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Development and Content Validity Testing of a Patient-Reported Treatment Acceptance Measure for Use in Patients Receiving Treatment via Subcutaneous Injection

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ABSTRACT

Background: New therapies in development for lowering low-density lipoprotein cholesterol, such as alirocumab, require administration by subcutaneous injections. There is a need to assess the acceptance of such treatments and their mode of administration. **Objectives:** To develop a novel patient-reported outcome measure, the Injection-Treatment Acceptance Questionnaire (I-TAQ), and assess its content validity using qualitative methods. **Methods:** Concepts generated from a literature and instrument review informed the initial drafting of 17 items in the I-TAQ, with item wording adapted from three existing instruments. Three rounds of qualitative interviews were conducted with 29 US-English speaking patients at high cardiovascular risk. Concept elicitation questioning was used to explore patients' treatment experiences followed by cognitive debriefing of the I-TAQ using "think-aloud" methods. Verbatim transcripts were analyzed using thematic analysis. **Results:** Qualitative analysis of concept elicitation data identified the following relevant concepts: perceived efficacy, side effects, self-efficacy, convenience, and overall acceptance. Seven (24%) patients discussed an initial fear of needles, but described this as subsiding with no impact on adherence. Five items were added after round one interviews, three of which were retained after round two testing in which two further items were added, forming the conceptually comprehensive 22-item I-TAQ. Patients demonstrated good understanding of item wording, instructions, response scales, and recall period. **Conclusions:** Successive rounds of in-depth interviews resulted in a treatment acceptance measure with strong content validity. Pending demonstration of its psychometric properties, the I-TAQ may prove to be a valuable measure of patients' perspectives toward being treated with low-density lipoprotein cholesterol–lowering therapies requiring subcutaneous injections.

Keywords: acceptance, instrument development, patient-reported outcome, qualitative research.

Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) levels are associated with an increase in the risk of cardiovascular (CV) events, including myocardial infarction, unstable angina, need for coronary revascularization procedures, ischemic stroke, and death. Evidence from numerous randomized clinical trials have demonstrated that LDL-C reduction, via statin- and non–statin-based therapies, leads to a reduction in CV events [1–5]. Recently, treatment with monoclonal antibodies to proprotein convertase subtilisin–kexin type 9, such as alirocumab, has been shown to reduce LDL-C levels in phase 3 studies with populations at moderate to very high levels of baseline CV risk who are being treated with statins or are unable to tolerate statins [6,7]. These therapies are being further tested for their impact on reducing CV outcomes [8]. These agents, however, require patients to self-administer the medication with subcutaneous injections, a treatment strategy that has seldom been used in the management of CV disease. Given the novelty of this treatment strategy, understanding patients' perspectives about using injection treatments, as opposed to oral medications, is important, but difficult to quantify with existing measures.

The aim of this work was to develop a patient-reported outcome (PRO) to assess patients' acceptance of a subcutaneous injection treatment for lowering LDL-C in a high CV risk population, following the Food and Drug Administration patient-reported outcome guidance as a framework [9]. A literature review, followed by three rounds of patient interviews, was

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conducted to develop and assess the content validity of a newly drafted measure, the Injection-Treatment Acceptance Questionnaire (I-TAQ).

Methods

Drafting of the I-TAQ

The first conceptual step was to consider whether it would be more appropriate to assess patient "satisfaction" or "acceptance" toward an injection treatment for an asymptomatic condition as both concepts have been used in previous studies of populations receiving injectable treatments [10,11]. Given the asymptomatic nature of hypercholesterolemia, it was felt to be more appropriate and relevant to assess whether patients are willing to "accept" taking their injection treatment, as opposed to asking patients how "satisfied" they are with having to inject a treatment.

After defining the overall measurement concept the conceptual domains of the Health Belief Model were used as a framework for developing the I-TAQ, including perceived severity, perceived susceptibility, perceived benefits, perceived barriers, modifying variables, cues to action, and self-efficacy [12]. In addition, five existing PRO instruments of greatest relevance were identified from the literature and reviewed in detail: the Treatment Satisfaction Questionnaire for Medication (TSQM) [13], the Treatment Satisfaction with Medication Questionnaire (SATMED-Q) [14], the Preference and Satisfaction Questionnaire (PSQ) [15], the Self-Injection Assessment Questionnaire (SIAQ) [16], and the Acceptance by the Patients of their Chronic Treatment Acceptance Questionnaire (ACCEPT) [17]. The instruments, however, were not deemed to have appropriate content validity for this population as none was adequately focused on assessing treatment acceptance *specifically in relation to injection treatments*. Therefore, it was felt that patients' concerns or experiences related to this treatment modality might not be adequately captured. In addition, the unique nature of elevated LDL-C level as a "silent" condition warranted a renewed effort to understand patients' perspectives of using subcutaneous injection therapies. Initial items were therefore drafted to capture relevant concepts identified from the literature and existing instruments and within the constructs articulated in the Health Belief Model.

Qualitative Study Design

A non-interventional qualitative study was conducted with 29 US-English speaking patients at high CV risk who had experience of self-administering their treatment for lowering LDL-C every 2 weeks via subcutaneous injection. Qualitative face-to-face interviews were conducted in three rounds (n = 9, n = 10, and n = 10 patients in each round, respectively) by trained interviewers and were audio recorded. The first two rounds involved patients who had self-administered their treatment with pre-filled pens (PFPs; n = 19), and the last round involved patients who had self-administered their treatment with pre-filled syringes (PFSs; n = 10). Interim analysis was performed after each round of interviews to enable consideration of additional items and subsequent testing of revisions. The first part of each interview, conducted before the patient had been shown the questionnaire, focused on concept elicitation. The second part focused on cognitive debriefing of the I-TAQ.

Patient recruitment

All participants were recruited through purposeful sampling from either a randomized double-blind, placebo-controlled clinical trial or an open-label extension trial for alirocumab. Inclusion criteria for the interview study required all patients to have been diagnosed with elevated LDL-C, be 18 years of age or older, and have experience of self-administering alirocumab or placebo via PFP or PFS. Quotas relating to diagnosis (heterozygous familial hypercholesterolemia, high or very high CV risk), treatment, ethnicity, and education were used to recruit a sample with a broad range of clinical and demographic characteristics. Categorization of high and very high CV risk was based on the National Cholesterol Education Program Adult Treatment Panel III guidelines [18].

Concept elicitation

To support the capture of a broad range of concepts articulated in the Health Belief Model, an interview guide was constructed containing a number of broad, open-ended, and non-leading questions to guide the interviewer (see Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.09.2937). The questions were designed to encourage patients to describe their experiences using their own language and to prohibit any possible bias. The discussions were exploratory and focused on eliciting spontaneous comments from patients regarding their treatment experience and the factors that (positively or negatively) affected their treatment acceptance and adherence. If the patients did not spontaneously mention a concept of interest identified from the literature in response to the broad questioning, more direct questions were used to explore that concept toward the end of the interview. In addition, the relevance of the concepts 'satisfaction' and 'acceptance' was explored with patients in terms of how they described their treatment experience.

Cognitive debriefing

After the concept elicitation (CE) section of the interview, cognitive debriefing (CD) was performed. Patients were asked to complete the I-TAQ using a "think-aloud" approach, requiring the patients to read each instruction, question, response option, and recall period out loud while verbally sharing their reasoning for selecting each response [19,20]. Patients were also asked detailed debriefing questions about their understanding of terms and response scale wording, relevance of concepts, and appropriateness of the response options and the recall period. More time was spent on the CE part of the interview in round one to ensure all relevant and important concepts were captured. As saturation was achieved, more time was spent on thoroughly debriefing the I-TAQ, and revisions made following interim analysis, in the subsequent interviews.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved and overseen by a centralized independent review board in the United States (reference: ADEL-13-347). Written informed consent was obtained from all participants before the collection of any data and before any study-related activities.

Qualitative Analysis

All interviews were transcribed verbatim with all identifiable information removed to protect anonymity of the patients. Thematic analysis of the verbatim transcripts was performed using computer-assisted qualitative data analysis software, ATLAS.Ti [21], and each transcript was quality assessed, coded, and analyzed by the researchers. Using an inductive approach, a code list was created and adapted as new codes were added [22]. Patient quotes were grouped by code/theme to enable findings to be summarized and conclusions drawn. Saturation of concepts was evaluated for the CE results, defined as the point at which no