5-1-2013

Cinacalcet as adjunctive therapy for hereditary 1,25-dihydroxyvitamin D-resistant rickets.

Tarak Srivastava
Children's Mercy Hospital

Uri S. Alon
Children's Mercy Hospital

CASE REPORT

JBMR

Cinacalcet as Adjunctive Therapy for Hereditary 1,25-Dihydroxyvitamin D–Resistant Rickets

Tarak Srivastava and Uri S Alon

Section of Nephrology, Bone and Mineral Disorder Clinic, Children's Mercy Hospitals and Clinics, University of Missouri at Kansas City, Kansas City, MO, USA

ABSTRACT

Secondary hyperparathyroidism from inadequate calcium absorption in the gut, is the underlying pathophysiology for rachitic changes in hereditary vitamin D–resistant rickets (HVDRR). We describe a novel use of Cinacalcet to treat a child with HVDRR in whom conventional modes of therapy had to be discontinued. Cinacalcet therapy with high-dose oral calcium effectively normalized the metabolic abnormalities and bone condition. The relative ease of administration of the calcimimetic as a once- or twice-daily oral preparation, compared with traditional intravenous calcium administration, should encourage its move to the frontline of treatment of the disorder. © 2013 American Society for Bone and Mineral Research.

KEY WORDS: HVDRR; CINACALCET; INTRAVENOUS CALCIUM; VDR; RICKETS

Introduction

Hereditary vitamin D–resistant rickets (HVDRR) is a rare autosomal recessive disease (OMIM 277440), and is characterized by early-onset rickets, hypocalcemia, hypophosphatemia, and secondary hyperparathyroidism in the face of elevated serum $1,25(OH)_2$-D_3 concentration.[1–3] A subset of children have total/partial alopecia and dermal cysts.[1–3] The disorder results from loss of function mutation in vitamin D–receptor (VDR) gene, leading to target organ resistance to $1,25(OH)_2$-D_3.[1] Several mutations have been described, and individuals with alopecia are generally unresponsive to oral calcium and $1,25(OH)_2$-D_3 therapy, and are currently being treated with intravenous calcium via a central line.[4–7] Secondary hyperparathyroidism from inadequate calcium absorption in the gut, is the underlying pathophysiology for rachitic changes in HVDRR.[8] Preliminary studies showed the calcimimetic Cinacalcet to be safe and effective therapy in children with secondary hyperparathyroidism, as a result of other conditions, such as renal failure, X-linked hypophosphatemic rickets (XLH), and familial hypocalciuric hypercalcemia.[9–12] In this report, we describe our novel experience with Cinacalcet therapy in a child with HVDRR that is resistant to $1,25(OH)_2$-D_3, as a result of a missense mutation affecting the DNA-binding domain of VDR, in which all other modes of therapy were exhausted.

Case Report

A 13-month-old male child was brought to the hospital for evaluation of failure to thrive. At presentation, his weight was 8.025 kg (Z-score –4.8) and length 65 cm (Z-score –2.6). He had rachitic rosary over the chest wall, widening of wrists and ankles, and bowing of upper and lower extremities. His head appeared disproportionately large (head circumference 51 cm, Z-score 3.2) with open anterior fontanel and frontal bossing. He had patches of scalp that were devoid of hair, whereas other regions had sparse hair, and scant eyebrows. He also exhibited delayed dentition, a large umbilical hernia, and generalized developmental delay. At presentation, his serum chemistry panel showed normal serum electrolytes, albumin, magnesium, BUN, and creatinine. Serum calcium (Ca) was 7.4 mg/dL, iCa 0.96 mmol/L (normal 1.13 to 1.37), phosphorus (P) 2.4 mg/dL, parathyroid hormone (PTH) 1103 pg/mL, and alkaline phosphatase (ALP) 893 U/L (Table 1). His serum $25(OH)$-D_3 concentration was 15 ng/mL and $1,25(OH)_2$-D_3 200 pg/mL. The skeletal survey showed generalized osteopenia with advanced features of rickets manifested by cupping and fraying at the metaphyseal ends of long bones of upper and lower extremities, and widening of growth plates (Fig. 1*C*). Kidney ultrasound showed no evidence of nephrocalcinosis.

Received in original form August 29, 2012; revised form November 5, 2012; accepted November 26, 2012. Accepted manuscript online December 4, 2012.
Address correspondence to: Uri S Alon, MD, Section of Nephrology, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108, USA.
E-mail: ualon@cmh.edu

Journal of Bone and Mineral Research, Vol. 28, No. 5, May 2013, pp 992–996
DOI: 10.1002/jbmr.1838

Table 1. Effect of Therapy With Elemental Calcium, Ergocalciferol, Calcitriol, and Cinacalcet Over Four Time Periods on Serum Total Calcium, Phosphorus, Parathyroid Hormone, and Alkaline Phosphatase

Age (months)	Elemental Calcium (mg/day)	Ergocalciferol (units/day)	Calcitriol (μg/day)	Cinacalcet (mg/day)	Serum Ca (mg/dL)	Serum P (mg/dL)	Serum ALP (U/L)	Serum PTH (pg/mL)
	Reference Range				8.6–10.5	3.5–6.8	110–320	7–75
	Period I: Oral Treatment with Vitamin D, Calcium, and Calcitriol							
13	0	0	0		7.4	2.4	893	1103
15	800	8000	0.4		8.4	2.8	1165	641
17	1600	800	1		8.6	2	920	1055
18	2400	800	1.5		7.3	2.1	529	1147
18	4000	800	6		8.6	2.2	725	642
19	8000	800	6		7.8	2.9	485	895
Median for the period					**7.8**	**2.4**	**725**	**815**
Mean for the last three visits					**7.9**	**2.4**	**580**	**895**
	Period II: Treatment with Intravenous Calcium							
20	550 mg over 10 hrs	400	0		7.8	2.9	851	799
21	600 mg over 10 hrs	400	0		8.3	2.2	1039	360
22	450 mg over 15 hrs	400	0		8.2	2.8	805	158
23	400 mg over 20 hrs	400	0		8.5	5.0	532	193
24	400 mg over 20 hrs	400	0		9.0	4.0	348	99
25	400 mg over 20 hrs	400	0		9.2	6.6	383	94
26	400 mg over 20 hrs	400	0		8.8	4.9	332	136
27	400 mg over 20 hrs	400	0		9.1	5.9	294	115
Median for the period					**8.5**	**4.0**	**432**	**165**
Mean for the last three visits					**9.0**	**5.8**	**336**	**115**
	Period III: Off Intravenous Calcium Therapy							
28	None	400	0		8.9	4.9	256	59
30	None	400	0		8.7	4.5	277	172
32	None	400	0		9.3	5.5	392	239
33	1800	400	0		9.0	4.9	382	92
34	2400	400	0		9.1	5.4	370	134
36	3000	400	0		8.8	4.0	379	218
38	3000	400	0		8.9	4.7	522	496
40	3000	400	0		8.9	3.7	556	412
42	3750	400	10		8.9	3.0	547	479
44	3750	400	10		8.5	3.7	530	530
46	3750	400	10		9.0	3.4	520	375
48	3750	400	20		8.9	3.5	490	545
49	3750	400	20		9.2	4.0	508	516
Median for the period					**8.9**	**4.5**	**460**	**268**
Mean for the last three visits					**9.0**	**3.6**	**506**	**479**
	Period IV: Novel Therapy with Cinacalcet							
51	3750	400	20	09	8.5	3.5	387	423
52	3750	400	20	18	8.2	4.4	332	378
54	4500	400	20	16	8.8	5.0	345	148
56	4500	400	20	16	8.3	5.4	272	85
58	6000	400	20	16	8.0	5.1	251	77
60	6000	400	20	16	7.9	4.6	230	108
62	6000	400	20	16	8.4	4.8	209	72
64	6000	400	0	16	8.7	6.7	246	113
66	6000	400	0	08	9.4	6.0	225	84
68	6000	400	0	08	9.3	4.1	178	12
70	6000	400	0	08	8.7	4.0	286	9
Median for the period					**8.4**	**4.5**	**280**	**122**
Mean for the last three visits					**9.1**	**4.7**	**230**	**35**

Serum creatinine and albumin concentrations remained normal for age throughout these periods.

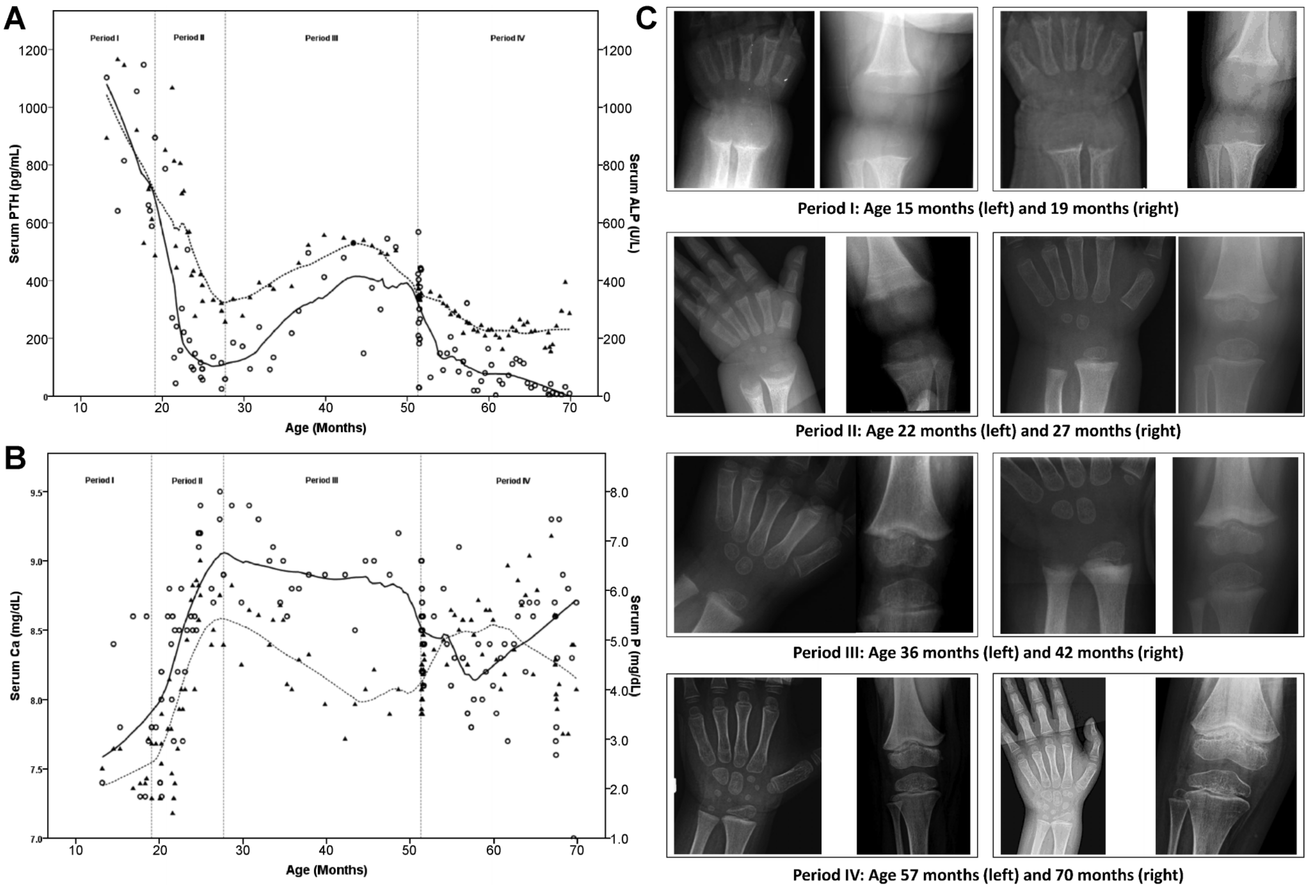

Fig. 1. The clinical course of the child with HVDRR has been divided into four periods based on key therapies during each period. The locally weighted regression-smoothing scatter plot (LOESS) regression, based on the Epanechnikov kernel function and piecewise change-point regression model, was used to best fit the data for serum PTH, ALP, Ca, and P. (*A*) Scatter plot for serum parathyroid hormone (PTH) and serum alkaline phosphatase (ALP). Individual results of serum PTH are represented by (○) and LOESS regression line by (–), and of serum ALP by (△) and LOESS regression line by (---). (*B*) Scatter plot for serum calcium (Ca) and serum phosphorus (P). Individual results of serum Ca are represented by (○) and LOESS regression line by (–), and for serum P by (△) and LOESS regression line by (---). (*C*) Radiological changes over the four time periods. Period I: Oral treatment with vitamin D, calcium, and calcitriol, during which the child had received ergocalciferol and escalating doses of calcium and calcitriol with minimal/poor response to therapy, as shown by persistent marked elevation in serum PTH and ALP; low serum P concentration; and rachitic changes on X-rays. Period II: Treatment with intravenous calcium for HVDRR, during which the child achieved almost normalization of serum PTH, ALP, Ca, and P, and healing of rachitic changes on X-ray. Period III: Off intravenous calcium therapy because of recurrent line infections/sepsis. The child received high oral dose of calcium and, subsequently, extremely high doses of calcitriol therapy, which could not prevent slow deterioration of his mineral metabolism and recurrence of early changes of rickets on X-ray. Period IV: Cinacalcet combined with oral calcium therapy led to normalization of all biochemical parameters with complete healing of rickets.

Period I: Oral treatment with vitamin D, calcium, and calcitriol

To eliminate the possibility of nutritional rickets, the child was initially treated with standard doses of ergorcalciferol, calcium, and calcitriol (Table 1). However, even after normalization of 25(OH)-D_3 level, there was no evidence of healing of rickets on X-rays, nor correction of serum Ca, P, ALP, and PTH levels. Next, an attempt was made to treat with incrementally increasing supra-physiological doses of calcium and calcitriol reaching elemental calcium of 8000 mg/day and calcitriol 6 μg/day. During this 6 months of oral therapy, his 25(OH)-D_3 levels rose to 117 ng/mL and 1,25$(OH)_2$-D_3 to 669 pg/mL, but no improvement on X-rays was observed, and the child's chemistry panel continued to show unresponsiveness. Toward the end of this period we evaluated him for VDR gene mutation. A single G to A missense mutation was identified in exon 2 that changed the codon for valine to methionine at amino acid 26 (V26M) in the DNA-binding domain confirming the diagnosis of HVDRR.[13] The functional impact of this mutation has been previously described.[13]

Period II: Treatment with intravenous calcium

Once HVDRR was confirmed, and with family's consent, we embarked on intravenous calcium therapy. Calcium gluconate was initiated at 550 mg of elemental calcium daily, infused via a central line over a period of 10 hours. Over the next 8 months, the dose of calcium was titrated based on biochemical response, ranging between 450 and 600 mg per day, infused over 10 to 20 hours. He responded to treatment with significant improvement, albeit not complete normalization, of his serum Ca, P, ALP, and PTH, and radiological healing of rickets (Table 1 and Fig. 1*A–C*. During this period, 25(OH)-D_3 levels ranged between 33 and 47 ng/mL and 1,25$(OH)_2$-D_3 between 99 and 243 pg/mL. However, intravenous calcium therapy was complicated by repeated severe central-line infections with various organisms, including Serratia, Citrobacter, Enterobacter, Enterococcus, and Staphylococcus species that failed to respond to conventional antibiotic therapy, each time necessitating central-line removal and replacement. An extensive work-up failed to detect any immunological malfunction. After the seventh life-threatening line infection, we agreed with the family to discontinue intravenous treatment.

Period III: Off intravenous calcium therapy

After discontinuation of intravenous calcium therapy, and while on maintenance dose of 400 units of ergocalciferol, we observed a gradual increase in ALP and PTH despite normal serum calcium levels (Table 1). The addition of high-dose of oral calcium did not affect the trend of rising ALP and PTH, and decline in serum P. It was evident that the improvement achieved previously with intravenous calcium therapy was slowly dissipating by increasing severity of secondary hyperparathyroidism, and therefore calcitriol at highly supra-physiological doses was added.[14] However, after 20 months of this mode of treatment, no significant impact on serum levels of ALP and PTH could be observed, and X-rays showed increased flaring and cupping of the metaphyses consistent with early manifestations of rickets. Serum 25(OH)-D_3 levels ranged between 32 and 52 ng/mL, and 1,25$(OH)_2$-D_3 level ranged between 129 and 2430 pg/mL during this period. FGF-23 was undetectable.

Period IV: Cinacalcet therapy

After a thorough discussion with the family, a decision was made to try Cinacalcet as part of the child's treatment. Although the manufacturer does not recommend crushing the tablet, having no other choices of how to administer it, we prepared a suspension daily by crushing 30 mg tablet into 10 mL water. The treatment was started in the hospital for close monitoring of serum iCa, because of the possibility of hypocalcemia induced by Cinacalcet therapy. The starting dose of Cinacalcet was 4 mg ($\sim$0.25 mg/kg) once a day. We did not appreciate a significant decrease in serum iCa, and the dose was incrementally increased based on serum PTH levels, reaching 4.5 mg twice a day by the end of the week, when the child was discharged. The dose was further increased over the next 6 weeks to 9 mg twice a day ($\sim$1 mg/kg/day) as an outpatient. Over the next year, we observed sustained control of secondary hyperparathyroidism and healing of the patient's rachitic changes on X-rays (Table 1 and Fig. 1*A–C*. At the age of 62 months, calcitriol therapy was discontinued. Nevertheless, the patient continued to maintain normal values of all biochemical parameters and normal-appearing bones on radiographs, and consequently the Cinacalcet dose was decreased to once a day at 8 mg ($\sim$0.4 mg/kg/day) (Table 1). The bone turnover markers obtained before the initiation of Cinacalcet therapy were elevated; namely Bone Specific-ALP was 187.1 μg/L (normal 25 to 124), osteocalcin was 48 ng/mL (normal 9 to 38), and urine N-telopeptide was 1412 nmol/mmolCr (normal 56 to 1763). They decreased to 78.9 μg/L, 29 ng/mL, and 530 nmol/mmolCr, respectively, on last follow-up. Serum FGF-23 was undetectable throughout this period, while 25(OH)-D_3 levels ranged between 38 and 64 ng/mL (64 ng/mL on last follow-up), and 1,25$(OH)_2$-D_3 ranged between 246 and 2630 pg/mL (246 ng/mL on last follow-up). On last follow up the patient's weight was 20.7 kg (Z-score 0.1), length 102.3 cm (Z-score –2.4); he had normal chemistries, resolution of rachitic changes and no nephrocalcinosis, but no change in alopecia.

Discussion

HVDRR results from loss of function of VDR leading to target organ resistance to 1,25$(OH)_2$-D_3.[1] The nature of the mutation impacts alopecia and response to therapy.[1] As described before, in vitro studies on our patient's fibroblasts revealed that the mutant V26M VDR failed to induce *CYP24A1* gene in response to treatment with up to 1000 nM 1,25$(OH)_2$-D_3.[13] Indeed, as was found in period I, and again while on extremely high oral doses of elemental calcium ($\sim$200 to 250 mg/kg/day) and calcitriol 20 μg/day in period III, there was no improvement in the patient's biochemical and radiological abnormalities, indicating complete resistance to 1,25$(OH)_2$-D_3, similar to other children with alopecia and mutation in the DNA-binding domain.[1]

Recently Tiosano and Hochberg have proposed a mechanistic classification of rickets, namely PTH-dependent, FGF 23–dependent, and Renal, all leading to a common denominator of hypophosphatemia causing rickets by interfering with apoptosis of chondrocytes.[8] They proposed HVDRR to be a form of PTH-dependent rickets. The secondary hyperparathyroidism develops because of decreased gastrointestinal calcium absorption and leads to both hypophosphatemia and increased bone turnover, as was evident in our patient while he was off effective treatment (Table 1). In HVDRR the defect in calcium absorption can be overcome by intravenous calcium infusion, which bypasses the gut.[4–7] We could replicate this observation in period II, when the child received intravenous calcium therapy resulting in marked, albeit incomplete, reversal of the biochemical and skeletal abnormalities. The fulminant life-threatening infections led to a comprehensive immunological workup, which failed to detect any abnormality and consequently resulted in withdrawal of this line of therapy.

In period III, we attempted to maximize the use of vitamin D–independent, nonsaturable paracellular pathway of calcium absorption in the gut by supplementing our patient with 200 to 250 mg/kg/day of oral calcium, in spite of which there was a slow and steady worsening of his mineral and skeletal status (Table 1 and Fig. 1*A–C*). Thus, because of circumstances beyond our control, period III resulted in an ineffective treatment providing a "washout" period between periods II and IV.

The VDR mutation causing HVDRR results in poor calcium absorption from the gut.[15] Based on the concept that skeletal pathophysiology is a form of PTH-dependent rickets, which develops in response to the poor absorption of calcium in the gut, we considered the use of a calcimimetic as a mean to normalize serum PTH. The safety and efficacy of Cinacalcet in children has been shown in a few small series and anecdotal cases of secondary hyperparathyroidism in other disorders.[9–12]. Because of the concern that Cinacalcet therapy might cause hypocalcemia, the high dose of oral calcium supplementation was not interrupted. However, because of the potential adverse effect of sequestration of dietary phosphate in the gut, we recommend that future studies try to use lower doses of supplementary calcium. Supplementation with phosphate was not necessary because serum phosphate normalized with suppression of the parathyroid gland with either intravenous calcium or Cinacalcet therapy (Table 1 and Fig. 1).[2,3,15–17] Cinacalcet exerted its effect rapidly, resulting in suppression of PTH and resolution of the radiological changes of rickets. This effect was further corroborated by suppression of bone turnover markers, and also by an apparent increase in bone mineralization on X-rays. Not unexpected, the beneficial effect of the calcimimetic agent was unaffected by the discontinuation of supplementation with 1,25$(OH)_2$-D_3. We did not observe any difficulties in the preparation or administration of the medication to the young child.

The patient described in this report exhibited the classical clinical pattern of HVDRR from a VDR mutation that caused complete target organ resistance to 1,25$(OH)_2$-D_3. The successful treatment with Cinacalcet shows that the skeletal pathophysiology of rickets in HVDRR is PTH dependent, and that successful control of the secondary hyperparathyroidism is sufficient to heal the rickets, even though resistance to 1,25$(OH)_2$-D_3 remains unaffected. Considering its relative easiness of the administration as a once-a-day or twice-a-day oral preparation, compared with the cumbersome and at times risks-associated intravenous calcium therapy, one can consider Cinacalcet to be an adjunct to calcium therapy in management of children with HVDRR.

Disclosures

All authors state that they have no conflicts of interest.

Acknowledgments

The study was supported by the Sam and Helen Kaplan Research Fund in Pediatric Nephrology and the Eric McClure Research Fund in Pediatric Bone and Mineral Disorders. Informed consent was given by the patient's family to share our experience with Cinacalcet in HVDRR. We appreciate their support and confidence in us over these years. We acknowledge Dr. Peter J. Malloy and Dr. David Feldman at Stanford University School of Medicine for their assistance in identifying the *VDR* gene mutation, and the functional impact of the mutation on mineral metabolism.

Authors' roles: TS and USA both contributed to the patient's clinical care, the data analysis, and the writing up of the manuscript.

References

1. Malloy PJ, Feldman D. Genetic disorders and defects in vitamin D action. Endocrinol Metab Clin North Am. 2010;39:333–6.
2. Malloy PJ, Pike JW, Feldman D. The vitamin D receptor and the syndrome of hereditary 1,25-dihydroxyvitamin D-resistant rickets. Endocr Rev. 1999;20:156–88.
3. Malloy PJ, Pike JW, Feldman D. Hereditary 1,25-dihydroxyvitamin D resistant rickets. In: Feldman D, Pike JW, Glorieux F, editors. Vitamin D 2nd ed. San Diego: Elsevier; pp. 1207–38. 2005.
4. Weisman Y, Bab I, Gazit D, Spirer Z, Jaffe M, Hochberg Z. Long-term intracaval calcium infusion therapy in end-organ resistance to 1,25-dihydroxyvitamin D. Am J Med. 1987;83:984–90.
5. Balsan S, Garabédian M, Larchet M, Gorski AM, Cournot G, Tau C, Bourdeau A, Silve C, Ricour C. Long-term nocturnal calcium infusions can cure rickets and promote normal mineralization in hereditary resistance to 1,25-dihydroxyvitamin D. J Clin Invest. 1986;77:1661–7.
6. al-Aqeel A, Ozand P, Sobki S, Sewairi W, Marx S. The combined use of intravenous and oral calcium for the treatment of vitamin D dependent rickets type II (VDDRII). Clin Endocrinol (Oxf). 1993;39:229–37.
7. Hochberg Z, Tiosano D, Even L. Calcium therapy for calcitriol-resistant rickets. J Pediatr. 1992;121:803–8.
8. Tiosano D, Hochberg Z. Hypophosphatemia: the common denominator of all rickets. J Bone Miner Metab. 2009;27:392–401.
9. Alon US, Levy-Olomucki R, Moore WV, Stubbs J, Liu S, Quarles LD. Calcimimetics as an adjuvant treatment for familial hypophosphatemic rickets. Clin. J Am Soc Nephrol. 2008;3:658–64.
10. Muscheites J, Wigger M, Drueckler E, Fischer DC, Kundt G, Haffner D. Cinacalcet for secondary hyperparathyroidism in children with end-stage renal disease. Pediatr Nephrol. 2008;23:1823–9.
11. Silverstein DM, Kher KK, Moudgil A, Khurana M, Wilcox J, Moylan K. Cinacalcet is efficacious in pediatric dialysis patients. Pediatr Nephrol. 2008;23:1817–22.
12. Alon US, Van De Voorde RG, Beneficial effect of cinacalcet in a child with familial hypocalciuric hypercalcemia. Pediatr Nephrol. 2010;25: 1747–50.
13. Malloy PJ, Wang J, Srivastava T, Feldman D. Hereditary 1,25-dihydroxyvitamin D-resistant rickets with alopecia resulting from a novel missense mutation in the DNA-binding domain of the vitamin D receptor. Mol Genet Metab. 2010;99:72–9.
14. Portale A, Miller WL. Rickets due to hereditary abnormalities of vitamin D synthesis or action. In: Glorieux F, Pettifor J, Juppner H, editors. Pediatric Bone: Biology & Diseases. San Diego: Academic Press (Harcourt); 583–602. 2003.
15. Xue Y, Fleet JC. Intestinal vitamin D receptor is required for normal calcium and bone metabolism in mice. Gastroenterology. 2009; 136:1317–27.
16. Feldman D, Malloy PJ. Hereditary 1,25-dihydroxyvitamin D resistant rickets: molecular basis and implications for the role of 1,25$(OH)_2D_3$ in normal physiology. Mol Cell Endocrinol. 1990;72:C57–62.
17. Ma NS, Malloy PJ, Pitukcheewanont P, Dreimane D, Geffner ME, Feldman D. Hereditary vitamin D resistant rickets: Identification of a novel splice site mutation in the vitamin D receptor gene and successful treatment with oral calcium therapy. Bone. 2009; 45:743–6.