Original Research

Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach

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ABSTRACT

Purpose: Telotristat etiprate, a tryptophan hydroxylase inhibitor, was previously evaluated in a Phase II randomized, placebo-controlled clinical trial in patients with carcinoid syndrome (CS) and diarrhea not adequately controlled by octreotide. The objective of the current study was to characterize the symptom experiences of patients participating in that trial.

Methods: Consenting patients participated in one-on-one, qualitative interviews focused on eliciting symptoms they had experienced in association with their CS diagnosis and recollection of symptom changes they experienced while participating in the Phase II trial.

Findings: Among the 23 patients who participated in the previous 4-week dose-escalation study, 16 were eligible for interviews and 11 participated in the present study. The median time from study completion to the interview was 31 months; 4 of 11 patients were receiving telotristat etiprate in a follow-up, open-label trial at the time of interview. All of the patients (100%) described diarrhea as a symptom of CS, with effects on the emotional, social, and physical aspects of their lives. Improvement in diarrhea during the study was described by 82% of participants, and was very impactful in several patients. Results led to the design and implementation of a larger interview program in Phase III and helped to establish a definition of *clinically meaningful change* for the clinical development program.

Implications: The diarrhea associated with CS can have a large impact on daily lives, and patient interviews can characterize and capture clinically meaningful improvements with treatment. ClinicalTrials.gov Identifier: NCT00853047. (*Clin Ther*. 2016;38:759–768) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

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INTRODUCTION

Neuroendocrine tumors (NETs) are thought to arise from neuroendocrine cells and are often found in the gastrointestinal tract; these tumors occur in ~2 per 100,000 persons.[1] Approximately 3 in 10 people with NETs will develop symptoms known as *carcinoid syndrome* (CS).[2] Patients with CS generally have advanced, metastatic disease and a survival rate lower than that in patients without CS.[3] Common symptoms of CS include diarrhea; flushing of the upper chest, neck, and face; abdominal pain; difficulty breathing; and heart valve dysfunction.[4]

Because CS is relatively rare, there is little experience in formally characterizing the condition with standardized patient-reported outcomes questionnaires. Furthermore, clinical trials in CS have small sample sizes, making it difficult to capture statistically significant and clinically meaningful changes with standardized instruments. In this situation, careful review of individual responses becomes especially important, and an interview approach in which the patient can provide a first-hand description of their clinical trial experience is particularly valuable.

Telotristat etiprate is a tryptophan hydroxylase inhibitor developed to treat CS by reducing the production of serotonin within the metastatic neuroendocrine tumor cell. Initial evidence of efficacy was obtained in a 4-week placebo-controlled Phase II clinical study of telotristat etiprate.[5] In that study, patients were treated in escalating-dose cohorts, and were randomly assigned in a 3:1 ratio to receive either telotristat etiprate or placebo. Clinical response (defined as at least a 50% reduction in bowel movement frequency for at least 2 weeks) was observed in 5 of 18 patients (28%) treated with telotristat etiprate compared with 0 of 5 patients on placebo. There was only 1 overall evaluation of the patient experience, a weekly question (with a "yes" or "no" answer) about the presence of adequate relief of gastrointestinal symptoms of CS. Adequate relief was reported in 10 of 18 telotristat etiprate–treated patients (56%) during at least 1 of the first 4 weeks of treatment, compared with zero patients on placebo.

While these observations clearly suggested that telotristat etiprate has biological activity, key questions remained as to the clinical relevance of these findings. Furthermore, the optimal strategy to assess patient-reported outcomes in Phase III clinical development was unclear. To help address these issues, retrospective interviews of Phase II clinical trial participants were performed.

The objectives of the interviews were to characterize the participants' CS experiences and to identify the important changes they experienced in their symptoms during the clinical trial of telotristat etiprate, during the 4-week, blinded, dose-escalation phase and/or the open-label extension phase.

PATIENTS AND METHODS

Participants

All recruiting sites from the Phase II clinical trial (LX1606.202)[5] were invited to join the present qualitative interview study, and 2 of the 8 sites chose to participate. A member of each site's study staff contacted potential participants to explain the purpose, procedures, benefits, and risks of the present interview-based study using a standardized recruitment script. If the patient was interested in participating, the site's staff member documented eligibility and obtained written informed consent and the participant was scheduled for an interview. All study procedures were approved by an institutional review board.

Participants meeting the following inclusion criteria were eligible for the study: participation in the previous telotristat etiprate Phase II clinical trial[5]; 18 years of age or older; able to participate in a one-on-one telephone interview; able to read, speak, and understand English and complete all study assessments; and willing and able to provide written informed consent before the interview. Participants with a cognitive or other impairment (eg, vision or hearing) that would have interfered with completing the interview were not eligible for the study.

Interview Procedures

Before each participant's telephone interview, he or she received a packet that contained an introductory letter, the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal NET questionnaire (GI.NET-21),[6,7] the EORTC Quality of Life (QOL) Questionnaire (QLQ-C30; EORTC 2012),[8] and a Sociodemographic and Clinical Characteristics form. The questionnaires were in a sealed envelope and participants were directed not to open these materials until instructed to do so by the interviewer. Participants were asked to return the materials at the conclusion of the interview.

Trained and experienced interviewers, blinded to treatment arm, conducted the one-on-one interviews over the telephone using a prescripted interview