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Improving Function in Age-related Macular Degeneration: A Randomized Clinical Trial.

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Running head: Improving Function in Age-Related Macular Degeneration

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Abstract

Purpose: To compare the efficacy of Problem-Solving Therapy (PST) with Supportive Therapy

(ST) to improve Targeted Vision Function in Age-Related Macular Degeneration (AMD).

Design: Single-masked, attention controlled randomized clinical trial with outcome assessments at 3 months (main trial endpoint) and 6 months (maintenance effects).

Participants: Patients with AMD (N = 241) attending retina practices.

Interventions: PST uses a structured problem-solving approach to reduce vision-related task difficulty. ST is a standardized attention control treatment.

Main Outcome Measures: Targeted Vision Function (TVF); National Eye Institute Vision Function Questionnaire - 25 plus Supplement (NEI VFQ); Activities Inventory (AI); and Vision-Related Quality of Life.

Results: There were no significant between-group differences in TVF scores at 3 months (p = 0.47) or 6 months (p = 0.62). For PST subjects, mean [standard deviation (SD)] TVF scores improved from 2.71 (0.52) at baseline to 2.18 (0.88) at 3 months (p = 0.001) and were 2.18 (0.95) at 6 months (change from 3 to 6 months, p = .74). For ST subjects, TVF scores improved from 2.73 (0.52) at baseline to 2.14 (0.96) at 3 months (p = 0.001) and were 2.15 (0.96) at 6 months (change from 3 to 6 months, p = .85). Similar proportions of PST and ST subjects had less difficulty performing a TVF goal at 3 months (77.4% vs. 78.6%, respectively; p = 0.83) and 6 months (76.2% vs. 79.1%, respectively; p = 0.61). There were no significant changes in the NEI VFQ or AI. Vision-related quality-of-life improved for PST relative to ST subjects at 3

months [$F_{(4,192)} = 2.46$; $p = 0.05$] and 6 months [$F_{(4,178)} = 2.55$; $p = 0.05$)]. PST subjects also developed more adaptive coping strategies than ST subjects.

Conclusions: We found that PST was not superior to ST at improving vision function in patients with AMD but PST improved their vision-related quality of life. Despite the benefits of anti-VEGF treatments, AMD remains associated with disability, depression, and diminished quality of life. This clinical reality necessitates new rehabilitative interventions to improve the vision function and quality of life of older persons with AMD.

Key Words: Vision Function, Age-Related Macular Degeneration, Clinical Trial, Coping

Introduction

Age-Related Macular Degeneration (AMD) is a chorioretinal disease that can lead to geographic atrophy and choroidal neovascularization and hemorrhage.[1] These advanced stages of AMD account for most cases of severe vision loss in older adults and affect almost 2 million people in the United States.[2,3] Aging of the population will double the prevalence of AMD by 2020, dramatically increasing the number of older adults who are visually impaired and at risk for blindness, disability, depression, hip fracture, nursing homes residence, and reduced quality of life.[4-7] The anti-vascular endothelial growth factor (anti-VEGF) antibodies ranibizumab and bevacizumab have greatly improved the prognosis of neovascular AMD but many patients continue to have disabling vision impairment.[8,9] For example, in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), about 35% of subjects had substantially improved vision function and 50% had improved mental health but the converse is also informative: the vision function of 65% of subjects and the mental health of 50% did not improve to that extent.[8, 9] Patients with visual acuity worse than 20/70 in the better eye after treatment still have disabling impairment and rehabilitative needs.[10]

Complementing the biomedical treatments for AMD are low vision rehabilitation (LVR) interventions which maximize visual ability using vision-enhancing devices, environmental modifications, and compensatory strategies.[11] The recent VA Low Vision Intervention Trial (LOVIT), a randomized controlled trial of outpatient LVR, demonstrated its efficacy to improve reading and other functional abilities.[12] Most visually impaired persons are unaware of LVR, however, and few ophthalmologists are able to provide comprehensive vision care to their patients.[13] Without national policies to integrate ophthalmologic and rehabilitative care, patients with AMD miss the opportunity to prevent disability, depression, and other medical complications of vision loss.

To address this problem, we conducted a randomized, controlled clinical trial entitled, "Improving Function in AMD" (IF-AMD), which compared the efficacy of Problem-Solving Therapy (PST) with Supportive Therapy (ST) to improve Targeted Vision Function (i.e., ability to perform valued vision-related daily living activities) in patients with AMD. PST teaches a structured approach to problem-solving that we adapted to reduce vision-related task difficulty.[14] ST is a structured, standardized, psychological treatment that controls for the nonspecific effects of attention.[15] In this clinical trial, we evaluated the immediate (3-months) and longer term (6-months) efficacy of PST to improve the primary outcome of Targeted Vision Function and the secondary outcome of vision-specific quality of life.

Methods

The aim of the IF-AMD Trial was to test the efficacy of PST to improve the primary outcome of

Targeted Vision Function (TVF) in older patients with AMD at 3 months. We recruited 247

patients with AMD from the retina clinics associated with the Wills Eye Institute (WEI) in

Philadelphia, PA from October 2006 to February 2010. The inclusion criteria were: 1) age 65

years or older; 2) bilateral AMD (neovascular and/or geographic atrophy); 3) visual acuity

between 20/70 and 20/400 [inclusive; (best corrected)] in the better-seeing eye, and no lower

acuity limit in the fellow eye; and 4) moderate difficulty in at least one valued vision-function goal (e.g., reading mail, attending social activities).   The exclusion criteria were: 1) presence of uncontrolled glaucoma, diabetic retinopathy, or planned cataract surgery within 6 months; 2) cognitive impairment on an abbreviated version of the Mini-Mental Status Examination (MMblind) that omits vision-dependent items;[16] 3) presence of a medical condition that would preclude participation; and 4) residence in a skilled nursing facility.   Eligible subjects were randomly assigned to PST or ST in a 1:1 allocation ratio stratified on severity of AMD (visual acuity better vs. worse than 20/100 in the better eye).   We used a random numbers table and serially numbered, sealed, opaque envelopes containing the treatment allocations to assign subjects within each stratum. The randomization schedule was based on a permuted random block design to ensure balance between treatment groups on time of subject enrollment. To attain 80% power for a 2-sided alternative hypothesis using a F-test to compare the 2 treatment groups at 3 months, we required 200 subjects (100 per group) to detect an effect size of 0.4. We over-sampled by 20% to account for attrition, bringing the total sample size to 240. Staff masked to treatment assignment was involved in central data collection; only the project director, statistician, and therapists were aware of treatment assignment. Thomas Jefferson University's Institutional Review Board approved this study and all subjects signed an approved informed consent form.

Study Treatments

Problem-Solving Therapy (PST): PST teaches problem-solving skills in a structured way to enable a patient to systematically identify his or her problems, generate alternative solutions for each problem, select the best solution, develop and conduct a plan, and evaluate whether the problem is solved.[14]   In this study, the PST therapist and subject discussed the functional problems caused by vision loss and used the following problem-solving steps to reduce the difficulty of vision-dependent tasks: 1) clarifying the problems associated with the task;

2) establishing a realistic goal toward improvement of task performance; 3) generating multiple solution alternatives; 4) implementing decision-making guidelines; 5) choosing the preferred solution(s); 6) implementing the preferred solutions(s); and 7) evaluating the outcome. The PST therapist helped subjects to develop feasible solutions and reviewed available rehabilitative services and devices to inform the process of generating solutions. The aim was to have subjects incorporate the problem-solving method of reasoning as a routine, often-recruited approach to solving future as well as current function-related problems.

Supportive Therapy (ST)

ST is a structured, standardized, psychological treatment that controls for nonspecific treatment effects.[15] ST resembles PST in all ways but for PST's problem-solving skills training. Both interventions are based on written treatment manuals and similar in dose and intensity of attention (i.e. number and duration of sessions). ST is nondirective, supportive, and facilitates personal expression and conveys empathy, respect, and optimism (i.e. a general sense that things can get better). The ST therapist informs subjects that ST's purpose is to explore the impact of vision loss on their lives. The goals were to facilitate and deepen knowledge of subjects' life situations and their relationship to illness, disability, retirement, social isolation and vision loss. The ST therapists created an accepting, non-judgmental, empathic environment by using supportive statements, reflective listening, and empathic communications. In contrast to PST, there was no discussion of vision function goals, problem solving, or low vision rehabilitative strategies.

Fidelity, Supervision, Masking, and Adherence

PST and ST therapists had bachelors or masters level degrees in the social sciences and were trained by a clinical psychologist (MTH) to deliver both interventions to reduce therapist effects. Both PST and ST are manual driven treatments; thus training concentrated on properly adhering to the treatment manuals. The training program consisted of workshops, review and discussion of the treatment manuals, and supervision of 5 training cases. All therapists met satisfactory levels of competence before delivering study treatments. To monitor treatment fidelity, all treatment sessions were audio-taped and 30% were randomly selected for fidelity ratings. To assess subjects' adherence to PST, therapists rated whether PST subjects understood and applied PST principles, complied with homework, and accomplished requisite problem-solving tasks. ST subjects did not focus on vision goals or have homework as part of their treatment. The research nurse who conducted outcome assessments became unmasked to the treatment assignment of 9 subjects (3.7%) when the latter revealed their assignments.

Study Measures:

A research nurse masked to treatment assignment obtained the following data during in-home interviews at baseline and months 3 and 6.

Personal characteristics: These included age, sex, race, marital status, living arrangements, and education.

Primary Outcome: To assess the primary outcome of vision function, we identified and quantified the Targeted Vision Function (TVF) goals that subjects valued but found difficult to achieve. To derive the TVF measure, at baseline subjects completed the Activities Inventory, which is a structured vision function questionnaire that asks patients to rate the value and

difficulty of 48 vision function goals (e.g., daily meal preparation) and the tasks (e.g., seeing stove settings) that are required to achieve them.[17,18] If a goal is important (range not important "0" to very important "4"), the subject rates its "difficulty" [on a scale of 0 (not difficult) to 4 (impossible)].   The average TVF score is the sum of the difficulty ratings of the (up to) 4 self-selected goals divided by the number of goals (from 1 to 4). Higher average scores indicate greater disability. At each outcome assessment subjects again rated the difficulty of the same targeted goals and the average TVF score was calculated. In this way, TVF was targeted and tailored, measured in a standardized way, and allowed subjects to vary in the number of TVF goals they select at baseline.

Secondary Outcomes: We administered the National Eye Institute Vision Function Questionaire-25 plus Supplement (NEI VFQ).[19] This version of the NEI VFQ consists of 39 items that assess self-reported vision function and vision-related quality of life (QoL). The latter yields a multidimensional index of vision-related health comprised of social functioning (i.e., social interactions), mental health (i.e., worry, frustration), role difficulties (i.e., accomplishing less), and dependency (i.e., relying more on others) due to vision loss. Scores range from 0 to 100, with higher scores indicating better function.

Vision Status: We assessed vision using a standardized battery of vision tests and standardized lighting to assess distance and near visual acuity, contrast sensitivity, and the size and location of central scotomas. To measure distance visual acuity, we used the Lighthouse Ferris-Bailey Early Treatment Diabetes Retinopathy Study (ETDRS) chart at a distance of 10 feet. For near acuity we used a reduced version of the ETDRS chart calibrated for 40 cm. For contrast sensitivity, we used the Pelli-Robson Contrast Sensitivity chart. To measure the size of central scotomas we used a tangent screen and modified Amsler grid technique.

Physical Health Status: We calculated the Chronic Disease Score, which provides an objective measure of medical comorbidity based on a weighted sum of medications taken for chronic illness.[20] Higher scores indicate worse medical morbidity.

Psychosocial Status: To assess depression, we used the Patient Health Questionnaire-9, which yields a continuous measure of depression severity.[21] Scores range from 0 to 27, with higher scores indicating worse depression. We used the Optimization in Primary and Secondary Control Scale (OPS) to assess subjects' control (i.e., coping) strategies.[22-24] The OPS is divided into 4 control strategies, each comprised of 8 items rated from 0 ("never true") to 4 ("almost always true"), yielding a range of 0 to 32; higher scores indicate greater use of the particular strategy. <u>Selective primary control</u> refers to the investment of behavioral resources (i.e., time, effort, skills) to pursue a goal (e.g., "I do whatever I can to continue my everyday activities despite my vision problem."). <u>Selective secondary control</u> serves to maintain commitment to a goal in the face of obstacles (e.g., "I think how important it is to me to keep up my daily activities in spite of my vision problem."). <u>Compensatory primary control</u> refers to asking for help from others or using assistive devices (e.g., "If I'm having trouble doing something because of my vision problem, I look for a device or aid that will help get it done."). <u>Compensatory secondary control</u> refers to goal disengagement when goals become unattainable (e.g., "I can accept that there are things I can no longer do since I started having problems with my vision.").

Data Analyses

We used descriptive statistics and bivariate comparisons of subjects in the two treatment groups to characterize the sample, and assess the success of randomization. To test the efficacy of PST to improve TVF functional reserve measures at 3 months, we used an analysis of covariance (ANCOVA) in which group differences (PST vs. ST) in 3-month average TVF scores were examined, adjusting for baseline TVF score and the vision severity stratification variable. To approximate an interval scale and compensate for ceiling and floor effects, we linearized TVF scores using a logit transform.[24] We also conducted subsidiary analyses examining treatment group effects on total NEI VFQ scores and AI measures estimated from Rasch analysis. We repeated all analyses to assess the maintenance effects of the study treatments at 6 months. To determine whether PST and ST were associated with clinically meaningful changes in function, we compared the proportions of subjects in the two treatment groups who rated a TVF goal at 3 or 6 months as less difficult compared with baseline. To determine PST's impact on vision-related quality-of-life at 3 and 6 months (in separate analyses), we used a multivariate analysis of covariance (MANCOVA) in which the dependent variables were the NEI-VFQ social functioning, mental health, role difficulties, and dependency subscales, with the visual acuity stratification variable and baseline NEI-VFQ scores as covariates. We analyzed rank-transformed scores because the distribution of scores was highly skewed. Mixed effects linear regression was used to model change in TVF and Optimization of Primary and Secondary Control variables over time. Fixed effects included time (baseline, 3 months, 6 months), treatment group, time by treatment interaction, and the vision severity stratification variable. A first-order auto-regressive structure was assumed to model the correlation among repeated measurements from the same subject.

Results

Figure 1 depicts the study flow chart. A total of 1,155 patients met ophthalmologic eligibility

criteria and were approached for further screening. Of these, 247 (21%) were enrolled and 914

(79%) were excluded. Of the latter, 414 (36%) refused participation; 214 (19%) did not have

difficulty achieving valued goals; 12 (1%) were deceased; and 273 (24%) had other reasons

(e.g., could not be reached, medical illness, cognitive impairment). Six enrolled subjects dropped from the study prior to randomization. Two hundred eleven subjects (87.6%) had neovascular disease in at least one eye; the remainder had bilateral geographical atrophy. In the better vision stratum (i.e., better eye acuity 20/70 – 20/100), there were 76 PST and 73 ST subjects. In the worse vision stratum (better eye acuity <20/100), there were 45 PST and 47 ST subjects. The attrition rates at 3 months for PST and ST subjects were 12% and 7%, respectively; at 6 months they were 13% and 9%, respectively. At baseline, 53% of PST subjects and 46% of ST subjects reported previously receiving anti-VEGF treatment. At 3 months, 48% of PST and 40% of ST subjects reported receiving injections after the baseline assessment, and 43% of PST and 42% of ST subjects reported receiving injections between the 3 and 6 month assessments.

Table 1 compares the demographic and clinical baseline characteristics of randomized subjects by treatment group. Notable are the advanced age of the subjects (average age about 82 years) and the severity of their vision loss. The average near visual acuity in the better-seeing eye (logMAR score of 0.62) corresponds to a Snellen visual acuity of about 20/80. Subjects in the PST and ST groups identified similar valued vision function goals to address in treatment: read newspaper (48% in both groups; leisure/entertainment activities: 38% and 48%, respectively; correspondence: 31% and 23%, respectively; personal communication: 31% and 23%, respectively; and manage finances: 22% and 21%, respectively. PST and ST subjects received a similar number of treatment sessions [5.8 (.8) and 5.9 (.5), respectively]. PST subjects addressed a mean of 4.5 (1.6) vision function goals. Over the 6 month study period there were no significant within or between group changes in visual acuity, contrast sensitivity, or scotoma size (data not shown).

Table 2 shows the primary and secondary outcomes by treatment group at baseline and 3 and 6 months. For PST subjects, mean [standard deviation (SD)] TVF scores (primary outcome) improved from 2.71 (0.52) at baseline to 2.18 (0.88) at 3 months (p = 0.001) and were 2.18 (0.95) at 6 months (change from months 3 to 6, p = .74). For ST subjects, TVF scores improved from 2.73 (0.52) at baseline to 2.14 (0.96) at 3 months (p = 0.001) and were 2.15 (0.96) at 6 months (change from 3 to 6 months, p = .85). There were no statistically significant between-group differences at 3 months (p = 0.47) or 6 months (p = 0.62). The results were the same using transformed TVF scores (data not shown).   Similar proportions of PST and ST subjects experienced less difficulty performing a TVF goal at 3 months (77.4% vs. 78.6%, respectively; p = 0.83) and 6 months (76.2% vs. 79.1%, respectively; p = 0.61).

On the secondary multivariate outcome of vision-related quality-of-life (i.e., a composite of the NEI VFQ-25 social functioning, mental health, role difficulties, and dependency subscales), there was a significant treatment group difference at 3 months favoring PST [F (4,192) = 2.46; p = 0.05] that was maintained at 6 months [F (4,178) = 2.55; p = 0.05]. On the secondary outcomes of total NEI VFQ-25 scores and Activity Inventory scores, there were no significant between-group or within-group changes from baseline to 3 months or from 3 months to 6 months. Levels of depression (i.e., PHQ-9 scores) were very low at baseline; there was no significant changes in depressive symptoms in either treatment group over time. There were also no statistically significant changes or treatment group differences in the use of low vision devices resources (e.g., device use, home modifications, or low vision rehabilitation).

Table 2 also shows mean scores on the Optimization of Primary and Secondary Control subscales by treatment group at 3 and 6 months. Treatment group differences in two control strategies, Compensatory Secondary Control and Selective Primary Control, indicate that

subjects who received PST developed more adaptive coping strategies than subjects who received ST.   For Compensatory Secondary Control, ST subjects had a significant decline in this coping strategy from baseline to 3 months ($p \leq 0.0001$) and to 6 months ($p = 0.015$). This suggests that ST subjects' ability to disengage from goals when they were no longer attainable declined (i.e., they were less accepting of vision loss) whereas PST subjects had no significant changes in this strategy over time (3 months; $p \leq 0.92$) and 6 months; ($p \leq 0.66$).   The comparison of PST vs. ST subjects on change in this variable was significantly different at both 3 months ($p = 0.01$) and 6 months ($p = 0.04$).   These data indicate that PST subjects' use of "acceptance" to compensate for vision loss remained stable over time whereas ST subjects' use of this strategy declined. On the control strategy of Selective Primary Control, which refers to devoting time, effort, and skills to pursue a goal, PST subjects decreased use of this strategy from baseline to 6 months ($p = 0.0007$) whereas ST subjects did not ($p = 0.69$). The between group comparison was significant ($p = 0.03$). This finding suggests that PST subjects were less likely than ST subjects to invest time and effort to pursue goals that they likely could not attain, and is congruent with PST subjects' acceptance of disability as per their greater use of Compensatory Secondary Control noted above.

Discussion:

We found that PST was not superior to ST at improving the vision function of older patients with AMD but PST did increase the use of adaptive coping strategies and improve vision-related quality of life. As a "talking treatment," PST emphasized independent problem solving but did not directly advise on low vision rehabilitative interventions. We believe that this characteristic

of PST limited its effectiveness to improve vision function. Although most subjects adhered to the treatment plans that they devised, the latter were insufficient to reduce their functional deficits.   The significant changes in coping strategies that we observed suggest, however, that the problem-solving approach may have helped PST subjects regain a sense of control over their situation by developing realistic appraisals of their disability, disengage from goals that they could no longer attain, free them to pursue goals that they could attain, and improved the quality of their lives.

The patients we studied had bilateral AMD and high levels of visual disability. Although such patients are common in clinical practice, they are not representative of most patients with AMD given our eligibility criteria and high refusal rate. These factors introduce possible selection biases and limit generalizability. Nevertheless, the average NEI VFQ scores in the sample were comparable to subjects enrolled in MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD), indicating the general similarity of the two AMD patient groups.[9]   The strengths of the study include systematic sampling, successful recruitment, randomization, and masking, protocol-driven treatments, assessment of multiple relevant outcomes, and maintenance of treatment fidelity. We enrolled a sufficient number of subjects to ensure adequate power to detect treatment effects on the primary outcome.

Our approach to assess vision function recognized that no single, universally accepted measure or methodology exists. Instruments such as the NEI-VFQ tap several diverse dimensions of vision loss (e.g., difficulty with daily activities, social functioning, and quality of life) but may be insensitive to the effects of interventions that target personally valued goals. Achieving these goals, which may be meaningful to an individual, may not translate to a statistically significant

change on a multi-item, multi-dimensional rating instrument. For that reason we used both a targeted outcome approach (i.e., TVF) as well as the NEI VFQ to detect changes in vision function. The TVF approach asked subjects to rate the difficulty of specific vision-dependent goals that they valued and wished to address in treatment. Although we believed that this approach was conceptually sound, we found that subjects' ratings of difficulty levels were inconsistent. In a subsample of 108 subjects, we reassessed TVF difficulty ratings two weeks after baseline (before receiving any treatment) and found that the intraclass correlation between the baseline and 2 week ratings was 0.45 (p < .001).   In fact, 16 subjects (14.8%) changed their first goal's difficulty rating from "moderate or greater" at baseline to "slightly or not difficult" on re-test 2 weeks later; 11 subjects (10.2%) changed their first goal's difficulty rating from "moderate" at baseline to "very difficult" or "impossible to do" on re-test. These data suggest that TVF difficulty ratings were unstable. Although TVF scores declined in both treatment groups over time, this within-group finding may reflect regression to the mean or a nonspecific positive effect of study participation.

The IFAMD trial adds to other studies demonstrating the value of psychosocial and rehabilitative treatments. Brody et al (2002) found that an AMD self-management program improved function, decreased emotional distress, and enhanced self-efficacy, particularly for depressed patients.[25] We previously reported that PST prevented depression and improved vision function in patients with recent vision loss due to AMD although its effect was short-lived because, we believe, PST did not increase use of low vision rehabilitation devices or services.[26] Likewise, in the this clinical trial, PST did not increase subjects' use of low vision resources even though PST therapists reviewed available devices and services. These findings are important in light of the VA Low Vision Intervention Trial (LOVIT), which demonstrated the efficacy of LVR to improve the functional visual ability of moderately-to-severely visually impaired outpatients.[12]

To improve vision function, we believe that an intervention that activates subjects and directly enhances rehabilitative skills is needed. We are currently conducting the "Low Vision Depression Prevention Trial," which tests the efficacy of a low vision intervention that combines rehabilitative and psychological treatments to prevent depression and improve function in patients with AMD.[27] Taken together, the clinical and public health significance of these studies is clear: the disability of AMD will become more prevalent, costly, and burdensome to patients, families, and ophthalmologists as the population ages. Despite the unprecedented benefits of anti-VEGF treatments, AMD remains associated with disability, depression, and diminished quality of life in some patients.[8-10, 28] These clinical realities necessitate devising and testing new rehabilitative interventions to improve the visual function and quality of life of older persons with AMD.

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