PROSPECTIVE STUDY ON SAFETY AND EFFICACY OF ORAL BISPHOSPHONATE, ZOLEDRONIC ACID AND DENOSUMAB IN POSTMENOPAUSAL OSTEOPOROSIS

Presented by

Dr. Shoma Sharker

Assistant Professor

Department of Medicine

Sylhet Women's Medical College

Name of the Authors

1. Shoma Sharker, DEM, MRCP, FCPS, Assistant Professor Medicine, SWMC
2. MD. Ismail Patwary, FCPS, MD, Professor of Medicine, SWMC
3. Mahjuba Umme Salam, FCPS, Professor of Medicine, SWMC

Declaration

- There was no conflict of interest

- Funding

Investigations and Interventions are funded by patients.

Objective

- The objective of the study was to compare safety and efficacy of oral bisphosphonates, denosumab and Zoledronic acid on bone mineral density (BMD). This retrospective follow up study aims to trace differences between bisphosphonates and denosumab treatment in a sample of women with postmenopausal osteoporosis in our population, concerning bone densitometry.

Study design

- This was a prospective, randomized, non-blind trial.

Study Period

- March 2017 to January 2023

Participants

- A total of 256 postmenopausal women with osteoporosis included in this study.

Selection Criteria

Inclusion criteria:

1) The presence of postmenopausal osteoporosis, as defined by T-score <-2.5 either in the lumbar spine or the femoral neck or the presence of an osteoporotic fracture

2) No previous anti osteoporotic treatment

Exclusion criteria:

Patients with cancer or glucocorticoid-induced osteoporosis or any acute severe illness

Materials and Methods

- The age of the participants was 52 to 92 years and was post menopausal.
- The menopausal status was defined for study after 12 consecutive months without menstruation.

Materials and Methods (cont'd)

- All women received advice on complementary treatment with calcium and vitamin D supplements (1000 mg/800 IU/day).
- Data were retrieved from the database of our Clinic and concerned the baseline visit, before the initiation of the medication and the 12 months and 24 month visit post-treatment.
- Women signed an informed consent for the use of their data for statistical analysis and the Study was approved by the Ethics Committee of the Al Haramain hospital and Ibn Sina Hospital at Sylhet.

Materials and Methods (cont'd)

- Weight was measured on an electronic scale and height was measured in a stadiometer in the upright position in order to estimate the Body Mass Index (BMI).
- Bone densitometry Bone mineral density (BMD) of total, the lumbar spine, femur-Tibia and Radius- Ulna was measured by dual energy absorptiometry (DXA; Excell Plus, Norland Corp, Arm Model 433A063) and expressed as the amount of mineral (g) divided by the area scanned (cm2).
- All DXA measurements were performed by the same densitometer at initial visit and 12 months and 24 months.

Materials and Methods (cont'd)

- Laboratory evaluations Serum levels of total calcium, phosphate as well as 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) were assessed enzymatically by an autoanalyzer.
- According to our laboratory, the reference values range as follows (using the following normal ranges): calcium (8.4-10.2 mg/dL), phosphate (2.4-4.1 mg/dL), serum 25-hydroxyvitamin D (25-OHD, 30-74 ng/mL) and parathyroid hormone (PTH, 10-61 pg/mL). Vitamin D deficiency was defined as serum levels ≤10 ng/mL, while serum levels of vitamin D≤20 ng/mL were defined as suboptimal.

Interventions

- Subjects were randomized 64 patients for each group, in group one Zoledronate (Z) 5 mg iv once yearly, second group oral bisphosphonate Ibandronate (I) 150 mg monthly, third group subcutaneous Denosumab(D) 60 mg given every 6, fourth group only calcium -vitamin D supplementation (C).

Main outcome measures

- Changes in BMD was measured

Statistical Analysis

- Statistical analysis was performed by SPSS Version 21.
- Baseline comparisons between groups were performed by Student's t-test for unpaired observations concerning continuous variables and by X-square concerning categorical variables.
- Skewed variables were log-transformed before entered in the analysis.
- Baseline and follow up bone density parameters mean levels were compared within therapy groups by t test for paired observations.
- Percent changes in outcome variables were compared between groups with Student's t-test for unpaired observations.
- Non-parametric tests were used in cases where the distribution deviated significantly from normality.
- The impact of different treatment arms on bone density was evaluated.

Fig:1 Age of the Patients of different intervention groups

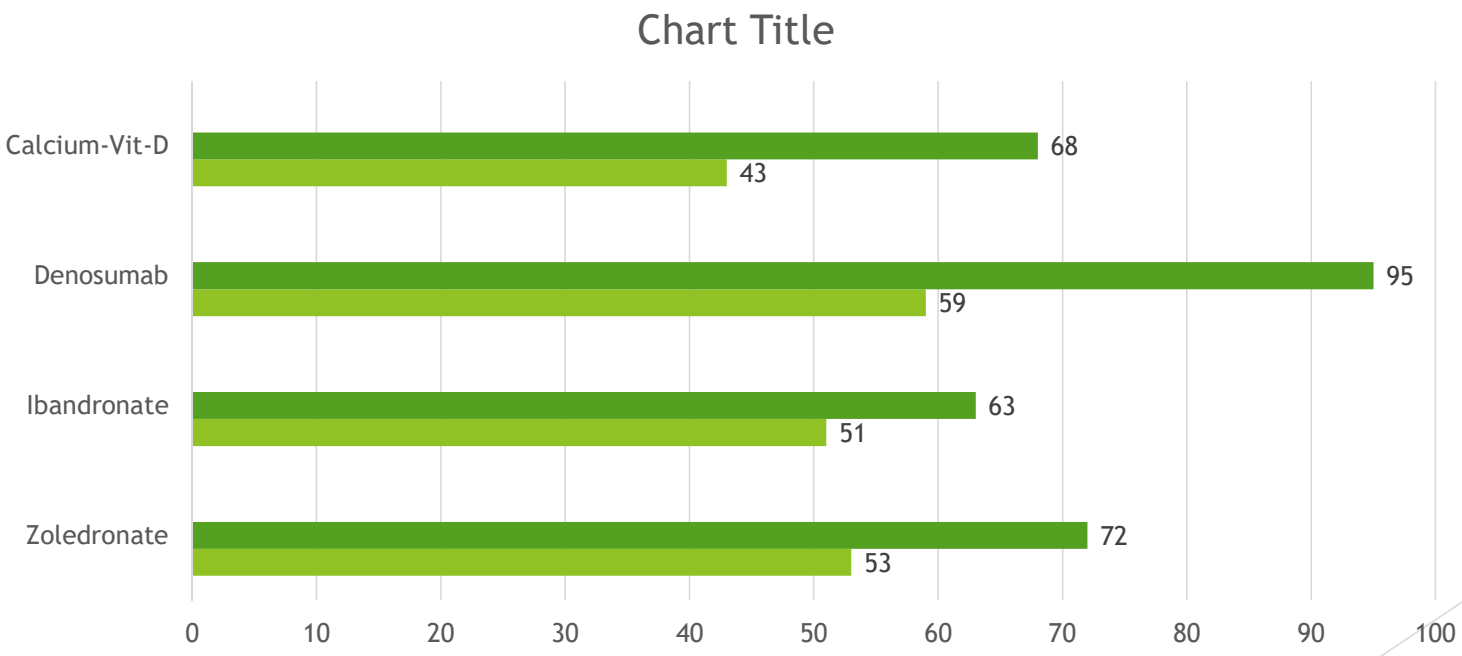


Fig: 2 Demographic Variables

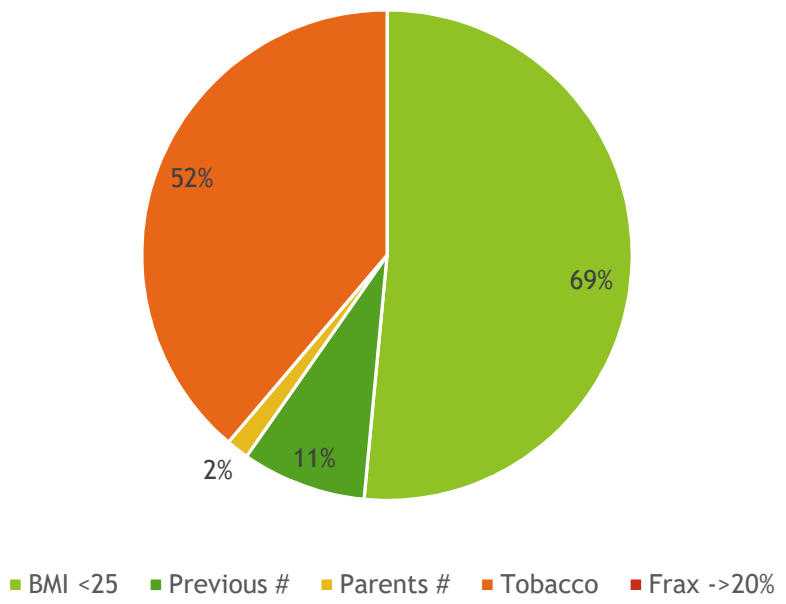
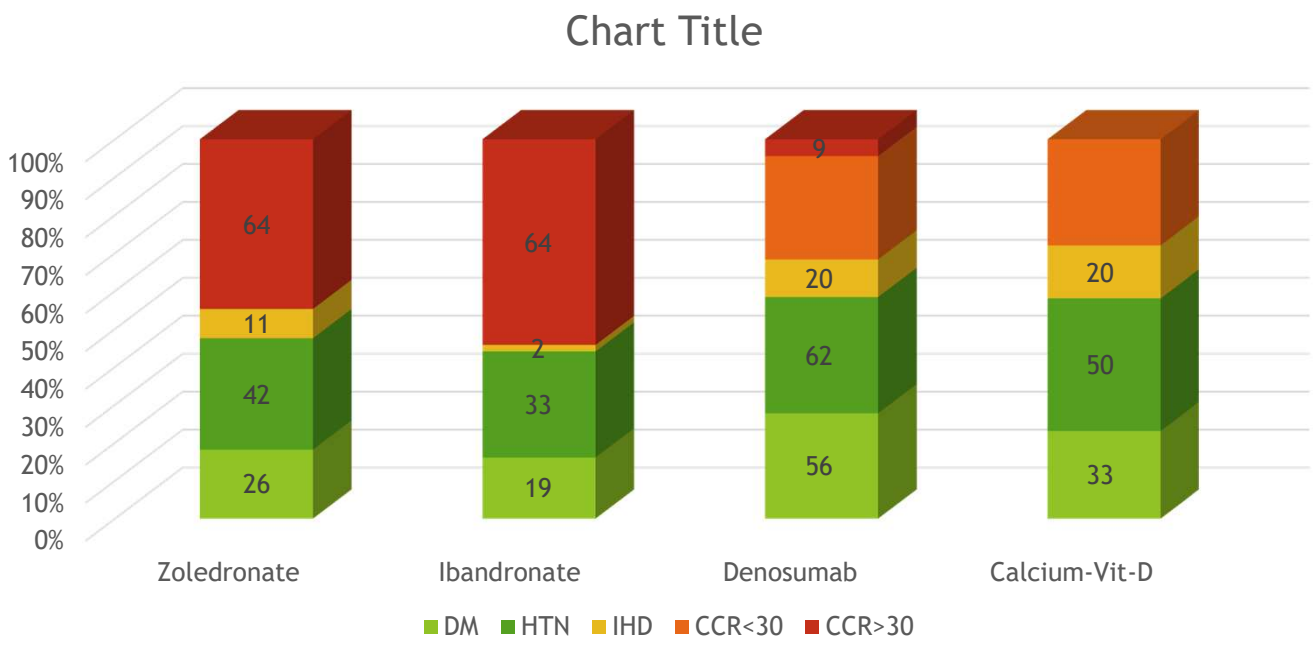


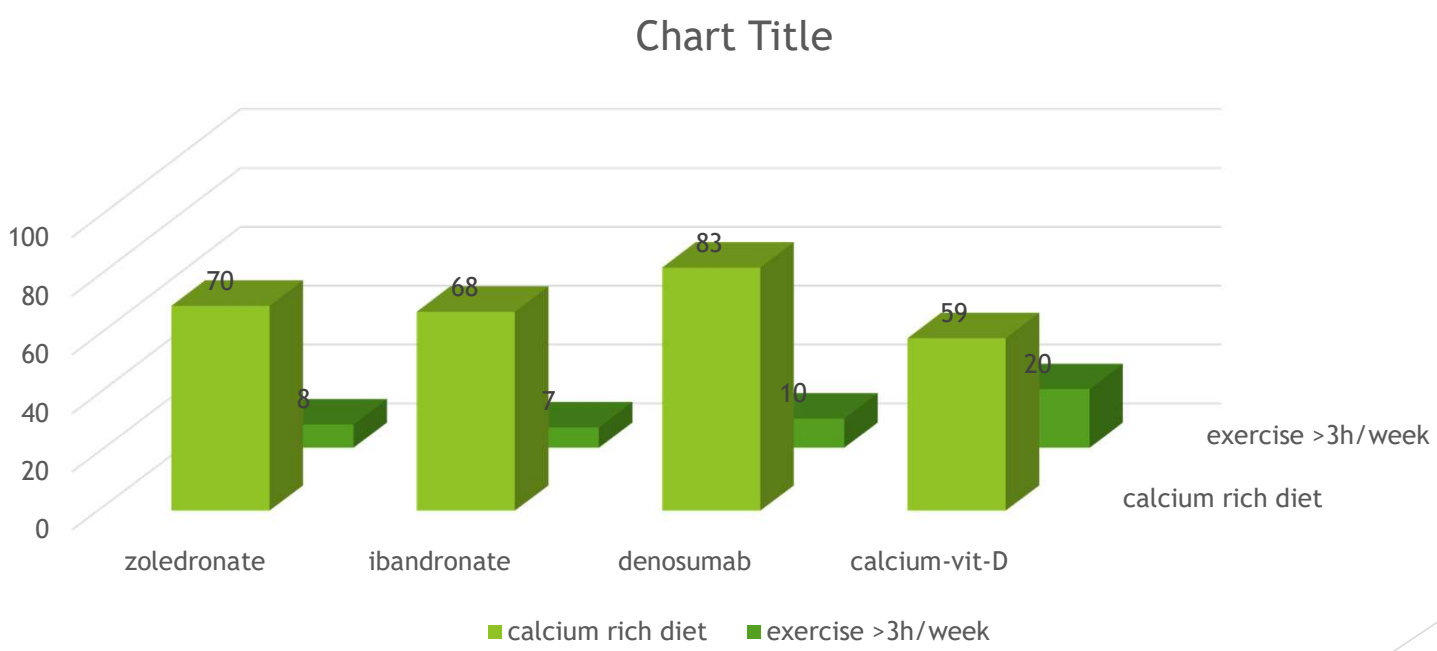
Fig: 3 Comorbidities in different intervention group



Baseline demographic characteristics of 256 postmenopausal women participating in the study.

Name of intervention (no. of participant)			
Zoledronate (64)	Ibandronate (64)	Denosumab (64)	Calcium Vit-D(64)
Continuous variables(%) Z	I	D	C
Age (years) 60.41	58.50	62.32	55.1
Menopause (years) 11.25	10.26	15.5	13.1
BMI (Kg/m2) 21.99	23.42	20.4	25.1
Weight 60.42	59.11	57.57	60.4
Mean BP 92.99	96.84	99.83	92.62

Calcium rich diet and Exercise more than 3h/week

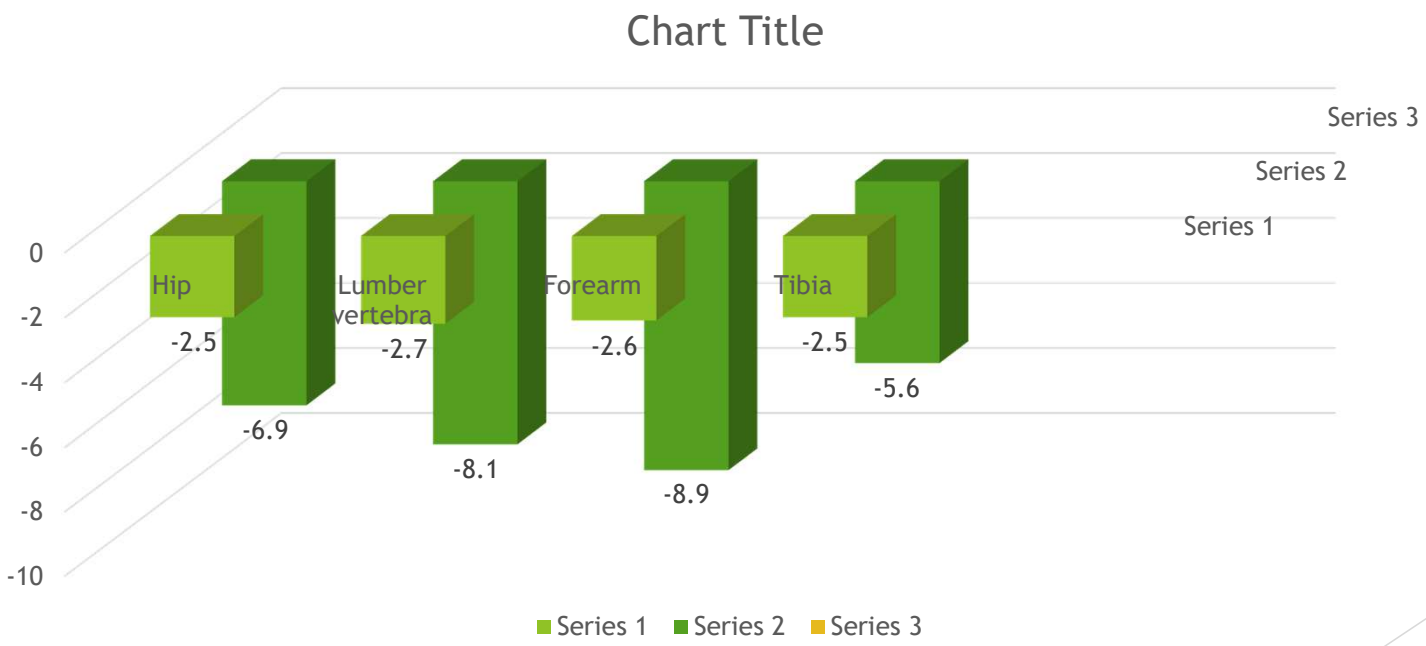


Baseline demographic characteristics of 256 postmenopausal women participating in the study. (cont'd)

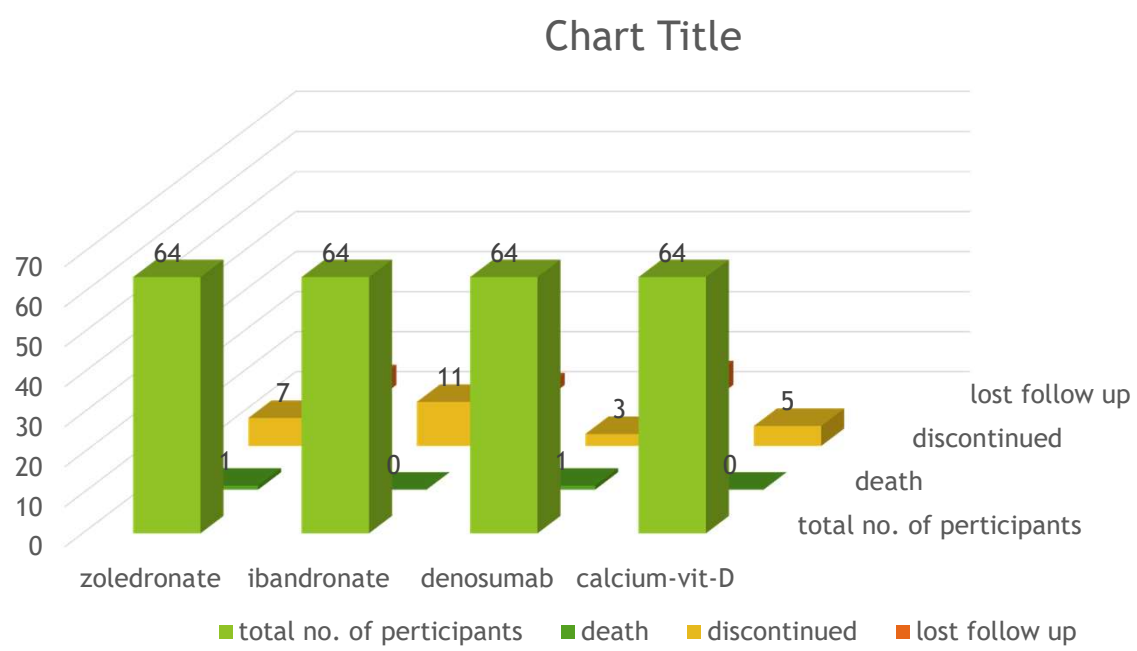
Categorical Variables (%)	Z	D	I	C	p-value
Tobacco consumption	21.9	28.8	31.7	22.6	0.86
Diet rich in calcium*	41.1	54.5	46.7	21.8	0.18
Alcohol (daily)**	0	0	0	0	
Physical exercise (>3h/week)	19.2	15.8	13.9	30.2	

32.23% of women under zoledronate and 22.2% of women under Ibandronate , 15.4% denosumab and 29.4% of calcium-vitamin D group had suboptimal levels of vitamin D at baseline. The difference between groups was not statistically significant.

BMD value at initial Visit



Study completion no. of patient



Results

- Baseline and follow-up mean levels of BMD and T-scores in lumber-spine, hip, femoral neck, tibia and forearm, calcium, phosphate, PTH and 25-hydroxyvitamin D were represented.
- Baseline values concerning T-score did not differ between the treatment groups.

Results cont’d

- Zoledronate and Denosumab resulted in significant increases in femoral neck BMD (denosumab 0.69±0.07 g/cm2 to 0.75±0.09 g/cm2 p=0.0001, Zoledronate 0.69±0.06 g/cm2 to 0.71±0.07 g/cm2 p=0.001), also ibandronate shows increased BMD 0.68±0.01 to 0.70±0.08 p=0.001).

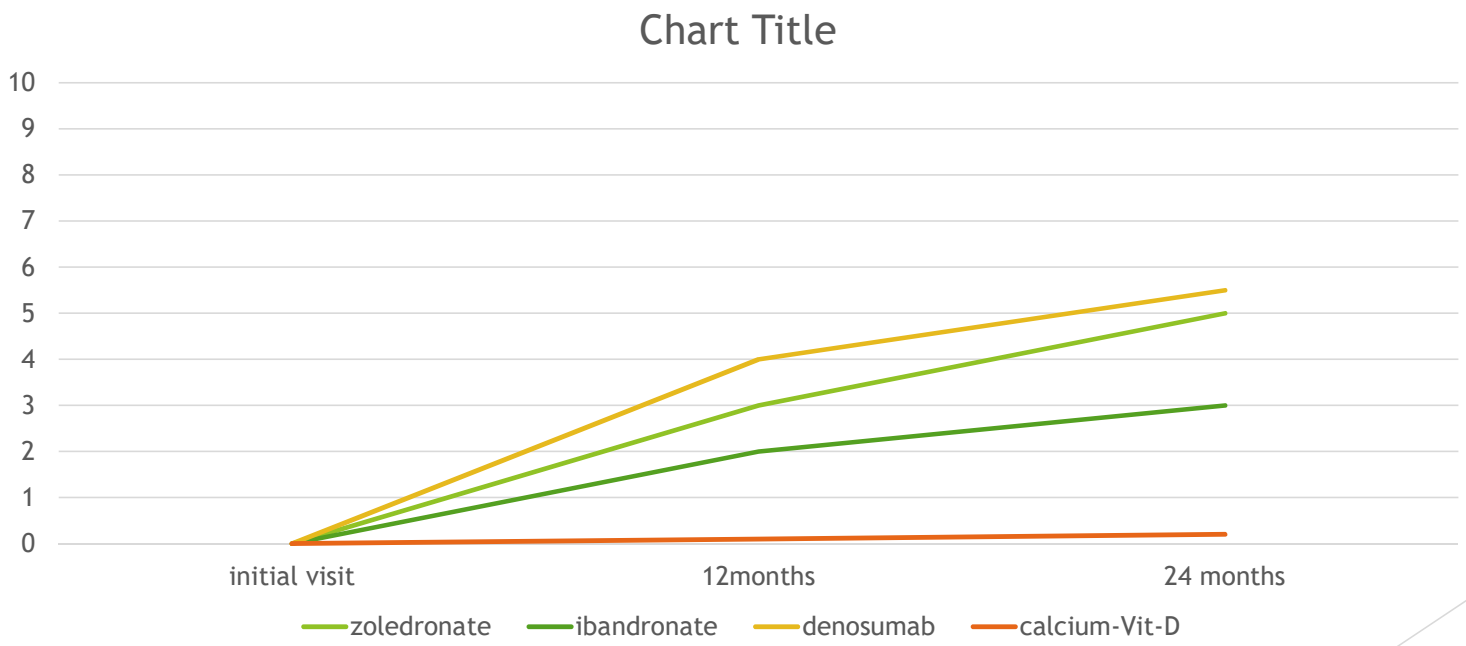
Results (cont'd)

- Lumbar spine BMD increased significantly in the denosumab group (0.83±0.14 g/cm2 to 0.89±0.14 g/cm2 p=0.0001) and marginally significantly in the Zoledronate group (0.84±0.10 g/cm2 to 0.87±0.11 g/cm2 p=0.09) less significant in Ibandronate group group (0.82±0.10 g/cm2 to 0.82±0.11 g/cm2 p=0.1) .

Results (cont'd)

- Denosumab was associated with a significant increase in serum PTH (44.87±17.54 pg/mL to 53.27±15.77 pg/mL p=0.04), an effect not observed in the bisphosphonate group (45.79±14.74 pg/mL to 49.64±20.67 pg/mL p=0.25). No changes in serum calcium, phosphate or 25OHD were observed in either of the two treatment groups.

Fig: 1 Change in total hip BMD from baseline, mean,%



Results (cont'd)

- Percent changes from baseline in the study groups concerning BMD in the total hip are presented in Figure 1. In accordance, T-score increases were higher in the denosumab group compared to the bisphosphonate group, the difference being significant only for femoral neck (% change T-score femoral neck: denosumab 21.2%±20.14, bisphosphonates 7.43%±17.4, p=0.003; % change T-score lumbar spine: denosumab 12.4%±23.0, bisphosphonates 6.3%±29.2, p=0.91). No significant differences between calcium-vit d group.

Results

- BMD change from baseline at month 24 was significantly greater with denosumab compared with Zoledronic acid at the lumbar spine (primary end point; 3.2% vs 1.1%; P < .0001), total hip (1.9% vs 0.6%; P < .0001), femoral neck (1.2% vs -0.1%; P < .0001), and one-third radius (0.6% vs 0.0%; P < .05). Median percentage changes from baseline in serum intact PTH were significantly greater at months 3 and 9 with denosumab compared with Zoledronic acid (all P < .05).

Results (cont'd)

- Flu like events are major concern among Zoledronic acid. Adverse events were similar between groups. One event of mandibular necrosis with ibandronate. One event of arrythmia in Zoledronate, and one cardiac arrest in a IHD diagnosed patients in Denosumab. 48 patients of oral preparations have GI adverse effects. Better adherence to therapy also observed in denosumab group.

Conclusions

- In postmenopausal women with osteoporosis denosumab was associated with greater BMD increases at all measured skeletal sites compared with oral ibandronate and Zoledronic acid also calcium - vitamin D supplementation group.
-

Discussion

- Osteoporosis (OP) is a common contributor to hip and spine fractures estimated 8.9 million fracture annually in worldwide patients
- Among them 1/3rd of all female and 1/5th of all male of more than 50 years have fracture in some point of life
- But under diagnosed and under treated in Asia.
- The burden will increase by 2-3 fold by 2050 due to aging.
- Hip fracture are the most serious with 12% mortality immediately.

Discussion cont'd

- Bisphosphonates, a classic antiresorptive agent, is currently the most common therapy for osteoporosis.
- However, compliance was the major concern of bisphosphonates.
- Prolonged medication and possible complications limited the effects of bisphosphonate.
- Denosumab is a fully human monoclonal antibody to RANKL, the final common effector of osteoclast formation, activity and survival.

FREEDOM study results

- Despite the availability of safe and effective anti-osteoporosis therapies, osteoporosis continues to be underdiagnosed and undertreated.
- Denosumab is a potent antiresorptive medication for treatment of osteoporosis, with clinical trial data for up to 10 years of treatment that demonstrate its safety and efficacy in reducing fracture risk.
- The continued gain in bone density differentiates denosumab from bisphosphonates, for which there is generally a plateau in hip bone mineral density after 3–4 years of treatment. Despite aging of the study population, non-vertebral fracture rates upon 4–10 years of treatment with denosumab were lower than initially observed with 3 years of therapy.
- Long-term bone turnover inhibition with denosumab treatment for up to 10 years demonstrated a favorable benefit/risk profile when comparing fractures prevented per skeletal adverse event (e.g., osteonecrosis of the jaw and atypical femoral fracture) observed. Furthermore, the subject incidence of adverse events, including infection and malignancy, remained low over time in the aging study population.
- If denosumab therapy is discontinued, transition to a different class of anti-osteoporosis medication, such as a bisphosphonate, can help prevent complete loss of the BMD gained with denosumab and maintain anti-fracture efficacy

JMNI: Comparative effects of denosumab or bisphosphonate treatment on BMD and Calcium Metabolism

- Eleven studies involving 5446 patients (denosumab = 2873, bisphosphonates = 2573) were included in the present meta-analysis. There was no significant difference between the risk of fracture (risk ratio (RR), 1.13; 95% confidence interval (CI), 0.82–1.55; P = 0.466), adverse events (AEs) (RR 1.00; 95% CI 0.96–1.04; P = 0.957) and withdrawn due to AEs (RR 0.68; 95% CI 0.34–137; P = 0.280). Denosumab compared with bisphosphonates significantly increased change in total hip, femoral neck, lumbar spine, and one-third radius bone mineral density (BMD) for postmenopausal osteoporosis patients (P < 0.05).

References

- 1. Golob AL, Laya MB. Osteoporosis: screening, prevention, and management. Med Clin North Am. 2015;99:587–606. [PubMed] [Google Scholar]
- 2. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone. 2011;48:677–692. [PubMed] [Google Scholar]
- 3. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med. 2008;148:197–213. [PubMed] [Google Scholar]
- 4. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182:1864–1873. [PMC free article] [PubMed] [Google Scholar]
- 5. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev. 2002;23:508–516. [PubMed] [Google Scholar]
- 6. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int. 2008;19:733–759. [PubMed] [Google Scholar]
- 7. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. Bone. 1999;25:97–106. [PubMed] [Google Scholar]
- 8. Moen MD, Keam SJ. Denosumab: a review of its use in the treatment of postmenopausal osteoporosis. Drugs Aging. 2011;28:63–82. [PubMed] [Google Scholar]
- 9. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: mechanism of action and clinical outcomes. Int J Clin Pract. 2012;66:1139–1146. [PMC free article] [PubMed] [Google Scholar]
- 10. Miller PD, Pannacciulli N, Brown JP, et al. Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates. J Clin Endocrinol Metab. 2016;101:3163–3170. [PMC free article] [PubMed] [Google Scholar]

References

- 11. Beaudoin C, Jean S, Bessette L, Ste-Marie LG, Moore L, Brown JP. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. Osteoporos Int. 2016;27:2835–2844. [PubMed] [Google Scholar]
- 12. Kostenuik PJ, Smith SY, Jolette J, Schroeder J, Pyrah I, Ominsky MS. Decreased bone remodeling and porosity are associated with improved bone strength in ovariectomized cynomolgus monkeys treated with denosumab, a fully human RANKL antibody. Bone. 2011;49:151–161. [PubMed] [Google Scholar]
- 13. Maalouf NM, Heller HJ, Odvina CV, Kim PJ, Sakhaee K. Bisphosphonate-induced hypocalcemia: report of 3 cases and review of literature. Endocr Pract. 2006;12:48–53. [PubMed] [Google Scholar]
- 14. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86:50–60. [PMC free article] [PubMed] [Google Scholar]
- 15. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009;24:153–161. [PubMed] [Google Scholar]
- 16. Seeman E, Delmas PD, Hanley DA, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res. 2010;25:1886–1894. [PMC free article] [PubMed] [Google Scholar]
- 17. Papapoulos S, Lippuner K, Roux C, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. Osteoporos Int. 2015;26:2773–2783. [PMC free article] [PubMed] [Google Scholar]
- 18. Dore RK. Data from extension trials: denosumab and zoledronic acid. Curr Osteoporos Rep. 2012;10:16–21. [PubMed] [Google Scholar]
- 19. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350:1189–1199. [PubMed] [Google Scholar]

References

- 20. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004;75:462–468. [PubMed] [Google Scholar]
- 21. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354:821–831. [PubMed] [Google Scholar]
- 22. Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res. 2007;22:1832–1841. [PubMed] [Google Scholar]
- 23. Makras P, Polyzos SA, Papatheodorou A, Kokkoris P, Chatzifotiadis D, Anastasilakis AD. Parathyroid hormone changes following denosumab treatment in postmenopausal osteoporosis. Clin Endocrinol (Oxf) 2013;79:499–503. [PubMed] [Google Scholar]
- 24. Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res. 2004;19:1059–1066. [PubMed] [Google Scholar]
- 25. Kostenuik PJ, Smith SY, Samadfam R, Jolette J, Zhou L, Ominsky MS. Effects of denosumab, alendronate, or denosumab following alendronate on bone turnover, calcium homeostasis, bone mass and bone strength in ovariectomized cynomolgus monkeys. J Bone Miner Res. 2015;30:657–669. [PubMed] [Google Scholar]
- 26. Kemmler W, Bebenek M, Kohl M, von Stengel S. Exercise and fractures in postmenopausal women. Final results of the controlled Erlangen Fitness and Osteoporosis Prevention Study (EFOPS) Osteoporos Int. 2015;26:2491–2499. [PubMed] [Google Scholar]
- 27. Wen HJ, Huang TH, Li TL, Chong PN, Ang BS. Effects of short-term step aerobics exercise on bone metabolism and functional fitness in postmenopausal women with low bone mass. Osteoporos Int. 2016;9:9. [PubMed] [Google Scholar]
- 28. Charansonney OL. Physical activity and aging: a life-long story. Discov Med. 2011;12:177–185. [PubMed] [Google Scholar]

Questionnaire

- ID no. Address contact no. Age- Date of birth:
- Sex male female
- Weight-kg
- Height- m BMI-
- Previous Fracture- yes No
- Parents fracture history- Yes No
- Current smoking- Tobacco leaves-
- Alcohol Yes No Unit per day-
- Menopause Yes No duration-
- Glucocorticoid Yes No dose- Duration- Name-
- Secondary osteoporosis Yes No
- Frax score-
- BMD- 1st visit T score L. spine- Hip- Femoral neck- Forearm- tibia-
- 2nd visit T score L. spine- Hip- Femoral neck- Forearm- tibia-
- 3rd visit T score L. spine- Hip- Femoral neck- Forearm- tibia-
- Medications: 1. Zoledronate 2. Ibandronate 3.Denosumab 4. Calcium-Vitamin-D
- Follow up visit time-
- New fracture-
- Investigation results- 1st visit – calcium Phosphate vitamin D PTH Xray jaw & OPG Xray femur ECG- CCR-
- 2nd visit
- 3rd visit
- Food Habit- Milk Nut Meat Fish Egg Leafy Vegetable Fruits calcium fortified food
- Comorbidities- DM HTN IHD CKD CLD connective tissue disease COPD/DPLD/bronchiectasis IBD Arrythmia Dental problem Endocrine disease Malignancy Cellulitis PUD Esophagitis TB Renal stone
- Side effects - GIT symptoms Flulike Symptoms tooth ache Arrythmia ACS Cellulitis uveitis others
- Any treatment needed due to side effects-
- Completed study Stopped due to 1.Side effects 2. Financial issue 3. Denied to continue 4. Lack of support 5. others Untraced

THANKS