Methods: 127 patients (aged 62±18 years, 63% women, 46% postmenopausal) on GC treatment (prednisone ≥5mg/day, >3 months) were included. Clinical data collected included: risk factors for OP and fractures, dose and GC-treatment duration, previous fractures and disease activity, anthropometric data, bone metabolism parameters (including gonadal axis study), BMD analysis (DXA; OP: T-score ≤-2.5), TBS (degraded microarchitecture [DMA]: <1.230), dorsolumbar X-ray (assessing vertebral fractures [VF]) and FRAX risk (GC-adjusted)¹.

Results: Most patients received GC treatment for vasculitis or polymyalgia rheumatica during 47.7±69 months (mean daily dose: 14.5mg). 17% had VF, 28% had fragility fracture (VF + non-VF), 29% OP and 71% DMA. Patients with VF received more GC-boluses (57.1% vs. 29.5%, p=0.03), were older (68±13 vs. 60±19 years, p=0.02), postmenopausal (100% vs. 67%, p=0.015) and/or men with testosterone <250ng/dL (57% vs. 11%, p=0.017) and had lower TBS values (1.100 vs. 1.220, p<0.001) and higher FRAX risk (17 vs. 9, p=0.003); patients with fragility fractures showed higher accumulated GC-doses (6.1±13 vs. 8±18g, p=0.046). On multivariate analysis, hypogonadism (OR 14.3; IC95% 2.2->100, p=0.01) and having received GC-boluses (OR 3.40; IC95% 1.1-11.8, p=0.01) were the principal factors associated with VF. Hypogonadism (OR 7.1; IC95% 1.5-38.7, p=0.01) and having a FRAX >20 (OR 6.97; IC95% 1.3-51.7, p=0.02) were factors related to the presence of fragility fractures. Men with testosterone <250ng/dL had higher BMI (29.4 vs. 26.3, p=0.005) and disease activity (ESR 23 vs. 12, p=0.005) and lower TBS (1.050 vs. 1.210, p<0.001); age, daily and cumulated GC doses were similar to subjects with normal testosterone levels.

Conclusion: Hypogonadism is a major risk factor for developing fractures in GC-treated men and women, whereas receiving GC-boluses is related to VF, indicating the importance of evaluating the gonadal axis in these patients.

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Disclosure of Interests: Helena Florez: None declared, José Hernández-Rodríguez: None declared, Africa Muxi: None declared, Josep Lluís Carrasco: None declared, Sergio Prieto-González: None declared, Silvia Ruiz-Gaspà: None declared, Maria C. Cid Grant/research support from: Kiniksa Pharmaceuticals, Consultant for: Roche, GSK, Janssen, Abbvie, Speakers bureau: Boehringer-Ingelheim, Vifor, Ana Monegal Speakers bureau: Eli Lilly, Amgen, Núria Gualabens Consultant for: Advisory Boards from Amgen, Alexion and UCB, Speakers bureau: Fees and lectures from Eli Lilly, Pilar Peris Speakers bureau: Personal Fees and Non-financial support (attendance to congresses) from Amgen and Eli Lilly

DOI: 10.1136/annrheumdis-2019-eular.3019

FR10467

THE DISTRIBUTION OF PREVALENT AND INCIDENT VERTEBRAL FRACTURES IN THE TERIPARATIDE VERSUS RISEDRONATE "VERO" CLINICAL TRIAL

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Background: Biomechanical analyses indicate that compressive load is heterogeneous throughout the thoraco-lumbar spine, with maximal loads during daily activities on T₇-T₈ and T₁₁-L₁. Population-based studies have shown a bimodal spinal distribution of prevalent and incident vertebral fractures (VFXs) at the mid-thoracic and thoraco-lumbar junction levels. However, prevalence and incidence of individual VFXs according to both their location and severity have not been reported in randomised clinical trials with anti-osteoporosis drugs.

Objectives: The aim of this study was to describe the distribution of prevalent and 12- and 24-month incident new and/or worsening VFXs according to location and severity in the teriparatide versus risedronate VERO clinical trial¹.

Methods: 1360 postmenopausal women with at least 2 moderate (SQ2: 25% ≤ vertebral body height loss ≤ 40%) or 1 severe (SQ3: vertebral body height loss > 40%) VFX according to the semiquantitative (SQ) scale by Genant², and a BMD T-score ≤ -1.50 were randomised to SC

daily teriparatide (20 µg) or oral weekly risedronate (35 mg) in a double-blind, double-dummy 2-year trial. A new VFX was defined as a vertebral body height loss of at least 20% (and 4 mm) of a vertebra that was unfractured at baseline, based on a 6-point placement of the vertebral bodies from T₄ to L₄, and confirmed by an increase by 1 or more severity grades according to the SQ scale². Worsening of a baseline pre-existing fracture was diagnosed if the decrease in vertebral height was at least 1 severity grade in the SQ assessment. Vertebrae with Schmorl's nodules, Scheuermann's disease and platyspondyly were excluded. Spine x-rays were centrally assessed by radiologists at BioClinica.

Results: Mean (SD) age was 72.1 (8.7) years (min-max: 45-93 years). Spine x-rays were available at baseline, 12, and 24 months for 1,360, 1,159 and 1,049 patients respectively, for a total of 17,413, 14,987 and 13,454 evaluable vertebral bodies. The location of the prevalent VFX by SQ severity degree is shown in Fig.1. At baseline, VFXs were preferentially located at L₁, T₁₂, L₂, T₁₁ and T₈ (38.5%, 37.4%, 25.3%, 23.5% and 23.1% of the patients, respectively). A total of 524 (3.0%) of all the assessed vertebral bodies had a fracture at L₁, the most frequently affected level. There were 126 new and/or worsened incident VFXs during the course of the study (35 in the teriparatide and 91 in the risedronate groups) affecting 100 patients (9.5%) at 24 months. Eighty-nine of these patients presented a new moderate (SQ2) or severe (SQ3) incident VFX. The most frequently fractured vertebral body was T₁₂ (1.6% of patients), followed by L₁ and T₁₁ (1.3% both), T₉ (1.2%) and T₈ (1.1%). The frequency of incident VFX was lower at all levels with teriparatide (Fig.2). T₁₂ was also the most frequently fractured vertebral body at 12 months of follow-up (0.7% of patients).

Conclusion: These results from the VERO clinical trial confirm previous results from epidemiological studies that VFXs occur most frequently in the mid-thoracic and thoraco-lumbar regions of the spine. Given the study eligibility criteria, mild (SQ1) VFXs are likely under-represented. Teriparatide is more effective in reducing the incidence of the commonest VFXs (T₁₂, L₁) as compared to risedronate.

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Fig. 2: % Patients with Incident VFX by Level and Treatment Arm

Disclosure of Interests: Piet Geusens Grant/research support from: Research support, consultant and/or speaker fees from: Pfizer, Abbott, Eli Lilly, Amgen, MSD, Roche, UCB, BMS, Novartis, Will-Pharma, Grant/research support from: Pfizer, Abbott, Lilly, Amgen, MSD, Will, Bio Minerals and Roche, Consultant for: Research support, consultant and/or speaker fees from: Pfizer, Abbott, Eli Lilly, Amgen, MSD, Roche, UCB, BMS, Novartis, Will-Pharma, Speakers bureau: Research support, consultant and/or speaker fees from: Pfizer, Abbott, Eli Lilly, Amgen, MSD, Roche, UCB, BMS, Novartis, Will-Pharma, Speakers bureau: Pfizer, Abbott, Lilly, Amgen, MSD, Will, Bio Minerals and Roche, David Kendler Grant/research support from: Research grants, and/or consultant fees from: Amgen, Lilly, AstraZeneca, Astellas, UCB, Consultant for: Research grants, and/or consultant fees from: Amgen, Lilly, AstraZeneca, Astellas,

UCB, Speakers bureau: Research grants, and/or consultant fees from: Amgen, Lilly, AstraZeneca, Astellas, UCB, Astrid Fahrleitner-Pammer Speakers bureau: Speaker fees from: Amgen, Alexion, BMS, Lilly, Fresenius, Pedro López-Romero Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Fernando Marin Shareholder of: Lilly, Employee of: Lilly
DOI: 10.1136/annrheumdis-2019-eular.808

FRI0468

EFFECTS OF DIFFERENT VITAMIN D SUPPLEMENTATION SCHEMES IN POSTMENOPAUSAL WOMEN

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Background: Vitamin D exerts different extra-skeletal effects, including a positive effect on muscle function. Circulating levels of the 25 hydroxylated Vitamin D - 25(OH)D - reflect the body Vitamin D reserves; to reach the optimal serum 25(OH)D threshold, Vitamin D supplementation is often requested. The commonest Vitamin D supplementation is represented by cholecalciferol (D3), but the hydroxylated Vitamin D metabolite calcifediol (HyD) represents a therapeutic alternative.

Objectives: The aim of the study was to evaluate the efficacy of the calcifediol supplementation compared to various cholecalciferol administration schedules in increasing the 25(OH) vitamin D serum levels and the effects on muscular function in post-menopausal women.

Methods: 60 post-menopausal women aged ≤ 65 years with low serum 25(OH)D levels (8-24 ng/ml) were included in the study. Recruited patients were randomly assigned to receive oral Vitamin D 1000 UI/day according to four different regimens. 1) cholecalciferol (D3) 300.000 UI, single oral dose; 2) monthly cholecalciferol 100.000 UI for three consecutive months; 3) weekly cholecalciferol 7000 UI; 4) weekly HyD 7000 UI. At baseline and every three months, for 12 months, the following parameters were evaluated: serum levels of 25(OH)D; PTH, calcium, phosphates; at baseline and every 15 days muscular function was evaluated using the Timed Up and Go (TUG) and the Sit to Stand test.

Results: Weekly administration of HyD induced a significantly faster and greater increase of 25(OH)D levels, compared to the other treatment groups (at 12 months: +384% vs +145%, + 220%, + 248% in groups 1, 2, 3, respectively); the increase appeared after 1 month from baseline. D3 300.000 UI single dose induces a slower increase of 25(OH)D compared to monthly and weekly supplementation. An increase of muscular strength was observed after 12 months in all supplementation groups, starting from 1 months from baseline, with a greater effect in subjects treated with weekly HyD compared to D3 treated subjects (TUG 6 second vs 7.3, 7.7, 7.9 in groups 1, 2, 3, respectively; Sit to Stand 16.2 vs 15.4, 15.3, 15.7 in groups 1, 2, 3 respectively). Overall, the effects on 25(OH)D levels and on muscular function were greater in subject treated with weekly D3 compared to subject treated with monthly or single dose D3. No differences in PTH, calcium and phosphate serum levels were found between supplementation groups.

Conclusion: Supplementation with calcifediol is more effective and faster compared to cholecalciferol in increasing 25(OH)D serum levels; further, weekly cholecalciferol is more effective and faster compared to single dose or monthly administration. Increase in circulating levels of 25(OH)D is associated to an improvement of muscular strength.

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Disclosure of Interests: Stefano Berardi: None declared, Addolorata Corrado: None declared, Angiola Mele: None declared, Cinzia Rotondo: None declared, Antonello Trotta: None declared, Natalia Mansueto: None declared, Francesco Paolo Cantatore Speakers bureau: PFIZER, ROCHE
DOI: 10.1136/annrheumdis-2019-eular.4785

FRI0469

CHANGES IN DKK-1, SCLEROSTIN, AND RANKL SERUM LEVELS FOLLOWING DISCONTINUATION OF LONG-TERM DENOSUMAB TREATMENT IN POSTMENOPAUSAL WOMEN

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Background: The positive effects of denosumab (DMAB) on bone mineral density (BMD) are quickly reversible after its discontinuation and concerns about the possible increase in vertebral fracture after stopping denosumab have been recently raised. Indeed, a rebound in bone turnover markers have been described after DMAB discontinuation. Dickkopf-1 (Dkk-1), and sclerostin, Wnt inhibitors, are considered master regulators of bone remodeling and directly influence the Receptor Activator of Nuclear factor Kappa B Ligand (RANKL) serum levels.

Objectives: We sought to determine whether the rebound of bone turnover following DMAB discontinuation is associated with dysregulation of the Wnt canonical pathway and/or with the increase in the receptor-activator of nuclear factor-kappa B ligand (RANKL) serum levels in long-term DMAB postmenopausal users.

Methods: The present study included patients (n = 15) with postmenopausal osteoporosis to whom DMAB was administered for 78 months and then discontinued. We collected BMD data at DMAB administration month 60 (M60), M84 (6 months after last DMAB administration, coinciding when the next DMAB dose would typically be due), and after discontinuation, 3 and 12 months of follow-up (FU-M3 and FU-M12, respectively). Serum C-terminal telopeptide of type 1 collagen (CTX-I), Dkk-1, and sclerostin were measured at M60, M84, FU-M3, and FU-M12. Serum N-terminal propeptide of type 1 procollagen (PINP) and RANKL were dosed at M60, M84, FU-M3, and FU-M12.

Results: We found a significant decrease in the T-score at all sites at FU-M12, when compared to M84 (-0.51 ± 0.91 at the lumbar spine; -0.72 ± 0.33 at the total hip; and -0.42 ± 0.27 at the femoral neck, $p < 0.05$). After DMAB discontinuation (M84 vs FU M12), RANKL, CTX-I and PINP significantly increased ($+0.041 \pm 0.062$ ng/mL; $+0.846 \pm 0.590$ and $+124.6 \pm 62.72$, $p < 0.05$, respectively), while Dkk-1 and sclerostin significantly decreased (-10.90 ± 11.80 and -13.00 ± 10.52 pmol/L, respectively, $p < 0.01$) (Figure 1). No changes in BMD or any of the markers were found between M60 and M84.

Conclusion: RANKL serum levels progressively increased after discontinuation of long-term DMAB while Dkk-1 and sclerostin serum levels decreased. The increase in RANKL serum levels supports the hypothesis of a sudden loss of inhibition of the resting osteoclast line after DMAB clearance, with a hyperactivation of these cells. Our results suggest that the decrease in serum Wnt inhibitors after DMAB suspension might represent a mere feedback response to the increased bone turnover.

Figure 1. Absolute values of Dickkopf-1 (Dkk-1), sclerostin and Receptor Activator of Nuclear factor Kappa B Ligand (RANKL) following discontinuation. * $p < 0.01$ vs M84; ** $p < 0.05$ vs M84

Disclosure of Interests: Giovanni Adami: None declared, Angelo Fassio Speakers bureau: Abiogen Pharma, Camilla Benini: None declared, Elisabetta Vantaggiato: None declared, Kenneth Saag Grant/research support from: Amgen, Ironwood/AstraZeneca, Horizon, SOBI, Takeda, Consultant for: Abbvie, Amgen, Ironwood/AstraZeneca, Bayer, Gilead, Horizon, Kowa, Radius, Roche/Genentech, SOBI, Takeda, Teijin, Alessandro Giollo: None declared, Irma Lippolis: None declared, Luca Idolazzi: None declared, Giovanni Orsolini Speakers bureau: Grunenthal, Maurizio Rossini: None declared, Davide Gatti Speakers bureau: Abiogen, Amgen, Janssen-Cilag, Mundipharma, Pfizer

DOI: 10.1136/annrheumdis-2019-eular.1596