

0072 - CLINICOPATHOLOGICAL AND MOLECULAR PROFILE OF BRAZILIAN PATIENTS WITH CUSHING SYNDROME DUE TO PRIMARY PIGMENTED MICRONODULAR ADRENAL HYPERPLASIA

Mode: Research paper

Thematic Unit: Adrenals

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Background/Objectives: To describe the clinicopathological and molecular characteristics of Brazilian patients with pigmented nodular adrenocortical disease (PPNAD) with or without Carney complex (CNC), a population yet not reported in the literature.

Methods: Single-center cohort of patients with Cushing syndrome caused by histopathologically confirmed PPNAD. Molecular strategy: PRKAR1A gene sequencing by Sanger followed by whole-exome sequencing (WES). Clinicopathological features were compared using Welch's test and proportions by Fisher's test.

Results: 85.7% of the 14 patients had CNC, and 28.6% had a family history of PPNAD or CNC. Most were women (64.3%), with a median symptom-onset age of 9.7 years (range: 2-29.8). The median age at diagnosis was 14.9 years (range: 3.3-67.1), and the median symptom duration was 2.8 years (range: 0.3-37.3). Weight gain (50%), lentiginosis (21.4%), and short stature (14.2%) were the most frequent complaints. Following the diagnosis, in CNC patients, lentiginosis was found in 50%, breast nodules in 43%, and cardiac myxomas in 29%. On adrenal imaging (n= 12), 66.7% had hyperplasia or nodules, 50% had both, and 2 patients had normal imaging. Median baseline cortisol was

23.4 µg/dL (7.7–26, n=10). ACTH was suppressed (4; MIKS HOSPITAL⁵; CENTRE HOSPITALIER UNIVERSITAIRE SAINTE-JUSTINE⁶; CHILDREN'S HOSPITAL, TOULOUSE UNIVERSITY HOSPITAL⁷; OSLO UNIVERSITY HOSPITAL⁸; UCSF BENIOFF CHILDREN'S HOSPITAL OAKLAND⁹; HAUKELAND UNIVERSITY HOSPITAL¹⁰; KK WOMEN'S AND CHILDREN'S HOSPITAL¹¹; HOSPITAL UNIVERSITARIO VIRGEN DE LA VICTORIA¹²; NHS GREATER GLASGOW AND CLYDE¹³; FONDAZIONE POLICLINICO A GEMELLI IRCCS¹⁴; VANDERBILT HEALTH¹⁵; HOSPITAL DE PEDIATRÍA GARRAHAN¹⁶; HÔPITAL FEMME MÈRE ENFANT, HOSPICES CIVILS DE LYON¹⁷; BRIDGEBIO PHARMA¹⁸; JOHNS HOPKINS UNIVERSITY¹⁹

Background/Objectives: Infigratinib is an oral FGFR1–3 inhibitor under evaluation for the treatment of achondroplasia (ACH) in the PROPEL clinical program, which includes an observational run-in study (PROPEL), followed by interventional phase 2 (PROPEL 2), phase 3 (PROPEL 3), and open-label extension (PROPEL OLE) studies. This longer-term efficacy



analysis (LTEA) aims to evaluate the longitudinal therapeutic effects of treatment with infigratinib 0.25 mg/kg/day.

Methods: Participants from PROPEL, PROPEL 2, and PROPEL 3 were potentially eligible to roll over to the open-label extension study, PROPEL OLE, to receive infigratinib 0.25 mg/kg/day until adult height. The LTEA is a descriptive pooled analysis of prospectively collected data from participants in the PROPEL program who received infigratinib 0.25 mg/kg/day for at least one year (efficacy population). The primary endpoint is absolute value and change from baseline (CFBL) in height z-score relative to CLARITY ACH reference data, and a key secondary endpoint is absolute value and CFBL in upper-to-lower body segment ratio. Safety data are summarized for all participants who initiated treatment at 0.25 mg/kg/day and received at least one dose of infigratinib in PROPEL OLE (safety population).

Results: The efficacy population included 94 participants, and the safety population included 146 participants. Mean (SD) height z-score relative to CLARITY was 0.09 (0.85) at baseline (n=94), 0.50 (0.84) at Year 1 (CFBL, 0.41 [0.24]; n=94), 0.71 (0.83) at Year 2 (CFBL, 0.66 [0.32]; n=22), and 1.28 (0.50) at Year 3 (CFBL, 0.92 [0.39]; n=11). Mean (SD) upper-to-lower body segment ratio was 2.07 (0.23) at baseline (n=94), 2.00 (0.17) at Year 1 (CFBL, -0.07 [0.12]; n=94), 1.98 (0.20) at Year 2 (CFBL, -0.15 [0.19]; n=22), and 1.84 (0.14) at Year 3 (CFBL, -0.15 [0.09]; n=11). In the safety population, treatment-emergent adverse events (TEAEs) were reported in 102 (69.9%) participants, and most events were mild or moderate. Grade 3 and serious TEAEs were infrequent (n=5 [3.4%] and n=3 [2.1%], respectively), with no grade 4 or 5 TEAEs. No treatment-related grade 3 or serious TEAEs, or TEAEs leading to discontinuation, were reported.

Conclusion: Infigratinib demonstrated sustained improvements in growth and body proportionality, with a well-tolerated safety profile, in children with ACH. Ongoing follow-up will further characterize the long-term efficacy and safety of infigratinib as data mature.

