Continuous Subcutaneous Recombinant Parathyroid Hormone (1-34) Infusion in the management of childhood Hypoparathyroidism associated with Malabsorption

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Short Title: CSPI rhPTH $^{1-34}$ therapy in hypoparathyroidism associated with malabsorption

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Established facts:

- Hypoparathyroidism associated with malabsorption can be particularly challenging to manage in children due to limited and often erratic intestinal absorption of calcium and vitamin D analogues.
- Conventional treatment in these children is often associated with symptomatic hypocalcaemia and hypo/ hypercalcaemia-related hospital admissions.

Novel insights:

- Continuous subcutaneous recombinant parathyroid (rhPTH $^{1-34}$) hormone infusion results in the normalisation and stabilisation of serum calcium and phosphate and therefore is a promising and effective alternative treatment option for children with hypoparathyroidism associated with intestinal malabsorption.

Abstract:

Background/ Aims: Hypoparathyroidism associated with malabsorption can be particularly challenging to manage due to limited and erratic intestinal absorption of calcium and vitamin D analogues, resulting in episodes of hypo- or hypercalcaemia. We evaluated the role of continuous subcutaneous recombinant parathyroid (rhPTH 1-34) hormone infusion (CSPI) in children with hypoparathyroidism associated with intestinal malabsorption resistant to conventional therapy.

Method: Four patients (8 - 13 years), with symptomatic hypocalcaemia resistant to conventional therapy were started on CSPI (follow up 3-8 years), in two paediatric endocrinology units in Europe.

Results: Serum calcium normalised within 48 hours of commencing treatment in all 4 patients. An average rhPTH 1-34 dose of 0.4 μg/kg/day resulted in a substantial reduction in symptomatic hypocalcaemia and hypo/ hypercalcaemia-related hospital admissions. An increased alkaline phosphatase activity was noted in the first six months on CSPI, indicating increase in bone turnover. In 2 patients with elevated urinary calcium excretion pre CSPI, this normalised in the first year on treatment. No significant side effects were noticed in the short or long term, with patient-reported preference of CSPI over conventional treatment.

Conclusion: CSPI is a promising and effective treatment option for managing hypocalcaemia and hyperphosphatemia in children with hypoparathyroidism associated with intestinal malabsorption.

1. Introduction:

Hypoparathyroidism is a rare endocrine disorder characterized by low serum calcium with an inappropriately low or normal serum parathyroid hormone (PTH) level. [1] In children, it is commonly associated with either defects in genes involved in parathyroid gland development (*TBX1*/22q11.2 del, *GCMB*), function (calcium-sensing receptor *CaSR*, *GNA11* and *PTH*), or auto-immune polyglandular syndrome type 1 (*AIRE*). [2, 3]

Along with maintaining calcium and phosphate homeostasis through stimulation of osteoclastic bone resorption, PTH plays a vital role in calcium reabsorption and phosphate excretion in the renal tubules. PTH also facilitates conversion of 25 hydroxy vitamin D (25OHD) to the active 1,25 dihydroxy vitamin D [1,25 $(OH)_2D$] which enhances intestinal calcium and phosphate absorption. [4]

Unlike other hormone deficiency states, replacing the missing hormone in hypoparathyroidism is not routine practice. Instead, conventional therapy with oral calcium supplements and vitamin D analogues remains the mainstay of treatment. [5] The role of synthetic subcutaneous PTH injections in the treatment of hypoparathyroidism was first reported in adults in 1996 [6, 7] followed by children in 2008. [8] Since then, short [9] and long term studies [10]

have demonstrated the efficacy and safety of Continuous Subcutaneous Recombinant PTH^{1-34} Infusion (CSPI) in the management of hypocalcaemia in children with activating mutations in *CaSR* and with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

Managing hypocalcaemia with conventional therapy can be particularly challenging in children with hypoparathyroidism associated with intestinal malabsorption, where calcium and active vitamin D analogue absorption capacity is both limited and highly variable. Here we report the favourable effects of CSPI in four children with resistant hypocalcaemia secondary to hypoparathyroidism associated with malabsorption, managed in two tertiary paediatric endocrinology units in Europe, Birmingham Children's Hospital, Birmingham, United Kingdom (patient 1) and Bicêtre Hospital, Paris, France (patient 2-4).

2. Subjects and Methods:

2.1. Case Reports:

Patient 1 (P1): A 13-year-old boy, born to consanguineous South-Asian parents was diagnosed with congenital hypoparathyroidism in infancy. He was subsequently diagnosed with sensory neural hearing loss, developmental delay and cryptogenic liver disease requiring liver transplant at the age of 2 years. He developed persistent diarrhoea with hypoalbuminaemia, lymphopaenia, hypomagnesaemia and recurrent severe hypocalcaemia by the age of 3 years. Video capsule endoscopy confirmed extensive intestinal lymphangectasia, not amenable to surgery. Genetic analysis has not identified any significant abnormalities to date. Despite high doses of alfacalcidol (200ng/kg), oral

calcium (300mg/kg/day) and magnesium supplements (15mg/kg/day) his serum calcium remained between 1.26 and 1.98 mmol/L. High doses of oral calcium supplements led to worsening diarrhoea. Multiple hospital admissions with hypocalcaemic seizures or symptomatic refractory hypocalcaemia requiring i.v. calcium infusions ensued. At the age of 13 years, he was commenced on CSPI delivered via a Medtronic™ pump and successfully weaned off alfacalcidol, magnesium and calcium supplements. His serum calcium normalised and stabilised within 2 days of commencing s.c. rhPTH$^{1-34}$. His calcium homeostasis is carefully managed with a combination of 2 litres of medium chain triglyceride (MCT) feeds (calcium 35 mg/kg/day) via gastrostomy in conjunction with rhPTH $^{1-34}$. He also receives regular oesophageal dilatation secondary to oesophageal strictures and recently underwent fundoplication due to severe gastroesophageal reflux. He has remained on CSPI for 3 years.

Patient 2 (P2): This 13 year old boy born to non-consanguineous Caucasian parents, first presented at the age of 7 years with hypocalcaemic seizures. He was diagnosed with and treated for hypoparathyroidism with conventional therapy. He subsequently developed adrenal insufficiency aged 8.4 years, when a diagnosis of APECED was confirmed with a compound heterozygous mutation in *AIRE* gene inherited from parents. He also developed intermittent diarrhoea and hypercalciuria [urine Calcium: Creatinine ratio (Ca:Cr, in mmol/mmol) 1.3] on a modest dose of 40ng/kg of alphacalcidol. Despite a short trial on thiazide diuretics, hypercalciuria persisted with serum calcium of 1.9mmol/L. He subsequently developed renal cysts. In view of intestinal malabsorption, poor growth and family history of polycystic kidney disease, he was commenced on

CSPI and pancreatic enzyme replacement (pancrelipase) therapy at the age of 9 years, on which he has remained for 6 years. He is otherwise on a normal diet, his serum calcium stabilised and hypercalciuria resolved subsequently.

Patient 3 (P3) and Patient 4 (P4) are 15 and 19 year old siblings, born to consanguineous Senegalese parents, with a diagnosis of APECED (homozygous *AIRE* gene mutation inherited from both parents) and glucose-6-phosphate dehydrogenase deficiency. P3 presented at 4 years of age with hypocalcaemic seizures (serum calcium 1.54 mmol/l). Despite being started on high doses of alphacalcidol (125ng/kg/day) and oral calcium (85mg/kg/day), he had recurrent hospital admissions with episodes of hypocalcaemia alternating with hypercalcaemia and hypercalciuria. These problems persisted on a brief trial of twice daily subcutaneous injections (40µg) of $rhPTH^{1-34}$. Intestinal malabsorption was confirmed due to elevated faecal calprotectin and low faecal elastase levels **(Table 1).** High doses of oral calcium resulted in worsening diarrhoea and the decision to commence CSPI was made. P4 presented at the age of 11 years in status epilepticus secondary to hypocalcaemia. Following normalisation of serum calcium with i.v calcium infusions, he was commenced on CSPI, for the purpose of consistency in the management of the two siblings. He subsequently developed diarrhoea and malabsorption was confirmed by elevated faecal calprotectin and low faecal elastase levels **(Table 1).** Primary adrenal insufficiency was diagnosed in P3 aged 8 years and P4 at the age of 12 years. Both were commenced on treatment with hydrocortisone and fludrocortisone as well as on pancrelipase. Both siblings required intermittent intramuscular vitamin D injections, when adequate serum 25 OHD level was not

achieved on monthly oral vitamin D supplements (100,000 IU) alone. To our knowledge, P3 and 4 were the first reported children to be commenced on CSPI and P3 has remained on it for the longest duration of 8 years.[10] Here we focus on the initiation of their PTH therapy and highlight the challenges in managing resistant hypocalcemia in the context of malabsorption.

P4 deceased at the age of 19 years, 6.5 years on CSPI treatment, due to acute adrenal insufficiency from septic shock secondary to a dental abscess.

2.2. CSPI dosing and management:

All patients were commenced on a continuous s.c. infusion of rhPTH$^{1-34}$ (teriparatide, European union trade name Forsteo, 20µg/80µl, Lilly France) delivered via a Medtronic™ pump. The device was attached to the abdomen or lower back, and parents trained to fill the pump cartridge with teriparatide and change the cannula and infusion set every 72 hours. The pump was programmed to deliver a standard basal rate throughout the day and carers trained to either increase basal rate in increments of 10-20% during illness or self administer a bolus following discussion with the medical team. Patient 1 was commenced on an rhPTH$^{1-34}$ dose of 0.16µg/kg/day, currently requiring a higher maintenance dose of 0.3 µg/kg/day. Patient 2 was on an initial dose of 1µg/kg/day, gradually weaned down to 0.35µg/kg/day. P3 and P4, the very first patients to have commenced CSPI were started on a higher initial dose of 2.6µg/kg/day and weaned down to a maintenance dose of 0.5µg/kg/day in P3 **(Table 2)**.[10]

As this was not a clinical trial, no ethical approval was required. However as CSPI was commenced in these patients under exceptional circumstances, a

multidisciplinary team of experts approved this decision and individual patient funding requests were obtained from the respective national bodies. Consent was obtained from parents of all 4 children prior to commencing CSPI treatment and informed of the desired effects, potential side effects and uncertainties of long- term safety of treatment with CSPI in children.

3. Results:

Serum calcium normalized in all patients within 36-48 hrs of commencing CSPI. All patients were successfully weaned off alfacalcidol and only P3 remains on a reduced dose of oral calcium supplements (40 mg/kg/day). A similar effect was noted with serum phosphate (**Figure 1**). P2 and P4 had elevated Ca:Cr at the start of CSPI, which normalized in the first year of treatment **(Figure 1)**. Episodes of hypercalcaemia and elevated urinary Ca:Cr in P3-4, 3-6 months into treatment guided rhPTH $^{1\text{-}34}$ dose reduction **(Figure 1)**.

P1, P3-4 had normal renal ultrasound scans with no evidence of nephrocalcinosis pre CSPI and this continues to remain the case on serial renal ultrasounds (1-3 yearly) on treatment. Grade II nephrocalcinosis was detected in P2 in the first year of treatment but did not progress on subsequent ultrasound evaluations. Serum creatinine and estimated GFR remains normal for age in all 4 patients on CSPI.

While P1 receives gastrostomy feeds, P2-3 are on a normal diet. Serum calcium throughout treatment remained correlated to $1,25(OH)_2D$ activity in all patients (**Figure 2**). The $1,25(OH)_2D$ concentrations were also elevated in all patients during therapy, which in the setting of malabsorption indicates that maximum

198 intestinal calcium absorption capacity is limited. As expected, serum calcium did
199 not correlate with 25 OHD concentrations.

200 All 4 patients had normal age- and sex- specific ALP activity at start of CSPI. A 60
201 -180 % increase from baseline in ALP activity was noted at 1 month following
202 start of treatment, which returned to baseline by 6 months on CSPI **(Figure 3)**.

203 Lumbar Spine Bone mineral apparent density (LSBMAD) z score of P1 decreased
204 from +3.0 pre CSPI to +2.8 and +2.1, 1 and 2 years on CSPI treatment,
205 respectively. P2-4 only had LS BMAD measured 12-18 months on CSPI with z
206 scores of -0.5, +1.5 and +1 respectively. There were no fractures reported in any
207 of the patients on CSPI.

208 A substantial reduction in hypocalcaemia-related hospital admissions were
209 noted from approximately 5 admissions in the year prior to commencing CSPI, to
210 2 calcium related admissions in the 1st year of treatment **(Table 2).**

211 None of the patients have had to discontinue CSPI and reported preference of
212 CSPI therapy over conventional treatment due to the perceived improvement in
213 quality of life. P3 has remained on CSPI treatment for 8 years, with no clinically
214 significant treatment-related adverse events observed.

215 In our cohort, episodes of hypocalcaemia on CSPI were associated with 1)
216 mechanical obstruction (catheter blockage or kinking) 2) insufficient vitamin D
217 supplementation 3) systemic illness, which often requires temporary increase in
218 basal rhPTH$^{1-34}$ infusion rates to avoid hypocalcaemia or 4) insufficient oral
219 calcium intake/ gastrostomy milk feeds and 5) pubertal growth spurt requiring
220 temporary higher rhPTH$^{1-34}$ doses to maintain normocalcemia. In most instances,

these episodes occurred secondary to a combination of the above mentioned factors. No cannula insertion site reactions or infections were recorded in any of the four patients.

4. Discussion:

Symptomatic hypocalcaemia associated with under treatment is a common occurrence with conventional treatment of hypoparathyroidism. Large doses of oral calcium supplements and alfacalcidol can result in worsening diarrhoea as observed in P1 and P3. In addition, erratic intestinal calcium absorption can lead to fluctuating serum calcium and hypercalciuria resulting in nephrocalcinosis. Here we report our experience demonstrating that this challenging subgroup of patients responds well to CSPI therapy with normalisation and stabilisation of serum calcium and phosphate resulting in reduced hospital admissions. The daily rhPTH$^{1-34}$ maintenance dose varied **(Table 2),** likely related to the extent of malabsorption. CSPI is also the preferred mode of rhPTH$^{1-34}$ delivery in these patients since stabilisation is difficult to achieve with twice daily subcutaneous injections. The fixed rhPTH$^{1-34}$ doses available as injections are often several times higher than the total daily dose needed during CSPI in these children.

From our experience, it is advisable to maintain 25OHD levels above 75 nmol/L in order to provide adequate substrate for PTH-induced conversion of 25OHD into active calcitriol ($1,25(OH)_2D$). In the setting of malabsorption, it is often challenging to achieve adequate serum 25OHD by oral supplementation alone. Therefore, regular intramuscular vitamin D administration should be considered earlier on in the management of these patients as required in P3-4.

A significant increase in alkaline phosphatase activity was noted within the first month of starting CSPI in our patient cohort, in keeping with the increased bone turnover associated with rhPTH$^{1-34}$ treatment in hypoparathyroidism . This however returned to pre-treatment levels within 6 months of commencing CSPI. We recognise the lack of consistent 24-hour urine calcium assessments in our cohort, as well as the challenges in measuring fasting serum calcium due to overnight feed requirement in P1.

All four patients reported preference of CSPI over conventional treatment due to the ease of use, fewer episodes of symptomatic hypocalcaemia, and substantial reduction in hospitalisation perceived as an improvement in quality of life. Future studies will have to carefully assess quality of life, alongside other functional outcomes and long-term safety monitoring.

Use of conventional treatment remains the mainstay in the treatment of hypoparathyroidism in children, due to the difficulty in dosing with recombinant parathyroid hormone and the boxed warning regarding the risk of osteosarcoma noted in rat toxicology studies [11, 12] but in no other animal models [13, 14]. It is essential to inform parents/ carers of the possible risks of CSPI treatment. The safety and efficacy of using rhPTH$^{1-84}$ as an alternative treatment option needs to be further explored. [15, 16]

In the absence of other new treatment options on the horizon in children, we propose CSPI as a promising and effective treatment method for children with hypoparathyroidism associated with intestinal malabsorption. However, we recommend careful monitoring of serum calcium daily for the first week, thrice weekly until serum calcium stabilizes in the normal range, later fortnightly,

monthly and 3 monthly or as clinically indicated. To avoid overtreatment urinary calcium excretion and renal ultrasound should be monitored periodically. Until further evidence becomes available, we recommend bone density scans, total body less head and lumbar spine [17] every 2 years. CSPI should be managed in tertiary rare disease centres with the required expertise. Due to the substantially higher drug costs and uncertainties of long term adverse events, CSPI is currently restricted to patients unresponsive and/ or having serious complications of conventional therapy.

Declaration of Interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Table 1: Clinical and biochemical characteristics of the cohort

M = male, APECED – Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy

Patient	**P1**	**P2**	**P3**	**P4**
Sex	M	M	M	M
Age at diagnosis	8 m	7 y	4 y	11 y
Diagnosis	Congenital hypoparathyroidism, sensory-neural deafness, intestinal lymphangectasia, cryptogenic liver disease	APECED	APECED	APECED
Gene mutation	No abnormality detected	Compound Heterozygous *AIRE* gene mutation (c.415 C>T exon 3 + c.967_979del exon 8)	Homozygous *AIRE* gene mutation (c.958del exon 8)	Homozygous *AIRE* gene mutation (c.958del exon 8)
Coeliac screen	negative	negative	negative	negative
Faecal calprotectin activity (µg/L)*	_	16	258	62
Faecal elastase (µg/g)**	> 500	408	82	40
Other investigations for malabsorption	Intestinal biopsy confirmed extensive lymphangectasia	_	_	_

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364 * Normal faecal calprotectin activity < 50 µg/L, **normal faecal elastase level >

365 200 µg/g

366 **Table 2: Dosing, metabolic response and duration of Continuous**

367 **Subcutaneous Recombinant PTH (1-34) Infusion (CSPI)**

Patient	**P1**	**P2**	**P3**	**P4**

Age at start of CSPI (years)	13	9	8	11
Initiation dose (µg/kg/day)	0.16	1	2.6	2.6
Maintenance dose 1yr on CSPI (µg/kg/day)	0.3	0.35	0.5	0.5
Serum calcium normalised post CSPI initiation (days)	2	2	2	2
Calcium-related hospital admissions, 1 year pre CSPI	8	3	10	1
Calcium-related hospital admissions, 1 year on CSPI	2	1	6	1
Duration of CSPI therapy to date (years)	3	6.5	8	6.5

Figure Legends:

Figure 1: Normalisation and maintenance of serum calcium and phosphate [mean (SD)] and urinary calcium: creatinine ratio in the first two years on CSPI. Shaded area represents normal reference range. High urinary calcium excretion in P3 and P4, six months into treatment guided rhPTH $^{1\text{-}34}$ dose reduction.

Figure 2: Serial measurements of serum calcium correlate significantly with rhPTH-driven serum $1,25(OH)_2D$ concentrations (estimated R^2 value 0.39, 95% confidence interval, 0.08-0.68 and two sided p value 0.001 using metacor package [18]). Normal range for $1,25(OH)_2D$ (20-62.5pg/mL) [19]. A similar correlation with serum 25OHD concentrations was not evident in children on CSPI.

Figure 3: Effect of CSPI on serum alkaline phosphatase (ALP) activity. The transient rise in ALP activity in the first month demonstrates the restoration of bone turnover followed by normalisation of activity by 6 months on treatment. Note that the ALP assay used for P1 results in ALP levels approximately twice the ALP activity of assays used for P2-4. At start of therapy, ALP was within the normal range in all patients.