به نام خداوند جان و خرد
کزین برتر اندیشه برنگذرد

Challenges after denosumab discontinuation

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Outline:

- Case presentation
- Dmab action and efficacy in various studies
- What happen to bone after dmab discontinuation?
- Effects of dmab discontinuation on btms,bmd and fracture by review of evidences
- Review of evidences about different sequential therapies after dmab discontinuation
- What evidences say about treatment after dmab discontinuation?
- Take home message

Case introduction

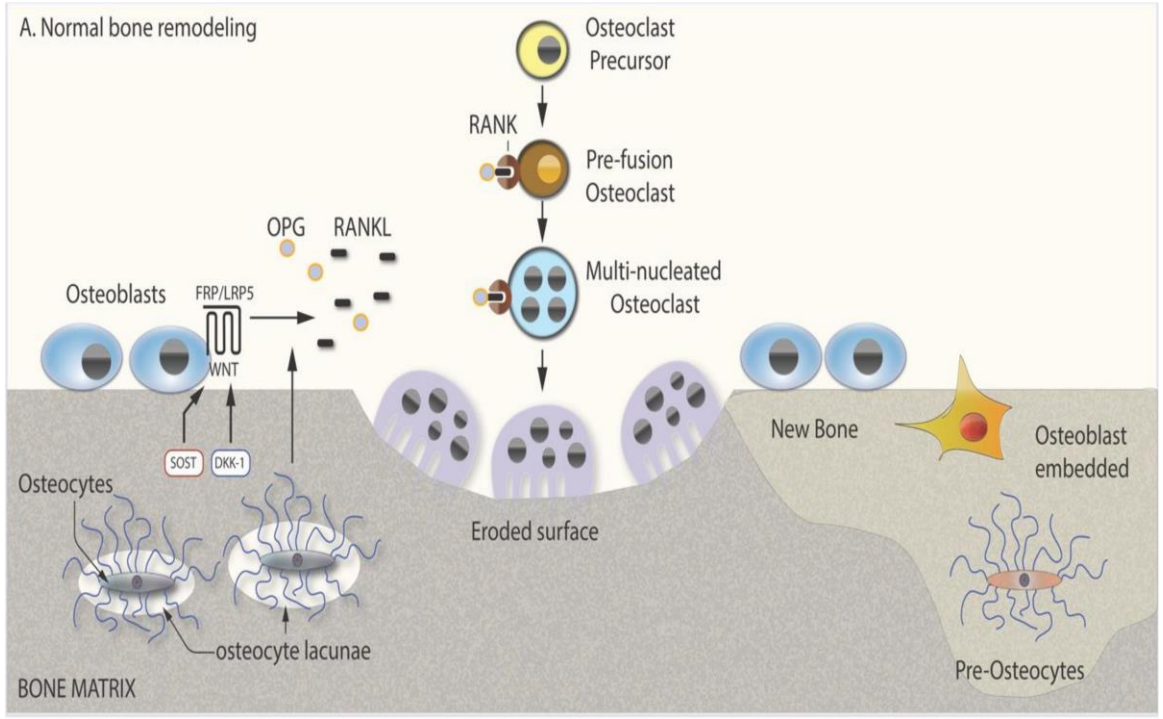
- The patient is a 72-year-old woman with diagnosis of postmenopausal osteoporosis who has been receiving denosumab for three years. In the initial BMD, the T-score in the lumbar spine was -3 and in the femoral neck was - 2.6. The patient mentions a history of fracture in the T12 vertebra before starting treatment.
- She is currently responding to treatment and has no specific complications. However, she has recently been unable to obtain the medication due to financial difficulties. The patient has referred to your office for advice on discontinuing treatment and next steps.

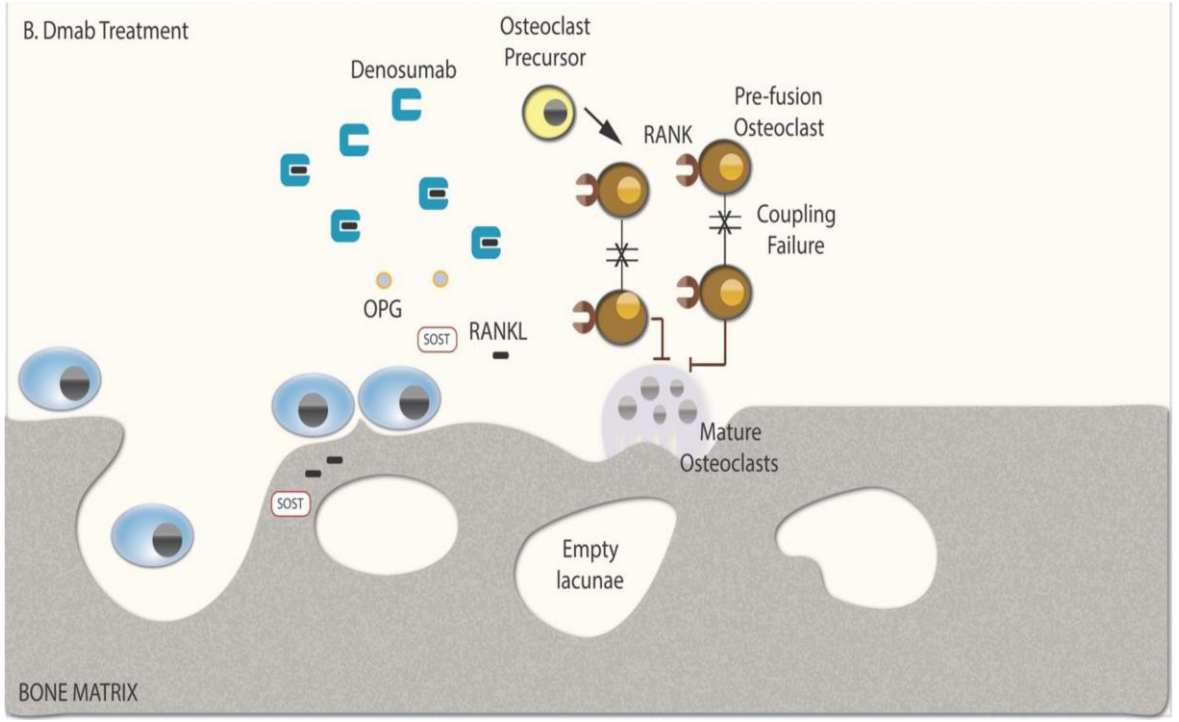
Denosumab action and efficacy

- Denosumab, approved for the treatment of osteoporosis since 2010, is a fully humanised monoclonal antibody against a cytokine, receptor activator of nuclear factor kappa B ligand (RANKL), involved in bone resorption.
- Dmab binds RANKL, thus preventing its binding to RANK on the surface of cells of the osteoclastic lineage. Consequently, Dmab suppresses osteoclast recruitment, maturation, function, and survival, and significantly decreases bone resorption and subsequent bone loss.
- It circulates in the bloodstream, binding to RANKL in the extracellular fluid, and is cleared via the reticuloendothelial system with a half-life of approximately 26 days.

- (1)Wei Lin Tay et alDiscontinuing Denosumab: Can It Be Done Safely? A Review of the Literature,, Endocrinol Metab 2022 Forthcoming. Posted online 2022
- (2)D. Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

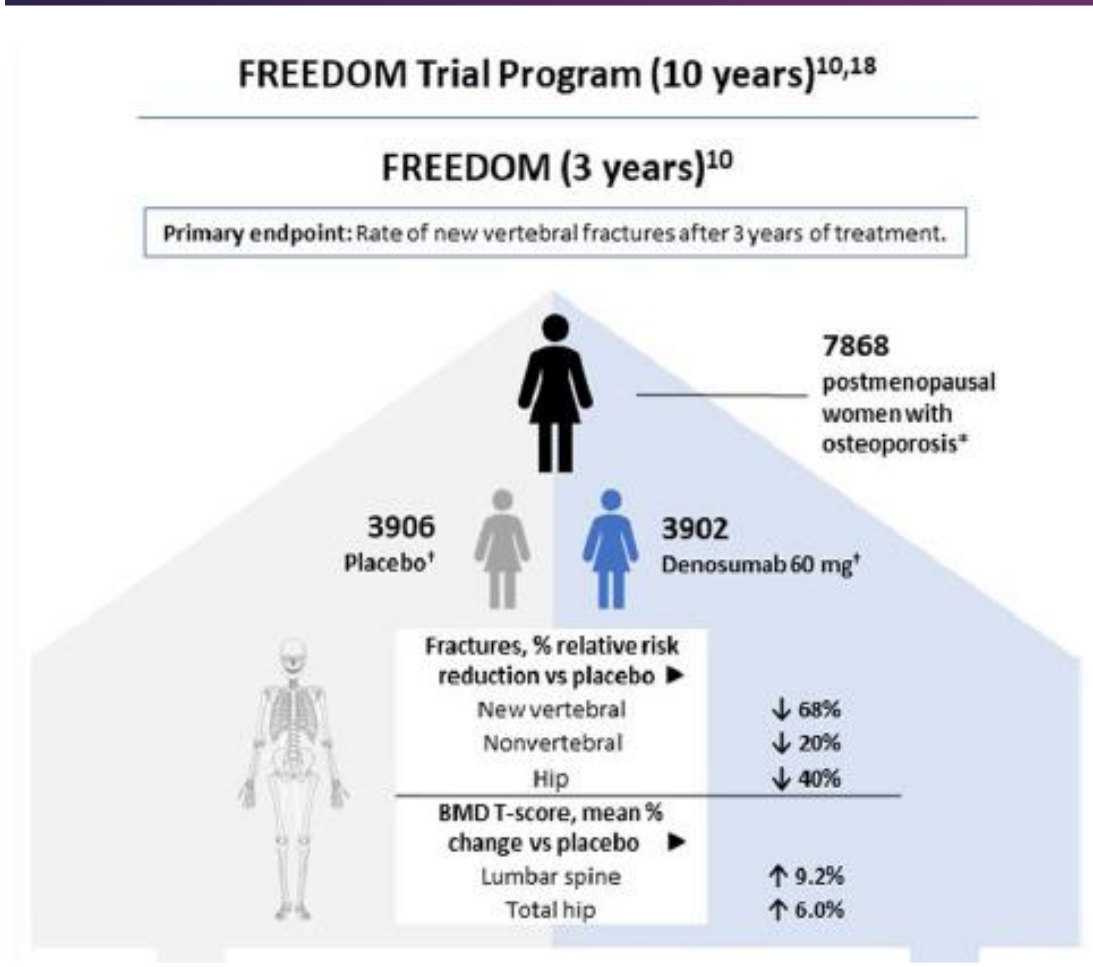
Normal bone remodeling vs DMAB treatment

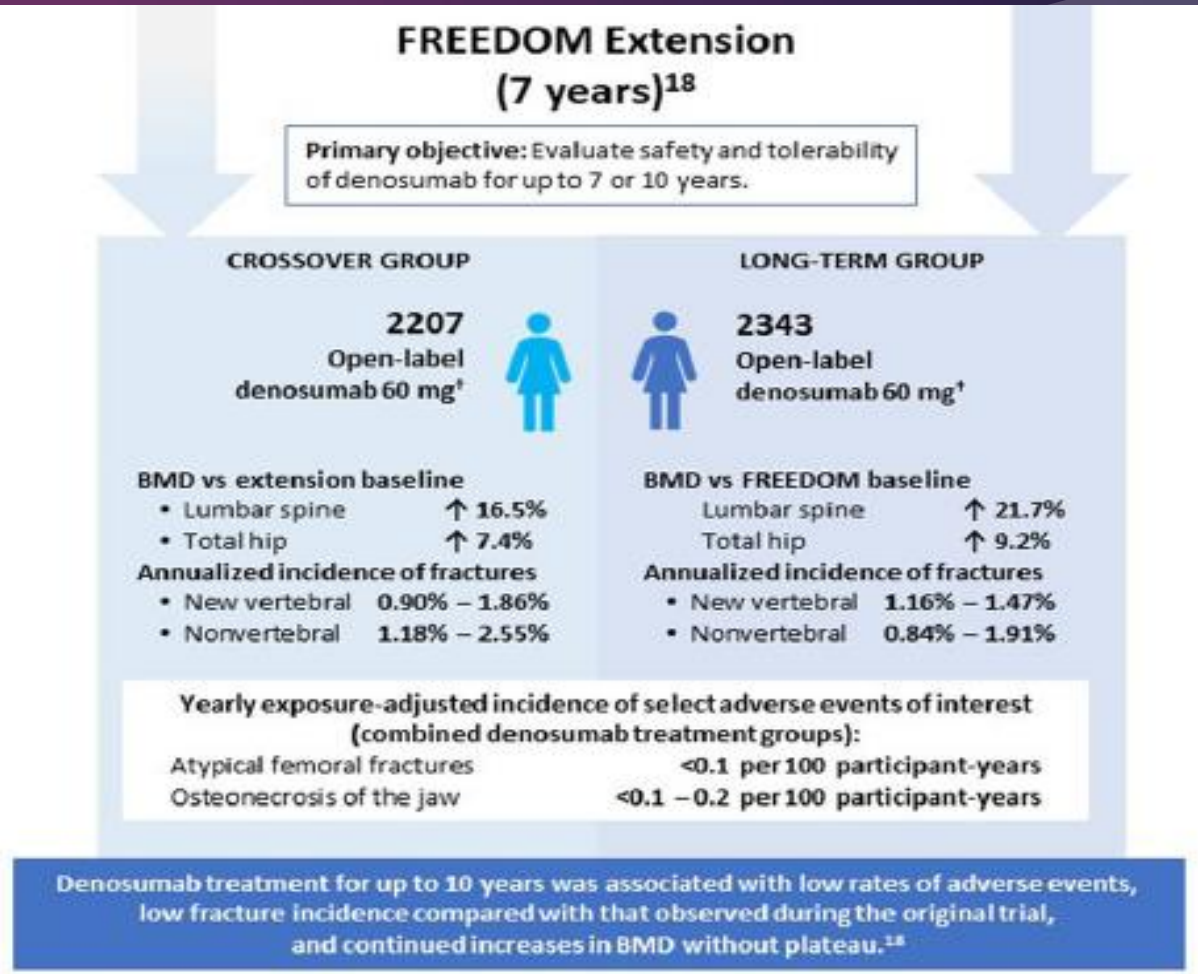




- D. Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

FREEDOM & FREEDOM Extension Trial





- David L. Kendler et alDenosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review, Adv Ther (2022) 39:58–74

Trial for DMAB efficacy in various clinical indications

Table 1. Trial evidence for denosumab efficacy across various clinical indications.

Patient population	Trial-participant characteristics	Efficacy
Postmenopausal osteoporosis[2]	$N = 7868$ Duration: 3 yr Inclusion: Postmenopausal women between 60 and 90 yr BMD T-score between –2.5 and –4.0 SD	BMD gain (vs placebo) LS 9.2% (95% CI: 8.2-10.1) TH 6.0% (95% CI: 5.2-6.7) Fracture risk reduction (vs placebo) Vertebral 68% (95% CI: 59-74) Hip 40% (95% CI: 3-63) Non-vertebral 20% (95% CI: 5-33)
Male osteoporosis[7]	$N = 242$ Duration: 1 yr Inclusion: Men between 30 and 85 yr BMD T-score between –2.0 and –3.5 SD, or T-score between –1.0 and –3.5 SD with osteoporotic fracture	BMD gain (vs placebo) LS 4.8% (95% CI: 4.0-5.6) TH 2.1%* FN 2.1%*
Osteoporosis in setting of chronic kidney disease[9]	$N = 3750$ Duration: 7-10 yr Inclusion: Postmenopausal women between 60 and 90 yr with Stage 2 or 3 CKD BMD T-score between –2.5 and –4.0 SD	BMD gain (vs baseline) LS 14.9%-23.7%*,# TH 6.2%-9.8%*,# Fracture risk reduction at 3 yr (vs placebo) Vertebral 82%-100%& Non-vertebral 10%-25%&
Glucocorticoid-induced osteoporosis[5]	$N = 795$ Duration: 2 yr Inclusion: Patients ≥18 yr receiving ≥7.5 mg prednisolone or equivalent daily Patients ≥50 yr included if BMD T-score ≤ –2.0 SD, or ≤ –1.0 SD with history of osteoporotic fracture Patients <50 yr included if history of osteoporotic fracture	BMD gain (vs risedronate) LS 3.2%-4.5% (95% CI: 2.0-5.8)^ TH 2.5%-3.1% (95% CI: 1.7-3.9)^ FN 1.8%-2.5% (95% CI: 0.7-3.6)^
Aromatase inhibitor therapy-induced bone loss[6]	$N = 252$ Duration: 2 yr Inclusion: Women ≥18 yr with hormone receptor positive non-metastatic breast cancer on aromatase inhibitor therapy BMD T-score between –1.0 and –2.5 SD	BMD gain (vs placebo) LS 7.6%* TH 4.7%* FN 3.6%*
Androgen deprivation therapy-induced bone loss[8]	$N = 1468$ Duration: 3 yr Inclusion: Men with non-metastatic prostate cancer on Androgen Deprivation Therapy (ADT) Men ≥70 yr with any BMD T-score Men <70 yr with BMD T-score < –1.0 SD or history of osteoporotic fracture	BMD gain at 2 yr (vs placebo) LS 6.7%* TH 4.8%* FN 3.9%* Fracture risk reduction at 3 yr (vs placebo) Vertebral 62% (95% CI: 22-81) Any fracture 28% (not significant)

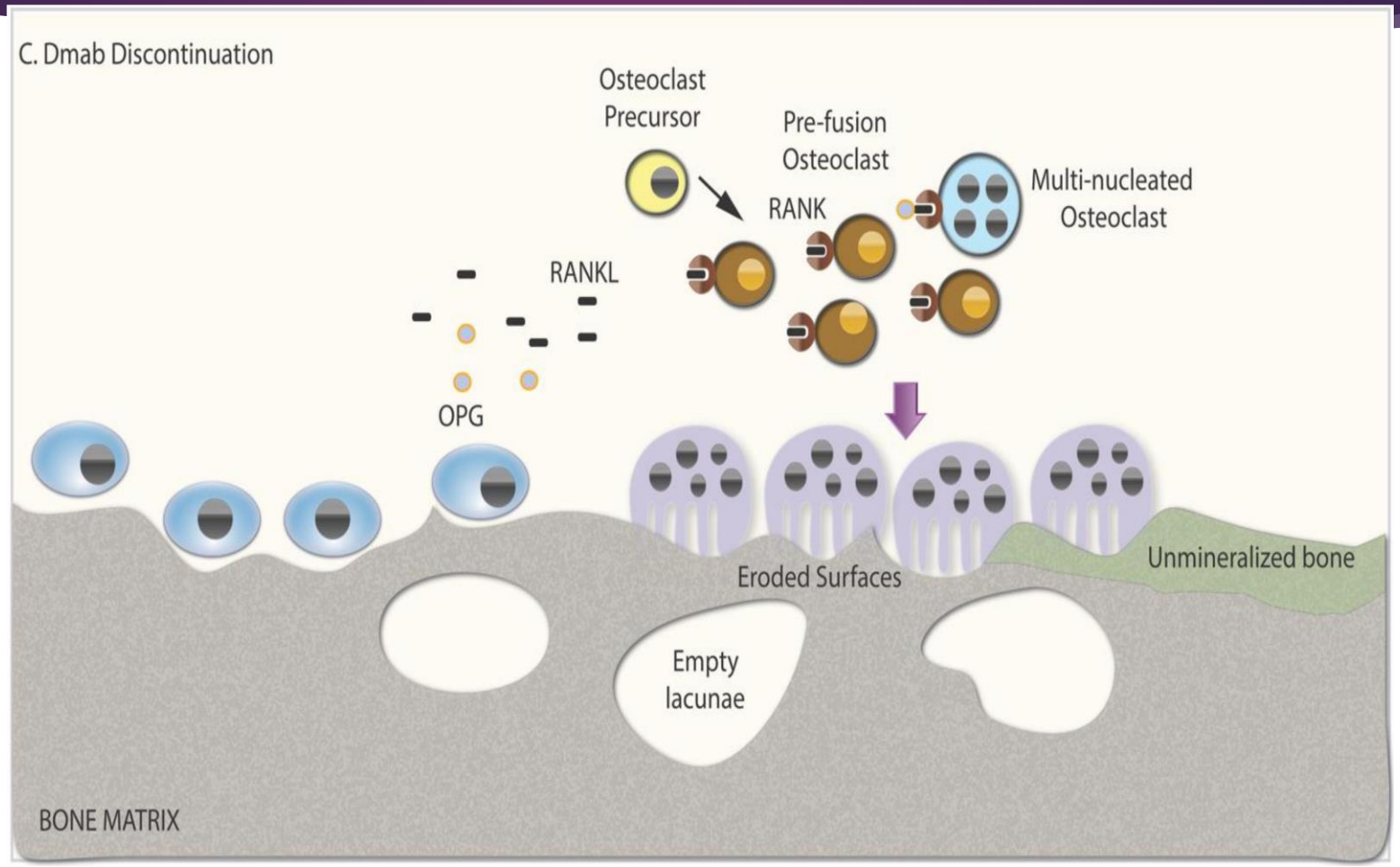
- Shejil Kumar et al, Denosumab discontinuation in the clinic: implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures, Journal of Bone and Mineral Research, 2025, 00, 1–18

DMAB discontinuation and rebound phenomenon

- During the robust inhibition of RANKL, immature preosteoclasts that are unable to resorb bone accumulate in the bone tissue leading to a mass increase in osteoclastogenesis and RANKL release after stopping Dmab (rebound phenomenon)
- Histomorphometric analyses of patients who discontinued Dmab without subsequent medication demonstrated increased osteoclast number, osteoclast surface, and eroded bone surface, together with increased osteoblast numbers and osteoblast-covered bone surface.
- The discontinuation of Dmab leads to significant and abrupt changes in bone remodeling. Enhanced osteoclastogenesis and osteoblastogenesis is evident at tissue level leading to seriously compromised bone structure.

• (2)D. Athanasios Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

DMAB discontinuation



- David L. Kendler et alDenosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review, **Adv Ther (2022) 39:58–74**

Discontinuation Effect on Bone Turnover Markers

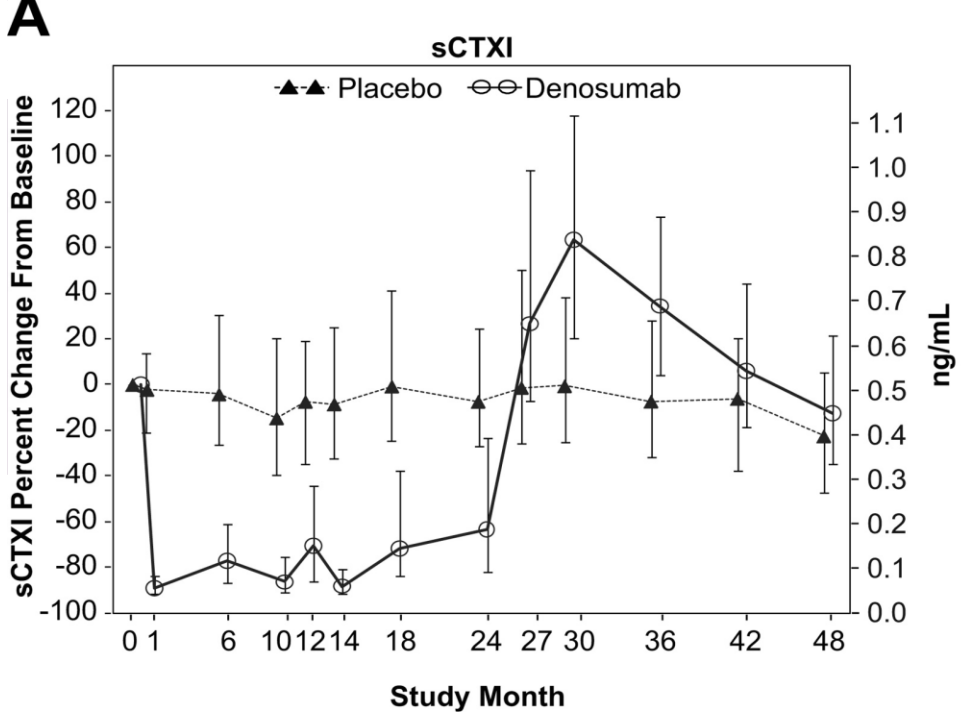
- Dmab discontinuation leads to a rapid, profound increase in the concentrations of BTM, frequently to above pre-treatment baseline levels
- In postmenopausal women participating in phase 2 and phase 3 trials, investigators described a fluctuating trend for serum CTX that began rising within a mean of 3 months after Dmab discontinuation (9 months following the last injection), with a peak after a mean of 6 months, and returned to pre-treatment concentrations after a mean of 24 months. A similar pattern was found for P1NP, suggesting that remodeling remained coupled during the discontinuation phase.
- The pathophysiology of the "rebound effect" on BTMs still remains uncertain. Previous treatment with BPs may have a protective role.

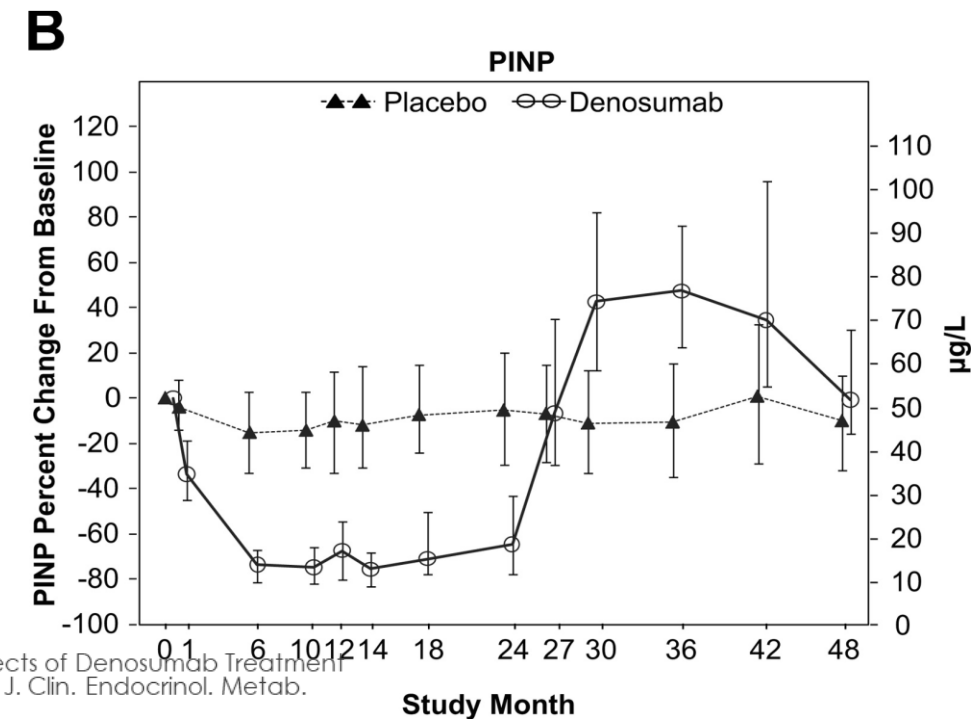
(2)D. Athanasios Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass

Henry G. Bone, Michael A. Bolognese, Chui Kin Yuen, David L. Kendler, Paul D. Miller, Yu-Ching Yang, Luanda Grazette, Javier San Martin, and J. Christopher Gallagher

- Participants: 256 postmenopausal women with a mean age of 59 yr and a mean lumba spine T-score of -1.61 .
- Interventions: received placebo or 60 mg denosumab every 6 months for 24 months,
- Results:After DMAB discontinuation, BTM increased above baseline within 3 months (serum C-terminal telopeptide of type 1 collagen) or 6 months (N-terminal propeptide of type 1 procollagen) and returned to baseline by month 48.
- Conclusions: In postmenopausal women with low BMD,the effects Of 60mg DMAB treatment for 24 months on BMD and BTM are reversible upon discontinuation.





Bone, H.G.; Bolognese, M.A.; Yuen, C.K.; Kendler, D.L.; Miller, P.D.; Yang, Y.-C.; Grazette, L.; Martin, J.S.; Gallagher, J.C. Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass. J. Clin. Endocrinol. Metab. 2011, 96, 972–980.

Discontinuation Effect on Bone Mineral Density

- Discontinuation of Dmab is typically associated with a decline in BMD at all skeletal sites.beginning from 6 months after discontinuation and continue 18 months for L.S and 30 months for hip and 1/3 distal radius.
- Reports from single centers who monitored their patients following the completion of the pivotal denosumab trials (FREEDOM and its Extension) concluded that the rate and amount of bone loss might be predicted by the total duration of Dmab use: patients treated for a longer period had more pronounced BMD loss at all skeletal sites. The rate of BMD loss observed in patients who had stopped Dmab therapy and did not receive any subsequent osteoporosis medication was about 5–11% at all sites during the first year off-treatment.
- To date, it is still uncertain if pre-treatment with BPs preserves BMD gain after Dmab discontinuation.
- In fact, BMD gains at the lumbar spine, total hip, femoral neck and distal radius were all lost within 2 years of discontinuation . Most of this decrease occurs rapidly, within 6 months of the last injection .

• (2)D. Athanasios Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

ORIGINAL ARTICLE

Significant bone loss after stopping long-term denosumab treatment: a post FREEDOM study

M. B. Zanchetta[1,2] · J. Boailchuk[1] · F. Massari[1,2] · F. Silveira[1] · C. Bogado[1,2] · J. R. Zanchetta[1,2]

- Summary We evaluate 38 elderly women who had received long-term denosumab treatment after stopping the drug. Taking into account the gain during treatment and the loss after stopping treatment, they lost 35.5% of the total gain in the spine, 44.6% of the total gain in the femoral neck, and 103.3% in the total hip.
- Results:Bone mineral density (BMD) decreased significantly in all regions: − 8.1% in LS, − 6% in FN, and − 8.4% in TH.

Table 2 BMD measured by DXA (media ± D.S.) in 38 patients at the end of FREEDOM/extension study and after 17 months of denosumab discontinuation

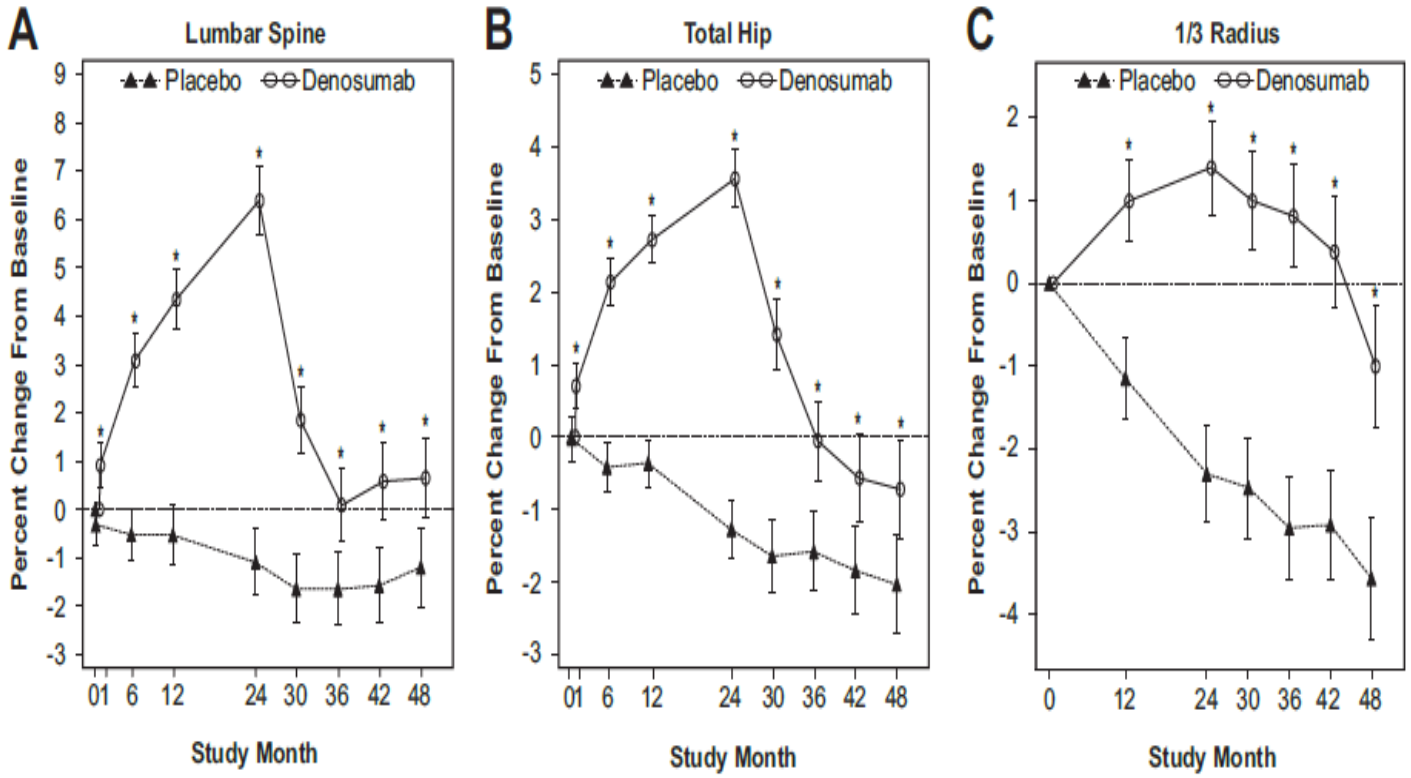
	End of treatment	Follow-up	Change %	*P*
L1-L4				
BMD (g/cm^2)	1.005 ± 0.108	0.923 ± 0.090	− 8.1 ± 4.1	< *0.01*
T-score	− 1.5 ± 0.9	− 2.1 ± 0.7		< *0.01*
Z-score	0.3 ± 1.0	− 0.3 ± 0.8		< *0.01*
FN				
BMD (g/cm^2)	0.820 ± 0.081	0.770 ± 0.083	−6.0 ± 4.7	< *0.01*
T-score	− 1.3 ± 0.7	− 1.7 ± 0.7		< *0.01*
Z-score	0.6 ± 0.7	0.2 ± 0.8		< *0.01*
TH				
BMD (g/cm^2)	0.866 ± 0.08	0.794 ± 0.091	− 8.4 ± 4.6	< *0.01*
T-score	− 1.1 ± 0.7	− 1.7 ± 0.8		< *0.01*
Z-score	0.7 ± 0.7	0.1 ± 0.8		< *0.01*

- M. B. Zanchetta et al, Significant bone loss after stopping long-term denosumab treatment: a post FREEDOM study, Osteoporos Int (2018) 29:41–47

Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass

Henry G. Bone, Michael A. Bolognese, Chui Kin Yuen, David L. Kendler, Paul D. Miller, Yu-Ching Yang, Luanda Grazette, Javier San Martin, and J. Christopher Gallagher

- Design: We conducted an off-treatment extension of a phase 3, randomized, double-blind, parallel- group study.
- Participants: A total of 256 postmenopausal women with a mean age of 59 yr and a mean lumbar spine T-score of 1.61 at randomization participated in the study.
- Interventions: Participants received placebo or 60 mg denosumab every 6 months for 24 months, followed by 24 months off treatment.
- Results: Of the 256 participants enrolled in the posttreatment phase, 87% completed the study.
- After discontinuation, BMD declined, but the previously treated denosumab group maintained higher BMD than the previously treated placebo group at these sites ($P < 0.05$). Final BMD at month 48 strongly correlated with month 0 BMD.



Henry G. Bone et al, Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass, J Clin Endocrinol Metab, April 2011, 96(4):972–980

Discontinuation Effect on Fracture Risk

- Discontinuation of Dmab is associated with a 3- to 5-fold higher risk for vertebral, major osteoporotic, and hip fractures.
- This might be simply a relapse of a given unopposed fracture risk as in the placebo-controlled trials, the off-treatment fracture risk among patients who had received Dmab was not different than that of the placebo group.
- However, the multiple vertebral fractures are specifically and significantly increased amongst those discontinuing Dmab
- The fractures in this setting are typically clinical, occurring a few months after the effect of the last Dmab injection has been depleted , and are often described as rebound associated vertebral fractures (RAVFs).

(2)D. Athanasios Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

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Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension

Steven R Cummings,[1] Serge Ferrari,[2] Richard Eastell,[3] Nigel Gilchrist,[4] Jens-Erik Beck Jensen,[5] Michael McClung,[6] Christian Roux,[7] Ove Törring,[8] Ivo Valter,[9] Andrea T Wang,[10] and Jacques P Brown[11]

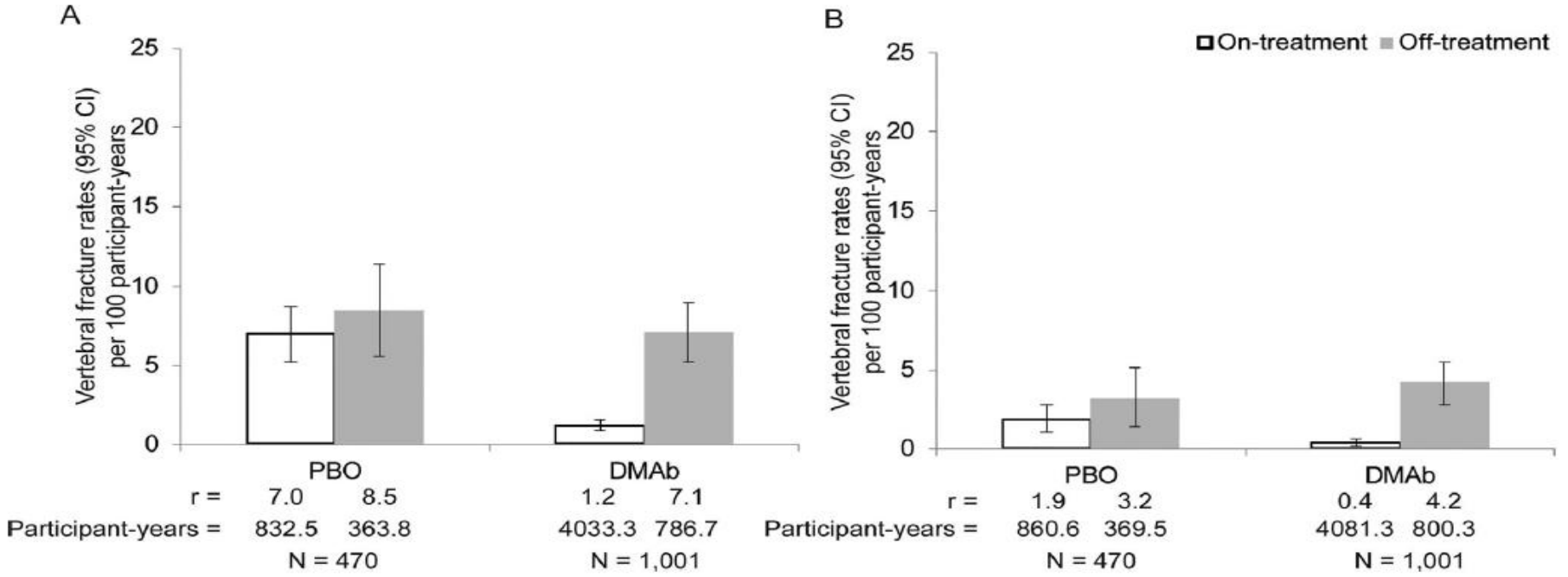

Fig. 2. Exposure-adjusted rates of (*A*) any and (*B*) multiple vertebral fractures in participants who received placebo or denosumab in the FREEDOM study and denosumab in the Extension before (white bar) and after (gray bar) discontinuing treatment. DMAb = denosumab; PBO = placebo; r = rate per 100 participant-years.

- Steven R Cummingset al, Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension, Journal of Bone and Mineral Research, Vol. 33, No. 2, February 2018, pp 190–198

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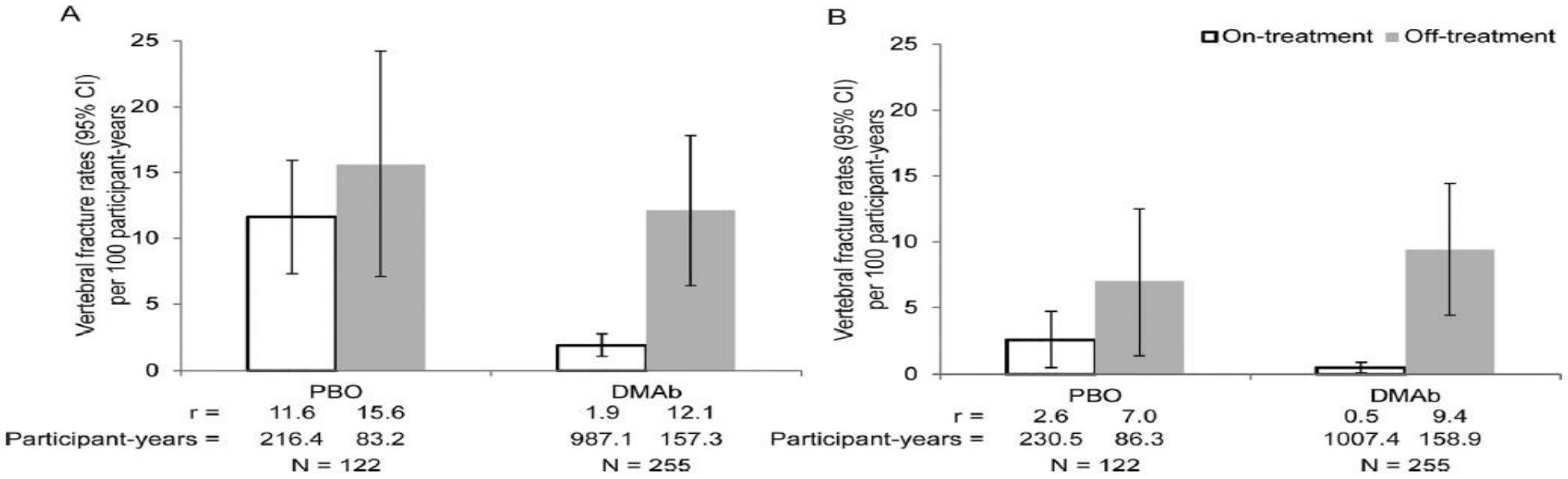


Fig. 3. Exposure-adjusted rates of (*A*) any and (*B*) multiple vertebral fractures in participants with prevalent vertebral fractures who received placebo o denosumab in the FREEDOM study and denosumab in the Extension before (white bar) and after (gray bar) discontinuing treatmen DMAb = denosumab; PBO = placebo; r = rate per 100 participant-years.

- Steven R Cummingset al, Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension, Journal of Bone and Mineral Research, Vol. 33, No. 2, February 2018, pp 190–198

- A post hoc analysis of the FREEDOM trial and its extension study examined this in detail by comparing the vertebral fracture rates of 1,001 subjects who discontinued denosumab after having at least two doses with the vertebral fracture rates of 470 participants who received placebo.
- After withdrawal of denosumab, the vertebral fracture rate increased from 1.2 per 100 participant-years to 7.1 per 100 participant-years . The vertebral fracture rate after stopping denosumab was similar to the rates before and after stopping placebo, which were 7.0 per 100 participant-years and 8.5 per 100 participant-years , respectively.
- Among those who had vertebral fractures after denosumab was stopped, 34 out of 56 participants (61%) had multiple vertebral fractures as compared to 12 out of 31 participants (39%) in the placebo group ($p<0.049$), corresponding to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively .
- Nonetheless, the incidence of any vertebral fractures upon discontinuation of denosumab was still lower than the incidence reported in the placebo group.

- Wei Lin Tay, Donovan Tay, Discontinuing Denosumab: Can It Be Done Safely? A Review of the Literature, Endocrinol Metab 2022 Forthcoming. Posted online 2022
- Steven R Cummingset al, Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension, Journal of Bone and Mineral Research, Vol. 33, No. 2, February 2018, pp 190–198

Limitation of study

- in this post hoc analysis, the annualized risk might be underestimated by the relatively short follow-up period (mean 0.2–0.5 years).
- Another cause of underestimation may be the fact that most studies reporting VFs after Dmab withdrawal were based on follow-up lateral X-rays to identify new fractures and not on MRI which depicts vertebral deformities with greater sensitivity among patients with RAVFs .
- Recent reports of cohorts from large registries confirmed the increased risk for VFs in Dmab discontinuers , while the effect of discontinuation on the risk for fractures at other skeletal sites is not clearly estimated as yet. The incidence of VFs after Dmab discontinuation is estimated around 8–10%, with a relative risk of multiple VFs per 100 patient-years of 14.63 (95% confidence interval (CI) 3.3–65.3)
- The latest evidence shows that even a 4-month delay in the injection significantly increases VF risk

(2)D. Athanasios Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

Review Article

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS

Elena Tsourdi [a,b], Bente Langdahl [c], Martine Cohen-Solal [d], Bérengere Aubry-Rozier [e], Erik Fink Eriksen [f], Nuria Guañabens [g], Barbara Obermayer-Pietsch [h,i], Stuart H. Ralston [j], Richard Eastell [k], M. Carola Zillikens [l,*]

Table 1
Effects of Denosumab Treatment Discontinuation on Bone Turnover Markers, Bone Mineral Density and Fracture Risk.

Design	Phase	No	Duration of Treatment (months)	Duration of Discontinuation (months)[c]	↑BTMs	↓BMD LS	↓BMD Hip	↑Vertebral Fx or ↑ multiple vertebral Fx	↑ Non-vertebral Fx	Reference
Open-label single arm in postmenopausal women with osteopenia/osteoporosis	2	200	24	24	+	+	+	N/A	N/A	[16]
Randomized blinded placebo controlled in postmenopausal women with osteopenia	3	256	24	24	+	+	+	–	–	[17]
Observational follow-up study after 8 years of denosumab treatment in patients with osteoporosis	N/A	82	96	12	N/A	–	+	N/A	N/A	[14]
Observational follow-up study after 10 years of denosumab treatment in women with osteoporosis	N/A	9[a]	120	12	+	N/A	+	+	–	[18]
Observational follow-up study after 7 to 10 years of denosumab treatment in women with osteoporosis	N/A	38	84–120	10–14	+	+	+	+	+	[19]
RCT blinded placebo controlled in postmenopausal women with osteopenia/osteoporosis	2	307	24	24	+	+	+	–	–	[20]
Retrospective analysis of participants of FREEDOM trial [12]	N/A	797	12–30	24	N/A	N/A	N/A	–	–	[27]
Case report	N/A	1	36	2	+	N/A	N/A	+	–	[28]
Case series	N/A	3	30–36	4–10	N/A	N/A	N/A	+	–	[29]
Case report	N/A	1	36	6	+	+	+	+	–	[30]
Case series	N/A	9	12–48	3–10	N/A	N/A	N/A	+	–	[31]
Case series	N/A	2	12–24	6–8	N/A	N/A	N/A	+	–	[32]
Case series	N/A	24[b]	12–30	2–10	N/A	N/A	N/A	+	–	[33]
Retrospective analysis based on administrative claims data	N/A	7.855	N/A	>6	N/A	N/A	N/A	+	+	[34]
Retrospective analysis of participants of FREEDOM and FREEDOM Extension trials [12,13]	N/A	1.001	>12	>7	N/A	N/A	N/A	+	–	[35]

Abbreviations: BMD LS, Bone Mineral Density at Lumbar Spine; BMD Hip, Bone Mineral Density at Total Hip/Femoral Neck; BTMs, Bone Turnover Markers; n/a, not applicable; N/A, not available; No, Number of patients; vertebral Fx; vertebral fractures; non-vertebral Fx, non-vertebral fractures.

[a] Patients from the FREEDOM and FREEDOM Extension Trials.

[b] 11 new patients, remaining patients already described [28–32].

[c] Duration of discontinuation in months is calculated from the time point the next injection of denosumab would be due.

M. Carola Zillikens et al, Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by EC
Bone 105 (2017) 11–17

Factors Predisposing to Bone Loss and Fractures Following Discontinuation

- According to currently existing evidence, prevalent VF(s) before or during the treatment period are the strongest predictor of new VFs upon discontinuation
- The rate of BMD loss off-treatment per se could be a risk factor,
- Other factors associated with increased risk of RAVFs, that were identified at the post-hoc analysis of FREEDOM and its Extension follow-up study, include longer duration of the off-treatment period, greater gain in hip BMD with Dmab treatment, and greater loss of hip BMD after discontinuation
- Vertebroplasty has also been identified as another factor setting patients who discontinue Dmab at risk for VFs, especially at the adjacent vertebrae
- Although younger age has been reported to be a risk factor for bone loss after discontinuation
- Weak evidence suggests that concomitant AI administration in breast cancer patients may aggravate the withdrawal effect of Dmab on the skeleton, even in normal BMD values, predisposing to VFs.

• (2)D. Athanasios Anastasilakis et al, Denosumab Discontinuation and the Rebound Phenomenon A Narrative Review, J. Clin. Med. 2021, 10, 152.

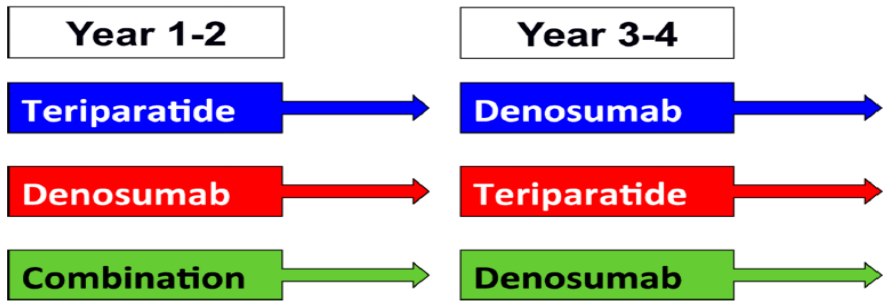
“REVIEW OF STUDIES ABOUT DIFFERENT ANTIOSTEOPOROTIC AGENTS AFTER DMAB DISCONTINUATION”

Denosumab and Teriparatide Transitions in Postmenopausal Osteoporosis (The DATA-Switch Study): a Randomised Controlled Trial

Benjamin Z. Leder, MD, Joy N. Tsai, MD, Alexander V. Uihlein, MD, Paul Wallace, BA, Hang Lee, PhD, Robert M. Neer, MD, and Sherri-Ann M. Burnett-Bowie, MD

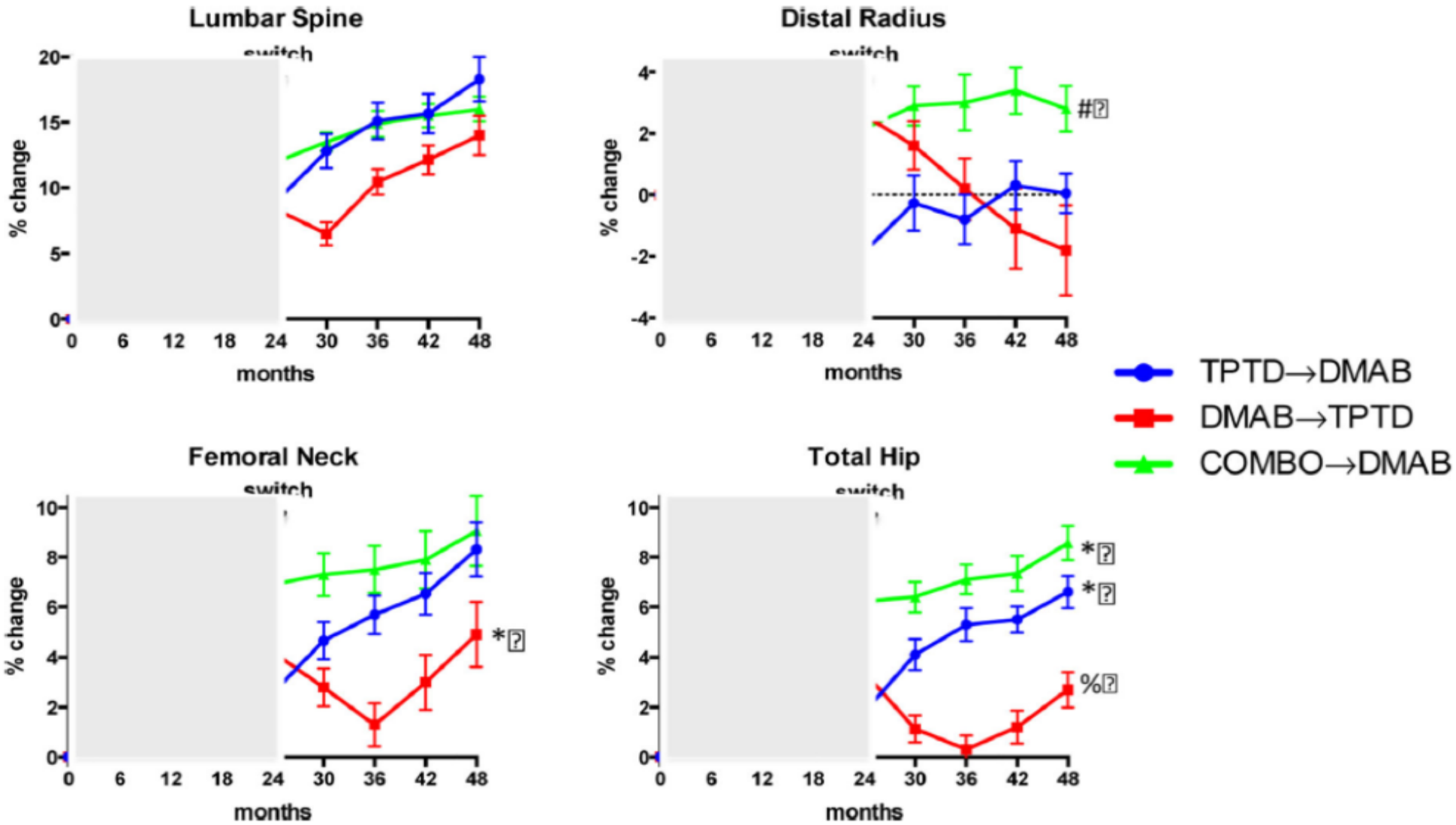
- METHODS:This study is a pre-planned extension of the Denosumab and Teriparatide Administration study (DATA)
- FINDINGS: After 48-months, spine BMD increased by18.3±8.5%, 14.0±6.7%, and 16.0±4.1% in the teriparatide-to-denosumab, denosumab-to-teriparatide, and combination-to-denosumab groups, respectively (P=NS for between-group comparisons).
- Conversely, total hip BMD increased most in the combination-to-denosumab group (8.6±3.0%), intermediately in the teriparatide-to-denosumab group (6.6±3.3%) and least in the denosumab-to-teriparatide group (2.7±3.3%), (P<0.05 for all between-group comparisons). Femoral neck BMD changes resembled those at the total hip. After 48-months, radius BMD was unchanged in the teriparatide-to-denosumab group (0.0±2.9%), decreased by −1.8±5.9% in the denosumab-toteriparatide group, and increased by 2.8±3.2% in the combination-to-denosumab group (P<0.01 combination-to-denosumab versus both other groups).

DATA-Switch Study Design



- INTERPRETATION—In postmenopausal osteoporotic women switching from teriparatide to denosumab, BMD continued to increase whereas switching from denosumab to teriparatide results in progressive or transient bone loss. Combination denosumab/teriparatide therapy followed by denosumab alone results in the largest 4-year increases in hip and wrist BMD.

Benjamin Z. Leder et al, Denosumab and Teriparatide Transitions in Postmenopausal Osteoporosis (The DATA-Switch Study): a Randomised Controlled Trial. Lancet. 2015 September 19; 386(9999): 1147–1155



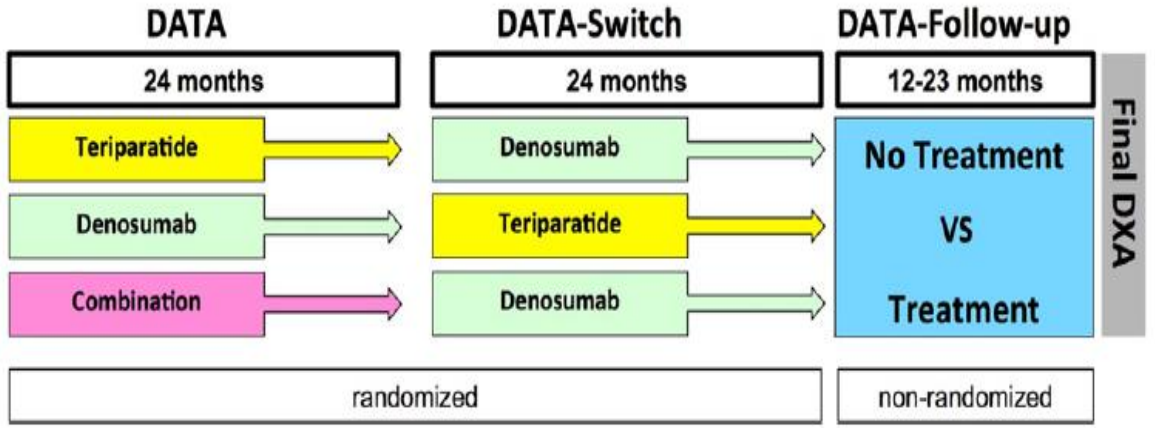
- Benjamin Z. Leder et al, Denosumab and Teriparatide Transitions in Postmenopausal Osteoporosis (The DATA-Switch Study): a Randomised Controlled Trial, Lancet. 2015 September 19; 386(9999): 1147–1155.

Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up)

Benjamin Z. Leder *, Joy N. Tsai, Linda A. Jiang, Hang Lee

Harvard Medical School, Endocrine Unit, Massachusetts General Hospital, United States

- Fifty of 69 women who completed DATA-Switch returned after a mean of 15.4 ± 3.5 months. Of the 28 women who received antiresorptive therapy (10 denosumab, 10 oral bisphosphonates, 8 intravenous zoledronic acid), the mean interval between ending DATA-Switch and beginning antiresorptive therapy was 3.8 ± 3.1 months. In the 22 women not receiving follow-up therapy, femoral neck, total hip, and spine BMD decreased by −4.2±4.3%,−4.5±3.6%, and−10.0±5.4%, respectively,while BMDwas maintained in those who did receive follow-up antiresorptive drugs (femoral neck, total hip, and spine BMD changes of −0.6 ± 2.7%, −0.8 ± 3.1%, and−1.2±4.7%, respectively, P b 0.001 for all between-group comparisons). Total hipBMD, but not spine BMD, showed a similar pattern.



- In summary, the large teriparatide and denosumab-induced gains in BMD achieved with 4 years of intensive therapy in the DATA and DATA-Switch studies were maintained in patients who received prompt antiresorptive therapy but not in those left untreated. These results demonstrate the negative consequences of delaying consolidation therapy in women treated with these drugs and underscore the importance of timely medication transitions in such patients.

- Benjamin Z. Leder et al, Importance of prompt antiresorptive therapy in postmenopausalwomen discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up) , Bone 98 (2017) 54–58

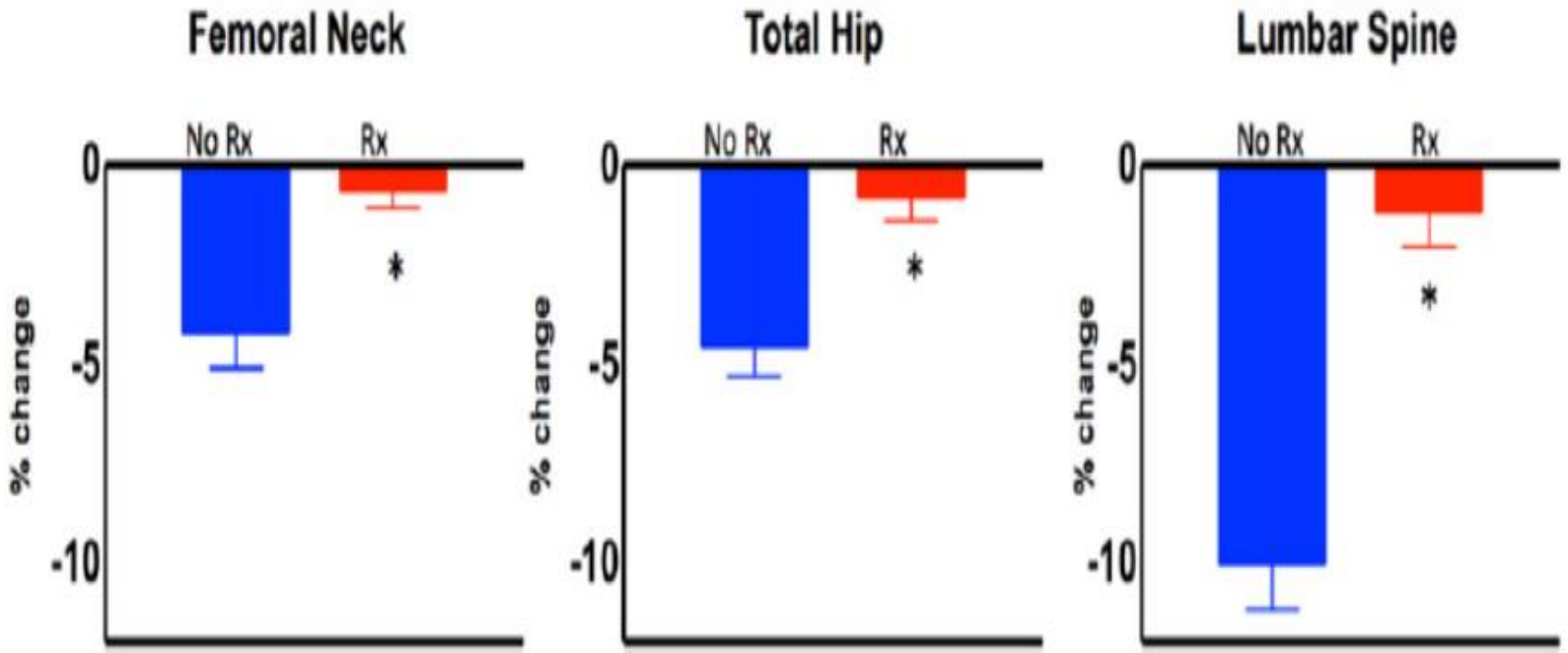


Fig. 3. Percent change in BMD in patients who did (Rx, $n = 28$) or did not (No Rx, $n = 22$) receive consolidation therapy (mean ± SE). *$P < 0.001$ versus No Rx.

- Benjamin Z. Leder et al, Importance of prompt antiresorptive therapy in postmenopausalwomen discontinuing teriparatide or denosumab: The Denosumab and Teriparatide Follow-up study (DATA-Follow-up) , Bone 98 (2017) 54–58

Osteoporos Int (2012) 23:317–326
DOI 10.1007/s00198-011-1780-1

ORIGINAL ARTICLE

Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women

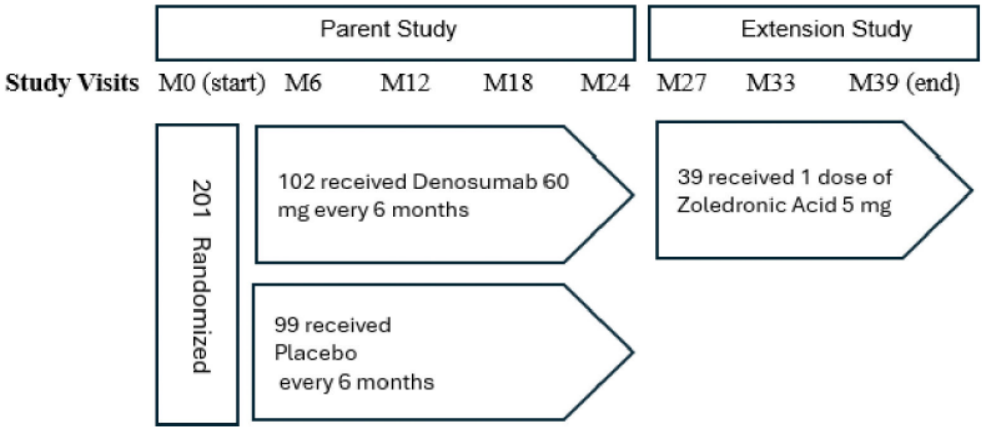
N. Freemantle · S. Satram-Hoang · E.-T. Tang · P. Kaur · D. Macarios · S. Siddhanti · J. Borenstein · D. L. Kendler · on behalf of the DAPS Investigators

- The effects of alendronate after denosumab were assessed in the DAPS (Denosumab Adherence Preference Satisfaction) study
- . In this 24-month, randomized, open-label crossover study, 250 postmenopausal women with low BMD were randomly assigned to either alendronate for 1 year followed by denosumab for 1 year or vice versa.
- Patients who received 1 year of alendronate after 1 year of denosumab maintained the BMD gained wit denosumab during the first year.

Impact of Zoledronic Acid on Bone Mineral Density and Trabecular Score Following Denosumab Discontinuation in Older Adults in Long-Term Care

Nami Safai Haeri, MD[1,2], Subashan Perera, PhD, FGSA[1,3], Susan L. Greenspan, MD[1,2]

- Method: an open-label, one-year extension study following a two-year double-blind, placebo-controlled, randomized clinical trial, 39 older adults aged 65 years and above, who were residents of LTCCs and participants in the PROUD (PReventing Osteoporosis Using Denosumab) trial, received a single 5 mg dose of zoledronic acid after completing four doses of denosumab 60 mg during the PROUD trial.
- We aim to evaluate the effects of a single 5 mg dose of zoledronic acid on bone mineral density (BMD) at the lumbar spine, total hip, femoral neck, and one-third radius, as well as on the spine trabecular bone score (TBS), over a one-year period. Additionally, we surveyed patients for fractures
- results:Our study included 27 women and 12 men, with a mean age of 81.5 years. Twelve months after the administration of zoledronic acid, the mean percent changes from the end of the denosumab trial showed no significant decline in any of the BMD sites in both women and men.
- These findings indicate no evidence of rebound bone loss. In women, TBS significantly increased by 3.9% (95% CI: 0.8 to 5.8, p=0.007), suggesting improved bone microarchitecture. In men, there was a trend toward improvement in TBS, with an increase of 3.3% (p=0.0545).
- There were no reported fragility fractures among participants during the post-denosumab period.
- Conclusions: In residents of LTCCs with osteoporosis receiving a single 5 mg dose of zoledronic acid following two years of denosumab, we found no evidence of a loss in BMD or TBS. Further, participants experienced enhanced bone microarchitecture.



Twelve Months Post-Zoledronic Acid Changes in Bone Mineral Density and Trabecular Bone Score

Bone Index	Women				Men				All Participants			
	Month 27 Mean±SE	Month 39 Mean±SE	Percent Change Mean±SE	*p*-Value	Month 27 Mean±SE	Month 39 Mean±SE	Percent Change Mean±SE	*p*-Value	Month 27 Mean±SE	Month 39 Mean±SE	Percent Change Mean±SE	*p*-Value
Lumbar Spine BMD (g/cm^2)	1.137±0.033	1.190±0.036	0.97±0.80	0.242	1.306±0.077	1.289±0.098	−0.32±1.47	0.832	1.189±0.035	1.221±0.039	0.57±0.71	0.426
Total Hip BMD (g/cm^2)	0.819±0.021	0.822±0.028	−0.10±1.03	0.927	0.940±0.044	0.981±0.055	1.79±1.08	0.139	0.856±0.022	0.871±0.029	0.49±0.79	0.545
Femoral Neck BMD (g/cm^2)	0.707±0.021	0.717±0.024	1.71±0.98	0.099	0.775±0.036	0.786±0.050	1.52±2.17	0.505	0.727±0.019	0.738±0.023	1.65±0.93	0.087
One-third Radius BMD (g/cm^2)*	0.602±0.015	0.605±0.018	−1.04±0.76	0.186	0.736±0.031	0.744±0.038	1.38±0.44	0.015	0.643±0.017	0.647±0.021	−0.30±0.58	0.613
TBS	1.349±0.024	1.423±0.021	3.91±1.25	0.007	1.353±0.033	1.376±0.028	3.33±1.08	0.054	1.350±0.019	1.409±0.019	3.79±1.01	0.001

- Nami Safai Haeri et al. Impact of Zoledronic Acid on Bone Mineral Density and Trabecular Score Following Denosumab Discontinuation in Older Adults in Long-Term Care

Table 3. Clinical studies investigating strategies to mitigate rebound after short-term (≤2.5-3.0 yr) denosumab use.

First author year	Study design	Study population	Prior Dmab exposure	Medication	Time since last Dmab	BMD outcomes	BTM outcomes	VF outcomes
Tsai 2024[44]	Extension of open-label RCT (CARD)	$N=18$ Postmenopausal osteoporosis Mean age = 66 yr	1.0 yr	ALN 1 yr ($N=8$)~ ALN 2 yr ($N=10$)~	6 mo	BMD maintained in both groups at 2 yr	BTMs suppressed in both groups	Nil VFs (radiographic)
Anastasilakis 2023[41]	Extension of prospective open-label randomized (AfterDmab)	$N=16$ Treatment-naïve postmenopausal osteoporosis Mean age = 65 yr	Mean 2.5 yr	ZOL ($N=16$)↓	NR	$N=9$ – BMD stable for 5 yr $N=7$ – retreated for BMD loss	N/A	Nil VFs (clinical & radiographic)
Ramchand 2024[43]	Open-label RCT (CARD)	$N=51$ Postmenopausal osteoporosis Mean age = 66 yr	1.0 yr	ALN ($N=26$)~ RLX ($N=25$)↓	6 mo	BMD maintained with ALN ~50% decline at LS and TH, maintained at FN with RLX	CTx, P1NP suppressed with ALN and returned to baseline with RLX	One VF (radiographic) with ALN
Tutaworn 2023[37]	Retrospective observational (real-world)	$N=121$ 93% female Mean age = 71 yr	Mean 2.5 yr	ZOL ($N=32$)~ ALN ($N=34$)~ RIS ($N=22$)↓ Nil ($N=33$)↓↓	6 mo	BMD mostly preserved with ZOL and ALN >50% gains lost with RIS		One VF with ZOL, 1 VF with ALN (clinical)
Hong 2022[48]	Observational (real-world) Propensity score matching	$N=66$ Postmenopausal women Mean age = 69 yr	0.5-2.0 yr	RLX ($N=33$)↓ Nil ($N=33$)↓↓	NR	RLX attenuated BMD loss at LS vs nil treatment, but not TH or FN	N/A	Nil VFs (clinical & radiographic)
Ha 2022[47]	Retrospective observational (real-world)	$N=61$ Postmenopausal women Mean age = 66 yr	1.0-2.5 yr	RLX ($N=61$)↓↓	6 mo	Loss of all BMD gains at LS, TH, and FN	Overshoot in CTx, P1NP	Nil VFs (radiographic)
Everts-Graber 2022[51]	Retrospective case series	$N=32$	0.5 yr	ZOL ($N=32$)~	6 mo	BMD maintained	BTMs declined	Nil VFs
Ramchand 2021[40]	Extension of prospective open-label randomized (DATA-HD)	$N=53$ Postmenopausal osteoporosis Mean age = 66 yr	1.0 yr Overlap with 9-mo TPTD	ZOL ($N=53$)~	5.5-8.0 mo	BMD maintained at 12-mo at LS, TH, and FN BMD maintained at 27-mo (other than small loss at LS)	BTMs increased but not back to baseline	Nil VFs (clinical)
Ebina 2021[38]	Retrospective multicentre observational (real-world)	$N=64$ Postmenopausal osteoporosis Mean age = 73.1 Previously treated with BPs/TPTD for mean 18-mo	1.0-1.5 yr	RLX ($N=13$)↓ Oral BPs ($N=26$)~ ZOL ($N=11$)~	Mean 7 mo	No sig. diff. in LS BMD Greater FN BMD loss with RLX	Trend to greater rise in serum TRAP5b using RLX	More frequent clinical VFs with RLX ($n=3$ vs $n=1$ vs $n=0$)
Kadaru 2021[35]	Retrospective case series	$N=12$ Postmenopausal women Mean age = 77 yr	Median 2.5 yr	ZOL ($N=12$)↓	Median 7 mo	BMD mostly preserved at LS ~50% gains lost at TH, FN	N/A	Nil VFs (clinical)
Kendler 2020[42]	Randomized multicentre open-label cross-over (DAPS)	$N=115$ Treatment-naïve postmenopausal women Mean age = 65 yr	1.0 yr	ALN ($N=115$)~	6 mo	BMD maintained at LS, TH and FN	Stable CTx and P1NP	Nil VFs (clinical)

Table 3. Continued

First author year	Study design	Study population	Prior Dmab exposure	Medication	Time since last Dmab	BMD outcomes	BTM outcomes	VF outcomes
Laroche 2020[46]	Prospective cohort study	$N = 18$ Postmenopausal women Mean age = 70 yr	Mean 3.0 yr	RIS ($N = 18$)$^{\downarrow}$	6 mo	Loss of ~50% BMD gains at LS and TH	Mean CTx 303 ng/L	One clinical VF
Kondo 2020[36]	Retrospective multicentre observational (real-world)	$N = 18$ Postmenopausal women Mean age = 76 yr	Mean 1.5 yr	ZOL ($N = 18$)$^{\sim}$	Mean 9 mo	BMD maintained at LS and FN	No increase in TRAP5b	Nil VFs (clinical/ radiographic)
Anastasilakis 2019[34]	Prospective open-label randomized (AfterDmab)	$N = 27$ Treatment-naïve postmenopausal osteoporosis Mean age = 65 yr	2.0-2.5 yr	ZOL ($N = 27$)$^{\sim}$	Mean 6.5 mo	BMD maintained at LS and FN	Stable CTx and P1NP	One clinical VF
Zanchetta 2019[87]	Prospective observational (real world)	$N = 33$ Postmenopausal women	≥1 yr	BPs ($N = 10$)$^{\downarrow}$ Nil ($N = 23$)$^{\sim}$	NR	BMD declined at LS but remained stable at FN with BPs	CTx more than tripled with BPs	Nil VFs (radiographic)
Horne 2018[45]	Observational post-RCT (FRAME)	$N = 19$ Postmenopausal osteoporosis Rmab/placebo 1 yr → Dmab	2.0 yr	ZOL ($N = 11$)$^{\sim}$ RIS ($N = 5$)$^{\downarrow}$ Nil ($N = 3$)$^{\downarrow\downarrow}$	Median 8 mo	BMD mostly preserved with ZOL Loss of >50% gains with RIS	N/A	Nil VFs

- Christian M. Girgis et al, Denosumab discontinuation in the clinic: implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures, Journal of Bone and Mineral Research, 2025, 00, 1–18

Table 4. Clinical studies investigating strategies to mitigate rebound after medium-to-long-term (≥3.0 yr) denosumab use.

First author year	Study design	Study population	Prior Dmab exposure	Medication	Time since last Dmab	BMD outcomes	BTM outcomes	VF outcomes
Lee 2024[32]	Prospective open-label randomized (DST)	$N = 76$ randomized to ZOL Predominantly women Mean age = 71 yr	Median 2.0 yr	ZOL ($N = 61$) <3 yr Dmab~ ZOL ($N = 15$) ≥3 yr Dmab↓	6 mo	BMD maintained in group with <3 yr Dmab BMD declined by ~3% at LS in group with ≥3 yr Dmab	No sig. diff. in CTx or P1NP between groups	Three clinical/ morphometric VFs
Grassi 2024[29]	Retrospective observational study	$N = 52$ Predominantly women Mean age = 71 yr	Mean 4.0 yr	ZOL ($N = 13$) CTx <280 ng/L 6-mo post~ ZOL ($N = 39$) CTx ≥280 ng/L 6-mo post and needing second infusion↓	6-7 mo	BMD maintained in group receiving 1 ZOL dose BMD declined by ~5% at LS, ~3%-4% at TH and FN in group with high bone turnover prompting second ZOL dose	BTMs at end of follow-up not recorded	Three clinical VFs and 1 morphometric VF in group needing second ZOL dose
Tutaworn 2023[37]	Subgroup analysis of retrospective real-world study	$N = 33$ Predominantly women Mean age = 73 yr	Mean 4.0 yr	ZOL ($N = 11$)↓ ALN ($N = 22$)~	6 mo	BMD maintained at LS, TH and FN with ZOL and ALN other than ~4% decline in LS BMD with ZOL	N/A	N/A
Everts-Graber 2022[51]	Single centre prospective observational study (ProOff)	$N = 282$ Postmenopausal women Mean age = 66 yr	Mean 2.5 yr ($N = 144$) Mean 5.0 yr ($N = 84$) Mean 7.5 yr ($N = 54$)	ZOL ($N = 144$) ~2.5 yr Dmab~ ZOL ($N = 84$) ~5 yr Dmab↓ ZOL ($N = 54$) ~7.5 yr Dmab↓	6 mo	Greater BMD loss at LS, TH, and FN after medium and long-term Dmab cessation	CTx, P1NP increased after first ZOL dose and decreased after subsequent ZOL dose	VF rates post-Dmab –7.4% after long Dmab –2.4% after medium Dmab –2.1% after short Dmab Three out of four cases of multiple VFs occurred in long Dmab group
Makras 2021[49]	Multicentre prospective cohort study (including post hoc data from AfterDmab)	$N = 47$ Treatment-naïve postmenopausal osteoporosis Mean age = 65 yr	≤3.0 yr ($N = 27$) >3.0 yr ($N = 20$)	ZOL ($N = 27$) ≤3 yr Dmab~ ZOL ($N = 20$) >3 yr Dmab↓	6 mo	BMD maintained at LS and FN after ≤3.0 yr Dmab BMD declined by ~7% and ~3% after >3.0 yr Dmab Longer duration of Dmab correlated with % decline in LS BMD	CTx and P1NP increased similarly in both groups	One clinical VF in group with longer Dmab exposure

- Christian M. Girgis et al, Denosumab discontinuation in the clinic: implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures, Journal of Bone and Mineral Research, 2025, 00, 1–18

Table 4. Continued

First author year	Study design	Study population	Prior Dmab exposure	Medication	Time since last Dmab	BMD outcomes	BTM outcomes	VF outcomes
Solling 2021,[50] 2020[28]	Prospective open-label randomized (ZOLARMAB)	$N = 61$ Postmenopausal women and men >50 yr with osteopenia Mean age = 69 yr	Mean 5.0 yr	ZOL ($N = 61$)↓	6 mo ($N = 20$) 9 mo ($N = 20$) Treatment threshold or 12 mo ($N = 21$)	Similar LS BMD loss in all groups (~4%-5%) from end of Dmab to 12 mo after ZOL BMD stable in second year (although several patients had repeat ZOL or rescue Dmab)	CTx, P1NP and osteocalcin increased in all groups	Two clinical VFs in 9-mo group
Everts-Graber 2021[30]	Retrospective study	$N = 219$ Women with osteoporosis Mean age = 66 yr	Mean 2.5 yr	ZOL ($N = 171$)↓ BPs/SERM ($N = 22$)↓ Nil ($N = 26$)↓↓	6 mo	No sig. Diff. in BMD loss between groups Greater BMD loss at LS and TH associated with longer Dmab (>2.5 yr)	Greater CTx rise associated with longer Dmab (>2.5 yr)	ZOL associated with fewest VFs (HR 0.16, $p = .02$) compared to nil treatment Multiple VFs only observed in nil treatment group
Grassi 2021[33]	Retrospective real-world single centre study	$N = 120$ Predominantly women Mean age = 69 yr	Mean 3.0 yr	ZOL ($N = 73$)↓ ALN ($N = 28$)↓ Nil ($N = 19$)↓↓	NR	No sig. Diff. in BMD loss between ZOL and ALN groups Partial loss of LS BMD gains and loss of majority of TH and FN BMD gains	N/A	VF rates: –5.9% in combined BP-treated groups –21.1% in untreated group
Reid 2017[53]	Case series post-FREEDOM RCT extension	$N = 6$ Postmenopausal women Mean age = 83 yr	7.0 yr	ZOL ($N = 6$)↓↓	6 mo	Loss of >50% LS BMD gains Loss of all TH BMD gains	Mean P1NP 52 ug/L	NR

- Christian M. Girgis et al, Denosumab discontinuation in the clinic: implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures, Journal of Bone and Mineral Research, 2025, 00, 1–18

What is the optimal treatment duration with denosumab for patients at high risk for fracture?

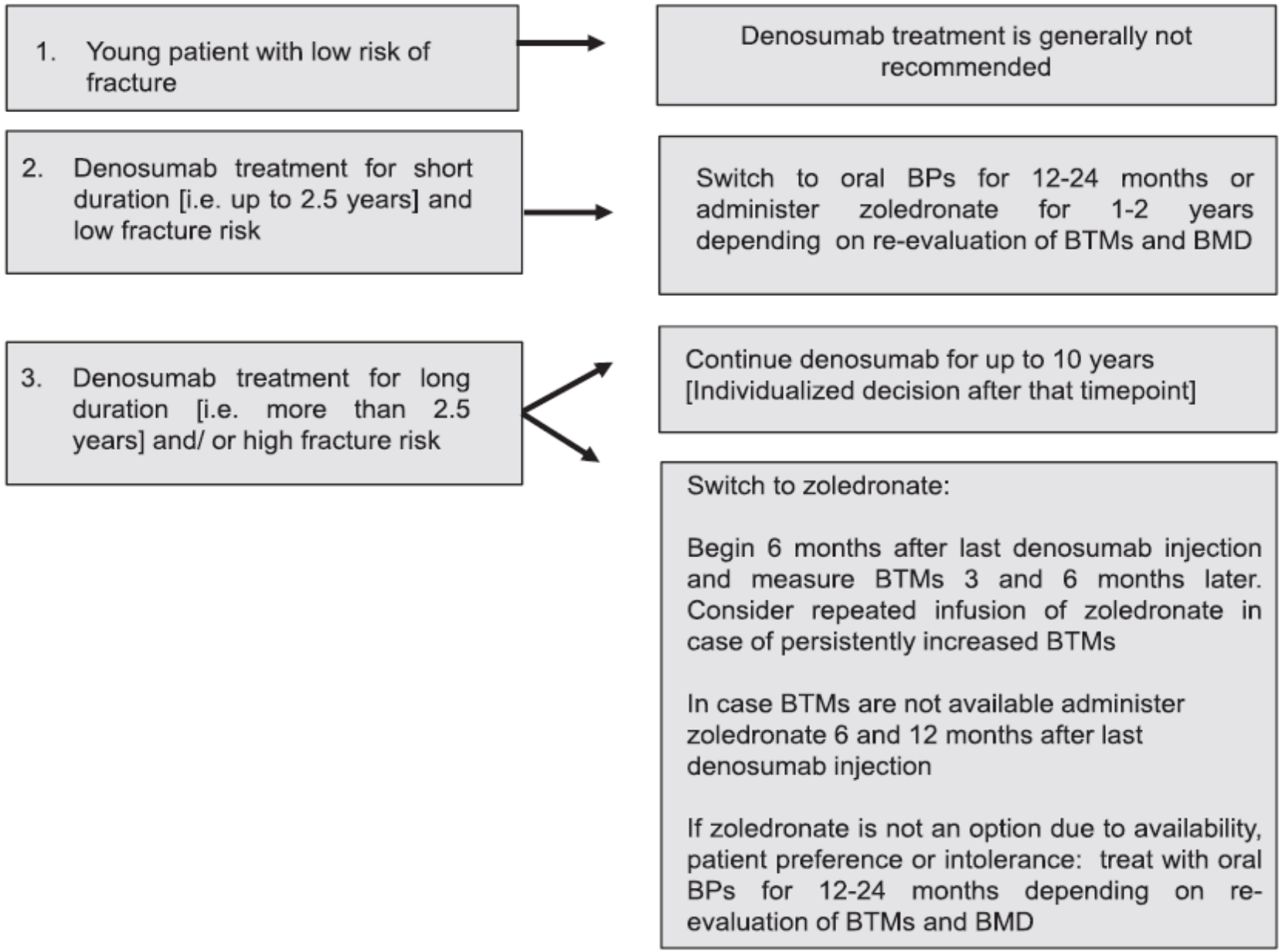
- The treat to target concept for osteoporosis suggests that treatment decisions should be made with the goal of achieving an acceptable level of fracture risk .
- In recent years, BMD has been propagated as a useful treatment target, and an ASBMR–National Osteoporosis Foundation working group on goal-directed treatment for osteoporosis has suggested a hip T score target of greater than –2.5, with a higher level of confidence for a T score target of greater than –2.0 , although even higher thresholds, that is, a T score target of greater than –1.5, have been proposed
- Thus, in patients considered to be at high risk for fracture, the efficacy and safety profile of denosumab allows for long-term treatment, with existing data supporting a duration of up to 10 years.

- Elene tsourdi et al, Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement by ECTS, The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 1, 264–281

SO WHAT DO WE DO?

- Given all the available information and recent recommendations, a rational approach would be the initiation of either oral BPs or zoledronate following Dmab discontinuation.
- As oral BPs might not adequately consolidate the BMD gains, the measurement of BTM is suggested after 3 months in order to monitor the efficacy and adherence through a level below the mean of healthy premenopausal women (CTX < 280 ng/L, P1NP < 35 g/L).
- BTM measurement could also be useful 6 months after zoledronate infusion, and a second infusion might be considered if a level above the mean of the age and gender-matched controls is found .
- In any case, treatment should last at least one year while the subsequent annual BMD could guide the decision for the continuation of BPs or not.

• Athanasios D. Anastasilakis etal, Denosumab Discontinuation and the Rebound Phenomenon: A Narrative Review, J. Clin. Med. 2021, 10, 152.



- Elene tsourdi et al, Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement by ECTS, The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 1, 264–281

Take home m essage

- Dmab is one of the most potent anti osteoporotic agents that reduce bone resorption and sustainably incresces bmd and redudes fx at all skletal sites.
- Unfortunately after discontinuation of the drug bmd loss accelerates due to rebound phenomen which may increase risk of fx especially vertebral fx.
- Many facror put paients at risk of fx after stopping the drug especially prevalent vertebral fx , duratioin of teratrment and time since stopping of the drug…
- Based on limited evidences teriparatide is not able to maintain bmd after dmab treatment and do not recommend as sequential therapy after dmab.
- Currently, It seems that alendonate and zoledronate are the most effective sequential therepies after dmab discontinuation and should be considered depending on the patients condition.