TREATMENT WITH PTH 1-84 IN MALE PATIENTS WITH SEVERE OSTEOPOROSIS
RESULTS FROM A PROSPECTIVE 24 MONTH OPEN-LABEL TRIAL

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Purpose:

Osteoporosis in men is an important and often underestimated problem. Generally accepted is the administration of antiresorptives which influence bone metabolism by reducing bone resorption and increasing bone mineral density (BMD).
Recent findings identified decreases in trabecular number, connectivity density or enhanced trabecular separation as a possible reason for microstructural alterations. Furthermore reduced expression of osteoblast-related genes (ie WNT10B, RUNX2, Osterix, SOST, OPG) support the hypothesis of osteoblast dysfunction leading to enhanced fracture risk in male osteoporosis as recently published by our group [1].
Anabolic agents such as rhPTH 1-84 or rhPTH 1-34 stimulate bone formation and subsequently bone resorption, thereby increasing BMD by rapid and sustained maturation of osteoblast precursors.
A number of osteoporotic patients under bisphosphonate treatment present persistent fragility fractures and bone loss despite good compliance and are considered as inadequate responders [2]. Furthermore glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. The antiresorptive mechanism of bisphosphonates does not address the major pathophysiological mechanisms of impaired bone formation during chronic glucocorticoid treatment [3].
According to these pathological pathways anabolic treatment by PTH is reimbursed when new osteoporotic fractures occur during antiresorptive treatment, in glucocorticoid induced osteoporosis (GIO) and in patients with low BMD and severe clinical risk factors (CRF).
This study is considered as a pilot project to prove the clinical relevance of our recent published basic research results in a clinical setting.

	All (n=26)	Prior BPH (n=14)	Prior GC (n=6)	Treatment naïve (Tn) (n=6)	P value (vs all)
Age (years)	63.3 ± 14.3	60.2 ± 8.4	39.4 ± 9.3†	68.5 ± 5.8	.05†
BMI (kg/cm²)	25.4 ± 4.7	26.4 ± 3.9	24.4 ± 3.7	26.0 ± 4.2	n.s.
Vertebral fractures (n, % pts vs all)	2.3 ± 0.8 (20; 76.9%)	2.1 ± 0.6 (14; 53.8%)	2.2 ± 0.9 (4; 15.4%)	1.9 ± 0.3 (2; 7.6%)	n.s.
Non-vertebral fractures (n, % pts vs all)	1.8 ± 0.7 (11; 42.3%)	1.3 ± 0.2 (8; 30.8%)	1.4 ± 0.4 (2; 7.7%)	0.5 ± 0.4 (1; 3.8%)	n.s.
Hip Fractures (n, % pts vs all)	5; 19.2%	4; 15.4%	0	1; 3.8%	n.s.
Calcium (2.10 – 2.58 mmol/l)	2.36 ± 0.14	2.34 ± 0.24	2.37 ± 0.11	2.37 ± 0.33	n.s.
Phosphorus (0.60 – 1.55 mmol/l)	1.16 ± 0.18	1.21 ± 0.21	1.17 ± 0.13	1.17 ± 0.10	n.s.
25-OH vitamin D (> 30 ng/ml)	35.1 ± 9.6	27 ± 2.2†	31.1 ± 9.1	31.5 ± 12.3	.001†
P1NP (27.7 – 127.6 µg/l)	28.3 ± 15.5	21.4 ± 11.2†	23.5 ± 9.4	44.7 ± 11.3†	.05†
S-CTX (< 0.6 ng/ml)	0.347 ± 0.217	0.153 ± 0.121†	0.487 ± 0.274	0.359 ± 0.127	.05†
iPTH (15.3 – 55.0 pg/ml)	45.3 ± 15.2	49.4 ± 12.7	42.9 ± 8.7	39.7 ± 12.4	n.s.
BMD lumbar spine (g/cm²)	0.81 ± 0.14	0.74 ± 0.32	0.89 ± 0.27†	0.83 ± 0.45	.05†
BMD femoral neck (g/cm²)	0.75 ± 0.12	0.71 ± 0.28	0.82 ± 0.33	0.79 ± 0.17	n.s.
BMD total hip (g/cm²)	0.79 ± 0.12	0.82 ± 0.18	0.84 ± 0.27	0.81 ± 0.22	n.s.

Tab 1: Baseline characteristics. (BPH = bisphosphonates, GC = glucocorticoids)

Methods:

We prospectively assigned 26 men (mean age 63.3 ± 14.3 ys) to daily subcutaneous injections of 100 µg of full length PTH 1-84 for 24 months. All patients received daily supplementation of 1000 mg calcium and 800 IU vitamin D. Vitamin D deficient subjects (defined as serum level <30 ng/ml) received oral loading with 25(OH) vitamin D3 prior to initiation of anabolic treatment.
Mean T-score at baseline was -3.24 ± 0.92 at lumbar spine and -2.31 ± 0.94 at hip. Fractured vertebrae were excluded from evaluation. 81% had prevalent fractures including vertebral fractures (20 pts, mean 2.3 ± 0.8), non-vertebral fractures (11 pts) and hip fractures (5 pts).

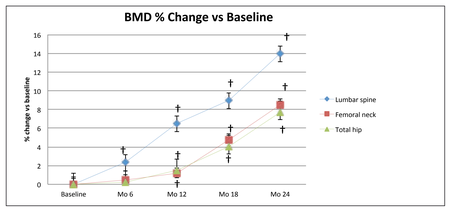

Fig 1: BMD increase of spine and hip (n = 26); † P < .05 vs baseline

According to prior medical history all patients were divided into three groups. 6 pts had long term steroid medication (9.3 ± 5.3 ys). 14 pts had prior antiresorptive treatment (6.3 ± 2.6 ys) and 6 were treatment naïve (low BMD, ≥ 2 CRF).
We investigated the overall study population and the effects of PTH 1-84 within these three groups [Tab 1].
Primary objectives were the increase of BMD at lumbar spine and hip/femoral neck and the changes of bone turnover markers (P1NP, S-CTX).
Secondary objectives were reduction of new osteoporotic fractures and the evaluation of safety and tolerability in men.
Patients had BMD measurements (DXA), X-ray of spine, assessment of P1NP, S-CTX at baseline and at months 6, 12, 18 and 24. Numeric Rating Scale (NRS) for back pain and EuroQol 5D (EQ-5D) Health Questionnaire scores were used to collate descriptive data on the patient population.

Results:

In the whole group the increase of lumbar spine BMD at month 12 was 6.51% and at month 24 finally 13.98%, at femoral neck from 1.17% and 8.5% and at total hip 1.5% and 7.72% compared to baseline (P<.05 for spine at any time, hip at mo 12 subsequently) [Fig 1]. P1NP rapidly increased up to 421% at month 12 compared to baseline and remained at elevated level until to the end of the observation period; S-CTX increased between 181% and 301% (maximum 322% at month 18) [P<.001 for all].[Fig 2]

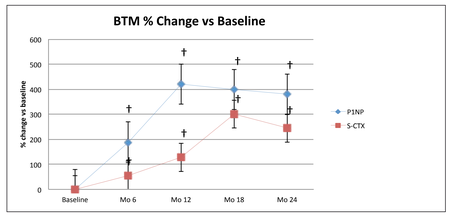

Fig 2: Increase of bone turnover markers (n = 26); † P < .001 vs baseline

After partition into the three groups (prior bisphosphonates, prior glucocorticoids, traiment naïve) we could not observe any delayed or impaired effect of PTH 1-84 on BMD increase or enhancement of bone turnover markers No significant changes of BMD increase could be observed when the three groups were compared separately to each other [Fig 3-5].
One patient (GIO) had a new morphometric vertebral fracture (spine facture I°) and one patient (treatment naïve) sustained a hip fracture after a major trauma (car accident).
PTH 1-84 was generally well tolerated. The most frequently reported adverse drug reactions (ADR) were nausea, headache and mild hypercalcemia without clinical consequence in 34% of the patients within the first 6 months. The majority of the ADRs occurred after initiation of treatment and faded away after the first quartile.
NRS score declined from 72.5 ± 11.4 to 31.2 ± 8.2 (P<.05). Similarly the EQ-5D scores improved up to 30% within the second half of therapy.

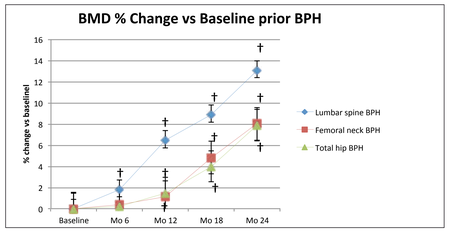

Fig 3: BMD increase of spine and hip – prior bisphosphonates (n = 14); † P < .05 vs baseline

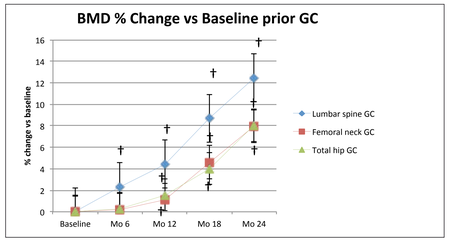

Fig 4: BMD increase of spine and hip – prior glucocorticoides (n = 6); † P < .05 vs baseline

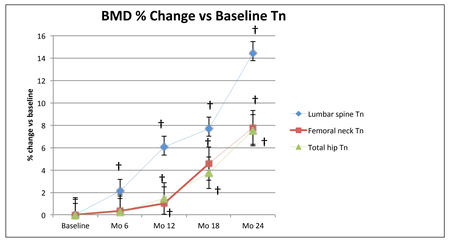

Fig 5: BMD increase of spine and hip – treatment naïve (n = 6); † P < .05 vs baseline

Conclusions:

Our data in men with osteoporosis suggest that PTH 1-84 rapidly increases BMD at different skeletal sites regardless of prior long-term treatment with bisphosphonates or steroid medication. We also found similar responses in all groups. Neither the treatment naïve group, nor the prior long term bisphosphonate induced suppression of the bone turnover or the suppression of osteoblasts by glucocorticoids reduces the anabolic effect of PTH 1-84 in male patients with severe osteoporosis

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