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The challenge of eliciting opinions of gene therapy for SCD

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Comment on Gonzalez Sepulveda et al, page 7371

In this issue of *Blood Advances*, Gonzalez Sepulveda et al describe respondents' preferred treatment options as they pertain to gene therapy for sickle cell disease (SCD).[1] Gene therapy, an autologous form of hematopoietic cell transplantation (HCT) in which a patient with SCD serves as their stem cell donor, is a curative strategy in several ongoing clinical trials. There is a wave of enthusiasm for gene therapy for SCD. In this report, the authors use a discrete-choice experiment (DCE) to tackle the challenge of understanding how adult patients and parents of patients with SCD approach the risk-benefit analysis and make decisions regarding the acceptability of gene therapy. The authors' aim is twofold: first, to understand patient acceptance of potential risks and benefits early in gene therapy technology development, presumably to ensure gene therapy can be designed with knowledge of an acceptable risk-benefit ratio, and second, to understand how disease severity affects risk assessment and risk aversion.

A DCE survey instrument was administered to adult patients with SCD and parents of pediatric patients with SCD. The survey asked study participants to choose between pairs of hypothetical gene therapies, which were defined by varying degrees of effectiveness and risk of toxicity. A third option, "no gene therapy," was also available for participants to choose and represented outcomes of standard-of-care therapy. Respondents also answered questions about their symptom severity and, based on their answers, were categorized as either group A (mild SCD symptoms) or group B. Data from a cohort of 283 patients and their parents were analyzed.

This carefully designed and meticulously executed study uses a novel approach to elicit patient preferences and gain insight into decision-making attributes among patients with SCD and parents of children with SCD. There are a variety of stated-preference techniques to study patient and stakeholder predilections; DCEs have become the most frequently applied approach in health care in recent years.[2] The authors followed standards developed by an international task force; they employed focus groups and one-on-one pre-test interviews to develop the survey instrument.

The study also presents significant challenges. The survey includes questions to assess respondent comprehension. Importantly, 15% to 18% of study participants answered at least half of the 4 comprehension questions incorrectly. Low numeracy is a challenge: Americans have difficulty making decisions based on statistical information and abstract numerical data representations.[3] The author's use of graphical representations is an effective strategy previously used to communicate risk to patients with SCD.[4] However, with surveys, there is an absence of the typical clinical bedside conversation that one would have about curative therapy. If the family would accept a 1-in-3 risk of death for a child when the actual risk of death is 1 to 2 in 100, one would suspect the family may not understand the numbers. The reader needs to be reassured that participants understand the tradeoffs and that the long-term outcomes of gene therapy are not known.

Prior work has demonstrated that patients with SCD have limited knowledge of gene therapy but are eager for more education.[5] Indeed, concerns raised historically by patients with SCD regarding the risk of malignancy after gene therapy were inadequately addressed in this analysis, given the lack of data at the time this study was designed. Strong et al previously reported that cancer risk was a major concern for patients with SCD considering gene therapy.[5] Notably, an increased risk of hematologic malignancy after certain curative therapies for patients with SCD, including gene therapy, has recently been described.[6] Furthermore, Strong et al report that the risk of infertility is a major concern for patients considering gene therapy. Gonzalez Sepulveda et al underestimate the risk of infertility, describing the

risk of fertility problems as rare though HCT recipients with SCD who receive myeloablative conditioning are at substantial risk of gonadal damage and infertility.[7]

Furthermore, although the survey by Gonzalez Sepulveda et al was designed based on factors identified by a focus group, previous work has highlighted other factors not explored in this one. The risks of gene therapy are vague and described in the survey as limited to the risks associated with chemotherapy: tiredness, nausea and vomiting, hair loss, and loss of appetite. There is no mention of the myriad other complications, some potentially lethal, associated with myeloablative chemotherapy.

The description of the effects of gene therapy is also fraught. The survey instrument states gene therapy could correct the cause of SCD and permanently eliminate all symptoms and future complications associated with SCD. Although HCT may stabilize some organ dysfunction and ameliorate some SCD manifestations, more data are necessary to understand the long-term effects of the reversal of SCD.[8] Furthermore, because of the use of myeloablative chemotherapy, many of the patients surveyed, particularly adults with more severe SCD manifestations, may not be eligible for ongoing gene therapy trials due to preexisting organ damage.

The survey instrument by Gonzalez Sepulveda et al was developed based on data available as of 2018. The last 5 years have seen significant development in curative therapies for SCD. A summary of haploidentical HCT results for SCD since 2017 demonstrates excellent effects in the era of post-transplant cyclophosphamide.[9] Thus, comparing gene therapy with the standard of care is no longer most appropriate. For patients without a matched sibling interested in curative treatment, the choice is most often between haploidentical transplant and gene therapy.[10]

Importantly, this article invites more patient education to the gene therapy setting. James et al describe the role of eliciting patient preference information with solid organ transplants.[11] DCEs can, thus, be used in the context of gene therapy for SCD to facilitate shared decision-making, strengthen patient-centered research, and determine priorities for outcomes after transplantation. The SCD population is eager to learn more about gene therapy technology. At this early stage in gene therapy development, this report by Gonzalez Sepulveda et al should help inform research priorities and establish a framework for patient involvement in study design.

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