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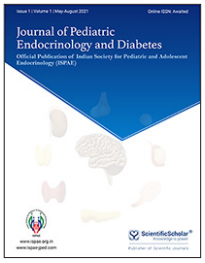

Ped Endo Journal Scan

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Oral Infigratinib Therapy in Children with Achondroplasia

Savarirayan R, De Bergua JM, Arundel P, Salles JP, Saraff V, Delgado B, *et al. N Engl J Med*. 2025 Feb 27:392(9):865-874.

Objective: Infigratinib is an orally bioavailable fibroblast growth factor receptor 3 selective tyrosine kinase inhibitor in the development for patients with achondroplasia. The objective of this study was to assess the safety and efficacy of once-daily oral infigratinib therapy in children with achondroplasia between the ages of 3 and 11 years and to identify the dose of infigratinib to be explored in future studies.

Study Methodology and Results: This was a phase 2, multicenter, multinational, open-label dose-finding study. Patients were enrolled sequentially in five dose cohorts to receive daily oral infigratinib at 0.016 mg/kg of body weight (cohort 1), 0.032 mg/kg (cohort 2), 0.064 mg/kg (cohort 3), 0.128 mg/kg (cohort 4), or 0.25 mg/kg (cohort 5) for 6 months. These patients continued treatment for an additional 12 months (extended-treatment period), during which time the dose in cohorts 1 and 2 could be escalated to the next ascending level at month 6 and month 12 (maximum, two increases allowed). The primary safety outcome was the incidence of adverse events that led to a decrease in the dose or discontinuation of infigratinib. The primary efficacy outcome was the change from baseline in the annualized height velocity. A total of 72 patients were enrolled sequentially in the five dose cohorts. A total of 67 patients completed 18 months of infigratinib treatment. All the patients had at least one adverse event during treatment, most of which were mild (in 39 of 72 patients [54%]) or moderate (in 28 of 72 patients [39%]) in severity (worst severity reported). The incidence and severity of adverse events were similar across all dose cohorts. The frequency and severity of adverse events were similar in the two trial groups. In cohort 5, an increased annualized height velocity was observed, which persisted throughout the duration of the study, with a mean change from baseline at 18 months of 2.50 cm/year (95% confidence interval [CI], 1.22–3.79; $P = 0.001$). The mean upper-to-lower body segment ratio also decreased, from 2.02 at baseline to 1.88 at month 18 (mean change, −0.12; 95% CI, −0.18 to −0.06).

Critical Review: This trial demonstrated that once-daily administration of infigratinib had a side-effect profile that was generally mild and resulted in a sustained increase in the annualized height velocity and a decrease in the upper-to-lower body segment ratio in children with achondroplasia. This is an important trial that explores a new oral therapeutic option for patients with achondroplasia, who face substantial disease burden and adverse health outcomes throughout their lives. The improvement in disproportion is noteworthy as that is an important factor contributing to challenges in motor functioning.

Treatment regimens and glycaemic outcomes in more than 100 000 children with type 1 diabetes (2013-22): a longitudinal analysis of data from paediatric diabetes registries

Zimmermann AT, Lanzinger S, Kummernes SJ, Lund-Blix NA, Holl RW, Fröhlich-Reiterer E, *et al*. *Lancet Diabetes Endocrinol*. 2025 Jan;13(1):47-56.

Objective: The objective of this study was to perform a longitudinal comparison of hemoglobin A1c (HbA1c), treatment regimens, and acute metabolic complications between registries, in children (aged ≤18 years) with type 1 diabetes over a 10-year period between 2013 and 2022 using data from eight well-established national longitudinal pediatric diabetes registries and the SWEET initiative.

Study Methodology and Results: This study included longitudinal analysis, the investigators obtained data from the Australasian Diabetes Data Network, ČENDA, Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids), Diabetes Prospective Follow-up Registry, Norwegian Childhood Diabetes Registry, England and Wales' National Paediatric Diabetes Audit, Swedish Childhood Diabetes Registry (Swediabkids), T1D Exchange Quality Improvement Collaborative (T1DX-QI), and the SWEET initiative. All children (aged ≤18 years) with type 1 diabetes with a duration of longer than 3 months were included in the analysis. In 2022, data were available for 109,494 children from the national registries and 35,590 from SWEET. The aggregated mean HbA1c of all registries decreased over the duration of the study period from 8.2% (95% confidence interval [CI] 8.1–8.3; 66.5 mmol/mol [95% CI 65.2–67.7 mmol/mol]) in 2013 to 7.6% (7.5-7.7; 59.4 mmol/mol [58.2–60.5]) in 2022 (least-squares mean difference 0.6% [0.5–0.8]; 7.1 mmol/mol [5.4–8.8]), $P < 0.0001$. The aggregated mean proportion of participants achieving the target HbA1c of <7%; increased over the duration of the study period from 19.0% (95% CI 15.7–22.4) in 2013 to 38.8% (35.7–22.0) in 2022 (least-squares mean difference 19.8% [15.2–24.4%], $P < 0.0001$). The aggregated mean proportion of participants with a HbA1c higher than 9% (>75 mmol/mol) across all registries decreased over the duration of the study period from 24.1% (95% CI 21.9–26.3) in 2013 to 13.1% (95% CI 11.0–15.1%) in 2022 (least-squares mean difference 11.0% [8.1–14.0], $P < 0.0001$). The aggregated proportion of participants with CSII use during the study period increased across all registries from 42.9% (95% CI 40.4–45.5) in 2013 to 60.2% (57.9–62.6) in 2022 (mean difference 17.3% [13.8–20.7], $P < 0.0001$). The aggregated proportion of participants using CGM increased across all registries from 18.7% (95% CI 9.5–28.0) in 2016 to 81.7% (73.0–90.4) in 2022 (mean difference 63.0% [50.3–75.7], $P < 0.0001$).

Critical Review: This study demonstrates that there was an improvement in mean HbA1c and the proportion of children with type 1 diabetes meeting HbA1c targets, in all eight well-established, national pediatric diabetes registries and the SWEET initiative during the 10-year study period. This was in line with increasing technology use in this cohort and is likely a major factor contributing to the glycemic improvement noted in this analysis.

Setmelanotide in patients aged 2–5 years with rare MC4R pathway-associated obesity (VENTURE): a 1-year, open-label, multicenter, phase 3 trial

Argente J, Verge CF, Okorie U, Fennoy I, Kelsey MM, Cokkinias C, *et al*. *Lancet Diabetes Endocrinol*. 2025 Jan;13(1):29-37.

Objective: The objective of this study was to evaluate the efficacy and safety of setmelanotide in pediatric patients aged 2–5 years with obesity due to either biallelic variants in proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1, or leptin receptor (LEPR) deficiency, or in patients with Bardet–Biedl syndrome (BBS).

Study Methodology and Results: This was a phase 3, open-label, multicenter trial. Eligible patients were aged 2–5 years with obesity (i.e., body mass index [BMI] ≥97th percentile for age and sex, and a body weight of ≥15 kg at enrolment) and the presence of symptoms or behaviors of hyperphagia due to either POMC or LEPR deficiency, confirmed by genetic testing. Following an 8-week screening period, all enrolled patients began treatment with 0.5 mg subcutaneous setmelanotide once daily. Doses were increased every 2 weeks in 0.5 mg increments until reaching the maximum dose based on weight. The co-primary efficacy endpoints were the proportion of patients with a decrease in BMI Z score of 0.2 points or more per the World Health Organization (WHO) Child Growth Standards at week 52 and the mean percentage change from baseline BMI at week 52. Secondary efficacy endpoints evaluated at week 52 included the mean absolute change in BMI Z score per WHO methodology and the mean change in percent of the 95th BMI percentile (%BMI$_{95}$) per Centers for Disease Control and Prevention reference populations. The study enrolled 12 participants of which 11 completed the study. Seven (58%) were diagnosed with POMC or LEPR deficiency; the remaining five patients (42%) had BBS. All patients had obesity at the time of enrolment, with an overall mean BMI of 29.9 kg/m^2 (standard deviation [SD] 7.9) and a mean WHO BMI Z score of 8.0 (4.4). Mean treatment adherence was 85% (SD 18.0) in the overall population. For the first co-primary endpoint, 10 (83%) participants reached a 0.2-point reduction or more in BMI Z score per WHO methodology at week 52 (95% CI 58.7–99.8;). This included 6 (86%) patients with POMC or LEPR deficiency and 4 (80%) patients with BBS. For the second co-primary endpoint, the mean percent change in BMI from baseline at week 52 was −18% (SD 13) in the overall safety population (n = 11 at week 52). The mean percent change in BMI at week 52 was

−26% (SD 11) in patients with POMC or LEPR deficiency and −10% (9) in patients with BBS. The mean change in BMI Z score per WHO methodology was −3.4 (SD 2.5) for the overall population at week 52 (POMC or LEPR deficiency −5.2 [1.9]; BBS −1.3 [1.2]). Reductions in hunger at week 52 were reported by caregivers in 10 (91%) of 11 evaluable patients. All patients in the safety population reported one or more treatment-emergent adverse events, all of which were mild or moderate in severity. The most common treatment-emergent adverse events were skin hyperpigmentation; vomiting; nasopharyngitis, upper respiratory tract infection, injection site bruising, injection site pruritus, pyrexia, fall, and melanocytic nevus; and injection site discoloration and cough. No serious adverse events or adverse events leading to study discontinuation or death were reported.

Critical Review: This is the first clinical trial of setmelanotide in patients under 6 years of age with rare MC4R pathway diseases and is one of the first trials of any obesity pharmacotherapy in this age group. The medication led to clinically meaningful weight-related responses in this cohort though greater relative reductions in weight-related measures were observed in patients with POMC or LEPR deficiency than in those with BBS. This is possibly attributable to the degree of effect on signaling through the MC4R pathway. Limitations include a small study size given the rarity of the disease and the lack of long-term follow-up data.

Lomitapide for the treatment of paediatric patients with homozygous familial hypercholesterolaemia (APH-19): results from the efficacy phase of an open-label, multicenter, phase 3 study

Masana L, Zambon A, Schmitt CP, Taylan C, Driemeyer J, Cohen H, *et al. Lancet Diabetes Endocrinol*. 2024 Dec;12(12):880-889.

Objective: The objective of this study was to investigate the clinical efficacy and safety of lomitapide in pediatric patients with homozygous familial hypercholesterolemia (HoFH) receiving lipid-lowering therapy.

Study Methodology and Results: This was an open-label, single-arm, phase 3 study performed at 12 study centers in Germany, Israel, Italy, Saudi Arabia, Spain, and Tunisia. It included a 6–12-week run-in period, followed by a 24-week efficacy phase and an 80-week safety phase. Eligible patients were aged 5–17 years, on stable lipid-lowering therapy, with HoFH diagnosed using the criteria from the 2014 European Atherosclerosis Society (EAS) Consensus Panel on HoFH. Lomitapide was administered orally in capsule form for all patients, starting at 2 mg for patients aged 5–15 years and at 5 mg for patients aged 16–17 years. The dose was escalated following a titration scheme based on the patient's age. The primary outcome measure was the percentage change from baseline to week 24 in low-density lipoprotein (LDL) cholesterol. The secondary outcomes were the percentage change from baseline to week 24 in total cholesterol, non-high-density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides, lipoprotein(a), and ApoB. A total of 43 patients (20 aged 5–10 years and 23 aged 11–17 years) entered the 24-week efficacy phase and were included in the full analysis set and safety set. Of the 43 patients, 38 (88%) had a genetic diagnosis of HoFH, and five (12%) patients were diagnosed using other criteria from the 2014 EAS Consensus Panel on HoFH. The median baseline LDL cholesterol concentration in the whole cohort was 390.5 mg/dL (interquartile range [IQR] 279.5–571.9; range 152.3–902.4 mg/dL), with a higher median baseline LDL cholesterol concentration in patients aged 5–10 years than in those aged 11–17 years (526.8 mg/dL [IQR 363.5–726.9] vs. 346.4 mg/dL [245.5–457.8]). A significant overall mean LDL cholesterol percentage change from baseline at week 24 of −53.5% (95% CI −61.6–−45.4; $P < 0.0001$) was noted. Results were similar in the younger and older patient subgroups. The overall mean percentage change in non-HDL cholesterol was −53.9% (95% CI −61.7 to −46.1, $P < 0.0001$). The overall mean percentage change in total cholesterol was –50.0% (95% CI −57.6 to −42.4 $P < 0.0001$) and that in VLDL cholesterol was −50.2% (−59.1 to −41.2, $P < 0.0001$). The overall mean percentage change in ApoB was −52.4% (95% CI −60.3 to −44.5, $P < 0.0001$), and that in triglycerides was −49.9% (−58.8 to −41.0, $P < 0.0001$). At any time up to week 24, 18 (42%) of 43 patients had reached the prespecified EAS-recommended target LDL cholesterol concentration of <135 mg/dL. Treatment-emergent adverse events were noted in 58% of patients. They were mostly mild and gastrointestinal or hepatic in nature. One serious treatment-emergent adverse event was reported (also classed as an adverse event of special interest): an increase in hepatic enzymes, resulting in two dose interruptions, two dose reductions, and a repeated dose escalation.

Critical Review: This study shows the efficacy of lomitapide in pediatric patients, with a significant overall reduction in LDL cholesterol after 24 weeks of treatment and an acceptable safety profile. This is marked in the context of a cohort that was receiving maximally tolerated statin or ezetimibe lipid-lowering therapy, with the use of lipoprotein apheresis widespread among the cohort. The degree of lipid reduction is similar to evinacumab. The addition of an oral agent to the list of LDL-receptor-independent therapies is useful. The potential hepatic effects of lomitapide are of clinical interest and longer-term hepatic safety in pediatric patients needs to be defined.

Loss-of-function GHSR variants are associated with short stature and low IGF-I

Punt LD, Kooijman S, Mutsters NJM, Yue K, van der Kaay DCM, van Tellingen V *et al*. J Clin *Endocrinol Metab*. 2025 Jan 9:dgaf010. Epub ahead of print.

Objective: The objective of this study was to describe the phenotype of patients carrying partial or complete loss-of-function variants in growth hormone secretagogue receptor

(GHSR) and their response to recombinant human growth hormone (rhGH) therapy.

Study Methodology and Results: This was a descriptive case series which included 26 patients from 24 families who had short stature and carried GHSR variants. In all patients, an extensive gene panel was performed to exclude other prevalent genetic causes of growth failure. *In vitro* functional studies for studying pathogenicity were performed for assessment of total protein levels, cell surface expression, and receptor activity in basal, stimulated, and inhibited states. The study included 26 patients (19 boys and 7 girls) who were heterozygous for variants in GHSR, with an average age of 8.0 years (range, 4.0–15.1 years). Eight missense variants (all variants of unknown significance), one frameshift, and one non-sense variant (both likely pathogenic) were identified in GHSR, of which six were novel. Variants showed either partial or complete loss of function, primarily through loss of constitutive activity.

Patients generally had a normal birth length with decreasing height Standard Deviation Score (SDS) during the first 2 years of life. The average height at presentation was −2.8 SDS (range, −4.1 to −1.9 SDS). The average serum insulin-like growth factor-I (IGF-I) and insulin-like growth factor-binding protein 3 were −1.6 SDS (range, −2.7 to 0.3 SDS) and −1.0 SDS (range, −2.3 to 0.2 SDS), respectively. A GH stimulation test was performed in 15 patients, and all showed a sufficient or even exaggerated rise (range, 10.8–32.7 μg/L). Three subjects had a history of prematurity and five were born small for gestational age (SGA). Four patients had a history of failure to thrive. Genetic evaluation was available for both parents in 17 of 23 families. In seven families the variant was segregated with short stature, as the affected parent had a height between −1.5 and −2.0 SDS (n = 3) or < −2.0 SDS (n = 4). Nine patients had received rhGH therapy. Their average gain in height after 1 year was 0.9 SDS (range, 0.5–1.6 SDS and 1.5 ± 0.4 SDS after 2 years (n = 5).

Critical Review: The observations of proportionate short stature, low IGF-I, and good response to rhGH are in line with the reported function of GHSR and fit with the hypothesis of growth hormone (GH) neurosecretory dysfunction in patients carrying pathogenic variants. These results exemplify the importance of GHSR in GH secretion and therefore provide additional support for investigating treatment with oral GHSR agonists in patients with a relatively intact pituitary axis.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Kriti Joshi is on the Editorial Board of the Journal.

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

The author confirms 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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