ABSTRACT

Contrast sensitivity and quality of life are evaluated in some clinical trials and have relevance to clinical practice. Contrast sensitivity measurements are more helpful than visual acuity values in predicting which patients will have difficulty performing tasks that involve visual orientation, such as moving around in unfamiliar surroundings, recognizing faces, and watching television. Quality of life is an important concern for patients, particularly if they have a chronic medical condition, such as age-related macular degeneration (AMD). This article addresses the impact of contrast sensitivity on visual function, explains how it is measured, and reviews the available contrast sensitivity data from studies evaluating verteporfin versus placebo in the treatment of choroidal neovascular lesions. The article also describes the National Eye Institute Visual Function Questionnaire and its subscales, compares overall and subscale scores in 4 studies and a reference group, and explains which changes in the overall score are clinically relevant. The prevalence of anxiety and depression in patients with neovascular AMD also is addressed, as is the significance of preference values for selected medical conditions, including subfoveal choroidal neovascularization.

Although visual acuity correlates better with visual discrimination (ie, the ability to read printed text and subtitles on a television screen), visual acuity values are not helpful in predicting problems with visual orientation (ie, the ability to move around in unfamiliar surroundings, recognize faces, and watch television). Conversely, contrast sensitivity measurements are better than visual acuity values in identifying patients who have difficulty with activities involving visual orientation.

WHAT THE MEASUREMENTS MEAN

The Pelli-Robson Contrast Sensitivity Chart (Figure 1) is used to measure contrast sensitivity in patients with AMD and other retinal disorders. Unlike charts used to measure very fine gradients of contrast sensitivity at a visual acuity of 20/20 in conditions treated with refractive surgery, Pelli-Robson charts have very large letters that are the Snellen equivalent of a visual acuity of approximately 20/750 at 1 meter. Contrast sensitivity decreases every 3 letters, and a 6-letter loss translates into a doubling of the amount of contrast required to see test chart letters.

A 6-letter loss increases the odds that a patient will report difficulty with everyday visual tasks by a factor of 3 to 5. A 15-letter loss in contrast sensitivity translates into a 5.5-fold increase in the amount of contrast required to see test chart letters and has approximately the same impact on visual disability as a 30-letter loss of visual acuity.

TAP INVESTIGATION FINDINGS

Contrast sensitivity was measured in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation, which involved patients with subfoveal CNV secondary to AMD who received verteporfin (n = 402) or placebo (n = 207) at the first visit, with retreatment at each 3-month follow-up visit if angiography revealed fluorescein leakage from CNV. Patients treated with verteporfin were less likely to lose moderate or severe levels of visual acuity and contrast sensitivity than those receiving placebo. At 1 and 2 years, 21% of patients receiving verteporfin lost 6 letters or more of contrast sensitivity versus 41% at 1 year (P <.001) and 45% at 2 years (P <.001) of patients receiving placebo.

A more sensitive way of looking at this clinically relevant outcome is to compare the mean change in contrast sensitivity from baseline at 3, 6, 9, 12, 15, 18, 21, and 24 months in the verteporfin and placebo groups in the TAP investigation, as shown in Figure 2 for all CNV lesions and in Figure 3 for predominantly classic and minimally classic lesions.

For all CNV lesions (Figure 2), patients receiving verteporfin essentially had no change in contrast sensitivity following treatment over 2 years compared to patients receiving placebo who lost an average of 5 letters from baseline—a large loss.

For predominantly classic CNV lesions (Figure 3, left panel), there was a better outcome for visual acuity that also translated into a better outcome for contrast sensitivity in the verteporfin group compared to the placebo group. Although 40% of verteporfin-treated patients with predominantly classic lesions lost 3 lines or more by 2 years, they lost almost no contrast sensitivity (mean loss 0.4 letters). The placebo group, however, lost a mean of 5.6 letters of contrast sensitivity (P <.001), and this is a clinically relevant change.

With respect to patients with minimally classic CNV lesions (Figure 3, right panel), those treated with verteporfin lost fewer letters of contrast sensitivity at 2 years (mean loss 2 letters) than patients who received placebo (P <.013). In addition, a greater proportion of patients in the placebo group lost 6 letters or more of contrast sensitivity than those receiving verteporfin (data not shown).
The superiority of verteporfin therapy over placebo in reducing the risk of a clinically relevant loss of contrast sensitivity was most pronounced in patients with predominantly classic CNV lesions at baseline, although patients with minimally classic CNV lesions also had better contrast sensitivity outcomes.1 Moreover, the contrast sensitivity findings associated with verteporfin therapy were consistent with the visual acuity outcomes observed in the study.

Given the association between contrast sensitivity and visual disability, the beneficial effects of verteporfin therapy on contrast sensitivity outcomes are expected to have a favorable impact on patients with respect to daily activities involving visual orientation. In addition, the findings underscore that contrast sensitivity measurements may provide additional information regarding the efficacy of a specific treatment for CNV.

**QUALITY OF LIFE**

Quality of life is an important issue for patients, particularly if they have a chronic medical condition.

**VISUAL FUNCTION QUESTIONNAIRE**

For patients with AMD or other conditions affecting vision, the National Eye Institute Visual Function Questionnaire (NEI-VFQ) is a generally accepted method of assessing how vision—an important determinant of overall quality of life for many patients—affects the ability to perform vision-dependent tasks.

The NEI-VFQ provides an overall visual function score that is a composite of 8 subscale scores. Because any subscale may be driven in one direction or another by another subscale, it is important to look at each subscale (ie, general vision, driving, near activities, distance activities, role difficulties, mental health, dependency, and social functioning) individually to get a better picture of how each is affecting the patient’s quality of life.
Mean NEI-VFQ scores from 5 studies of specific subjects are shown in Table 1 and discussed in greater detail below. The scores reflect 2 groups of subjects in the SST (Group N with subfoveal predominantly classic or minimally classic neovascular lesions in the study eye, and Group B with predominantly hemorrhagic lesions in the study eye); AREDS\(^8\) subjects with good vision in 1 or both eyes or drusen in 1 or both eyes; CAPT\(^9\) subjects with large drusen in both eyes who received laser treatment in 1 eye; reference values from a group of patients about to undergo refractive surgery\(^{12}\); and patients with diabetic retinopathy.\(^{13}\)

**WHAT THE NEI-VFQ SCORES SIGNIFY**

Overall and subscale visual function questionnaire scores are most meaningful when they are compared with reference values in subjects without neovascular lesions and scores in individual patients with neovascular lesions or other retinal disorders but less vision loss.

As shown in Table 1, mean subscale scores for subjects in the reference group, who are otherwise normal and have a visual acuity of 20/20, are generally in the high 80s and 90s.\(^{12}\) Although mean overall and subscale scores in AREDS\(^8\) and CAPT\(^9\) subjects with good vision, despite some drusen in both eyes (CAPT) or drusen in 1 or both eyes or neovascularization in 1 eye (AREDS), are lower than the scores in the reference group, they are higher than the scores in subjects in Groups N and B of the SST who had subfoveal neovascular or hemorrhagic lesions.\(^{2}\) The lower scores in Groups N and B of the SST reflect the impact of vision loss from neovascularization or hemorrhage on all aspects of visual function.

The NEI-VFQ scores in patients with diabetic retinopathy also reflect the impact of vision loss on visual function. Whereas these scores are lower in diabetic retinopathy\(^{12}\) than the scores in the reference group, AREDS, and CAPT, they are higher than those in Groups N and B of the SST, indicating that diabetic retinopathy, although it impairs vision and reduces visual function, may have less of an impact on visual function than CNV in AMD.

The widely accepted premise that unilateral CNV involvement has considerably less impact on vision function than bilateral CNV involvement was not borne out in the SST.\(^2\) There was a 6-point difference in overall NEI-VFQ score between subjects with unilateral CNV and those with bilateral CNV in Group N, with the overall score still far below “normal” in the unilateral cases. A 9-point difference existed between subjects with unilateral versus bilateral hemorrhagic lesions in Group B, with the overall score again far below “normal” in the unilateral cases.

As suggested by the results in Groups N and B of the SST, there was a 2-point difference in overall NEI-VFQ score for each line of visual acuity, suggesting that a clinically relevant change of losing at least 3 lines on a chart in which the size of the letters doubles in size every 3 lines translates into a difference of approximately 6 points on the overall score, suggesting that a change of at least 6 points likely represents a clinically relevant change in a patient’s perception of vision function. Interestingly, experts in quality-of-life assessment had determined, in several focus groups evaluating the NEI-VFQ before it was used in the SST, that a 5- to 7-point change in an NEI-VFQ score probably represented a clinically relevant difference.

**ANXIETY AND DEPRESSION**

The SST also assessed other aspects of quality of life and symptom-specific outcomes of CNV that are not measured by visual acuity, contrast sensitivity, and visual function tests—namely, anxiety and depression.\(^2\) The investigators used the Hospital Anxiety and Depression Scale, which defines a score of 11 or more.

**Table 1. Mean Vision Function Questionnaire Scores in Groups with Age-Related Macular Degeneration and Other Ocular Disorders**

<table>
<thead>
<tr>
<th>Scale</th>
<th>SST(^a) Group N</th>
<th>SST(^a) Group B</th>
<th>Reference Values(^b)</th>
<th>AREDS(^8)</th>
<th>DR(^{11})</th>
<th>CAPT(^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>65</td>
<td>63</td>
<td>-</td>
<td>87</td>
<td>-</td>
<td>88</td>
</tr>
<tr>
<td>General vision</td>
<td>52</td>
<td>49</td>
<td>81</td>
<td>76</td>
<td>61</td>
<td>79</td>
</tr>
<tr>
<td>Driving</td>
<td>41</td>
<td>37</td>
<td>89</td>
<td>77</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>Near activities</td>
<td>55</td>
<td>53</td>
<td>93</td>
<td>84</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Distance activities</td>
<td>61</td>
<td>69</td>
<td>95</td>
<td>87</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>Role difficulties</td>
<td>62</td>
<td>58</td>
<td>96</td>
<td>88</td>
<td>72</td>
<td>87</td>
</tr>
<tr>
<td>Mental health</td>
<td>59</td>
<td>56</td>
<td>91</td>
<td>87</td>
<td>68</td>
<td>85</td>
</tr>
<tr>
<td>Dependency</td>
<td>70</td>
<td>65</td>
<td>99</td>
<td>94</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>Social functioning</td>
<td>78</td>
<td>77</td>
<td>99</td>
<td>95</td>
<td>84</td>
<td>97</td>
</tr>
</tbody>
</table>

AREDS = Age-Related Eye Disease Study; CAPT = Complications of Age-Related Macular Degeneration Prevention Trial; DR = diabetic retinopathy; SST = Submacular Surgery Trials. Data from Dong et al\(^2\); Clemons et al\(^8\); Maguire et al\(^9\); and Mangione et al.\(^{12}\)
points as a definite case of anxiety or depression and a score of 8 to 10 points as a doubtful case of anxiety or depression. Psychiatrists have suggested that the use of the summary term “doubtful” may not be the best adjective to describe scores of 8 to 10 points and that perhaps the term “probable” should have been used. Regardless, the number and proportion of subjects with definite or doubtful (possible) cases of anxiety and depression in Groups N and B of the SST are outlined in Table 2.

The proportion of individuals reporting anxiety appears to be lower than what might be expected in this population. However, these subjects may have had less anxiety because they had agreed to participate in a surgical trial and were perhaps better able to cope in that setting.

The proportion of people in the SST reporting depression may seem high. However, it is unknown whether the proportion is higher or lower than that in patients of similar age with other ocular conditions.

**PREFERENCE VALUES**

Scaled preference values for selected medical conditions are an index of quality of life. The value scale ranges from 0 to 100, with 0 equaling death and 100 equaling perfect health with perfect vision.

A total of 792 patients with subfoveal CNV participating in 2 of the SST involving patients with AMD were asked to rate their condition on the preference value scale; 64 was the average rating. By comparison, patients with congestive heart failure on a similar scale rated their condition at 75, and patients with symptomatic HIV/AIDS and those with chronic renal failure requiring home dialysis rated their conditions at 66. Preference values are good indicators of how much a patient is willing to pay for effective treatment—the lower the preference value, the more a patient is willing to spend as an individual. Given the high prevalence of subfoveal CNV in adults older than 65 years, the increasing number of older adults in this country who will develop this condition, and its preference value of 64, the economic and health policy implications of preference values in treating subfoveal CNV to prevent vision loss are enormous. That is, patients are willing to pay for relatively expensive treatments for neovascular AMD. However, given the very high incidence of neovascular AMD in the United States, whether third-party payors can afford these treatments is another question.

### Table 2. Anxiety and Depression in Groups N and B in the Submacular Surgery Trials

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group N</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite case (score of ≥11)</td>
<td>15 (3%)</td>
<td>19 (4%)</td>
</tr>
<tr>
<td>Doubtful case (score of 8–10)</td>
<td>45 (10%)</td>
<td>38 (8%)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (13%)</td>
<td>57 (12%)</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite case (score of ≥11)</td>
<td>18 (6%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Doubtful case (score of 8–10)</td>
<td>37 (11%)</td>
<td>42 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>55 (17%)</td>
<td>59 (18%)</td>
</tr>
</tbody>
</table>

HADS = Hospital Anxiety and Depression Scale. Data from Dong et al.

**CONCLUSIONS**

Contrast sensitivity and quality-of-life outcomes are evaluated in some clinical trials, and their results have relevance to clinical practice that are often underrated. As demonstrated in the TAP investigation, contrast sensitivity outcomes in patients treated with verteporfin appeared to be better than in patients treated with placebo for all classic-containing CNV lesions (predominantly classic and minimally classic lesions) at 1 and 2 years. Health-related quality-of-life data from the SST indicate relatively low NEI-VFQ scores of 65 in Group N subjects (classic-containing subfoveal CNV lesions) and 63 for Group B subjects (predominantly hemorrhagic lesions) even in unilateral cases (CNV in 1 eye, no CNV in the other eye), with an approximate 2-point change in overall score for each line of visual acuity loss. Study findings also show that anxiety and depression are present in patients with neovascular AMD.

These findings confirm the need to pursue more effective prevention and treatment options.

**DISCUSSION**

**DISCREPANT OUTCOMES**

Dr Olsen: In the SST, there was a statistically significant difference in the quality of life of the surgical treatment group versus the nontreatment group. However, based on visual acuity outcomes, there was no statistical difference except in 1 small subgroup analysis. If the primary outcome of a study is visual acuity and visual function and shows no difference in treatment arms, but the secondary quality-of-life out-
comes are statistically significantly different, what value do you place on the secondary outcome in managing a patient?

Dr Bressler: Because we’ve had 35 years of experience with visual acuity outcomes, we concluded at the start, and even at this time, that that was going to drive our decision as to whether a treatment was beneficial or not. However, we also wanted to know what the instruments to measure vision function showed.

The issue is what to do with the disconnect between no visual acuity benefit for Group N and the quality-of-life outcome benefit approaching the 5-point difference that we said was important to individuals. I put it aside and say, “Now we need to learn more. Let’s see what the next study shows.”

If we begin to see that same disconnect in other studies, then we have to ascertain if the patient was unmasked to treatment and reported feeling better because something was done, or if the patient was masked to treatment but the results assessed by the vision function questionnaire were more important to the patient than just visual acuity. On the other hand, if other studies show that a visual acuity outcome correlates with a visual function outcome, then that will be important.

The third possibility is considerable benefit with respect to visual acuity but no difference in the vision function questionnaire. That’s going to make us wonder if treatment was really worthwhile for that particular patient or if the questionnaires themselves need further development.

This is just the beginning. We’re just scratching the surface. I think that 10 years from now, we’ll understand more. It doesn’t make me want to operate on someone yet because we don’t know enough about it. Maybe 10 years from now, if we have an outcome like that, we can be very confident that a quality-of-life difference in the absence of a visual acuity difference really makes a difference for the patient.

Dr Klein: I find it hard to understand the validity of the visual function questionnaires when you say that the scores for unilateral and bilateral visual loss are so similar in some of these patients, including subgroups. It’s hard to visualize anybody with bilateral involvement having the same score as someone with unilateral involvement when it comes to driving, reading, and so on. How do you explain that?

Dr Bressler: For one thing, they are not the same. They were worse for bilateral compared to unilateral cases. However, it’s important to note that the scores were decreased even for unilateral cases. For near vision activities we need to collect more information. Clearly, patients have been bothered in some way by changes in vision in unilateral cases, and the questionnaire reflects how they are responding to it. In fact, some small studies looking at 360° macular translocation confirmed that near vision outcomes were closely associated with quality-of-life outcomes. We don’t know enough about it yet.

Dr Klein: I mention near vision or reading vision and driving because that’s what our patients really want to do.

Dr Bressler: That’s important. They want to be able to drive, and they certainly want to be able to read, so we have to figure out how to prevent vision loss in the first place. But I also think we underestimate the impact of vision loss on social functioning where people cancel events they were going to attend because they do not want to walk into a room and not be able to recognize other people who are there; it’s just uncomfortable. The same holds true for business meetings and networking where they can’t recognize the person they are speaking with or find the person they wanted to speak with. It really changes their vision function. This may be just as important as driving and reading.

Dr MacCumber: I was struck by these data when I first heard them during the SST data summary roundup. One important thing about quality of life is that it has a ripple effect, particularly in dependency. Macular degeneration is a chronic disease. It not only affects the quality of life of the individual, but also of the caregivers, the spouse, and the family members. That’s why we should take this beyond vision outcomes to see how it affects the family and the patient’s whole life.

Dr Bressler: We’re just at the beginning in terms of understanding the impact of AMD on quality of life, but it’s worth presenting this information in an educational format to let people know what’s been learned so far.

As for preference values, I think some of that information will be very important in terms of medical care costs in the future. Although policymakers will be charged with making decisions as to what we should and should not be spending our money on, they will need to come to ophthalmologists and say, “Help us make a decision.” This is where preference value information comes in.

Dr Mieler: What impressed me about the quality-
of-life data was the fact that patients perceive even a unilateral visual loss as having more impact on their life than some life-threatening processes, whether it’s cardiovascular disease or certain types of cancer. It’s one of those issues that we really have to look at much more critically. We can’t just use vision alone.

**CONTRAST SENSITIVITY**

**Dr Klein:** Were the contrast sensitivity measurements related to quality of life in any of the studies you talked about?

**Dr Bressler:** There was a relationship. It wasn’t any stronger or weaker than the visual acuity, but the details are in the SST papers.2-7

**Dr Klein:** I’m still trying to appreciate the value of the contrast sensitivity measurements. If contrast sensitivity generally tracks with visual acuity, and if it’s not any better in predicting quality of life, I would question its value.

**Dr Bressler:** I disagree. Visual acuity does not always track with contrast sensitivity. We can see lack of change in contrast sensitivity and loss of visual acuity. For example, we showed little or no change in the average contrast sensitivity, among patients with minimally classic lesions treated with photodynamic therapy within the TAP investigation, but we did show, on average, a loss of visual acuity for these lesions 1 and 2 years after study entry. So, they don’t always track together.

Another example of this discrepancy may be found if you look at various vision tasks. At different levels of contrast sensitivity for the same visual acuity, you can have different abilities in terms of visual orientation, the ability to walk around, to get through a corridor, and so on. I think there are good data to suggest that contrast sensitivity and visual acuity don’t track together, and there are also good data to suggest that they measure different functions.

**QUALITY-OF-LIFE ASSESSMENT INSTRUMENTS**

**Dr Olsen:** There are a number of quality-of-life measures or tests reported in the literature. How do they compare with each other? Which one do we rely on most? Is there a time efficiency scale built into the various tests?

**Dr Bressler:** There are several quality-of-life instruments. Some are organ-specific to vision or hearing, and obviously, we’re only interested in the organ-specific instruments for vision. There are some that are generic, like the 36-Item Short Form Health Survey. Generic questionnaires are not very sensitive with respect to changes versus no changes in vision, or to other ophthalmologic conditions.

There are different vision-specific function questionnaires, including the Visual Functioning Index (VF-14), a short form that was designed mainly for pre- and postcataract procedures but has been used in other areas. Because many thought that the VF-14 was not broad enough to capture the various problems of people with lower levels of vision, the NEI-VFQ has been used in these patients instead. That being said, it’s probably true that many different questionnaires, if they are validated, could be used. Because the NEI-VFQ has been validated, it’s probably worth using it so that we can compare across studies. Imagine what would happen if we each used different charts to test visual acuity. It wouldn’t work as well.

Other instruments in various languages have been used in European studies, but they have not been validated in the United States. One such instrument is the EuroQual quality-of-life questionnaire.

**REFERENCES**

1. Rubin GS, Bressler NM; Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Effects of verteporfin therapy on contrast sensitivity: results from the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) investiga-
7. Childs AL, Bressler NM, Bass EB, et al. Surgery for hemor-


