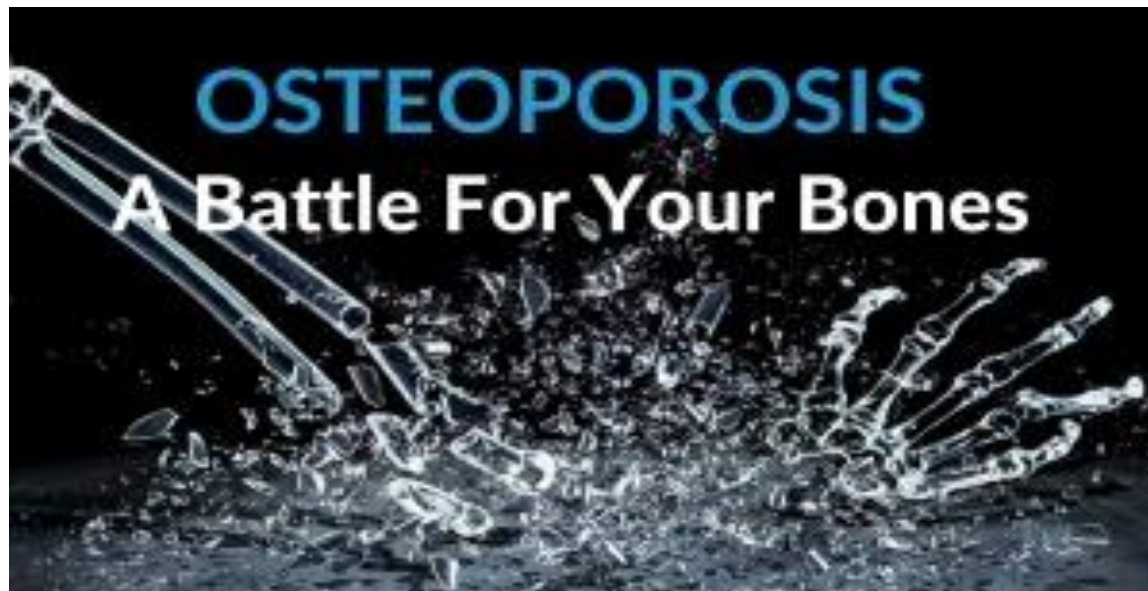




ΣΤΡΑΤΗΓΙΚΕΣ ΔΙΑΧΕΙΡΙΣΗΣ ΟΣΤΕΟΠΟΡΩΣΗΣ - ΕΝΑΡΞΗ ΑΓΩΓΗΣ

***ΔΕΔΟΜΕΝΑ ΚΑΙ ΠΡΟΒΛΗΜΑΤΙΣΜΟΙ ΓΙΑ ΤΗΝ ΑΡΧΙΚΗ
ΕΠΙΛΟΓΗ ΦΑΡΜΑΚΕΥΤΙΚΗΣ ΑΓΩΓΗΣ***

**ΚΑΤΕΡΙΝΑ ΜΑΤΣΟΥΚΑ
ΡΕΥΜΑΤΟΛΟΓΟΣ
ΟΚΤΩΒΡΙΟΣ 2020**

ΔΗΛΩΣΗ ΣΥΜΦΕΡΟΝΤΩΝ

Τιμητική αμοιβή από AMGEN HELLAS

ΠΕΡΙΣΤΑΤΙΚΟ ΠΡΟΣ ΣΥΖΗΤΗΣΗ

- Γυναίκα **ηλικίας 68 ετών** συνταξιούχος ΔΥ

- **Ατομικό αναμνηστικό**

Ηπια οροθετική **ΡΑ** από 10ετίας υπό αγωγή με μεθοτρεξάτη 12,5 mgr/εβδομάδα με χαμηλή ενεργότητα νόσου την τελευταία 5ετία. Παλαιότερα -μετά την αρχική διάγνωση - λήψη για 2 έτη πρεδνιζολόνης 5mgr ημερησίως

Από 4ετίας λήψη SSRIs . Υπέρταση υπό αγωγή .Λοιπό ιστορικό [-]

- Υψος = 161cm
- Βάρος = 57 kgr [πρόσφατη απώλεια βάρους 14 κιλά σε 12μήνες]
- Κάπνισμα [-]
- Αλκοόλ [-]
- Ιστορικό # μητέρας [-]
- Ηπια άσκηση - Ισορροπημένη διατροφή
- Εμμηναρχή σε ηλικία 13 ετών - Εμμηνόπαυση σε ηλικία 51 ετών

ΠΕΡΙΣΤΑΤΙΚΟ ΠΡΟΣ ΣΥΖΗΤΗΣΗ

- DEXA προ 10ετίας $T_{sc} \text{ ΟΜΣΣ} = -1,2$
 $T_{sc} \text{ ΑΡ ΙΣΧΙΟΥ} = -0,8$
ασβεστίου/D3

Λήψη

- DEXA προ 2ετίας $T_{sc} \text{ ΟΜΣΣ} = -2,3$
 $T_{sc} \text{ ΑΡ ΙΣΧΙΟΥ} = -2.1$
Οριακός FRAX - Λήψη ασβεστίου/D3

- DEXA 2020 $T_{sc} \text{ ΟΜΣΣ} = -2,7$
 $T_{sc} \text{ ΑΡ ΙΣΧΙΟΥ} = -2,6$

ΔΙΑΓΝΩΣΤΙΚΗ ΚΑΙ ΘΕΡΑΠΕΥΤΙΚΗ ΠΡΟΣΕΓΓΙΣΗ ???

ΣΥΓΚΕΝΤΡΩΣΗ ΣΤΟΙΧΕΙΩΝ ΠΡΟΣΦΑΤΟΥ ΕΛΕΓΧΟΥ

- **Ro ΟΜΣΣ PR/ ΘΜΣΣ PR** = χωρίς παθολογικά ευρήματα

- **ΕΡΓΑΣΤΗΡΙΑΚΟΣ ΕΛΕΓΧΟΣ**

Ht=39,5 Λ=5780 ΤΚΕ=15 cRP=0,36mgr/dL

Ca =9,6 P=3,8 Alb=4,1 23(OH)D3=28ng/ml

γgt=28 SGOT=20 SGPT=21 ALP=88 TSH=1,7

Κρεατινίνη=0,79 Σ=92 Η/Φ λευκ =χωρίς
παθολογικά ευρήματα

Χώρα: Ελλάδα

Όνομα/Κωδικός: Ε.Δ.

[Σχετικά με τους παράγοντες κινδύνου](#)

Ερωτηματολόγιο:

1. Ηλικία (μεταξύ 40 και 90 ετών) ή την ημερομηνία γέννησης

Ηλικία:

68

Ημερομηνία γέννησης:

E: 1952

M:

H:

2. Φύλο

☐ Άνδρας ☒ Γυναίκα

3. Βάρος (κιλά)

57

4. Ύψος (εκατοστά)

161

5. Προηγούμενο κάταγμα

☒ Όχι ☐ Ναι

6. Ιστορικό κατάγματος ισχίου σε γονέα

☒ Όχι ☐ Ναι

7. Κάπνισμα

☒ Όχι ☐ Ναι

8. Γλυκοκορτικοειδή

☒ Όχι ☐ Ναι

9. Ρευματοειδής αρθρίτιδα

☐ Όχι ☒ Ναι

10. Δευτεροπαθής οστεοπόρωση

☒ Όχι ☐ Ναι

11. 3 ή περισσότερες μονάδες αλκοόλ ημερησίως

☒ Όχι ☐ Ναι

12. BMD αυχένα μηριαίου (g/cm²)

GE-Lunar

0.678

T-score: -2.6

Καθαρισμός πεδίων

Υπολογισμός

ΔΜΣ: 22.0

Η δεκαετής πιθανότητα κατάγματος (%)



με BMD

Μείζον οστεοπορωτικό κάταγμα

15

Κάταγμα ισχίου

5.7

Εάν έχετε μια τιμή TBS, κάντε κλικ εδώ:

Ρυθμίστε με TBS



ΓΕΝΙΚΗ ΓΡΑΜΜΑΤΕΙΑ ΥΠΟΥΡΓΕΙΟΥ ΥΓΕΙΑΣ

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ΤΗ ΔΗΜΙΟΥΡΓΙΑ ΜΗΤΡΩΩΝ ΑΣΘΕΝΩΝ
(ΦΕΚ 505/ΥΟΔΔ/13.10.2017)

ΕΠΙΣΤΗΜΟΝΙΚΗ ΟΜΑΔΑ ΕΡΓΑΣΙΑΣ
ΟΣΤΕΟΠΟΡΩΣΗΣ

Κατόπιν αυτών, οι περιπτώσεις ασθενών με ανάγκη αγωγής είναι οι εξής:

1. Σπονδυλικό κάταγμα χαμηλής βίας
2. Κάταγμα ισχίου χαμηλής βίας
3. Περισσότερα από ένα έτερα κατάγματα χαμηλής βίας (πχ κάταγμα κερκίδας)
4. Μέτρηση οστικής πυκνότητας ισχίου (ολικό ισχίο ή αυχένιας μηριαίου) ή/και Ο.Μ.Σ.Σ. με T score $\leq -2,5$
5. Μέτρηση οστικής πυκνότητας με T score μεταξύ -1,0 και -2,5 (οστεοπενία) αλλά με 10-ετή καταγματικό κίνδυνο (FRAX) $\geq 10\%$ για μείζον οστεοπορωτικό κάταγμα ή/και $\geq 2,5\%$ για κάταγμα ισχίου, για άτομα ηλικίας 50-75 ετών.
6. Μέτρηση οστικής πυκνότητας με T score μεταξύ -1,0 και -2,5 (οστεοπενία) αλλά με 10-ετή καταγματικό κίνδυνο (FRAX) $\geq 15\%$ για μείζον οστεοπορωτικό κάταγμα ή/και $\geq 5\%$ για κάταγμα ισχίου, για άτομα ηλικίας άνω των 75 ετών.

Σε κάθε άλλη περίπτωση συνιστάται επανεκτίμηση σε χρονικό διάστημα όχι μικρότερο του ενός έτους, εκτός εάν στο μεσοδιάστημα προκύψει κάταγμα χαμηλής βίας, συννοσηρότητα ή άλλη φαρμακευτική αγωγή.

ΠΡΟΣΔΟΚΙΕΣ ΚΑΙ ΣΤΟΧΟΙ ΕΝΑΡΞΗ ΘΕΡΑΠΕΙΑΣ ΟΣΤΕΟΠΟΡΩΣΗΣ

Βέλτιστη αποτελεσματικότητα στη μείωση καταγμάτων

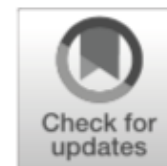
Ασφάλεια και ανοχή

Μη κατωτερότητα και ει δυνατόν ανωτερότητα έναντι άλλων θεραπειών

Ικανοποιητική συμμόρφωση ασθενούς - Εύκολη χρήση

Αναλογία προσδοκιών όσον αφορά τιμή φαρμάκου-αποτελεσματικότητας [cost effectiveness evidence]

ORIGINAL ARTICLE



The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece

Polyzois Makras^{1,2} • Athanasios D. Anastasilakis^{2,3} • George Antypas^{2,4} • Efstathios Chronopoulos^{2,5} • Evangelia G. Kaskani^{2,6} • Aikaterini Matsouka² • Dimos K. Patrikos^{2,7} • Konstantinos D. Stathopoulos^{2,8} • Symeon Tournis^{2,9} • George Trovas⁹ • Christos Kosmidis^{2,10}

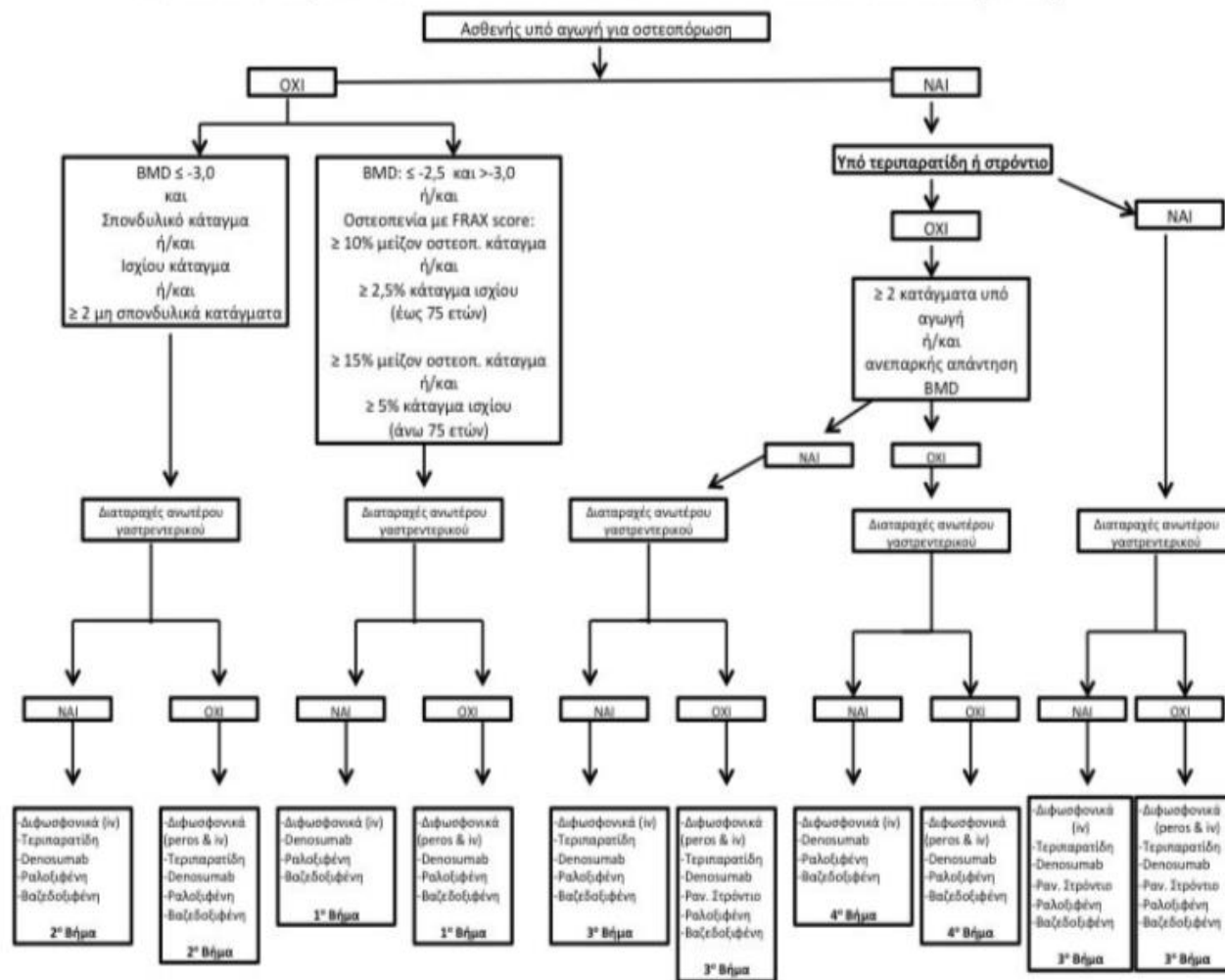


ΓΕΝΙΚΗ ΓΡΑΜΜΑΤΕΙΑ ΥΠΟΥΡΓΕΙΟΥ ΥΓΕΙΑΣ

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ΟΣΤΕΟΠΩΡΩΣΗΣ

ΑΛΓΟΡΙΘΜΟΣ ΦΑΡΜΑΚΕΥΤΙΚΗΣ ΑΝΤΙΜΕΤΩΠΙΣΗΣ ΟΣΤΕΟΠΩΡΩΣΗΣ (2017)

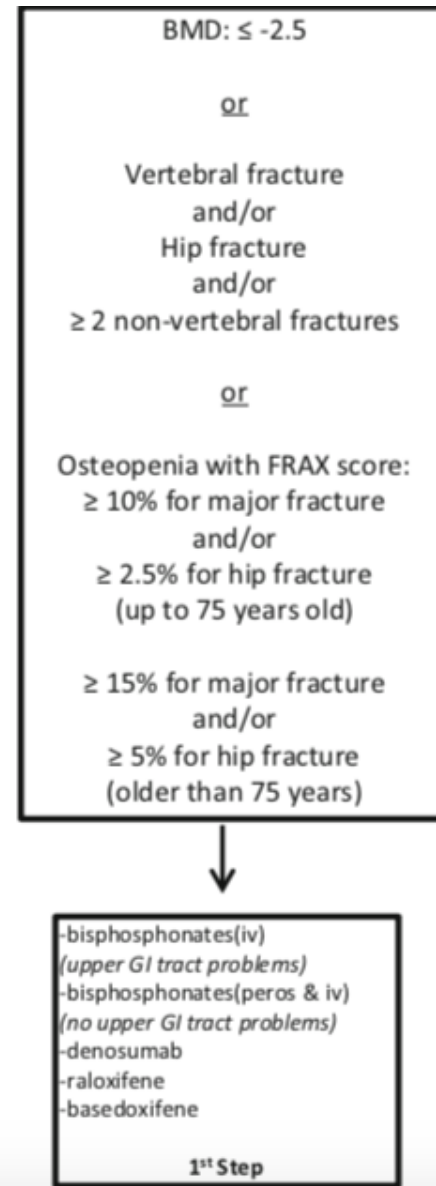




The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece

Polyzois Makras^{1,2} · Athanasios D. Anastasilakis^{2,3} · George Antypas^{2,4} · Efstathios Chronopoulos^{2,5} · Evangelia G. Kaskani^{2,6} · Aikaterini Matsouka² · Dimos K. Patrikos^{2,7} · Konstantinos D. Stathopoulos^{2,8} · Symeon Tournis^{2,9} · George Trovas⁹ · Christos Kosmidis^{2,10}

ΠΡΩΤΟ ΒΗΜΑ:
Διφωσφονικά (per os, IV),
Denosumab, SERM's





ΓΕΝΙΚΗ ΓΡΑΜΜΑΤΕΙΑ ΥΠΟΥΡΓΕΙΟΥ ΥΓΕΙΑΣ

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ΟΣΤΕΟΠΩΡΩΣΗΣ

ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΓΩΓΗ

1. Στις μετεμμηνοπαυσιακές γυναίκες έχουν διεξαχθεί πολλαπλές πολυκεντρικές μελέτες αλλά και μετα-αναλύσεις αναφορικά στην αντικαταγματική δράση διαφόρων φαρμακευτικών ουσιών. Οι ενδείξεις της αντικαταγματικής δράσης των φαρμακευτικών ουσιών που κυκλοφορούν στη Ελλάδα, παραθέτονται στον Πίνακα που ακολουθεί.

ΕΠΙΣΤΗΜΟΝΙΚΗ ΟΜΑΔΑ ΕΡΓΑΣΙΑΣ ΟΣΤΕΟΠΩΡΩΣΗΣ

12

Φαρμακευτική αγωγή	Αντικαταγματική δράση		
	Σπονδυλικά	Μη σπονδυλικά	Ισχίου
Αλενδρονάτη	+	+	+
Ρισεδρονάτη	+	+	+
Ιμπανδρονάτη	+	+*	
Ζολεδρονάτη	+	+	+
Denosumab	+	+	+
Ραλοξιφαίνη	+		
Βαζεδοξιφαίνη	+	+*	
Ρανελικό στρόντιο (αγωγή 2 ^{ης} γραμμής)	+	+	+*
Τεριπαρατίδη	+	+	

* Post hoc ανάλυση: (η ένδειξη αφορά ειδικές κατηγορίες ασθενών με συγκεκριμένη ηλικία, T-score ή προηγούμενο κάταγμα).

DENOSUMAB VS ΔΙΦΩΣΦΟΝΙΚΑ

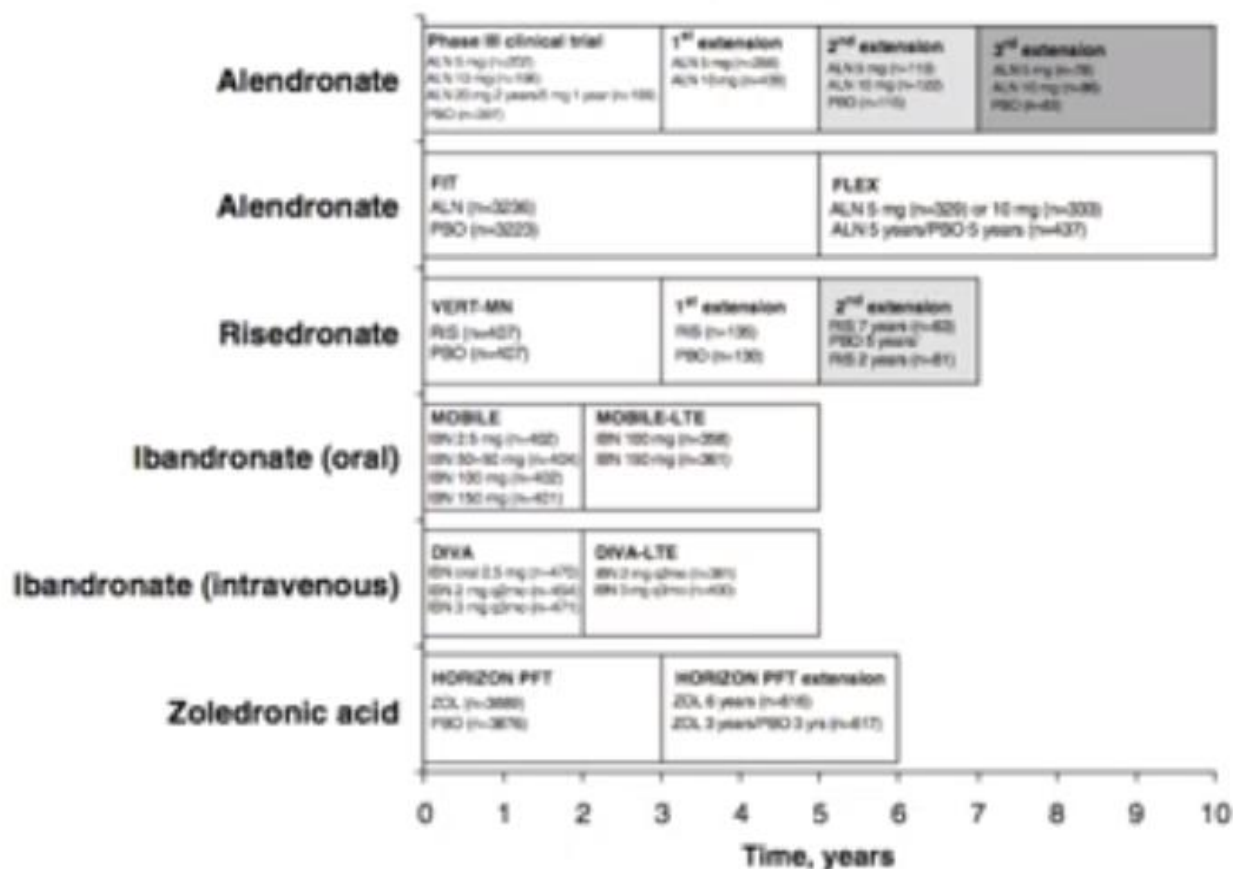
- Αποτελεσματικότητα -Αντικαταγματική δράση
- Δεδομένα μακροχρόνιας χορήγησης
- Ασφάλεια και ανοχή
- Συμμόρφωση – ικανοποίηση ασθενών

Δεδομένα μακροχρόνιας χορήγησης

Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: A systematic review

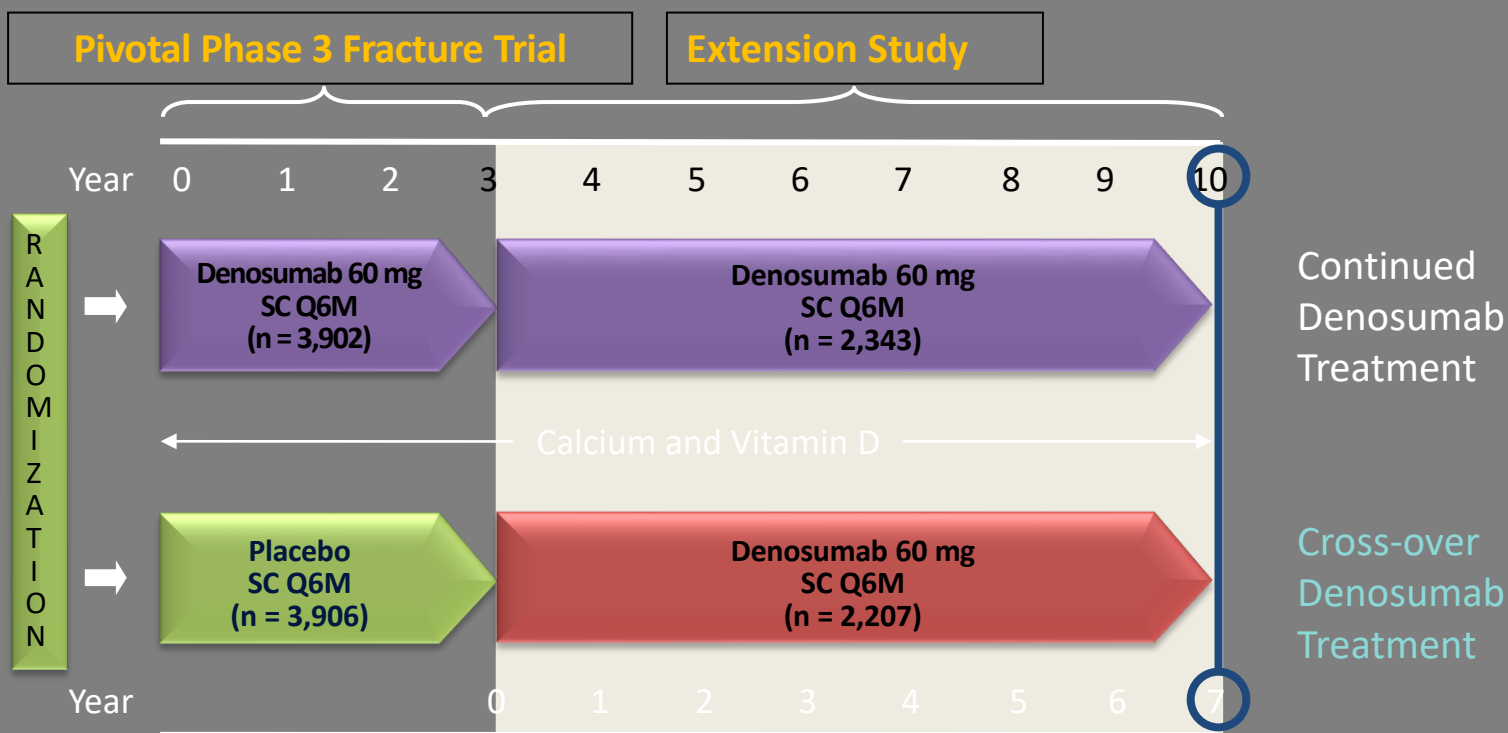
Erik F. Eriksen ^{a,*}, Adolfo Díez-Pérez ^b, Steven Boonen ^{c,1}

E.F. Eriksen et al. / Bone 58 (2014) 126–135



Study Design

Pivotal Phase 3 Study – Extension



- All patients who completed the pivotal phase 3 fracture trial (completed their 3-year visit, did not discontinue investigational product, and did not miss more than 1 dose) were eligible to participate.

SC = subcutaneous; Q6M = once every 6 months

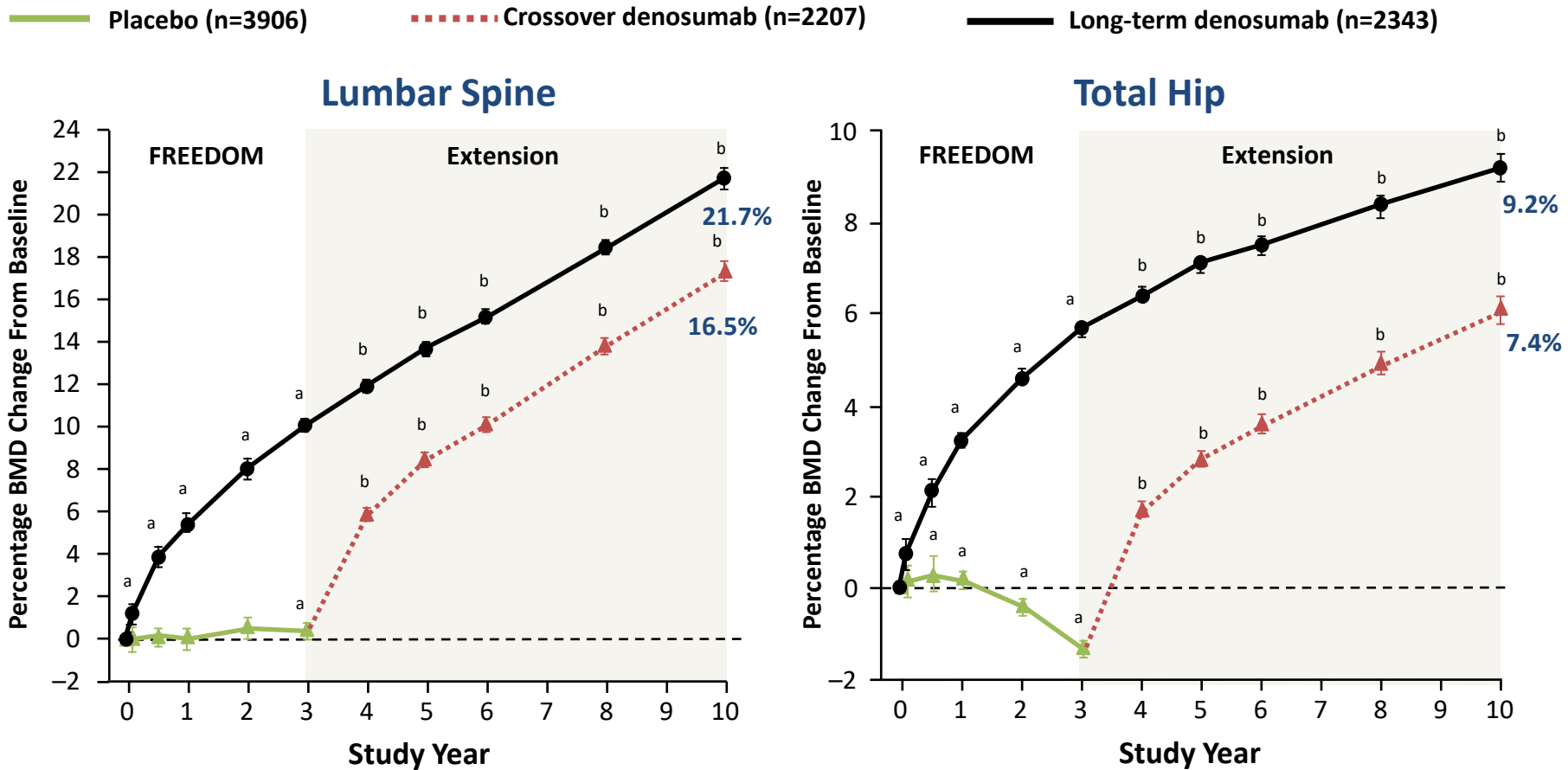
Adapted from: Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017; 5: 513-523.

2.

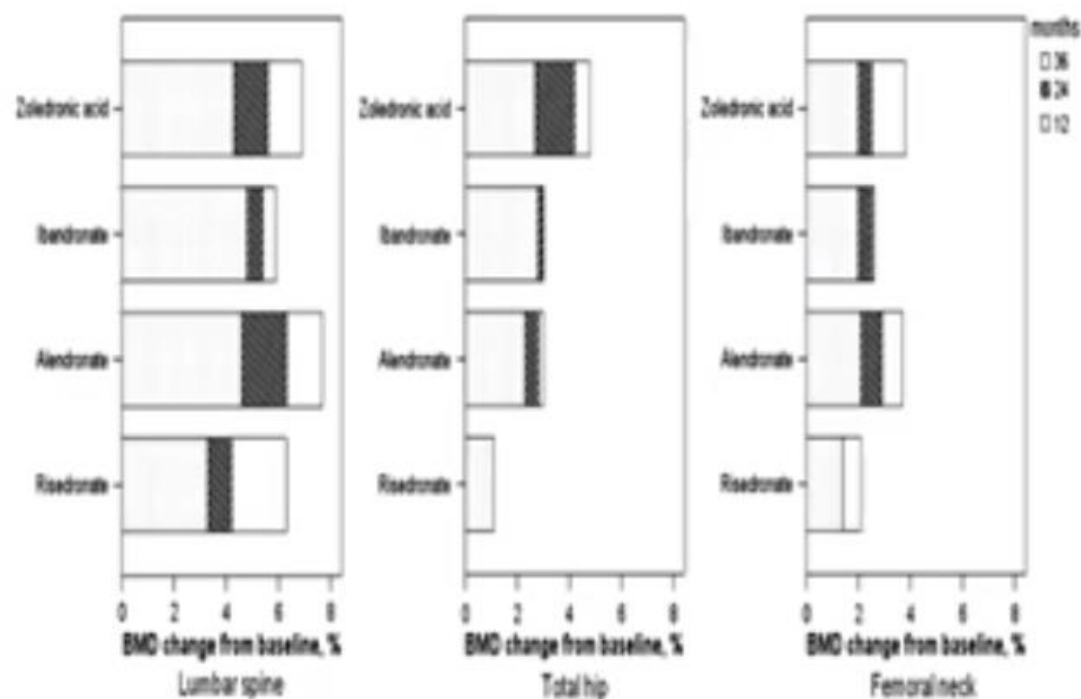
**Αποτελεσματικότητα
Αντικαταγμματική δράση**

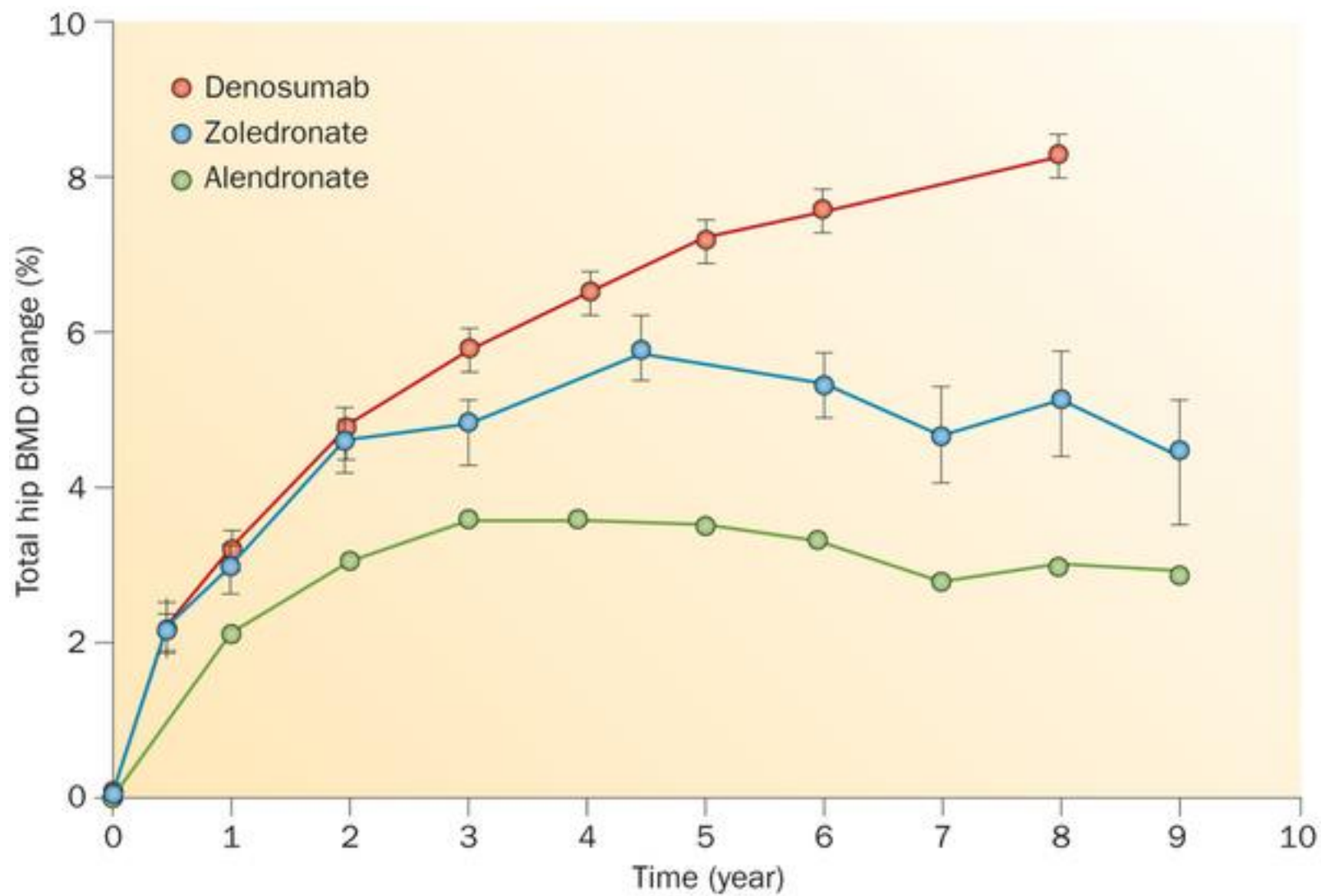
Change in Lumbar Spine and Total Hip BMD Through 10 Years With Denosumab Treatment

FREEDOM and the Open-Label FREEDOM Extension

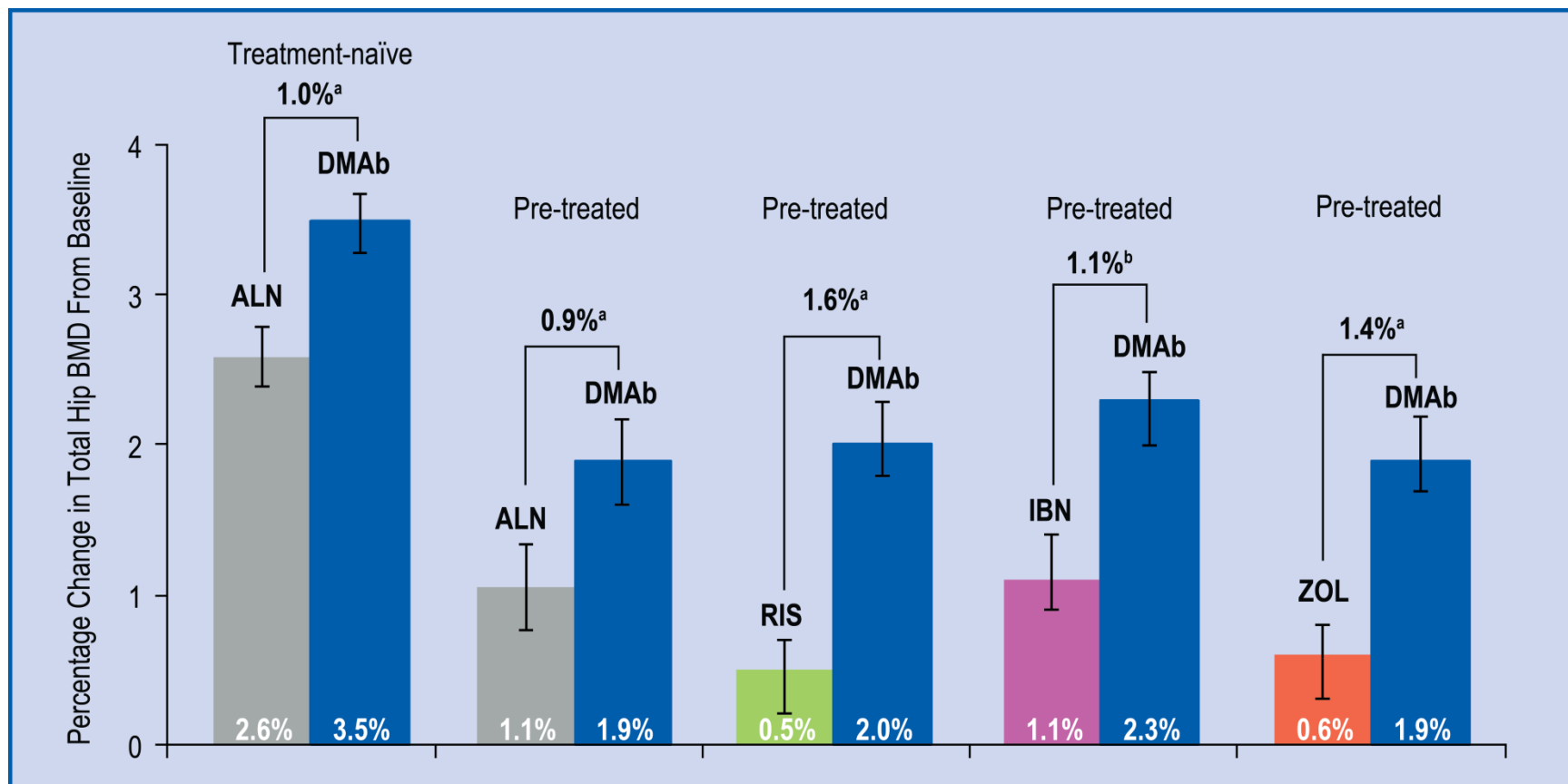


^ap<0.05 compared with FREEDOM baseline. p<0.05 compared with FREEDOM and extension baselines.

Bisphosphonates for postmenopausal osteoporosis [Ⓢ]Richard Eastell ^{1,2*}, Jennifer S. Walsh ¹, Nelson B. Watts ³, Ethel Sirin ¹



Results: Figure 5. Percentage Change from Baseline in Total Hip BMD at Month 12 in Head-to-Head Studies of DMAb vs Bisphosphonates^{1-3,5}



Data are least-squares means and 95% confidence intervals. ^a $p < 0.0001$; ^b $p < 0.001$.

ALN, alendronate; BMD, bone mineral density; DMAb, denosumab; IBN, ibandronate; RIS, risedronate; ZOL, zoledronic acid.

Μεγαλύτερη αύξηση της οστικής πυκνότητας σε σχέση με τα διφωσφονικά



Journal of Bone and Mineral Research, Vol. 34, No. 6, 2019, p. 1033–1040

Relationship Between Bone Mineral Density T-Score and Nonvertebral Fracture Risk Over 10 Years of Denosumab Treatment

S Ferrari,^{1*} C Libanati,² Celia Jow Fang Lin,³ JP Brown,⁴ F Cosman,⁵ E Czerwiński,⁶ LH de Gregório,⁷ J Malouf-Sierra,⁸ J-Y Reginster,⁹ A Wang,³ RB Wagman,³ and EM Lewiecki¹⁰

ΒΕΛΤΙΣΤΗ ΑΝΑΜΕΝΟΜΕΝΗ
ΕΛΑΤΤΩΣΗ ΚΙΝΔΥΝΟΥ ΜΗ
ΣΠΟΝΔΥΛΙΚΟΥ ΚΑΤΑΓΜΑΤΟΣ
ΜΕ ΥΨΗΛΟΤΕΡΗ ΤΙΜΗ T-score
ΟΛΙΚΟΥ ΙΣΧΙΟΥ (ΚΑΤΩΦΛΙ:-1,5)

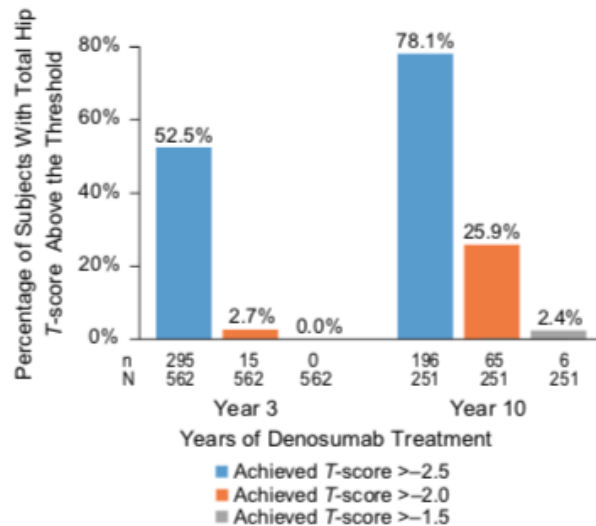
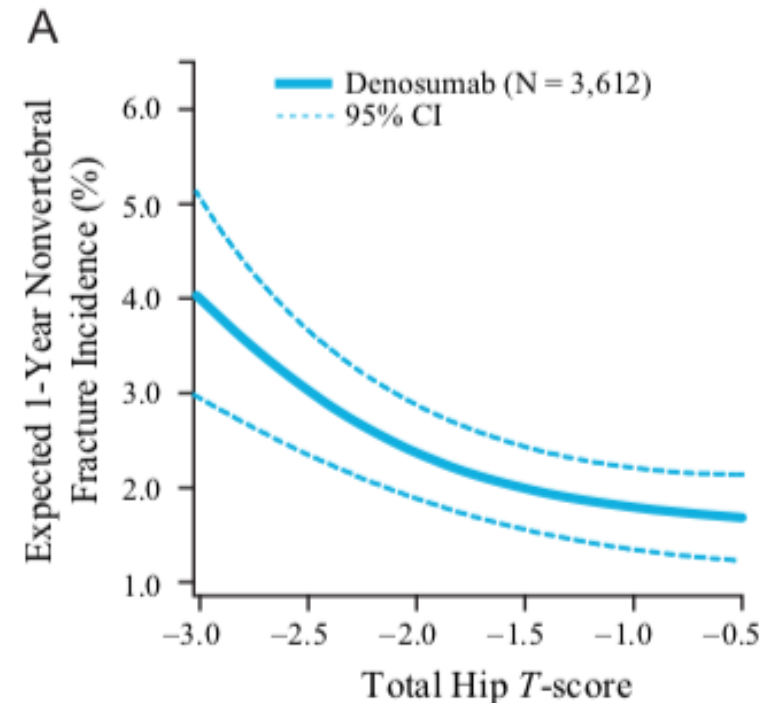


Fig. 3. Percentage of subjects with a total hip T-score ≤ -2.5 at FREEDOM baseline attaining T-scores of > -2.5 , > -2.0 , and > -1.5 after 3 and 10 years of denosumab treatment. N = number of subjects randomized to denosumab in the FREEDOM study and enrolled in the Extension who had a T-score of ≤ -2.5 at the total hip at FREEDOM baseline and an observed T-score at the time point of interest; n = number of subjects with a total hip T-score above threshold; BL = baseline



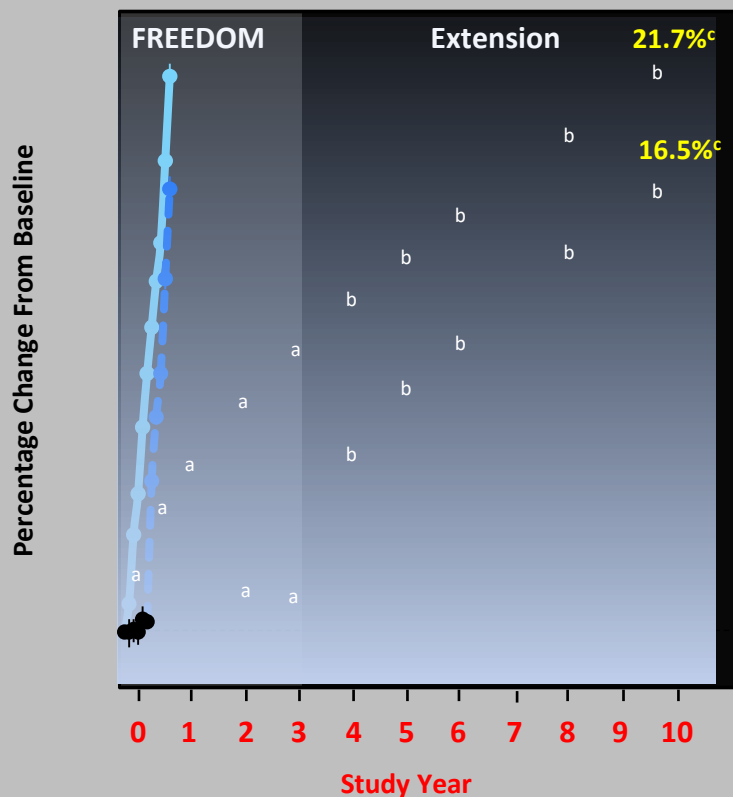
Η ΜΑΚΡΟΧΡΟΝΙΑ ΘΕΡΑΠΕΙΑ ΜΕ DENOSUMAB - 10 ΕΤΗ- ΑΥΞΑΝΕΙ ΤΗΝ ΒΜΔ ΤΗΣ ΣΣ ΚΑΙ ΜΕΙΩΝΕΙ ΤΗ ΣΥΧΝΟΤΗΤΑ ΕΜΦΑΝΙΣΗΣ ΝΕΩΝ ΣΠΟΝΔΥΛΙΚΩΝ ΚΑΤΑΓΜΑΤΩΝ

■ Placebo

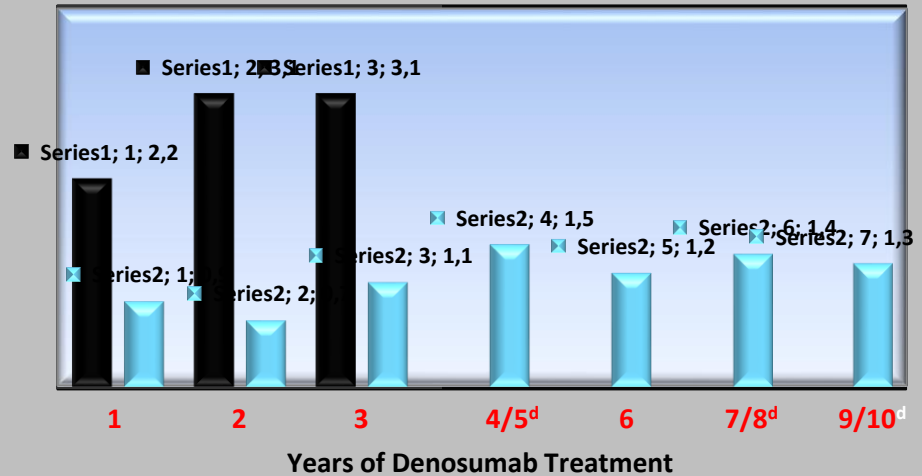
■ Long-term Denosumab

■ Cross-over Denosumab

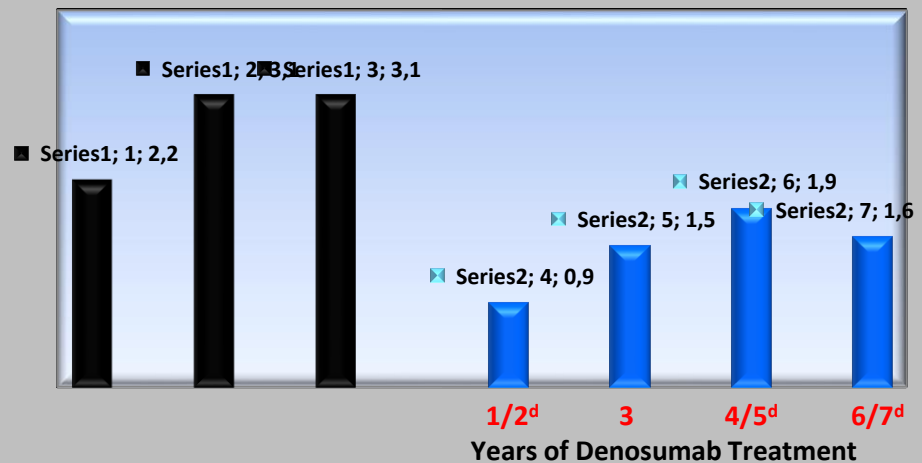
Lumbar Spine



Yearly Incidence of New Vertebral Fractures (%)



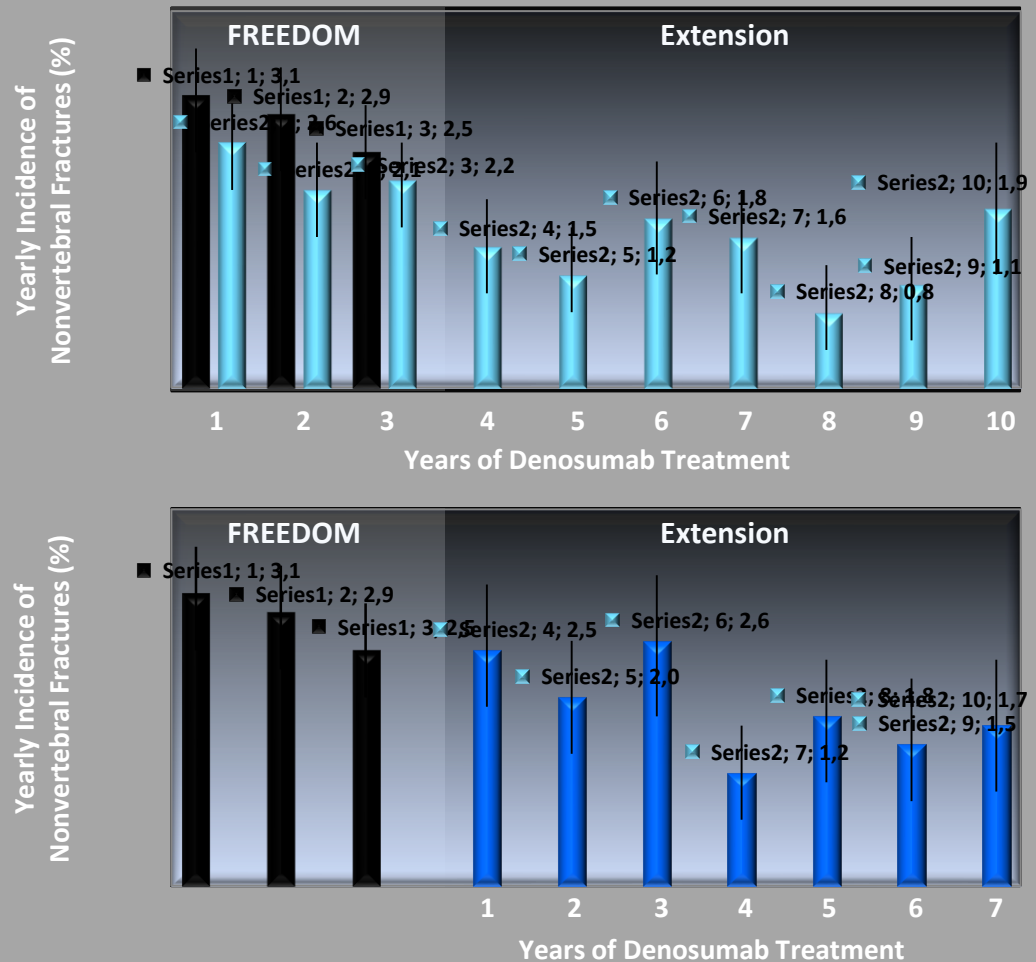
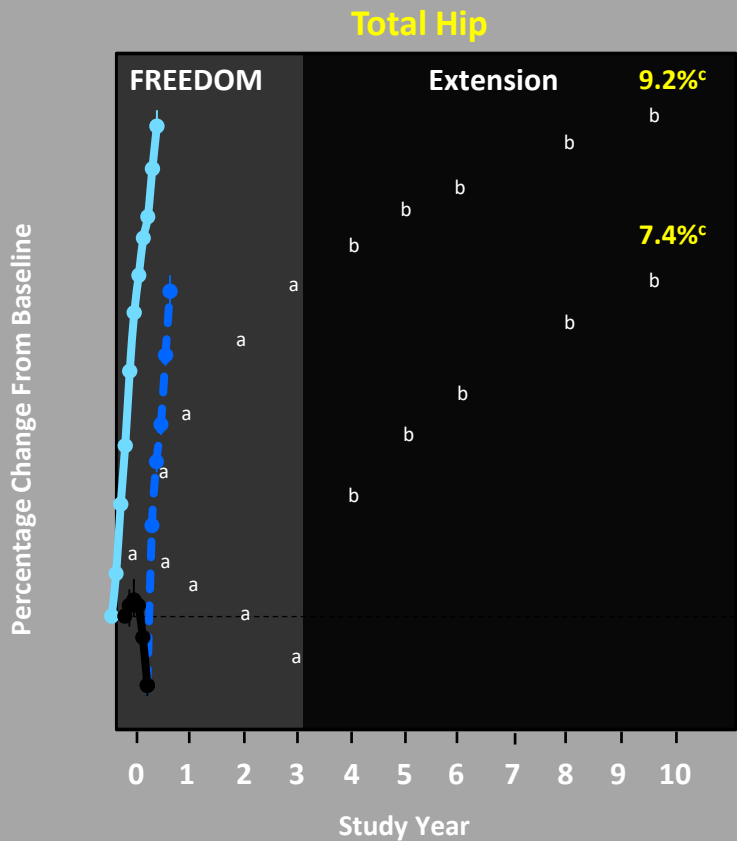
Yearly Incidence of New Vertebral Fractures (%)



BMD data are LS means and 95% confidence intervals. ^a $P < 0.05$ vs FREEDOM baseline. ^b $P < 0.05$ vs FREEDOM and Extension baselines. ^cPercentage change while on denosumab treatment. ^dAnnualized incidence: (2-year incidence) / 2. Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension).

Η ΜΑΚΡΟΧΡΟΝΙΑ ΘΕΡΑΠΕΙΑ ΜΕ DENOSUMAB - 10 ΕΤΗ -ΑΥΞΑΝΕΙ ΣΥΝΕΧΩΣ ΚΑΙ ΧΩΡΙΣ ΠΛΑΤΕΑΥ ΤΗΝ BMD ΤΟΥ ΟΛΙΚΟΥ ΙΣΧΙΟΥ ΚΑΙ ΟΔΗΓΕΙ ΣΕ ΜΕΙΩΜΕΝΗ ΣΥΧΝΟΤΗΤΑ ΜΗ ΣΠΟΝΔΥΛΙΚΩΝ ΚΑΤΑΓΜΑΤΩΝ

■ Placebo
▣ Long-term Denosumab
▣ Cross-over Denosumab



BMD data are LS means and 95% confidence intervals. ^a $P < 0.05$ vs FREEDOM baseline. ^b $P < 0.05$ vs FREEDOM and Extension baselines. ^cPercentage change while on denosumab treatment. Percentages for nonvertebral fractures are Kaplan-Meier estimates.

10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension

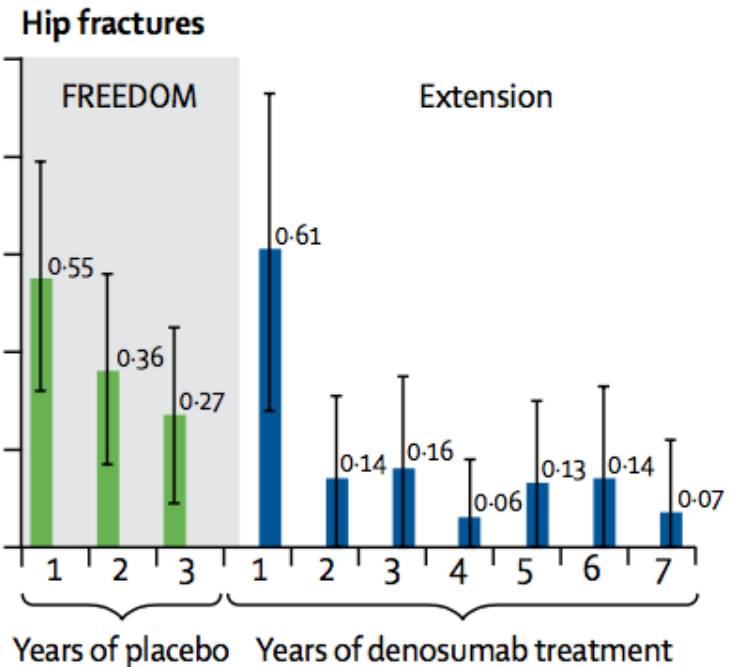
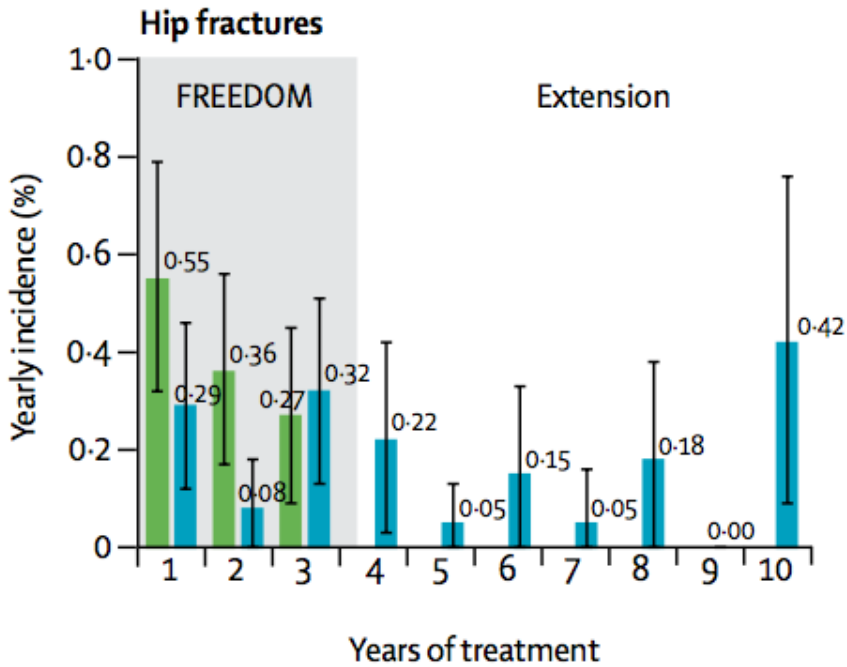


Henry G Bone, Rachel B Wagman, Maria L Brandi, Jacques P Brown, Roland Chapurlat, Steven R Cummings, Edward Czerwiński, Astrid Fahrleitner-Pammer, David L Kendler, Kurt Lippuner, Jean-Yves Reginster, Christian Roux, Jorge Malouf, Michelle N Bradley, Nadia S Daizadeh, Andrea Wang, Paula Dakin, Nicola Pannacciulli, David W Dempster, Socrates Papapoulos

Summary

Background Long-term safety and efficacy of osteoporosis treatment are important because of the chronic nature of the disease. We aimed to assess the long-term safety and efficacy of denosumab, which is widely used for the treatment of postmenopausal women with osteoporosis.

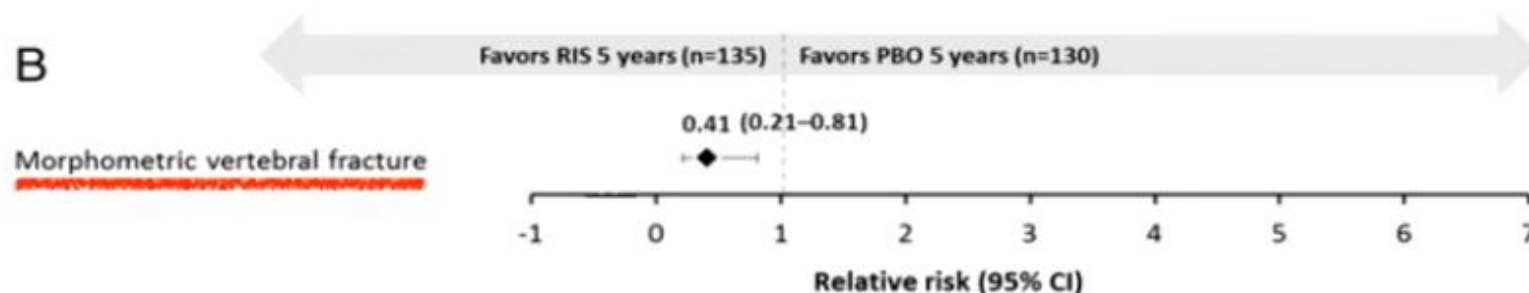
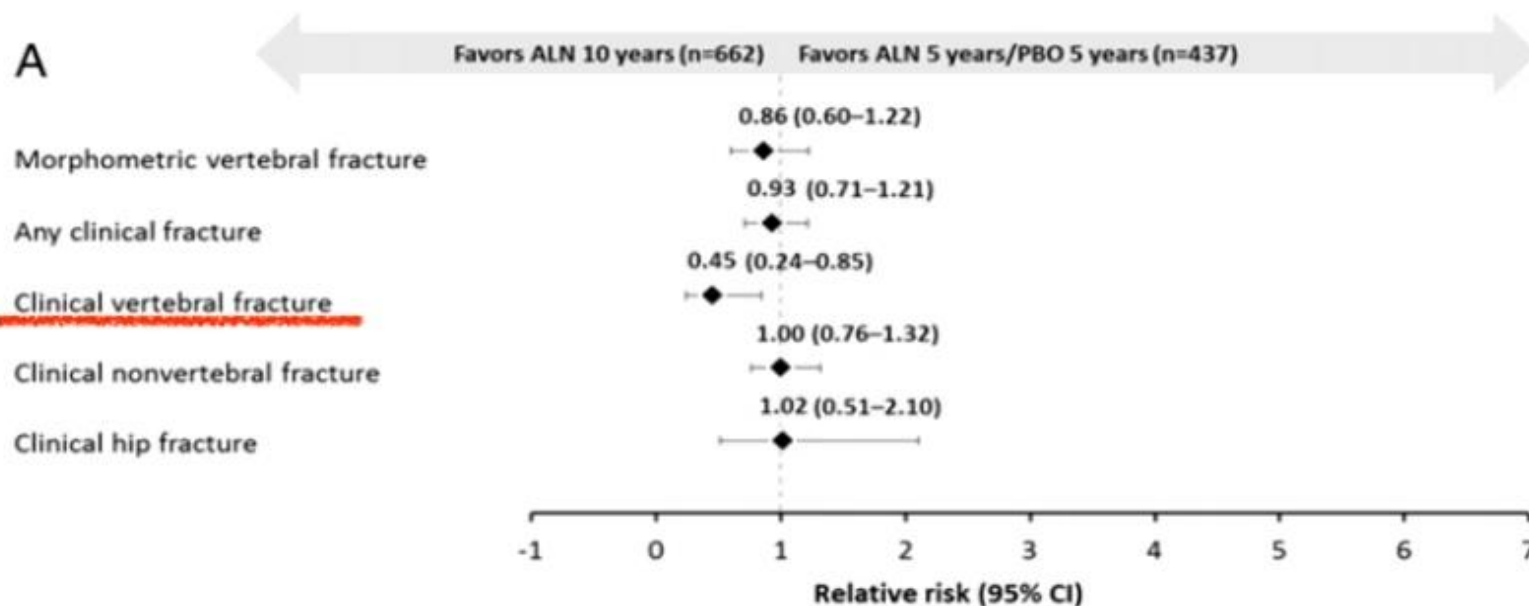
Lancet Diabetes Endocrinol 2017
Published Online
May 22, 2017



Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: A systematic review

Erik F. Eriksen ^{a,*}, Adolfo Díez-Pérez ^b, Steven Boonen ^{c,1}

E.F. Eriksen et al. / Bone 58 (2014) 126–135



Effects of Long-Term Denosumab on Bone Histomorphometry and Mineralization in Women With Postmenopausal Osteoporosis

David W. Dempster,^{1,2} Jacques P. Brown,³ Astrid Fahrleitner-Pammer,⁴
David Kendler,⁵ Sebastien Rizzo,⁶ Ivo Valter,⁷ Rachel B. Wagman,⁸ Xiang Yin,⁸
Susan V. Yue,⁸ and Georges Boivin⁶

J Clin Endocrinol Metab, July 2018, 103(7):2498–2509

Table 1. Bone Histology and Histopathology

	FREEDOM		Extension	
	Placebo Year 2 and/or 3	Denosumab Year 2 and/or 3	Denosumab Year 5	Denosumab Year 10
	N = 45 ^a	N = 47 ^a	N = 28 ^b	N = 22 ^b
Evaluable biopsies ^c	62	53	28	22
Normal lamellar bone, n (%)	62 (100)	53 (100)	28 (100)	22 (100)
Normal mineralization, n (%)	62 (100)	53 (100)	28 (100)	22 (100)
Present osteoid, n (%)	62 (100)	48 (91)	23 (82)	18 (82)
No visible osteoid, n (%)	0 (0)	5 (9.4)	5 (17.9)	4 (18.2)
Osteomalacia, n	0	0	0	0
Marrow fibrosis, n	0	0	0	0
Woven bone, n	0	0	0	0

^aNumber of subjects who enrolled in the FREEDOM bone biopsy substudy, received ≥ 1 dose of investigational product during FREEDOM, and had an evaluable biopsy at year 2 or year 3.

^bNumber of subjects who enrolled in the extension bone biopsy substudy, received ≥ 1 dose of investigational product during the extension, and had an evaluable biopsy at the time point(s) of interest.

^cNumber of evaluable biopsies, which serves as the denominator for percentage values in parentheses; some subjects had ≥ 1 evaluable biopsy during the FREEDOM trial.

DENOSUMAB

**Πολύ καλά δεδομένα αποτελεσματικότητας στη μείωση
των καταγμάτων**



3. Ασφάλεια και ανοχή



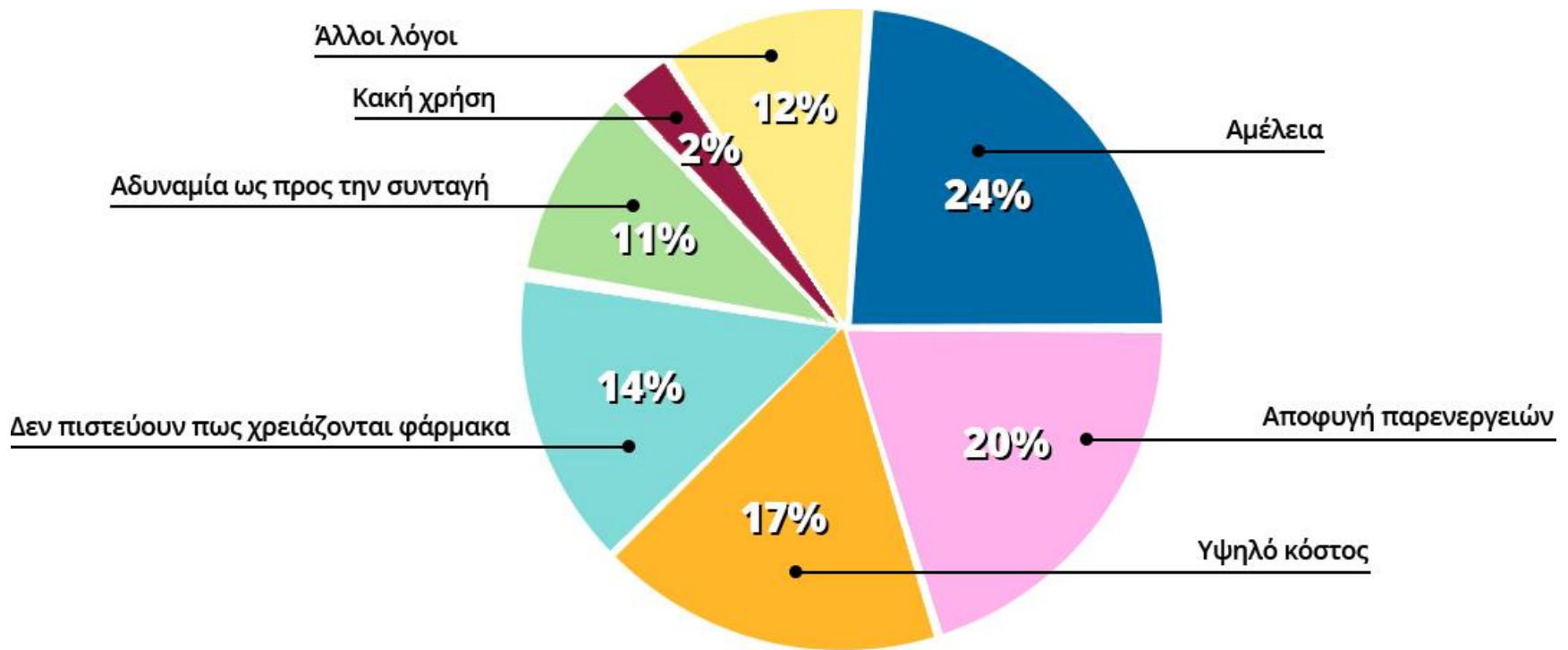
Yearly Exposure-adjusted Participant Incidence of Adverse Events per 100 Participant-years of Follow-up

FREEDOM and the Open-Label FREEDOM Extension

Years of treatment	Placebo				Long-term and crossover denosumab groups combined									
	1	2	3		1	2	3	4	5	6	7	8	9	10
N =	3,883	3,687	3,454		6085	5787	5452	4099	3890	3582	3261	1743	1585	1451
All adverse events	189.5	156.3	132.8		165.3	137.8	124.6	129.9	110.9	110.0	108.4	107.6	109.5	95.9
Infections	38.6	33.9	31.7		35.1	30.3	29.5	29.1	26.0	27.2	26.5	27.0	27.0	23.0
Malignancies	1.8	1.6	1.5		1.9	1.5	2.2	2.3	2.4	2.2	2.7	1.7	2.6	1.6
Eczema	0.8	0.5	0.6		1.4	1.1	1.0	1.1	1.2	0.9	0.7	0.8	0.9	1.3
Hypocalcemia	<0.1	0	<0.1		<0.1	<0.1	0	<0.1	0.1	0	<0.1	<0.1	0	0.1
Pancreatitis	<0.1	<0.1	0		<0.1	<0.1	<0.1	0	<0.1	0.1	<0.1	0.1	<0.1	0
Serious adverse events	11.7	11.9	10.8		12.0	11.5	12.3	11.5	12.9	12.6	14.4	11.5	13.1	12.3
Infections	1.1	1.4	1.4		1.5	1.6	1.4	1.4	1.3	1.9	2.3	1.2	1.5	2.6
Cellulitis or erysipelas	0	0	<0.1		<0.1	<0.1	0.2	<0.1	<0.1	0.1	<0.1	0.2	<0.1	0.1
Atypical femoral fracture	0	0	0		0	0	<0.1	0	0	0	<0.1	0	0	0
Osteonecrosis of the jaw	0	0	0		0	<0.1	0	<0.1	0	0.2	<0.1	0	<0.1	<0.1
Fatal adverse events	0.8	0.8	1.0		0.7	0.6	0.7	0.5	0.8	0.9	1.5	0.7	1.0	0.9

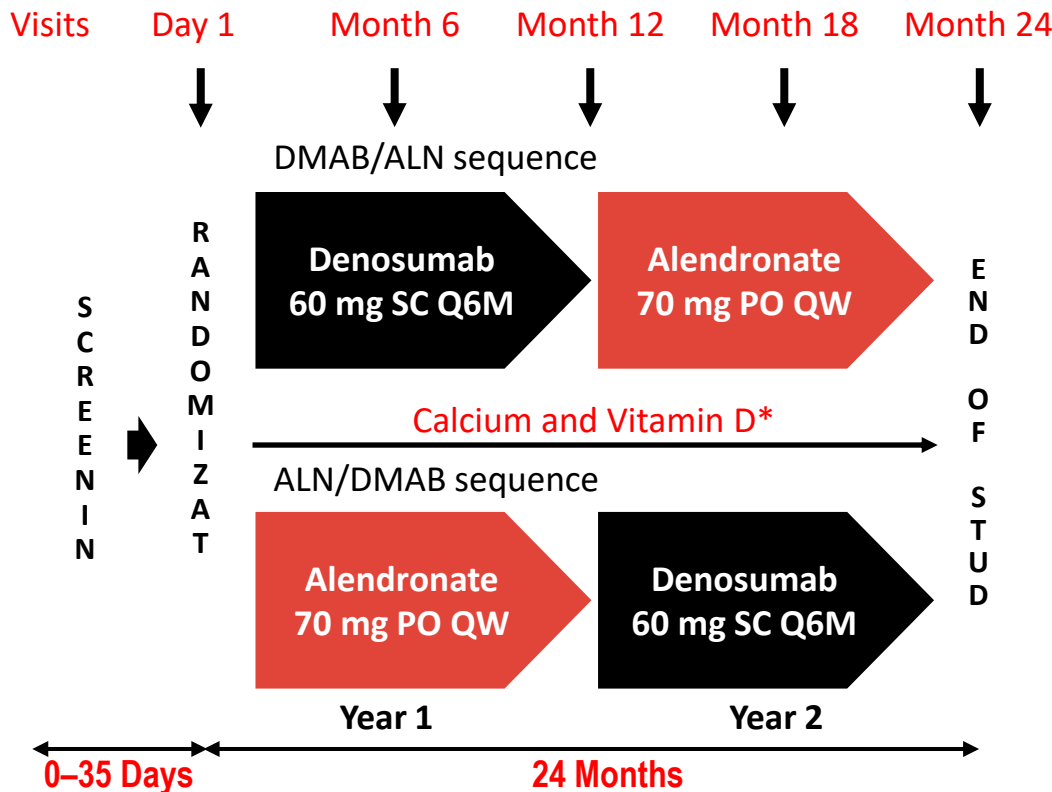
Analyses were based on the original randomized treatments in FREEDOM. All adverse and serious adverse events were coded using MedDRA v13.0. N = number of women who received ≥1 dose of investigational product in FREEDOM or the Extension. All subjects treated with denosumab during FREEDOM are included in the first 3 years. Years 1-7 of denosumab exposure include the first 7 years for the long-term group, and the 7 years of the active treatment extension for the cross-over group. Years 8-10 are the last 3 years for the long-term group only.

4. Συμμόρφωση – ικανοποίηση ασθενών



Study Design

DAPS Study



Study population

- Postmenopausal women ≥ 55 years
- BMD T-scores ≤ -2.0 to ≥ -4.0 at the spine, hip, or femoral neck

Objectives

- To evaluate adherence (including compliance and persistence)
- To also evaluate patient treatment beliefs, preference, satisfaction, and bother

Primary endpoint

- Adherence during the first year

■ Open-label, randomized, cross-over study

All subjects were instructed to take daily supplements of $\geq 1,000$ mg calcium and ≥ 400 IU vitamin D.

DMAB = denosumab; ALN = alendronate; SC = subcutaneous; Q6M = once every 6 months; PO = by mouth ; QW = once a week;

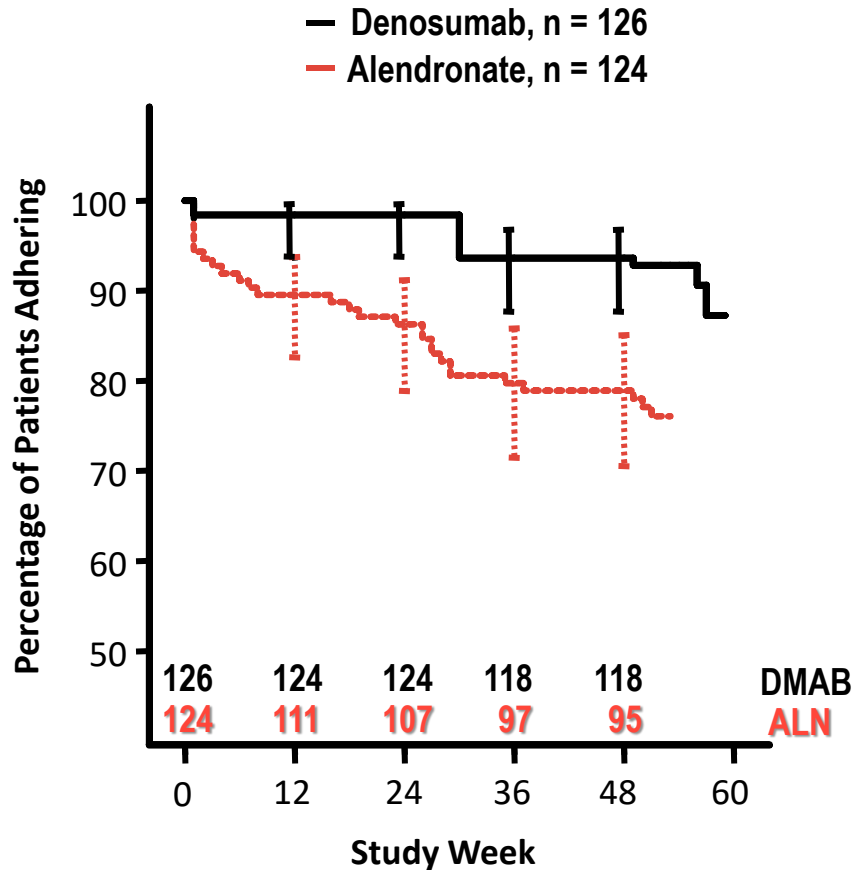
BMD = bone mineral density

Freemantle N, et al. *Osteoporos Int*. doi 10.1007/s00198-011-1780-1.

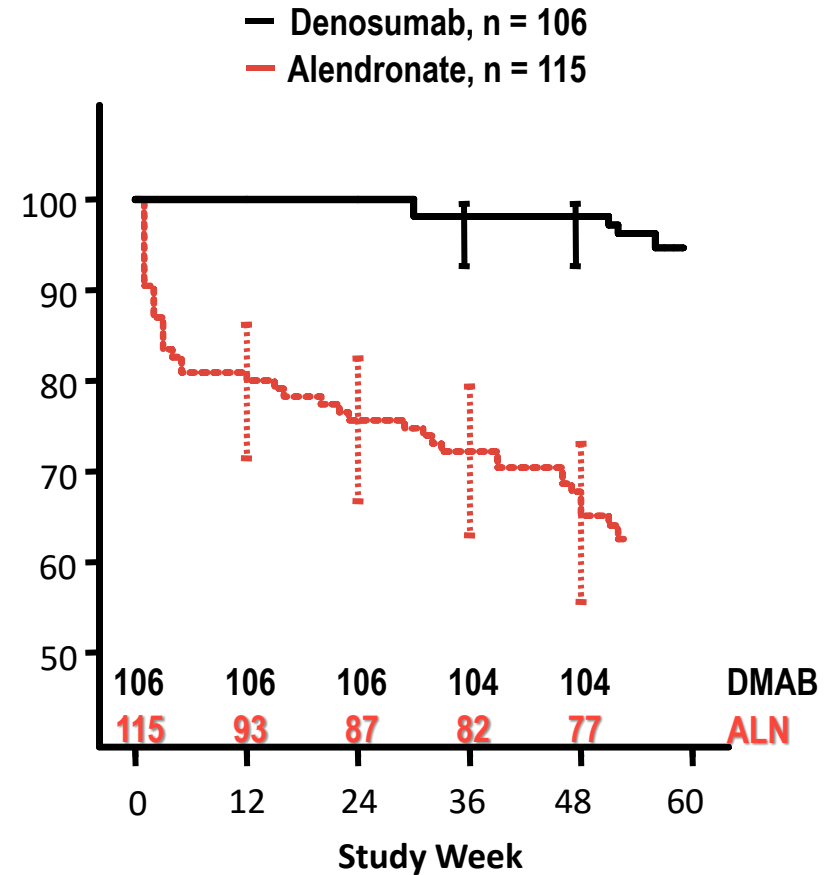
Time to Treatment Non-adherence

DAPS Study

Year 1



Year 2



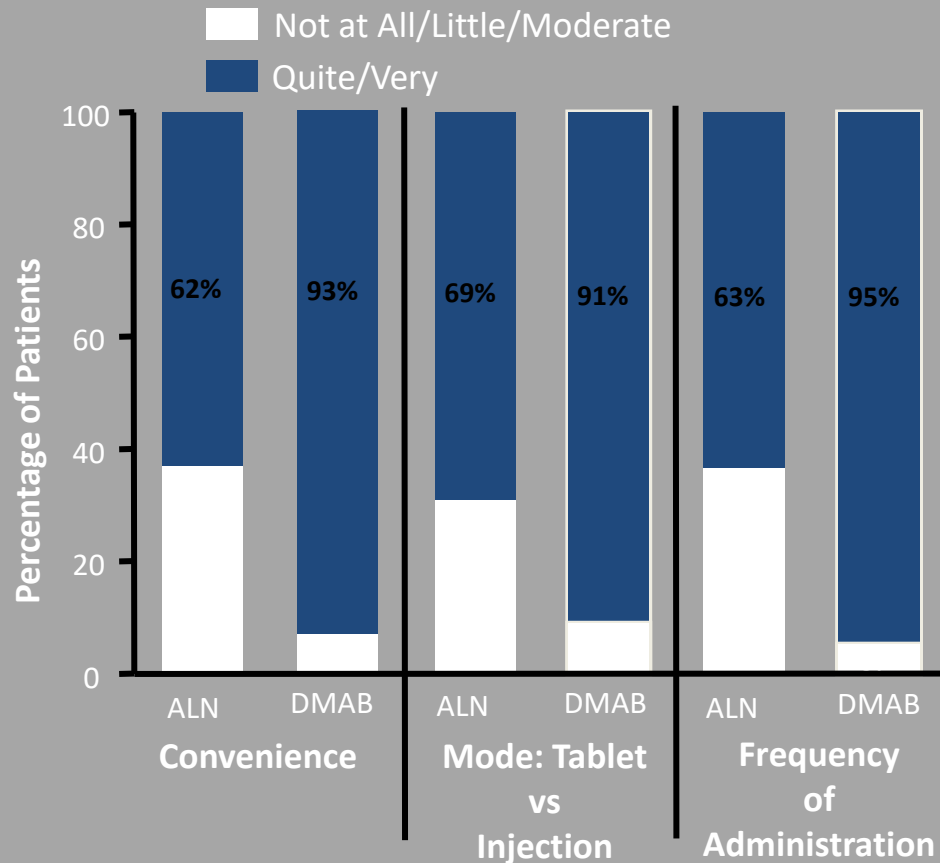
For each treatment group, time points with > 95% cumulated subjects were excluded.

Freemantle N, et al. *Osteoporos Int*. doi 10.1007/s00198-011-1780-1.

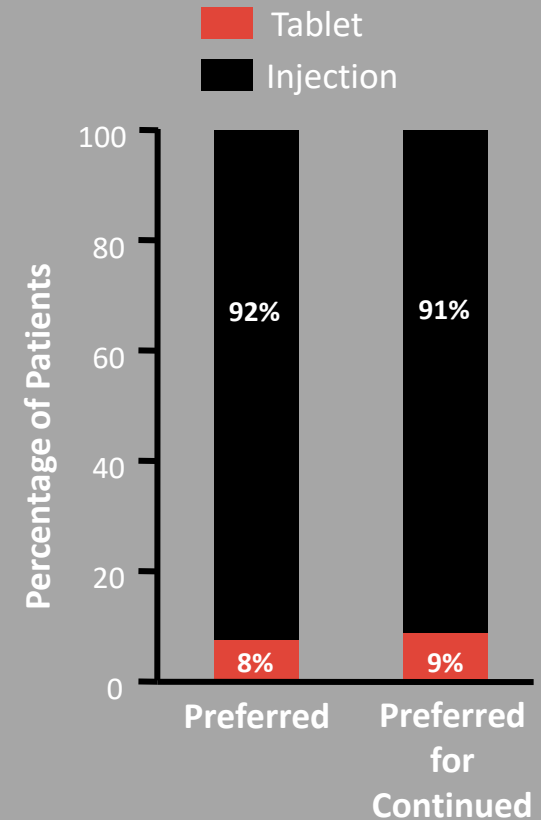
Patient-Reported Satisfaction and Preference

DAPS Study

Satisfaction



Preference



Preference was assessed only in Year 2.

Freemantle N, et al. *Osteoporos Int*. doi 10.1007/s00198-011-1780-1.

DENOSUMAB

Εύκολος τρόπος λήψης

Ικανοποίηση και συμμόρφωση ασθενών



ΚΑΙ Ο ΠΡΟΒΛΗΜΑΤΙΣΜΟΣ ΤΟΥ ΡΕΥΜΑΤΟΛΟΓΟΥ...

ΑΝ Η ΑΣΘΕΝΗΣ ΠΑΡΟΥΣΙΑΣΕΙ ΑΥΞΗΜΕΝΗ ΕΝΕΡΓΟΤΗΤΑ ΤΗΣ ΡΑ ΜΗ ΕΛΕΓΧΟΜΕΝΗ ΑΠΟ ΤΗ ΜΕΘΟΤΡΕΞΑΤΗ ΚΑΙ ΧΡΕΙΑΣΘΕΙ ΝΑ ΧΟΡΗΓΗΘΕΙ ΒΙΟΛΟΓΙΚΟΣ ΠΑΡΑΓΟΝΤΑΣ ΤΙ ΘΑ ΓΙΝΕΙ ΜΕ ΤΗ ΧΟΡΗΓΗΣΗ ΤΟΥ DENOSUMAB...???



Risk of Hospitalized Infection Among Rheumatoid Arthritis Patients Concurrently Treated With a Biologic Agent and Denosumab

Jeffrey R. Curtis, Fenglong Xie, Huifeng Yun, Kenneth G. Saag, Lang Chen,
and Elizabeth Delzell

Objective. Denosumab is a biologic agent used to treat osteoporosis. Its safety profile given concurrently with biologic drugs for rheumatoid arthritis (RA) has not been well studied. We evaluated hospitalized infections among patients treated with biologic agents for RA who initiated denosumab or zoledronic acid (ZA), a parenteral bisphosphonate without known associations with infection. We hypothesized that the rate of hospitalized infection with denosumab would be noninferior to ZA.

Methods. We identified RA patients enrolled in Medicare in 2006–2012 treated with biologic agents who initiated denosumab or ZA. Cox proportional hazards models compared the risk for hospitalized infection, comparing denosumab users to ZA users and adjusting for potentially confounding factors. A noninferiority margin was specified a priori to demonstrate that denosumab had no greater infection risk than ZA if the upper bound of the 95% confidence interval (95% CI) of the hazard ratio (HR) was <1.5 .

Results. Eligible RA patients receiving biologic agents initiated denosumab ($n = 1,354$) or ZA ($n = 4,460$). Characteristics of the denosumab users were as follows: mean $\pm$ SD age 73.0 ± 8.9 , 98.2% women, with a majority

receiving infliximab (35.7%) or abatacept (18.6%). Denosumab users had a higher prevalence of prior infections (11.5% hospitalized and 48.3% outpatient) and infection-related risk factors. The crude rate of hospitalized infections for denosumab (14.9/100 person-years [95% CI 12.2–18.1]) was comparable to that for ZA (13.9/100 person-years [95% CI 12.5–15.4]). After adjustment, the HR of hospitalized infection for denosumab users was noninferior to that for ZA users (HR 0.89 [95% CI 0.69–1.15]).

Conclusion. The rate of hospitalized infection among RA patients receiving denosumab concurrently with biologic agents for RA was not increased compared to those receiving zoledronate.

Denosumab is a novel parenteral agent used for the treatment of osteoporosis. Given at a dose of 60 mg subcutaneously every 6 months, it has been shown to increase bone mineral density and to prevent fractures in both women and men (1–4). It is a fully human monoclonal antibody that binds to RANKL and inhibits the ability of RANKL to bind to osteoclast RANK receptors (5). Both osteoclast formation and activation are thereby inhibited. Denosumab is a biologic agent and, unlike

Occurrence of Serious Infection in Patients with Rheumatoid Arthritis Treated with Biologics and Denosumab Observed in a Clinical Setting

Arthur N. Lau, Matthew Wong-Pack, Rod Rodjanapiches, George Ioannidis, Sally Wade, Leslie Spangler, Akhila Balasubramanian, Nicola Pannacciulli, Celia J.F. Lin, Patrick Roy-Gayos, William G. Bensen, Robert Bensen and Jonathan D. Adachi

J Rheumatol 2018;45:170-176
<http://www.jrheum.org/content/45/2/170>

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ABSTRACT. Objective. Previous studies combining biologic disease-modifying antirheumatic drugs (bDMARD) to treat rheumatoid arthritis (RA) have shown an increased risk of infection. However, the risk of infection with concurrent use of denosumab, a biologic agent for the treatment of osteoporosis, and a bDMARD remains unclear. Here, we evaluated the incidence of serious and opportunistic infections in patients treated concurrently with denosumab and a bDMARD and patients treated with a bDMARD alone.

Methods. A chart review of patients with RA from 2 Canadian rheumatology practices between July 1, 2010, and July 31, 2014, identified 2 groups of patients: those taking denosumab and a bDMARD concurrently (concurrent group) and those taking only a bDMARD (biologic-alone group). Patients were followed from the time of initiation of denosumab, or a matched index date for the biologic-alone group, to the end of the study or loss to followup. Instances of serious or opportunistic infections were recorded.

Results. A total of 308 patients ($n = 102$ for the concurrent group and $n = 206$ for the biologic-alone group) were evaluated. Within the concurrent group, 3 serious infection events occurred. Within the biologic-alone group, 4 serious infection events and 1 opportunistic infection event occurred. In both groups, all patients with serious or opportunistic infection recovered, and there were no instances of death during the study period.

Conclusion. This study demonstrated a low occurrence of serious and opportunistic infections in patients with RA taking bDMARD, including patients with concurrent denosumab use. (First Release November 15 2017; J Rheumatol 2018;45:170-6; doi:10.3899/jrheum.161270)

Table 3. Incidence of serious and opportunistic infections within the concurrent and biologic-alone groups.

Event Category Type	Concurrent, $n = 102$		Biologic Alone, $n = 206$	
	Event No./Total No. Patient-Yrs	Events per 100 Patient-Yrs (95% CI)	Event No./Total No. Patient-Yrs	Events per 100 Patient-Yrs (95% CI)
Serious infection requiring hospitalization				
Pneumonia	2/246	0.81 (0.10-2.94)	2/509	0.39 (0.05-1.42)
Bronchitis	—	—	1/509	0.20 (0.01-1.09)
Serious infection requiring ER visit and IV antibiotics				
Pneumonia	1/246	0.41 (0.01-2.26)	1/509	0.20 (0.01-1.09)
Opportunistic infection requiring hospitalization				
Pleural <i>Mycobacterium avium</i> complex	—	—	1/509	0.20 (0.01-1.09)
Serious infections	3/246	1.22 (0.25-3.56)	4/509	0.79 (0.21-2.01)
Serious or opportunistic infections (total)	3/246	1.22 (0.25-3.56)	5/509	0.98 (0.32-2.29)

ER: emergency room; IV: intravenous.

(25.0 per 100 patient-yrs) versus those treated with denosumab in addition to a bDMARD (15.7 per 100 patient-yrs)²³. However, the sample size in that study was also limited ($n = 20$ patients in the combination group; $n = 43$ in the denosumab-alone group), and no adjustment was made for potential confounding factors.

Access to detailed clinical information is a strength of our study, which provides a unique evaluation of a cohort of patients with RA in a real-world clinical practice setting. Previous studies have used large administrative databases or RA registries that provide large sample sizes, but often do not provide enough information regarding potential events of interest to confirm the occurrence and severity of such events. In our study, the patients' full medical records were used to gather details surrounding potential events of interest. Further, patients taking a bDMARD were routinely asked about recent infections, hospitalizations, and use of antibiotics at each clinic visit, which maximized the total number of events identified. In addition, having 2 designated adjudicators of outcomes allowed for consistency and reproducibility of the adjudication of outcomes of interest.

The results of our study should be interpreted in light of particular limitations. First, the relatively small sample size and short followup duration may have contributed to the low number of events observed in both groups. Because of our limited sample size, the study was underpowered to detect differences between groups, and the interpretation of

osteoporosis treatment in this group. However, our findings suggest that the incidence of serious infections was low in both groups. The clinics that contributed patient data to our study are highly vigilant regarding vaccination protocols and counseling patients to stop their bDMARD in response to impending signs of infection; therefore, the observed rates of infection may have been lower than those in other clinic populations with different practice standards. Further, as a result of such proactive patient monitoring, infections occurring in this patient population may have been less likely to require hospital admission or IV antibiotics in the emergency room, thereby lowering the number of serious infections observed. Finally, event rates may have been underreported, especially given the definition of a serious infection in our study. This is a general limitation to retrospective studies in general, and is also applicable to our study.

Results from our study suggest that few patients with RA concurrently treated with a bDMARD and denosumab had serious infections or opportunistic infections. The small number of infections observed is consistent with that reported in previous cohort studies and provides additional evidence of the safety of concurrent treatment with denosumab and a bDMARD. Future studies using larger cohorts could shed further light on this important question.

ACKNOWLEDGMENT

Lisa A. Humphries, PhD, of Amgen Inc. and Martha Mutomba (on behalf

ΣΑΣ ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ

