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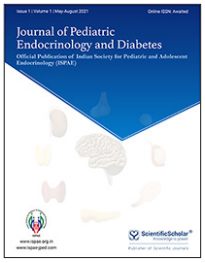

Ped Endo Journal Scan

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Baricitinib and β-cell function in patients with new-onset type 1 diabetes

Waibel M, Wentworth JM, So M, Couper JJ, Cameron FJ, MacIsaac RJ, *et al. N Engl J Med.* 2023 Dec 7;389(23):2140-2150. doi: 10.1056/NEJMoa2306691.

Objective: The objective of this study was to assess if baricitinib could preserve β-cell function and improve metabolic measures in patients with new-onset type 1 diabetes mellitus (TID).

Study Methodology and Results: This was a phase 2, multicenter, investigator-initiated, double-blind, randomized, and placebo-controlled trial that enrolled individuals between the ages of 10–30 years with T1D diagnosed within 100 days of enrolment. Participants were randomized in a 2:1 manner to receive baricitinib (4 mg/day) or matched placebo orally for 48 weeks. The primary outcome was the mean C-peptide level, calculated with the use of the trapezoidal rule as the area under the concentration-time curve (AUC) divided by 120 min during a 2-hours mixed-meal tolerance test at week 48. Secondary outcomes were the glycated hemoglobin (HbA1C) level, the total daily insulin dose, and continuous glucose monitoring metrics. The study enrolled 91 participants, 60 in the baricitinib and 31 in the placebo group. At week 48, the median of the mixed-meal-stimulated mean C-peptide level in the baricitinib group was 0.65 nmoL/L/min (interquartile range, 0.31–0.82) versus 0.43 nmoL/L/min (interquartile range, 0.13–0.63) in the placebo group (adjusted mean difference in the ln [AUC + 1], 0.13; 95% confidence interval [CI], 0.06–0.20; $P = 0.001$). The mean daily insulin dose at week 48 was 0.41 U/kg body weight/day (95% CI, 0.35–0.48) in the baricitinib group and 0.52 U/kg body weight/day (95% CI, 0.44–0.60) in the placebo group. The HbA1C level at week 48 was 7.0% (95% CI, 6.6–7.4) in the baricitinib group and 7.5% (95% CI, 6.9–8.0) in the placebo group. The frequency and severity of adverse events were similar in the two trial groups.

Critical Review: This trial demonstrates that a 48-week treatment with baricitinib in individuals with T1D preserved beta cell function as evinced by the mixed-meal–stimulated mean C-peptide level. This is a very important study that adds to the armamentarium of immune-modulatory treatments in T1D, particularly as baricitinib is an oral medication with a favorable safety profile. This trial should pave the way for larger trials involving younger children and earlier stages of T1D.

Clinical characteristics and outcomes of prolactinomas in children and adolescents: A large retrospective cohort study

Yang Y, Ke X, Duan L, Yang H, Gong F, Pan H, *et al.* J Clin Endocrinol Metab. 2024 Jan 2:dgad769. doi: 10.1210/clinem/dgad769.

Objective: The objective of this study was to describe the characteristics and outcomes of a large cohort of pediatric prolactinomas from China.

Study Methodology and Results: This study was a retrospective review of prolactinoma cases under 20 years of age from a single center in China. The investigators collated clinical, biochemical, and radiological data from these patients. Tumors were classified according to size as microadenomas (diameters <10 mm), macroadenomas (10 mm ≤ diameters ≤40 mm), and giant adenomas (diameters >40 mm). Dopamine agonist (DA) resistance was defined as the absence of prolactin (PRL) control after DA treatment for at least three months, with a maximal dose ≥ 15 mg/d for bromocriptine or 2 mg/w for cabergoline. PRL control was determined by PRL normalization (≤ 30 ng/mL) with or without DA treatment. Cure was defined as long-term PRL normalization without the need for DAs after medication, surgery, or radiotherapy.

The study enrolled 170 patients, of which 67.6% were females and 32.4% were males. Of these, four subjects had an underlying genetic cause, three had multiple endocrine neoplasia type I syndrome, and one had McCune–Albright syndrome, with all patients presenting with DA-responsive macroprolactinomas. Basal prolactin levels were found to be significantly higher in boys than in girls (median 383.0 ng/mL vs. 198.8 ng/mL, $P = 0.031$). A total of 34.2% were microadenomas, 61.2% macroadenomas, and 4.6% giant adenomas and were not different between genders. However, males demonstrated larger tumors, maximal median diameter 21.0 mm vs. 12.0 mm, $P = 0.005$. In the 110 patients (64.7% of the total 170) with documented neuroradiological characteristics, invasive growth (Knosp grade ≥3) was detected in 24.5% of patients, more frequently in males than in females (41.9% vs. 17.7%, $P = 0.016$). Most girls presented with menstrual disturbances (84.5%) and galactorrhea in 45.7%, with boys presenting with headache (42.6%), visual disturbance (27.8%), reduced height velocity (25.9%), and gynecomastia (31.5%). About 79.2% of patients received DA as first-line therapy, among whom 30.8% (41/133) underwent second-line surgery. Surgery as primary treatment was needed in 20.8% of patients. About 22.5% (25/111) of patients were resistant to DA therapy. Patients with DA resistance had higher PRL levels (median 1461.4 ng/mL vs. 182.2 ng/mL, $P < 0.001$), larger tumor maximal diameters (median 18.5 mm vs. 11.0 mm, $P < 0.001$), and more cavernous sinus invasion (50.0% vs. 13.0%, $P = 0.007$) compared with the responsive ones. Patient preference was the main reason for first-line surgery, with DA resistance the main one for second-line surgery. A total of 32.9% of post-surgical patients achieved long-term remission, with cavernous sinus invasion showing a negative correlation with remission in multivariate analysis ($P = 0.025$).

Critical Review: This study provides important data on a large cohort of children with prolactinomas in children. The study highlights that while medical management still appears to be effective in a vast proportion of children, a select subgroup of patients might benefit from surgical management.

Dasiglucagon for the treatment of congenital hyperinsulinism: A randomized phase 3 trial in infants and children

Thornton PS, De Leon DD, Empting S, Zangen D, Kendall DM, Birch S, *et al. J Clin Endocrinol Metab*. 2023 Nov 1:dgad648. doi: 10.1210/clinem/dgad648.

Objective: The objective of this study was to study the efficacy and safety of dasiglucagon delivered through a subcutaneous infusion pump on rates of hypoglycemia in infants and children with congenital hyperinsulinism (CHI) (aged 3 months–12 years) when added to the standard of care (SoC) therapies.

Study Methodology and Results: This was an open-label and multicenter randomized trial that enrolled children between the ages of 3 months–12 years with a diagnosis of CHI who had ≥3 episodes of hypoglycemia/week (self-measured plasma glucose [SMPG] <3.9 mmoL/L). Patients were randomly assigned to continue receiving SoC alone or SoC plus dasiglucagon (10–70 μg/h through an infusion pump) for four weeks (Part 1). In Part 2, all patients received SoC plus dasiglucagon for four weeks. The primary endpoint was the rate of hypoglycemia (average weekly number of episodes of SMPG <3.9 mmoL/L) during weeks 2–4. A total of 16 participants were randomized to each arm of the study. No statistically significant difference was found in the rate of SMPG-detected hypoglycemia episodes between dasiglucagon + SoC versus SoC alone during weeks 2–4 (primary analysis: Mean [95% confidence interval, CI] 0.85 [0.54; 1.36], $P = 0.5028$. Dasiglucagon treatment resulted in a 43% reduction in CGM-detected hypoglycemia (<3.9 mmoL/L) compared to SoC alone during weeks 2–4 (*post hoc* analysis: mean [95% CI] 0.57 [0.39; 0.83], $P = 0.0029$). The mean total weekly gastric carbohydrate intake decreased from baseline for the dasiglucagon + SoC (−146.56 g) but increased for patients receiving SoC alone (+160.44 g) during weeks 2–4. Gastrointestinal and skin disorders were the most common side effects noted with the use of dasiglucagon. Vomiting was the most common gastrointestinal symptom. There were two confirmed cases of necrolytic migratory erythema.

Critical Review: This is an important study that explores newer therapeutic options for the management of congenital CHI. While the study did not achieve its primary outcome, there were improvements noted in CGM measures of glycemia. The study drug was, however, associated with the expected side effects. This study adds to the limited number of medications used for CHI; however, it needs longer follow-up studies to determine ongoing efficacy and tolerability.

Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: Analysis of secondary outcomes from a multicenter, double-blind, randomized, and placebo-controlled trial

Ganmaa D, Khudyakov P, Buyanjargal U, Tserenkhuu E, Erdenenbaatar S, Achtai CE, *et al. Lancet Diabetes Endocrinol*. 2024 Jan;12(1):29-38. doi: 10.1016/S2213-8587(23)00317-0.

Objective: The objective of this study was to assess whether weekly oral vitamin D supplementation for three years affected the incidence of bone fractures in Mongolian school children.

Study Methodology and Results: This was a two-arm, double-blind, randomized, and placebo-controlled trial conducted in Mongolian public schools that enrolled children between the ages of 6–13 years. All eligible participants received weekly doses of either 14,000 international units (IU) of vitamin D3 or placebo. All subjects had assessments of 25-hydroxyvitamin D [25(OH)D] levels, and a subset had a measurement of radial speed of sound (SOS) Z-scores, a marker of bone strength. Calcium, albumin, parathyroid hormone, total alkaline phosphatase (ALP), and bone ALP levels were analyzed in a smaller subset of those who had SOS measurements. Fracture incidence was a pre-specified secondary outcome of the trial. The study enrolled 8851 participants, of which 8348 participants (4176 [945%] in the vitamin D group and 4172 [941%] in the placebo group) were included in the analysis of fracture outcomes. At baseline, 7975 (95·5%) participants had baseline 25(OH)D concentrations of <50 nmoL/L, and 2664 (319%) participants had 25(OH)D concentrations of <25 nmoL/L. 5191 (64.2%) of the participants had a calcium intake of <500 mg/day. A total of 268 (64%) participants in the vitamin D group and 253 (61%) participants in the placebo group had at least one fracture (adjusted relative risk 1.10, 95% confidence interval 0.93–1.29; $P = 0{\cdot}27$). There was no statistically significant effect modification by sex, baseline 25(OH)D concentration, or calcium intake (P interaction >0.05). There was no statistical difference in the radial SOS Z-scores or unadjusted SOS values, either overall or in subgroups defined by sex, baseline 25(OH)D concentration, or calcium intake. The incidence of adverse events was similar in participants in the vitamin D and placebo groups.

Critical Review: This is an important study that demonstrates that in schoolchildren, Vitamin D supplementation might not influence fracture risk or bone strength for three years. Therefore, vitamin D use should be reserved for conditions like rickets where there is demonstrable evidence of benefit from randomized control trials.

Incidence and risk factors for adrenal crisis in pediatric-onset adrenal insufficiency: A prospective study

Hosokawa M, Ichihashi Y, Sato Y, Shibata N, Nagasaki K, Ikegawa K, *et al. J Clin Endocrinol Metab*. 2023 Dec 21:dgad753. doi: 10.1210/clinem/dgad753.

Objective: The objective of this study was to determine the incidence and risk factors for adrenal crisis (AC) in patients with pediatric-onset adrenal insufficiency (AI).

Study Methodology and Results: This was a multicenter prospective cohort study conducted in Japan that enrolled patients who were diagnosed with primary or secondary AI at ≤ 15 years of age. All patients were educated about stress dosing for glucocorticoids. The primary outcome measures included the incidence of AC as events per 100 person-year (PY) and the risk factors for AC. Secondary outcome measures included mortality and morbidity rates. The study included data from 349 participants (164 males and 185 females), with a total follow-up of 961 PY. About 61% of participants had primary AI, and 39% had secondary AI.

Forty-one AC events occurred in 31 patients during the study period. The incidence of AC was calculated to be 4.27/100 PY (95% confidence interval [CI] 3.15–5.75). The incidence of AC in those participants who were in the <25th percentile age group was significantly higher as compared to older age groups. Sixty-one percent of the AC events followed oral intake of stress-dosing glucocorticoids. Younger age at the start of the observation period (relative risk [RR] 0.93 [95% CI 0.89–0.97]) and increased number of infections (RR 1.17 [95% CI 1.07–1.27]) were identified as significant risk factors on multivariable regression analysis. Primary AI (RR 0.65 [95% CI 0.30–1.41]) or hydrocortisone dosages per square meter of body area (RR 1.02 [95% CI 0.96–1.08]) was not a significant risk factor.

Critical Review: This is a useful study that validates previous studies that have demonstrated that AC is common in AI, with younger children being at the highest risk. Thus, this study revealed that particular attention should be devoted to younger patients and those who experience recurrent infections, irrespective of the etiology of AI.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's 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.

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