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ORIGINAL ARTICLE

Cinacalcet for secondary hyperparathyroidism in children with end-stage renal disease

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Abstract The efficacy and acceptability of cinacalcet for treatment of secondary hyperparathyroidism (SHPT) was assessed in seven pediatric patients suffering from end-stage renal disease (ESRD) presenting with inadequately controlled SHPT despite conventional management. Patients received daily treatment with cinacalcet (dosage 0.25 mg/kg body weight) for a total of 4 weeks. Within 4 h after application of the first dose, median levels of serum parathyroid hormone (PTH) had decreased from 932 pg/ml (range 511–1,938 pg/ml) to 584 pg/ml (88–937 pg/ml), and final pre-dose values after 4 weeks were 199 pg/ml (121–940 pg/ml; each $P<0.05$ versus baseline). Median concentrations of serum calcium (Ca) decreased within 4 h of the first administration, from 2.56 mmol/l to 2.38 mmol/l, returning to 2.58 mmol/l at 24 h, and they remained slightly decreased compared to baseline values thereafter (each $P<0.05$ versus baseline). Both the median levels of serum phosphorus (P) and the Ca×P ion product decreased significantly during the 4-week period. Cinacalcet was well tolerated and without drug-related adverse effects. Thus, even with approximately half of the dose usually given to adult dialysis patients, PTH and the Ca×P ion product were markedly reduced in pediatric ESRD patients presenting with inadequately controlled SHPT. Therefore, our results support the initiation of a randomized, controlled, long-term trial in children.

Keywords End-stage renal disease · Secondary hyperparathyroidism · Hyperphosphatemia · Hypercalcemia · Calcimimetics · Cincacalcet

Abbreviations

Alk. Ptases	alkaline phosphatase
ARPKD	autosomal-recessive polycystic kidney disease
Ca	calcium
Ca × P	calcium-phosphorus ion product
CaSR	Ca sensing receptor
CKD	chronic kidney disease
P	phosphorus
PTH	parathyroid hormone
SHPT	secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism (SHPT) is a major complication in children with end-stage renal disease (ESRD) and is characterized by persistently elevated levels of circulating parathyroid hormone (PTH), causing metabolic bone disease, skeletal deformities and impairment of longitudinal growth [1–5]. Conventional management of SHPT includes treatment with active vitamin D metabolites and phosphate binders. However, as a result of enhanced intestinal calcium (Ca) and phosphate (P) retention, their use may exacerbate

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hypercalcemia and hyperphosphatemia, resulting in markedly increased Ca×P ion product requiring cessation of vitamin D and/or calcium-containing phosphate binders [6]. Together with persistently elevated PTH levels these complications are major contributors to the development of extraskeletal/vascular calcifications and increased cardiovascular mortality in these patients [7–9]. In addition, high doses of active vitamin D metabolites have been accused of impairing linear growth in children and adolescents with ESRD [10].

Cinacalcet is an allosteric modulator of the calcium-sensing receptor (CaSR) which is expressed in great abundance in the chief cells of the parathyroid gland and several other tissues. Cinacalcet increases sensitivity of the CaSR, lowers the threshold for activation by calcium, and decreases PTH secretion [11]. Several clinical trials in adult SHPT patients on dialysis or after renal transplantation have demonstrated that cinacalcet is effective in lowering PTH levels with simultaneous decrease in Ca and P serum concentrations [12–21]. So far, cinacalcet has not been used in children with SHPT. Activation of the CaSR in the parathyroid glands theoretically could produce greater decreases in serum Ca and P levels in children as they are undergoing active skeletal development [22]. Therefore, the impact of calcimimetics on serum Ca and P levels is of special importance when such treatment is being considered for children.

Here, we report on a 4-week treatment with cinacalcet of seven pediatric patients aged 1.1–19 years with ESRD and suffering from inadequately controlled SHPT despite conventional management with calcitriol and phosphate binders.

Material and methods

Patients

Between July 2005 and December 2007 seven children and adolescents suffering from chronic kidney disease (CKD) stage 5 and inadequately controlled SHPT were treated with cinacalcet (off-label use) for a period of 4 weeks. Prior to the initiation of cinacalcet, the patients and/or their parents had given assent and written informed consent. The analysis and publication of the clinical data of this off-label use received appropriate ethics committee approval from the Institutional review board in accordance with the Declaration of Helsinki, and patients and/or their parents gave assent and written informed consent for publication.

All patients had presented with severely elevated PTH levels (>500 pg/ml from at least two consecutive measurements during the previous 2 months), despite standard treatment with calcitriol and calcium-free/calcium-containing phosphate binders. Baseline patient characteristics are given in Table 1. In two of the seven patients calcitriol has been withdrawn 3 weeks prior to the onset of cinacalcet treatment, due to hypercalcemia (>2.79 mmol/l) and/or hyperphosphatemia [>2 standard deviations (SDs) above the normal range]. The dialysate calcium concentration in hemo- and peritoneal dialysis patients was 1.25 mmol/l. The primary renal diseases were nephronophthisis (n=3), hypoplasia (n=1), autosomal-recessive polycystic kidney disease (ARPKD, n=1), Pierson syndrome (n=1), and pauci-immune glomerulonephritis (n=1).

Treatment protocol

The subjects received oral treatment with cinacalcet (Mimpara, Breda, Netherlands) at a dosage of 0.25 mg/kg body weight once daily during a 4-week period. The local pharmaceutical department prepared the capsules, i.e. tablets (30 mg) were ground, diluted with lactose monohydrate, and re-pressed into tablets containing 2.5 mg, 5 mg, and 7.5 mg of cinacalcet. The dosages of calcitriol and phosphate binders remained unchanged unless patients showed hypocalcemia (<2.20 mmol/l) or their PTH levels decreased below 100 pg/ml. In the case of hypocalcemia, calcium acetate or calcitriol treatment was started, depending on whether the serum P level was above or below 2

Table 1 Base-line demographic characteristics

Characteristic	Result
Age (range) in years	17.0 (1.1–19.0)
Gender (male/female)	3/4
Pubertal stage (prepubertal/pubertal)	3/4
Mode of renal replacement therapy (hemodialysis/peritoneal dialysis/conservative)	3/3/1[a]
Duration of dialysis (range) in years	2.7 (0.9–4.4)[b]
Height (SD score)	-0.75 (−1.06 to 2.01)
Weight (range) in kg	45.0 (9.4–72.0)

[a] Glomerular filtration rate=12 ml/min per 1.73 m^2 body surface area
[b] n=6

SDs of the age-related normal range, respectively. In the case of low PTH levels, concomitant calcitriol treatment was stopped. Patients were kept in hospital for the first 48 h of therapy so that they could be monitored for adverse events. Serum chemistry and hematology parameters were assessed at baseline, after 1 week, and after 4 weeks of treatment. Furthermore, due to the fact that only limited experience of cinacalcet treatment in children is available, serum PTH and Ca levels were regularly checked on a narrow time scale (i.e. 4 h, 12 h, 24 h, 36 h, 48 h, and 4 weeks after initiation of cinacalcet treatment). In addition, serum calcium levels were determined 4 h after the second and third doses of cinacalcet (i.e. at 28 h and 52 h), and after 1 week and 2 weeks. Serum P values were determined at baseline and after 24 h, 48 h, 1 week, 2 weeks, and 4 weeks. Serum Ca, P, and alkaline phosphatase (Alk. Ptase) levels were determined with a Beckmann Synchron LX analyzer. Serum PTH values were measured by an immunometric assay that detects full-length PTH (1–84) and amino-truncated PTH fragments (Nichols, San Juan Capistrano, CA, USA; normal range 15–65 pg/ml). Serum calcium concentrations were corrected for variations in plasma albumin levels according to the procedure of Payne et al., and corrected values are reported [23].

Statistical analysis

All data are summarized by means of descriptive statistics, including median, range and number of available observations for continuous variables, and boxplots were used to visualize the results. Wilcoxon's test for paired samples was applied to compare patient-specific data related to different time points, and Fisher's exact test was used to evaluate differences in proportions. The SPSS/PC software package, version 15.0 (SPSS GmbH, Munich, Germany), was used for processing and statistical analysis of all data. All P values resulted from two-sided statistical tests, and a P value of <0.05 was considered to be significant.

Results

Effects of cinacalcet on PTH, Ca, and P concentrations

Median serum PTH values decreased rapidly after 4 h and 12 h by 43% (−7% to 83%) and 39% (−15% to 76%), respectively (Fig. 1a). During the 4-week treatment period median levels of serum PTH constantly further declined, from the initial 932 pg/ml (range 511 pg/ml–1,938 pg/ml) to final pre-dosage values of 199 pg/ml (range 121 pg/ml–940 pg/ml; $P<0.05$ versus baseline).

The median decrease amounted to 74% (−59% to 89%). In all except one 4-year-old patient on automated peritoneal dialysis, presenting with markedly elevated serum P levels ranging from 2.39–3.07 mmol/l during the study period, a decrease in serum PTH levels of at least 40% was noted. The decrease in serum PTH levels after the first dose of cinacalcet and at the end of the 4-week treatment period, expressed either in absolute concentration units or as a percentage of pre-treatment values, was unrelated to the pre-dose level of either Ca or PTH (data no shown).

Median concentrations of serum Ca showed a significant decrease 4 h after the dose, from 2.69 mmol/l (2.46–2.82 mmol/l) to 2.38 mmol/l (2.18–2.89 mmol/l), returning to 2.46 mmol/l (2.23–2.92 mmol/l) and 2.58 mmol/l (2.22–2.73 mmol/l) at 12 h and 24 h, respectively (4 h and 24 h versus baseline, $P<0.05$; 12 h versus baseline $P=0.128$). A similar decrease in serum Ca levels after the second and third cinacalcet doses was observed (Fig. 1b). Pre-dose levels of serum Ca remained constantly decreased compared to baseline values throughout the 4-week treatment period (Fig. 1b, Table 2).

Both serum P levels and the Ca×P ion product showed a rapid and sustained decrease, which occurred within the first week of cinacalcet treatment and lasted throughout the treatment (Fig. 1c, d, Table 2). The median decrease in serum P levels and Ca×P ion product at the end of the 4-week treatment period was 0.71 mmol/l (−0.27 mmol/l to 1.34 mmol/l) and 2.53 $mmol^2/l^2$ (0.06 $mmol^2/l^2$–3.72 $mmol^2/l^2$), respectively. Serum levels of alkaline phosphatase did not change significantly (Table 2).

After the 4-week treatment period, target PTH and/or P levels according to the guidelines of the Kidney Disease Outcomes Quality Initiative (K/DOQI) [24] were reached in four of the seven patients (Table 3). All patients showed serum Ca levels within the target range. Simultaneous achievement of all K/DOQI guidelines (i.e. values for PTH, P, Ca and Ca×P ion product) was reached in two of the seven patients.

Safety and medication use

During the 4-week treatment period, no adverse events, e.g. symptomatic hypocalcemia, gastrointestinal symptoms (nausea, vomiting, and diarrhea), were noted. Cinacalcet was well tolerated. In two patients showing non-symptomatic hypocalcemia (<2.20 mmol/l) during the first treatment week, calcium acetate or calcitriol treatment was started on day 7. In two patients concomitant calcitriol treatment was stopped after 24 h due to PTH levels below 100 pg/ml. In these patients PTH levels increased subsequently to 103 pg/ml and 215 pg/ml, respectively. Overall, the number of patients receiving vitamin D metabolites and calcium-containing/calcium-free phosphate binders, and the dosages of these drugs, remained grossly constant during the 4-week treatment period (Table 2).

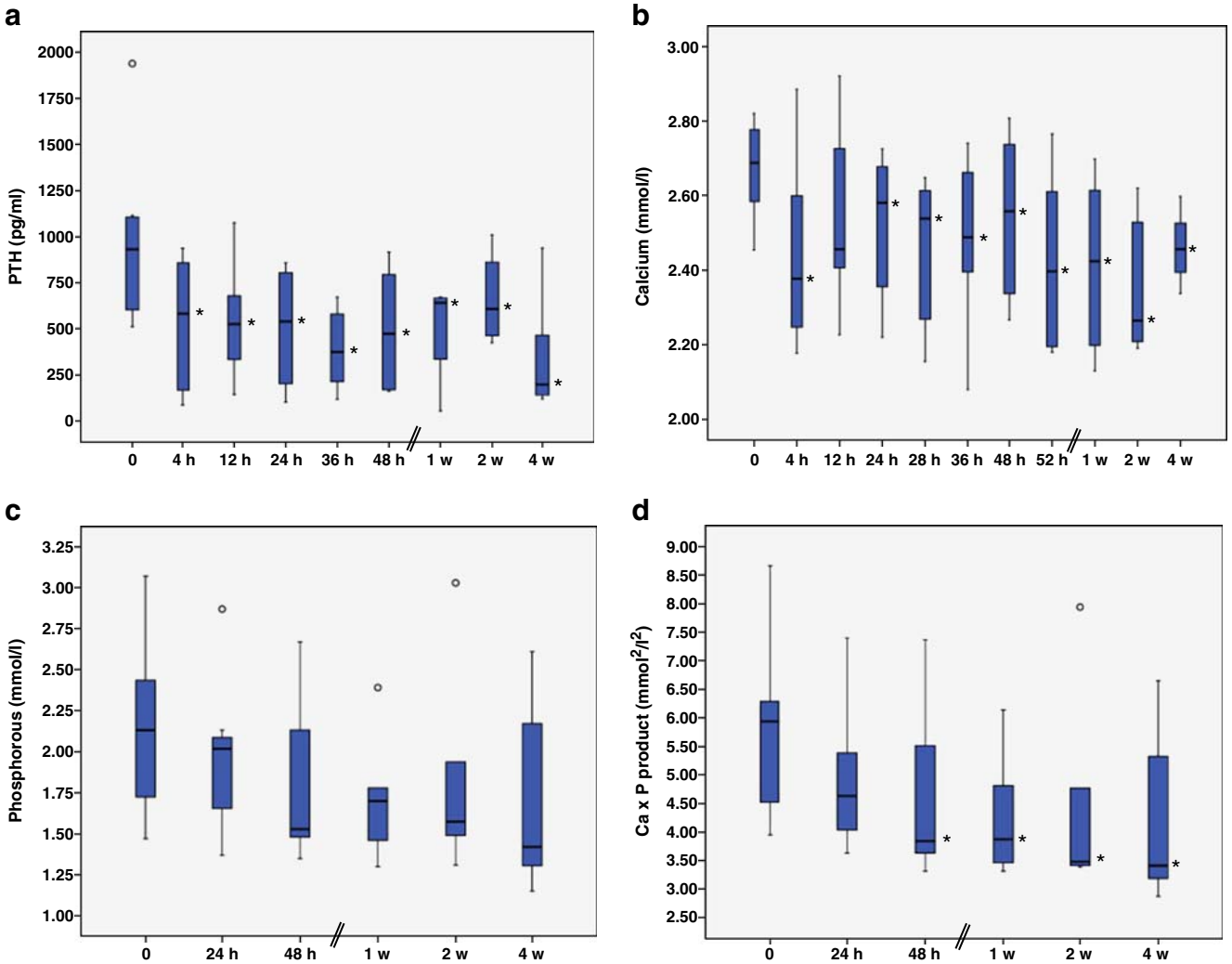

Fig. 1 **a**–**d** Effect of cinacalcet (dosage 0.25 mg/kg body weight once daily) on serum concentrations of intact PTH (**a**), calcium (**b**), phosphorus (**c**), and Ca×P ion product (**d**) in seven pediatric patients with secondary hyperparathyroidism. Data are given as boxplots indicating median and 25th and 75th percentiles (*shaded bars*), outliers are indicated by *open circles*, smallest and largest values which are not outliers are marked by *vertical ticks*; * $P<0.05$ versus baseline values

Discussion

Pediatric patients with CKD stage 5 and inadequately controlled SHPT despite conventional management with active vitamin D metabolites and phosphate binders received cinacalcet as an off-label treatment. This resulted in a rapid and sustained decrease in serum PTH levels (median 74%). This was associated with a decrease in serum Ca levels (median 0.31 mmol/l), within 4 h of the first cinacalcet dose, and a gradual rise thereafter. However, pre-dose serum Ca levels remained below baseline levels throughout the 4-week treatment period. In addition, both median P concentrations and Ca×P ion products decreased, respectively, by 33% and 43% within 4 weeks.

To the best of our knowledge this is the first report on cinacalcet treatment in pediatric ESRD patients with SHPT. In six of the seven patients at least a 40% reduction in serum PTH levels was achieved. The non-responding patient was a 4-year-old girl on automated peritoneal dialysis due to ARPKD presenting with constantly elevated serum P levels (range 2.39–3.07 mmol/l) despite prescription of high doses of phosphate binders and continuous dietary advice. Although a rapid decline in Ca levels from 2.82 mmol/l at baseline to a final pre-dose value of 2.55 mmol/l was noted in this girl, no concomitant reduction in serum PTH levels was observed (baseline 590 pg/ml; 4-weeks, 940 pg/ml). Whereas this finding might suggest that cinacalcet can only partly overcome the PTH-stimulating effects of markedly elevated P levels in patients with SHPT, general non-compliance with medical treatment must be considered.

The 74% decrease in pre-dose PTH levels during the 4-week treatment period is quite remarkable in view of the

Table 2 Changes in serum biochemistry and treatment

	Week 0	Week 4	*P*
PTH (pg/ml)	932 (511–1938)	199 (121–940)	0.028
Ca (mmol/l)	2.54 (2.4–2.66)	2.36 (2.13–2.47)	0.018
P (mmol/l)	2.13 (1.47–3.07)	1.42 (1.3–2.61)	0.091
Ca×P ($mmol^2/l^2$)	5.67 (3.76–7.37)	3.35 (3.18–5.57)	0.043
Alk. Ptases (U/l)	212 (56–1038)	244 (72–1022)	0.090
Use of calcitriol	5/7	4/7	
Dosage (ng/kg per day)	8.6 (7.0–140)	8.8 (7.8–140)	1.000
Use of cholecalciferol	4/7	5/7	
Dosage (IU/day)	400 (400–800)	400 (400–800)	1.000
Use of calcium acetate	2/7	3/7	
Dosage (g/kg per week)	0.90 (0.34–1.46)	0.76 (0.24–2.2)	0.180
Use of sevelamer	6/7	4/7	
Dosage (g/kg per week)	0.67 (0.35–1.63)	0.61 (0.35–1.16)	0.317

results reported for adult ESRD patients. This might be at least partly related to the shorter duration of SHPT in our patients than in adults. Previous studies of adult hemodialysis patients on single oral doses of cinacalcet (25–100 mg) showed a clear dose-dependent PTH lowering effect [15, 19]. The minimum effective dose was 25 mg, resulting in a 25% reduction in PTH levels during 8 days of treatment. In two large randomized trials using step-wise increasing cinacalcet doses (30 mg up-to 180 mg per day) the mean decrease in PTH levels amounted to approximately 30% and 40% after 4 weeks and 12 weeks, respectively [12, 17]. Notably, the dosage used by us was only approximately 50% of that usually given at onset of treatment to adult ESRD patients, due to the lack of experience with cinacalcet in children. In fact, the dosage of 0.25 mg/kg per day corresponds to 17.5 mg for an adult weighing 70 kg.

In our patients, serum PTH levels rapidly declined within 4 h of the first cinacalcet dose, and, although a subsequent increase was noted, PTH levels remained below baseline values throughout the day. The same phenomenon was noted after the second and third cinacalcet doses. However, even more importantly, pre-dose PTH levels declined continuously during the 4-week treatment period. Previously, in adult hemodialysis patients receiving between 25 mg and 100 mg of cinacalcet, a rapid decline in PTH levels, with maximum responses at 2 h to 4 h, followed by a constant rise, has been described [15, 16, 19]. This oscillating PTH suppression by cinacalcet, which is not observed during vitamin D treatment, may have stimulatory effects on bone formation and bone strength [25–27]. Recent studies investigating long-term effects of cinacalcet on adult hemodialysis patients have demonstrated a decline in pre-dose PTH concentrations during the first 3 to 6 months of treatment, with stable values thereafter [12, 17, 18]. Therefore, the PTH-suppressing effect of cinacalcet in pediatric patients might be underscored in our report. This is due to the low dosage of cinacalcet and the rather short treatment interval.

Although median concentrations of serum Ca declined by approximately 0.3 mmol/l after the first administration of cinacalcet, none of the patients experienced symptoms of hypocalcemia. These calcium-lowering effects were attenuated by the use of a rather small cinacalcet dose and the concomitant adjustment of calcium-containing phosphate

Table 3 Achievement of the K/DOQI guidelines

Parameter	Week 0	Week 4	*P*
PTH	0/7	4/7	0.070
P	2/7	4/7	0.592
Ca	3/7	7/7	0.070
Ca×P	3/7	4/7	1.000
Simultaneous achievement	0/7	2/7	0.462

Ranges according to the K/DOQI guidelines are: PTH 200–300 pg/ml
P 1.46–2.1 mmol/l (1–5 years); 1.16–2.2 mmol/l (6–12 years); 0.74–1.46 mmol/l (13–20 years)
Ca 2.35–2.7 mmol/l (1–5 years); 2.35–2.57 mmol/l (6–12 years); 2.2–2.55 mmol/l (13–20 years)
Ca×P <5.25 $mmol^2/l^2$ (<12 years); <4.44 $mmol^2/l^2$ (>12 years)

binders and calcitriol therapy, which was necessary in two of the seven patients.

Vitamin D metabolites had been withheld from two of the seven patients at the onset of cinacalcet treatment, owing to elevated levels of serum P, Ca, or both. Whereas, at baseline, none of the patients fulfilled the K/DOQI guidelines with respect to values for PTH, Ca, P, and Ca×P ion product, this was achieved in two of the seven patients at the end of the 4-week treatment. Thus, the fact that cinacalcet lowers PTH levels while reducing Ca and P levels represents a potentially important therapeutic development for children with ESRD.

Treatment with cinacalcet was generally well tolerated, and no episodes of nausea or vomiting were observed. Serum Ca levels below the normal range were not associated with symptoms of hypocalcemia and were rapidly managed by means of adjustments in the dosage of calcium-containing phosphate binders and/or calcitriol.

Although the treatment of only seven pediatric patients does not allow us to draw sound conclusions with respect to safety and efficacy of cinacalcet in this setting, our results are encouraging. However, important issues such as the impact of cinacalcet on bone histology, arterial and soft-tissue calcification, and cardiovascular morbidity, must be addressed in future clinical trials. Moreover, in a recent phase 3 study of male adult hemodialysis patients, a 30% reduction in serum testosterone levels after 6 months of cinacalcet treatment was observed (unpublished results; Amgen, Europe). Although the mechanism by which cinacalcet may reduce serum testosterone levels remains to be elucidated, this possible side effect is of major importance for the use of cinacalcet in adolescents with ESRD. In this population, alterations of the gonadotropic hormone axis, which can be summarized as a hypergonadotropic hypogonadism, are already present in a significant proportion of patients, which results in delayed puberty and diminished pubertal height gain [28–30]. Finally, epiphyseal growth plate chondrocytes express the CaSR, but the role of the CaSR as a potential modifier of chondrocyte proliferation, differentiation, and differentiated function, remains uncertain. Of note, the administration of calcimimetics to growing non-uremic and uremic rats apparently did not induce any major growth disturbances when they were compared with pair-fed controls, but the observation periods may have been too short for minor changes to be detected, and this issue has not been addressed specifically [31].

In conclusion, a 4-week treatment with cinacalcet, at dosages of 0.25 mg/kg, effectively reduced serum concentrations of PTH, Ca, P, and Ca×P ion product in pediatric ESRD patients with inadequately controlled SHPT despite conventional management. The fact that cinacalcet lowered PTH levels while reducing Ca and P levels and Ca×P ion product represents a potentially important therapeutic development for children with ESRD. Our results support the initiation of a randomized, controlled, long-term trial in children.

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