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Patients with acromegaly not cured by surgery are often initially treated with injected peptide long-acting somatostatin receptor ligands (SRLs). Non-peptide small molecules can also activate the somatostatin receptor and do so with a high degree of precision for the target therapeutic receptor subtype. Paltusotine (formerly CRN00808) is a small molecule somatostatin type 2 (SST2) receptor agonist with high oral bioavailability (70%) and pharmacokinetic profile suitable for once daily dosing. In healthy volunteers, paltusotine has been shown to lower growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels. We hypothesized that patients with acromegaly could switch from injected SRLs to once daily oral paltusotine while maintaining baseline IGF-1 levels. ACROBAT Edge (NCT03789656) was a single-arm study designed to evaluate the safety and efficacy of switching from injected SRLs to paltusotine in patients with acromegaly. The primary analysis population consisted of those who had not achieved normal IGF-1 levels despite stable therapy with long-acting octreotide or lanreotide. Eligible patients received their last injection of SRL 4 weeks prior to switching to once daily oral paltusotine monotherapy for a 13-week treatment period. The starting dose of 10 mg per day was uptitrated in 10 mg increments at specified study visits to a maximal dose of 40 mg per day based on protocol specified study drug toleration and IGF-1 criteria. The primary endpoint was change in IGF-1 from baseline to the completion of the 13-week treatment period. Statistical testing was based on non-parametric Wilcoxon Sign Rank test of whether the median change is different from zero. In addition, the rise in IGF-1 during a 4-week washout period was used to provide supportive evidence of efficacy. Twenty-five patients were enrolled in the primary analysis group, three patients discontinued from the study for non-study drug related reasons, two during the treatment period and one during the washout period after completing treatment. The primary endpoint was achieved as paltusotine treatment resulted in no significant change in IGF-1 levels at week 13 compared to baseline [change in IGF-1 =-0.034 (-0.107, 0.107), median (IQR), p>0.6]. Of the 23 patients who completed the dosing period, 20 (87%) achieved IGF-1 levels at the end of treatment that were within 20% of baseline or lower. Median IGF-1 values rose significantly after paltusotine washout (p<0.0001). The most common treatment-emergent adverse events (>10%) included: headache, arthralgia, fatigue, peripheral swelling, paresthesia and hyperhidrosis. There were no discontinuations due to adverse events and no treatment related serious adverse events. These results suggest that patients with acromegaly treated with injected SRLs can switch to oral paltusotine while maintaining IGF-1 and that paltusotine appeared to be well tolerated.

Neuroendocrinology and Pituitary

CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Safety Results From MPOWERED, a Phase 3 Trial of Oral Octreotide Capsules in Adults With Acromegaly

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Background: Injectable somatostatin receptor ligands (iSRLs) have been a mainstay in acromegaly treatment. Oral octreotide capsules (OOC; MYCAPSSA®) were recently approved in the United States. Results from the placebo-controlled CHIASMA OPTIMAL and open-label CH-ACM-01 studies showed an OOC safety profile consistent with that of iSRLs with no new or unexpected safety signals. Results of the MPOWERED trial have enabled a comparison of OOC safety and efficacy with iSRLs.
Methods: To enter MPOWERED, patients must have the following: acromegaly diagnosis, biochemical control of acromegaly (insulin-like growth factor I <1.3 × upper limit of normal; mean integrated growth hormone <2.5 ng/mL), and ≥6 months' iSRLs treatment (octreotide or lanreotide). Eligible patients entered a 26-week Run-in phase to determine the effective OOC dose; responders at week 24 then entered a 36-week randomized controlled treatment (RCT) phase receiving OOC or iSRLs. Safety was monitored as adverse events (AEs) in both arms throughout the trial, including the RCT.
Results: In the RCT, incidence of treatment-emergent adverse events (TEAEs) was similar between groups; 39

patients (70.9%) in the OOC group and 26 (70.3%) in the iSRL group had ≥1 TEAE. 19 patients (34.5%) in the OOC and 15 (40.5%) in the iSRL group had treatment-related TEAEs. Occurrence was similar for serious AEs (OOC, 5.5%; iSRL, 8.1%) as well as TEAEs classified as severe (OOC, 9.1%; iSRL, 10.8%). One patient in the OOC group discontinued due to a TEAE. The most common gastrointestinal TEAEs were flatulence (OOC, 25.5%; iSRL, 21.6%), nausea (OOC, 20.0%; iSRL, 8.1%), diarrhea (OOC, 10.9%; iSRL, 13.5%), abdominal pain (OOC, 9.1%; iSRL, 8.1%), and constipation (OOC, 5.5%; iSRL, 13.5%). AEs of interest were infrequent, including cholelithiasis (OOC, n=0; iSRL, n=1 [2.7%]) and secondary hypothyroidism (OOC, n=1 [1.8%]; iSRL, n=0). In the iSRL group, 32.4% of patients reported injection site reactions (ISRs) during the RCT, and 47% of patients reported ISRs as part of the Acromegaly Treatment Satisfaction Questionnaire, a newly validated patient-reported outcome tool.[1]

Conclusion: Safety results from MPOWERED align with prior trials, showing that the OOC safety profile is consistent with that of iSRLs as well as the acromegaly disease burden. No new or unexpected safety signals were identified during the trial. Safety results were mostly similar between OOC and iSRLs, although patients in the OOC group did not experience any ISRs.

[1]Fleseriu M, et al. *Pituitary*. 2020 Aug;23(4):347-358.

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CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Treatment of Postsurgical Clinically Nonfunctioning Pituitary Adenomas Remnants With Cabergoline

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Background: The standard first-line therapy for clinically nonfunctioning adenomas (NFPA) is transsphenoidal surgery, however there is no consensus of the optimal postsurgical treatment for residual adenoma. Medical therapy, such as cabergoline (CAB), may be an alternative for preventing growth of postoperative pituitary tumor remnants. The moment of introduction dopamine agonist (DA) is still uncertain. **Objective:** To assess tumor behavior in patients who used CAB in the postoperative period. Design and methods: A retrospective cross-sectional study was performed with twenty one patients with NFPA treated surgically. All patients stayed with residual tumor and were divided in two groups: patients who received CAB early in postoperative period (Group A, n=6) and when tumor growth were detected during follow-up (Group B, n=15). CAB dosage was 1.5mg or 3.5mg per week. A change in tumor size was considered significant and recorded as such if a difference of at least 5 mm in major diameter was observed. MRI was performed four months after surgery and yearly thereafter in all patients. Subjects in treatment groups also underwent MRI 6 months following medical therapy. No patients were treated by irradiation before or during the follow-up. Statistical analysis was performed using the Fisher's exact test. **Results:** From 21 patients, 11 were men and 10 women with similar mean age in two groups (p=0.651). MRI in group A showed stabilization of residual tumor in 50% (3/6) and tumor reduction in 50% (3/6) in group A. In group B, tumor shrinkage was observed in 47% (7/15), stabilization in 27% (4/15) and enlarged in 27% (4/15). No statistical difference between groups was obtained regarding tumor shrinkage and stabilization with the treatment (Group A n=6 *versus* Group B n=11, p=0.281). In contraste Batista *et al*., 2016, have already shown that CAB was effective alternative in residual tumor reduction in a study with 74 patients. **Conclusion:** A multicenter study is necessary to define the role of CAB in the treatment of residual tumor in postsurgical patients with NFPA.

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CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Use of Oral Concomitant Medications in Patients With Acromegaly

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Background: Acromegaly is a rare condition characterized by excess GH and IGF-I levels.[1] Injectable somatostatin analogs (SSAs) are recommended as first-line medical treatment.[2] Comorbidities including diabetes, hypertension and hypopituitarism reduce quality of life in patients with acromegaly;[3,4] treatment for these includes oral medications. We assessed the most common oral medications used by patients with acromegaly during treatment with lanreotide autogel 120 mg (LAN).

Methods: This post-hoc analysis reports data from the PRIMARYS[5] (NCT00690898) and LEAD[6] (NCT00701363) open-label trials in which adult patients with acromegaly received LAN. PRIMARYS patients were SSA/surgery-naïve with uncontrolled acromegaly, LEAD patients were previously treated with octreotide long-acting release with normal age-adjusted IGF-I levels for two consecutive measurements.

Results: PRIMARYS included 90 patients: mean (standard deviation [SD]) age 49.5 (12.4) years; 47.8% male; mean (SD) baseline IGF-I 809.9 (300.0) µg/L, 97.8% had IGF-I >1.3xULN. LEAD included 124 patients: mean (SD) age 55.4 (10.9) years; 37.1% male. Median (range) time since diagnosis was 99.0 (27.0-1,261.0) days (PRIMARYS) and 7.1 (0.5-27.0) years (LEAD). 51.1%, 24.4% and 3.3% of participants in PRIMARYS had a history of cardiovascular disorders (including hypertension), diabetes/glucose intolerance, and hypopituitarism/hypothalamic disorders; the corresponding values in LEAD were 69.4%, 33.9% and 18.5%. 83.3% of participants in PRIMARYS and 86.3% in LEAD used ≥1 concomitant oral medication with LAN. Of these participants, >50% used >3 types (PRIMARYS: 53.3%;