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Endocrinology

TELEPRO: Patient-Reported Carcinoid Syndrome Symptom Improvement Following Initiation of Telotristat Ethyl in the Real World

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine tumors • Carcinoid tumor • Malignant carcinoid syndrome • Telotristat ethyl • Octreotide • Lanreotide

Abstract

Background. When carcinoid syndrome (CS) diarrhea (CSD) is inadequately controlled with long-acting somatostatin analogs (SSAs), clinical practice guidelines recommend addition of the tryptophan hydroxylase inhibitor telotristat ethyl (TE). In a 12-week multinational, randomized controlled trial, TE added to SSA reduced peripheral serotonin and the frequency of CSD. We evaluated real-world effectiveness of TE using patient-reported data from a nurse support program over 3 months.

Materials and Methods. This study used a deidentified data set of patients initiating TE who opted into a nurse support program between March and November 2017 and reported CS symptom burden at baseline and at least one follow-up time point at months 1, 2, and 3. Patients reported demographic and medical history information as well as frequency of bowel movements (BMs) and flushing episodes, severity of nausea, urgency and abdominal pain (0 "no/not at all" to 100 "worst imaginable/very urgent"), and stool form (1 "very hard" to 10 "watery"). Mean changes from baseline in CS symptom burden were reported using paired-sample *t* tests and Wilcoxon signed-rank tests.

Results. Most patients initiating TE enrolled in the nurse program (791/898, 88%), of whom 369 (47%) were included in the analysis. Patients treated with TE reported significant reductions in CSD and other CS symptoms (all $p < .001$). At least half of patients treated with TE experienced ≥30% improvement from baseline in BM frequency and an average reduction of at least two BMs per day within 3 months.

Conclusion. Patients taking SSA therapy showed substantial burden of disease before initiating TE and significant improvements with the addition of TE treatment in this real-world effectiveness study. ***The Oncologist*** 2019;24:1446–1452

Implications for Practice: Patients with carcinoid syndrome diarrhea uncontrolled by high doses of long-acting somatostatin analogs may be candidates for additional therapy with the tryptophan hydroxylase inhibitor telotristat ethyl. Understanding the real-world prevalence of uncontrolled symptoms and the effectiveness of telotristat ethyl in clinical practice may further support clinical and policy decisions for these patients. This study investigated self-reported carcinoid syndrome symptom burden and improvements among patients initiating telotristat ethyl and participating in a voluntary nurse support program. Disease burden and off-label somatostatin analog treatment before initiating telotristat ethyl were high, and symptoms improved markedly over 1, 2, and 3 months of treatment.

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Introduction

Carcinoid syndrome (CS) is known to cause significant clinical morbidity with substantial effects on quality of life [1–4]. Patients with carcinoid syndrome diarrhea (CSD) require more medical care and have more hospitalizations and higher health care costs than their peers without CSD [5]. The prevalence of pretreatment CS symptoms among patients enrolled in a recent phase III clinical trial was considerable, including bowel movement-related issues (97%), flushing (86%), and abdominal pain (63%) [2]. The majority of patients (80%) reported meaningful reductions in quality of life and work productivity (43%) [2].

Since the 1980s, somatostatin analog (SSA) therapy has been the first-line medical management approach for CS symptoms and CSD [6–8]. Approximately 60% of patients may be responsive to initial SSA long-acting release (LAR) treatment, but they have shown a loss of effect over time, resulting in refractory symptoms [9–12]. Other treatment options with the potential to palliate CS or delay its progression include hepatic arterial embolization and peptide receptor radiotherapy, which are generally recommended for patients with radiographic progression rather than those with symptom progression in the setting of stable disease [13].

Telotristat ethyl (TE; Xermelo, Lexicon Pharmaceuticals, Inc., The Woodlands, TX) is a novel oral tryptophan hydroxylase inhibitor that mediates the rate-limiting step in serotonin biosynthesis [14]. TE reduces the production of peripheral serotonin, which helps to mediate the secretion, motility, and inflammation of the gastrointestinal tract, and, in turn, TE reduces the frequency of CSD. TE is approved for the treatment of CSD in combination with SSA therapy in adults whose CSD is not adequately controlled by SSA alone [14]. TE demonstrated significant reductions in daily bowel movement frequency and improvements in other markers of disease among patients with refractory CSD in the randomized, controlled, 3-month phase III pivotal TELESTAR study [15]. TE is recommended in combination with long-acting SSA therapy for persistent CSD in the National Comprehensive Cancer Network (NCCN) Guidelines for Neuroendocrine and Adrenal Tumors (Version 3.2018) and in the NCCN Drugs & Biologics Compendium [13, 16]. The 2017 consensus guideline of the North American Neuroendocrine Tumor Society for midgut neuroendocrine tumors recommends TE in patients with stable radiographic disease and refractory CSD before escalating SSA doses, adding short-acting octreotide, or using nonspecific antidiarrheals [17].

Although TELESTAR was the largest study conducted in patients with CS, the analytic sample was still too small for robust evaluation of secondary endpoints. As with other medical interventions, patient selection, treatment administration, and compliance differ between clinical trials and clinical practice. We investigated patient-reported burden and treatment benefits using a large sample of patients initiating TE in clinical practice over a 3-month period.

Materials and Methods

Analysis of data collected through a nurse support program was conducted to assess patient-reported CSD and CS symptom burden before initiating TE and over 3 months of TE treatment. Because TE is distributed by a specialty pharmacy, patients had the option to participate in the specialty pharmacy nurse support program at the time of first TE prescription fill. Nurse support programs are common offerings designed to help patients properly administer and manage advanced therapeutics distributed by specialty pharmacies. Patients who voluntarily opted into the nurse program provided basic demographic and clinical information (e.g., functional status, time since diagnosis, type and frequency of SSA therapy), including disease burden and current treatment before initiating TE (baseline).

During monthly follow-up nurse calls, patients reported their current CS symptom burden at 1, 2, and 3 months after initiating TE. Data were collected during telephone interviews as part of the nurse program from March through November 2017. Non-English speakers could participate by using the translation service provided by the specialty pharmacy for all of its patient interactions. The primary objective was to assess changes in patient-reported daily bowel movement (BM) frequency from baseline. Secondary objectives included other diarrhea-related (urgency and stool form) and CS symptom-related burden (daily flushing episodes, nausea, and abdominal pain). Frequency of BM and flushing episodes were reported as number of events or episodes per day. Stool form was reported on a scale of 1 ("very hard") to 10 ("watery"). Nausea, urgency, and abdominal pain were reported on a scale of 0 ("no/not at all") to 100 ("worst imaginable/very urgent"). CS symptom improvements were also evaluated among patients who did or did not experience meaningful reduction in daily BM frequency.

Patients could discontinue their participation in the nurse support program at any time after TE initiation if they did not require clinical advice or did not have questions about TE treatment. To be included in the final analysis, patients had to be on TE for 3 months (determined by shipment of TE to the patient by the specialty pharmacy) and contribute clinical symptom data at baseline prior to TE initiation and at least one other time point in the follow-up period. Each patient served as his or her own control. A sample size of 62 participants was required to detect a significant difference ($\alpha = .05$) in daily BM episodes based on the sample size calculations used for the TELESTAR trial (effect size, 50%; SD, 1.4) [15].

Descriptive statistics were used to report patient demographic and clinical characteristics including medical and treatment history. Univariate statistics using paired-sample *t* tests and Wilcoxon signed-rank tests were conducted to evaluate changes from baseline. We evaluated the number of patients experiencing at least 30% improvement from baseline, as reported to be a meaningful threshold for improvement by TELESTAR participants and as approved by the U.S. Food and Drug Administration as an acceptable threshold for clinical effect [18, 19]. A cumulative distribution function was conducted to evaluate the proportion of patients achieving different levels of BM frequency reduction from baseline. We also evaluated improvements in CS symptoms in the overall TE population and among those who did and did not achieve BM frequency reductions. Missing data were computed using the last observation carried forward methodology. These analyses

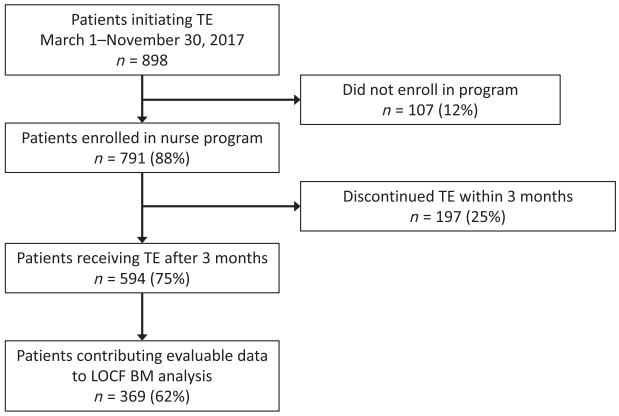

Figure 1. Patient attrition.
Abbreviations: BM, bowel movement; LOCF, last observation carried forward; TE, telotristat ethyl.

Table 1. Reported adverse events related to reasons for study discontinuation

Reported adverse event or side effect	Proportion of patients, %
Nausea	21.2
Constipation	17.6
Abdominal pain	13.3
Diarrhea	13.3
Malaise	10.3
Vomiting	10.3
Headache	9.1
Abdominal pain, upper	4.8

were conducted in a deidentified data set with no patient identifiers. The study was determined to be exempt from institutional review board oversight (Advarra, Columbia, MD).

Results

Of the 898 patients initiating TE during the study period, 791 (88%) enrolled in the nurse support program and provided baseline survey responses. Seventy-five percent (n = 594) of patients received 3 months of TE shipments from the specialty pharmacy, whereas 25% (n = 197) discontinued TE shipments within 3 months of initiation (Fig. 1). The top five reasons reported by the specialty pharmacy for stopping shipment of TE to the patient were side effect or adverse event (21%), patient decision (19%), unable to contact patient (16%), prescriber decision (14%), and patient deceased (8%). The most frequently reported adverse events related to discontinuation are provided in Table 1. Among the 25% of patients who discontinued within 3 months, 3.2% reported "drug ineffective" and 1.5% reported "off-label use" as a reason. Of the 594 patients that were enrolled in the nurse support program and received TE for 3 months, 369 patients met all study criteria and were included in the analysis.

Demographic and clinical characteristics including SSA treatment and baseline CS symptom burden were similar among those enrolled in the nurse support program, those who discontinued within the first 3 months of TE initiation, and those included in the analysis cohort (Table 2). Approximately half of enrolled patients were women (55%), the average age was 65 years, and most patients had commercial (42%) or Medicare (37%) insurance as their primary insurer. Patients had been diagnosed with CSD for an average of 6 years, and the majority (92%) were taking long-acting SSA therapy. Patients reported average baseline long-acting SSA doses of 41 mg (±25.6 mg) for octreotide LAR and 117 mg (±27.3 mg) for lanreotide. Nearly one-third (27%) of all patients and of those in the analysis cohort (29%) were receiving above-label doses of octreotide (>30 mg) or lanreotide (>120 mg) or above-label dosing frequency (more than one dose every 4 weeks). Mean (±SD) baseline patient-reported functional status according to Eastern Cooperative Oncology Group performance status was 1.4 (±0.65).

At baseline, patients receiving SSA therapy reported substantial burden of CS diarrhea with a mean (±SD) of 6.3 (±3.47) bowel movements per day and a mean (±SD) urgency severity score of 29.7 (±34.59; Table 2). Patients reported approximately three flushing episodes per day and a mean (±SD) nausea severity score of 39.4 (±26.29). Patients receiving TE demonstrated consistently significant improvements from baseline in diarrhea-related symptoms (Fig. 2) and in other CS symptoms (Fig. 3; all $p < .001$).

Approximately half of patients treated with TE experienced at least 30% improvement from baseline in BM frequency at months 1 (51%), 2 (55%), and 3 (54%). At the end of month 3, at least half of patients treated with TE (52%) experienced a reduction of at least two BMs per day, and nearly one-quarter of all patients treated with TE had a reduction of at least four BMs per day (Fig. 4). The majority of patients with meaningful reduction of BM frequency at month 3 also had improvements in secondary CS symptoms, including urgency (83%), nausea (79%), stool form (75%), flushing (64%), and abdominal pain (58%; Fig. 5). Approximately half of those who did not experience reductions in daily BM frequency reported improvements in urgency (58%), nausea (73%), stool form (49%), flushing (50%), and abdominal pain (44%; Fig. 5).

Discussion

This real-world effectiveness study showed that patients receiving standard of care SSA LAR therapy had substantial symptomatic CS burden. Over a 3-month period, the addition of TE to SSA LAR significantly improved CSD and other CS-related symptoms. After 3 months of TE therapy, the majority of patients who completed at least one follow-up interview had a reduction of at least two BMs per day, and one-quarter reported at least four fewer BMs per day. Urgency severity scores averaged 29.7/100 at baseline and showed improvements ranging from 63% to 85%. Baseline daily BM frequency reported in this study was comparable to that of the TELESTAR population receiving TE 250 mg (mean 6.1 vs. 6.3, respectively), and the observed benefit was slightly higher in this study compared with the TE 250 mg arm in TELESTAR (1.7 vs. 2.1 reduction in daily BMs) over 3 months [15].

Table 2. Patient characteristics and CS symptoms prior to initiating TE for patients enrolled in the nurse support program[a]

Characteristic	All patients treated with TE (*n* = 791)	Analysis cohort (*n* = 369)	Discontinued TE (*n* = 197)
Female, *n* (%)	433 (55%)	204 (55%)	114 (58%)
Age, mean (SD)	65.2 (11.79)	65.7 (11.07)	65.1 (11.51)
Insurance type, *n* (%)			
Commercial	336 (42%)	137 (37%)	91 (46%)
Medicare	292 (37%)	151 (41%)	79 (40%)
Medicaid	30 (4%)	19 (5%)	5 (3%)
Other or missing	133 (17%)	62 (17%)	22 (11%)
Number of years since diagnosis, *n*, mean (SD)	657, 6.3 (5.8)	324, 5.8 (5.24)	36, 7.1 (4.18)
SSA IR therapy, *n* (%)	63 (8%)	29 (8%)	12 (6%)
Long-acting SSA therapy, *n* (%)			
Octreotide	491 (62%)	240 (65%)	123 (62%)
Lanreotide	206 (26%)	100 (27%)	51 (26%)
Above-label dosing[b]	212 (27%)	106 (29%)	—
None	94 (12%)	29 (8%)	23 (12%)
CS symptom burden, *n*, mean (SD)			
Daily bowel movement frequency	770, 6.3 (3.47)	359, 6.3 (3.30)	192, 6.3 (3.48)
Urgency severity score (1–100)	744, 29.7 (34.59)	346, 33.9 (37.13)	187, 28.7 (34.10)
Stool consistency score (1–10)	777, 6.7 (2.02)	365, 6.6 (1.88)	192, 6.8 (2.02)
Abdominal pain score (1–100)	527, 19.7 (25.41)	250, 22.6 (26.79)	130, 19.4 (22.63)
Nausea severity score (1–100)	144, 39.4 (26.29)	77, 40.3 (28.49)	34, 38.4 (26.94)
Daily flushing episodes	633, 2.9 (3.13)	300, 3.0 (3.26)	152, 3.1 (3.09)

[a]Data are not available for patients who did not enroll in the nurse support program.
[b]Defined as octreotide dose >30 mg, lanreotide dose >120 mg, or dosing frequency greater than one dose every 4 weeks.
Abbreviations: —, not available; CS, carcinoid syndrome; IR, immediate release; SSA, somatostatin analog; TE, telotristat ethyl.

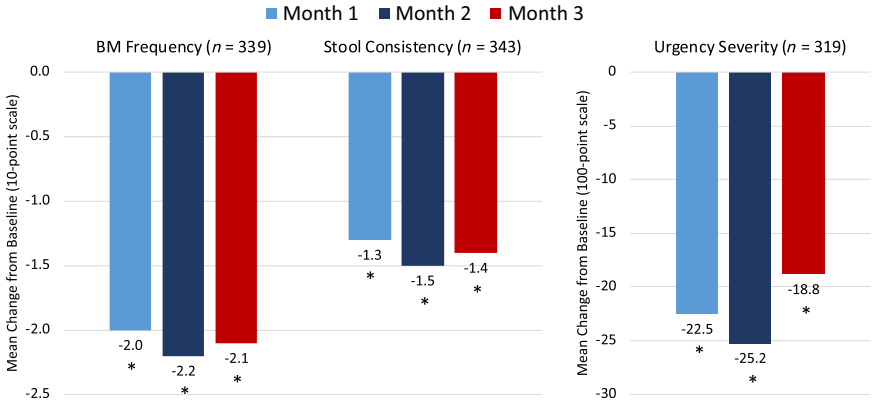

Figure 2. Carcinoid syndrome diarrhea symptom-related changes from baseline through 3 months. The symbol * indicates a significance level of $p < .001$.
Abbreviation: BM, bowel movement.

Other CS symptoms showed similar baseline burden and improvement patterns as diarrhea-related symptoms, with substantial ranges of improvement across 3 months of TE treatment in daily flushing episodes (41%–52% reductions), abdominal pain severity (67%–84% reductions), and nausea severity (69%–82% reductions). Among patients with meaningful reductions in daily BM frequency, the majority also reported meaningful improvements in all other CS symptoms (58%–83%).

Patient-reported burden of CS has been collected using standardized scales and instruments in clinical trials but seldom characterized among patients with CS receiving care in clinical practice. This study contributes meaningful observations of CS symptom burden among these patients in the real-world clinical practice setting. Nearly all patients included in the analysis cohort were taking some form of long-acting SSA therapy at baseline (92%), with CSD and other symptoms persistent even though 30% of the patients

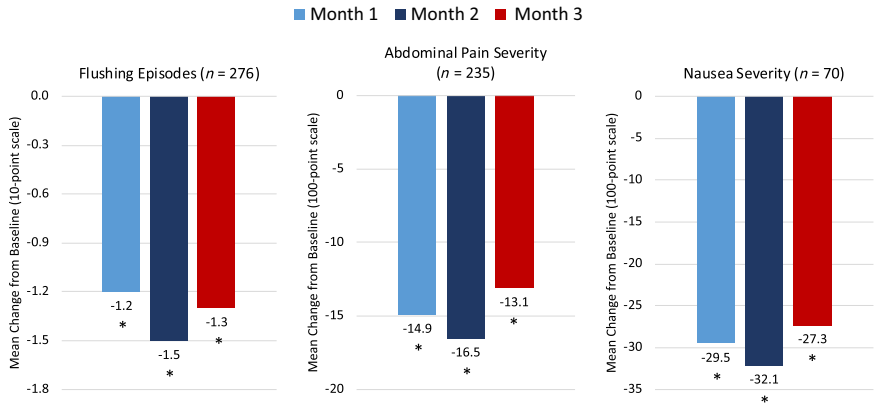

Figure 3. Other carcinoid syndrome symptom changes from baseline through 3 months. The symbol * indicates a significance level of $p < .001$.

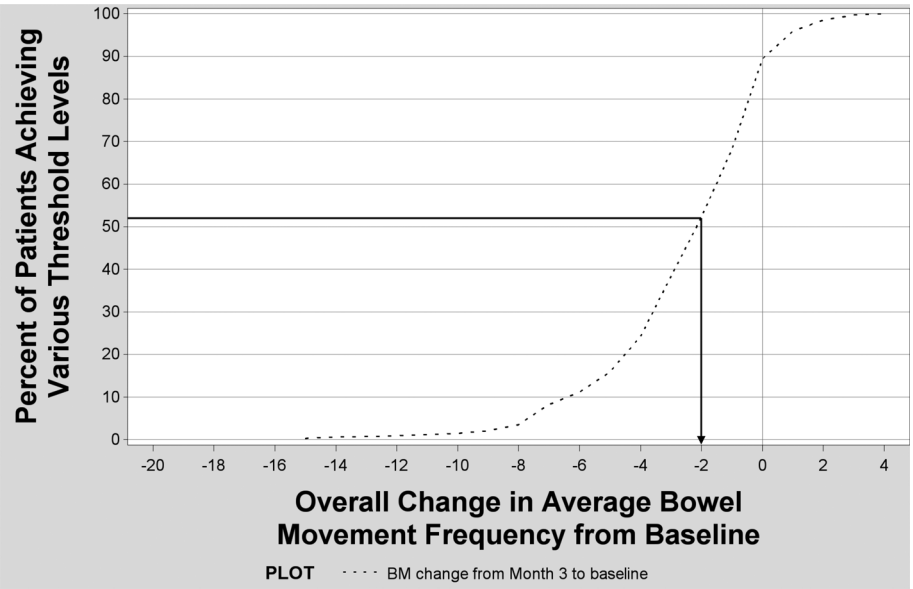

Figure 4. Cumulative distribution of overall BM frequency reductions at month 3.
Abbreviation: BM, bowel movement.

were receiving average doses in excess of those approved for labeled indications. Our findings of baseline symptom burden were consistent with those of participants in the TELESTAR clinical trial, including for high daily BM frequency (97% and 97%, respectively), abdominal pain (67% vs. 63%), and flushing (80% vs. 86%) [2]. In this sense, CSD and other symptom burden observed in real-life practice and among TELESTAR clinical trial participants appear to be quite similar.

There are certain strengths and limitations of this study. Observational research with patient-reported outcomes can make meaningful contributions to the knowledge of disease and care patterns and to the interpretation of evidence from randomized, controlled trials, which often enroll selective patient populations. The large sample size of this study has allowed for some precision in examining secondary endpoints that were not sufficiently powered in the TELESTAR study, the largest clinical trial in CSD to date. Analyses of flushing and abdominal pain, for example, showed potential for benefit over 3 months of TE treatment and may warrant further investigation.

This was a single-arm observational study with no control group in which both patients and nurses administering the survey instruments were unblinded to the patient's treatment regimen. Moreover, loss to follow-up among some study participants may have introduced a degree of selection bias. However, this limitation reflects therapeutic choices and benefits assessed in real-world clinical practice. Although not all patients initiating TE during the study period enrolled in the nurse support program or contributed data across all time points, the baseline patient characteristics were similar across all subgroups. Concerns of external generalizability and selection bias are common to observational studies that do not incentivize consistent participation and follow-up, as is common in clinical trials. In this clinical practice setting, however, response to treatment may be considered a marker for continuation of therapy. In this case, the high prevalence of continued TE treatment after 3 months suggests that patients receive meaningful benefit in the real world. The number of evaluable patients in this study compared with previous TE clinical trials provides useful insight into the

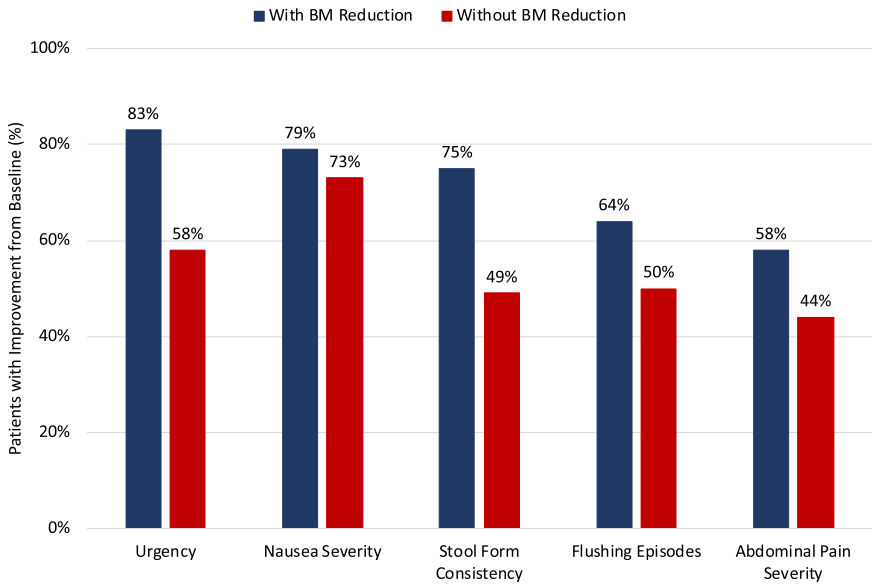

Figure 5. Improvements in carcinoid syndrome symptoms among patients with and without ≥30% reduction in BM frequency. Abbreviation: BM, bowel movement.

unmet need of symptomatic patients with CSD and into the real-world effectiveness of TE in these patients.

Overall, patient-reported burden of CS and CSD and the benefits of adding TE therapy suggest that TE is being used in an appropriate patient population. Although compliance was not formally estimated, it appears to have been sufficient for the benefits of TE treatment to be realized. Future research should evaluate the long-term benefit of TE in terms of overall improvement in health and well-being of patients.

Conclusion

In a real-world clinical setting, patients with CS treated with TE reported significant improvements in diarrhea and other CS symptoms. Future observational studies should investigate long-term treatment adherence and outcomes in these patients.

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Disclosures

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For Further Reading:

Lowell B. Anthony, Matthew H. Kulke, Martyn E. Caplin et al. Long-Term Safety Experience with Telotristat Ethyl Across Five Clinical Studies in Patients with Carcinoid Syndrome. ***The Oncologist*** 2019;24:e662–e670.

Implications for Practice:

Carcinoid syndrome can cause persistent diarrhea, even in patients treated with somatostatin analogs. Across five clinical trials in patients with carcinoid syndrome, telotristat ethyl has been well tolerated and efficacious, providing clinicians with a new approach to help control carcinoid syndrome diarrhea, in addition to somatostatin analog therapy. By reducing the stool frequency in patients with carcinoid syndrome whose diarrhea is refractory to anticholinergics, such as loperamide and atropine/diphenoxylate, and somatostatin analog dose escalation, improvement in quality of life becomes an achievable goal.