A patient preference study to inform regulatory decision-making for islet cell therapy in hard-to-control type 1 diabetes mellitus

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Abstract

Purpose: To design a PPI tool and collect quantitative PPI that can help inform regulatory decision-making for islet cell therapy for treating patients with hard-to-control TIDM. **Methodology**: The study recruited a convenience sample of patients with T1DM who had ever experienced a severe hypoglycemic episode to complete a choice-based conjoint survey instrument. The survey consisted of 18 paired treatment choice questions that required patients to choose based on different levels of eight attributes. These attributes were selected based on literature review and inputs from different stakeholder groups through individual interviews. The survey instrument was pretested before finalized for data collection. Preference weights were estimated using random parameters logit models and the conditional relative importance scores (CRIS) were calculated. **Results:** 92 participants (50% female, 77% white, mean length of diagnosis= 22 years) completed the survey. The five most important attributes to patients were: (1) increase in risk of serious complications requiring hospital treatment and rare death from 0 to 15% (CRIS: 10.0); (2) gaining insulin independence from 0 to 5 years, (CRIS: 7.9); (3) extending duration of treatment success from 0.5 to 5 years (CRIS: 6.3); (4) increasing probability of treatment success from 40 to 90% (CRIS: 5.0); and (5) the increase in risk of treatable procedure-related AEs from 0 to 40% (CRIS: 5.0). **Conclusion:** This study quantified the benefit-risk tradeoff preferences for islet cell therapy that can help inform regulatory decision-making.

Background

- Approximately 40,000 Americans have “hard-to-control” type 1 diabetes mellitus (T1DM) in which patients experience periods of “hypoglycemia unawareness” or frequent episodes where the blood glucose drops below normal levels. These events can result in poor quality of life (QoL), poor prognosis and fatality[1,2].
- Islet cell therapy is a novel treatment that could potentially treat patients with hard-to-control T1DM for which insulin-based management is no longer optimal.
- While islet cell therapy has its benefits in preventing hypoglycemia, the procedure can come with short-term (e.g., procedure risks, risk of infection) and long-term complications (e.g., lifelong immunosuppression to prevent graft-rejection).
- CBER is interested in understanding how patients make trade-offs regarding the benefits and risks of islet cell therapy and how this can inform benefit-risk assessment for regulatory decision-making.

Materials and Methods

Study Design:

- This is a cross-sectional study where an online survey instrument was administered to patients with hard-to-control T1DM.
- A convenience sampling method was used to recruit study participants between January 2020 and April 2020 from UCSF Diabetes Clinics and national diabetes research centers
- Patients eligibility criteria: English-speaking, physician confirmed T1DM, previously experienced a severe hypoglycemic episode.
- Informed consent was collected, and a $20 incentive was provided to completers. The study was approved by the UCSF IRB (#18-26355).

Table 1. Final list of eight attributes and corresponding levels.

Attributes	Levels
Chance of achieving clinical treatment success as defined by a normal range HbA1c (≤ 7.0%) and elimination of severe hypoglycemia by end of year 1 after final islet cell infusion period	40 out of 100 people
	60 out of 100 people
	90 out of 100 people
Success duration as defined by duration of time that a normal range HbA1c and elimination of severe hypoglycemia lasts after the final infusion without additional actions	0.5 year or less
	1 year
	2 years
	5 years
Extent of insulin independence defined as not needing any insulin doses or to monitor sugars or adjust insulin to maintain your blood glucose within the first 5 years after your transplantation procedure	Never independent
	2 years of independence
	5 years of independence
Expected reduction in the risk of long-term complications such as high risk of developing vision loss, or moderate risk of developing kidney damage, or low risk of developing nerve damage	Eye
	Kidney
	Nerve
Risk of treatable procedure-related adverse effects such as nausea, vomiting, diarrhea, moderate bleeding, anemia, pain treated with medications, headache, tremors, confusion, high blood pressure or cholesterol	0 out of 100 people
	5 out of 100 people
	15 out of 100 people
	40 out of 100 people
Risk of serious complications requiring hospital treatment and rare death (serious infections, liver bleeds, kidney damage, development of antibodies making additional transplant more difficult or cytomegalovirus infections or viral heart inflammation)	0 out of 100 people
	1 out of 100 people
	5 out of 100 people
	15 out of 100 people
Restrictions due to life time immunosuppression (anti-rejection) medications required as long as your islet cells are working (up to 5 years or longer)	Medication to prevent Mouth sores, anemia
	Constant need for Renal complications monitoring
	Need to take precautions to because of a Higher infection risk
	Monitoring for increased risk of Cancer
Time and support needed if 1-3 islet cell procedures are required each requiring 3 months of extra time and support to manage your diabetes including 3-5 days hospital stay, 2 weeks intensive monitoring of diabetes, and monthly physician visits each time	3 months
	6 months
	9 months

Survey Instrument:

- A choice-based conjoint (CBC) survey instrument was designed using Sawtooth™ software (v9.5.3) following a balanced overlap experimental design and consisted of 18 paired treatment choice questions. Within each question (Figure 1), patients had to choose their most preferred treatment profile from the presented pair.
- The treatment profiles were characterized by different levels of 8 features (i.e., attributes). These 8 attributes were selected to describe the benefits and risks associated with islet cell therapy (see Table 1). Selection of attributes and corresponding levels were based on a literature review and input from different stakeholder groups through an iterative process that included individual interviews with clinicians, subject matter experts (SMEs), regulatory SMEs, and a patient/caregiver advisory committee.
- Sociodemographic and self-reported clinical characteristics were also collected in the survey.
- The CBC instrument was pre-tested (N=12) to ensure comprehension, readability, and appropriate length prior to its use for data collection.

Data Analysis:

- Preference weights (PW) for each attribute level were estimated using random parameters logit models (RPL). The PW is a unit-less scale that measures the relative value of the attribute level to other attribute levels of the study. A larger PW indicates a stronger preference, meaning that respondents would be more likely to choose a profile with that level over another with a level that has a lower PW, all else equal.
- Using the PWs, conditional relative importance scores (CRIS) were calculated as follows:

$$\text{CRIS} = \frac{\text{Maximum difference in PWs within levels of Attribute X}}{\text{Maximum difference in PWs within levels of Reference attribute}} \times 10$$

- Where the reference is the attribute with the largest difference in PWs across its levels among all 8 attributes, and is assigned a value of 10
- The CRIS provides a relative measure of the impact that a change in level of a specific attribute, from the most to least preferred level, has on treatment choices
- The R package ‘gmnl’ was used for the RPL analysis.

Figure 1. Sample choice-task question from the DCE survey instrument for islet cell therapy PPI study.

Results and Discussion

- 184 invitations were sent to eligible patients
- Participants were excluded based on their willingness to participate, completion of the full DCE survey instrument, and correctly answering the fixed comprehension questions.
- 92 participants (50% female) completed the survey and were included in the final analyses. Most of the sample are white (77%), full-time employed (57%), have private health insurance through work (68%), and hold a bachelor’s degree (41%).
- Mean duration of time since diabetes diagnosis was 22-years. All patients were on insulin therapy, with 56% using an insulin pump. 31% of patients reported checking their blood glucose more than 6 times per day.

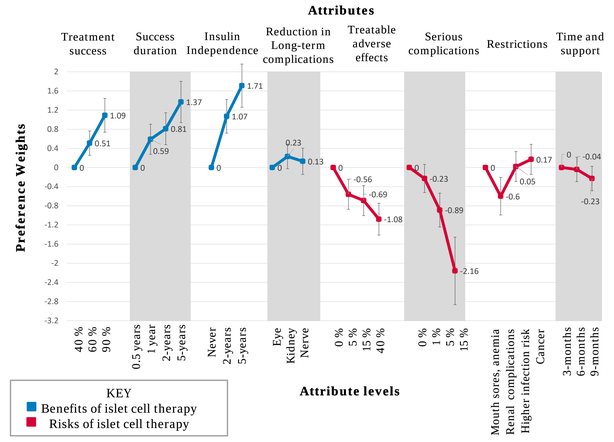

Figure 2. Preference weights for attributes and levels for survey participants (n = 92).

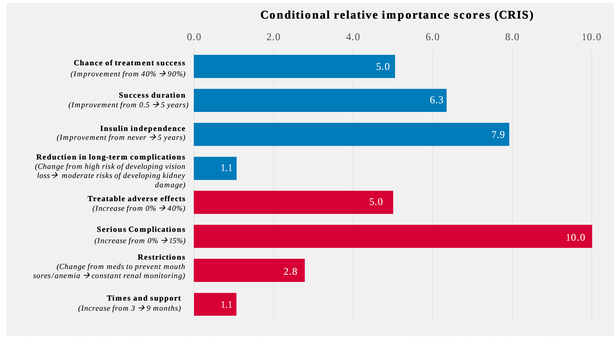

Figure 3. Conditional relative importance scores (CRIS) for islet cell therapy for sample of hard-to-control T1DM patients (n = 92).

Conclusion

- Patients wanted to avoid the highest levels of islet cell transplant risks but were willing to trade lower-level risk for insulin independence.
- This suggests that hard-to-control T1DM patients may be willing to accept a certain level of risk (e.g., 5% risk of serious complications) to achieve a certain extent of benefit (the possibility of having 5-years of insulin independence).
- This study quantified the benefit-risk tradeoff of hard-to-control T1DM patient preferences for islet cell therapy that can help inform the benefit-risk assessment of this product for regulatory approval.
- This study serves to enrich the evidence on how PPI studies can inform decision-making for future CBER regulated therapeutic products.

References

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