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5-Hydroxyindoleacetic Acid (5-HIAA) and Chromogranin A (CgA) as Biomarkers Secreted by Neuroendocrine Tumors (NETs): a Pooled Analysis of the ELECT and CLARINET Studies

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BACKGROUND: NETs are associated with elevated urinary 5-HIAA and plasma CgA. Pooled data from two studies (CLARINET, ELECT) were analyzed to assess relationships between urinary 5-HIAA and plasma CgA levels and treatment responses with lanreotide depot/Autogel in patients with NETs.

METHODS: CLARINET and ELECT were double-blind, placebo-controlled, randomized trials that evaluated progression-free survival (CLARINET) and symptom control (ELECT) with lanreotide (120 mg SQ monthly) in patients with nonfunctioning (CLARINET) and functioning (ELECT) NETs. Urinary 5-HIAA (liquid chromatography/tandem mass spectrometry) and plasma CgA (radioimmunoassay) were assessed at baseline and every 12 weeks for 96 weeks (CLARINET; if elevated at baseline or 48 weeks) or 48 weeks (ELECT). Biochemical response was defined as ≥50% reduction from baseline. Upper limit of normal (ULN) was prespecified as 41.6 µmol/d (CLARINET) and 77.9 µmol/d (ELECT) for 5-HIAA and 98.1 µg/L and 245 µg/L, respectively, for CgA; levels were standardized between trials. Changes from baseline were assessed with ANOVA and treatment effects with t-tests.

RESULTS: The pooled population (N=319) included 204 patients with nonfunctioning NETs (CLARINET) and 115 with NETs with carcinoid symptoms (ELECT). At baseline, 47% (128/273) had 5-HIAA levels >ULN; 74% (222/302) had CgA levels >ULN. At weeks 12 through 96, statistically significant reductions were observed with lanreotide vs placebo in 5-HIAA and CgA (Table 1). Biochemical response rates in patients with 5-HIAA >ULN were 70% (49/70) for lanreotide vs 31% (18/58) for placebo (P=0.0042), and for CgA >ULN were 57% (63/111) vs 23% (25/111) (P<0.0001). Patients with baseline levels >ULN and biochemical responses had longer median PFS than nonresponders (for both biomarkers: not reached vs 17.6 months, P<0.0001 for 5-HIAA, P=0.0069 for CgA).

CONCLUSION: Lanreotide significantly reduced 5-HIAA and CgA in functioning and nonfunctioning NETs, reductions which correlated with prolonged PFS. These biomarkers may be useful indicators in managing patients with NETs.

Table 1. Geometric Least-Squares Mean Changes, Adjusted for Baseline, in Urinary 5-HIAA (μmol/d) and Plasma CgA (μg/L) by Visit for Pooled CLARINET and ELECT Studies (ITT Population).

Time point	Treatment group (n)	GLSM ratio LAN/PBO (95% CI)	t-test P-value
Week 12 (5-HIAA)	LAN (100)/PBO (89)	0.63 (0.49, 0.81)	0.0003
Week 24 (5-HIAA)	LAN (99)/PBO (86)	0.55 (0.43, 0.69)	<0.0001
Week 36 (5-HIAA)	LAN (89)/PBO (76)	0.63 (0.46, 0.86)	0.0042
Week 48 (5-HIAA)	LAN (97)/PBO (80)	0.46 (0.35, 0.60)	<0.0001
Week 96 (5-HIAA)	LAN (69)/PBO (45)	0.48 (0.35, 0.66)	<0.0001
Week 12 (CgA)	LAN (139)/PBO (131)	0.55 (0.47, 0.66)	<0.0001
Week 24 (CgA)	LAN (125)/PBO (121)	0.58 (0.47, 0.71)	<0.0001
Week 36 (CgA)	LAN (117)/PBO (104)	0.52 (0.42, 0.64)	<0.0001
Week 48 (CgA)	LAN (106)/PBO (89)	0.57 (0.45, 0.73)	<0.0001
Week 96 (CgA)	LAN (79)/PBO (47)	0.53 (0.40, 0.70)	<0.0001

CgA, chromogranin A; CI, confidence interval; GLSM, geometric least-squares mean; ITT, intention-to-treat; LAN, lanreotide depot/Autogel; PBO, placebo; SE, standard error of GLSM.