The effectiveness of cinacalcet as an adjunctive therapy for hereditary 1-25 dihydroxyvitamin D3 resistant rickets

Aysehan Akinci[1], Ismail Dundar[1], Meltem Kivilcim[2]
Inonu University Medical Faculty, Pediatric Endocrinology[1] and Developmental and Behavioral Pediatrics Department[2] Malatya, Turkey

Bacground: Patients with vit-D resistant rickets (VDRR)due to vitD receptor mutations have extreme rickets along with alopesia, severe hypocalcemia, hypophosfatemia secondary to hyperparathroidism and elevated 1,25(OH)2vitD3. Although there is no standart therapy for this patients, long-term or intermittant i.v. or high dose oral calcium suplementations are recommended to correct the hypocalcemia and secondary hyperparathyroidism. Preliminary studies showed the calcimimetics to be safe and effective therapeutic choise in children with secondary hyperparathyroidism.

Objectives: To observe the efficacy of cinacalcet on the normalization of secondary hyperparathroidism and hypophosphatemia in two siblings with VDRR who did not respond to traditional models of therapy.

Patients : Two siblings, one at the age of 2 years - 6 months and the other at 4 months old were admitted to the hospital with severe hypocalcemia. The skeletal survey and biochemical findings showed advanced features of rickets. 1-25(OH)2D3 levels were near upper limits in both siblings. Mutation analaysis of the VDR gene revealed a homozygote C to T transition in exon 4 (c.148C<T) in both siblings. Parents were heterozygous for the same mutation. They were treated with high dose calcitriol and intermittant i.v. calcium infusions. Hyperparathroidism was normalized temporarly, but not completly. We started cinacalcet (0.25 mg/kg) once a day along with high dose oral calcium and calcitriol, after 3 months biochemical and radiologic findings were return to normal status.

Figure 1 1a 1b 1c

Figure 1: Alopecia and rickets in case 1

1-a: Anterio-posterior radiography of the patient's hand with rickets demonstrates cupping and frying of the metaphysial region(before treatment);

1-b: After treatment with high dosages of i.v. calcium infusion ,the x-ray of the wrist is showing partial healing of the rickets findings;

1-c: The x-ray of the wrist is showing progressive healing of rickets while the child was receiving high dose oral calcium, calcitriol and cinacalcet.

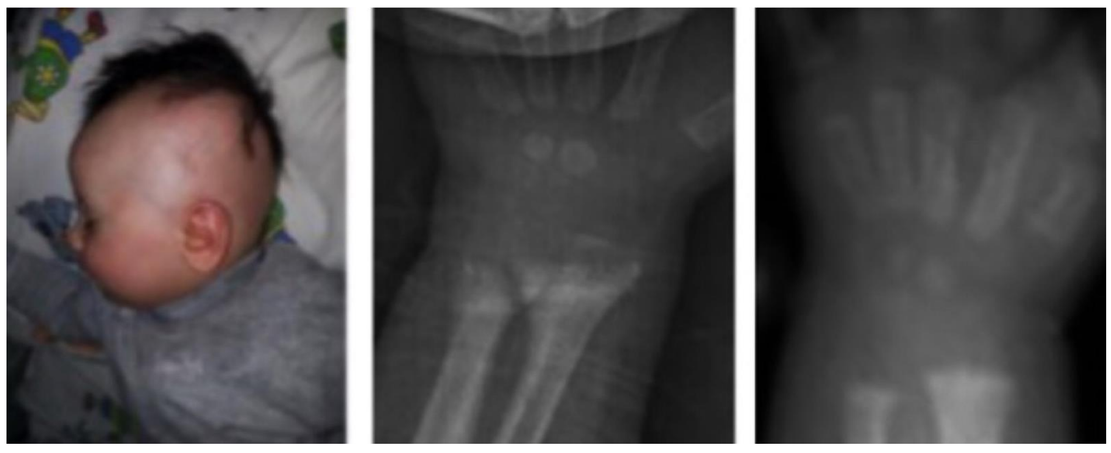

Figure 2 2a 2b

Figure 2: Alopecia and rickets in case 2.

2-a: the baseline x-rays at the age of 4 months are showing changes consistent with rickets,

2-b: Bone roentgenogram was showing markedly improved signs of rickets with high dose calcitriol, oral calcium and cinacalcet.

Tablo 1. The effect of theraphy with elemental Ca (oral/i.v.), calcitriol and cinacalcet on serum Ca, P, ALP and PTH levels in case 1

Date	Ca (mg/dl)	P (mg/dl)	ALP (U/L)	PTH (pg/ml)	Treatment
First admission	7.2	2.3	2278	1194	elemental ca oral: 2gr/day calcitriol: 2 µg/day phosphor 1 gr/day
4th week (second visit)	7.8	2.4	2127	1078	elemental ca oral : 4 gr/day calcitriol: 4 µg/day fosfor :1.5 gr/day
8th week (third visit)	8.5	2.8	2047	1036	Continued with same protocol no radiological changes
After 6 weeks of 3th visit First step i.v. ca infusion for 5 days in a month	6.8	1.8	1427	940	elemental ca: i.v. (150µg/kg/day) phosphor:2gr/day calcitriol: 6µg/day
After first step of i.v.calcium therapy for 5 days	9.4	2.7	1540	95	elemental ca oral: 4 gr/day calcitriol: 6µg/day phosphor: 2 gr/day
After 4 weeks of i.v. calcium therapy	7.9	3	1887	887	elemental ca oral: 4 gr/day calcitriol: 6µg/day phosphor: 2 gr/day
After oral drugs for 2 month, second step i.v. ca therapy applied	7.2	1.5	1651	1085	elemental ca i.v.: (150 µg/kg/day) calcitriol: 6µg/day phosphor: 2gr/day
After 5 days i.v. elemental ca infusion	9.4	2.1	1433	90	elemental ca oral: 4gr/day calcitriol:6µg/day phosphor: 2gr/gün
After 4 weeks i.v. ca infusion off	7.1	2.4	1638	681	elemental ca i.v.:(150mg/kg/day) calcitriol: 6µg/day fosfor: 2gr/day
After 4 steps i.v. ca infusion	7.5	2.6	1480	716	partial radiological healing cinacalcet applied(0.25mg/kg/day)
After 15 days of cinacalcet applied	7.9	2.7	1335	503	elemental ca oral: 4gr/day calcitriol: 6µg/day phosphor: 1gr/day cinecalcet : 0.4 mg/kg/ mg/day
After 1 month of cinacalcet applied	8.9	3	1100	184	oral elemental ca:2gr/day calcitriol 4µg/day cinacalcet: 0.4 mg/kg/day
After 4 months of cinacalcet applied	9	3.1	200	64	oral elemental ca:2gr/day calcitriol 2µg/day cinacalcet: 0.25mg/kg/day radiological healing was observed

Tablo 2. The effect of therapy with elemental Ca (oral/i.v.) calcitriol and cinacalcet on serum Ca,P,ALP and PTH levels in case 2

Date	Ca (mg/dl)	P (mg/dl)	ALP (U/L)	PTH (pg/ml)	Treatment
First visit	9.2	4.1	522	234	
After 1 month of first visit	7.8	3.5	847	555	calcitriol 1.5µg/day oral calcium 1gr/day
After 2 months of first visit Radiological findings of rickets was appeared	7.2	1.8	1427	940	first step of elemental Ca i.v. (150mg/kg/day) for 5 days oral phosphor: 1.5gr/day calcitriol: 2 µg/day
After 5 days of first step i.v. Ca infusion	9.4	2.7	1540	115	elemental Ca oral: 1gr/day calcitriol: 4µg/day oral phosphor : 1.5 gr/day
After one week i.v. ca infusion off	7.8	3	1887	887	elemental Ca oral: 2gr/kg/day calcitriol: 4 µg/day oral phosphor:2gr/day
After 1 month first step i.v. ca infusion off	6.9	1.5	1651	785	second step elemental Ca i.v.: 150mg/kg/day for 5 days calcitriol 4 µg/day fosfor: 2gr/day
After second step Ca infusion for 5 days	9.6	3.1	1433	165	elemental Ca oral: 2gr/day phosphor:2gr/day calcitriol: 4 µg/ day
After 1 month second step Ca infusion off	7.1	2.4	1638	681	elemental Ca i.v.: 150mg/kg/day for 5 days calcitriol:4µg/day fosfor1.5gr/day cinecalcet : (0.25mg/kg/day)
After 2 months of cinecalcet applied	9.2	3.7	215	95	elemental Ca oral: 1gr/day calcitriol 2 µg/day cinacalcet 0.25 mg/kg/day
After 3 months of cinacalcet applied	8.9	3.2	220	62	Continue same treatment protocol radiological healing was observed

Conclusion: We observed that cinacalcet is succesfull to normalize of hyperparathyroidism and hypophosphatemia and to restore bone findings in patients with HVDRR.

References: 1-Huang K,Malloy P, Feldman D, Pitukcheewanont P. Enteral calcium infusion used successfully as treatment for a patient with hereditary vitamin D resistant rickets (HVDRR) without alopecia: A novel mutation.Gene. 2013; 512: 554-559.
2-Srivastava T,Alon US. Cinacalcet as adjunctive therapy for hereditary 1,25-dihydroxyvitamin D-resistant rickets. J Bone Miner Res . 2013; 28(5): 992-996.

55ESPE 147--P2
Bone & Mineral Metabolism
Aysehan Akinci
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS
PosterSessionOnline.com