimizing vision loss and maintaining overall quality of life in patients with dry AMD (38). However, many of the principles regarding QOL in AMD will apply regardless of the particular treatment modality.

Another limitation was that measures of general health were not included. Researchers have found that general health, as measured by SF-36 physical component summary and mental component summary scores influenced score on the VFQ-25 (39). These researchers in a separate article reported that adjusting for comorbidities such as diabetes, arthritis/rheumatism, and hypertension did not change the magnitude of the treatment effect on NEI-VFQ scores, but that adjustment for Short Form-36 physical and mental component summaries produced changes in the estimated treatment effect (40). Moreover, the results of previous studies have indicated that interventions aimed at improving QOL should include a component directed at improving physical and mental health (41).

Challenges would exist in adding additional measures to the study; it is likely that response rate is inversely proportional to time needed to complete the measure(s). For patients interviewed in clinic, in particular, administration of the VFQ-25 often occurred during, and filled, wait time during the visit. Moreover, it stands to reason that the longer

the questionnaire(s), the more bias might be introduced toward patients who are younger, more functional, and perhaps better-educated. These challenges notwithstanding, adjustment for general health might be a plausible improvement to future similar studies.

A final limitation was that we only examined visual acuity in the better-seeing eye. Some researchers have found independent contributions to vision-related quality of life from the worst-eye visual acuity (VA) and the best-eye visual acuity (14). Potentially increased risk for depression among those with unilateral AMD, as described above, is another important factor to consider with regard to QOL in AMD.

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