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BRIEF COMMUNICATION

A viewpoint describing the American Society of Transplantation rationale to conduct a comprehensive patient survey assessing unmet immunosuppressive therapy needs

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Abstract

This viewpoint aims to "set the stage" and provide the rationale for the proposed development of a large-scale, comprehensive survey assessing transplant patients' perceived unmet immunosuppressive therapy needs. Research in organ transplantation has historically focused on reducing the incidence and impact of rejection on allograft survival and minimizing or eliminating the need for chronic immunosuppressive therapies. There has been less emphasis and investment in therapies to improve patient-reported outcomes including health-related quality of life and side-effects. Patient-focused drug development (PFDD) is a new and important emphasis of the Food and Drug Administration (FDA) that provides a guiding philosophy for incorporating the patient experience into drug development and evaluation. The American Society of Transplantation (AST) Board of Directors commissioned this working group to prepare for the conduct of a comprehensive patient survey assessing unmet immunosuppressive therapy needs. This paper aims to describe the basis for why it is important to conduct this survey and briefly outline the plan for broad stakeholder engagement to ensure the information gained is diverse, inclusive, and relevant for advancing PFDD in organ transplant recipients.

KEYWORDS
patient characteristics, quality of life (QOL), rejection, side effects

This viewpoint provides a foundation as to why the professional transplant community should support efforts to develop and disseminate a patient-centered survey assessing their experience with immunosuppressive therapy and current unmet needs regarding these treatments.

Organ transplantation remains an imperfect, time-limited treatment that commonly falls short of restoring durable health, vibrancy, and functionality for patients with end-stage organ disease. As an example, the estimated median survival of a deceased donor kidney allograft is only 11.7 years,[1] and the standardized mortality ratios

for kidney transplant recipients are two to eightfold higher than age-matched persons from the general US population.[2] Moreover, although kidney transplantation improves health-related quality of life (HRQOL) compared to remaining on dialysis,[3] transplant recipients experience numerous deleterious symptoms and medication side effects,[4] and a substantial proportion of heart, lung, liver, and kidney recipients remain chronically disabled after transplantation.[5,6] Non-adherence to medications among transplant recipients due to common and severe immunosuppressive therapy side effects is an important barrier to achievement of long-term transplant survival. However, few therapeutic options are available to address these side effects.[7,8] Further, the relatively small number of therapies that have demonstrated significantly improved side effect burden profiles, such as belatacept, tend to be under-utilized in transplantation.[9] This underutilization is possibly due to the improved safety profile with belatacept, which was not an established FDA-approved clinical trial endpoint, and thus could not be marketed as such by the manufacturer. Belatacept underutilization may also be related to cost barriers that preclude access to this medication. Medicare Part B has a 20% copay for medications and belatacept is only available as brand name Nulojix®[9]; commonly used oral immunosuppressive therapy is now generic and available at a lower cost. For innovators to overcome the cost difference between generic agents and newly approved branded therapies, clear therapeutic advantage must be established. Given the low rates of acute rejection and graft loss that occur during the first-year post-transplant, advantages must focus on alternate outcomes: side effects and tolerability.

The last novel immunosuppressive therapy used in solid organ transplant was approved in 2011, and immunosuppressant regimens have remained virtually unchanged for two decades.[10] Historically, therapeutic development in transplantation has traditionally focused on regimens that limit acute rejection and prolong allograft survival. These efforts have led to the approval of potent therapies that result in excellent short-term allograft survival. But for many recipients, these drugs have simply replaced the life-threatening disease of end-organ failure with other chronic diseases (such as diabetes, hypertension, and chronic kidney disease) and debilitating side effects that limit quality of life, functionality, life participation, and long-term survival. Importantly, the medications required to treat these chronic diseases and side effects compound the formidable pill burden that life-long immunosuppressive regimens already induce.

The transplant field's success in limiting acute rejection and achieving excellent short-term allograft survival (i.e., 1-year allograft survival) has set a very high benchmark for approval of new immunosuppressive therapy based on the established primary efficacy endpoints displayed in Table 1. The Critical Path Institute's Transplant Therapeutics Consortium (TTC), co-founded by the AST and the American Society of Transplant Surgeons (ASTS) in 2017, was developed to accelerate the medical product development process for transplantation. The TTC is seeking regulatory endorsement with the FDA and the European Medicines Agency (EMA) of a composite surrogate endpoint for use in kidney transplant clinical trials (iBox, see Table 1). Toward that end, in 2018, the FDA and the TTC convened a public workshop to address drug development in transplantation, titled "Evidence-based Treatment Decisions in Transplantation: The Right Dose & Regimen for the Right Patient/Individualized Treatment." This workshop focused on biomarker use in transplantation and incorporating patient voice in transplant drug development.[11] *The AST Board recognizes the need to broaden efforts to advance alternate clinical trial endpoints to address the patient experience in organ transplantation, beyond acute rejection and allograft failure.* This includes safety-related outcome endpoints listed in the third column of Table 1 and Patient-Reported Outcome Measures (PROMs), detailed in the fourth column of Table 1.

Predominant safety-related outcomes include side effects or new health conditions, such as diabetes, hypertension, dyslipidemia, diarrhea, tremor, headache, and gastrointestinal symptoms that significantly impact how transplant recipients feel and function. These issues often require the addition of long-term medications and treatments. Many of these conditions are recognized disease entities with specific approved treatments, supporting the concept that these outcomes can be considered differentiators for novel immunosuppressive therapies, and potentially lead to regulatory approved label claims. The safety-related outcomes also include well-known and common complications of immunosuppressive therapies, most notably infections, cytopenias, and impaired kidney function in non-renal organ transplant recipients, that later frequently necessitates reductions in immunosuppressive therapies predisposing patients to acute and chronic rejection and premature allograft failure. Currently, none of the safety outcomes listed in Table 1 are endorsed by the FDA as acceptable transplant endpoints to obtain approved label claims for new immunosuppression therapies. Endorsement of these safety outcomes may re-invigorate interest in developing novel therapeutics and provide clinicians with more options to manage the well-known complications of current immunosuppressive therapies.

The FDA and EMA have accepted patient symptom assessments or physical signs representing symptom improvement as endpoints for other conditions, most notably, cancer.[12] For signs and symptoms to be accepted as outcomes, they typically must be related to the disease process rather than drug toxicity. New information about the relationship between how immunosuppressive therapies make transplant recipients feel and function and their impact on treatment adherence may persuade regulators to accept safety outcomes for the approval of novel immunosuppressive therapies. Further, given the importance of sustaining an appropriate level of immunosuppressive therapy to prevent acute and chronic rejection and limit side effects, new endpoints that measure the adequacy and consistency of immunosuppression exposure and limit high intra- and interpatient variability should also be evaluated as potential outcomes for regulatory approval. Such measures may facilitate development of new therapies to be approved based on improved achievement of target drug exposure from better recipient tolerability, pharmacokinetic profiles, or lower burden of administration (i.e., improve the patient treatment experience and reduce the monitoring burden).

Patient-focused drug development (PFDD), defined as a "systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into

TABLE 1 Examples of endpoints used in transplantation, including traditional measures currently approved by FDA and EMA (Column 1), surrogates or those proposed to regulators for use (Column 2), and examples of potential endpoints that may be considered to facilitate development of novel therapies in organ transplantation (Columns 3 and 4)

Primary efficacy endpoints	Secondary efficacy or surrogate endpoints	Safety outcome endpoints	Patient reported outcome endpoints
Patient survival	eGFR (kidney transplant)	Diabetes	SF36, SF12[17]
Graft survival	Biopsy findings	Hypertension	SONG-TX,[18] SIP[19]
Biopsy-proven rejection (BPAR)	Proteinuria (kidney transplant)	Hyperlipidemia	EQ-5D-5L,[20] WHOQOL,[21] PROMIS,[22] GLOBAL-10[23]
Efficacy failure (composite of death, graft loss, BPAR and loss-to-follow-up)	Donor-specific antibody (DSA)	Malignancy	MTSOSD-59R[4]
	iBox Scoring System[16] (kidney transplant)	Infections	KTQ-25[24]
		Cytopenias	KDQOL-SF[25]
		Diarrhea, gastrointestinal symptoms	ESRD-SCL-TM[26]
		eGFR (non-kidney transplant)	SAGIS,[27] GIQLI,[28] GSRS[28]
		Growth, nutrition, and reproductive health, particularly in adolescents and young adults	QUEST,[29] NIH Toolbox and Neuro-QOL[30]

Abbreviations: eGFR, estimated glomerular filtration rate; EQ-5D-5L, Euro quality of life, 5-dimensions, 5-levels; ESRD-SCL-TM: end-stage renal disease symptom checklist- transplantation; GIQLI: Gastrointestinal quality of life index; Global-10: Global 10 question health related qualify of life survey; GSRS: Gastrointestinal symptom rating scale; KDQOL-SF: Kidney disease quality of life – short form; KTQ-25: Kidney transplant questionnaire – 25 items; MTSOSD-59R: Modified transplant symptom occurrence and distress 59 items revised; PROMIS: Patient-reported outcomes measurement information system; QUEST: Quality of life in essential tremor questionnaire.; SAGIS: Structured assessment of gastrointestinal symptoms; SF-12: Short form-12 health related quality of life instrument; SF-36: Short form-36 health related quality of life instrument; SIP: Sickness impact profile; SONG-TX: Standardized Outcomes in Nephrology – Transplantation; WHOQOL: World Health Organization quality of life instrument.

drug development and evaluation," is a major emphasis of the FDA. FDA guidance documents on the advancement of new tools to measure the patient experience that may be utilized in PFDD emphasize collecting patient information about unmet therapeutic needs, including PROMs.[13] The FDA defines PROMs as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by the clinician or anyone else.[14]" As displayed in Table 1, PROMs may include established symptom rating scales for specific conditions as well as functional outcomes and multi-dimensional constructs such as HRQOL and well-being that may be harder to attribute to a specific immunosuppressive therapy. Advancement of novel PROMs related to the daily burden of lifelong immunosuppression and chronic disease management, which can impact physical and psychological health as well as treatment adherence, may be of specific interest because of the direct and robust link between treatment non-adherence and transplant outcomes.[15] For example, better characterization of the burden of medication-taking may be useful in advancing the development of maintenance biologics that have the potential to reduce or obviate the need for daily oral immunosuppressant therapy. FDA guidance documents outline the process for developing and validating PROMs for use in clinical trials, including leveraging existing PROMs or developing a new PROM.[14] Though the regulatory qualification of PROMs will be a challenging multi-year process, advancing these important clinical trial outcomes may be essential to address the unmet immunosuppressive therapy needs of transplant recipients. PFDD presents a promising opportunity to advance novel therapeutics while improving the tolerability of existing immunosuppressant drug regimens. The PFDD program provides an important rationale for the transplant professional community to support the development and dissemination of a large-scale survey to assess transplant recipients' and patients' perspectives of how immunosuppressive drug regimens impact their lives. The AST Board of Directors approved the development and comprehensive dissemination of this survey, which will be developed and disseminated to a diverse population of adult and pediatric transplant patients and caregivers over the next 12 to 24 months.

Efforts to develop this survey are ongoing. This paper is a first step to outline the rationale and initial planning components of the survey. Thus far, an expert panel of 8 transplant professionals has already identified 15 key constructs that wholistically measure the patients' transplant experience regarding immunosuppression therapy. This panel also ranked the constructs from 1 (most important) to 15 (least important) in an iterative fashion and added two additional constructs for patients to consider. These 17 constructs were shared with 22 transplant recipients (14 adult, 8 pediatric, 13 heart, 5 kidney, 4 liver, 1 lung, and 1 pancreas; mean age 48 yo adult and 9 yo pediatric). Patients and caregivers were identified from the AST Transplant Community Advisory Counsel (TCAC) and the Transplant Families Organization, providing verbal consent to voluntarily participate. As displayed in Figure 1, there was strong congruence between these independent rankings. Side effects, comorbidity burden, quality of life, adherence to strict regimen, and interference with important parts of your life, including family, work, hobbies, were ranked as important issues related to current immunosuppressive therapies by both the transplant professionals and the recipients (or guardians).

Once complete, this survey work product is expected to inform advocacy efforts for the regulatory endorsement of safety outcomes that have the potential to renew investment in novel therapeutics to

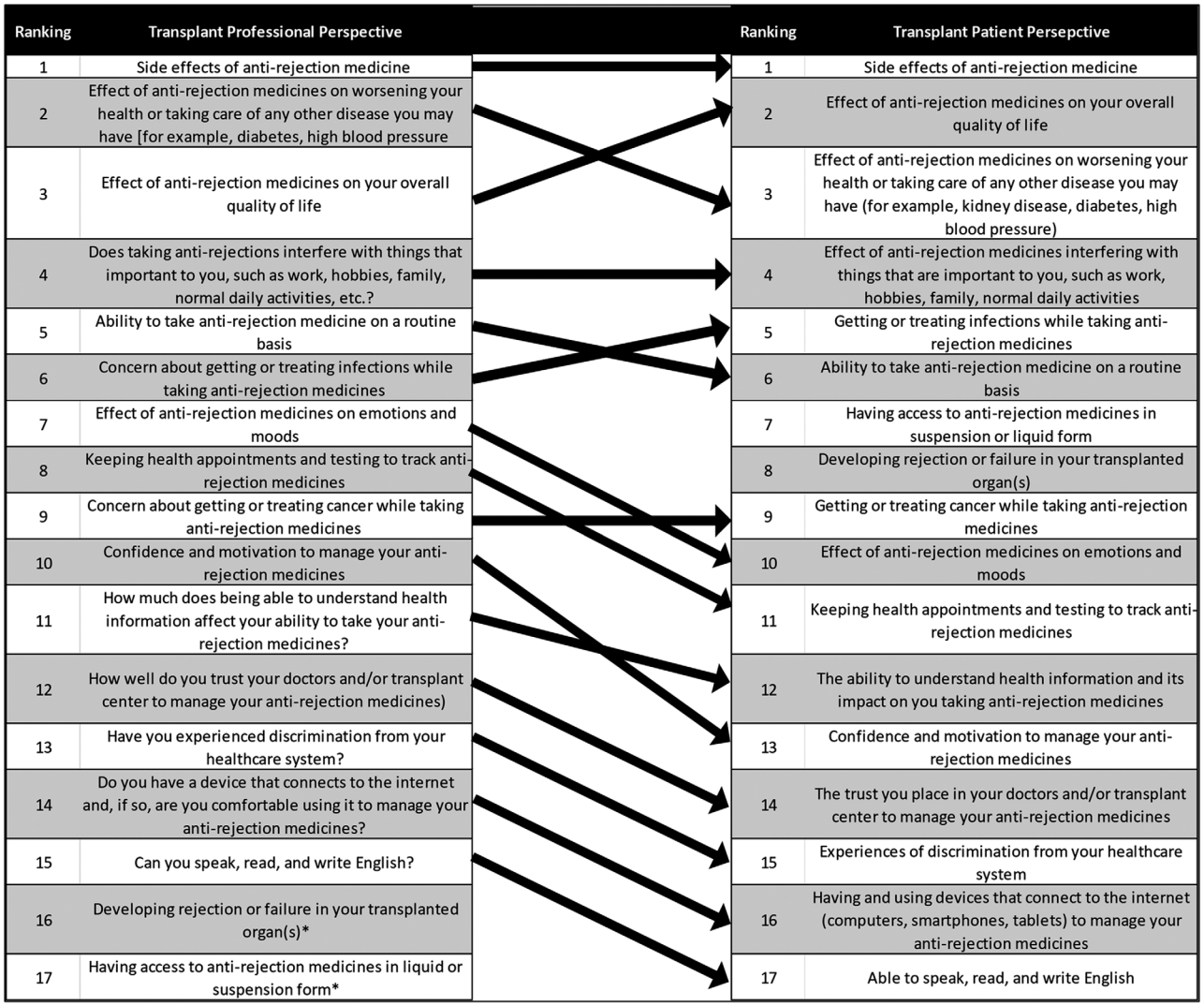

FIGURE 1 17 key constructs identified and ranked by transplant professions (left column) and recipients (right column). Of note, the transplant professions only ranked 15, as two constructs were added later (those with an * at the end of left column were added later).

better address the holistic transplant recipients' post-transplant experience. Novel therapeutics that decrease the burden and side effects of long-term immunosuppression may also address treatment nonadherence and improve transplant survival. This work is also expected to inform a long-term strategy regarding advancing PROMs as formal and recognized clinical trial outcome endpoints. Strategies include understanding the extent to which existing PROMs can enable a broad new investment in therapeutic drug development and the need to validate novel PROMs to capture recipient post-transplant experiences and immunosuppressive therapy tolerability that can be reliably linked to treatment adherence.

In summary, there is a clear and urgent need to better understand the transplant patients' perspectives regarding their experiences and concerns with current immunosuppressive therapies. This paper provided a detailed rationale to support the development and dissemination of a new survey in the hopes of spurring research and development into innovative therapies that may improve transplant patients' post-transplant experience. The AST Board recognizes the success of this work will depend on the collaboration of the global transplant community and will seek the engagement and support of the AST Transplant Community Advisory Council, as well as organizations outside the Society to ensure strong, broad, diverse, transparent, and equitable partnerships in advancing this work and invites feedback from interested stakeholders. Our goal is to have a survey ready to disseminate by June 2023 at the American Transplant Congress and to leave it open for at least 6 months.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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