

# CLINICAL UPDATE

Advances in the Treatment of Carcinoid Syndrome

## Advances in the Management of Patients With Carcinoid Syndrome



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### **H&O** What are the symptoms of carcinoid syndrome?

**MK** Carcinoid syndrome can occur in patients who have carcinoid tumors. Carcinoid tumors have the ability to secrete peptides and hormones, such as serotonin. The symptoms of carcinoid syndrome are in large part related to the secretion of serotonin. The main symptom is diarrhea. In some cases, patients will also experience flushing. In the later stages of carcinoid syndrome, patients may develop scarring and fibrosis of the heart valves, as well as fibrosis in the mesentery surrounding the primary tumor, which is often located in the small bowel. It is thought that fibrosis is caused by serotonin that is secreted by the tumor.

### **H&O** How do the symptoms impact quality of life?

**MK** The diarrhea associated with carcinoid syndrome can have a big impact on quality of life. Patients can experience fairly profound secretory diarrhea and frequent bowel movements throughout the course of the day. It is not uncommon for my patients to have memorized the location of every rest stop along the drive from their home to the hospital.

### **H&O** What are the traditional approaches to management, and do they leave any unmet needs?

**MK** The traditional approach to carcinoid syndrome has been to initiate treatment with a somatostatin analogue. Somatostatin analogues have been available since the

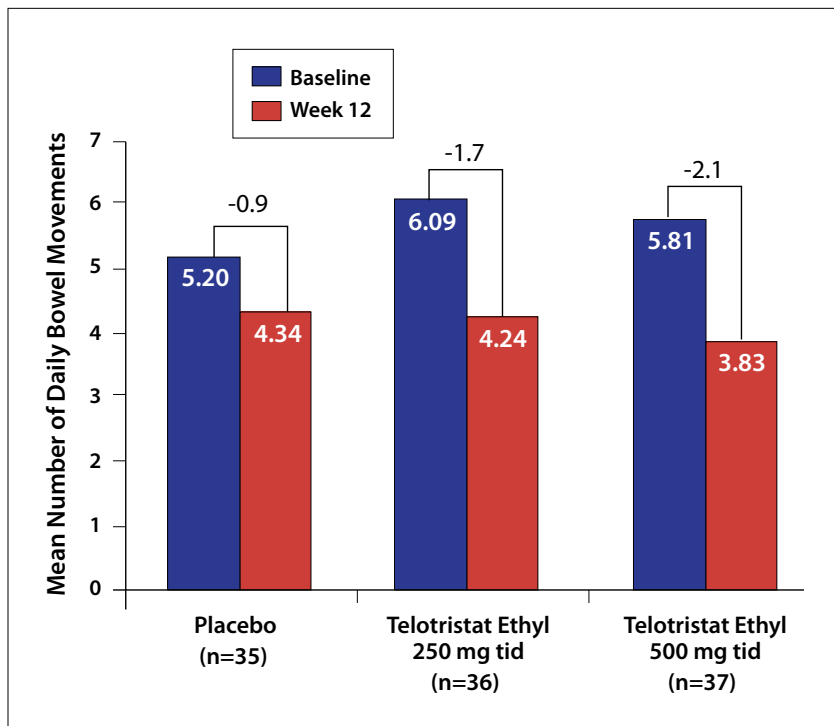
mid-1980s, and they have had an important impact on the treatment of carcinoid syndrome. When they are first administered, somatostatin analogues are often associated with a very good benefit. However, treatment can continue for years, and over time, patients may develop recurrent symptoms of diarrhea and sometimes flushing.

Patients can experience fairly profound secretory diarrhea and frequent bowel movements throughout the course of the day.

Although somatostatin analogues clearly have had an important benefit for patients with carcinoid syndrome, they are not completely effective. New treatments are therefore needed.

### **H&O** What is the mechanism of action of telotristat ethyl, and what led to its evaluation in these patients?

**MK** The association between serotonin secretion and carcinoid syndrome has been known for a long time. In fact, one of the tests used to diagnose and monitor carcinoid syndrome is measurement of 5-hydroxyindoleacetic acid



**Figure.** Mean number of daily bowel movements in the TELESTAR trial. Data include patients with assessments at both baseline and week 12. The arithmetic mean reduction in daily bowel movement frequency from baseline to week 12 was  $-0.9$  with placebo,  $-1.7$  with telotristat ethyl 250 mg, and  $-2.1$  with telotristat ethyl 500 mg. TELESTAR, Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome; tid, 3 times daily. Reprinted with permission from Kulke MH et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol.* Volume 35 (Issue 1), 2017:14-23. © 2017 American Society of Clinical Oncology. All rights reserved.

(5-HIAA), a serotonin metabolite that can be measured in the urine. Telotristat ethyl (Xermelo, Lexicon Pharmaceuticals) is an inhibitor of tryptophan hydroxylase, a key enzyme involved in serotonin synthesis. The evaluation of telotristat ethyl in patients with carcinoid syndrome was based on the hypothesis that inhibition of the synthesis of serotonin in the tumor could effectively treat carcinoid syndrome.

#### H&O What was the design of the TELESTAR trial?

**MK** The phase 3 TELESTAR trial (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) was designed with a primary endpoint of bowel movement frequency. This endpoint was chosen because increased bowel movement frequency is a key symptom that impacts patients with carcinoid syndrome, and it is mediated by serotonin. The trial enrolled patients who were receiving treatment with somatostatin analogues but were still experiencing symptoms of diarrhea. Enrollment criteria required 4 or more bowel movements per day despite treatment with a somatostatin analogue.

Patients were randomly assigned to receive placebo, telotristat ethyl at a dose of 250 mg 3 times a day, or telotristat ethyl at a dose of 500 mg 3 times a day. There were 45 patients assigned to each arm. Bowel movement frequency was measured for a 12-week double-blind period. At the end of that period, all patients had the

option to receive telotristat ethyl at a dose of 500 mg 3 times a day.

#### H&O What were the results?

**MK** Telotristat ethyl was associated with a decrease in bowel movement frequency. At week 12, the daily bowel movement frequency in the 250-mg group decreased by 1.7 (Figure). In the 500-mg group, frequency decreased by 2.1 bowel movements per day. It was exciting to see that a drug with a new mechanism of action was efficacious in carcinoid syndrome, particularly in patients who were experiencing symptoms despite standard treatment.

#### H&O Did the improvement in symptoms impact quality of life?

**MK** There were improvements in the diarrhea subscale scores. Patients who responded to telotristat ethyl reported modest improvements in overall quality of life compared with nonresponders.

#### H&O Does the decrease in bowel movement frequency represent a true clinical benefit?

**MK** It does appear to represent a true clinical benefit. Patients who received telotristat ethyl reported that they felt better. This improvement was certainly clear when

treating these patients. Results from the TELESTAR trial show that telotristat ethyl represents an important opportunity for treating the diarrhea associated with carcinoid syndrome. In February 2017, the US Food and Drug Administration approved telotristat ethyl in combination with somatostatin analogue therapy for the treatment of adults with diarrhea related to carcinoid syndrome that is not adequately controlled by somatostatin analogue therapy alone.

### H&O What were some other findings from the study?

**MK** Another endpoint of the study was measurement of the serotonin metabolite urinary 5-HIAA. Decreases in urinary 5-HIAA reflect reductions in serotonin synthesis. In a post hoc analysis of the trial, a decrease in urinary 5-HIAA of 30% or more was reported in 78% of the 250-mg arm and 87% of the 500-mg arm, vs 10% of the placebo arm. This decrease in urinary 5-HIAA validated the mechanism of action of telotristat ethyl. It was a clear indication that telotristat ethyl was hitting its target.

A potential benefit of decreasing serotonin levels in patients with carcinoid syndrome relates to the long-term consequences of high levels. Patients can develop scarring and fibrosis of the heart valves and perhaps in the mesentery of the small intestine. These events are common in patients with carcinoid syndrome, although they were not assessed in the TELESTAR trial. There is the possibility that reducing serotonin levels over the long-term might decrease some complications of long-standing carcinoid syndrome.

### H&O What were the adverse events in the trial?

**MK** Telotristat ethyl was well-tolerated. There were increases in alanine transaminase in 2.2% of the 250-mg telotristat ethyl arm and 6.7% of the 500-mg telotristat ethyl arm (vs 0% in the placebo arm). Nausea was seen

in 11.1% of the placebo arm, 13.3% of the 250-mg arm, and 31.1% of the 500-mg arm. Treatment-emergent adverse events led to study discontinuation in 13.3% of patients receiving placebo and in 6.7% of patients in both telotristat ethyl arms.

An adverse event of special interest is depression, given the mechanism of action of telotristat ethyl and its effect on serotonin synthesis. Telotristat ethyl was specifically designed not to cross the blood-brain barrier, to avoid any effects on the central nervous system. Episodes of depression-related adverse events (eg, depression, depressed mood, and decreased interest) were observed among 6.7% of patients receiving placebo or the 250-mg dose of telotristat ethyl. The rate of depression was slightly higher, at 15.6%, among patients treated with the 500-mg dose of telotristat ethyl. No patient discontinued telotristat ethyl owing to depression. The incidence of depression will be followed in extension studies and future trials.

### Disclosure

*Dr Kulke has served as a consultant for Lexicon, Novartis, and Ipsen.*

### Suggested Readings

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