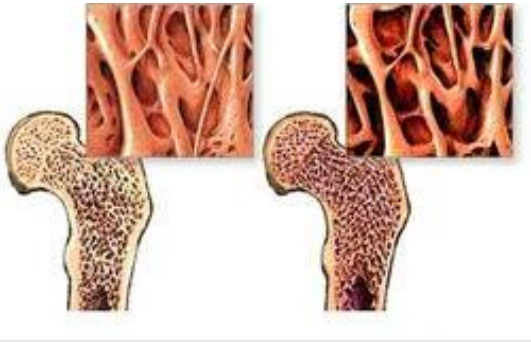


Επιδράσεις των βιολογικών παραγόντων στον οστικό μεταβολισμό

Σπύρος Ν Νίκας

Ρευματολόγος
Ιωάννινα

Βιολογικοί παράγοντες

- Etanercpet (FDA : 11/98)
- engineered proteins derived from human genes
- μονοκλωνικά αντισώματα στην θεραπεία διαφόρων νοσημάτων
  - εξειδικευμένο τρόπο δράσης
  - επίδραση στις αυτοάνοσες διαδικασίες
  - είναι έτσι σχεδιασμένα ώστε να αναστέλλουν ειδικά συστατικά του ανοσοποιητικού συστήματος , τα οποία διαδραματίζουν σημαντικό ρόλο στη ανάπτυξη φλεγμονής

Βιολογικοί παράγοντες

Δράση:

- Μείωση ενεργότητας νόσου (DAS28)
- Ποιότητα ζωής
- Καρδιαγγειακό

Avouac J, Allanore Y. Cardiovascular risk in rheumatoid arthritis: effects of anti-TNF drugs. Expert Opin Pharmacother.2008 May;9(7):1121-8.

Βιολογικοί παράγοντες

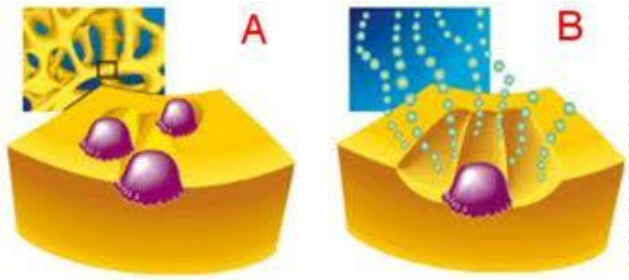
Οστά – αρθρώσεις : αναστολή της ακτινολογικής εξέλιξης

Κοινός μηχανισμός

Δράση των βιολογικών παραγόντων στο μεταβολισμό των οστών

Οστεοπόρωση

Φλεγμονώδη νοσήματα

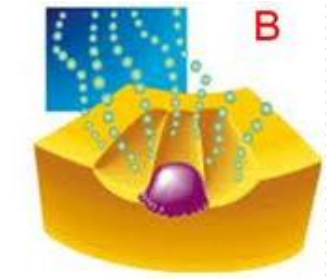


Φλεγμονώδη νοσήματα

- ΡΑ
- ΣΕΛ
- ΦΝΕ
- Κοιλιοκάκη
- ΧΑΠ
- Κυστική ίνωση

} Αυξημένη οστική απορρόφηση

Κοινός μηχανισμός οστεοπόρωσης & διαβρώσεων



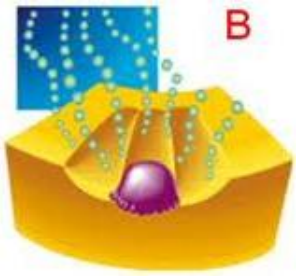
Rheumatoid arthritis (RA) is characterised by the presence of an **inflammatory synovitis** accompanied by destruction of

- joint cartilage
- Bone

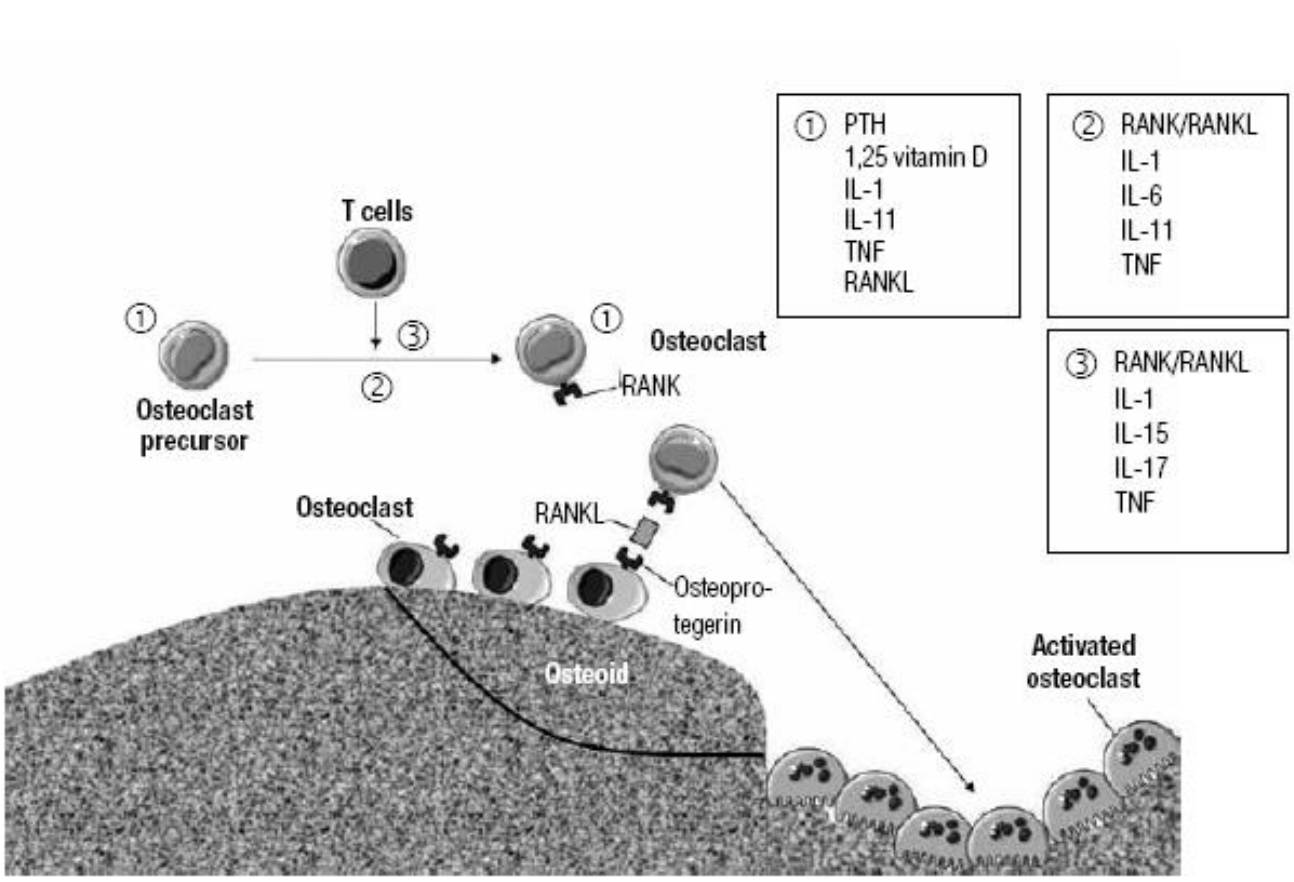
Destruction of **cartilage** matrix results predominantly from the action of connective tissue *proteinases* released by RA synovial tissues, chondrocytes, and pannus tissue

Several lines of evidence in RA and in animal models of arthritis support a role for *osteoclasts* in the pathogenesis of **bone erosions**

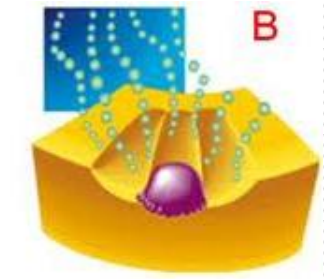
Gravallese EM. Bone destruction in arthritis. Ann Rheum Dis. 2002 Nov;61 Suppl 2:ii84-6.



Κοινός μηχανισμός οστεοπόρωσης & διαβρώσεων



Μηχανισμός οστικής απώλειας στην PA



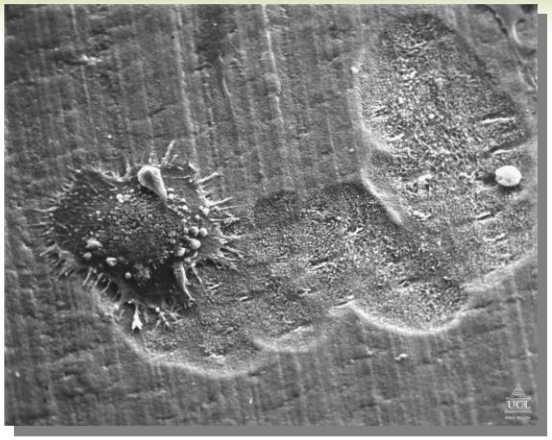
as a result of increased production of (**RANKL) in the bone marrow**, which activates osteoclast to

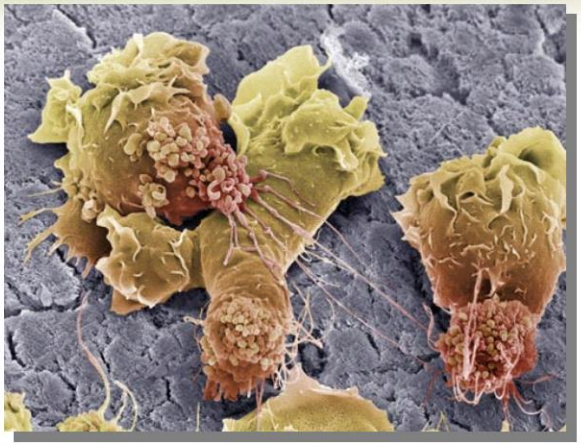
- resorb bone and
- cause erosions

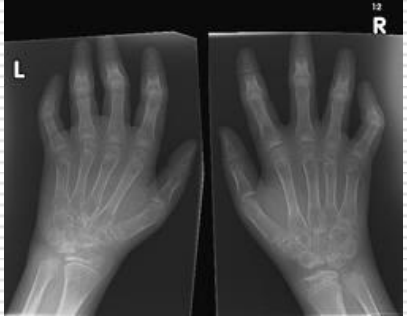
- **osteoblasts** are stimulated by **TNF-a,** it guides the expression of RANKL.

- **TNF-a** directly activates the macrophages, which are the antecedents of osteoclasts, and finally guides the **differentiation of macrophages into osteoclasts**

Activated Osteoclasts at Work







Οστεοκλάστης στην RA

- Διαβρώσεις

- Οστεοπόρωση

Περιαρθρική

Γενικευμένη Συμμετέχουν : ακινησία
στεροειδή
εμμηνόπαυση

Πειραματικές αποδείξεις

Treatment with TNFbp completely prevented

- bone loss
- increase in both osteoclast formation & bone resorption

induced by OVX

Kimble RB, Bain S, Pacifici R. The functional block of TNF but not of IL-6 prevents bone loss in ovariectomized mice. J Bone Miner Res. 1997 Jun;12(6):935-41.

Πειραματικές αποδείξεις

Πειραματόζωα με

- ανεπάρκεια οστεοκλαστών (osteoclast-deficient) και
- υπερ-παραγωγή TNF-α

ανέπτυξαν φλεγμονώδες νόσημα **αλλά όχι διαβρώσεις**

Redlich K, Hayer S, Ricci R, David JP, Tohidast-Akrad M, Kollias G, Steiner G, Smolen JS, Wagner EF, Schett G (2002) Osteoclasts are essential for TNF-alpha-mediated joint destruction. J Clin Invest 110:1419–1427

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RA & Οστεοπόρωση

- Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. Lancet 1994;344:23–7.
- Shenstone BD, Mahmoud A, Woodward R, Elvins D, Palmer R, Ring EF, et al. Longitudinal bone mineral density changes in early rheumatoid arthritis. Br J Rheumatol 1994;33:541–5.
- Sambrook PN, Cohen ML, Eisman JA, Pocock NA, Champion GD, Yeates MG. Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study. Ann Rheum Dis 1989;48:535–8.
- Aman S, Hakala M, Silvennoinen J, Manelius J, Risteli L, Risteli J. Low incidence of osteoporosis in a two year follow-up of early community based patients with rheumatoid arthritis. Scand J Rheumatol 1998;27:188–93.
- Cortet B, Guyot MH, Solau E, Pigny P, Dumoulin F, Flipo RM, et al. Factors influencing bone loss in rheumatoid arthritis: a longitudinal study. Clin Exp Rheumatol 2000;18:683-90.
- Mazzantini M, Di Munno O, Incerti-Vecchi L, Pasero G. Vertebral bone mineral density changes in female rheumatoid arthritis patients treated with low-dose methotrexate. Clin Exp Rheumatol 2000;18:327–31.
- Van Schaardenburg D, Valkema R, Dijkmans BA, Papapoulos S, Zwinderman AH, Han KH, et al. Prednisone treatment of elderlyonset rheumatoid arthritis: disease activity and bone mass in comparison with chloroquine treatment. Arthritis Rheum 1995;38: 334–42.
- Kroot EJ, Nieuwenhuizen MG, de Waal M, van Riel PL, Pasker-de Jong PC, Laan RF. Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. Arthritis Rheum 2001;44:1254–60.
- Kvien TK, Haugeberg G, Uhlig T, Falch JA, Halse JI, Lems WF, et al. Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis. Ann Rheum Dis 2000;59:805–11.

ARTHRITIS & RHEUMATISM
Vol. 46, No. 7, July 2002, pp 1720–1728
DOI 10.1002/art.10408

Bone Loss in Patients With Rheumatoid Arthritis

Results From a Population-Based Cohort of 366 Patients Followed Up for Two Years

Glenn Haugeberg,[1] Ragnhild E. Ørstavik,[1] Till Uhlig,[1] Jan A. Falch,[2] Johan I. Halse,[3] and Tore K. Kvien[1]

Bone Loss in Patients With Rheumatoid Arthritis

Results From a Population-Based Cohort of 366 Patients Followed Up for Two Years

- 366 ασθενείς
  - ηλικία 55 ετών
  - Διάρκεια νόσου : 13 y
  - 48% στεροειδή
  - 37% αντι-οστεοκλαστική αγωγή

Μείωση BMD (γενικά)

- - 0,77 % ισχίο
- - 0,29 % ΟΜΣΣ

Bone Loss in Patients With Rheumatoid Arthritis

Results From a Population-Based Cohort of
366 Patients Followed Up for Two Years

- Αντι-οστεοκλαστική αγωγή : αύξηση BMD
- Ca & Vit D3 : μείωση BMD (-2% , -1,4%)
- Καμία αγωγή για ΟΠ : μείωση BMD (-1,2 %, -0,43%)
- Στεροειδή : κίνδυνο για απώλεια BMD ισχίο: 2,63

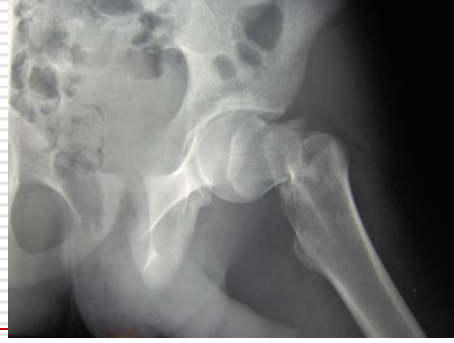
Πρώιμη αρθρίτιδα

Over the next 12 months, **bone mineral density loss** was greater in patients with rheumatoid arthritis compared with controls; **significantly so for early disease**

- -2.4 [0.8] vs -0.6 [0.4] g/cm2, $p < 0.05$ in the spine
- - 4.3 [0.8] vs -0.4 [0.5] g/cm2, $p < 0.001$ in the trochanter

Generalised bone loss in patients with early rheumatoid arthritis. *Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Lancet. 1994 Jul 2;344(8914):23-7.*

ΡΑ & κάταγμα



- van Staa TP, Geusens P, Bijlsma WJ, Leufkens HGM, Cooper C (2006) Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum 54:3104–3112

- Orstavik RE, Haugeberg G, Uhlig T, Mowinckel P, Falch JA, Halse JI et al (2004) Self reported non-vertebral fractures in rheumatoid arthritis and population based controls: incidence and relationship with bone mineral density and clinical variables. Ann Rheum Dis 63:177–182

- Huusko TM, Korpela M, Karppi P, Avikainen V, Kautiainen H,Sulkava R (2001) Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland. Ann Rheum Dis 60:521–522

ACR 2011
CHICAGO
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1155 ασθενείς σε κάθε ομάδα :

- *Women* younger than 50 years of age at RA diagnosis (304 women; mean age at diagnosis, 39 years) were more likely than their counterparts without RA to have their first new **fracture** even before age 50

- *Men* with RA were also at increased risk for fractures, but that risk was not evident until they were older than age 50

Shreyasee Amin, American College of Rheumatology 2011 Annual Meeting;
Abstract #1632. To be presented Monday November 7, 2011.

Βιολογικοί παράγοντες

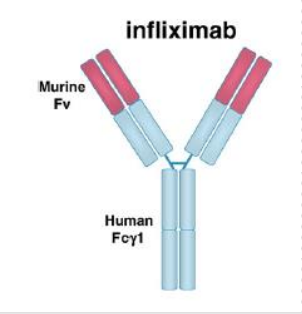
- Infliximab
- Etanercept
- Adalimumab
- Golimumab
- Certolizumab

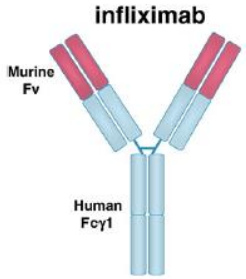
- Anakinra
- Abatacept
- Rituximab
- Tocilizumab

- Belimumab
- canakinumab

- Denosumab

Infliximab





Rheumatology 2005;44:1546–1548
Advance Access publication 1 November 2005
doi:10.1093/rheumatology/kei082

Concise Report

Increase in bone mineral density of patients with rheumatoid arthritis treated with anti-TNF-α antibody: a prospective open-label pilot study

U. Lange, J. Teichmann[1], U. Müller-Ladner and J. Strunk

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Concise Report

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U. Lange, J. Teichmann[1], U. Müller-Ladner and J. Strunk

- 26 ασθενείς με PA
  - χωρίς ΟΠ
  - χωρίς θεραπεία για ΟΠ
  - 9: στεροειδή

- BMD στους 12 μήνες
- δείκτες (osteocalcin , crosslaps)

Rheumatology 2005;44:1546–1548 doi:10.1093/rheumatology/kei082
Advance Access publication 1 November 2005

Concise Report

Increase in bone mineral density of patients with rheumatoid arthritis treated with anti-TNF-α antibody: a prospective open-label pilot study

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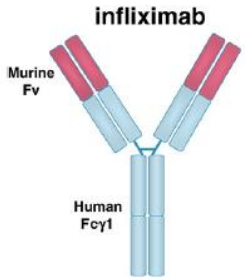
TABLE 1. Changes in DXA parameters during the study period

	Baseline	After 12 months	*P*
BMD left femoral neck (g/cm^2)	0.84 ± 0.33	0.95 ± 0.15	0.001
T-score left femoral neck (g/cm^2)	−0.93 ± 1.06	−0.77 ± 0.97	0.001
Z-score left femoral neck (g/cm^2)	−0.24 ± 0.77	−0.16 ± 0.68	0.010
BMD L1–4	1.07 ± 0.14	1.10 ± 0.23	0.001
T-score L1–4	−0.92 ± 1.09	−0.71 ± 1.07	0.001
Z-score L1–4	−0.58 ± 1.23	−0.49 ± 1.14	0.001

- *Στατιστικά σημαντική αύξηση BMD* (ΟΜΣΣ & ισχίο)
- Σημαντική αύξηση οστεοκαλσίνης
- Σημαντική μείωση δεικτών οστικής απορρόφησης

Infliximab



Rheumatology 2006;45:761–764
Advance Access publication 25 January 2006
doi:10.1093/rheumatolog

The effect of infliximab on bone metabolism markers in patients with rheumatoid arthritis

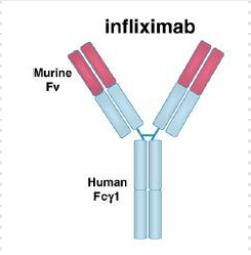
E. Torikai, Y. Kageyama, M. Takahashi, M. Suzuki, T. Ichikawa, T. Nagafusa and A. Nagano

Rheumatology 2006;45:761–764 doi:10.1093/rheumatolog
Advance Access publication 25 January 2006

The effect of infliximab on bone metabolism markers in patients with rheumatoid arthritis

E. Torikai, Y. Kageyama, M. Takahashi, M. Suzuki, T. Ichikawa, T. Nagafusa and A. Nagano

- 17 ασθενείς
- NTX **μειώθηκαν** σημαντικά στις 6 w και παρέμειναν χαμηλά στους 6 m ~ SJC & mHAQ
- DPD **μειώθηκαν** σημαντικά στις 6 m ~ ESR
- ALP χωρίς διαφορές



EXTENDED REPORT

Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFκB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis

M Vis, E A Havaardsholm, G Haugeberg, T Uhlig, A E Voskuyl, R J van de Stadt, B A C Dijkmans, A D Woolf, T K Kvien, W F Lems

Ann Rheum Dis 2006;65:1495–1499. doi: 10.1136/ard.2005.044198

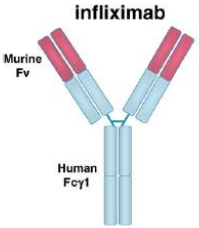
Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFκB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis

102 ασθενείς – 1 χρόνος infliximab

- Η BMD σε ΟΜΣΣ & ισχίο : σταθερή
- Η BMD στα **χέρια** (μετακάρπια) μειώθηκε κατά 0.8 % (p< 0,01)
- Μείωση β-CTx & RANKL
  - β-CTx ~ DAS & CRP

		Good EULAR response	
	All	No	Yes
Vertebral-spine (n = 102)	0.20 (5.1)	−0.57 (5.0)	0.74 (5.3)
Total hip (n = 89)	−0.20 (3.6)	−0.68 (3.8)	0.77 (3.4)*
Hand (n = 53)	−0.82 (2.4)	−1.2 (2.6)	−0.63 (2.3)

*p<0.001 versus those without good response.



Research article

Open Access

A 1-year case-control study in patients with rheumatoid arthritis indicates prevention of loss of bone mineral density in both responders and nonresponders to infliximab

Hubert Marotte[1], Beatrice Pallot-Prades[2], Laurent Grange[3], Philippe Gaudin[3], Christian Alexandre[2] and Pierre Miossec[1]

[1]Hospices Civils de Lyon-bioMérieux Research Unit on Rheumatoid Arthritis, Hopital Edouard Herriot, place d'Arsonval, 69437 Lyon Cedex 03, France
[2]Department of Rheumatology, University Hospital, Hopital Bellevue, 42000 Saint-Etienne, France
[3]Department of Rheumatology, University Hospital, Hopital Sud, 38000 Grenoble, France

Corresponding author: Pierre Miossec, miossec@univ-lyon1.fr

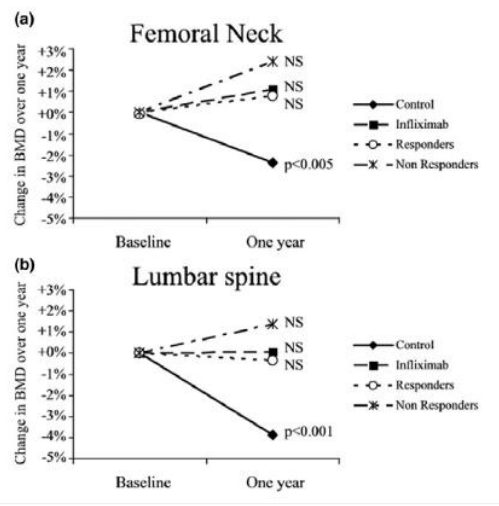
Received: 23 Jan 2007 Revisions requested: 5 Mar 2007 Revisions received: 19 Jun 2007 Accepted: 27 Jun 2007 Published: 27 Jun 2007

Arthritis Research & Therapy 2007, **9**:R61 (doi:10.1186/ar2219)

A 1-year case-control study in patients with rheumatoid arthritis indicates prevention of loss of bone mineral density in both responders and nonresponders to infliximab

Hubert Marotte[1], Beatrice Pallot-Prades[2], Laurent Grange[3], Philippe Gaudin[3], Christian Alexandre[2] and Pierre Miossec[1]

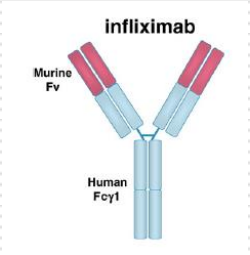
- 90 PA ασθενείς υπό infliximab Vs 99 χωρίς (controls, MTX)
- 1 χρόνο παρακολούθηση



- ✓ Μείωση BMD OMSS & ισχίο (controls)
- ✓ Χωρίς αλλαγή BMD στη ομάδα Infliximab
  - Χωρίς αλλαγές στους οστικούς δείκτες
  - Χωρίς συσχέτιση με την κλινική ανταπόκριση

Ακόμη και αυτοί που δεν ανταποκρίθηκαν κλινικά
δεν είχαν οστική απώλεια

Ότι συμβαίνει και με τις διαβρώσεις



Long-term effects of infliximab on bone and cartilage turnover markers in patients with rheumatoid arthritis

F Chopin,[1] P Garnero,[2] A le Henanff,[3] F Debiais,[4] A Daragon,[5] C Roux,[6] J Sany,[7] D Wendling,[8] C Zarnitsky,[9] P Ravaud,[3] T Thomas[1]

Ann Rheum Dis 2008;**67**:353–357. doi:10.1136/ard.2007.076604

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48 γυναίκες

- *N-terminal propeptide* (PINP), => bone formation
- serum *C-terminal cross-linked telopeptide of type I*

collagen (CTX-I), a marker of cathepsin K-mediated bone

collagen degradation => systemic bone resorption

- serum *C-terminal cross-linked telopeptide of*

type I collagen (ICTP), an index of matrix metalloprotease

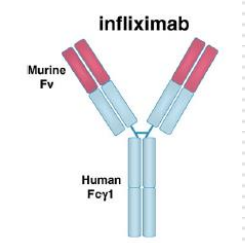
(MMP) mediated type I collagen degradation => preferential joint metabolism

- urinary *CTX-II* biochemical markers of cartilage degradation

Long-term effects of infliximab on bone and cartilage turnover markers in patients with rheumatoid arthritis

F Chopin,[1] P Garnero,[2] A le Henanff,[3] F Debiais,[4] A Daragon,[5] C Roux,[6] J Sany,[7] D Wendling,[8] C Zarnitsky,[9] P Ravaud,[3] T Thomas[1]

- Η BMD έμεινε σταθερή
- Ταχεία πτώση CTX-1 (19% - 28%)
- ICTP : προοδευτική μείωση (MMP)
- PINP : σταθερό
- CTX –II ούρων : σταθερό
- Βελτίωση στην οστική ανακατασκευή (PINP / CTX)



Infliximab inhibits bone resorption by circulating osteoclast precursor cells in patients with rheumatoid arthritis and ankylosing spondylitis

M Gengenbacher,[1] H-J Sebald,[2] P M Villiger.[3] W Hofstetter.[4] M Seitz[3]

Ann Rheum Dis 2008;**67**:620–624. doi:10.1136/ard.2007.076711

Infliximab inhibits bone resorption by circulating osteoclast precursor cells in patients with rheumatoid arthritis and ankylosing spondylitis

M Gengenbacher,[1] H-J Sebald,[2] P M Villiger,[3] W Hofstetter,[4] M Seitz[3]

- **Καλλιέργειες** osteoclast precursor cells σε ασθενείς με PA & ΑΣ και έλεγχος οστικής απορρόφησης (in vitro)
- 0 – 24 w

- Ισχυρή **μείωση οστικής απορρόφησης των OPC**
  - Πιο γρήγορα στην PA
  - Παράλληλα με την κλινική βελτίωση
  - Αύξηση OC , μείωση NTX στη PA

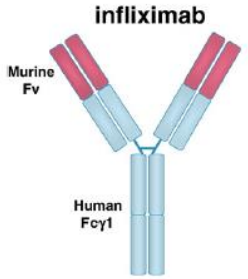
Infliximab BEST

- After 1 year of follow-up in the BeSt study, we did not find differences in BMD loss between the four treatment strategies, including
  - high doses of corticosteroids
  - anti-tumour necrosis factor-alpha

Güler-Yüksel M, et al . Changes in bone mineral density in patients with recent onset, active rheumatoid arthritis.Ann Rheum Dis. 2008 Jun;67(6):823-8

Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis

M Güler-Yüksel,[1] C F Allaart,[1] Y P M Goekoop-Ruiterman,[1] J K de Vries-Bouwstra,[2] J H L M van Groenendael,[3] C Mallée,[4] M H W de Bois,[5] F C Breedveld,[1] B A C Dijkmans,[2,6] W F Lems[2,6]

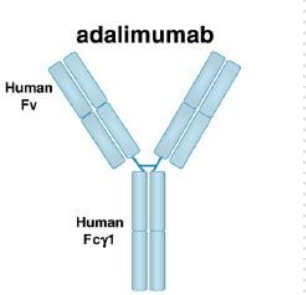


- After 1 and 2 years, there was significant BMD loss in all locations
  - with significantly greater BMD loss in the hands than generalised BMD loss in the hip and spine.

- Initial **combination** therapy with prednisone or infliximab were associated with less hand BMD loss compared with initial monotherapy

Ann Rheum Dis 2009;**68**:330–336. doi:10.1136/ard.2007.086348

Adalimumab



Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss

C A Wijbrandts,[1] R Klaasen,[1] M G W Dijkgraaf,[2] D M Gerlag,[1] B L F van Eck-Smit,[3] P P Tak[1]

Ann Rheum Dis 2009;**68**:373–376. doi:10.1136/ard.2008.091611

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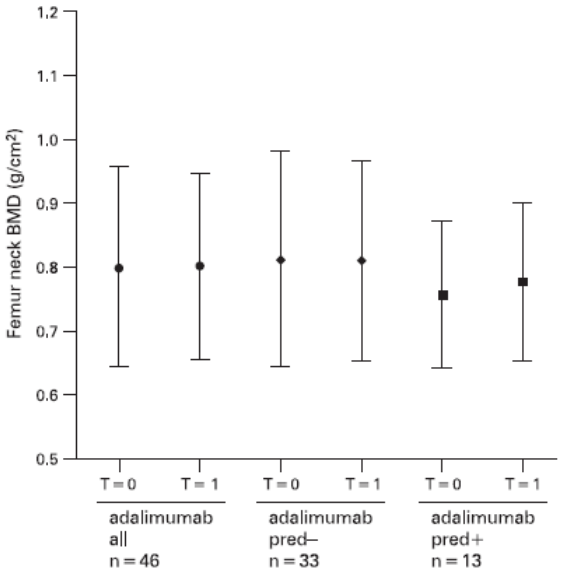
Ann Rheum Dis 2009;**68**:373–376. doi:10.1136/ard.2008.091611

- 50 ασθενείς με PA
- BMD (ΟΜΣΣ & ισχίο) έμεινε **σταθερή**
- Ευεργετική δράση στεροειδών



Adalimumab reduces hand bone loss in rheumatoid arthritis independent of clinical response: Subanalysis of the PREMIER study

Mari Hoff[1,2*], Tore K Kvien[3], Johan Kälvesten[4], Aake Elden[5], Arthur Kavanaugh[6], Glenn Haugeberg[2,7]

BMC Musculoskeletal Disorders 2011, **12**:54

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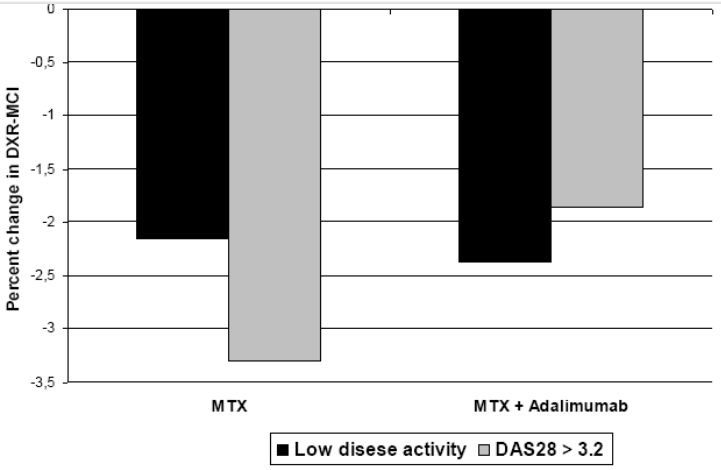
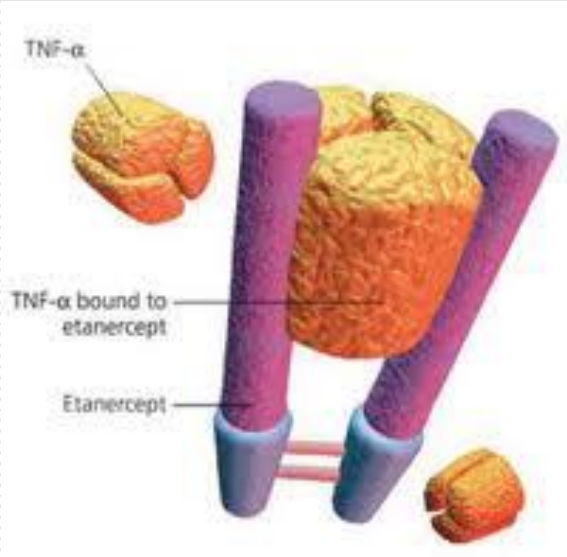
Mari Hoff[1,2*], Tore K Kvien[3], Johan Kälvesten[4], Aake Elden[5], Arthur Kavanaugh[6], Glenn Haugeberg[2,7]

MTX + ADA (214) Vs MTX (198): 52 w

- **DRX – MCI απώλεια στην MTX ήταν υψηλή σε ασθενείς με αυξημένη ενεργότητα νόσου (-3,3 Vs -2,2%)**
- **DRX – MCI απώλεια στην MTX + ADA ήταν μικρότερη (-1,9%)**
  - **ανεξάρτητη της ενεργότητας**



Etanercept



ASBMR 2007
Exploring New Horizons

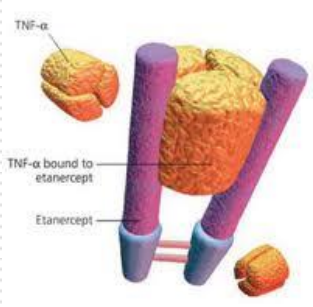
The American Society for Bone and Mineral Research

W434

The Effect of Etanercept on Bone Metabolism in Patients with Rheumatoid Arthritis. D. Kida*, Y. Eto*, M. Tsukamoto*, T. Sato*, A. Kaneko*, G. Ishihara*, H. Sugishita*, K. Saito*. Department of Orthopedic surgery and Rheumatology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan.

- **NTx levels** did not differ significantly in 6 months after initial treatment with ETN
- **BAP levels (p<O.01) were significantly increased** and higher p<0.01) in patients treated with ETN compared to others.
- ETN therapy may **not inhibit bone resorption** but stimulate bone formation in patients with RA.

Etanercept



Clin Rheumatol (2008) 27:1093–1101
DOI 10.1007/s10067-008-0870-8

ORIGINAL ARTICLE

Reduction of urinary levels of pyridinoline and deoxypyridinoline and serum levels of soluble receptor activator of NF-kappaB ligand by etanercept in patients with rheumatoid arthritis

Kageyama Yasunori · Takahashi Masaaki · Nagafusa Tetsuyuki · Kobayashi Hayato · Nagano Akira

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Kageyama Yasunori · Takahashi Masaaki · Nagafusa Tetsuyuki · Kobayashi Hayato · Nagano Akira

- urinary excretion levels of pyridinoline (PYD)
- deoxypyridinoline (DPD)
- cross-linked N-telopeptides of type I collagen (NTX)
- and serum levels of bone alkaline phosphatase (BAP)
- osteoprotegerin (OPG)
- soluble receptor activator of NFκB ligand (sRANKL)

at the baseline and at 3 and 6 months after

Clin Rheumatol (2008) 27:1093–1101
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Kageyama Yasunori · Takahashi Masaaki · Nagafusa Tetsuyuki · Kobayashi Hayato · Nagano Akira

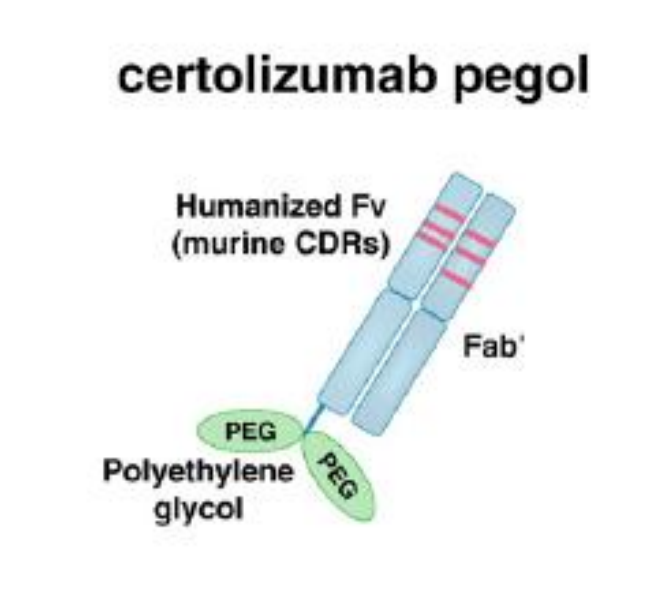
- **Reduction** of
  - urinary excretion levels of PYD and DPD
  - serum sRANKL levels, with a significant difference at 6 months
  - ΄Οχι NTX
- an **increase of serum BAP** levels at 3 and 6 months after the initial treatment with etanercept

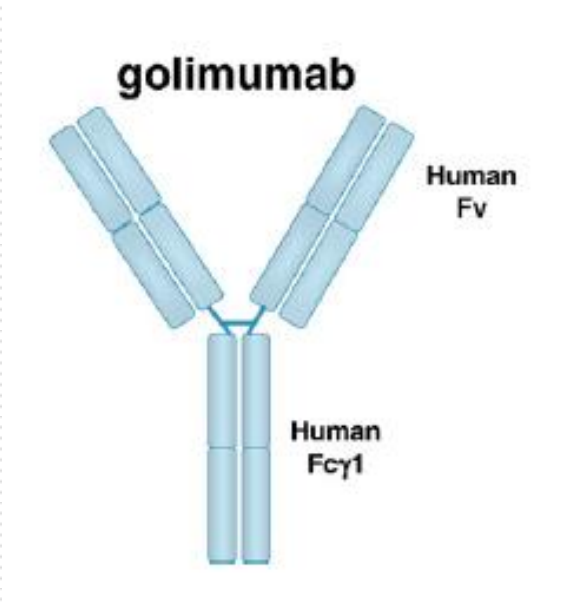
Etanercept

Etanercept Normalizes Systemic Bone Metabolism in Rheumatoid Arthritis Patients

- lower level of serum CTX and sclerostin in RA patients than in control group, which
  - suggested slow bone resorption rate coupled with low bone production
- after etanercept use, both serum CTX and sclerostin markedly increased
- Therefore we conclude that etanercept **stimulates depressed bone metabolism** in RA patients as it suppresses inflammation

Park, et al ;. Arthritis Rheum 2010;62 Suppl 10 :1813


certolizumab pegol
Humanized Fv
(murine CDRs)
Fab'
PEG
PEG
Polyethylene
glycol


golimumab
Human
Fv
Human
Fcγ1

PA & κάταγμα

- Among subjects diagnosed with RA, the adjusted risk of non-vertebral fracture was **similar** across persons starting a TNFi, MTX, or other nbDMARD

Kim SY, Schneeweiss S, Liu J, Solomon DH. Effects of disease-modifying antirheumatic drugs on non-vertebral fracture risk in rheumatoid arthritis: a population-based cohort study. J Bone Miner Res. 2011 Dec 8

abatacept

ARD ONLINE

CTLA-4 directly inhibits osteoclast formation

Roland Axmann, Sonja Herman, Mario Zaiss, Sandra Franz, Karin Polzer, Jochen Zwerina, Martin Herrmann, Josef Smolen and Georg Schett

Ann Rheum Dis published online 18 Jan 2008;
doi:10.1136/ard.2007.080713

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Ann Rheum Dis published online 18 Jan 2008;
doi:10.1136/ard.2007.080713

- CTLA-4 ενώνεται με την επιφάνεια αντιγονοπαρουσιαστικού κυττάρου (δενδριτικά – μονοκύτταρα) στο CD80-86
- Περιφερικά μονοκύτταρα ποντικιού
- Με CTLA-4 υπάρχει δοσοεξαρτώμενη αναστολή οστεοκλαστογένεσης (RANKL & TNF εξαρτώμενη)

Abatacept

- abatacept could prevent PTH-induced bone loss

Bedi B, Li JY, Grassi F, Tawfeek H, Weitzmann MN, Pacifici R (2010) Inhibition of antigen presentation and T cell costimulation blocks PTH-induced bone loss. Ann NYAcad Sci 1192:215–221

Anakinra

- IL-1, TNF and other proinflammatory cytokines **stimulate osteoclast** differentiation and activation, resulting in bone loss
- stimulate synovial fibroblasts and chondrocytes to produce **proteinases** that degrade cartilage
- In **animal** arthritis models, blocking IL-1 significantly reduces
  - bone erosions
  - cartilage degradation

Strand V, Kavanaugh AF. The role of interleukin-1 in bone resorption in rheumatoid arthritis. Rheumatology (Oxford).2004 Jun;43 Suppl 3:iii10-iii16.

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Number 5, 2007
Published online on February 12, 2007; doi: 10.1359/JBMR.070207

Effect of Blockade of TNF-α and Interleukin-1 Action on Bone Resorption in Early Postmenopausal Women

Natthinee Charatcharoenwitthaya,[1] Sundeep Khosla,[1] Elizabeth J Atkinson,[2] Louise K McCready,[1] and B Lawrence Riggs[1]

JOURNAL OF BONE AND MINERAL RESEARCH
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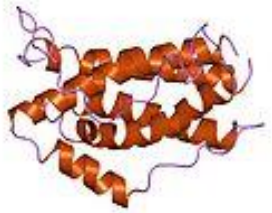
Natthinee Charatcharoenwitthaya,[1] Sundeep Khosla,[1] Elizabeth J Atkinson,[2] Louise K McCready,[1] and B Lawrence Riggs[1]

- The data are consistent with a role for TNF-a, and possibly for IL-1, in mediating increased bone resorption during estrogen deficiency in women

IL-6



ELSEVIER

Bone 37 (2005) 601–606

BONE

www.elsevier.com/locate/bone

Review

Interleukin-6: An osteotropic factor influencing bone formation?

Nathalie Franchimont*, Sylvie Wertz, Michel Malaise

STAT signaling pathway. However, from all the data we have now available, one might consider that IL-6 is not essential for bone remodeling in physiological conditions, but that this cytokine plays a role in osteoblast generation in conditions of high bone turnover.

ARTHRITIS & RHEUMATISM
Vol. 54, No. 11, November 2006, pp 3551–3563
DOI 10.1002/art.22175

Impaired Skeletal Development in Interleukin-6–Transgenic Mice

A Model for the Impact of Chronic Inflammation on the Growing Skeletal System

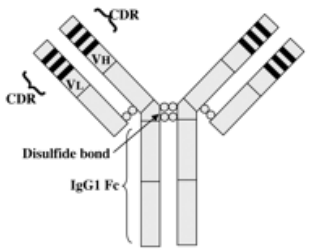
ARTHRITIS & RHEUMATISM
Vol. 54, No. 11, November 2006, pp 3551–3563
DOI 10.1002/art.22175

Impaired Skeletal Development in Interleukin-6–Transgenic Mice

A Model for the Impact of Chronic Inflammation on the Growing Skeletal System

- Chronic overexpression of IL-6 alone induces a skeletal phenotype closely resembling growth and skeletal abnormalities observed in children with chronic inflammatory diseases

- pointing to IL-6 as a pivotal mediator of the impact of chronic inflammation on postnatal **skeletal** development



Tocilizumab
(TCZ)

ARTHRITIS & RHEUMATISM
Vol. 60, No. 9, September 2009, pp 2747–2756
DOI 10.1002/art.24781

Inhibition of Interleukin-6 Receptor Directly Blocks Osteoclast Formation In Vitro and In Vivo

Roland Axmann,[1] Christina Böhm,[1] Gerhard Krönke,[1] Jochen Zwerina,[1]
Josef Smolen,[2] and Georg Schett[3]

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Vol. 60, No. 9, September 2009, pp 2747–2756
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Roland Axmann,[1] Christina Böhm,[1] Gerhard Krönke,[1] Jochen Zwerina,[1] Josef Smolen,[2] and Georg Schett[3]

1. Ab έναντι IL-6R in blocking **osteoclast differentiation** of mononuclear cells stimulated with RANKL was tested (K/a)

2. arthritic human **TNF-transgenic mice** were treated with anti-IL-6R antibody

ARTHRITIS & RHEUMATISM
Vol. 60, No. 9, September 2009, pp 2747–2756
DOI 10.1002/art.24781

Inhibition of Interleukin-6 Receptor Directly Blocks Osteoclast Formation In Vitro and In Vivo

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- dependently reduced
  - osteoclast differentiation
  - bone resorption in monocyte **cultures** stimulated with

RANKL or RANKL plus TNF

- In human TNF-transgenic **mice**, IL-6R blockade
  - did not inhibit joint inflammation
  - but it strongly reduced osteoclast formation in inflamed joints & bone erosion in vivo

ARTHRITIS & RHEUMATISM
Vol. 60, No. 9, September 2009, pp 2747–2756
DOI 10.1002/art.24781

Inhibition of Interleukin-6 Receptor Directly Blocks Osteoclast Formation In Vitro and In Vivo

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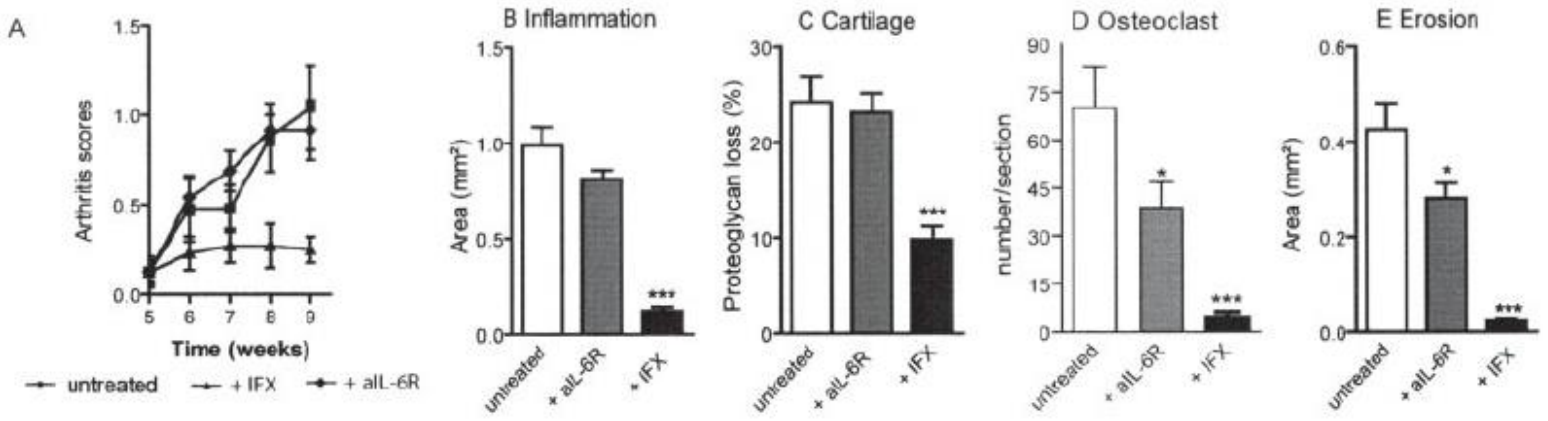
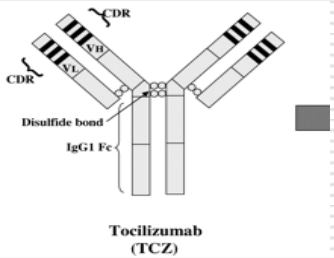


blockade of IL-6R directly affects osteoclast formation in vitro and in vivo, suggesting a direct and specific effect of anti– IL-6R therapy on osteoclasts



Tocilizumab
(TCZ)

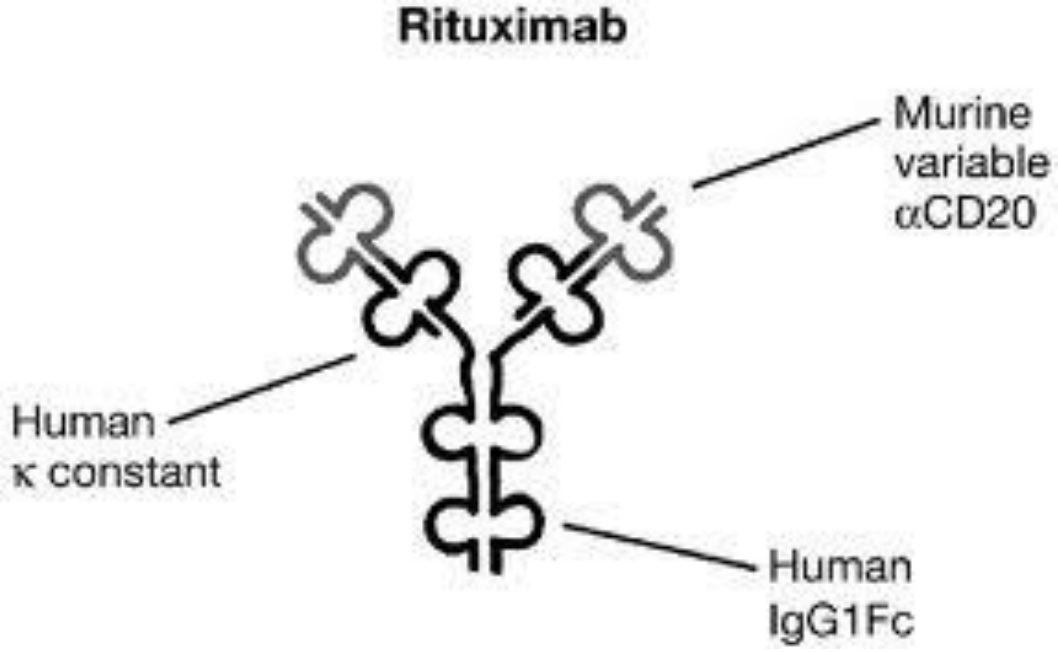
ARTHRITIS & RHEUMATISM
Vol. 62, No. 1, January 2010, pp 33–43
DOI 10.1002/art.25053

Rapid and Sustained Improvement in Bone and Cartilage Turnover Markers With the Anti–Interleukin-6 Receptor Inhibitor Tocilizumab Plus Methotrexate in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate

ARTHRITIS & RHEUMATISM
Vol. 62, No. 1, January 2010, pp 33–43
DOI 10.1002/art.25053

Rapid and Sustained Improvement in Bone and Cartilage Turnover Markers With the Anti–Interleukin-6 Receptor Inhibitor Tocilizumab Plus Methotrexate in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate

- TCZ induced marked dose-dependent **reductions** in PIIANP, HELIX-II, and MMP-3 levels at week 4 that were maintained until week 24
- increased levels of **bone formation markers** that were significant as compared with placebo only for PINP and only at 4 weeks ($P < 0.01$ for both TCZ doses)
- TCZ induced significant decreases in the **bone degradation** markers CTX-I and ICTP, providing initial evidence of a beneficial effect on bone turnover
- TCZ-treated patients who **met the American College of Rheumatology 50%** improvement criteria (achieved an ACR50 response) or achieved clinical remission (as determined by a Disease Activity Score in 28 joints <2.6) at week 24 had greater reductions in ICTP, HELIX-II, and MMP-3 levels as compared with ACR50 nonresponders


Rituximab
Murine
variable
αCD20
Human
κ constant
Human
IgG1Fc

SAT0179 SUPPRESSION OF BONE TURNOVER BY RITUXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS

G. Wheater [1,*], V. Hogan [2], O. Teng [3], J. Tekstra [4], S. Tuck [1], F. Lafeber [4], T. Huizinga [3], J. Bijlsma [4], R. Francis [2], H. Datta [2], J. van Laar [2]

[1]The James Cook University Hospital, Middlesbrough, [2]Newcastle University, Newcastle, United Kingdom, [3]Leiden University Medical Centre, Leiden, [4]University Medical Centre Utrecht, Utrecht, Netherlands

Background: Recent investigations have provided abundant evidence for an intricate interaction between the immune and skeletal systems[1]. Rheumatoid arthritis (RA) is the most prevalent inflammatory joint disease, in which B cells play an important role. It is tempting to speculate that B cell depletion has a beneficial effect on bone loss. On the other hand, based on extrapolation from preclinical studies [2], it can be argued that B cell depletion may result in progressive bone loss. To our knowledge no studies have yet been undertaken to address the role of human B cells in bone turnover.

Objectives: To analyse changes in bone markers in serum before and after B cell depletion in patients with rheumatoid arthritis.

Methods: Serum samples from 46 patients with refractory RA were analysed before and six months post rituximab for biochemical markers of; bone formation (procollagen type I N propeptide (PINP) and osteocalcin); bone resorption (carboxyterminal cross-linking telopeptide of bone collagen (βCTx)); and osteoprotegerin (OPG).

Results: A significant decrease in bone resorption was observed at 6 months post rituximab (median change βCTx -50 ng/L, 95%CI -8,-136, p<0.001). These results were mirrored by a significant reduction in inflammation (median change CRP -8.5mg/L, 95%CI -16, -1, p=0.001; ESR -11.5 mm/hr, 95%CI -21, -5, p=<0.001) and disease activity (median change DAS28 score -0.82, 95%CI -1.26, -0.47, p<0.001). There was a significant increase in PINP (median change 5.0 µg/L, 95%CI -1.0, 11.2, p=0.02), a marker of bone formation, but no significant change in osteocalcin or OPG levels. Premenopausal females had the lowest baseline results overall and least change at 6 months for all bone markers. The percentage change from baseline of βCTx was significantly correlated with DAS28 score (r_s=0.570, p=0.014) and there was a trend towards significance between βCTx and CRP (r_s=0.485, p=0.057) and between PINP and DAS28 (r_s=0.422, p=0.081).

Conclusion: Patients with refractory RA show a significant decrease in bone resorption and increase in bone formation, depicted by PINP, six months post rituximab therapy. Significant correlations between the percentage change from baseline between βCTx and DAS28 score suggest that improvement in disease activity accounts in part for the reduction in bone turnover.

References: 1 Datta HK, Ng FW, Walker JA, et al. The cell biology of bone metabolism-a review. *J Clin Pathol*, 2008;61:577-587.

2 Jimenez-Boj E, Redlich K, Türk B, et al. Interaction between Synovial Inflammatory Tissue and Bone Marrow in Rheumatoid Arthritis. *J Immunol*. 2005;175: 2579-2588.

AB0733 VARIATIONS IN LUMBAR AND FEMURAL BMD AFTER RITUXIMAB THERAPY IN ACTIVE RHEUMATOID ARTHRITIS

S. Salvin [1,*], L. Quartuccio [1], M. Maset [1], L. Corazza [1], G. De Marchi [2], S. Lombardi [1], S. De Vita [1]

[1]CLINICA DI REUMATOLOGIA, Udine, [2]Ospedale Civile, San Daniele del Friuli (Udine), Italy

Background: Frequently systemic and local osteoporosis (OP) complicates rheumatoid arthritis (RA). B lymphocytes promote the survival of osteoclasts in RA and anti-TNFalpha therapy seems to improve bone loss.

Objectives: To evaluate possible changes in lumbar and/or femoral BMD in pts with active RA treated with rituximab (RTX).

Methods: 16 patients with active longstanding RA (all females, mean age 56 ± 12 years, mean duration's disease 15 ± 12 years, mean baseline DAS28 6,36 ± 1,04) were treated with RTX (1 gr x 2). There were no differences in the use of steroid or biphosphonates. BMDs (gr/cm^2) were evaluated with Explorer Hologic® (S/N 90954) before RTX and after 18 months.

Results: A major clinical response (ACR≥50) ad a minor o no response (ACR≤20) at month +6 were identified. An ACR≥50 was seen in 8/16 RA pts (50%). 10/16 pts were retreated with RTX between months +6 and +18, confirming an ACR≥50 (8/10 pts) or improving the clinical response (2 pts with previous ACR≤20). At the same time, 5/6 no responders pts were treated with Abatacept, 4/6 pts with an anti-TNFalpha agent (2/4 pts with Etanercept, 1/4 pts with Adalimumab and 1/4 pts with Infliximab) and 1/6 pts with Anakinra.

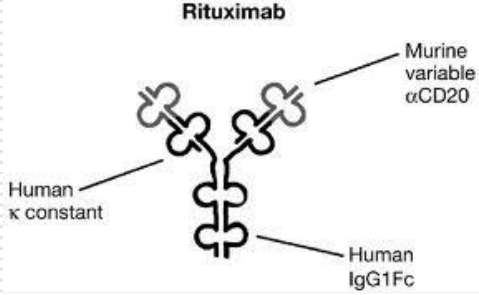
At baseline 69% (11/16) and 31% (5/16) of pts present an osteoporotic or osteopaenic lumbar or femoral BMD, respectively.

After 18 months, in all pts an improvement in lumbar BMD (0,872±0,162 gr/cm^2 baseline vs 0,881±0,152 gr/cm^2 on L1-L4, p ns) was seen. Lumbar BMD improves more in responders pts (0,910±0,169 gr/cm^2 vs 0,936±0,159 gr/cm^2 on L1-L4, p ns). Femoral BMD worsens in no-responders pts (0,627±0,096 gr/cm^2 vs 0,591±0,104 gr/cm^2 on femoral neck, p ns).

Conclusion: RTX could improve or stabilize lumbar BMD in pts with active longstanding RA, with more effect in responder pts.

Disclosure of Interest: None declared

Rituximab



Rheumatol Int (2011) 31:269–272
DOI 10.1007/s00296-010-1560-9

SHORT COMMUNICATION

Influence of Rituximab on markers of bone remodeling in patients with rheumatoid arthritis: a prospective open-label pilot study

Gert Hein · Thorsten Eidner · Peter Oelzner · Michael Rose · Alexander Wilke · Gunter Wolf · Sybille Franke

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- 13 ασθενείς με PA

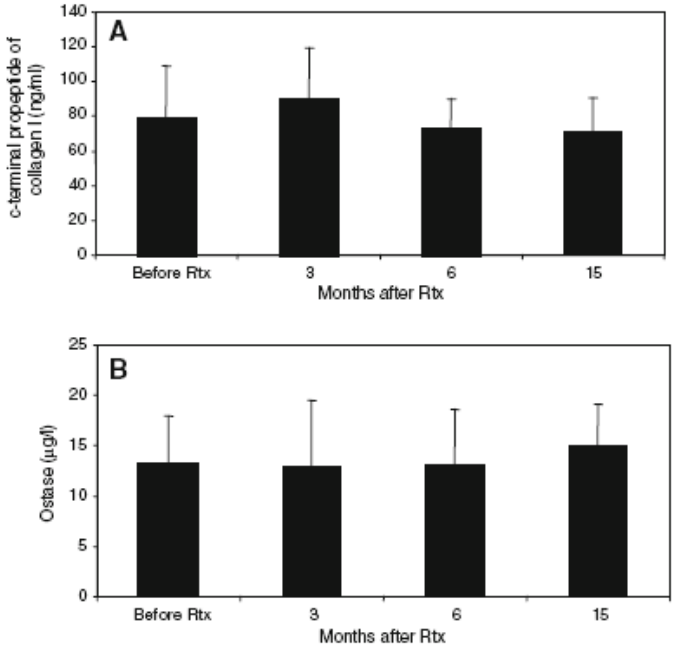

Fig. 1 Bone formation markers

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Influence of Rituximab on markers of bone remodeling in patients with rheumatoid arthritis: a prospective open-label pilot study

Gert Hein · Thorsten Eidner · Peter Oelzner · Michael Rose · Alexander Wilke · Gunter Wolf · Sybille Franke

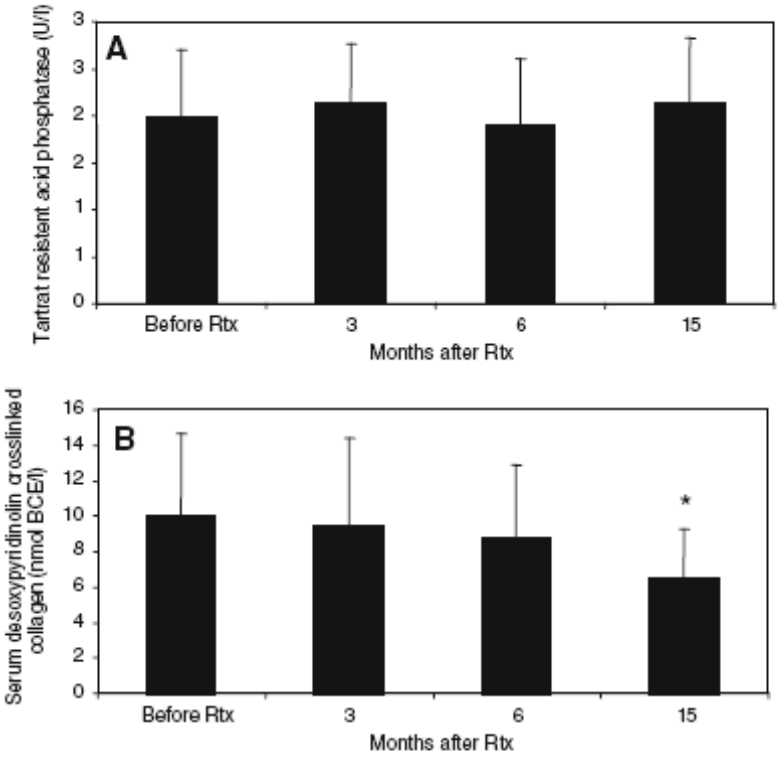

Fig. 2 Bone resorption markers (* $P < 0.001$ vs. patients before Rtx)

ARD Online First, published on November 8, 2011 as 10.1136/annrheumdis-2011-200198

Extended report

Rituximab abrogates joint destruction in rheumatoid arthritis by inhibiting osteoclastogenesis

Maria J H Boumans,[1] Rogier M Thurlings,[1] Lorraine Yeo,[2] Dagmar Scheel-Toellner,[2] Koen Vos,[1,3] Danielle M Gerlag,[1] Paul P Tak[1]

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- 26 ασθενείς – α-α έλεγχος – SHS score
- Βιοψίες υμένα πριν και 16 w μετά (ανοσοϊστοχημεία)
- Μετρήθηκαν στον ορό :
  - osteoprotegerin
  - receptor activator of nuclear factor κB ligand (RANKL)
  - osteocalcin
  - cross-linked N-telopeptides of type I collagen (NTx)

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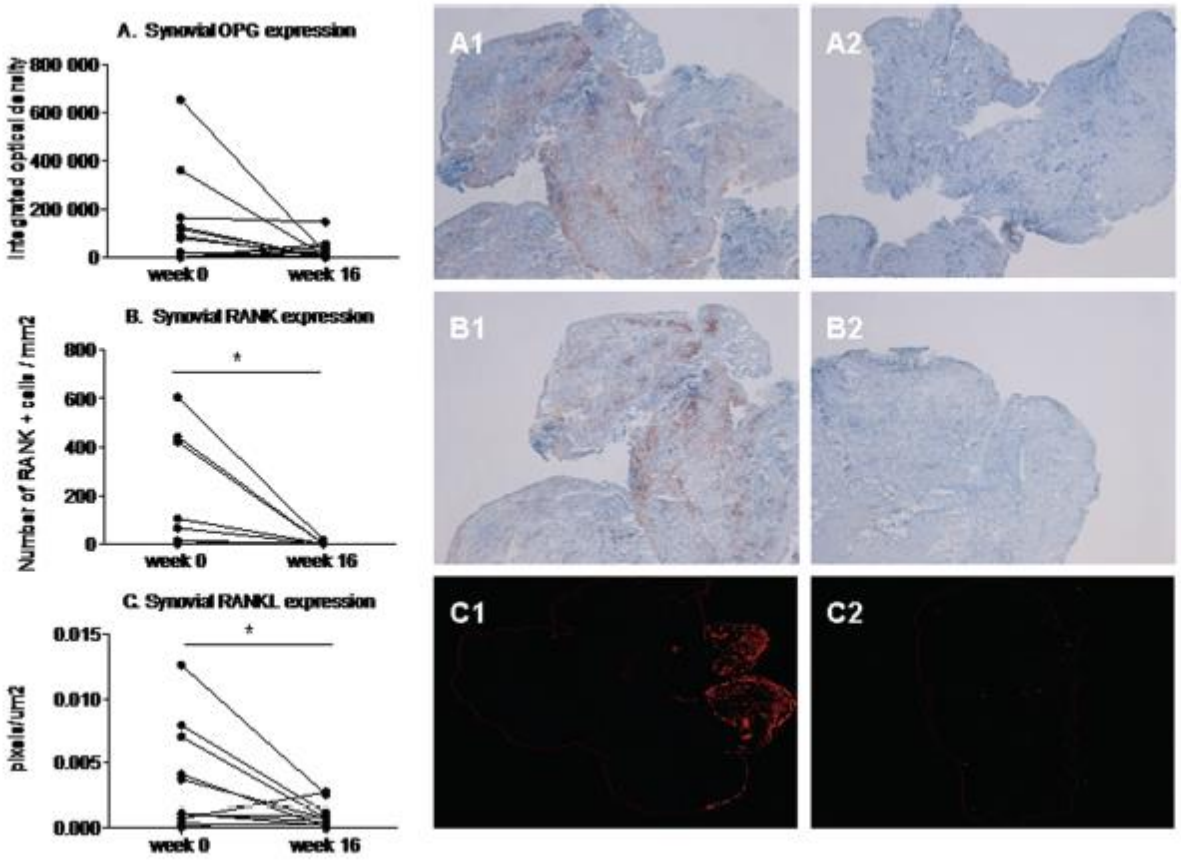

The number of RANK-positive osteoclast precursors in synovial tissue was decreased by 99%

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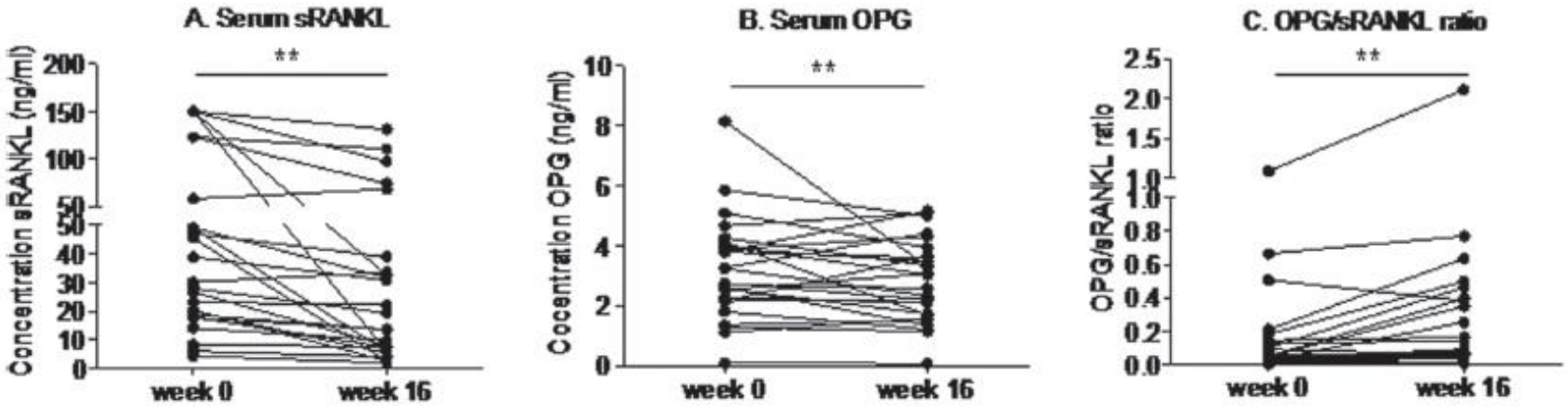


osteoprotegerin/ RANKL ratio increased (157%, p=0.006).

Denosumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., and Claus Christiansen, M.D., for the FREEDOM Trial*

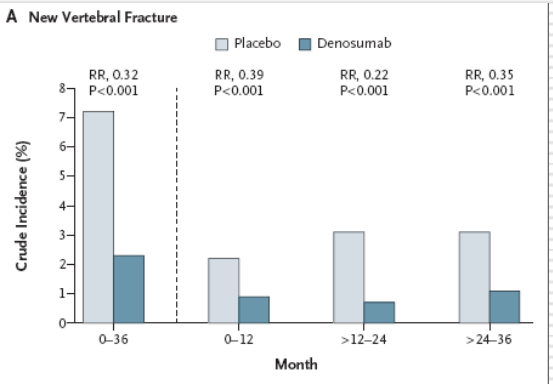
N Engl J Med 2009;361:756-65.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

- Νέο σπονδυλικό κάταγμα
  - 2,3 % DEN
  - 7,2 placebo
  - P<0,001
  - Μείωση σχετικού κινδύνου : 68%



- Νέο κάταγμα ισχίου : μείωση 40% (ρ= 0,04)

- Μη σπονδυλικό κάταγμα : μείωση 20% (ρ = 0,01)

The NEW ENGLAND JOURNAL of MEDICINE

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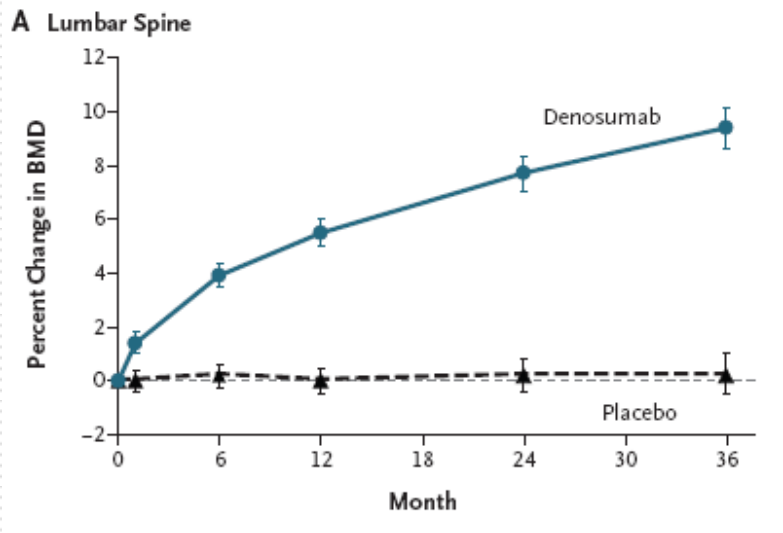
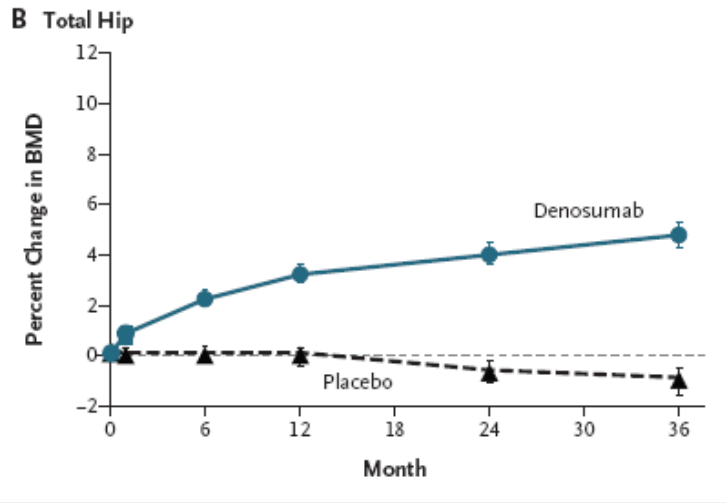
Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis





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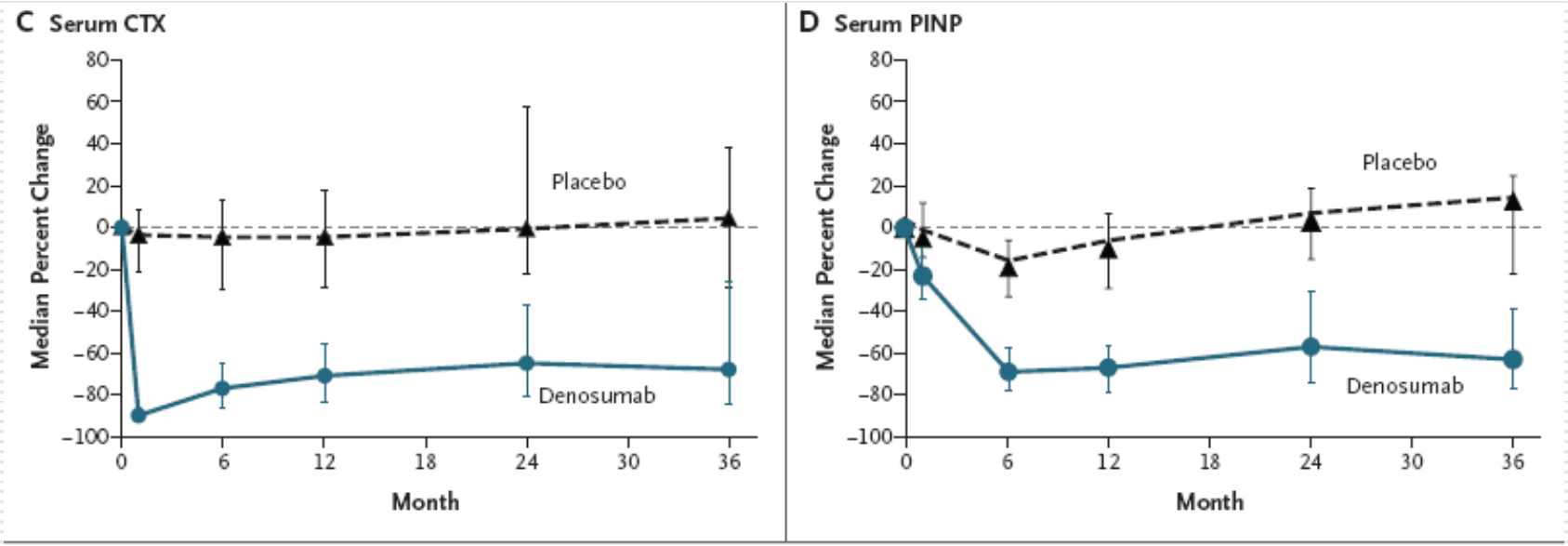

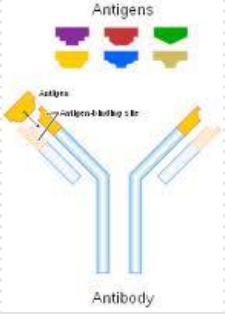

ARTHRITIS & RHEUMATISM
Vol. 58, No. 5, May 2008, pp 1299–1309
DOI 10.1002/art.23417

Denosumab Treatment Effects on Structural Damage, Bone Mineral Density, and Bone Turnover in Rheumatoid Arthritis

A Twelve-Month, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase II Clinical Trial

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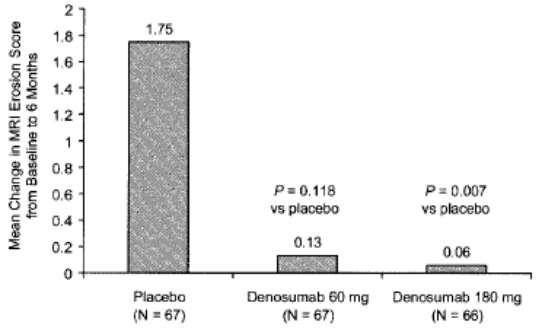
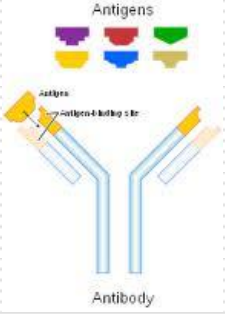
- Μείωση δεικτών οστικού μεταβολισμού
- Στατιστικά σημαντική μείωση με 180 mg στους 6 μήνες (P = 0,007)
  - mod sharp Score
  - MRI erosions score



- Δεν προέκυψαν δεδομένα για δράση :
  - Στένωση αρθρικού διαστήματος
  - PA ενεργότητα



Αύξηση BMD άκρων χειρών

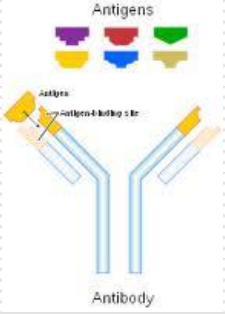
Mean changes in **hand BMD** at 6 and 12 months were:

- +0.8% and +1.0%, respectively, for denosumab 60 mg
- +2.0% and +2.5%, respectively, for denosumab 180 mg
- and -1.2% and -2.0%, respectively, for placebo

Erosion scores

- **remained near baseline** in the denosumab groups and
- increased from baseline in the placebo group

Deodhar A et al. Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients. Arthritis Care Res (Hoboken). 2010 Apr;62(4):569-74.

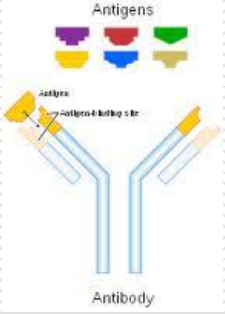


BMD άκρων χειρών

Twice-yearly injections of denosumab with ongoing methotrexate treatment significantly

- **reduced cortical bone loss** (digital x-ray radiogrammetry) in RA patients for up to 12 months
- denosumab 180 mg: 0.0001 gain

Sharp JT, et al . Denosumab prevents metacarpal shaft cortical bone loss in patients with erosive rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010 Apr;62(4):537-44.



Αύξηση BMD σε PA

Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates

Robin K Dore,[1] Stanley B Cohen,[2] Nancy E Lane,[3] William Palmer,[4] William Shergy,[5] Lifen Zhou,[6] Huei Wang,[6] Wayne Tsuji,[7] Richard Newmark[6]; on behalf of the Denosumab RA Study Group

Ann Rheum Dis 2010;**69**:872–875. doi:10.1136/ard.2009.112920

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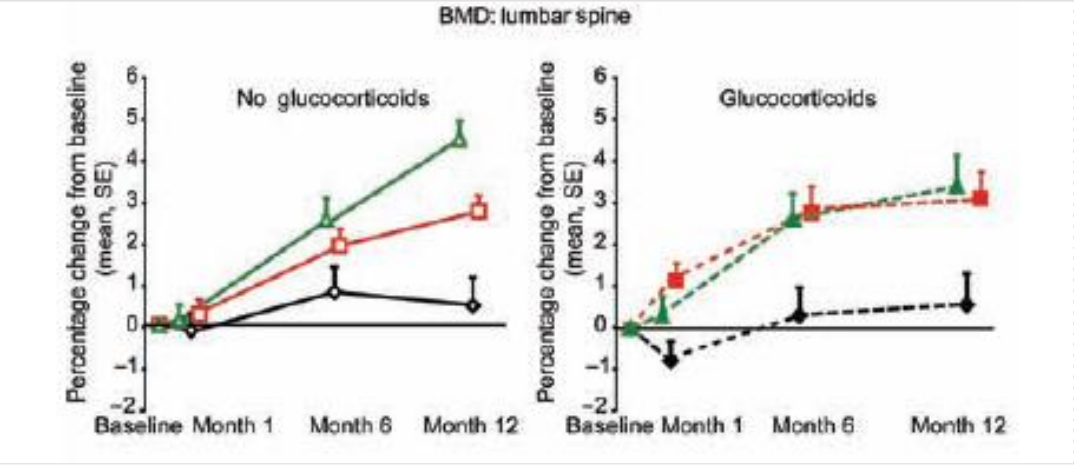

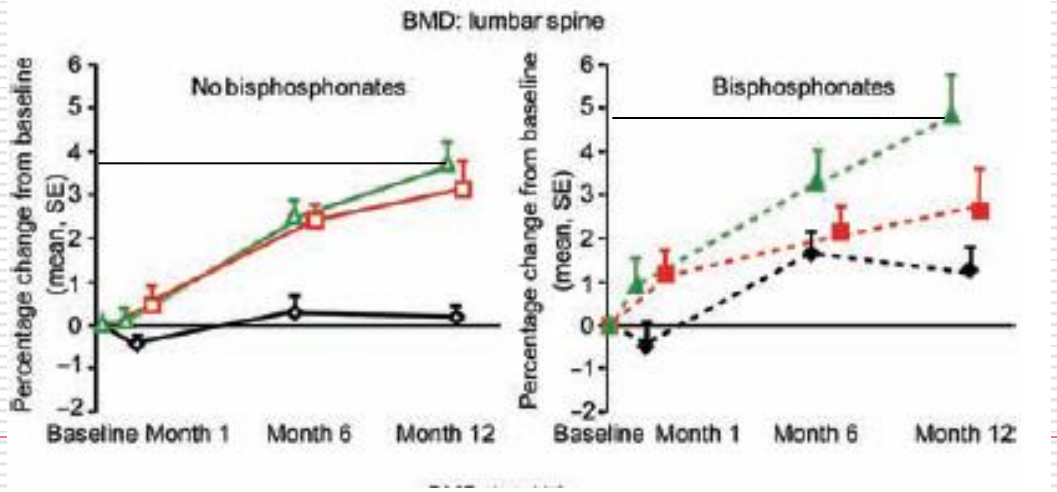

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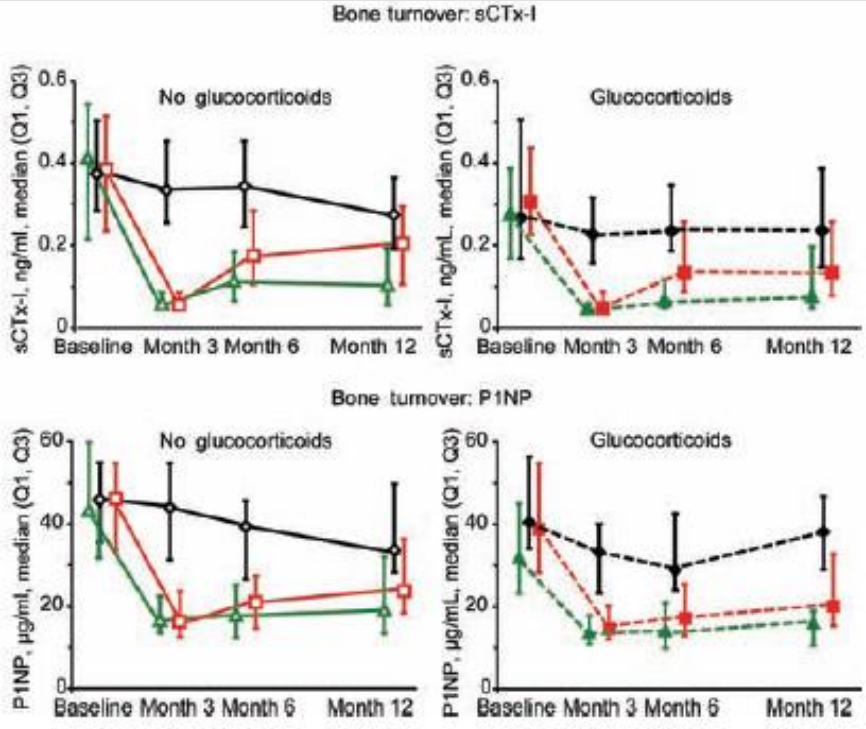

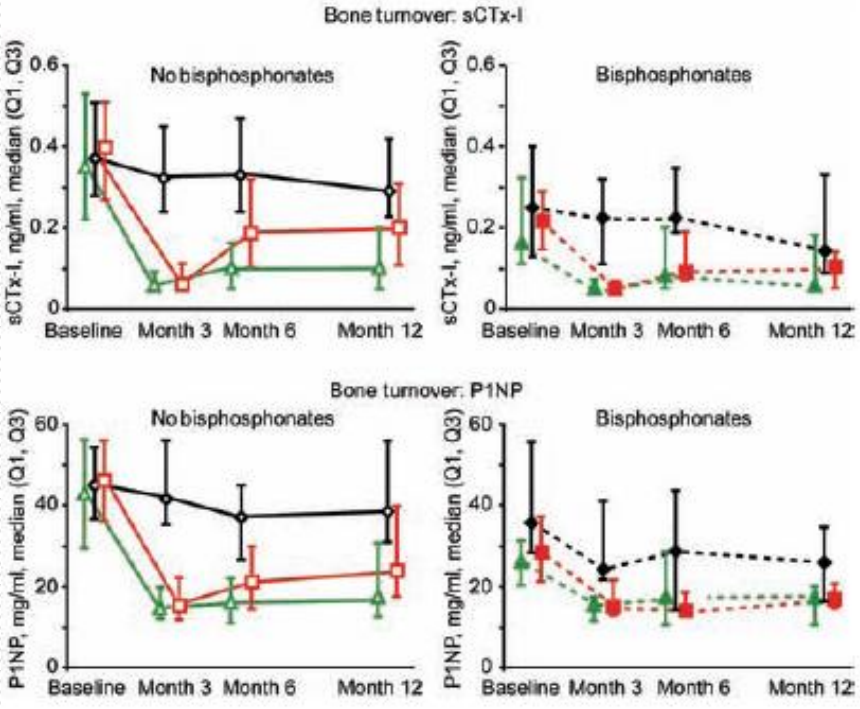

Take home messages

Τα φλεγμονώδη νοσήματα (PA) σχετίζονται από διαταραχές στον οστικό μεταβολισμό:

- Περιοχική οστική απώλεια
- Γενικευμένη οστική απώλεια **οστεοκλάστης**
- Διαβρώσεις

Take home messages

Μελέτες με βιολογικούς παράγοντες έχουν δείξει

- μείωση της οστικής απώλεια μέσω μείωσης της οστεοκλαστικής δραστηριότητας (και φλεγμονής)
- Βελτίωση profil οστικών δεικτών
- Σταθεροποίηση της *γενικευμένης* οστικής πυκνότητας (Dexa)
- Η *περιοχική* οστική απώλεια φαίνεται να είναι πιο «ευαίσθητη» στη νόσο => ανεκτική στη θεραπεία

ΕΥΧΑΡΙΣΤΩ !