Exploring Telotristat Ethyl's Antiproliferative Effects in Patients with Carcinoid Syndrome: A Real-World Observational Study (TELEACE)

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Background

- Elevated serotonin has proliferative effects on neuroendocrine tumors (NETs) and is associated with increased mortality in patients with NETs and carcinoid syndrome (CS).[1,2]
- Inhibition of tryptophan hydroxylase 1 (TPH1), the first enzyme in the synthesis of serotonin, may have antitumor effects.[3-6]
- Telotristat ethyl (TE) is a TPH1 inhibitor indicated for carcinoid syndrome diarrhea inadequately controlled with somatostatin analogs; we hypothesized that TE might affect NET growth rate.

Methods

- Retrospective, pre/post design chart review of patients who received TE in US clinical practice
  - Physicians had to have treated ≥1 patient with TE who was diagnosed with advanced (unresectable, locally advanced or metastatic) NET and CS in the previous 12 months; eligible records had to include tumor size before and after TE initiation
- Eligible patients were ≥18 years of age at the time of TE initiation (the index date) with:
  - Confirmed diagnosis of advanced NET and documented CS or history of CS
  - TE treatment for ≥ 6 months after advanced NET and CS diagnosis
  - ≥2 radiological scans in the 12 months prior and ≥1 scan after TE initiation
  - NET and CS treatment information until death or for ≥ 6 months after TE initiation
  - Patients were excluded if they had a poorly differentiated NET based on grade (G3) or Ki67 index >20%; mixed tumor types; any clinical trial participation during the 6 months following TE initiation
- Primary endpoint was change in primary tumor size between pre- and post-TE periods
  - Average primary tumor size was defined as the largest diameter obtained from ≥2 radiological scan reports recorded in the medical chart within 12 months prior to TE initiation and ≥1 scan after TE initiation (**Figure 1**)
  - Secondary outcomes (not presented) included physician assessment of tumor response and CS symptoms, progression-free survival, time to tumor progression, body weight, and ECOG Performance Status

Statistical Analysis

- Sample size of 95 patients was required based on a 2-sided Wilcoxon signed-rank test with 80% power to detect a 3-percentage point change in tumor size between pre- and post-TE periods
- Descriptive statistics summarized participant characteristics
- Linear regression models assessed changes in tumor size after TE initiation, controlling for SSA treatment and additional NET treatment prior to TE initiation
- Longitudinal analyses of changes in tumor size used a generalized estimation equation with a log link and unstructured covariance matrix to model the repeated tumor scans in the pre- and post-TE periods, controlling for background NET and CS treatments

$$\log(y_{ij}) = \beta_0 + \beta_1 t_{ij} + \beta_2 SSA\_pre_{ij} + \beta_3 Additional\ tx\_pre_{ij} + \beta_4 Post\_TE_{ij}$$

Where, y_{ij} = tumor size for patient i at time j
t_{ij} = months since first tumor scan for patient i at time j
SSA_pre_{ij} = SSA treatment during pre-TE initiation period for patient i at time j
$Additional\ tx\_pre_{ij}$ = Additional NET treatment during pre-TE initiation period for patient i at time j
$Post\_TE_{ij}$ = Indicator for post-TE period for patient i at time j

Demographic and Clinical Characteristics

- 114 physicians participated, predominantly from community settings, and nearly all were oncologists (**Table 1**)
- Medical charts for 200 patients who initiated TE during the study period were included
  - Most patients had well differentiated NETs with primary gastrointestinal tumor site
  - Those with NET treatment information tended to receive SSAs before and after initiating TE
  - Patients received TE for an average of 12 months; 82% were still receiving TE at the time of data collection

Radiological Scans Before and After TE Initiation

- Patients had a mean of 2.3 documented radiological scans before TE and 1.2 after TE initiation
- Mean time from first scan to TE initiation was 5.6 months; 7.2 months from TE initiation to last scan (**Figure 1**)

Table 1. Demographic and clinical characteristics abstracted from medical records

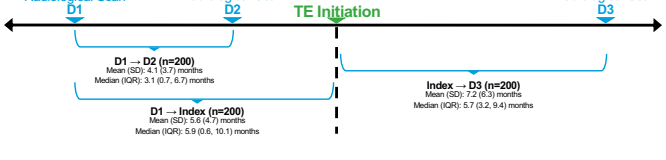
Characteristic	Patients (N=200)
Age at TE initiation, mean (SD)	60.6 (10.2)
Male, n (%)	113 (57)
Race or Ethnicity, n (%)	
White	148 (74)
Black or African-American	35 (18)
Asian	13 (7)
Native American or American Indian	3 (2)
Unknown/not sure	3 (2)
Ethnicity, Hispanic	24 (12)
Ethnicity, Non-Hispanic	176 (88)
NET histologic differentiation, n (%)	
Well differentiated	122 (61)
Moderately differentiated	78 (39)
Primary site of tumor, n (%)	
Gastrointestinal tract[a]	121 (61)
Pancreas	52 (26)
Lung, bronchus, larynx, trachea, other respiratory organ	19 (10)
Unknown primary origin	8 (4)
ECOG Performance Status, n (%)	
0	61 (31)
1	111 (56)

Characteristic	Patients (N=200)
Pre-TE tumors response by physician assessment, n (%)	
Worsened (progressed)	33 (17)
Stable	103 (52)
Improved (partial or complete response to treatment)	61 (31)

Treatment and Radiological Scans	Pre-TE initiation	Post-TE initiation
Patients with SSA treatment, n (%)	**(n=95)**	**(n=160)**
Octreotide, short-acting or rescue use	5 (5)	15 (9)
Octreotide, long-acting release, depot or infusion	66 (70)	95 (59)
Lanreotide	28 (30)	51 (32)
Pasreotide	0	3 (2)
Patients with non-SSA NET treatment, n (%)	**(n=35)**	**(n=52)**
Liver-directed therapy (nonsurgical)	12 (34)	9 (17)
Surgery	12 (34)	13 (25)
Chemotherapy	10 (29)	15 (29)
Targeted therapy	4 (11)	13 (25)
Interferon	2 (6)	5 (10)
Other therapy[b]	2 (6)	10 (19)
Radiological scans performed, n (%)	**(n=450)**	**(n=241)**
CT	256 (57)	135 (56)
^{68}Ga-DOTATOC SSTR PET	78 (17)	42 (17)
MRI	62 (14)	22 (9)
Other	119 (26)	68 (28)

Percentages may not sum to 100% due to multiple treatments per patient or due to rounding
[a] Gastrointestinal tumor sites included: appendix, cecum, colon, duodenum, ileum, jejunum, rectum, small bowel, small bowel mesentery, and stomach
[b] Other therapies included peptide-receptor radionuclide therapy (Lu-177), external beam radiation, and peptide-receptor radionuclide therapy (yttrium-90)

Figure 1. Timing of radiological scans during the pre- and post-TE treatment periods (Overall population)



Change in Tumor Size after TE Treatment

- A significant mean tumor size reduction of –0.59 cm (95% CI: –1.01 to –0.17) was estimated post-TE initiation after adjusting for background NET treatment (**Table 2**)
- Confirmatory analysis in a subgroup of patients (n=65) who had the same documented NET treatment before and after TE initiation yielded similar results (–0.63 cm; 95% CI: –1.24 to –0.02; P=0.044; **Figure 2**)
- Longitudinal analysis estimated an 8.5% decrease in tumor size after TE initiation (P=0.04; **Table 3**)

Table 2. Estimates of impact on post-TE changes in tumor size

Model Parameter	Estimate	95% CI	P value
TE treatment	–0.59	–1.01, –0.17	0.006*
SSA prior to TE initiation	0.25	–0.19, 0.68	0.263
NET treatment prior to TE	0.08	–0.49, 0.65	0.793

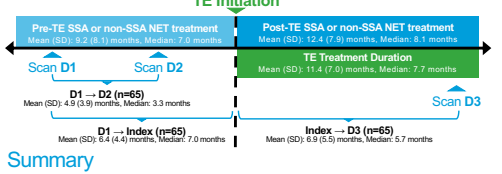
*Statistically significant at P<0.05
The average of documented tumor sizes pre- and post-TE initiation were used for each patient

Table 3. Longitudinal analysis of change in tumor size

Model Parameter	Estimate	95% CI	P value
Difference in tumor size pre- vs. post-TE initiation	–8.5%	–16.1%, –0.2%	0.045*
Covariate Estimates			
Time since first scan (mo)	0.5%	0, 1.1%	0.057
SSA prior to TE initiation	–7.6%	–19.0%, 5.3%	0.235
Pre-TE NET treatment	9.4%	–8.9%, 31.5%	0.335

*Statistically significant at P<0.05
Time of the first tumor scan during the pre-TE period was used as baseline
Negative estimate indicates a decrease in tumor size after TE initiation

Figure 2. Treatment duration and adjusted tumor size reduction in patients with the same SSA and/or NET treatment in the pre- and post-TE periods (n=65)



D1, date of first pre-TE radiological scan; D2, date of last pre-TE scan; D3, date of last post-TE scan. Figure is not drawn to scale.
The documented SSA and/or non-SSA treatments were initiated prior to D2 and were continued after TE initiation; 14 patients without documented SSA or non-SSA treatments pre- and post-TE initiation were included.
Only systemic therapies (ie, chemotherapies, targeted therapy, liver-directed therapy (non-surgical), interferon, PRRT) were included. Surgical procedures were excluded as they usually occurred at 1 time point and not were administered continuously.
Linear regression model was fitted for each patient subgroup, separately, assessing tumor size change between the pre- and post-TE periods adjusting for documented SSA and non-SSA NET treatment before TE. Tumor size from the pre- and post-TE period was evaluated as the average of documented tumor sizes pre-TE initiation and the average of documented tumor sizes post-TE initiation, respectively, for each patient. P values from the models were obtained using the Wald test.

Summary

Limitations

- Possible selection bias; the proportion of eligible charts submitted by each participating physician was unknown
- Data abstraction was limited to records with scan reports
- Heterogeneity in assessment of radiological scans and assessment schedules across clinical sites and physicians

Strengths

- Sample size was adequate for primary analysis of tumor size
- Pre/post design reduced potential for confounding and eliminated challenges of control group selection
- All scans were utilized in the longitudinal analysis of tumor size

Conclusions

- While additional prospective clinical studies are needed, these findings are consistent with the known preclinical mechanisms of serotonin as a potential tumor promoter
- This exploratory real-world study showed a possible role for TE to inhibit tumor growth in patients with advanced NETs and CS

References
1. Siddiqui EJ, et al. *BJU Int.* 2008; 2. Joish VN, et al. *Clin Ther.* 2019; 3. Huang L, Mellor A. *Curr Opin Oncol.* 2014; 4. Jiang S-H, et al. *Gastroenterol.* 2017; 5. Gautam J, et al. *Mol Cancer.* 2018; 6. Matthes S, Bader M. *Trends Pharmacol Sci.* 2018.