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# *Ενδιαφέροντα Άρθρα Βιβλιογραφίας*

**Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized blinded phase 3 trial**

Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH et al.
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Το Denosumab είναι ένα πλήρες ανθρώπινο μονοκλωνικό αντίσωμα, το οποίο, δεσμεύοντας το RANKL, αναστέλλει την οστική απορρόφηση. Σε πολυκεντρική μελέτη φάσεως 3 με μετεμμηνοπαυσιακές γυναίκες με χαμηλή οστική μάζα (T score ≤-2.0 στην ΟΜΣΣ ή στο ισχίο), το Denosumab αύξησε σημαντικά την οστική πυκνότητα, έδειξε σημαντική μείωση στους δείκτες οστικού μεταβολισμού και ήταν εξίσου ασφαλές σε σύγκριση με την αλενδρονάτη κατά τη διάρκεια χορήγησής τους για ένα έτος.

Denosumab is a fully human monoclonal antibody that inhibits bone resorption by neutralizing RANKL, a key mediator of osteoclast formation, function and survival. This phase 3, multi-center, double-blind study compared the efficacy and safety of denosumab with alendronate in postmenopausal women with low bone mass. One thousand one hundred eighty-nine postmenopausal women with a T score ≤-2.0 at the lumbar spine or total hip were randomized 1:1 to receive subcutaneous denosumab injections (60mg every 6 months-Q6M) plus oral placebo weekly (n=594) or oral alendronate weekly (70mg) plus subcutaneous placebo injections Q6M (n=595). Changes in BMD were assessed at the total hip, femoral neck, trochanter, lumbar spine, and 1/3 radius at 6 and 12 months and in bone turnover markers at months 1, 3, 6, 9, and 12. Safety was evaluated by monitoring adverse events and laboratory values. At the total hip, denosumab significantly increased BMD compared with alendronate at month 12 (3.5% versus 2.6%; p<0.0001) Furthermore, significantly greater increases in BMD were observed with denosumab treatment at all measured skeletal sites (12-month treatment difference: 0.6% femoral neck; 1.0% trochanter; 1.1% lumbar spine; 0.6% 1/3 radius; p≤0.0002 all sites). Denosumab treatment led to significantly greater reduction of bone turnover markers compared with alendronate therapy. Adverse events and laboratory values were similar for denosumab -and alendronate- treated subjects. Denosumab demonstrated significantly larger gains in BMD and greater reduction in bone turnover markers compared with alendronate. The overall safety profile was similar for both treatments.

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**The effect of alendronate on progression of spinal osteophytes and disc-space narrowing**

Neogi T, Nevitt MC, Ensrud KE, Bauer D, Felson DT.
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Μια δευτερογενής ανάλυση δεδομένων από τυχαιοποιημένες μελέτες πρόληψης οστεοπορωτικών καταγμάτων με τη χορήγηση αλενδρονάτης έδειξε ότι το φάρμακο συσχετίζεται με μικρότερου βαθ-

μού σχηματισμό σπονδυλικών οστεόφυτων και με μικρότερου βαθμού στένωση του μεσοσπονδύλιου διαστήματος, συγκριτικά με το εικονικό φάρμακο. Το στοιχείο αυτό υποδεικνύει ότι τα διφωσφονικά φαίνεται να έχουν κάποιον τροποποιητικό ρόλο στην παθολογική διεργασία της οστεοαρθρίτιδας.

Background: Bisphosphonates may have chondroprotective effects that could be of relevance in osteoarthritis. Using data from a large fracture prevention trial, we evaluated the effect of alendronate on the progression of radiographic spinal osteophytes (OST) and disc-space narrowing (DSN).

Methods: The Fracture Intervention Trial (FIT) evaluated the effectiveness of alendronate at 5mg/day (first 2 years) followed by 10mg/day (third year) vs placebo over 3-4 years in preventing osteoporotic fractures. In 200 randomly selected subjects from FIT, we read baseline and follow-up lateral x-rays for anterior OST and DSN (both scored 0-3 at each vertebral level) in the thoracic and lumbar spine. We calculated the mean difference in change in the sum of OST and DSN scores at T4 to L5 from baseline to follow-up, respectively, in each treatment arm using linear regression.

Results: The participants' baseline characteristics were similar in the alendronate and placebo arms. The adjusted mean change in summary OST score was less in the alendronate group compared to placebo (3.2 vs 4.7; p=0.04), indicating that OST progression was less in the alendronate group. The adjusted mean change in summary DSN score was less in the alendronate group vs placebo for the whole spine (0.4 vs 0.7; p=0.2), particularly when limited to the lumbar spine (0.3 vs 0.6; p=0.04).

Conclusions: In this secondary analysis of data from a randomised controlled trial, alendronate was associated with less spinal OST and DSN progression than placebo. This suggests a role for bisphosphonates in altering the pathological processes seen in osteoarthritis.

**Effects of long-term strontium ranelate treatment on the risk of non-vertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial**

Reginster J-Y, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi M-L et al.
*Arthritis Rheum 2008; 58:1687-95.*

Η θεραπεία της μετεμμηνοπαυσιακής οστεοπόρωσης με ρανελικό στρόντιο οδηγεί σε σταθερή μείωση της συχνότητας των οστεοπορωτικών σπονδυλικών και μη-σπονδυλικών καταγμάτων (π.χ. κατάγματα ισχίου) για περισσότερο από πέντε έτη.

Objective: This study was undertaken to assess the effect of strontium ranelate on non-vertebral and vertebral fractures in postmenopausal women with osteoporosis in a 5-year, double-blind, placebo-controlled trial.

Methods: A total of 5,091 postmenopausal women with osteoporosis was randomized to receive either strontium ranelate at 2gm/day or placebo for 5 years. The main efficacy criterion was the incidence of nonvertebral fractures. In addition, incidence of hip fractures was assessed, by post hoc analysis, in the subset of 1,128 patients who were at high risk of fractures (age 74 years or older, with lumbar spine and femoral neck bone mineral density T scores -2.4 or less). The incidence of new vertebral fractures was assessed, using the semi quantitative method described by Genant, in the 3,646 patients in whom spinal radiography (a non-mandatory procedure) was performed during the course of the study. Fracture data were analyzed using the Kaplan-Meier survival method.

Results: Of the 5,091 patients, 2,714 (53%) completed the study up to 5 years. The risk of non-vertebral fracture was reduced by 15% in the strontium ranelate group compared with the placebo group (relative risk 0.85; 95% confidence interval 0.73-0.99). The risk of hip fracture was decreased by 43% (relative risk 0.57; 95% confidence interval 0.33-0.97) and the risk of vertebral fracture was

decreased by 24% (relative risk 0.76; 95% CI 0.65-0.88) in the strontium ranelate group. After 5 years, the safety profile of strontium ranelate remained unchanged compared with the 3-year findings.

Conclusion: Our findings indicate that treatment of postmenopausal osteoporosis with strontium ranelate results in a sustained reduction in the incidence of osteoporotic non-vertebral fractures, including hip fractures and vertebral fractures over 5 years.

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**Rituximab combined with Peg-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis**

Saadoun D, Resche-Rigon M, Sene D, Perard L, Karras A, Cacoub P
*Ann Rheum Dis 2008; 67:1431-6.*

Ο συνδυασμός της ριτουξιμάμπης με πεγκυλιωμένη ιντερφερόνη και ριμπαβιρίνη αποτελεί μια ασφαλή και αποτελεσματική θεραπευτική επιλογή για την αντιμετώπιση της σοβαρής καταστροφικής μικτής κρυοσφαιριναιμικής αγγειίτιδας από τον ιό της ηπατίτιδας C.

Objectives: To report the results of a pilot study using rituximab combined with Peg-interferon (IFN) α2b-ribavirin in severe refractory hepatitis C virus (HCV) related mixed cryoglobulinaemia (MC) vasculitis.

Methods: Sixteen consecutive patients with severe HCV-MC vasculitis that were resistant (n = 11) or relapser (n = 5) to a previous combination treatment with standard (n = 10) or Peg-IFNa2b (n = 6) plus ribavirin were included. They were treated with rituximab (375mg/$m^2$ intravenously weekly for 4 weeks) combined with Peg-IFNa2b (1.5μg/kg per week subcutaneously) plus ribavirin (600-1200mg/day orally) for 12 months.

Results: Fifteen patients (93.7%) showed clinical improvement, 10 of whom (62.5%) were clinical complete responders (CR). HCV RNA and serum cryoglobulin became undetectable in all the clinical CR. Peripheral blood B cell depletion was achieved in all patients (CD19+ cells, 111 (SD 32)/$mm^3$ at baseline versus 2(2)/$mm^3$ after the fourth infusion of rituximab) with reconstitution starting at the end of antiviral treatment. Compared with clinical CR, the partial or non-responders had a 3.6 times longer duration of vasculitis prior to treatment and a lower rate of early virological response. Treatment was well tolerated with no infectious complications. After a mean follow-up of 19.4 (SD 3.6) months, two patients experienced clinical relapse associated with a simultaneous reappearance of HCV RNA and cryoglobulin and an increase in the number of B cells.

Conclusions: Rituximab combined with Peg-IFNa2b-ribavirin represents a safe and effective treatment option in severe refractory HCV-MC vasculitis.

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**Abnormal antinuclear antibody titers are less common than generally assumed in established cases of systemic lupus erythematosus**

Sjowall C, Sturm M, Dahle C, Bengtsson AA, Jonsen A, Sturfelt G et al.
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Οι αντιγονο-ειδική αντινουκλεοσωμιακή ανοσοενζυμική μέθοδος ανίχνευσης των ANA (ANSA-EIA) δεν έχει υψηλή διαγνωστική ειδικότητα για το ΣΕΛ ώστε να δικαιολογηθεί η χρήση της για διαγνωστικούς ελέγχους ρουτίνας.

Objective: To evaluate antinuclear antibody (ANA) tests in established cases of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) by indirect immunofluorescence microscopy (F-ANA) and enzyme-immunoassays detecting antinucleosomal antibodies (ANSA-EIA).

Methods: Sera from 50 patients with SLE and 65 patients with RA were analyzed regarding abnormal concentrations of F-ANA (serum dilution

≥1:200=95th percentile among 300 healthy blood donors). The sera were also analyzed with 2 commercial ANSA-EIA kits.

Results: An abnormal F-ANA titer occurred in 76% of the SLE sera compared to 23% in RA and was not related to present use of antirheumatic drugs. At dilution 1:50, 84% of the SLE sera were F-ANA-positive compared to 20% of healthy women. Forty percent and 56%, respectively, of the SLE sera tested positive in the 2 ANSA-EIA kits. By the most sensitive assay, 96% of the ANSA-positive SLE sera produced a homogenous (chromosomal) F-ANA staining pattern compared to 18% of the ANSA-negative SLE sera. Ten of the 15 F-ANA-positive RA sera (63%) generated homogenous F-ANA staining and 13 (20%) tested positive in the most sensitive ANSA-EIA, but with no correlation to the F-ANA staining pattern.

Conclusion: The sensitivity of F-ANA at an abnormal titer was surprisingly low (76%) in established cases of SLE. ANSA occurred in 56% of the SLE sera, but also in a fair number (20%) of RA sera. Practically all ANSA-positive SLE sera were identified by chromosomal F-ANA staining. We conclude that the antigen-specific antinucleosomal EIA does not have high enough diagnostic specificity to justify use of this analysis for routine diagnostic purposes.

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**Efficacy and safety of rilonacept (interleukin-1 trap) in patients with cryopyrin-associated periodic syndromes: Results from two sequential placebo-controlled studies**

Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A et al.
*Arthritis Rheum 2008; 58:2443-52.*

Η θεραπευτική εβδομαδιαία χορήγηση του rilonacept (interleukin-1 trap) δίνει ασφαλή, καλώς ανεκτή, σημαντική και παρατεταμένη βελτίωση της κλινικής συμπτωματολογίας και σημειολογίας των περιοδικών συνδρόμων που σχετίζονται με κρυοπυρίνες (CAPS) και μειώνει το αμυλοειδές SAA στα φυσιολογικά επίπεδα, απομακρύνοντας τον κίνδυνο ανάπτυξης αμυλοείδωσης.

Objective: To assess the efficacy and safety of rilonacept (Interleukin-1, IL-1, Trap), a long-acting and potent inhibitor of IL-1, in patients with cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

Methods: Forty-seven adult patients with CAPS, as defined by mutations in the causative NLRP3 (CIAS1) gene and pathognomonic symptoms, were enrolled in 2 consecutive phase III studies. Study 1 involved a 6-week randomized double-blind comparison of weekly subcutaneous injections of rilonacept (160mg) versus placebo. Study 2 consisted of 9 weeks of single-blind treatment with rilonacept (part A), followed by a 9-week, randomized, double-blind, placebo-controlled withdrawal procedure (part B). Primary efficacy was evaluated using a validated composite key symptom score.

Results: Forty-four patients completed both studies. In study 1, rilonacept therapy reduced the group mean composite symptom score by 84%, compared with 13% with placebo therapy (primary end point; P <0.0001 versus placebo). Rilonacept also improved significantly all other efficacy end points in study 1 (numbers of multi-symptom and single-symptom disease flare days, single-symptom scores, physician's and patient's global assessments of disease activity, limitations in daily activities, and C-reactive protein and serum amyloid A [SAA] levels). In study 2 part B, rilonacept was superior to placebo for maintaining the improvements seen with rilonacept therapy, as shown by all efficacy parameters (primary end point; P <0.0001 versus placebo). Rilonacept was generally well tolerated; the most common adverse events were injection site reactions.

Conclusion: Treatment with weekly rilonacept provided marked and lasting improvement in the clinical signs and symptoms of CAPS, and normalized the levels of SAA from those associated with risk of developing amyloidosis. Rilonacept exhibited a generally favorable safety and tolerability profile.