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Denosumab increases Bone Mineral Density in primary hyperparathyroidism treated with Cinacalcet.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the commonest endocrine disorder with a current estimated incidence in of about 22 new cases per 100 000 persons per year and a prevalence of 1–4 per 1000 individuals in the general population.

Parathyroidectomy (PTx) is the therapeutic procedure able to cure the disease and it should be considered in all patients with PHPT and recommended in those with moderate-to-severe. a A minority of patients may experience surgical failure, some patients may have contraindications to surgery, and some other patients simply do not wish to have surgery.

Cinacalcet, an allosteric modulator of the calcium-sensing receptor decreases and normalizes serum calcium levels across a broad severity range of primary hyperparathyroidism (PHPT), slightly reduces parathyroid hormone levels which generally remains elevated, whereas it has no effect on bone mineral density (BMD).

Therefore, when administering cinacalcet to a patient with PHPT, concomitant treatment with an anti-catabolic drug should be considered and Vitamin D deficiency, which appears to be associated with a more severe skeletal disease, should be corrected.

A recent meta-analysis showed that antiresorptive therapies increase BMD to the same extent as PTx in patients with mild PHPT, suggesting that this treatment may be considered in patients with Primary hyperparathyroidism with contraindications to surgery.

Denosumab is a fully human monoclonal anti-RANKL antibody that inhibits the binding of RANKL to RANK, thereby decreasing osteoclastogenesis and bone-resorbing activity of mature osteoclasts.

MÉTODOS

An open-labeled, prospective trial was conducted in 30 patients with PHPT with Cinacalcet treatment [contraindications to surgery: comorbidities, high surgical risk and age, clinical judgment of inappropriate parathyroid surgery (PTx): negative parathyroid imaging, persistent or relapsing PHPT after PTx- and refusal of PTx], to determine whether denosumab, maintains or improves BMD in patients with PHPT after a year of treatment.

PHPT patients with low BMD were treated with Cinacalcet (Mimpara, Amgen; titrated dose), 25-OH vitamin D (Hidroferol, Faes.) and denosumab (Prolia, Amgen) 60 mg sc injections given every six months.

Serum calcium, phosphorous PTH and bone turnover markers (alkaline phosphatase osteocalcin an crosslaps) were evaluates every three months, 25 hydroxyvitamin D, 1,25-dihydroxyvitamin BMD were evaluated at Reina Sofía laboratory

Dual-energy x-ray absorptiometry assessments using the Hologic QDR 4500 instrument were made at the L1–L4 lumbar spine (posteroanterior projection) (LS) , total femoral neck, every 12 months. Screening radiographs for vertebral compression fractures were not done. tatistical analysis

The treatment effect on BMD, and biochemical markers was tested by a paired t tests were used to detect differences pre and posttreatment

Hypothesis: Denosumab will increase or mantain bone mineral density in patients with in primary hyperparathyroidism with contraindications to surgery in medical treatment with cinacalcet after atwo years of treatment

RESULTS

Baseline characteristics hyperparathyroidism patients groups are shown in Table 1

After 24 months the treatment normalized calcium, phosphorous and 25(OH)D serum levels and urinary calcium excretion. Bone turnover markers remained suppressed for the duration of the trial. The treatment was also associated with a significant increase after 24 months in vs. baseline in LS BMD: 8% (p: 0.003) and in TF BMD: 7% (p: ,0001). Results are showed in table 2.

TABLE

PARAMETERS	BASAL VALUE	AFTER 1 YEAR TREATMENT	P VALUE	AFTER 2 YERAS TREATMENT	p VALUE
Calcium p (8,5-10,5 mg/dl)	11,43±0,79	10,06±0,61	P<0,0001	9,73 ± 0,74	P<0,0001
Phosphorate (2,3-4,7 mg/dl)	2,72±0,59	2,85±0,41	P<0,0001	2,94 ± 0,41	P<0,0001
Paratohormona (15-65 pg/ml)	124,16±59,46	96,92±40,14	P<0,1	90,86±37,81	P<0,05
Calcium/Cr urinary (0,08-0,20 mg/mg)	0,27±0,18	0,20±0,08	P<0,0001	0,19 ± 0,10	P<0,001
Betacrosslaps (0,02-0,55 ng/ml)	0,46±0,30	0,08±0,08	P<0,003	0,02 ± 0,009	P<0,004
Osteocacin (5-40 ng/ml)	20,51± 8,75	12,51±6,72	P<0,0001	20,2±14,55	P<0,1
25 OH Vitamin D (8-42 ng/ml)	32,17±15,26	36,18±19,93	P<0,12	44,1 ± 25,9	P<0,005
BMD Lumbar spine g/cm2	0,96±0,19	1,03±0,19	P<0,03	1,03±0,11	P<0,03
BMD Total Femoral g/cm2	0,82±0,17	0,85±0,17	P<0,03	0,88±0,11	P<0,06

CONCLUSIONS

- Association of Denosumab & vitamin D with cinacalcet is an excellent therapeutic option to normalize serum calcium and to treat the metabolic bone-disease in patients with PHPT who do not meet criteria for surgical treatment.
- Denosumab produces an increase in bone mineral density with suppressed remodeling markers from the beginning of treatment.
- PTH both builds and breaks down bone.
- Prior research suggests that RANKL is a critical molecule in bone catabolism in response to PTH. then if the RANKL is inactivated, PTH is shifted towards anabolic pathway building bone in patients with PHPT

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