Research Article

Telotristat Ethyl for Treatment of Carcinoid Syndrome

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ABSTRACT

Introduction: Carcinoid syndrome affects quality of life and prognosis of patients with neuroendocrine neoplasia. Diarrhea and flushing are the most frequent symptoms. Standard treatment of carcinoid syndrome is somatostatin analogs. However, during course of the disease, a significant proportion of patients become treatment resistant. Telotristaethyl is the first in his class medication inhibiting peripheral serotonin synthesis, the major transmitter associated with carcinoid syndrome. Phase II and phase III studies showed a significant reduction by Telotristaethyl in number of bowel movements and serotonin levels determined by measurement of urinary 5-HIAA, a serotonin metabolite. Telotristaethyl was shown to be safe in a dose of 250 mg tid and did not increase significantly adverse events related to depression, hepatic enzyme elevations and gastrointestinal disorders compared to placebo. Telotristaethyl at a dose of 250 mg tid is registered under the brand name Xermelo® for treatment of carcinoid syndrome in addition to somatostatin analogs.

Areas covered: All publications on Telotristaethyl have been searched and are included in the text

Expert opinion: Telotristaethyl has been shown to be an effective additional treatment option for notoriously difficult to treat carcinoid syndrome. Telotristaethyl reduces number of secretory diarrhea in carcinoid syndrome and improves quality of life. It is safe despite the concern of affecting central serotonin biosynthesis. Telotristaethyl may open additional treatment venues for functional bowel disorders or as an anti-neoplastic agent for treatment of serotonin producing neuroendocrine neoplasia.

FUNCTIONAL ACTIVE NEUROENDOCRINE NEOPLASIA CAUSING CARCINOID SYNDROME

Neuroendocrine neoplasia originate by malignant transformation of dispersed endocrine cells of the diffuse endocrine system, which is present in many organs to regulate numerous physiological functions such as blood glucose control or gastric acid secretion. Well and moderately differentiated neuroendocrine neoplasia are termed neuroendocrine tumors. Poorly differentiated neuroendocrine neoplasia are referred to as neuroendocrine carcinomas. Well differentiated neuroendocrine neoplasia G1 display a Ki67 index of less than 2%, G2 or moderately differentiated neuroendocrine neoplasia between 2-20% whereas neuroendocrine carcinomas are delineated by a proliferation rate of more than 20%. The new WHO classification of 2017 of pancreatic neuroendocrine neoplasias also includes well differentiated

neuroendocrine tumors G3 with a proliferation rate of more than 20% but preserved differentiation in contrast to poorly differentiated neuroendocrine carcinomas G3 [1- 3].

About 20-40% of G1 and G2 neuroendocrine neoplasia are functionally active by paraneoplastic aberrant secretion of peptide hormones or biogenic amines. The most frequent functional syndrome is carcinoid syndrome by excess secretion of serotonin leading to characteristic clinical symptoms of gastrointestinal tract, skin, lung and heart. Flushing is the leading symptom of carcinoid syndrome followed by secretory diarrhea in 80%. Abdominal pain is observed in 35% of patients and bronchoconstriction in 15%. Fibrosis in mesentery is prevalent in 50% of patients and about half of all patients with carcinoid syndrome, develop carcinoid heart disease characterized by fibrosis of the right heart. Pellagra has been described as a symptom of carcinoid syndrome due to tryptophan depletion but is rarely observed in countries where somatostatin analogs are available. An exacerbation of carcinoid syndrome is carcinoid crisis caused by excessive secretion of bioactive amines inducing hypotension, tachycardia, flushing and bronchospasms. Carcinoid crisis is life-threatening and can be lethal if not treated as an emergency [4-7].

IMPACT OF DIARRHEA ON QUALITY OF LIFE IN PATIENTS WITH CS

Diarrhea associated with carcinoid syndrome is secretory and does not taper by fastening. Amount of bowel movements, stool consistency, volume, urgency and incontinence should be evaluated to judge impact on daily life. Especially urgency does interfere with daily activities and social life. In addition, diarrhea may be accompanied by cramping and pain. Multiple bowel movements in conjunction with large stool volumes may lead to dehydration and serious clinical problems. More than 3 bowel movements a day impair quality of life by reducing physical and social functioning and increasing fear, depression, fatigue, pain and sleep disturbances [8]. A survey on 538 patients and 151 oncologists treating patients with neuroendocrine neoplasia and carcinoid syndrome identified significant symptoms at more than 21 days a month in 38% of patients. Two thirds of patients reported depression due to symptoms, 88% reported daily stress and 83% as a day to day challenge. Symptoms by diarrhea were a strong burden for 35% of patients. In contrast, treating physicians judged impact of diarrhea lower than patients [9].

TREATMENT OPTIONS FOR PATIENTS WITH CARCINOID SYNDROME

Somatostatin was identified by its growth hormone inhibiting characteristics. Subsequently, it was shown that somatostatin acts as an anti-secretory hormone inhibiting release of additional hormones. Neuroendocrine neoplasia causing carcinoid syndrome overexpress somatostatin receptors. Subsequently, it was shown that somatostatin acts anti-secretory in functional active neuroendocrine neoplasia. However, clinical utility of somatostatin is hampered by its short half live in vivo. Somatostatin analogs with high affinity for somatostatin receptor 2 and 5 were developed and tested in clinical studies. Of these, octreotide and lanreotide were registered for treatment of functionally active neuroendocrine neoplasia. Special formulations as long acting release and autogel allow 4 weekly injections of octreotide and lanreotide. If necessary, long acting somatostatin analogs may be combined with octreotide for intravenous or subcutaneous injections. A somatostatin analog with broader affinities for somatostatin receptors (Pasireotide) is also available although clinical studies showed no significant advantage compared to octreotide. Interferon has also a role in treatment of carcinoid syndrome. Despite treatment, about 20% of patients with carcinoid syndrome become resistant to somatostatin analoges during course of the disease [6,7,10].

BIOSYNTHESIS OF SEROTONIN AND ITS PHYSIOLOGICAL ROLE

Serotonin is synthesized in neurons and enterochromaffin cells, which are part of the diffuse neuroendocrine system of bowel and lung. Dietary essential amino acid L-thryptophan is converted into 5-hydroxythryptophan by tryptophan hydroxylase (TPH). 5-hydroxythryptophan is subsequently converted to biogenic amine serotonin by aromatic L-amino acid decarboxylase. TPH is the rate limiting enzyme in serotonin biosynthesis. Serotonin is stored in secretory granules which are released upon chemical or mechanical stimuli such as stretch or bacterial toxins. Serotonin acts in a paracrine manner via seven subtypes of serotonin receptors mediating physiological gut functions like secretion and peristalsis. Serotonin is secreted in a paracrine manner. Inactivation of

serotonin occurs by monoamineoxidase A in adjacent epithelial cells, whereas serotonin released in portal veins is inactivated by first pass effects in liver and lung to 5-hydroxyindoleacetic acid (5-HIAA), which is then emitted by the kidneys. Residual serotonin is taken up and stored in platelets [11,12].

TPH ISOFORMS AND THEIR ROLES IN PHYSIOLOGY AND PATHOPHYSIOLOGY

Two different isoforms of TPH were identified and characterized after a knockout of TPH gene revealed TPH1 and TPH2 genes with almost no overlap and distinct functions. TPH2 is expressed in cells of the neural system and TPH1 in non-neural cells. A knockout of TPH1 leads to a severe reduction in peripheral serotonin levels but no alterations in physiological gut functions. In contrast, in mice models of knockouts of TPH2 and TPH1/TPH2 double knockouts gastrointestinal functions such as gastric emptying, total intestinal transit and colonic motility are disturbed. However, serotonin generated by TPH1 has a proinflammatory role in experimentally induced colitis. Fundamental role of serotonin in gut functions is demonstrated by 5-HT3 receptor antagonists such as odansetrone, which are applied for prevention of nausea and diarrhea associated with chemotherapy. In addition, 5-HT4 receptor agonists like prucaloprid have been used for treatment of chronic constipation and non-diarrhea-predominant irritable bowel syndrome [13-18].

SEROTONIN AS A CAUSATIVE AGENT IN CARCINOID SYNDROME AND DEVELOPMENT OF TELOTRISTATETHYL AS A PERIPHERAL TPH INHIBITOR

Although causative messengers in carcinoid syndrome are multiple, serotonin has been regarded as major player in pathophysiology of carcinoid syndrome and carcinoid heart disease. Pharmacological studies using parachlorophenylalanine und methysergide reduced diarrhea in patients with carcinoid syndrome. Methysergide is a serotonin receptor antagonist and parachlorophenylalanine, an inhibitor serotonin synthesis. Development of parachlorophenylalanine was stopped due to its central nervous effects on serotonin synthesis causing depression. The serotonin agonist fenfluramine caused right sided heart fibrosis similar as observed in carcinoid heart disease and is no longer available for treatment of obesity [19,20].

Since knockout models of TPH indicated crucial roles of serotonin in gut physiology and pathophysiology, a small molecule inhibitor of peripheral serotonin biosynthesis was identified by screening molecular libraries with radiolabeled tryptophan. One compound (LP-533401) inhibited TPH1 and TPH2 at low micromolar levels. Ethyl estering of LP-533401 rendered LP-615819, which is acting as a prodrug with increased potency. LP-615819 decreased peripheral but not central serotonin levels in the mouse and was further characterized as Telotristaethyl [15,18].

Telotristaethyl does not cross the blood-brain barrier. It is produced as a hippurate salt, which is acting as a prodrug of Telotristaethyl. The chemical structure and pharmacological characteristics of Telotristaethyl are described elsewhere. Telotristaethyl is available as 250 mg tablets [21,22].

Phase I studies in healthy volunteers revealed that Telotristaethyl at 500 mg tid decreased serotonin levels in blood and urinary 24-hour 5-HIAA levels. A phase 1 study with patients with CS, Telotristaethyl at 250 mg tid reduced urinary 5-HIAA levels after 6 and 12 weeks of treatment compared to placebo. Telotristaethyl has a half-life of 0.6 hours and the active metabolite telotristat one of five hours. Telotristaethyl does not affect QT interval and is no substrate of CYP enzymes. It is highly bound to plasma proteins and better absorbed after fatty meals. Metabolisation of Telotristaethyl is not affected by mild hepatic or nephrogenic impairment. Bioactivity may be reduced by co-administration of short acting octreotide although this is not clinically important [21,22].

Clinical phase I studies included three studies. Dose tolerability studies in single doses between 50 and 1500 mg (LX1606.1-101-NRM) and multiple doses (LX1606.1.102-NRM) between 100 mg (qd) to 500 mg tid with were performed. Another phase I study examined TE 250 mg as tablet or capsule formulation (LX1606.1-103-NRM). Nausea, diarrhea, headache, abdominal pain, abdominal distension constipation and dizziness were frequent adverse events and slight elevations in ALT and AST were noted in the ascending dose-study. Telotristaethyl was converted in telotrist rapidly and almost completely. Telotristaethyl did not accumulate after multiple doses while serotonin and urinary 5-HIAA levels were reduced [21,22].

PHASE II CLINICAL STUDIES

Two phase II studies have been performed in the US and Europe in patients with secretory diarrhea caused by carcinoid syndrome. Study LX1606.1-202-CS examined patients on stable doses of somatostatin analogs with additional doses of Telotristaethyl given tid (150 mg, 250 mg, 500 mg) for 28 days. LX1606.1-202-carcinoid syndrome was designed as a double-blind, proof-of-concept ascending multi-dose study to test safety, tolerability and effectiveness of Telotristaethyl. After completion of the double blind period, patients could continue on Telotristaethyl at their individual dose. Clinical endpoint was a ≥30% reduction in daily mean number of bowel movements/week for 2 or more during the 4 week trial compared to baseline and occurred in 5/28 patients taking Telotristaethyl and in 0/5 patients of the placebo group. Patients in the Telotristaethyl group had a reduction in bowel movements whereas no decrease was observed in the placebo group. Reduction in urinary 5-HIAA to normal or a ≥50% decrease was achieved in 9/16 patients in the TE group and 0/5 patients in the placebo group. Serious adverse events were rare and reported in 2/18 patients in the Telotristaethyl group and none in patients receiving placebo. Treatment-emergent adverse events were observed in all patients treated with Telotristaethyl and 4/5 patients receiving placebo. Adverse events were mostly gastrointestinal and no hepatic toxicities were reported [23].

The second phase II study LX1606.1-203-CS was performed in Europe in patients with diarrhea predominant carcinoid syndrome. LX1606.1-203-CS was designed as a 12 week open label dose-titration study. Somatostatin analog treatment was not mandatory. Of the 21 patients screened for the study, 15 were enrolled, 14 completed 12 weeks and 12 could be increased to 500 mg Telotristaethyl tid. Most patients in the 12 week study took somatostatin analogs (13/15) and 8/15 took additional loperamide hydrochloride. All patients observed a decrease in mean bowel movement frequency from mean 5.9 to 2.6 movements/day at the end of the study. Urinary 5-HIAA was reduced by a mean of 74.2%, stool consistency improved, flushing and abdominal pain decreased by a mean of 27% and 29%, respectively. For all patients completing the 12 weeks study, a long term extension study over 124 weeks was offered and 11 patients were enrolled. Concomitant medication with somatostatin analogs and loperamide hydrochloride did not affect treatment with Telotristaethyl. Adverse events were mostly gastrointestinal, mild and resolved during the study. Serious adverse events occurred in 3 patients and were not treatment related. Elevation of liver enzymes were lower than 2 x ULN with no increased bilirubin levels. Hematological adverse events were not noted [24].

PHASE III CLINICAL STUDIES

Two phase III clinical studies have been carried out. The pivotal trial for registration of Telotristaethyl, the TELESTAR trial (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) was the largest randomized placebeo-controlled study for patients with carcinoid syndrome. Patients with carcinoid syndrome diarrhea with a mean of more than 4 bowel movements/day despite somatostatin analog therapy at a stable dose for at least one month could be included. Reduction in bowel movements during double blind period compared to screening period was the primary endpoint. Secondary endpoints were change in urinary 5-HIAA levels and frequency of flushing and abdominal pain. Durable responders were defined as a more than 30% reduction in bowel movements during more than 50% of the treatment period. During the 12 week study period, patients were randomized 1:1:1 to Telotristaethyl 500 mg tid, Telotristaethyl 250 mg tid or placebo while continuing somatostatin analog therapy. Screening period was 3 or 4 weeks depending upon interval of somatostatin analog therapy. After double blind period, patients were offered open label extension with 500 mg Telotristaethyl tid. The study recruited 135 patients from 12 countries. Baseline and demographic characteristics were not different in treatment groups. Above label somatostatin analog treatment was reported in 43% of patients. Mean bowel movements during screening ranged from 5.2 to 6.1 per day. Elevated urinary 5-HIAA levels were present in 57% of patients and mean urinary 5-HIAA levels varied from 81.0 to 92.6 mg/24 hours. Completion of double blind period was achieved by 82.6-91.1% of patients. Compliance, defined as receipt of 75 to 125% of study drugs was reported in 86.7% to 93.3%. Open label extension was entered by 115 patients and 56 completed 48 weeks. Mean drug exposure in both studies was 26.7 weeks [25].

All doses of Telotristatethyl induced a reduction in number of bowl movements. Calculations by the Hodges-Lohmann estimator showed a reduction of -0.81 and -0.69 bowel movements of double blind phase in patients receiving 250 mg Telotristatethyl tid and 500 mg Telotristatethyl tid. Mean arithmetic daily reduction was -1.7 and -2.1 in 250 mg Telotristatethyl tid and 500 Telotristatethyl mg tid arms, respectively and -0.9 in the placebo arm. A durable response was observed in 44% and 42 % of patients in respectively Telotristatethyl 250 mg tid and 500 mg tid groups and in 20% of the placebo group. Urinary 5-HIAA levels were lowered by Telotristatethyl by 40.1 mg/24 h and 57.7 mg/24 hours at week 12 in the 250 mg tid and 500 mg tid groups respectively compared to baseline. In contrast, levels increased by 11.5 mg/24 hours in the placebo group. Abdominal pain and flushing were reduced in both verum groups, however these results were not statistically significant. Quality of life as assessed by EORTC QLQ-C30 questionaire showed improvement by Telotristatethyl in diarrhea subscale scores but not in other scores such as global health status, nausea and vomiting subscales [25].

Telotristatethyl in combination with somatostatin analog was safe and well tolerated in the TELESTAR trial. Vertigo, abdominal pain, headache and fatigue were the most common adverse events. Treatment-emergent adverse events occurred in similar frequency in all treatment arms but severe events were rare. Here, nausea was most frequent, however, severe nausea was rare. Discontinuation due to treatment-emergent adverse events was most frequent in the placebo-arm. Depression or depressed mood occurred in 3 patients (6.7%) in placebo arm, 2 patients (4.4%) in Telotristatethyl 250 mg tid arm and 8 patients (17.7%) in Telotristatethyl 500 mg tid. Depression did not require new study medication and did not lead to study discontinuation. There was one new case of depression during open label extension in one patient crossing over from placebo to 500 mg TE tid [25].

Weight loss may be associated with uncontrolled secretory diarrhea in carcinoid syndrome and may reduce survival. Weight change of more than 3% at week 12 was prespecified in the statistical analysis of TELESTAR trial. The post-hoc analysis showed that more patients treated with Telotristatethyl had a weight gain of more than 3% compared to placebo (5.1% placebo arm, 17.1% of patients on Telotristatethyl 250 mg tid and 32.5% on 500 mg Telotristatethyl tid). These results indicate that treatment with Telotristatethyl may improve nutritional status in patients with carcinoid syndrome. However, it has to be noted that these observations may include a recall bias [26].

Structured patients interviews in a blinded manner were performed in 35 patients at the end of the double blind treatment period in TELESTAR trial. These interviews indicated that quality of life is severely impaired by uncontrolled diarrhea carcinoid syndrome. If patients met criteria of durable responders, patients were very satisfied by treatment effects of Telotristatethyl [27]. Durable responders also reported sustained and significant improvements in EORTC QLQ-C30 global health status, nausea and vomiting, pain, diarrhea, and EORTC QLQ-GINET21 gastrointestinal symptoms [28].

To evaluate safety and efficacy of Telotristaethyl in patients with carcinoid syndrome, the Telotristat ethyl in carcinoid syndrome study (TELECAST) was designed as a phase 3, randomized, placebo-controlled, multicenter and double-blind study. Patients with symptomatic carcinoid syndrome with <4 BMs/day while on somatostatin analogs (or ≥4 if not on somatostatin analogs) could be included. The study was performed as a 12-week double-blind treatment period followed by a 36-week open-label extension. Except for 8 patients, all patients were treated with somatostatin analogs. Symptoms of carcinoid syndrome were gastrointestinal in 90% of patients (diarrhea in 70%), metabolic and nutritional in 58% and cardiac in 42% including carcinoid heart disease in 20 patients (26%) [29].

The TELECAST study enclosed 76 patients to the double-blind period and 67 patients went on to open-label extension. Mean study drug exposure in open label extension was 30 months. Patients were randomly assigned to placebo (n=26), Telotristaethyl 250 mg (n=25), or Telotristaethyl 500 mg (n=25) tid for 12 weeks. Incidence of treatment-emergent adverse events and percent change from baseline in 24-hour urinary 5-HIAA levels at Week 12 were primary endpoints. Secondary efficacy endpoints included the change from baseline averaged over the 12-week double blind period for daily bowel movement frequency, stool consistency, cutaneous flushing episodes, abdominal pain, and frequency of rescue

short-acting SSA treatment. Additional endpoints included durability of response to treatment as described above.

Both primary endpoints, safety and efficacy were met. Treatment related adverse events were similar in all groups during the double blind phase and were more frequently judged treatment-related by investigators in Telotristaethyl groups. Serious adverse events occurred in five patients of the placebo group and one and three patients in Telotristaethyl 250 mg tid and 500 mg tid groups, respectively. There were no deaths in all groups during double-blind and open label extension periods. Discontinuations of the study drug due to treatment related adverse events were noted in three patients, one in placebo arm and two in Telotristaethyl 250 mg tid arm. Severity of treatment related adverse events was mild to moderate and most treatment related adverse events were gastrointestinal. During open label extension, treatment related adverse events were similar to those of the double blind period and crossover from placebo to Telotristaethyl did not increase incidence of treatment related adverse events.

No increase in depression-related adverse events in Telotristaethyl groups with no severe or serious events. Two patients with known depression at baseline discontinued Telotristaethyl treatment during open label extension due to adverse events related to depression. Hepatic enzyme abnormalities were mild to moderate with two events leading to treatment discontinuation during open label extension. Gastrointestinal adverse events were frequent in all groups without a drug- or dose-dependent relationship.

At week 12, a significant reduction in urinary 5-HIAA levels were monitored in Telotristaethyl 250 mg tid and Telotristaethyl 500 mg tid groups compared to placebo and continued in the majority of patients during open label extension. Calculations with the Hodges–Lehmann estimator revealed treatment differences from placebo of –54.0% (95% Confidence Limits [CL] –85.0%, –25.1%) for the 250 mg Telotristaethyl group and –89.7% (95% CL –113.1%, –63.9%) for the 500 mg Telotristaethyl group ($p<0.001$ for both versus placebo). In addition, number of bowel movements/day was significantly reduced in Telotristaethyl groups. Durable responders as described above were only seen in Telotristaethyl groups and not in patients treated by placebo. There were no significant changes in frequency of flushing, abdominal pain and usage of rescue short acting somatostatin analog treatment by treatment with Telotristaethyl [29].

At the end of open label extension of TELESTAR and TELECAST, patients were offered continued treatment with Telotristaethyl in the TELEPATH extension study. Here, 124 subjects were enrolled and more than half of the study population completed the study. Incidence of treatment related adverse events was the primary endpoint and evaluation of long-term changes in patient-reported outcomes was the secondary endpoint. The mean cumulative duration of exposure was 102.63 weeks with a maximum of 234 weeks. Treatment compliance was high with 88.2%. Study drug discontinuation was observed in 17.7% of patients and 16.1% of patients died. Most frequent treatment related adverse events were diarrhea (35.5%), nausea (33.1%), and abdominal pain (32.3%). No statistically significant reduction from baseline in proportion of subjects reporting adequate relief of carcinoid syndrome symptoms associated with gastrointestinal events over the course of the study was reported. This study indicated that relief of gastrointestinal symptoms related to carcinoid syndrome was maintained during the course of TELEPATH study [30,31].

Clinical meaningful benefits of Telotristatethyl we also observed in the phase 4 study TELEPRO. Here, 369 patients were analyzed and experienced significant reductions in diarrhea and other carcinoid syndrome symptoms. Notably, at least 50% of patients reported a reductions of at least 30% in bowel movement frequency and a reduction of more than 2 bowel movements per day during a 3 months time frame [32]. Multiple studies are currently exploiting the potential of Telotristatethyl to reverse weight loss during treatment of cancers other than neuroendocrine neoplasias. Preclinical studies indicated that Telotristatethyl did not inhibit proliferation of neuroendocrine cancer cell lines [33]. However, the cell lines used my not reflect clinical behavior of neuroendocrine neoplasia. As such an exploitary clinical study to address such a potential effect is warranted. Medical treatment with Telotristatethyl in conjuction with somatostatin analogs in somatostatin analoge refrectory carcinoid syndrome has been included in current medical guidelines [34].

Telotristaethyl is registered under the brand name brand name Xermelo® on February 28th, 2017 in the US and September 2017 in Europe. Telotristaethyl is indicated for treatment of

carcinoid syndrome with somatostatin analog treatment in a dose of 250 mg tid, only due to lack of additional effect in the 500 mg tid group and increased adverse events. Telotristaethyl should be taken with food.

CONCLUSION

Telotristaethyl is the first in his class serotonin-synthesis inhibitor. Initially developed to treat diarrhea by multiple causes, it has been shown to effectively inhibit frequency of diarrhea associated with carcinoid syndrome. Telotristaethyl has little effects upon incidence of flushing episodes and abdominal pain. Since diarrhea is the main negative determinator of quality of life in patients with carcinoid syndrome, Telotristaethyl helps to improve all aspects of quality of life in these patients. Concerns were raised during development and conduit of clinical studies with Telotristaethyl in respect of incidence and worsening of depression. However, all clinical studies performed sofar have shown that Telotristaethyl is safe in regard of adverse events and treatment related adverse events. Telotristaethyl thus has become a valuable addition to somatostatin analogs for treatment of patients with carcinoid syndrome.

REGULATORY AFFAIRS

Telotristaethyl has been approved for treatment of diarrhea caused by carcinoid syndrome in combination with somatostatin analog therapies on February 28th, 2017 by FDA in the US and September 19th, 2017 by EMA in the EU, Norway and Iceland.

EXPERT COMMENTARY

Serotonin has a pivotal role in regulating intestinal peristalsis and secretion. Knockouts of tow isoforms of rate limiting enzyme of serotonin synthesis TPH1 and TPH2 indicated that peripheral serotonin production in intestinal L-cells and neurons is essential for regulation of gastrointestinal functions. Serotonin has also been shown to be main messenger of secretory diarrhea associated with carcinoid syndrome. Telotristaethyl has been developed as a small molecule inhibitor of TPH1 and TPH2 not crossing the blood brain barrier. Clinical studies indicated that serotonin levels are lowered by Telotristaethyl in healthy volunteers and reduced frequency of diarrhea in patients with carcinoid syndrome. Two phase II studies showed potential of Telotristaethyl in treating patients with carcinoid syndrome leading to two placebo-controlled double-blind and prospective phase III trials in patients with carcinoid syndrome. These trials, TELESTAR and TELECAST were the largest controlled clinical trials for patients with carcinoid syndrome so far and showed a significant reduction in frequency of bowel movements/day and serotonin levels determined by urinary serotonin metabolite 5HIAA. An extension of these trials, TELEPATH was an open label trial for patients continuing Telotristaethyl intake and was primarily designed to collect safety data. All trials up to date indicated that Telotristaethyl is safe in regard of adverse events and treatment related adverse events with very few incidents of newly diagnosed or worsening depression mainly in patients taking Telotristaethyl 500 mg tid. Since clinical studies indicated that Telotristaethyl at 250 mg tid and 500 mg tid had similar response rates on frequency of bowel movements, Telotristaethyl was registered at 250 mg tid in addition to somatostatin analog treatment in patients with secretory diarrhea associated with carcinoid syndrome in 2017 in US and europe under the brand name Xermelo®.

FIVE-YEAR VIEW

Telotristaethyl has been shown to be an effective additional treatment option for notoriously difficult to treat carcinoid syndrome. It is safe despite the concern of affecting central serotonin biosynthesis and may open additional treatment venues for functional bowel disorders or as an anti-neoplastic agent for treatment of serotonin producing neuroendocrine neoplasia.

DISCLOSURES

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