Positive Quality Intervention: Telotristat Ethyl for the Management of Carcinoid Syndrome Diarrhea

Description:
Treatment options for patients with carcinoid syndrome diarrhea that is refractory to somatostatin analog (SSA) therapy are limited. A first in class oral tryptophan hydroxylase inhibitor, telotristat ethyl (Xermelo), was approved in February for 2017 for use in combination with SSA therapy in adults with carcinoid syndrome diarrhea inadequately controlled by SSA.

Background:
Carcinoid tumors are well-differentiated neuroendocrine tumors that typically originate in the digestive track or lungs. These tumors may secrete as many as 40 different bioactive products, with the most pronounced being serotonin, histamine, tachykinins, kallikrein and prostaglandins. Carcinoid syndrome diarrhea is thought to be caused by the overproduction and release of serotonin by the carcinoid tumor, resulting in stimulation of intestinal secretions as well as motility and inhibition of intestinal absorption.

TELESTAR was a phase III placebo-controlled trial that demonstrated a significant decrease in bowel movement frequency with the addition of telotristat ethyl to SSA therapy in patients with uncontrolled carcinoid syndrome with a manageable adverse event profile. Bowel movement (BM) frequency decreased by approximately two movements a day, and a responder analysis identified that more than 40% of patients receiving telotristat ethyl had a ≥30% decrease in BM frequency compared with 20% of patient receiving placebo. The most common treatment-related adverse events reported in TELESTAR in patients receiving telotristat ethyl 250mg were nausea (13.3%), headache (11.1%), increased gamma-glutamyl-transferase (8.9%), depression (6.7%), peripheral edema (7%), flatulence (6.7%), decreased appetite (6.7%) and pyrexia (6.7%).

Clinicians should be aware of this oral option for carcinoid tumor patients who exhibit diarrhea symptoms that continue to be refractory to SSA therapy.

PQI Process:
Upon receipt of a new prescription for telotristat ethyl:
- Verify initial dosage is 250mg orally three times a day
- Ensure adult patient with the diagnosis of carcinoid syndrome is:
  - Currently receiving a long-acting SSA at a stable-dose (3 months of treatment at the same dose)

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- Depot octreotide
- Long-acting lanreotide
  - Suffering from inadequately controlled diarrhea
- Dosages >30mg for depot octreotide and >120mg for long-acting lanreotide may not be reimbursed by insurance companies as this is above the Food and Drug Administration (FDA)-approved dosages. Additionally, administering at an interval of <4 weeks is also outside of the prescribing guidelines and may cause reimbursement issues.
- Provide patients with refractory carcinoid symptoms (either during the dose escalation phase of the long-acting SSA or while waiting to receive telotristat ethyl) with a rescue short-acting octreotide prescription, if not already receiving, as well as an antidiarrheal. Initial dosing of short-acting octreotide is typically 100mcg subcutaneously three times a day. This dose may be titrated up to 600mcg per day.
- Telotristat ethyl can be administered concomitantly with antidiarrheals and/or short-acting octreotide, but the injection must be given at a minimum 30 minutes after the telotristat ethyl as octreotide may decrease the serum concentration of the medication.
- Consider screening for depression using an approved depression test questionnaire. Although preclinical trials with telotristat ethyl did not demonstrate significant central nervous system penetration, at higher doses (e.g., 500mg three times daily vs 250mg three times daily) an increase in depression-related adverse events were reported (placebo = 6.7% vs telotristat ethyl 500mg TID = 15.6%). Further examination of this adverse event is being explored in a phase III trial.

**Patient Centered Activities:**
- Educate patients receiving telotristat ethyl:
  - **Response times**
    - Response times vary, but they may need to allow the full 12 weeks of therapy to respond to the treatment
  - **Bowel Habits**
    - Monitor their BM closely and if they begin to experience constipation make their healthcare team aware
    - Report any severe or persistent bowel pain as intestinal perforation and bowel obstruction was observed in TELESTAR
  - **Nausea**
    - Report so that an anti-nausea medication can be prescribed
    - Important to remember that many anti-nausea medications can cause constipation, so counsel patients to monitor closely

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References:


Supplemental Information:
Background on Carcinoid Syndrome Diarrhea

Carcinoid syndrome is most commonly associated with metastatic tumors of the jejunum, ileum and cecum, most commonly in the setting of liver metastases, as the liver is responsible for inactivating the bioactive products secreted by the tumor into the bloodstream. These tumors secrete substances like serotonin which is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) and excreted in the urine. Patients suffering from carcinoid syndrome are known to have modified metabolism of tryptophan. In healthy individuals only about 1% of tryptophan is converted to serotonin, but in patients suffering from carcinoid syndrome up to 70% of tryptophan can be converted to serotonin. Serotonin however does not cause flushing in carcinoid syndrome; this symptom is thought to be due to other bioactive products released by the tumor. Figure 1 outlines the metabolism of tryptophan and serotonin.

Figure 1: Tryptophan and Serotonin Metabolism

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\begin{align*}
\text{Monoamine oxidase aldehyde dehydrogenase} & \quad \downarrow \\
\text{Tryptophan} & \quad \rightarrow \quad \text{5-hydroxytryptophan} & \quad \rightarrow \quad \text{Serotonin (blood)} & \quad \rightarrow \quad \text{5-hydroxyindoleacetic acid (urine)} \\
\text{Tryptophan hydroxylase} & \quad \uparrow \\
\text{Aromatic L-amino acid decarboxylase} & \quad \uparrow
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