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ORIGINAL ARTICLE

Measuring symptom experience of side-effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale

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Summary

Measurement of the patients' subjective experience of side-effects of immunosuppressants is a critical post-transplant outcome. This study aimed to update and validate the 45-item Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD) for novel immunosuppressive regimens. We used four steps: (1) literature review to identify immunosuppressant-related symptoms; (2) screening of adverse event forms; (3) international experts' evaluation of the appropriateness of each symptom; and (4) a pilot study in 24 renal transplant patients to test the clarity of instructions and items, and a pilot study in 84 lung transplant patients, to determine content and discriminant validity. Steps 1 and 2 produced a list of 76 symptoms. Clinical experts deemed 59 symptoms as being relevant for assessing symptom experience (step 3). Based on the first pilot testing, items and instructions were adapted to improve clarity. The second pilot testing showed that the updated MTSOSD-59R was easy to complete, that items and instructions were understandable, and that symptom profiles differed between males and females, and between depressed and nondepressed patients (step 4). The MTSOSD-59R is an instrument with established content and discriminant validity for assessing transplant patients' symptom experience of side-effects stemming from currently available immunosuppressive regimens.

Introduction

Clinical trials in transplantation (Tx) invariably include medically defined endpoints to demonstrate the effectiveness of immunosuppressive drugs in terms of graft function. These conventional clinical measures do not fully capture how immunosuppressive treatment affects the Tx recipients [1–3]. For example, a meta-analysis comparing tacrolimus to cyclosporine in kidney Tx recipients found that medical outcomes (e.g., graft function) were reported far more frequently than complications or side-effects of immunosuppression [4]. Yet, the latter are an important determinant of patients' quality of life and may be a trigger for nonadherence [5–13]. Evaluating immunosuppressive regimens, therefore, necessitates not only a focus on medical outcomes but also on side-effects associated with these drugs.

Side-effects can be evaluated both objectively (e.g., healthcare worker's perspective) and subjectively (e.g., patient's perspective) [14]. The objective evaluation refers

to clinicians' monitoring of side-effects (e.g., malignancy, infection, diabetes mellitus) [15], which are traditionally assessed in clinical trials using adverse event forms or checklists. Empirical evidence, however, has shown that adverse event forms identify only 7% of the symptoms that patients actually experience and report on a symptom scale [16], resulting in an underestimate of the true burden of immunosuppressive treatment [4,17].

The subjective evaluation refers to the patient's appraisal of the side-effects of immunosuppressive regimens. Including the patient's perspective is increasingly recognized as a key to understanding both the benefit and burden of immunosuppressive regimens, and should therefore be part of quality-of-life assessments [14]. A theoretically framed, clearly defined, standardized and validated instrument that assesses the subjective appraisal of the side-effects of immunosuppressive regimens greatly enhances interpretation of research evidence by both clinicians and patients. Such an instrument may also assist healthcare providers and patients in making decisions about immunosuppressive treatment. The 45-item Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD) is the only existing validated scale to assess Tx-related symptoms associated with the use of immunosuppressive drugs that is based on a conceptual framework (i.e., self-regulation theory) [8,18,19]. Self-regulation theory [19] posits that symptom experience should be measured along two pathways, i.e. *symptom occurrence*, which is measured in terms of frequency or severity, and *symptom distress*, which encompasses mental anguish or suffering caused by a specific symptom [20]. A patient, for example, may frequently experience spots on the face and neck but may report that these spots are not distressing at all.

Although other symptom scales have certain benefits and have been used successfully in past immunosuppression-related research, their focus on core subjective patient experiences is diluted by either conceptual or methodological shortcomings [21–28]. First, these scales lack a conceptual framework; second, some subjective scales include objective side-effects that cannot possibly be experienced by patients (e.g., hypercholesterolemia, renal problems), challenging its values as a patient-reported instrument [22,29]; third, several scales go beyond a narrow focus on side-effects of immunosuppressive drugs by also including broader quality of life issues, such as somatic symptoms related to Tx (e.g., exercise intolerance) or symptoms of Tx-related psychological distress (e.g., fear about complications, worry about family situation) [21–23,26–29]; and finally, some instruments have focussed on symptoms of specific drugs only, such as steroids [23,25]. In summary, no instrument to date, with the exception of the MTSOSD, has adopted a complete list of relevant symptoms that focusses exclusively on the patient's appraisal of the side-effects of all immunosuppressive drugs currently used in clinical practice. It can be used in the context of all organ transplant types [8,18].

Yet, the 45-item MTSOSD was last validated several years ago, before the clinical introduction of newer immunosuppressants. The purpose of the present study was to update the MTSOSD, incorporating new insights gained from clinical experience with the side-effects of current and newer immunosuppressive drugs, i.e. cyclosporine, corticosteroids, azathioprine, tacrolimus, mycophenolic-acid-containing formulation, mTOR inhibitors and belatacept. We also aimed to determine the content and discriminant validity of the updated MTSOSD and to assess its acceptability to patients in clinical practice.

Methods

This study consisted of four interrelated steps: in concordance with the FDA guidelines for development of patient-reported outcome (PRO) instruments (available online at http://www.fda.gov/cber/gdlns/prolbl.htm). The first three were related to the updating and expansion of the MTSOSD item pool and assessment of the adapted tool's content validity. The fourth procedure aimed to pilot-test the clarity of items and the clarity of scale construction, as well as the discriminant validity of the updated MTSOSD.

Step 1: Review of databases, literature, and other relevant sources to verify items and to generate new test items

We conducted a comprehensive literature review to update the current 45-item MTSOSD scale to include symptoms related to the side-effects of routinely used, oral immunosuppressive drugs (i.e., tacrolimus, cyclosporine, steroids, azathioprine, micophenolic-acid-containing formulation, mTOR inhibitors). We searched PubMed, the website of the US Food and Drug Administration (FDA), product information (e.g., package inserts) provided by pharmaceutical companies, and other various public sources, including web pages reporting on side-effect profiles.

Step 2: Review of adverse event forms of belatacept studies

As clinical experience with belatacept, a novel T-cell activation blocker, is limited to clinical trials, the adverse event forms were reviewed for side-effects experienced by patients in Phase-II trials conducted to date, i.e. adverse event data pertaining to the first 6 months after renal Tx

(i.e. open label, randomized controlled multiple-dose study of the efficacy and safety of belatacept compared to cyclosporine in de novo renal transplant patients [30]). Our analysis of these data focussed on symptoms related to side-effects that could be experienced by patients.

Step 3: International expert review

Next, we consulted international experts to review our updated information generated from steps 1 and 2. A convenience sample was formed of 21 international experts in clinical Tx of various organ types; including investigators involved in belatacept trials. We contacted experts personally by phone or by e-mail and explained the purpose of the study. After obtaining an agreement to participate, we mailed the updated MTSOSD symptom list (based on step 1 and 2) to the participating expert, along with instructions in an accompanying letter. Experts were asked to complete the questionnaires (see below) and return them within 14 days. They were paid 100 Euros or US Dollars for their time and effort.

The experts were asked to complete three tasks: (i) indicating whether a given symptom was relevant to the experience transplant patients might encounter as side-effects of immunosuppressive drugs (binary YES/NO rating); (ii) assigning each symptom to the applicable immunosuppressive medication [More than one answer was possible, as symptoms may be common across some or all of the immunosuppressants. Provision was made for the experts to list the names of other immunosuppressive medications (i.e., medications from medical trials)]; and (iii) listing of additional relevant symptoms (not already listed in the updated MTSOSD) associated with the side-effects of approved or late-stage development immunosuppressive drugs.

Items were included in the final updated version if at least three experts scored a specific item as relevant. This decision criterion was based on a previously used cut-off during the validation process of the original 45-item MTSOSD [8].

Step 4: Pilot testing of the updated MTSOSD

A pilot test with the 59 items of the MTSOSD in renal transplant and one in lung transplant recipients was carried out. The methodology for these two pilot tests is described next.

Pilot testing in 24 renal transplant patients

Design and sample.

We tested cross-sectionally the provisionally updated MTSOSD scale in a convenience sample of 24 renal transplant recipients enrolled at Emory University Hospital (EUH; Atlanta, GA, USA). The aim was to assess the clarity of the items and instructions as well as its completeness.

Inclusion criteria were: first renal Tx, being able to understand and write English, aged 18 years or older, and having received one of the following immunosuppressants either within the confines of a clinical trial or as part of routine care: belatacept, tacrolimus, or cyclosporine. Patients having received multi-organ Tx, patients with an active viral or bacterial infection, and HLA-identical living-related donor/recipient pairs were excluded.

Variables and measurements.

Demographic and clinical characteristics noted were: gender, age, race, marital status, educational level, cause of end-stage organ disease, and type of immunosuppressive regimen.

The *symptom experience* of transplant patients was assessed using the updated MTSOSD. Symptom occurrence was rated on a five-point scale, ranging from 0 (never occurring) to 4 (always occurring), and from 0 (not at all distressing) to 4 (extremely distressing) for symptom distress. Instrument layout was designed to enhance independent responses from patients by including a vertical scaling method for symptom occurrence and a horizontal scaling method for symptom distress. Gender-specific versions of the MTSOSD scale differed on one item: impotence for men and menstrual problems for women.

In addition to filling out the questionnaire, patients were asked to evaluate the clarity of the instructions, scaling methods, and items. Patients were also asked to evaluate the completeness of the questionnaire.

Data collection procedure.

A clinician at the EUH Transplant Center approached the eligible patients during a scheduled clinic visit to explain the purpose of the study. After oral informed consent, patients received a package containing the written informed consent form, demographic questionnaire, and updated MTSOSD. All questionnaires were coded by EUH to guarantee patient confidentiality. A cover letter explained the purpose of the study, included the contact information of the researchers, provided instructions on how to fill out the questionnaires, and asked patients to write comments next to items that lacked clarity. Patients could also list additional symptoms related to their immunosuppressive treatment that they experienced but were not mentioned in the symptom list. All participants were instructed to return the signed informed consent

form and the completed questionnaires in a prestamped, pre-addressed envelope within 14 days to the Tx center, after which a reminder was sent wherever the form had not been received. The IRB at EUH gave approval for this study.

Data management and statistical analysis.

The completed questionnaires and the clinical data of all participants were sent to the investigators for data entry and analysis. Data were kept in a locked filing cabinet in a research office at the University of Leuven (Belgium).

Demographic and clinical characteristics were described using mean values ± SD, median/interquartile ranges, and frequencies, as appropriate. Data were analyzed using SPSS version 14 for Windows (SPSS Inc., Chicago, IL, USA). In addition, content analysis was used to explore the clarity of items and instructions, addressing three issues:

1 Which items were not clear or were not completed by the patients (i.e., missing values)?

2 Were both the symptom occurrence and the symptom distress subscale completed?

3 Was the questionnaire completed in accordance with the instructions?

Completeness of the updated MTSOSD was evaluated by reviewing the additional symptoms listed by the patients.

Pilot testing in 84 lung transplant patients

Design and sample.

On the basis of the results of the first pilot testing, the items and instructions were adapted. The clarity of items and instructions was tested again in a second pilot testing in 84 lung transplant patients, as part of a study on long-term functioning, allowing also testing the discriminant validity of the updated MTSOSD. More specifically, it is known that women have a higher symptom experience compared to men [6,22,31,32]. Moreover, evidence in transplant and nontransplant populations shows a positive relationship between symptom experience and depression. Consequently, discriminant validity of the updated MTSOSD was tested by comparing symptom occurrence and distress in men versus women, and in patients with and without depressive symptoms, respectively. The adapted MTSOSD was translated into Dutch prior to this study in a culturally sensitive way, in concordance with the Brislin protocol. Using a cross-sectional design, all lung transplant patients being >3 years post-transplant, >18 years of age, and Dutch-speaking were included. Patients being hospitalized, on the waiting list for a retransplantation, or with a life expectancy of <6 months were excluded.

Variables and measurement.

Variables and measurement were similar to the ones described under pilot testing one. In addition, patients completed the depression subscale of the Hospital Anxiety and Depression Scale, a 7-item self-report instrument to assess presence and severity of depressive symptoms [33]. Each item is receiving a score between 0 and 3, yielding a total score between 0 and 21. Patients with a score below 8 were classified as not depressed, patients with a score of 8 or higher were considered to be depressed.

Data collection procedure.

The primary investigator (FD) contacted all eligible patients by phone and explained the purpose of the study. After oral consent, the questionnaires and an accompanying letter explaining the scoring instructions were sent to the home address of the patient (see also above). Patient could return the completed questionnaires to the researchers in a prestamped envelope. Patients who did not return their questionnaire were contacted again by phone after 3 weeks. The ethical review board of the University Hospitals of Leuven, Belgium approved this study.

Data analysis.

To evaluate the completeness and clarity of the questionnaire, the data analysis was similar to that described under pilot testing one. Because the items of both the occurrence and the distress part of the MTSOSD-59R are scored on an ordinal scale, it is not justified to merely sum up the item responses. We performed factor analysis to see if subscales emerged, allowing grouping of items in different meaningful categories. Yet, no factor structure emerged. The only correct way to calculate an overall score is ridit analysis. Ridit is a sensitive statistical technique for ordinal data [34]. Ridit analysis represents the Relative probability to an Identified Distribution. The use of ridits implies the selection of a reference distribution and so the ridit of a (sub)sample will always be compared to the ridit of that chosen reference group. Symptom experience scores for each patient can be computed by calculating ridit scores over all symptoms for occurrence and distress separately. A ridit is the result of comparing this individual item score distribution with the distribution of scores of the total sample. The ridit of a (sub)sample is the probability that a randomly selected individual from that group scores higher on the response variable than a randomly selected individual of the reference group. A ridit ranges from 0 to 1. For instance, a ridit for symptom occurrence of a depressed patients is

0.75, indicating that a randomly selected depressed patient will have a chance of 75% to have a higher symptom occurrence than a randomly selected patient from the reference group, i.e. nondepressed patients. De ridits of men and women, and of depressed versus nondepressed patients, were compared using a Mann–Withney *U*-test afterwards.

Results

The results of the four inter-related steps are described next.

Step 1: Review of databases, literature, and other relevant sources to verify items and to generate new test items

Our systematic search and review of databases yielded 63 possible symptoms of immunosuppressive drugs, that were compared to the symptoms reported within the original 45-item MTSOSD. The versions for male and female patients differed on one item, resulting in 46 symptoms in total. Six items in the original MTSOSD did not match items from the current literature review, yet as their clinical relevance had been established previously we retained these items in the updated MTSOSD, i.e. 'I have a feeling of warmth in my hands and feet', 'I have a reduced interest in sex,' 'My facial features have changed,' 'I have difficulty in concentrating,' 'I have warts,' and 'I feel tired.' We identified 22 candidate symptoms that were not part of the original 45-item MTSOSD.

A total of 68 symptoms (44 items + two gender-specific items of the original MTSOSD + 22 candidate items) related to side-effects of immunosuppression were thus included in the symptom list for further evaluation (Table 1).

Step 2: Review of adverse event forms of belatacept studies

Analysis of the adverse event forms mainly yielded side-effect symptoms of the immunosuppressive drugs congruent with the list in Table 1. Only eight additional symptoms were identified: dyspnea, abnormal skin color, dental abnormalities, dry mouth, genital pain, heartburn, dryness of skin, and tachycardia.

These new symptoms were added to the 68 items identified in step 1, resulting in 76 items available for expert review.

Step 3: International expert review

Seventeen out of 21 experts (81%) returned their questionnaires. Based on their feedback, six items were removed: hiccups, somnolence, decreased urge to urinate, painful or heavy menstrual periods, shortness of breath, and genital pain/discomfort.

Table 1. Overview of the 68 symptoms identified from the literature.

Items of the MTSOSD-45		New symptoms
Mouth infections	Joint pain	Sores on lips or in mouth
Skin rash	Low back pain	Black tarry stools
Nausea	Muscle cramps	Hives
Spots on face and neck	Muscle weakness	Oily skin
Diarrhea	Trembling hands	Constipation
Vomiting	Tingling in hands or feet	Flatulence, gas
Stomachache	Difficulty seeing well	Increased thirst
Tiredness	Changed sense of taste	Dizziness
Abdominal pain	Gum growth	Chest pain, heart cramps
Poor appetite	Cough	Itching
Excessive appetite	Unusual bruising	Changed built
Headache	Sensitivity to light	Swollen glands
Swollen ankles	Brittle skin	Hearing difficulties, hearing loss, deafness
Moon face	Fever	Sweating, night sweats, sweating of feet and legs
Difficulty sleeping	Pain when passing water	Face redness, flushing of face and neck
Nightmares	Hair loss	Hiccups
Increased hair growth on face and body	Feeling of warmth in hands and feet	Drowsiness, somnolence, unusual tiredness
Depression	Reduced interest in sex	Breast enlargement
Anxiety	Changed facial features	Voice alteration
Mood swings	Concentration difficulties	Sores around genitals
Listlessness	Warts	Brittle fingernails
Stress	Impotence (in men)	Yellow skin, changes in skin color
Hallucinations	Menstrual problems (in females)	

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Three additional items were suggested: nocturia, gout, and wound-healing problems. These items were rephrased to describe symptoms in lay terms, presumably more familiar to patients: 'increased urge to urinate,' 'pain in joints,' and 'brittle skin.'. Three experts addressed overlaps among items. Careful revision of the list of 76 symptoms resulted in an updated 59-item version (MTSOSD-59R).

Step 4: Pilot testing of the MTSOSD-59R in a sample of renal transplant patients

Pilot testing in 24 renal transplant patients

Table 2 contains the demographic and clinical characteristics of the renal T_x patient sample enrolled in the first pilot study.

Most patients responded to most items. Two patients did not rate one item, and two other patients did not rate two items. The items not scored were 'I have brittle skin,' 'I have breast enlargement,' 'My hands tremble,' 'I have an altered voice,' and 'I have an abnormal skin color.' Reasons for these omitted ratings were not evident, except for the item 'I have breast enlargement'. Two male patients did not rate this item, suggesting that they may have missed its applicability and the underlying physiological plausibility. This item was therefore replaced by 'My breasts are larger,' as suggested by two native English-speaking clinicians at EUH.

One patient did not complete two nonconsecutive pages and one patient did not complete the symptom-distress subscale of the questionnaire. To avoid future oversights and to ensure that patients complete the entire questionnaire, we adjusted the instructions by including a statement at the beginning and at the end of the questionnaire asking the patients to check that all items and pages have been completed.

Nine patients misunderstood the instructions on how to rate the symptom distress subscale. The instructions for this subscale asked subjects to circle the numerical value corresponding to how distressing their symptom was. However, instead of circling numbers, five patients put an 'X' next to a value and four patients put an 'X' between two values. To discourage this type of answering pattern in the future, we inserted an example into the instructions, illustrating how to correctly rate the distress scale.

All participants rated the items as clearly formulated. Two patients suggested new symptoms: 'osteoporosis' and 'memory loss.' As osteoporosis is a disease referring to a specific cluster of symptoms, only the associated pain symptoms, not osteoporosis as such, can be experienced by transplant patients. Therefore, we did not add osteoporosis to our item list. To address the issue of memory loss, we adjusted the item 'I have difficulty concentrating' to 'I have problems with concentration and/or memory.' An overview of symptoms included in the updated and validated 59-item MTSOSD (MTSOSD-59R) is provided in Table 3.

Pilot testing in 84 lung transplant recipients

As some problems related to clarity of instructions were noted during the pilot testing in renal transplant recipients, 84 lung transplant recipients were asked to check the clarity of items and instructions of the adapted version again (see Table 2 for their demographic and clinical characteristics). Only one patient forgot to complete one page, and one person only rated symptoms that occurred, but did not indicate a score for symptoms that she did not experience. Four patients forgot to score 1 item each.

Table 2. Demographic and clinical characteristics of the patients participating in the two pilot tests.

Demographics	Pilot test 1 (24 renal Tx patients)	Pilot test 2 (84 lung Tx patients)
Age (years)	Me = 51 (IQR = 22)	Me = 57 (IQR = 18)
Gender (% male)	10 (41.7)	49 (58.3)
Race (% white)	17 (70.8)	84 (100)
Marital status (% married)	11 (45.8)	62 (73.8)
Education level (≥bachelor degree)	10 (41.7%)	28 (33.3%)
Etiology of end-organ disease (%)	Glomerulonephritis: 3 (12.5)	Emphysema: 45 (53.6)
	Hypertension 4: (16.7)	Cystic fibrosis: 16 (19)
	Diabetes: 3 (12.5)	Fibrosis: 15 (17.9)
	Cystic, hereditary or congenital renal disease: 4 (16.7)	Other: 6 (9.6)
	Interstitial nephritis/pyelonephritis: 1 (4.2)	
	Unknown: 9 (37.5)	
Immunosuppressive regimen (%)	Cyclosporine: 8 (33.3)	Cyclosporine: 8 (9.5)
	Tacrolimus: 8 (33.3)	Tacrolimus: 76 (90.5)
	Belatacept: 8 (33.3)	

Me, Median; IQR, interquartile range.

Table 3. Overview of the 59 symptoms included in the MTSOSD-59R*.

1) Itching	21) Spots on face or back	40) Warts on hands or feet
2) Chest pain	22) Excessive appetite	41) Increased hair growth
3) Wind	23) Depression	42) Sleep difficulties
4) Increased thirst	24) Swollen gums	43) Muscle weakness
5) Restlessness/nervousness	25) Swollen glands	44) Changed sense of taste
6) Hearing loss	26) Thinning of hair/hair loss	45) Poor appetite
7) Abnormal skin color	27 A) Menstrual problems (for female persons only)	46) Tiredness
8) Increased sweating	27 B) Impotence (for male persons only)	47) Lack of energy
9) Redness of face or neck	28) Moon face	48) Stomach complaints/nausea/vomiting
10) Brittle fingernails	29) Swollen ankles	49) Joint pain
11) Larger breasts	30) Diarrhea	50) Skin rash
12) Sores on lips or in mouth	31) Tingling or numbness of hands or feet	51) Muscle cramps
13) Voice alterations	32) Back pain	52) Nightmares
14) Oily skin	33) Brittle skin	53) Shortness of breath
15) Dizziness	34) Anxiety	54) Dry skin
16) Trembling hands	35) Mood swings	55) Palpitations
17) Increased urge to urinate	36) Headaches	56) Constipation
18) Feeling of warmth in hands or in feet	37) Changed facial features	57) Difficulty seeing well
19) Bruises	38) Buffalo hump	58) Reduced interest in sex
20) Genital warts	39) Concentration or memory problems	59) Sensitivity to light

*The Katholieke Universiteit Leuven, Belgium holds the copyright of the MTSOSD-59R. A copy of the entire questionnaire and/or translated versions can be obtained upon e-mail request: sabina.degeest@unibas.ch.

Except for 1 patient who did not understand the symptom 'moon face', the other items were randomly missed (i.e. 'lack of energy', 'constipation', and 'itching'. Seventy-eight patients (93%) correctly completed the MTSOSD-59R.The results of this second pilot testing shows that the clarity of instructions and items has significantly been improved compared to the previous version, indicating excellent validity related to test content.

Moreover, female patients ($N = 35$; 41.7%) showed a tendency toward higher symptom occurrence ($U = 674$; $P = 0.096$), and significantly higher symptom distress ($U = 219$; $P = 0.017$) compared to men ($N = 49$; 58.3%). Patients with depressive symptoms ($N = 12$ with HADS score ≥ 8; 14.3%) had a significantly higher symptom occurrence ($U = 586$; $P = 0.030$), and higher symptom distress ($U = 187$; $P = 0.006$) compared to patients without depressive symptoms ($N = 72$; 85.7%). These results indicate that the MTSOSD-59R has excellent discriminant validity.

Discussion

As the immunosuppressive agents and combination immunosuppressive regimens are continuously evolving, new symptoms associated with side-effects may emerge. Likewise, as PROs gain in importance as study endpoints, instruments used to assess a patient's subjective symptom experience, in terms of frequency and distress, must be updated and validated. The revision of the MTSOSD-45 into the MTSOSD-59R reflects this process. We propose to replace the former version with the latter to obtain a comprehensive representation of side-effect symptoms stemming from approved or later-stage development immunosuppressive agents: cyclosporine, corticosteroids, azathioprine, tacrolimus, mycophenolic-acid-containing formulation, mTOR inhibitors, and belatacept. The MTSOSD-59R* is a validated instrument that exclusively focusses on the subjective appraisal of side-effects from immunosuppressive medications by transplant recipients.

Patients' subjective appraisal of medication side-effects is increasingly recognized as an important PRO in Tx as well as in other chronic illnesses [1,2]. Traditional clinical outcome measures fall short in capturing the ways in which immunosuppressive treatment affect patients. The availability to researchers and clinicians of an adequate and appropriate instrument to assess symptom experience of immunosuppression side-effects is critical. The FDA recently issued a draft report that provides proposed guidance on evaluating PRO measures, used as effectiveness

*The MTSOSD-59R has been translated into Dutch, English, French, German, Spanish, Brazilian Portuguese, Italian, Danish, Swedish, Polish and Hindi. All were translated in a culturally sensitive way by the MAPI Research Institute (France), which is in line with the principles of good practice for the translation and cultural adaptation process for PRO measures [3]. We would like to refer the interested reader to the website of MAPI (http://www.mapi-research.fr/index.htm) to learn more about the linguistic validation methodology used in this study. The Katholieke Universiteit Leuven holds the copyright of this questionnaire. Information regarding the use of this instrument may be obtained by e-mail: sabina.degeest@unibas.ch.

endpoints in clinical trials (available online at http://www.fda.gov/cber/gdlns/prolbl.htm). The MTSOSD-59R complies with the proposed FDA standards: It is based on a conceptual framework identifying the intended application; the procedures for item generation are clearly described; clarity of items and instructions has been tested in the target population; and the measurement properties such as content and discriminant validity have been established. Moreover, according to the FDA guidelines, validating a PRO instrument is an ongoing process. This means that the instrument needs to be validated whenever it is used in a new population. This means that validity will be explored in all new studies incorporating the MTSOSD-59R. The following hypotheses, for instance, will be explored in future studies: (i) Women have a higher symptom experience compared to men; (ii) depressed patients have a higher symptom experience than nondepressed patients; (iii) higher symptom experience is associated with a poorer quality of life; (iv) higher symptom experience (especially distress) is related to adherence with the immunosuppressive treatment; and (v) symptom profiles will differ across different immunosuppressive regimens.

Methodological shortcomings of the MTSOSD-59R

One possible shortcoming is that we did not use patient focus groups for item generation. Indeed, qualitative interviews with transplant recipients on different immunosuppressive regimens could have assisted in the updating and validation process. Yet, both renal and lung transplant patients on different immunosuppressive regimens tested the completeness of the instrument and clarity of instructions and item formulations.

Second, while the instrument intends to measure symptoms associated with side-effects of the immunosuppressive regimen, some items may refer to symptoms of the underlying disease or a worsening condition. It should be checked in future studies if the patients indeed believe the items are indeed caused by their immunosuppressive drugs.

Strengths of the MTSOSD-59R

We believe that the MTSOSD-59R has many scientific and clinical benefits. It will assist healthcare providers in understanding the true burden of immunosuppressive treatment in transplant recipients.

Measurement of symptom experience during routine clinical follow-up of transplant recipients allows the identification of patients with high levels of symptom distress, and patients at risk for nonadherence [5]. Regular screening of symptom experience also permits the implementation of interventions to reduce symptom distress; for instance, treatment of stomach complaints, prescription of hair removal creams, treatment of impotence through referral to specialized care, or organization of make-up sessions to teach camouflage techniques for facial redness or puffiness.

Assessing symptom experience may inform healthcare providers on whether treatment innovations also translate to subjective benefits for the patients [35,36]. Inclusion of a subjective measure of patient-reported side-effects in the evaluations of any new drugs or in equivalence studies of immunosuppressives is recommended [8,37,38]. Two treatments having comparable impact on graft function may cause different degrees of burden for the patient. Analyses can be performed at item level, as well as using a more general ridit score, a technique to summarize ordinal data based on the Relative Probability to an Identified Distribution. The meta-analysis by Webster *et al.* [4], for instance, showed that tacrolimus-treated patients were significantly more likely to report tremors, headache, dyspepsia, vomiting, and diarrhea, while patients on cyclosporine were more likely to report constipation, hirsutism, and gingival hyperplasia. The MTSOSD-59R is suitable for comparing treatment regimens in all types of transplant patients in view of symptom experience related to side-effects of immunosuppressive drugs.

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Authorship

FD: developed the study design, coordinated the data-collection, performed the analyses, and wrote the paper. PM: supervised the development of the study design, based on his expertise in symptom experience. IA: Contributed to the study design, and provided feedback on the content of the paper. CPL: coordinated and supervised the data-collection for pilot study 1 at Emory University. LD: coordinated and supervised the data collection. For pilot study 2 at the University Hospitals of Leuven. SDG: supervised the whole project, and was actively involved in the preparation of the manuscript.

References

1. Doward LC, McKenna SP. Defining patient-reported outcomes. *Value Health* 2004; **7**(Suppl. 1): S4.

2. McKenna SP, Doward LC. Integrating patient-reported outcomes. *Value Health* 2004; **7**(Suppl. 1): S9.
3. Wild D, Grove A, Martin M, *et al.* Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: Report of the ISPOR Task Force for translation and cultural adaptation. *Value Health* 2005; **8**: 94.
4. Webster AC, Woodroffe C, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomized trial data. *BMJ* 2005; **331**: 810.
5. Teixeira de Barros C, Cabrita J. Noncompliance with immunosuppressive therapy: prevalence and determinants. *Transplant Proc* 2000; **32**: 2633.
6. Moons P, De Geest S, Abraham I, Van Cleemput J, Vanhaecke J. Symptom experience associated with maintenance immunosuppression after heart transplantation: patients' appraisal of side effects. *Heart Lung* 1998; **27**: 315.
7. Moons P, Fairchild S, De Geest S. Patients' appraisal of side effects in quality of life assessments of immunosuppressive regimens. In: Cochat P, ed. *Immunosuppression Under Trial*. Dordrecht, the Netherlands: Kluwer Academic Publishing, 1999: 69 pp.
8. Moons P, De Geest S, Versteven K, *et al.* Psychometric properties of the "Modified Transplant Symptom Occurrence and Symptom Distress Scale". *J Nurs Meas* 2001; **9**: 115.
9. Moons P, Vanrenterghem Y, van Hooff JP, *et al.* Steroids may compromise quality of life of renal transplant recipients on a tacrolimus-based regimen: a multicentre study. *Transplant Proc* 2002; **34**: 1691.
10. Cleemput I, Kesteloot K, Moons P, *et al.* The construct and concurrent validity of the EQ-5D in a renal transplant population. *Value Health* 2004; **7**: 499.
11. Artz MA, Boots JM, Ligtenberg G, *et al.* Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function, and cardiovascular risk. *Am J Transplant* 2004; **4**: 937.
12. De Geest S, Abraham I, Moons P, *et al.* Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant* 1998; **17**: 854.
13. De Geest S, Moons P. The patient's appraisal of side-effects: the blind spot in quality-of-life assessments in transplant recipients. *Nephrol Dial Transplant* 2000; **15**: 457.
14. Burra P, de Bona M. Quality of life following organ transplantation. *Transpl Int* 2007; **20**: 397.
15. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. *Transpl Int* 2006; **19**: 607.
16. Anderson RB, Testa MA. Symptom distress checklists as a component of quality of life measurement: comparing prompted reports by patient and physician with concurrent adverse event reports via the physician. *Drug Inf J* 1994; **28**: 89.
17. Cuervo LG, Clarke M. Balancing benefits and harms in health care. *BMJ* 2003; **327**: 65.
18. Moons P, Vanrentherghem Y, van Hooff JP, *et al.* Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multicentre study. *Transpl Int* 2003; **16**: 653.
19. Leventhal H, Johnson JE. Laboratory and field experimentation: Development of a theory of self-regulation. In: Wooldridge PJ, Schmitt MH, Schipper JK, Leonard RC, eds. *Behavioral Science and Nursing Theory*. St Louis, MO: CV Mosby, 1983: 189–262.
20. Rhodes VA, Watson PM. Symptom distress, the concept: past and present. *Semin Oncol* 1987; **3**: 242.
21. MacNaughton KL, Rodrigue JR, Cicale M, Staples EM. Health-related quality of life and symptom frequency before and after lung transplantation. *Clin Transplant* 1998; **12**: 320.
22. Winsett RP, Arheart K, Stratta RJ, *et al.* Evaluation of an immunosuppressant side effect instrument. *Prog Transplant* 2004; **14**: 210.
23. Matthees BJ, Anantachoti P, Kreitzer MJ, Savik K, Hertz MI, Gross CR. Use of complementary therapies, adherence, and quality of life in lung transplant recipients. *Heart Lung* 2001; **30**: 258.
24. Unal G, de Boer JB, Borsboom GJ, Brouwer JT, Essink-Bot M, de Man RA. A psychometric comparison of health-related quality of life measures in chronic liver disease. *J Clin Epidemiol* 2001; **54**: 587.
25. Franke GH, Reimer J, Kohnle M, Luetkes P, Maehner N, Heemann U. Quality of life in end-stage renal disease patients after successful kidney transplantation: development of the ESRD symptom checklist – transplantation module. *Nephron* 1999; **83**: 31.
26. Grady KL, Jalowiec A, Grusk BB, White-Williams C, Robinson JA. Symptom distress in cardiac transplant candidates. *Heart Lung* 1992; **21**: 434.
27. De Vito Dabbs A, Hoffman LA, Dauber JH, Zullo T, Iacono AT. Evaluating the reliability and validity of the Questionnaire for Lung Transplant Patients. *Prog Transplant* 2002; **12**: 191.
28. De Vito DA, Kim Y, Vensak J, Studer S, Iacono A. Validation and refinement of the Questionnaire for Lung Transplant Patients. *Prog Transplant* 2004; **14**: 338.
29. Hathaway D, Winsett R, Prendergast M, Subaiya I. The first report from the patient outcomes registry for transplant effects on life (PORTEL): differences in side-effects and quality of life by organ type, time since transplant and immunosuppressive regimens. *Clin Transplant* 2003; **17**: 183.

30. Vincenti F, Larsen C, Durrbach A, *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; **353**: 770.
31. Gijsbers van Wijk CM, Kolk AM. Sex differences in physical symptoms: The contribution of symptom perception theory. *Soc Sci Med* 1997; **45**: 231.
32. Kroenke K, Spitzer RL. Gender differences in the reporting of physical and somatoform symptoms. *Psychosom Med* 1998; **60**: 150.
33. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1913; **67**: 361.
34. Sermeus W, Delesie L. Ridit analysis on ordinal data. *West J Nurs Res* 1996; **18**: 351.
35. Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. *Control Clin Trials* 2004; **25**: 535.
36. Russ G, Jamieson J, Oberbauer J, *et al.* Three-year health-related quality-of-life outcomes for sirolimus-treated kidney transplant patients after elimination of cyclosporine. *Transpl Int* 2007; **20**: 875.
37. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int* 2006; **19**: 705.
38. Becker YT, Samangieo-Picota M, Sollinger HW. The emerging role of rituximab in organ transplantation. *Transpl Int* 2006; **19**: 621.

