Comparison of the efficacy of denosumab and alendronate in glucocorticoid-induced osteoporosis

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INTRODUCTION

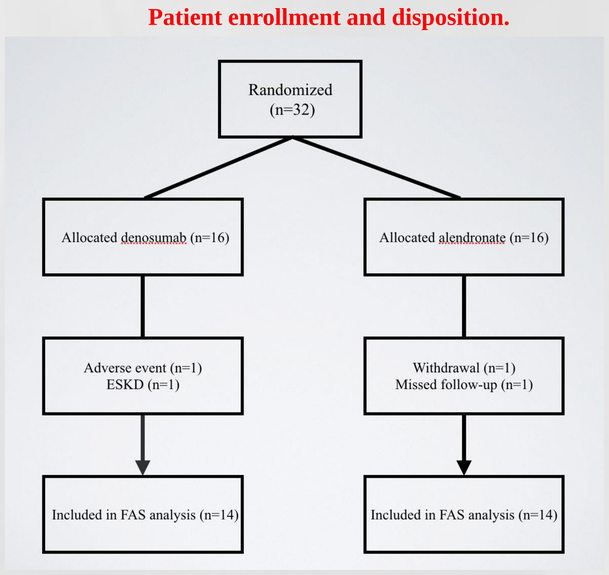
Denosumab is a fully humanized monoclonal IgG2 antibody against the receptor activator of nuclear factor-κB ligand (RANKL), which is a key effector of osteoclast formation, function and survival. Denosumab treatment rapidly decreased bone resorption, increased BMD at lumbar spine and total hip and reduced the risk of new fractures in postmenopausal women with osteoporosis.
To date, denosumab was widely used not only postmenopausal osteoporosis but also other types of osteoporosis such as secondary hyperparathyroidism, however limited information is available regarding the therapeutic potential of denosumab in patients with glucocorticoid-induced osteoporosis (GIOP).
The purpose of the present study was to investigate the efficacy and safety of denosumab compared to alendronate in glomerulonephritis patients with GIOP.

METHODS

We conducted a 12-month, single center, open-label, randomized controlled study that recruited 32 patients with glomerulonephritis who were diagnosed as glucocorticoid induced osteoporosis according to Japanese Society for Bone and Mineral Research criteria. Participants were randomized to either alendronate (35 mg orally once a week) or denosumab (60 mg subcutaneously once every 6 months), and all subjects were received calcitriol. Subjects were randomly assigned in a 1:1 ratio to receive denosumab subcutaneously every 6 months or oral alenedronate for 1 year. All patients received at least calcitriol 0.25 μg/day throughout the study.
The percentage change from baseline in BMD of the lumbar spine at 12 months was the primary endpoint. The secondary endpoints included the percentage change in BMD at other sites and relative changes in bone turnover markers (tartrate-resistant acid phosphatase 5b (TRACP-5b), bone-specific ALP (BAP) and total-type I collagen N-terminal propeptide (t-P1NP)) from baseline to 12 months.

RESULTS

Patient enrollment and disposition.



Clinical characteristics at baseline

	Total (N= 28)	Denosumab (N= 14)	Alendronate (N= 14)	*P*
Age — yr	60.3 ± 18.9	58.7 ± 19.8	61.8 ± 18.6	0.75
Body mass index (kg/m2)	22.4 ± 3.8	22.8 ± 3.9	22.0 ± 3.7	0.61
SMI (skeletal muscle index)	7.0 ± 1.8	7.3 ± 1.8	6.7 ± 1.8	0.32
Female/male	12 / 16	6 / 8	6 / 8	1.00
Postmenopausal women — no. (%)	9 (32.1%)	5 (35.7%)	4 (28.6%)	0.51
Previous drug therapy — no. (%)				
Glucocorticoid	20 (71.4%)	10 (71.4%)	10 (71.4%)	1.00
Prednisone equivalent daily dose — mg	7.2 ± 8.2	5.6 ± 3.1	8.8 ± 11.3	0.79
Duration of therapy — yr	10.1 ± 8.8	9.5 ± 8.0	10.7 ± 9.8	0.91
Vitamin D	18 (64.3%)	9 (64.3%)	9 (64.3%)	1.00
Duration of therapy — yr	5.0 ± 6.2	5.2 ± 6.7	4.8 ± 5.9	0.93
GIOP score	7.5 ± 4.1	7.1 ± 4.1	8.0 ± 4.2	0.59
Previous fracture — no. (%)				
Current Smoker— no. (%)	10 (35.7%)	5 (35.7%)	5 (35.7%)	1.00
Habitual drinking— no. (%)	2 (7.1%)	2 (14.3%)	0 (0%)	0.14
Parent Fractured Hip	1 (3.5%)	0 (0%)	1 (7.1%)	0.31
Rheumatoid arthritis	1 (3.5%)	0 (0%)	1 (7.1%)	0.31
Underlying disease				0.60
MCNS	9	4	5	
Lupus nephritis	7	3	4	
MN	5	2	3	
ANCA-GN	3	3	0	
FSGS	2	1	1	
IgAN	1	1	0	
HSPN	1	0	1	

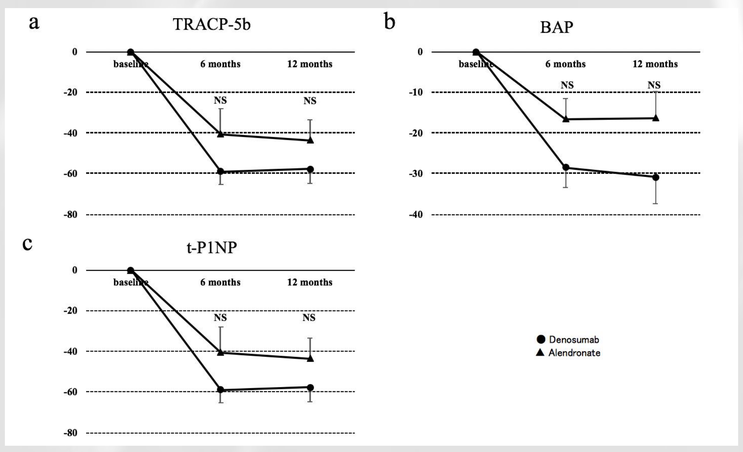
Data are presented as mean ± SD, or n (%). MCNS, minimal change nephrotic syndrome; MN, Membranous nephropathy; ANCA-GN, antineutrophil cytoplasmic antibody-associated glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy ; HSPN, Henoch-Schönlein purpura nephritis

Clinical parameters at baseline

	Total (N= 28)	Denosumab (N= 14)	Alendronate (N= 14)	*P*
Serum biochemical markers				
Albumin (g/dL)	3.4 ± 1.0	3.5 ± 1.0	3.4 ± 1.1	0.76
eGFR (ml/min/1.73㎡)	62.3 ± 25.9	72.0 ± 32.2	52.6 ± 12.3	0.08
Corrected Ca (mg/dl)	9.6 ± 0.5	9.6 ± 0.5	9.6 ± 0.5	1.00
P (mg/dL)	3.2 ± 0.6	3.3 ± 0.5	3.2± 0.6	0.73
Uric Acid	5.7 ± 1.3	5.6 ± 1.6	5.7 ± 1.1	0.70
ALP (U/L)	226.1 ± 69.6	219.0 ± 56.3	233.2 ± 82.4	0.78
TG (mg/dL)	169.4 ± 121.8	154.6 ± 75.6	184.1 ± 156.9	0.78
TC (mg/dL)	235.8 ± 117.5	222.3 ± 121.2	249.3 ± 116.7	0.08
HDL-C (mg/dL)	62.4 ± 16.4	59.9 ± 15.3	65.0 ± 17.6	0.60
LDL-C (mg/dL)	139.5 ± 106.1	131.4 ± 121.3	147.5 ± 92.3	0.10
LDL / HDL ratio	2.5 ± 2.3	2.4 ± 2.5	2.6 ± 2.2	0.63
HbA1c	5.9 ± 0.6	5.9 ± 0.7	5.9 ± 0.5	0.83
Intact PTH (pg/mL)	44.2 ± 25.0	41.5 ± 21.1	46.9 ± 28.9	0.80
TRACP-5b (mU/dL)	450.7 ± 334.6	438.2 ± 242.8	463.2 ± 416.2	0.80
Total P1NP (ug/L)	41.7 ± 19.5	41.8 ± 16.0	41.5 ± 23.2	0.78
BAP (ug/L)	11.4 ± 6.1	11.0 ± 4.1	11.8 ± 7.8	0.64
$1,25(OH)_2$ VitD	43.6 ± 21.1	39.1 ± 19.1	47.6 ± 22.8	0.38
Pentosidine (ug/L)	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.52
Homocysteine (nmol/mL)	19.3 ± 16.5	13.8 ± 5.0	24.8 ± 21.8	0.23
Bone mineral density				
Lumbar spine				
Measurement — g/cm²	0.901 ± 0.20	0.906 ± 0.25	0.894 ± 0.12	0.92
T score	-1.1 ± 1.7	-1.3 ± 1.3	-1.5 ± 0.9	0.76
Femoral neck				
Measurement — g/cm²	0.650 ± 0.14	0.672 ± 0.17	0.627 ± 0.11	0.72
T score	-1.5 ± 1.2	-1.1 ± 2.1	-1.2 ± 1.0	0.85
Ultra-distal radius				
Measurement — g/cm²	0.400 ± 0.11	0.409 ± 0.12	0.390 ± 0.09	0.32
T score	-1.7 ± 1.5	-1.5 ± 1.6	-1.9 ± 1.5	0.30

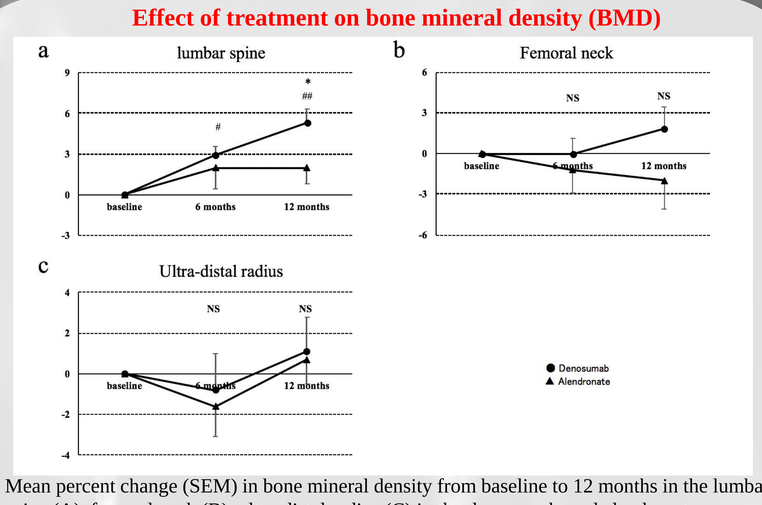
Data are presented as mean ± SD. eGFR, estimated glemerular filtration rate; P, phosphate; ALP, alkaline phosphatase; TG, triglyceride; TC, total cholesterol ; HDL-C, HDL-cholesterol ; LDL-C, LDL-cholesterol ;HbA1c, glycated hemoglobin; Intact PTH, ;TRACP-5b, tartrate-resistant acid phosphatase 5b ;Total P1NP, total- type I collagen N-terminal propeptide; BAP, bone-specific alkaline phosphatase

Effect of treatment on bone turnover markers



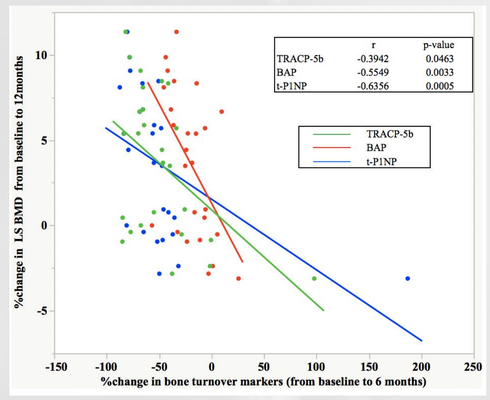
Mean percent change (SEM) in bone turnover markers from baseline to 12 months in the in the denosumab, and alendronate groups. NS, not significant.

Effect of treatment on bone mineral density (BMD)



Mean percent change (SEM) in bone mineral density from baseline to 12 months in the lumbar spine (A), femoral neck (B), ultra-distal radius (C) in the denosumab, and alendronate groups. *P <0.05 compared with alendronate group (by the Wilcoxon's signed rank test). #P <0 .05, ##P<0.01 compared with baseline (by the paired Student's t-test). NS, not significant.

Correlations between bone turnover markers and BMD responses



Correlation between the change from baseline to 6 months in bone turn over markers (TRACP-5b, BAP, t-P1NP) and the change from baseline to 18 months in lumbar spine BMD.

Discussion

✓**Denosumab increased lumbar spine and hip BMD and reduced sCTx- Ⅰ and P1NP compared to placebo in patients with rheumatoid arthritis (RA) receiving concurrent glucocorticoids through 12 months(1). In addition, switching from oral bisphosphonates to denosumab in chronic glucocorticoids users resulted in greater gain of the spinal BMD(2).**
⇨ These studies including the present study indicates that denosumab is superior to alendronate in increasing LS BMD for GIOP patients regardless of previous bisphosphonates use.

✓**Serious adverse events of cellulitis were more frequently observed in the denosumab treatment group compared to placebo in the postmenopausal women with osteoporosis (3). As for GIOP patients, a significantly higher number of adverse events were reported compared to bisphosphonates (2)**
⇨ In our study, hypocalcemia (n=2), worse of skin rash (n=1) and pulmonary tuberculosis (n=1) were observed in the denosumab group while there is no adverse event including gastric distress in the alendronate group. Further studies are needed to confirm the safety of denosumab in patients with GIOP.

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2. Mok CC, et al., Bone. 2015 ;75:222-228.
3. Cummings SR, et al., N Engl J Med. 2009; 361:756–65.

CONCLUSION

Denosumab treatment achieved marked suppression of bone turnover, which result in a great increase of lumbar spine BMD than alendronate treatment. These results suggest that denosumab is a promising therapeutic option for the treatment of GIOP.

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