Changes in Weight Associated With Telotristat Ethyl in the Treatment of Carcinoid Syndrome

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ABSTRACT

Purpose: In the placebo-controlled Phase III TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) trial, the oral tryptophan hydroxylase inhibitor telotristat ethyl significantly reduced bowel movement (BM) frequency during a 12-week, double-blind treatment period in 135 patients with metastatic neuroendocrine tumors with carcinoid syndrome and ≥4 BMs per day. Patients (mean [SD] age, 63.5 [8.9] years; mean [SD] body mass index, 24.9 [4.9] kg/m^2) received placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg 3 times per day (TID) in addition to somatostatin analogue therapy. Weight loss is associated with uncontrolled carcinoid syndrome and may be associated with reduced survival.

Methods: Assessment of the occurrence of weight change ≥3% at week 12 was prespecified in the statistical analysis plan.

Findings: In 120 patients with weight data available, weight gain ≥3% was observed in 2 of 39 patients (5.1%) taking placebo TID, 7 of 41 (17.1%) taking telotristat ethyl 250 mg TID, and 13 of 40 (32.5%) taking telotristat ethyl 500 mg TID ($P = 0.0017$) at week 12. Weight loss ≥3% was observed in 5 of 39 patients (12.8%) taking placebo TID, 4 of 41 (9.8%) taking telotristat ethyl 250 mg TID, and 6 of 40 (15.0%) taking telotristat ethyl 500 mg TID ($P = 0.77$). Biochemical and metabolic parameters of serum albumin and cholesterol significantly increased ($P = 0.02$ and $P = 0.001$, respectively) in patients gaining weight and decreased in patients who lost weight, suggesting an improvement in overall nutritional status.

Implications: Up to 32.5% of patients treated with telotristat ethyl experienced significant, dose-dependent weight gain, associated with reduced diarrhea severity and improved biochemical and metabolic

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parameters. Improved nutritional status could be an additional aspect of telotristat ethyl efficacy among patients with functioning metastatic neuroendocrine tumors. ClinicalTrials.gov identifier: NCT01677910. (*Clin Ther*. 2018;40:952–962) © 2018 The Authors. Published by Elsevier HS Journals, Inc. (*Clin Ther*. 2018;40:952–962) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: carcinoid syndrome, carcinoid syndrome diarrhea, malnutrition, neuroendocrine tumor, telotristat ethyl, weight.

INTRODUCTION

Telotristat ethyl is used to treat patients with neuroendocrine tumors (NETs) with carcinoid syndrome not adequately controlled by somatostatin analogs (SSAs).[1] Telotristat ethyl is an inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis that converts tryptophan to 5-hydroxytryptophan, which is subsequently converted to serotonin. Treatment with telotristat ethyl significantly reduces both urinary 5-hydroxyindole acetic acid (u5-HIAA) concentrations and bowel movement (BM) frequency compared with placebo.[1–3] Telotristat ethyl, in combination with SSA therapy, was recently approved for adults in the United States and Europe for the treatment of carcinoid syndrome diarrhea inadequately controlled by SSAs.[4,5]

Generally, weight loss is a manifestation of advanced malignancy and is evident in patients with carcinoid syndrome, who may experience profound diarrhea. Incidence of weight gain was added as an exploratory analysis in the TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) study to determine the effects of telotristat ethyl on weight. We report dose-dependent effects of treatment with telotristat ethyl on changes in weight, metabolic parameters, and patient-reported outcomes during the 12-week double-blind treatment period of the Phase III TELESTAR clinical trial.

PATIENTS AND METHODS

Patients

The TELESTAR study cohort has been described in detail previously.[1] Eligible patients were at least 18 years of age, had a histopathologically confirmed diagnosis of a metastatic NET, had a documented history of carcinoid syndrome with at least 4 BMs per day, and were receiving treatment with long-acting SSAs for ≥3 months before enrollment. Detailed inclusion and exclusion criteria have been published previously.[1]

Study Design and Treatment

Eligible patients entered a screening period of 3 or 4 weeks, depending on their SSA dose schedule, to establish baseline symptoms. Patients were randomly assigned 1:1:1 to orally receive placebo 3 times per day (TID), telotristat ethyl 250 mg TID, or telotristat ethyl 500 mg TID for the 12-week double-blind treatment period. Treatment with SSAs was continued. Rescue use of short-acting octreotide and antidiarrheal agents was unrestricted, but there was no significant difference in use among the treatment arms.[1] Downward dose adjustment of telotristat ethyl was not allowed during the double-blind treatment period. The study was approved by the respective institutional review boards or ethics committees at the participating centers. All patients gave written informed consent. The study complied with the ethical principles of the Declaration of Helsinki and with Good Clinical Practice guidelines.[6]

The study drug dosage form consisted of white-coated, debossed oval tablets that contained 250 mg of telotristat ethyl or matching inactive placebo of microcrystalline cellulose. There was no taste reported for the tablets. During the dose-escalation phases, the assigned study drug was provided in 8-day blister packs that contained 6 columns and 8 rows for a total of 48 tablets. After the dose-escalation phase, patients received their assigned study drug in 100-mL high-density polyethylene bottles with child-resistant polypropylene screwcaps and heat-induction seal liners. There was no official assessment of the success of matching performed.

Prior medical histories (before enrollment) were reviewed relating to weight gain, weight loss, and nutritional status by searching for relevant conditions among the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes of Gastrointestinal Disorders, General and Nutritional Disorders, and Metabolic Parameters. The potential associations of weight change with BM frequency reduction and changes in u5-HIAA concentrations were examined. Patient-reported outcomes were examined with the European Organisation for