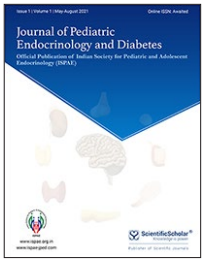
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ispae-jped.com/

Journal of Pediatric Endocrinology and Diabetes



Ped Endo Journal Scan

Ped Endo Journal Scan

Kriti Joshi[1]

[1]Department of Endocrinology and Diabetes, Queensland Children's Hospital, South Brisbane, Queensland, Australia.

***Corresponding author:**
Kriti Joshi,
Department of Endocrinology and Diabetes, Queensland Children's Hospital, South Brisbane, Queensland, Australia.

kriti.joshi@health.qld.gov.au

Received: 25 July 2024
Accepted: 25 July 2024
Published: 10 August 2024

DOI
10.25259/JPED_33_2024

Quick Response Code:

Phase 3 trial of crinecerfont in pediatric congenital adrenal hyperplasia

Sarafoglou K, Kim MS, Lodish M, Felner EI, Martinerie L, Nokoff NJ, *et al*. CAHtalyst pediatric trial investigators. *N Engl J Med*. 2024 Jun 2. doi: 10.1056/NEJMoa2404655. Epub ahead of print. PMID: 38828945.

Objective: The objective of this study was to evaluate the efficacy of crinecerfont, a new corticotropin-releasing factor type 1 receptor antagonist, in reducing androstenedione levels and ameliorating the need for supraphysiologic doses of glucocorticoids in children with congenital adrenal hyperplasia (CAH).

Study Methodology and Results: This was a phase 3, multinational, double-blind, randomized, and placebo-controlled trial followed by an open-label extension period. 2–17-year-old children with CAH receiving glucocorticoids in a dose of >12 mg/m^2/day of hydrocortisone equivalent were eligible for the study. Participants were randomized in a 2:1 manner to receive oral crinecerfont or matched placebo for 28 weeks. After 4 weeks, the glucocorticoid dosing was stepwise titrated down to a target of 8.0–10.0 mg/m^2/d in hydrocortisone dose equivalent if androstenedione levels remained in the target range (≤120% of the baseline level or within the reference range). The primary endpoint was the change in the androstenedione level from baseline to week 4. The key secondary endpoints were the change in the serum 17-hydroxyprogesterone (17OHP) level from baseline to week 4 and the percent change in the daily dose of glucocorticoid from baseline to week 28 while androstenedione was controlled. The study enrolled 103 participants, 69 in the crinecerfont, and 34 in the placebo group. At week 4, the crinecerfont group had a substantial least-squares mean decrease in the androstenedione level from baseline to week 4 (−197 ng/dL [−6.9 nmol/L]), as compared with an increase in the placebo group (71 ng/dL [2.5 nmol/L]) (least-squares mean difference, −268 ng/dL [−9.3 nmol/L]; $P < 0.001$). 17OHP also decreased substantially from baseline to week 4 in the crinecerfont group and increased slightly in the placebo group (least-squares mean difference, −6421 ng/dL [−195 nmol/L]; $P < 0.001$). In the crinecerfont group, the glucocorticoid dose was reduced from baseline to week 28 while control of the androstenedione level was maintained, whereas the dose in the placebo group was increased (least-squares mean percent change from baseline, −18.0% vs. 5.6%; least-squares mean difference, −23.5 percentage points; $P < 0.001$) body mass index standard deviation scores decreased in the crinecerfont group and increased in the placebo group at week 28. The frequency and severity of adverse events were similar in the two trial groups.

Critical Review: This trial demonstrated that in pediatric participants with CAH, reduction in the glucocorticoid doses to the target physiologic range could be accomplished with the use of crinecerfont with apparent safety. This is an important trial that explores a new therapeutic option for patients with CAH, who face substantial disease burden and adverse health outcomes

throughout their lives. A larger study of longer duration would be needed to assess meaningful improvement in bone age- and growth-related endpoints.

Setmelanotide for the treatment of acquired hypothalamic obesity: A phase 2, open-label, and multicenter trial

Roth CL, Scimia C, Shoemaker AH, Gottschalk M, Miller J, Yuan G, *et al*. *Lancet Diabetes Endocrinol*. 2024 Jun;12(6):380-389.

Objective: The objective of this study was to investigate the safety and efficacy of setmelanotide for the treatment of hypothalamic obesity.

Study Methodology and Results: This was a phase 2, open-label, and multicentric trial which enrolled participants between the ages of 6–40 years with obesity subsequent to hypothalamic damage following surgery, chemotherapy, or radiation for nonmalignant brain tumors affecting the hypothalamic region. Following 4 weeks of dose up-titration, participants were treated with 3 mg of daily subcutaneous setmelanotide as tolerated, once a day for another 12 weeks, for a total treatment duration of 16 weeks. The primary endpoint was the proportion of patients who had a reduction in body mass index (BMI) of at least 5% from baseline after 16 weeks of setmelanotide treatment, compared with a historic control rate of <5% for patients with hypothalamic obesity. Key secondary endpoints were the proportion of patients younger than 18 years who had a reduction in BMI Z-score of at least 0.2 points and the proportion of patients aged 18 years or older who had a reduction in body weight of at least 5% after 16 weeks of setmelanotide. Participants who reached the primary endpoint were eligible to continue in a long-term extension study. The study enrolled 18 participants of which 16 completed the trial. The mean age of the subjects was 15.0 years (standard deviation [SD] = 5.3) with a mean BMI of 38.0 kg/m^2 (SD = 6.5). Craniopharyngioma was the most common tumor type (n = 14); other tumor types included hamartoma (n = 3) and juvenile pilocytic astrocytoma (n = 1). Sixteen (89%) of 18 patients met the primary efficacy endpoint of a reduction in BMI of at least 5% from baseline after 16 weeks of treatment (90% confidence interval 69–98%, P < 0·0001. The collective mean percent change among all patients was −15% in BMI (SD = 10), −13% in bodyweight (SD = 9), and −10% in waist circumference. The mean change from baseline in maximal daily hunger scores was −2.9 (SD = 2.3) at week 16 (n = 11), a 45% decrease from the mean baseline score (6.6, SD = 1.6; n = 12). Mild-to-moderate treatment-related side effects were seen in all patients and included nausea (n = 11 [61%]), vomiting (n = 6 [33%]), skin hyperpigmentation (n = 6 [33%]), diarrhea (n = 4 [22%]), and COVID19 infection (n = 4 [22%]). Two patients discontinued the study due to adverse events (one hyperpigmentation and one increased levels of liver transaminases); both events were moderate in severity and related to the study drug. Twelve subjects who had completed at least 12 months of treatment at the time of publication had a mean change in BMI of −26% (SD = 12) from the index trial baseline.

Critical Review: This is an important study that explores novel therapeutic options for the management of this challenging condition. With setmelanotide therapy, adherent patients reversed the trajectory of weight gain and experienced a rapid and consistent decrease in BMI. A global phase 3 placebo-controlled randomized control trial of setmelanotide in patients with hypothalamic obesity is ongoing and will provide further information regarding efficacy and safety in this population.

The late effects of hematopoietic stem cell transplants in pediatric patients: A 25-year review

Lee SL, Nguyen QN, Ho C, James S, Kaur A, Lim A, *et al*. *J Clin Endocrinol Metab*. 2024 Mar 27: dgae196. doi: 10.1210/clinem/dgae196. Epub ahead of print. PMID: 38534046.

Objective: The objective of this study was to document endocrine sequelae and other late effects of all hemopoietic stem cell transplantation (HSCT) recipients.

Study Methodology and Results: This was a retrospective review of all patients who underwent allogeneic HSCT at the Royal Children's Hospital (RCH) Melbourne and had been followed up for at least 5 years post-transplant. The main outcomes were incidence of endocrinopathies, fertility, growth, bone, and metabolic status; and subsequent malignant neoplasms (SMNs). A total of 384 children and adolescents underwent the first allogeneic HSCT at RCH during the review period. One hundred and forty patients had died, and 16 were lost to follow-up within 5 years post-transplant. The remaining 228 formed the study cohort. Gonadotoxicity was significantly more common in females than males (P < 0.001) and after total body irradiation (TBI)-based conditioning than after myeloablative chemotherapy conditioning regimens (P < 0.001). Those with premature ovarian failure (POI) had received significantly higher cumulative cyclophosphamide equivalent doses. In men who had received TBI +/− additional testicular irradiation or therapeutic testicular irradiation without TBI, 97% had evidence of impaired spermatogenesis (raised follicle-stimulating hormone), with 29.7% having complete Leydig cell failure.

In contrast, among those conditioned with myeloablative chemotherapy without testicular irradiation, only 50% with available gonadotropin levels had impaired spermatogenesis; 7.5% had complete, and 8.3% compensated Leydig cell dysfunction. Younger age at HSCT was predictive of biochemically normal testicular function after HSCT. Of 37 sexually active females transplanted for malignancies, eight had naturally conceived pregnancies, and five of

these women had been diagnosed with POI 5–16 years before conception. Growth hormone axis disruption (including growth hormone-releasing hormone defect) was documented in 30% of those with short stature and 5.2% with normal final heights. About 51% had thyroid nodules at a median follow-up of 11.8 years (range 5.1–28) post-HSCT; the median time since first head/neck radiation exposure was 12 years (range 5.1–38). About 30% of these had carcinoma at a median of 9 years (range 5–17) after transplant. Both benign and malignant thyroid nodules were strongly associated with head and neck radiation ($P < 0.001$) and younger age at first head/neck radiation exposure (median 7.0 years vs. 10.9 years in those with no nodules. About 26.2% developed hypothyroidism post-transplant. Abnormal glucose metabolism developed in 7.3%, lipid abnormalities in 50%, hypertension in 20.2%, and both excess and underweight were reported. About 13% developed SMNs. The proportion of survivors with chronic health conditions after myeloablative conditioning increased with increasing duration of follow-up, with those conditioned with TBI being most severely affected. About 7.45% of 5-year survivors had died, with SMN being the predominant cause of death.

Critical Review: This study provided important long-term follow-up data on chronic health conditions affecting post-HSCT recipients and demonstrates that endocrinopathies, reproductive disorders, and second malignancy are three critical sequelae for survivors.

From Klinefelter syndrome to high-grade aneuploidies: Expanding the gene-dosage effect of supernumerary X chromosomes

Spaziani M, Carlomagno F, Tarantino C, Angelini F, Paparella R, Tarani L, *et al. J Clin Endocrinol Metab*. 2024 Jul 12;109(8):e1564-e1573. doi: 10.1210/clinem/dgad730.

Objective: The objective of this study was to investigate the effect of supernumerary X chromosomes (extra-Xs) on the clinical, hormonal, metabolic, and echocardiographic features of patients with high-grade aneuploidies (HGAs).

Study Methodology and Results: This was a cross-sectional study that compared 23 subjects with HGAs and 46 age-matched subjects with 47, XXY Klinefelter syndrome (KS). An additional cohort of 46 subjects with KS, matched by pubertal status, were included for validation of significant findings, as well as gonadal development and function parameters. All patients underwent a thorough clinical examination, a hormonal and metabolic evaluation, and a detailed ultrasonographic study of the testes. To assess the effect of extra-Xs on phenotype, patients with HGAs and KS were classified as follows: group 1, XX/- karyotypes (i.e., 47, XXY; 48, XXYY); group 2, XXX/- karyotypes (i.e., 48, XXXY; 49, XXXYY); and group 3, XXXX/- karyotypes (49, XXXXY). The pubertal stage was significantly delayed in HGAs subjects compared to age-matched KS individuals ($P = 0.023$). A negative trend was observed for height standard deviation score (SDS) with an increasing number of X chromosomes, whereas the HGA group demonstrated higher weight and body mass index SDS than the KS group. A difference was observed in ultrasonographic bitesticular volume between the KS and HGA age-matched groups, with a decreasing linear trend as the number of supernumerary Xs increased, that is, 5.93 mL (5.24, 6.27) for group 1 versus 3.89 mL (2.02, 6.33) for group 2 versus 1.26 mL (0.56, 1,98) for group 3. Serum testosterone (T) levels showed a linear decrease with the increasing number of extra-Xs, although LH, FSH, and sex hormone-binding globulin levels were similar.

Furthermore, the HGA group showed lower calculated free T concentrations and inhibin B levels, often at or below the limit of detection. A progressive linear increase in adrenocorticotropic hormone (ACTH) and a decrease in cortisol/ACTH ratios were found. The HGA group showed higher LDL and lower HDL cholesterol levels than the age-matched KS group. The HGA group showed higher glucose and insulin levels at both basal and 2-h post-oral glucose tolerance tests and a higher homeostatic model assessment index. The cardiac evaluation revealed a linear association with reduced left and right end-diastolic diameters and reduced ejection fraction.

Critical Review: This is one of the largest reports on subjects with HGA which demonstrates a dosage effect of extra-Xs on both gonadal and extra-gonadal clinical, endocrine, metabolic, and cardiac characteristics. However, the distribution across phenotypes was uneven, which could have limited the statistical power. While adrenal function abnormalities have been reported in this study, the mechanism of the same is not elucidated. A larger registry-based study might be needed to define these associations better.

Pediatric medullary thyroid carcinoma: Clinical presentations and long-term outcomes in 144 patients over six decades

Hensley SG, Hu MI, Bassett RL, Ying AK, Zafereo ME, Perrier ND, *et al. J Clin Endocrinol Metab*. 2024 Mar 4:dgae133. doi: 10.1210/clinem/dgae133. Epub ahead of print. PMID: 38441533.

Objective: The objective of this study was to describe the clinical presentations and long-term outcomes of a large cohort of children and young adults with sporadic medullary thyroid carcinoma (sMTC) compared with hereditary medullary thyroid carcinoma (hMTC).

Study Methodology and Results: This was a retrospective study of patients diagnosed with medullary thyroid carcinoma (MTC) between 1961 and 2019 at an age under or equal to 21 years at a single tertiary referral center. Patients were

classified as sMTC or hMTC based on germline RET proto-oncogene analysis, clinical phenotype, and/or family history of MTC, pheochromocytoma, and/or hyperparathyroidism. hMTC was further subdivided into MEN2A or MEN2B based on the specific RET pathogenic variant or the presence of the characteristic extra-endocrine clinical features of MEN2B. Forty-four patients ≤ age 21 years were identified, of which 20 (14%) had sMTC and 124 (86%) had hMTC. Among the hereditary cases, 79 (64%) had MEN2A and 45 (36%) had MEN2B. Patients with sMTC were older than patients with hMTC at the time of diagnosis (median of 19 years vs. 13 years, $P < 0.0001$) and they had higher baseline levels of calcitonin (CTN) (889 × upper limit of normal [ULN] vs. 14 × ULN, $P = 0.00026$) and carcinoembryonic antigen (191 × ULN vs. 1 × ULN, $P < 0.0001$). Patients with sMTC had a higher stage grouping at diagnosis (stage IV at diagnosis in 79% sMTC vs. 38% hMTC, $P = 0.001$). Primary tumors in patients with sMTC were also larger (median 2.5 vs. 0.8 cm, $P < 0.0001$), more likely to be unifocal (53% vs. 17%, $P = 0.0005$), and associated with a higher rate of lateral neck lymph node metastases (79% vs. 35%, $P = 0.0035$). However, rates of distant metastases (DM) at diagnosis were no different between groups (25% vs. 11%, $P = 0.12$). Patients with sMTC were more likely to have persistent disease (95% vs. 64%, $P = 0.0045$) and DM (79% vs. 37%, $P = 0.00084$). In contrast, patients with hMTC were more likely to have no evidence of disease at the last follow-up (36% vs. 5%, $P = 0.0045$). Among 77 patients diagnosed clinically, not by family history (20/20 sMTC and 57/124 hMTC), there was no difference in the initial stage ($P = 0.27$), presence of DM at diagnosis ($P = 1.0$), disease status at last follow-up ($P = 0.13$), overall survival ($P = 0.57$), or disease-specific survival ($P = 0.87$). Of 138 evaluable patients, 19 patients (14%) died during follow-up, including six sMTC, four MEN2A, and nine MEN2B patients. Twelve (9%) died from MTC. Of the 12 sMTC tumors that underwent somatic testing, 11 (91%) had an identifiable alteration: ten RET gene alterations and one anaplastic lymphoma kinase fusion.

Critical Review: This is an important study presenting the largest population and longest follow-up of pediatric MTC and expands our knowledge of the clinical phenotype of this rare neuroendocrine malignancy. The study reports that even sMTC do well over the short-term with a good overall and disease-free survival rate.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient consent was not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

How to cite this article: Joshi K. Ped Endo Journal Scan. J Pediatr Endocrinol Diabetes. 2024;4:45-8. doi: 10.25259/JPED_33_2024