

# CLINICAL UPDATE

Advances in the Treatment of Carcinoid Syndrome

## Emerging Treatment Options for Carcinoid Syndrome



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### **H&O** What are carcinoid tumors, and which types are most likely to lead to carcinoid syndrome?

**MK** Carcinoid tumors fall into the broader category of neuroendocrine tumors. Traditionally, neuroendocrine tumors have been subdivided into 2 main groups: pancreatic neuroendocrine tumors and carcinoid tumors. Carcinoid tumors are most commonly seen in the lungs and intestines, but can arise in many different sites in the body.

Carcinoid syndrome is most likely to occur in patients with carcinoid tumors that originate in the small intestine or appendix. Carcinoid syndrome is usually present in patients who have metastatic disease, particularly liver metastases. It is caused by the hormones, especially serotonin, that the tumors secrete into the systemic circulation.

### **H&O** How does carcinoid syndrome lead to morbidity and impact quality of life?

**MK** The classic symptoms of carcinoid syndrome are flushing and diarrhea. The flushing can manifest fairly suddenly; patients feel warm and their skin turns red, particularly on the torso and face. That can be bothersome. Flushing can have social consequences, particularly because it can be precipitated by stress. The diarrhea associated with carcinoid syndrome can be profound. Patients can have more than 10 bowel movements a day, which limits social functioning and can pose problems in the workplace.

A later consequence of carcinoid syndrome that is caused by the secretion of serotonin is scarring and fibro-

sis on the heart valves, typically the tricuspid valve. The scarring can lead to symptoms of valvular insufficiency. In some cases, patients must undergo valve replacement. The long-term effects of high serotonin secretion have not been well-studied. However, there is increasing evidence that serotonin can interact with the receptors on fibroblasts. It is likely that serotonin directly leads to the valvular fibrosis seen in patients who have longstanding carcinoid heart disease.

There is also increasing evidence that serotonin may cause local fibrosis, particularly in the intestines. This condition, known as mesenteric fibrosis, can lead to intermittent bowel obstruction and other complications.

### **H&O** Which patients would benefit from treatment of carcinoid syndrome?

**MK** Any patient who is symptomatic will benefit from treatment of carcinoid syndrome, for the simple reason that it will make him or her feel better and function better. Whether it is beneficial to decrease serotonin levels in patients who have no overt clinical symptoms of carcinoid syndrome is not as clear, and is an important area of future study. There is reason to think that reducing long-term exposure to high serotonin levels might prevent or reduce some of the complications seen in patients with carcinoid syndrome.

### **H&O** What is the standard of care for carcinoid syndrome?

**MK** The standard of care has been treatment with somatostatin analogues, which were initially developed in the 1980s. They have had a very beneficial impact on

patients with carcinoid syndrome. They decrease levels of serotonin and improve quality of life, and more recently have also been shown to slow tumor growth. The initial treatment of carcinoid syndrome often begins with somatostatin analogues, but over time, sometimes years, breakthrough symptoms occur. In some patients, somatostatin analogues fail to completely control the syndrome.

### H&O What are the newer treatment options for carcinoid syndrome?

**MK** For some time, somatostatin analogues were the only option. A recent development has been the introduction of telotristat etiprate, which is a tryptophan hydroxylase inhibitor. In the randomized, phase 3 TELESTAR trial (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome), telotristat etiprate was shown to decrease daily bowel movement frequency (the primary endpoint) and reduce levels of the serotonin metabolite urinary 5-hydroxyindoleacetic acid (5-HIAA; the secondary endpoint). The TELESTAR trial compared 2 doses of telotristat etiprate, 250 mg and 500 mg, administered 3 times daily vs placebo in 135 patients with carcinoid syndrome who were receiving treatment with somatostatin analogues. After 12 weeks of follow-up, statistically significant reductions in daily bowel movement frequency were observed in both the 250-mg arm and 500-mg arm compared with placebo. Durable response, defined as a reduction in daily bowel movements of at least 30% for more than 50% of the study period, was reported in 44% of the 250-mg arm and in 42% of the 500-mg arm, compared with 20% of the placebo arm ( $P < .02$  for both). From baseline to week 12, the mean urinary 5-HIAA change was 40.13 mg per 24 hours in the 250-mg arm and 57.73 mg per 24 hours in the 500-mg arm. In the placebo arm, 5-HIAA increased by a mean of 11.47 mg per 24 hours. Interim analysis of an open-label extension study, in which patients received the 500 mg dose 3 times daily, showed continued evidence of efficacy and safety. Telotristat etiprate is not yet approved by the US Food and Drug Administration. It was granted a priority review in May 2016.

### H&O How important is the decrease in bowel movement frequency?

**MK** Frequent bowel movements are an important issue for patients and can impact their quality of life and functioning. Some of my patients can name every rest stop on the highway because they have to carefully plan their drive to the clinic.

### H&O What does the decrease in urinary 5-HIAA suggest?

**MK** Urinary 5-HIAA is a serotonin metabolite commonly used as a biomarker in patients with advanced carcinoid tumors. High levels of 5-HIAA have been associated with poor prognosis. Tryptophan hydroxylase is the enzyme involved in serotonin synthesis. At a basic level, the decrease in 5-HIAA observed in the TELESTAR trial provided important scientific proof-of-concept data that telotristat etiprate, a tryptophan hydroxylase inhibitor, hit the target it was supposed to and decreased levels of serotonin.

Another important aspect is that elevated levels of 5-HIAA have been associated with the development of cardiac valvular disease, presumably because of the link to serotonin. At least in theory, it appears that decreasing 5-HIAA may have some of the longer-term benefits previously discussed. This is an important area for further study.

### H&O Is telotristat etiprate associated with any adverse events?

**MK** In clinical trials, the side effect profile of telotristat etiprate was very favorable. Telotristat etiprate does not cross the blood-brain barrier. It is therefore an exciting development.

### H&O What are some areas of future research?

**MK** Future research should focus on how to best use telotristat etiprate to improve quality of life. In addition, it should also determine whether the use of this therapy can ameliorate some of the longer-term consequences of high serotonin levels.

#### Disclosure

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

#### Suggested Readings

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