Assessing patient perception of risk in ocular stem cell therapies

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SUMMARY

A wide variety of stem cell-derived therapies are under development for the treatment of retinal degeneration. In order to better understand patient perspectives about these therapies, we assessed risk tolerance using an in-person survey of 178 patients at an academic eye center. Risk of malignancy served as a hypothetical, readily understood, and serious adverse event to be considered in trade for potential visual improvement from a stem cell-derived treatment. The results indicate that patients were willing to trade visual improvement against a risk of malignancy that far exceeds actual risk. Two novel findings were that older patients and those with an intermediate level of visual loss were particularly risk tolerant. The quantitative survey results provide a step toward understanding patient perspectives that will, over the long term, guide the development of ocular stem cell-derived therapies.

INTRODUCTION

The great promise of stem cell-derived therapy to replace retinal cells that are lost in degenerative disease has led to widespread global development of ocular stem cell-derived therapies. The willingness of patients to incur the risks associated with stem cell-derived therapy has an important role in developing these therapies. Although many patients are considering or have undergone stem cell-derived therapies, relatively few data are available to describe how patients assess the risk and benefit associated with ocular stem cell-derived therapies.

Vision is highly valued, with significant impact on quality of life (Brown et al., 2002; Mangione, 1998; Varma et al., 2006). In the United States, the public fears blindness only second to cancer and more than many other debilitating conditions (Research to Prevent Blindness, 2014; Scott et al., 2016). In this regard, the development of stem cell-derived therapies to restore vision serves an important clinical need. This is shown by strong public interest in regulated clinical trials to assess the safety of cell-based therapies for retinal disease (Kashani et al., 2018; Mandai et al., 2017; Schwartz et al., 2012; Song et al., 2015). The goal of our survey is to improve understanding of the patient perspective that underlies participation in clinical trials for ocular stem cell-derived therapies.

We used discrete-choice analysis, a method for modeling patient preferences, to determine patient risk tolerance for malignancy, a serious hypothetical adverse event associated with therapies using stem cell-derived tissue. The actual risk of malignancy with use of post-mitotic stem cell-derived tissue is exceedingly small (Kanemura et al., 2014) and multiple layers of regulation and surveillance minimize this risk for clinical-grade cell products (Sato et al., 2019). Nevertheless, malignancy serves as a readily understood serious risk that is useful to model risk tolerance. It should be made clear that our use of malignancy risk is to gauge patient willingness to incur risk relative to changes in visual acuity and is not intended to describe the actual type or occurrence rate of malignancy. Similarly, the survey design is agnostic to the exact type of stem cell-derived therapy, specifying only a generic stem cell-derived therapy. The survey did not compare available technologies but rather used a hypothetical risk and treatment to assess patient perspective of the risk-benefit balance applicable to any ocular stem cell-derived therapy.

RESULTS

Out of 243 patients approached in clinic waiting rooms and asked to participate, 178 agreed to complete the in-person
survey (73% response rate). Mean age of survey respondents was 62.2 years (standard deviation [SD] = 17.9 years), and 84 respondents (47%) were male (Table 1). Twenty-two respondents (12%) had a history of cancer (excluding non-melanoma skin cancer). Mean visual acuity was logMAR 0.4 (SD = 0.7), equivalent to Snellen visual acuity of 20/50 or a mild level of visual impairment. In 86% of survey respondents, the better-seeing eye had normal or near-normal visual acuity in the 20/20 to 20/40 range. For 38% of survey respondents, the worse-seeing eye had impaired visual acuity of 20/50 or worse. Mean visual function score on the National Eye Institute (NEI) Visual Function Questionnaire-9 (VFQ-9) was 72.5 (SD = 19.4), lower than the reference scores for patients without ocular disease, which range from 83 to 97 across several types of visual function such as near vision, distance vision, and peripheral vision (Kodjebacheva et al., 2010; Mangione, 2001). Recruited survey respondents had a wide range of reasons for visiting the eye clinic (Figure 1A), ranging from age-related macular degeneration (16%) and inherited retinal degeneration (14%) to routine comprehensive eye examination (24%).

The survey asked respondents what they believed the ideal stem cell-derived therapy would do for vision given the stated risks, which included risk of cancer in the eye (Figure 1B). Most (39%) believed that the ideal therapy should improve vision significantly. However, a significant minority believed that the ideal therapy should slow down vision loss (11%), stop vision loss (13%), or improve vision slightly (13%). Figure 2 shows estimates of the part-worth utilities for visual acuity and risk of malignancy calculated from discrete-choice analysis. Estimates for visual acuity were: 20/20, 2.36 (SE = 0.21); 20/40, 2.31 (SE = 0.18); 20/70, 1.60 (SE = 0.14); 20/100, 0.36 (SE = 0.12); and 20/200, 0 (reference). Pairwise comparisons of the differences between levels (20/40 compared with 20/70, 20/70 compared with 20/100, and 20/100 compared with 20/200) were statistically significant (p < 0.001) except for 20/20 compared with 20/40 (p = 0.66). Estimates of utility for risk of malignancy were: 1%, 0.63 (SE = 0.14); 5%, 0.84 (SE = 0.10); and 20%, 0 (reference). Pairwise comparisons were statistically significant for 1% risk versus 5% risk (p = 0.03) and 5% risk versus 20% risk (p < 0.001). The greatest changes in utility between adjacent levels of visual acuity occurred between 20/40 and 20/70 (0.71), and between 20/70 and 20/100 (1.24). Between 20/40 and 20/100, there was a loss of 1.95 units of utility (SE = 0.22). The magnitude of this effect was three times the magnitude of the effect of increasing the risk of malignancy from 1% to 20%. Based on the magnitude of utility effects, the relative importance of visual acuity was 71%, and the relative importance of risk of malignancy was 29%.

We also examined whether demographic or clinical factors were associated with how survey participants answered the discrete-choice questions. Higher VFQ-9 score was associated with greater importance of visual acuity (p < 0.01; Figure 3A), and older age was associated with lower importance of risk of malignancy (p < 0.05; Figure 3B). We compared the utility of visual acuity for patients who were one SD below and above the mean age and VFQ-9 score. Comparisons were made relative to the reference groups (20/200 visual acuity and 20% risk of malignancy) for which utilities were set to 0. For risk of malignancy, at the 1% risk level the utility was 0.71 (95%CI = 0.39–1.02) at age 45 years and 0.54 (95% confidence interval [CI] = 0.22–0.86) at age 80 years. At the 5% risk level, utility of risk of malignancy was 1.04 (95% CI = 0.78–1.29) at age 45 years, and 0.67 (95% CI = 0.41–0.92) at age 80 years. For VFQ-9 score, the utility of 20/20 visual acuity was 2.49 (95% CI = 2.01–2.97) with a score of 55, and 2.28 (95% CI = 1.81–2.76) with a score of 90. The utility of 20/70 visual acuity was 1.45 (95% CI = 1.12–1.79) with a score of 55, and 1.78 (95% CI = 1.43–2.12) with a score of 90.
utility of 20/100 visual acuity was 0.11 (95% CI = (−0.20, 0.41)) with a score of 55, and 0.63 (95% CI = 0.32–0.94) with a score of 90. In pairwise comparisons, the differences between levels of visual acuity and levels of malignancy risk remained statistically significant when separated by age and VFQ-9 score.

**DISCUSSION**

Understanding patient perspective is useful to guide the development of ocular stem cell-derived therapies to meet patient expectations and needs. As a step to assess patient perspective, we used discrete-choice analysis to describe patient decision making when weighing a hypothetical risk of malignancy against a potential visual improvement. We found that patients were willing to trade increased visual acuity against a risk of malignancy that far exceeded the actual risk from stem cell-derived therapy, indicating a risk-benefit balance that favored treatment in the overall study population. Furthermore, the risk tolerance was greater for older patients and for those with moderate (ranging from 20/40 to 20/100) loss of visual acuity.

Our survey population included patients with age-related macular degeneration and inherited retinal degenerations, who are most likely to participate in and benefit from stem cell-based therapy. Participants were asked to trade specific levels of visual acuity for specific risks of malignancy. They chose to weigh the utility of visual acuity (71%) greater than the utility of decreasing the risk of malignancy (29%). The level of risk accepted by patients was much higher than the actual risk from post-mitotic cells,
which is negligible (Kanemura et al., 2014). The high level of risk tolerated in trade for potential vision improvement may partly explain why patients are willing to participate in unregulated, dangerous treatments where the actual risk is undefined (Bauer et al., 2018). For properly regulated stem cell clinical trials, the level of risk tolerance far exceeds the actual risk of tumorigenesis that patients are willing to trade for potential visual improvement.

The greatest loss of utility from visual acuity occurs between visual acuity levels of 20/40 and 20/100. Over this acuity range, activities such as reading road signs, reading books, and ability to recognize faces become increasingly difficult. Further, the legal limit of visual acuity for driving is 20/70 in Michigan (Mangione, 2001). The significant loss of utility between 20/40 and 20/100 for everyday tasks may explain why patients with visual acuity at this level are most risk tolerant, which, in turn, may contribute to their seeking unproven stem cell therapies (Kuriyan et al., 2017). Similar to the findings reported here, other studies have reported significantly decreased utility in the 20/50 to 20/100 and 20/200 or worse categories (Brown et al., 2002; Sharma et al., 2003). Together, the results emphasize the great clinical need for safe and effective therapies that can restore vision, such as stem cell-derived therapies, even in patients with mild to moderate visual impairment. The finding that patients with better perceived visual function were more motivated to maintain their levels of vision could be explained by loss aversion, a finding from behavioral economics that describes how people tend to prefer avoiding losing something of value to gaining something of equivalent value (Courtney et al., 2014).

In addition to higher visual function scores correlated with increasing utility placed on visual acuity, we also found that the relative utility of visual acuity and risk tolerance for malignancy are modified by patient age. Increased age was correlated with decreased utility placed on risk of malignancy. For example, at the 5% risk level, utility of risk for malignancy was 1.04 (95% CI = 0.78–1.29) at age 45 years but decreased to 0.67 (95% CI = 0.41–0.92) at age 80 years. Patients with older age may be more likely to value the quality of life provided by good vision or more willing to incur a risk of malignancy. In this context, it is plausible that older patients with age-related macular degeneration would be more motivated to seek experimental treatments. A national survey showed that the main reasons patients elect to participate in clinical trials are advancing medical knowledge, access to improving own health, recommendation from a trusted person, and receiving adequate compensation (Zogby Analytics, 2013). Patient concerns about clinical trials include worry over side effects or safety, inconvenience of trial location, and concerns about receiving a placebo or taking part in an experimental treatment (Zogby Analytics, 2013). Further research is needed to understand how visual function scores and age factor into the patient decision to participate in stem cell trials to improve vision.

A major strength of our survey is that all questions were administered in person, allowing patients with visual impairment to accurately answer survey questions and ask clarifying questions when needed. Another strength was that survey responses were linked to the medical record, allowing assessment of the modifying effect of patient-level variables on survey responses. Limitations of the survey include that the scenarios depicted were theoretical in nature, although discrete-choice experiments are an accepted method to study such patient preferences (Reed Johnson et al., 2013). The study was conducted at a single academic eye center, and a larger study on a national cohort is needed to make the results more generalizable.

In conclusion, we used a patient-centered survey to find that patients are highly interested in gains in visual acuity,
even when having to trade against risk of malignancy in the eye. We found that the relative utility of visual acuity and risk of malignancy are modified by patient age and visual function survey score. Our findings indicate that current regulatory processes regarding malignancy for stem cell-derived ocular products far exceeds the standard of safety expected by patients with vision loss seeking a clinical trial or treatment. The quantitative measures of patient risk tolerance provided can be a useful resource for researchers, physicians, and policymakers to develop ocular stem cell-derived therapies that meet patient needs.

**EXPERIMENTAL PROCEDURES**

This study was approved by the University of Michigan Institutional Review Board (IRBMED #HUM00141662). We included English-speaking patients aged 18 years or older and excluded patients with neurologic disease. Since some participants had significantly decreased vision, the entirety of the survey was read aloud to all participants. The survey prompt asked patients to envision themselves in a scenario in which a stem cell treatment was offered to them (Figure S1). Risks of treatment were described as the standard risks of eye surgery, plus the unique risk of malignancy in the eye, which would need to be treated with radiation, chemotherapy, or surgery to remove the eye.

Each survey contained discrete-choice questions asking participants to choose between two possible options. Discrete-choice analysis has been used previously to model patient preferences (Rozier et al., 2019; Zickafoose et al., 2015). Each option had a level of visual acuity (20/20, 20/40, 20/70, 20/100, 20/200), each with a description of typical visual function and an associated hypothetical level of risk of malignancy developing in the eye (1% or 1 in 100; 5% or 1 in 20; 20% or 1 in 5). We chose these levels of risk based on levels of risk that patients would be able to easily understand, with the highest (20%) an unacceptably high level of risk. As previous laboratory studies have demonstrated, although pluripotent stem cells do carry risk of tumor formation, stem cell-derived post-mitotic cells carry negligible risk after proper differentiation protocols (Kanemura et al., 2014). The option choice combinations presented to patients were selected using a fractional factorial design (Reed Johnson et al., 2013) to eliminate frivolous combinations. Each survey included an assessment of visual function, the NEI VFQ-9 (Kodjebacheva et al., 2010). Surveys were administered by a trained individual (P.Y.Z., S.J., A.L., O.M.B., or D.Q.D.). This study was prospectively approved by the University of Michigan Institutional Review Board. Written informed consent was obtained from each patient for the survey and chart review, and the research complied with Health Insurance Portability and Accountability Act (HIPAA) regulations.

A retrospective clinical chart review was performed to record patient-level demographic and clinical variables, which were linked to survey answers. Conditional logistic regression was used to determine part-worth estimates of utility and the modifying effects of patient variables. Statistical analyses were performed using R (The R Foundation, Vienna, Austria).

**SUPPLEMENTAL INFORMATION**

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2021.09.001.

**AUTHOR CONTRIBUTIONS**

P.Y.Z., P.N.C., D.W.H., and R.C.R. conceptualized and designed the study. P.Y.Z., S.J., P.N.C., C.A.A., D.W.H., S.T., J.H.S., and R.C.R.
CONFLICT OF INTERESTS

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