Editorial

Patient-centered outcomes in treatment options for proliferative diabetic retinopathy

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The Diabetic Retinopathy Clinical Research (DRCR) Network Protocol S demonstrated, in a prospective, randomized, multicenter trial, the non-inferiority of intravitreal ranibizumab (IVR) compared to panretinal photocoagulation (PRP) in the treatment of proliferative diabetic retinopathy (PDR) (1).

The trial established IVR as a viable alternative treatment for what has been the mainstay, indeed only non-surgical, treatment for PDR. The primary outcome measure in the trial was change in visual acuity letter score, but secondary measures included rate of vitrectomy, diabetic macular edema (DME), and peripheral visual field loss, which were lower with IVR. Notably, patients treated with IVR had more intravitreal injections and doctor visits during the 2-year study duration. Interpretation of the PDR results was somewhat confounded by the coexistence of DME (although the cohorts were stratified for baseline DME) and its response to or subsequent need for IVR, not to mention protocol allowances for rescue treatments for PDR; hence there were significant degrees of overlap in the initially-assigned treatment cohorts. An embedded study was assessment of patient-centered outcomes in each of these two groups, with the inferred purpose of determining if the non-inferiority of IVR to PRP was present for these outcomes. The high level summary of the findings of that study, reported by Beaulieu *et al.* (2), is that PRP and IVR also have similar outcomes as measured by patient-centered instruments, corroborating the DRCR Protocol S objectively based findings of non-inferiority of IVR for PDR.

Clinicians have long been cognizant of the importance to a patient of subjective or functional ("patient-centered") outcomes after any treatment. While intuition suggests these usually parallel objective measures (notably visual acuity), an active area of investigation has been the standardization and application of a variety of surveys and self-assessed questionnaires. These types of evaluations may corroborate objective measures of outcomes, but might offer important insights not captured by standard outcome measures.

Beaulieu *et al.* (2), report on the results of self-perceived visual health and function administered to a subset of patients from the DRCR Protocol S cohort who had only one eye randomized to treatment with IVR or PRP (bilaterally affected patients who were assigned to different treatment groups by the protocol were excluded). The authors employ three surveys: the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), the University of Alabama Low Luminance Questionnaire (UAB-LLQ), and the Work Productivity and Activity Impairment Questionnaire (WPAIQ).

Both the NEI VFQ-25 and the UAB-LLQ focus on health and visual function as well as the psychosocial impact of visual disability. The NEI VFQ-25 is an abbreviated form of the long form 51-item NEI-VFQ (3). It is divided into several sections. Part 1 includes an assessment of

general health and vision, anxiety about vision, and ocular pain. Part 2 focuses on difficulties in accomplishing activities such as reading, hobbies, mobility, activities of daily living, and driving. Part 3 assesses for changes in daily function and habits secondary to visual impairment. The NEI VFQ-25 also includes vision-related subscales concerning general health, vision, social function, driving, role limitations, well-being/distress, and dependency. The UAB-LLQ is a 32-item questionnaire with six subscales on driving, extreme lighting, mobility, emotional distress, general dim lighting, and peripheral vision. A key difference between the two surveys is that the UAB-LLQ focuses on vision in low-light conditions and has historically been used in studies of age-related macular degeneration (AMD). While in the context of AMD, the UAB-LLQ has shown to be equivalent to the NEI VFQ-25 (4), the UAB-LLQ has not been used previously to evaluate vision loss in diabetic eye disease. In contrast, the NEI VFQ-25 more generally assesses visual function and has been utilized in prospective and randomized clinical trials, including in diabetic eye disease (5). It has been reported as a reliable indicator of vision related quality of life in diabetic retinopathy (6), and measureable gains in the NEI VFQ-25 have been associated with IVR in the treatment of DME (7). The WPAIQ, like the UAB-LLQ, has not previously been applied to diabetic eye disease. It is a 6-item questionnaire that assesses for impacts on work absenteeism, presenteeism (impairment while working), productivity loss, and activity impairment.

Beaulieu *et al*. find no statistically significant differences between the IVR and PRP cohorts in composite NEI VFQ-25 scores or in what would be expected to be important pertinent qualities of peripheral, color, or driving subscores. Similarly, the authors report no difference in UAB-LLQ composite scores. Of note, they identify a small but statistically significant decrease in work productivity at one year, identified by the WPAIQ, which was no longer significant at the two year mark.

Overall, patients have favorable outcomes with respect to those initially driving with both treatments. Eighty-four percent of patients in the IVR cohort and 89% of patients in the PRP cohort were still driving by the end of the study, with only 3% and 4% respectively having stopped driving because of their vision respectively (NEI VFQ-25). Although the study finds that the percentage of participants who changed their driving habits because of their vision did not differ between the treatment cohorts (NEI VFQ-25), objective measures that could be relevant to driving, such as vision of 20/40 or better in at least one eye and binocular visual acuity better than 20/40, were slightly better in the IVR cohort. Beaulieu *et al*. conclude that although differences were identified in some work productivity and driving-related outcomes were slightly more favorable with IVR, most other patient-centered outcomes were equivalent.

The data from this study also do not show a change in perception of peripheral field (by NEI VFQ-25 or UAB-LLQ). Moreover, there are no treatment cohort differences in peripheral vision subscales from the patients who had a history of PRP in the nonrandomized fellow eye. This finding contrasts to the DRCR Protocol S report which found mean peripheral visual field sensitivity loss was –23 dB in the IVR cohort versus –422 dB in the PRP group ($P<0.001$). It would have been interesting to know the average visual field outcomes of the subset of patients included in this study and whether they reflected those of the larger cohort. While field loss was clinically measurable in DRCR Protocol S, it is interesting that it was not detectable as a subjective detriment by survey response. This may represent issues with the sensitivity of the questionnaires' ability to identify subjective consequences of peripheral field changes. Alternatively, the differences identified by perimetry may not be clinically significant to daily functioning after patient adaptation to a smaller field. The lack of measurable deficits in perceived visual field is consistent with the results from a smaller British study that investigated the effect of PRP on Esterman binocular visual field score and found only a modest loss of sensitivity at 6 months after treatment (8).

An unexpected finding in this trial is that driving subscales (from the NEI VFQ-25) are better in eyes treated with PRP (compared to IVR) if they have preexisting DME but more favorable with IVR if they do not have existing DME. This effect also applies to mobility scores. This finding conflicts with the reports that PRP worsens DME (9). It is unclear whether this effect represents potential issues with the reliability of patients' subjective responses and requires further investigation in future studies. Alternatively this might be a consequence of limitations in performing post hoc analyses, especially in smaller subsets.

It is also surprising that eyes treated with IVR report less loss in work productivity (in the WPAIQ questionnaire) than those treated with PRP. In addition, neither treatment cohort shows a benefit in patient perceived absenteeism. In DRCR Protocol S, patients treated with IVR had more injections and doctor visits over the course of treatment

(median 10 injections and 22 visits compared to a median of 1 injection and 16 visits). This gap occurred even though 48% of patients randomized to PRP also required IVR for the treatment of DME. It is possible that outside of the realm of a protocol, in standard clinical practice, patients treated with PRP would require even fewer visits which could translate to less absenteeism.

There are previous reports of cost-utility analysis of laser and anti-VEGF therapy in the treatment of DME (10,11) and PDR (12). Treatment with IVR is significantly more costly than PRP in terms of gross healthcare dollar expenditures. Markov models of the cost-utility of IVR and PRP for the treatment of PDR do not account for the non-reimbursable costs accrued by patients such as for transportation to the doctor's office (13) and missed work which would be expected to increase the relative difference in cost given the need for increased visits in patients treated with IVR long-term. Assuming non-inferior visual outcomes for the two treatments, the cost per quality adjusted-life year clearly favors PRP (12). These differences are more considerable when the cost of treatment is extrapolated to lifetime therapy, with near a 10-fold premium in cost per QALY (poorer cost-utility) with IVR in comparison to PRP. The cost of therapy and physician visit burden, and non-reimbursed expenses (14-18) involved in more frequent office visits, may be important factors in compliance, and should also be considered in addition to objective and subjective visual outcomes associated with anti-VEGF therapy or PRP when making shared treatment decisions with patients.

In summary, Beaulieu *et al*. (2), report valuable patient-centered outcomes from the DRCR Protocol S cohort (1). Providing metrics indicative of patients' daily function and personal experiences is important to validate the total outcome picture of a therapeutic approach as presented in this context of PDR. While we acknowledge that survey responses are subjective in nature and must be viewed critically, it is reassuring that most of the differences between the IVR and the PRP cohorts were not statistically significant, or were minimal. It is especially reassuring that these findings were found in a rigorously performed, well-controlled clinical trial cohort with excellent compliance and follow-up data. This serves to validate visual acuity as a comprehensive surrogate measure for outcomes—something that has historically been presumed, but not proven, since the findings of Beaulieu *et al*. parallel the initial reports on objective visual outcomes reported in Protocol S.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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