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Original Investigation

Development of Focal Segmental Glomerulosclerosis Patient-Reported Outcome Measures: Symptom Diary and Symptom Impact Questionnaire

Susan D. Mathias, MPH,[1] Susan Vallow, MA,[2] Debbie S. Gipson, MS, MD,[3] Kevin S. Thorneloe, PhD,[4] and Dennis Sprecher, MD[2]

Background: Focal segmental glomerulosclerosis (FSGS) is a kidney disease that affects patients' functioning and well-being. This study aimed to develop patient-reported outcome questionnaires to measure patient experiences related to FSGS.

Study Design: Qualitative patient interviews to identify important symptoms and concepts (concept elicitation) formed the basis for the development of 2 questionnaires, one on symptoms and one on their impact. Additional qualitative interviews were implemented to evaluate/refine the questionnaires (cognitive debriefing). Transcripts of concept elicitation and cognitive debriefing interviews, conducted by telephone, were analyzed for concepts of interest using qualitative text analysis.

Setting & Participants: Patients with FSGS (aged 18-65 years with estimated glomerular filtration rates $\geq$ 40 mL/min/1.73 m^2) whose disease remained inadequately controlled after 2 or fewer courses of treatment.

Methodology: Qualitative concept elicitation and cognitive debriefing interviews.

Analytical Approach: Interview transcripts were analyzed using qualitative software, MAXQDA.

Results: 30 patients completed concept elicitation interviews; 9 patients completed cognitive debriefing interviews. Frequently mentioned symptoms included swelling from the waist down/legs/knees/feet/ankles (67%), fatigue (57%), stomach/abdomen swelling (43%), body pain/pressure (30%), and shortness of breath (20%), as well as impacts on physical (52%), emotional (68%), and social functioning (89%). Based on analyses of interview transcripts and clinical input, 2 questionnaires, one on symptoms and one on the impact of the symptom, were drafted. The 23-item FSGS Symptom Diary (assessing the frequency and severity of FSGS symptoms during the past 24 hours) and the FSGS Symptom Impact Questionnaire (17 items assessing interference with activities and emotions during the past 7 days) were iteratively revised based on cognitive debriefing interviews.

Limitations: The study was restricted to English-speaking adults located in the United States, and the concept elicitation interview group had a low number of African Americans.

Conclusions: The FSGS Symptom Diary and FSGS Symptom Impact Questionnaire are new FSGS-specific patient-reported outcomes measures designed to support a comprehensive assessment of symptoms and symptom impact in adults with FSGS. Future research is needed to evaluate their quantitative measurement properties.

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INDEX WORDS: Patient reported outcome (PRO); cognitive debriefing (CD); concept elicitation (CE); focal segmental glomerulosclerosis (FSGS); idiopathic FSGS; FSGS Symptom Diary; FSGS Symptom Impact Questionnaire; semi-structured interview; symptom impact; edema; swelling; side effect; qualitative research; kidney disease.

Assessing patients' views on their well-being without interpretation by clinicians by using patient-reported outcomes (PROs) has become increasingly important in clinical practice. In clinical trials, PROs as trial end points can enrich drug development and the approval process by incorporating the patient voice. Furthermore, in combination with routine clinical data, PRO data contribute to a comprehensive patient assessment and may inform clinical decision making.[1]

Focal segmental glomerulosclerosis (FSGS) is a condition that affects glomerular filtering and is characterized by excess urinary protein and glomerular scarring. The incidence of FSGS in the United States is estimated at 7 per million and as an underlying cause of nephrotic syndrome in 40% of adults and 20% of children, making a significant contribution to end-stage renal disease cases.[2,3]

Categorization of FSGS is as follows: primary/idiopathic (cause unknown), genetic, or secondary to

From [1]Health Outcomes Solutions, Winter Park, FL; [2]GlaxoSmithKline, Collegeville, PA; [3]University of Michigan, Ann Arbor, MI; and [4]NephCure Accelerating Cures Institute, King of Prussia, PA.

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Address correspondence to Susan Vallow, MA, MedAvante Inc, 100 American Metro Blvd #106, Hamilton Township, NJ 08619. E-mail: sue@vallow.com

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diseases/toxicities.[4] Prognosis highly depends on the level and persistence of proteinuria.[5-7] Type and severity of FSGS symptoms are reported to vary with extent of proteinuria; these symptoms include edema, fluid retention/weight gain, foamy urine, and shortness of breath.[5-7]

Despite the many impacts of FSGS, an expansive literature review revealed an absence of FSGS-specific PRO measures. The 36-Item Short-Form Health Survey (SF-36) has been used previously as a PRO questionnaire in studies of FSGS in adults.[8,9] Although the SF-36 measure may include questions relevant to patients with FSGS, SF-36 development did not commence with an elicitation of concepts important to the disease experience of patients with FSGS.[9]

We conducted this study according to current best practices[10] using qualitative research methods with patients with FSGS, with the goal of developing a content-valid FSGS-specific PRO measure for adults to accurately assess FSGS symptoms in support of a drug development program. The US Food and Drug Administration (FDA) PRO Guidance encourages that PRO measures be population specific, measure concepts important for both the targeted patients and context of use, and involve patients in qualitative research interviews of "concept elicitation" to understand what to measure and "cognitive debriefing" to ensure comprehensiveness and patient understanding of question items. In addition, we used expert clinical advisors to ensure that interview guide questions and questionnaire content were consistent with clinical experience. These are important first steps in the development of disease-specific PRO measures for use in clinical research and drug development, as used here for adults with primary FSGS.

METHODS

Overview

This was a prospective qualitative research study using concept elicitation interviews, qualitative analysis, PRO measure development, and semi-structured cognitive debriefing interviews to confirm that the items were relevant, comprehensive, and clear. The study protocol was approved by a central institutional review board (IRB) and local IRBs of participating centers.

Study Population

Patients were recruited through the University of Michigan, Harbor-UCLA Medical Center, NephCure Foundation, Nephrotic Syndrome Study Network (NEPTUNE) Patient Contact Registry, and referring nephrologists. The NephCure Foundation posted an IRB-approved advertisement on their website and sent an e-mail to its members in the United States, with both containing study information. Individuals were directed to a website to complete an Online Screening Questionnaire, which also included informed consent and medical release forms authorizing their nephrologist to complete a Clinical Case Report and a Background Demographic Questionnaire. Other patients were approached either in person or by telephone and screened by study staff. Eligible patients included men and women aged 18 to 65 years with a diagnosis of idiopathic FSGS confirmed by their treating physician, a maximum FSGS duration of 60 months before enrollment, estimated glomerular filtration rate $\geq$ 40 mL/min/1.73 m^2 at the most recent assessment before screening, for whom disease remained inadequately controlled after trying no more than 2 prior FSGS treatments (including steroids, calcineurin inhibitors, mycophenolate mofetil, or rituximab), and who were able to speak and read English, able to provide participation consent, and willing to participate in a 1-hour telephone interview. Individuals with any of the following conditions were excluded from the study: FSGS secondary to another condition, such as congenital heart anomaly; human immunodeficiency virus (HIV) infection; significant coexisting conditions (eg, malignancy, chronic obstructive pulmonary disease, or diabetes mellitus) that may influence reporting of FSGS symptoms; infection such as tuberculosis, or hepatitis B and C virus; and history of solid-organ or bone marrow transplantation.

The NephCure Foundation, academic institutions, referring nephrologists, and patients were remunerated at a fair market rate.

Patient Interviews and PRO Development

Based on literature review findings (no adequate measures available), concept elicitation interviews, and clinical advisor input, 2 questionnaires were drafted: the FSGS Symptom Diary and FSGS Symptom Impact Questionnaire.

Concept Elicitation Interviews

The concept elicitation interviews were conducted by telephone using a semi-structured interview guide developed specifically for this study. The interview guide contained open-ended questions about the patient's general health, FSGS diagnosis, current FSGS treatments, FSGS symptoms, treatment side effects, symptom management, and physical, emotional, and social functioning. Representative questions included: "Some people with FSGS have symptoms or side effects as a result of their disease or treatment. Have you ever experienced any symptoms or side effects? If yes, please describe (frequency, duration, severity, impact on daily activities). Are/were these symptoms/side effects related to FSGS or due to your treatment? How do you know? Are there any symptoms that you had previously that you don't have now? If yes, do you know what made them go away? Please describe." Patients' experiences with FSGS symptoms and symptom impacts were used to develop a draft conceptual framework for the FSGS Symptom Diary and FSGS Symptom Impact Questionnaire.

Cognitive Debriefing Interviews

The content of the FSGS Symptom Diary and FSGS Symptom Impact Questionnaire was evaluated via cognitive debriefing interviews to patients with FSGS. A semi-structured interview guide was developed and used to evaluate content, clarity, comprehensiveness, and relevance of the questions in the 2 newly developed PRO measures. During cognitive debriefing interviews, patients were asked how they interpreted the instructions, items, and response options; whether they had suggestions to revise for clarity; and whether there were any missing, irrelevant, or inappropriate items. Based on feedback, the 2 PRO measures were revised iteratively and then finalized. An item-tracking matrix was developed to document changes made based on cognitive debriefing interviews and included the rationale for revisions.

Data Analyses

Interviews were recorded, transcribed, and analyzed using the qualitative research software MAXQDA (VERBI GmbH).