

BISFOSFONATI

GRUPPO ITALIANO PER LO STUDIO DEI BISFOSFONATI

IN QUESTO NUMERO

L'osteoporosi da corticosteroidi

Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group

Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism

Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis

Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis

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EDITORIALE

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L'OSTEOPOROSI DA CORTICOSTEROIDI

I corticosteroidi (CS) hanno rivoluzionato il trattamento di un largo numero di patologie fra cui l'asma, varie forme di artrite, alcune malattie del tessuto connettivo, alcune malattie autoimmuni del tratto gastroenterico e alcune malattie del sistema nervoso centrale. I CS sono spesso dei veri e propri salva-vita, sia usati per terapie a breve termine, sia per terapie a medio e lungo termine. Soprattutto in quest'ultimo caso causano frequenti e importanti effetti collaterali, compresa l'osteoporosi (OP).

Estrapolando i dati di studi anglosassoni si può stimare che circa 300.000 italiani assumano CS per via orale in maniera continuativa e che circa 1.800.000 lo facciano per via inalatoria.

L'OP primitiva riguarda 3.000.000 di donne in postmenopausa, di cui 1/3 va incontro a fratture, ma la prevalenza di fratture nell'osteoporosi indotta da CS (CIO) è 20 volte superiore, come si può dedurre valutando i gruppi di controllo dei più recenti trial internazionali sull'uso di bisfosfonati nell'OP postmenopausale e nella CIO.

L'uso di CS si verifica maggiormente nel sesso femminile e tra i 50 e gli 80 anni, ossia in un momento critico per il metabolismo osteoscheletrico. La prevalenza di CIO dipende da numerosi fattori, legati alla dose cumulativa, alla durata del trattamento, alla presenza di altri fattori di rischio fra cui anche la malattia di fondo curata con i CS. Alcuni studi clinici hanno evidenziato una più rapida perdita di massa ossea nei primi 6-12 mesi che mediamente è del 7% annuo, mentre altri studi biotipici hanno evidenziato una demineralizzazione trabecolare che raggiunge il 30%.

Questi dati sono una media di valori molto variabili. A parità di dosaggio, età postmenopausale e attività e stadio di malattia di fondo vari soggetti possono essere diversamente sensibili all'impatto dei CS. In merito si sta studiando il polimorfismo del recettore dei CS. Un altro aspetto genetico riguarda il polimorfismo del recettore della vitamina D, che avrebbe un ruolo nel determinismo del picco di massa ossea e nella risposta ai CS.

Patogenesi della CIO

I CS influenzano l'omeostasi osteoscheletrica attraverso numerosi e complessi meccanismi in parte diretti sulle cellule ossee e in parte mediati da modificazioni degli ormoni calciotropi.

A livello cellulare i CS sopprimono il reclutamento degli osteoblasti e ne determinano la depressione funzionale, con conseguente riduzione della matrice non

calcificata neoformata. Ciò avviene per diretta inibizione dell'espressione genica a livello trascrizionale e post-trascrizionale del gene che codifica il collagene di tipo I, ma anche per stimolo alla produzione di mRNA del collagene di tipo 3. I CS, inoltre, riducono negli osteoblasti l'espressione genica dell'inibitore tissutale della metalloproteasi I (TIMP), che riduce la degradazione del collagene di tipo I. I CS inibiscono l'espressione del gene che codifica l'integrina B-1, che determina l'adesione degli osteoblasti alla matrice proteica e la sua mineralizzazione. I CS inibiscono la sintesi delle PGE₂, che stimolano la sintesi delle proteine collageniche e non collageniche dell'osso. Altri effetti riguardano i cosiddetti fattori di crescita.

I CS riducono direttamente l'IGF-1 e indirettamente, attraverso l'incremento della sintesi dell'IGFBP-6, l'IGF-2 con riduzione della matrice proteica e del riassorbimento osteoclastico. Inoltre, viene inibito il legame del TGF-beta con il suo recettore, con conseguente riduzione dell'attività osteoblastica e stimolo dell'attività osteoclastica e aumento della sensibilità alla IL-1.

Il numero dei recettori della vitamina D (VDR) negli osteoblasti è risultato drasticamente ridotto in presenza di CS.

L'effetto più sorprendente è stato dimostrato nel 1998 dal gruppo di Manolagas: i CS inducono, sia nell'animale sia nell'uomo, l'apoptosi degli osteoblasti e degli osteociti. La morte degli osteociti sarebbe tra l'altro la causa dell'osteonecrosi.

L'azione sugli osteoclasti è più controversa: l'effetto diretto sarebbe prevalentemente inibitorio, nonostante le modificazioni sulle citochine abbiano spesso segno opposto, mentre in caso di aumento del PTH, il riassorbimento può essere aumentato soprattutto nelle terapie a lungo termine.

Recentemente è stato dimostrato che i CS inibiscono l'osteoprotegerina (OPG), proteina che inibisce l'osteoclastogenesi, interagendo con il RANKL al posto del RANK. L'interazione fra RANK e RANKL normalmente provoca la differenziazione e la maturazione sia dei precursori degli osteoclasti sia degli osteoblasti.

Riguardo agli effetti sul metabolismo calcio-fosforo, i CS riducono l'assorbimento intestinale del calcio (per riduzione dei VDR e forse per ridotta attivazione renale della vitamina D) e aumentano la calciuria, determinando indirettamente un aumento del PTH. Inoltre, i CS avrebbero effetti diretti anche sulla secrezione di questo ormone e sulla sensibilità del relativo recettore osteoblastico.

I GC causano la riduzione degli ormoni sessuali sia indirettamente, riducendo la produzione pituitaria e surrenalica, sia direttamente sulla secrezione gonadica.

Prevenzione e trattamento della CIO

Nei pazienti che assumono CS la riduzione della massa ossea porta a un rischio di frattura che, come abbiamo detto all'inizio, è molto più alto di quello di soggetti affetti da OP postmenopausale o senile, ma anche di quello di soggetti con artrite non trattata con CS. Ciò avviene non solo per una maggiore demineralizzazione, ma anche a parità di massa ossea, a testimoniare la presenza di alterazioni biomeccaniche di tipo qualitativo oltreché quantitativo. Le fratture sono più comuni là dove prevale l'osso trabecolare (vertebre e coste), ma anche a livello femorale, dove risultano triplicate rispetto ai soggetti non sottoposti a terapia cortisonica. Nei soggetti trapiantati il rischio raddoppia ulteriormente anche per l'uso di immunosoppressori.

Ciò fa sì che nella CIO non si possa accettare quella di -2,5 DS come soglia densitometrica diagnostica e di intervento terapeutico, ma si debbano considerare valori di guardia quelli di -1 o -1,5 DS.

In due studi è stato osservato che solamente l'8-14% dei soggetti in trattamento cronico con CS si sottopone a una qualche terapia o prevenzione della CIO, per cui occorre sensibilizzare la classe medica, e di conseguenza i pazienti, a questo problema attraverso un'attenta informazione oltre che attraverso linee guida facilmente praticabili.

Non completamente soddisfacenti sono risultate le linee guida emanate nel 1996 e nel 1998, rispettivamente, dall'ACR e da un gruppo britannico appositamente costituitosi.

Le linee britanniche sono previste per chi assume la dose quotidiana di almeno 7,5 mg di prednisone o equivalente. In realtà tutta una serie di lavori, fra cui anche uno recente del gruppo SIR per lo studio dell'OP nelle malattie reumatiche, ha dimostrato che anche dosi quotidiane più piccole sono osteopenizzanti.

La riduzione del fumo e dell'alcol, lo svolgimento di una regolare attività fisica, la riduzione del rischio di cadute, personale e ambientale, la supplementazione di calcio e vitamina D in anziani istituzionalizzati e in caso di carenza alimentare devono essere considerate quali misure generali. Inoltre, è raccomandata la rivalutazione della dose minima efficace del CS e, in caso di intolleranza ai glucidi o di altri effetti collaterali, il passaggio a deflazacort.

In presenza di dosi di almeno 15 mg di prednisone o equivalente per almeno 6 mesi, in presenza di una frattura o di altri forti fattori di rischio (età >65 anni, menopausa antecedente i 45 anni, indice di massa corporea <20, fumo, anamnesi familiare di fratture da fragilità), si può prescindere da una valutazione densitometrica, sebbene occorra procedere a una serie di valutazioni di laboratorio che sono tese anche a escludere altre cause di OP secondaria (rx colonna, VES, calcemia, fosforemia, fosfatasi alcalina, emocromo, elettroforesi proteica, ormoni tiroidei, testosterone totale nei maschi, estradiolo nelle donne amenorroiche in premenopausa). In caso di ipogonadismo la terapia di prima scelta consigliata è l'estradiolo (in premenopausa), l'HRT (in postmenopausa), il testosterone (nel maschio). In assenza di ipogonadismo (quindi in premenopausa o nel maschio) o in caso di insuccesso o rifiuto da parte del paziente si consigliano bisfosfonati, calcitriolo, fluoro, calcitonina nasale.

In caso di dosi inferiori ai 15 mg di prednisolone o equivalente, in assenza di fratture e di altri fattori forti di rischio, la BMD indirizza il comportamento da seguire. Se il T-score è <-1,5 si rientra automaticamente nell'iter sopraesposto; se il T è compreso fra 0 e -1,5 bisogna valutare la perdita dopo un anno; se supera il 4% lombare o il 7% femorale si rientra nell'iter sopraesposto, altrimenti si rimisura la BMD ogni 3-5 anni. Se il T-score è >0 basta rimisurare la BMD dopo 3-5 anni.

Con particolare riferimento ai bambini viene consigliato l'uso di deflazacort, CS per via inalatoria o topica e somministrazione a giorni alterni.

Le linee guida dell'ACR sono simili e distinguono formalmente il paziente con o senza frattura da fragilità e, nella sostanza, presentano dei provvedimenti simili. Viene anche qui consigliata una valutazione clinica-laboratoristica, che è ancor più estesa (per esempio, il dosaggio della 25-OHvitD). La densitometria viene comunque consigliata (femorale in tutti i soggetti, lombare prima dei 60 anni), ma la terapia indicata è indipendente dal risultato densitometrico e dei test di laboratorio: calcio + vitamina D + HRT (estradiolo in premenopausa con irregolarità mestruali) + aumento dell'attività fisica. In assenza di fratture, in caso di T-score >-1, si consiglia l'HRT solo in postmenopausa. Solo in seconda battuta vengono consigliati bisfosfonati, calcitonina, fluoro e steroidi anabolizzanti. In presenza di calciuria >300

mg/die e in assenza di terapia con calcitriolo, viene indicato l'uso di un tiazidico, altrimenti deve essere corretta la dose di calcio e/o di calcitriolo.

Per concludere bisogna fare un cenno su alcune problematiche sollevate soprattutto dalle linee guida britanniche.

Riguardo all'ipotetico ruolo protettivo svolto da deflazacort sulla massa ossea, in letteratura non sono presenti dati concordanti su questa azione; forse è ipotizzabile per l'impiego di deflazacort ad alti dosaggi, mentre per bassi dosaggi esso è dubbio, anche perché il farmaco sembra troppo spesso essere stato sottodosato in virtù di un erroneo rapporto dose/equivalenza con prednisone (non 6/5 bensì 7-8/5).

Un altro aspetto riguarda la cosiddetta dose minima efficace. Alcuni studi hanno dimostrato che il sottodosaggio di CS soprattutto in presenza di artrite in fase attiva determina una maggiore demineralizzazione rispetto a un dosaggio minimo ma tale da abbattere gli indici di flogosi. Del resto è noto che i CS abbattano i livelli di IL-6 e TNF, che sono causa di OP nell'artrite reumatoide.

L'altra considerazione riguarda la terapia a giorni alterni, che non si è dimostrata protettiva anche in presenza di dosi cumulative più basse, rispetto alla terapia quotidiana.

Per quanto riguarda gli steroidi per via inalatoria, essi risultano particolarmente osteopenizzanti se vengono superate le dosi consigliate (da 2 a 8 spray al dì); comunque, seppur in minor misura rispetto alla terapia orale, determinano demineralizzazione anche a dosi di comune uso, soprattutto dopo alcuni anni di terapia. A tal riguardo esistono molecole che alle dosi comuni sono meno dannose, come budesonide e fluticasone, ma che purtroppo non sono assorbite per via orale e parenterale.

A tale proposito la ricerca si sta indirizzando nell'allestire molecole selettive che agiscano soprattutto come antiflogistici a livello dei fattori di trascrizione (trans-soppressione; origine degli effetti benefici dei CS) non avendo azioni endocrino-metaboliche mediate da meccanismi di legame col recettore (transattivazione; origine degli effetti collaterali).

Ma la cosa più importante è che, alla luce dei più recenti dati pubblicati, le linee guida risultano datate soprattutto per il ruolo secondario che attribuiscono ai bisfosfonati.

Infatti nel 1998 sono stati pubblicati i risultati della prevenzione e terapia della CIO a un anno di studio con alendronato in pazienti affetti da varie patologie e che assumevano mediamente 10 mg di prednisone. Tutti i pazienti assumevano calcio (800-1000 mg/die) e vitamina D (250-500 UI/die). La massa ossea risultava aumentata in tutto lo scheletro, indipendentemente dal sesso, dallo stato menopausale, dalla dose di CS e dalla patologia di fondo (*Figura 1*); la riduzione delle fratture vertebrali non risultava significativa, pur essendo del 40%. Lo studio, esteso al secondo anno, raggiungeva la significatività in termini di riduzione dell'incidenza di fratture (oltre il 60%) riunendo i dati di diversi dosaggi. Infatti, solo il 2% dei pazienti trattati, rispetto a quasi il 4% di quelli trattati con placebo, presentava fratture vertebrali (*Figura 2*). Alendronato risultava ben tollerato; in particolare non si registrava aumento degli effetti collaterali in associazione a FANS o a farmaci di fondo.

Risultati sovrapponibili sono stati recentemente pubblicati per residronato. Anche in questo caso la significatività statistica nella riduzione delle fratture è stata raggiunta

Figura 1. CIO: valutazione della BMD vertebrale a seconda del sesso/menopausa/impiego di estrogeni

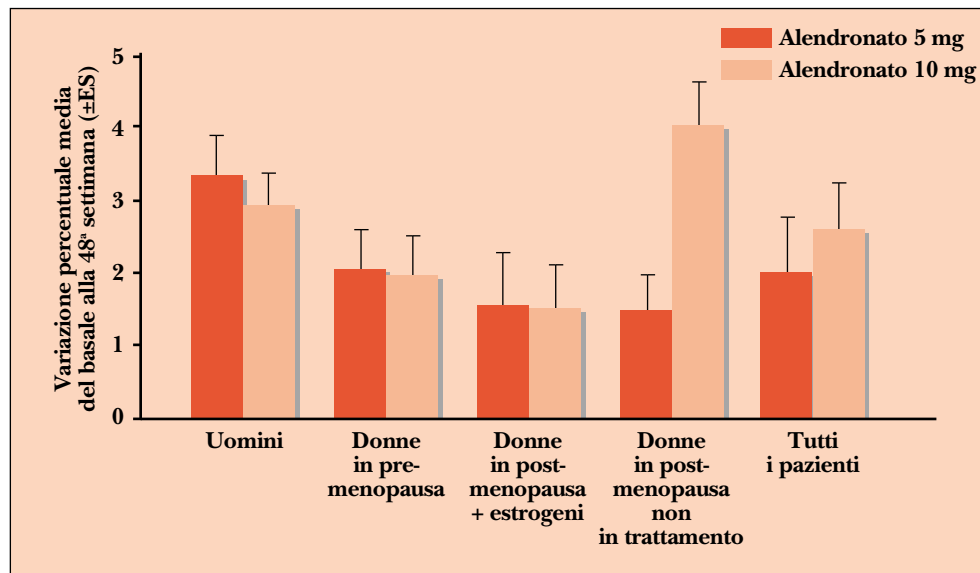
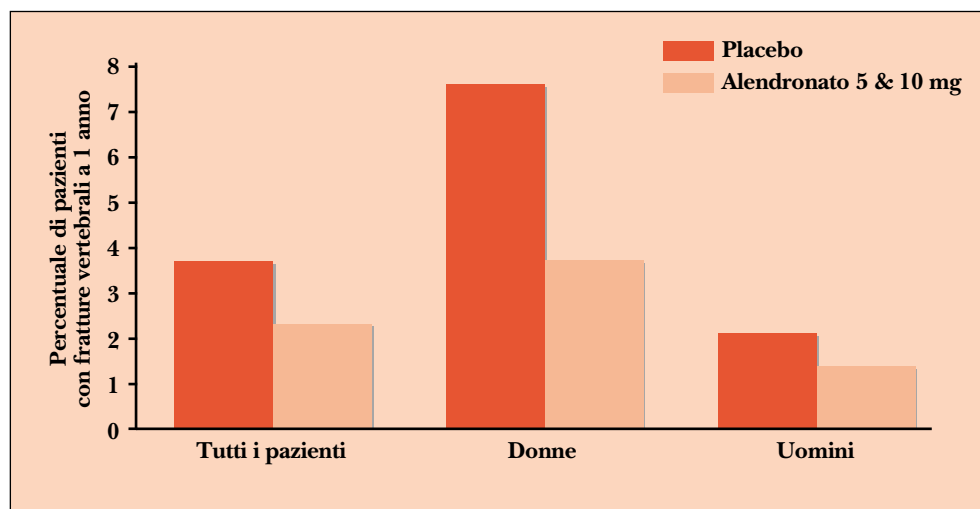


Figura 2. CIO: efficacia di alendronato sulle fratture vertebrali morfometriche a seconda del sesso



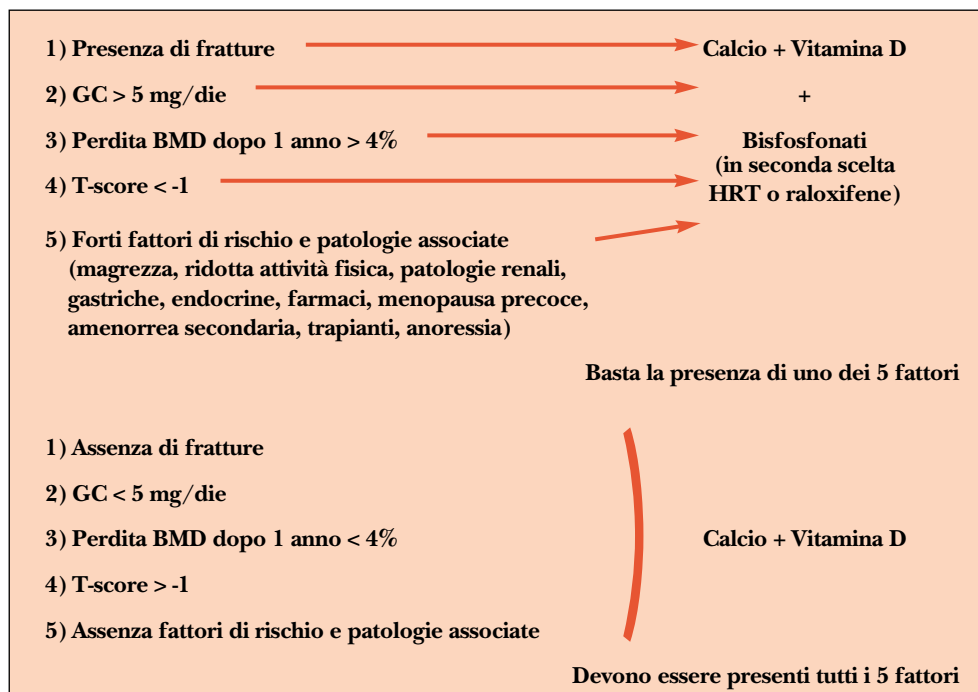
riunendo due sottogruppi di studio: quello di prevenzione e quello di trattamento.

Questi studi hanno portato in Italia, solamente per queste due molecole, all'indicazione "osteoporosi da corticosteroidi" e alla rimborsabilità (nota 79), in presenza di una frattura e nel caso di dosi di almeno 7,5 mg di prednisone o equivalente, protrattesi per almeno 6 mesi.

A nostro avviso, seguendo un comportamento più rispondente all'esperienza quotidiana e ad alcuni contributi scientifici, si potrebbe porre l'indicazione all'uso di un bisfosfonato, in presenza di un fattore di rischio già a dosi di 5 mg di prednisone protrattesi (o in previsione di protrarsi) per tre mesi (Figura 3).

Quello che stupisce in questi studi è che l'effetto di alendronato e risedronato sulla

Figura 3. Linee guida terapeutiche nel paziente da trattare a lungo termine con glucocorticoidi (GC) (> 3 mesi)



massa ossea, seppur significativo, non sia esaltante ad onta di un massiccio effetto sulla riduzione di incidenza di fratture. Questi risultati sono ancora più favorevolmente sorprendenti se si tiene conto dei meccanismi patologici della CIO (inibizione prevalentemente osteoblastica) e del meccanismo di azione più noto degli aminobisfosfonati (inibizione prevalentemente osteoclastica).

Tutto ciò fa ipotizzare che queste molecole abbiano un meccanismo di azione più complesso.

Recentemente è stato dimostrato che alendronato inibisce l'IL-6, uno dei fattori osteopenizzanti della flogosi soprattutto nell'artrite reumatoide; tale IL risulta comunque aumentata dalla carenza estrogenica e stimola il riassorbimento osteoclastico, ma inibisce anche l'attività osteoblastica.

Ancora più interessante è l'osservazione in vitro che alendronato inibisce l'apoptosi degli osteoblasti e degli osteociti indotta da CS. Un simile effetto è attribuibile al paratormone, che si è rivelato estremamente efficace nella CIO se associato a estrogeni.

L'associazione di un potente stimolatore degli osteoblasti (PTH) con un potente inibitore degli osteoclasti, che rispetta se non addirittura stimola l'attività osteoblastica (un aminobisfosfonato come alendronato o residronato) dovrebbe in futuro dare i migliori risultati nella terapia della CIO.

ABSTRACT

SEZIONE A

Questa sezione riporta abstract di articoli recentemente pubblicati, selezionati dal capo-redattore e completati da un commento editoriale.

Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group
 McChung MR, Geusens P, Miller PD et al. for the Hip Intervention Program Study Group
 N ENGL J MED 2001; 344 (5): 333-40

Background: Risedronate increases bone mineral density in elderly women, but whether it prevents hip fracture is not known.

Methods: We studied 5445 women 70 to 79 years old who had osteoporosis (indicated by a T score for bone mineral density at the femoral neck that was more than 4 SD below the mean peak value in young adults [-4] or lower than -3 plus a nonskeletal risk factor for hip fracture, such as poor gait or a propensity to fall) and 3886 women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low bone mineral density at the femoral neck (T score, lower than -4 or lower than -3 plus a hip-axis length of 11.1 cm or greater). The women were randomly assigned to receive treatment with oral risedronate (2.5 or 5.0 mg daily) or placebo for three years. The primary end point was the occurrence of hip fracture.

Results: Overall, the incidence of hip fracture among all the women assigned to risedronate was 2.8 percent, as compared with 3.9 percent among those assigned to placebo (relative risk, 0.7; 95 percent confidence interval, 0.6 to 0.9; P=0.02). In the group of women with osteoporosis (those 70 to 79 years old), the incidence of hip fracture among those assigned to risedronate was 1.9 percent, as compared with 3.2 percent among those assigned to placebo (relative risk, 0.6; 95 percent confidence interval, 0.4 to 0.9; P=0.009). In the group of women selected primarily on the basis of nonskeletal risk factors (those at least 80 years of age), the incidence of hip fracture was 4.2 percent among those

COMMENTO

L'importanza di questo studio è duplice. Viene confermata in uno studio "ad hoc" la capacità dei bisfosfonati di prevenire le fratture di femore. Per altro verso è stato osservato che pazienti con fattori di rischio di frattura di femore per cadute, hanno effettivamente (prospettivamente) un'elevata incidenza di queste fratture e non beneficiano in maniera significativa della terapia con bisfosfonati. Sfortunatamente i valori densitometrici in questo gruppo di pazienti era noto solo in meno del 50% dei casi, per cui rimane da stabilire se la presenza o meno di osteoporosi fosse corresponsabile dell'incapacità della terapia di ridurre il rischio di frattura.

assigned to risedronate and 5.1 percent among those assigned to placebo ($P=0.35$).

Conclusions: Risedronate significantly reduces the risk of hip fracture among elderly women with confirmed osteoporosis but not among elderly women selected primarily on the basis of risk factors other than low bone mineral density.

Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism

Rossini M, Gatti D, Isaia G et al.

J BONE MINER RES 2001; 16 (1): 113-9

In a large proportion of the patients with primary hyperparathyroidism (PHPT), a variable degree of osteopenia is the only relevant manifestation of the disease. Low bone mineral density (BMD) in patients with PHPT is an indication for surgical intervention because successful parathyroidectomy results in a dramatic increase in BMD. However, low BMD values are almost an invariable finding in elderly women with PHPT, who are often either unwilling or considered unfit for surgery. Bisphosphonates are capable of suppressing parathyroid hormone (PTH)-mediated bone resorption and are useful for the prevention and treatment of postmenopausal osteoporosis. In this pilot-controlled study, we investigated the effects of oral treatment with alendronate on BMD and biochemical markers of calcium and bone metabolism in elderly women presenting osteoporosis and mild PHPT. Twenty-six elderly patients aged 67-81 years were randomized for treatment with either oral 10 mg alendronate on alternate-day treatment or no treatment for 2 years. In the control untreated patients a slight significant decrease was observed for total body and femoral neck BMD, without significant changes in biochemical markers of calcium and bone metabolism during the 2 years of observation. Urine deoxypyridinoline (Dpyr) excretion significantly fell within the first month of treatment with alendronate, while serum markers of bone formation alkaline phosphatase and osteocalcin fell more gradually and the decrease became significant only after 3 months of treatment; thereafter all bone turnover markers remained consistently suppressed during alendronate treatment. After 2 years in this group we observed statistically significant increases in BMD at lumbar spine, total hip, and total body ($+8.6 \pm 3.0\%$, $+4.8 \pm 3.9\%$, and $+1.2 \pm 1.4\%$ changes vs. baseline mean \pm SD) versus both baseline and control patients. Serum calcium, serum phosphate, and urinary calcium excretion significantly decreased during the first 3-6 months but rose back to the baseline values afterward. Increase in serum PTH level was statistically significant during the first year of treatment. These preliminary results may make alendronate a candidate as a supportive therapy in patients with mild PHPT who are unwilling or are unsuitable for surgery, and for whom osteoporosis is a reason of concern.

COMMENTO

La terapia con alendronato determina rapidi e importanti aumenti della massa ossea in pazienti con iperparatiroidismo primitivo. Vale la pena di avviare questa terapia in tutti i pazienti che non vengono operati, o perché asintomatici, o perché non-idonei all'intervento? In realtà abbiamo ancora troppe incertezze riguardo all'entità del rischio fratturativo in pazienti con iperparatiroidismo primitivo non-operati a parità di massa ossea e d'età.

Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis

Pfeifer M, Begerow B, Minne HW et al.

EXP CLIN ENDOCRINOL DIABETES 2001; 109 (2): 87-92

The aim of this study was to identify factors associated with fractures in patients with postmenopausal osteoporosis. The overall hypothesis was that trunk muscle strength, body sway and hypovitaminosis D would influence daily activities and the likelihood of falls and fractures. - In 237 women (mean age 62.9±7.4 years) osteoporosis was defined by a T-score at the femoral neck below -2.5 SD. Trunk muscle strength was determined using isokinetic dynamometry and body sway was measured according to Lord et al. Limitations in everyday life were assessed and the history of falls was documented. A fracture was defined as a vertebral height reduction of more than 20% or at least 4 mm. The assessment was carried out using the Spine Deformity Index (SDI) and was confirmed by an experienced radiologist. Pearson coefficients of correlation were calculated. - After correction for age, significant associations were found for body sway and 25-hydroxyvitamin D (p<0.001), body sway and falls (p<0.001), body sway and rib fractures (p<0.01), trunk muscle strength and limitations in everyday life (p<0.001), trunk muscle strength and SDI (p<0.001), trunk muscle strength and bone density (p<0.001), and bone density and 25-hydroxyvitamin D (p<0.001). No significant correlation was found for trunk muscle strength and 25-hydroxyvitamin D (p=0.712). - Findings suggest that hypovitaminosis D is associated with increased body sway and an elevated risk for falls and falls-related fractures. Musculoskeletal rehabilitation should include strengthening exercises for the trunk muscles and training of neuromuscular co-ordination and balance.

Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis

Neer RM, Arnaud CD, Zanchetta JR et al.

N ENGL J MED 2001; 344 (19): 1434-41

Background: Once-daily injections of parathyroid hormone or its amino-terminal fragments increase bone formation and bone mass without causing hypercalcemia, but their effects on fractures are unknown.

Methods: We randomly assigned 1637 postmenopausal women with prior vertebral fractures to receive 20 or 40 microg of parathyroid hormone (1-34) or placebo, administered subcutaneously by the women daily. We obtained vertebral radiographs at base line and at the end of the study (median duration of observation, 21 months) and performed serial measurements of bone mass by dual-energy x-ray absorptiometry.

Results: New vertebral fractures occurred in 14 percent of

COMMENTO

In questo lavoro viene oggettivata la relazione tra compromissione funzionale muscolare e livelli di vitamina D. Anche in considerazione dell'elevata incidenza di ipovitaminosi D tra i nostri anziani, sarebbe opportuno riverificare questa associazione determinando anche se e in quanto tempo la somministrazione di vitamina D possa modificare la situazione muscolare.

COMMENTO

Il trial dimostra una straordinaria efficacia anti-fratturativa della terapia con PTH, smentendo dubbi relativi alla possibilità che questo ormone determinasse solo una ricompartimentazione della massa ossea. Il PTH offrirà nuove possibilità terapeutiche nei pazienti più gravi. Una più estesa utilizzazione rimane incerta per la necessità di meglio conoscere la sicurezza d'impiego a lungo termine. Un ulteriore problema potrebbe essere rappresentato dal costo della terapia.

the women in the placebo group and in 5 percent and 4 percent, respectively, of the women in the 20-microg and 40-microg parathyroid hormone groups; the respective relative risks of fracture in the 20-microg and 40-microg groups, as compared with the placebo group, were 0.35 and 0.31 (95 percent confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). New nonvertebral fragility fractures occurred in 6 percent of the women in the placebo group and in 3 percent of those in each parathyroid hormone group (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.86]). As compared with placebo, the 20-microg and 40-microg doses of parathyroid hormone increased bone mineral density by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck; the 40-microg dose decreased bone mineral density at the shaft of the radius by 2 more percentage points. Both doses increased total-body bone mineral by 2 to 4 more percentage points than did placebo. Parathyroid hormone had only minor side effects (occasional nausea and headache).

Conclusions: Treatment of postmenopausal osteoporosis with parathyroid hormone (1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated. The 40-microg dose increased bone mineral density more than the 20-microg dose but had similar effects on the risk of fracture and was more likely to have side effects.

SEZIONE B

Questa sezione riporta una serie di abstract selezionati dal capo-redattore, senza commento editoriale.

Clinical and radiological improvement of periodontal disease in patients with type 2 diabetes mellitus treated with alendronate: a randomized, placebo-controlled trial

Rocha M, Nava LE, Vazquez de la Torre C et al.

J PERIODONTOL 2001; 72 (2): 204-9

Background: Alendronate (ALN) is an aminobisphosphonate commonly used for osteoporosis in postmenopausal women. We studied the effect of ALN on bone loss prevention in type 2 diabetes mellitus patients with periodontal disease.

Methods: In a controlled double-blind, randomized study we evaluated prospectively diabetic patients paired by gender and years since diagnosis for 6 months. The study included 40 patients (20 men and 20 women), 50 to 60 years old, with more than 5 years since diagnosis of diabetes and established periodontitis. They were randomly allocated to alendronate (10 mg/daily) or placebo treatment for 6 months. The endpoints of treatment were: the distance between the alveolar bone border and the cemento-enamel-junction (CEJ) evaluated by means of digital radiographic imaging, a biochemical marker of bone resorption (urine N-telopeptide) (Ntx), and periodontal parameters. Metabolic control was assessed at baseline and after 6 months.

Results: Baseline and 6-month glycosylated hemoglobin levels were similar in both groups. Alendronate induced a

significant decrease in NTx at 6 months (P = 0.006). Periodontal parameters improved in both groups. However, they were significantly better for the ALN treated group. Alveolar bone border-CEJ distance increased in the placebo, but decreased in the ALN group (P = 0.0003).

Conclusions: In type-2 diabetic patients, alendronate induced more improvement in alveolar bone crest height than control therapy. No differences in urinary N-telopeptide or glycosylated hemoglobin were observed in this short-term randomized controlled pilot trial.

Alendronate and naproxen are synergistic for development of gastric ulcers

Graham DY, Malaty HM

ARCH INTERN MED 2001; 161 (1): 107-10

Background: Both alendronate sodium use and nonsteroidal anti-inflammatory drug use are associated with gastric ulcers. The aim of this study was to investigate whether alendronate and naproxen are synergistic as causes of gastric ulcers. **Methods:** We performed an endoscopist-blind, randomized, crossover, single-center comparison of 10 mg/d of alendronate sodium, 500 mg of naproxen sodium twice daily, or the combination taken orally for 10 days in volunteers aged 30 years or older. Videoendoscopy was used to evaluate the presence and degree of mucosal damage to the esophagus, stomach, or duodenal bulb before and after each treatment. There was a 1- to 4-week washout between evaluations.

Results: Twenty-six healthy volunteers participated (18 women and 8 men), aged 30 to 50 years. Gastric ulcers were present in 2 subjects receiving

alendronate (8%), in 3 receiving naproxen (12%), and in 10 receiving both (38%) (P<.05 for the combination vs either drug alone).

Conclusions: Both alendronate and naproxen can cause gastric ulcers. The combination appears synergistic. Alendronate should be used with caution in those who simultaneously require nonsteroidal anti-inflammatory drugs.

Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption

Price PA, Faus SA, Williamson MK

ARTERIOSCLER THROMB VASC BIOL 2001; 21 (5): 817-24

The present experiments were carried out to test the hypothesis that artery calcification is linked to bone resorption by determining whether the selective inhibition of bone resorption with the bisphosphonates alendronate and ibandronate will inhibit artery calcification. Artery calcification was first induced by treatment of 42-day-old male rats with warfarin, a procedure that inhibits the gamma-carboxylation of matrix Gla protein and has been shown to cause extensive calcification of the artery media within 2 weeks. These experiments revealed that ibandronate (0.05 mg. kg(-1). d(-1)) and alendronate (0.1 mg. kg(-1). d(-1)) completely inhibited calcification of all arteries and heart valves examined after 2 and 4 weeks of warfarin treatment. A 10-fold lower dose of alendronate reduced artery calcification by 50% (P<0.005). These bisphosphonate doses are comparable to those that inhibit bone resorption in rats of this age. More rapid artery calcification was induced by treatment with warfarin together with high doses of vitamin D, a procedure that causes extensive artery calcification by 84 hours. Alendronate and ibandronate again completely inhibited

calcification of all arteries and heart valves examined. The subcutaneous doses of alendronate and ibandronate necessary to inhibit artery calcification are comparable to the daily subcutaneous doses of these drugs that have previously been shown to inhibit bone resorption in rats of the same age, with 50% inhibition of artery calcification at 20 μ g alendronate. kg(-1). d(-1) and at 1 μ g ibandronate. kg(-1). d(-1). Bisphosphonate treatment did not affect serum calcium and phosphate, and so the inhibition of artery calcification cannot be due to a simple lowering of the serum calcium phosphate ion product. We conclude that bisphosphonates inhibit the calcification of arteries and heart valves at doses comparable to the doses that inhibit bone resorption. These results support the hypothesis that artery calcification is linked to bone resorption. The mechanism of this linkage remains to be established, however, and an alternative explanation for the present results is also considered.

Bisphosphonate therapy in fibrous dysplasia

Lane JM, Khan SN, O'Connor WJ et al. CLIN ORTHOP 2001; (382): 6-12

Fibrous dysplasia is proliferation of fibrous tissue within the bone marrow causing osteolytic lesions and pathologic fractures. Recently, second generation bisphosphonates have shown promise in the treatment of patients with fibrous dysplasia. In the current study, six patients with fibrous dysplasia were treated with either oral alone or oral and intravenous bisphosphonates. The participants were observed for changes in N-telopeptide, pain score, and radiographic changes. In the current study, the combination bisphosphonate therapy diminished pain, prevented fractures, lowered N-

telopeptide values, and led to partial resolution of fibrous dysplasia lesions.

Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles

Mashiba T, Turner CH, Hirano T et al. BONE 2001; 28 (5): 524-31

We recently demonstrated that suppression of bone remodeling allows microdamage to accumulate, leading to reduced bone toughness in the rib cortex of dogs. This study evaluates the effects of reduced bone turnover produced by bisphosphonates on microdamage accumulation and biomechanical properties at clinically relevant skeletal sites in the same dogs. Thirty-six female beagles, 1-2 years old, were divided into three groups. The control group was treated daily for 12 months with saline vehicle (CNT). The remaining two groups were treated daily with risedronate at a dose of 0.5 mg/kg per day (RIS), or alendronate at 1.0 mg/kg per day (ALN) orally. The doses of these bisphosphonates were six times the clinical doses approved for treatment of osteoporosis in humans. After killing, the L-1 vertebra was scanned by dual-energy X-ray absorptiometry (DXA), and the L-2 vertebra and right ilium were assigned to histomorphometry. The L-3 vertebra, left ilium, Th-2 spinous process, and right femoral neck were used for microdamage analysis. The L-4 vertebra and Th-1 spinous process were mechanically tested to failure in compression and shear, respectively. One year treatment with risedronate or alendronate significantly suppressed trabecular remodeling in vertebrae (RIS 90%, ALN 95%)

and ilium (RIS 76%, ALN 90%) without impairment of mineralization, and significantly increased microdamage accumulation in all skeletal sites measured. Trabecular bone volume and vertebral strength increased significantly following 12 month treatment. However, normalized toughness of the L-4 vertebra was reduced by 21% in both RIS (P = 0.06) and ALN (P = 0.05) groups. When the two bisphosphonate groups were pooled in a post hoc fashion for analysis, this reduction in toughness reached statistical significance (P = 0.02). This study demonstrates that suppression of trabecular bone turnover by high doses of bisphosphonates is associated with increased vertebral strength, even though there is significant microdamage accumulation and a reduction in the intrinsic energy absorption capacity of trabecular bone.

Efficacy of low dose schedule pamidronate infusion in children with osteogenesis imperfecta

Gonzalez E, Pavia C, Ros J et al. J PEDIATR ENDOCRINOL METAB 2001; 14 (5): 529-33

Background: Osteogenesis imperfecta (OI) is a rare condition in which bones are abnormally brittle with frequent fractures. A variety of therapeutic agents has been used with low efficacy. In this study, we present three patients treated for 4 years with i.v. pamidronate. Patients and Methods: Three prepubertal patients, aged 9 (M), 9 (F) and 11 (F) years old, with OI, were treated with 30-60 mg i.v. pamidronate every 6 months over four years. Determinations were made of plasma 1,25-dihydroxycholecalciferol, 25-hydroxycholecalciferol, insulin-like growth factor-I (IGF-I) and its transport protein (IGFBP3),

osteocalcin, total alkaline phosphatase and its osseous fraction, and parathormone (PTH) at baseline and after every pamidronate infusion, Densitometry and X-ray of the vertebral column were performed at the same intervals.

Results: Significant reductions of number of bone fractures and pain were observed in all patients, despite lack of any modification in biochemical parameters. Lumbar X-ray and densitometry showed a striking improvement by the end of the treatment period.

Conclusion: Pamidronate seems to be useful in the treatment of patients with osteogenesis imperfecta.

The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitaxel

Jagdev SP, Coleman RE, Shipman CM et al. BR J CANCER 2001; 84 (8): 1126-34

Bisphosphonates are well established in the management of breast-cancer-induced bone disease. Recent studies have suggested that these compounds are effective in preventing the development of bone metastases. However, it is unclear whether this reflects an indirect effect via an inhibition of bone resorption or a direct anti-tumour effect. The breast cancer cell lines, MCF-7 and MDA-MB-231 cells were treated with increasing concentrations of the bisphosphonate, zoledronic acid, for varying time periods, in the presence or absence of paclitaxel. The effects of zoledronic acid were determined by assessing cell number and rate of apoptosis by evaluating changes in nuclear morphology and using a fluorescence nick translation assay. Zoledronic acid caused a dose- and time-dependent

decrease in cell number ($P < 0.001$) and a concomitant increase in tumour cell apoptosis ($P < 0.005$). Short-term exposure to zoledronic acid was sufficient to cause a significant reduction in cell number and increase in apoptosis ($P < 0.05$). These effects could be prevented by incubation with geranyl geraniol, suggesting that zoledronic acid-induced apoptosis is mediated by inhibiting the mevalonate pathway. Treatment with zoledronic acid and clinically achievable concentrations of paclitaxel resulted in a 4-5-fold increase in tumour cell apoptosis ($P < 0.02$). Isobologram analysis revealed synergistic effects on tumour cell number and apoptosis when zoledronic acid and paclitaxel were combined. Short-term treatment with zoledronic acid, which closely resembles the clinical setting, has a clear anti-tumour effect on breast cancer cells. Importantly, the commonly used anti-neoplastic agent, paclitaxel, potentiates the anti-tumour effects of zoledronic acid. These data suggest that, in addition to inhibiting bone resorption, zoledronic acid has a direct anti-tumour activity on breast cancer cells in vitro.

Bisphosphonate treatment inhibits the growth of prostate cancer cells

Lee MV, Fong EM, Singer FR et al. CANCER RES 2001; 61 (6): 2602-8

The presence of skeletal metastases in patients suffering from cancer leads to a variety of clinical complications. Bisphosphonates are a class of drugs with a potent bone resorption inhibition activity that have found increasing utility in treating and managing patients with metastatic bone disease. Several clinical trials have demonstrated that

bisphosphonates have clinical value in the treatment and management of skeletal metastases derived from advanced prostate cancer. Currently, the mechanism(s) through which bisphosphonates exert their activity is only beginning to be understood. We have studied the effects of bisphosphonate treatment on the growth of prostate cancer cell lines in vitro. Treatment of PC3, DU145, and LNCaP cells with pamidronate or zoledronate significantly reduced the growth of all three cell lines. Using flow cytometry, pamidronate treatment (100 microM) was shown to induce significant amounts of cell death in all three cell lines studied. In contrast, treatment with zoledronate (100 microM) did not induce cell death, instead exerting dramatic effects on cell proliferation, as evidenced by a major increase in cells present in the G0-G1 and S phase. Although both drugs reduced prostate cancer cell growth in the presence of serum, zoledronate was more potent under these conditions, disrupting growth at doses as low as 25 microM in the presence of 5% fetal bovine serum. These results raise the intriguing possibility that the observed clinical utility of bisphosphonates in managing skeletal metastases may in part derive from direct inhibition of prostate cancer cell growth in the bone microenvironment.

Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial

Wilkinson JM, Stockley I, Peel NF et al. J BONE MINER RES 2001; 16 (3): 556-64

Acute periprosthetic bone loss occurs after total hip arthroplasty. Bone loss undermines the

support of the implant and may contribute to prosthetic failure. At present, there is no established prophylaxis for this process. We studied the effect of a single-dose infusion of 90 mg of pamidronate on early periprosthetic bone mineral density (BMD), biochemical markers of bone turnover, radiological, and clinical outcome in a 26-week, prospective, randomized, double-blinded study of 47 men and women undergoing total hip arthroplasty. Pamidronate therapy led to a significant reduction in bone loss compared with placebo for both the proximal femur and the pelvis (repeated measures analysis of variance [ANOVA]); $P = 0.001$ and $P = 0.01$, respectively). Pamidronate therapy was associated with suppression of all biochemical markers of bone turnover compared with placebo (repeated measures ANOVA; $P < 0.05$ for all comparisons), with the exception of urinary free deoxyypyridinoline. Pamidronate did not interfere with the clinical improvement in symptoms after total hip arthroplasty, or radiological outcome, and was not associated with an increase in adverse events. This study provides clinical data on the efficacy and safety of bisphosphonates for the prevention of bone loss after total hip arthroplasty and supports the establishment of larger-scale clinical trials to determine the long-term clinical efficacy of this intervention using implant failure as the primary endpoint.

Effect of intravenous pamidronate on bone mineral density in adults with cystic fibrosis

Haworth CS, Selby PL, Adams JE et al. THORAX 2001; 56 (4): 314-6

Background: Low bone mineral density (BMD) is prevalent in

adults with cystic fibrosis. The aim of this study was to assess the effect of intravenous pamidronate on BMD in these subjects.

Methods: Patients were invited to participate if they had a BMD Z score of -2 or less in the lumbar spine, proximal femur, or distal forearm. Patients were randomised to receive either 30 mg intravenous pamidronate every 3 months + 1 g calcium daily (pamidronate group) or 1 g calcium daily (control group). All pancreatic insufficient patients were prescribed oral vitamin D supplements.

Results: After 6 months of treatment the pamidronate group (n=13) showed a significant increase in absolute BMD compared with the control group (n=15) in the lumbar spine (mean difference 5.8% (CI 2.7% to 8.9%)) and total hip (mean difference 3.0% (CI 0.3% to 5.6%)). However, the pamidronate group showed a reduction in BMD compared with the control group in the distal forearm (mean difference -1.7% (CI -3.7% to 0.3%)). The use of pamidronate was associated with a high incidence of bone pain in non-corticosteroid treated individuals.

Conclusions: Intravenous pamidronate increases axial BMD in adults with cystic fibrosis, but the high incidence of bone pain associated with this treatment might limit its use.

Effects of clodronate on vertebral fracture risk in osteoporosis: a 1-year interim analysis

McCloskey E, Selby P, de Takats D et al. BONE 2001; 28 (3): 310-5

The aim of this study was to determine whether clodronate reduced the incidence of vertebral fractures in patients with osteoporosis. We report here

the interim analysis after 1 year of a 3-year double-blind placebo-controlled study. The objectives of the interim analysis were to determine whether there was a trend in fracture frequency and to examine the effects of clodronate on bone mineral density (BMD). Patients with densitometrically proven osteoporosis (T-score < -2.5 and < -3 for women and men, respectively) or with at least one prevalent vertebral fracture were recruited to a 3-year double-blind, controlled study. Patients were randomized to three strata, namely women with postmenopausal osteoporosis (stratum I, n = 483), women with secondary osteoporosis (II, n = 110), and men with osteoporosis of any causation (III, n = 84). They received either clodronate 800 mg daily by mouth or an identical placebo, and all patients received a calcium supplement of 500 mg daily. BMD was measured at six monthly intervals, and lateral spine radiographs for vertebral morphometry were obtained at baseline and 1 year. Treatment with clodronate was associated with a significant increase in BMD at the spine of $3.2 \pm 0.3\%$ ($P < 0.0001$ vs. baseline) compared with a nonsignificant change of $0.5 \pm 0.3\%$ in the placebo group ($P < 0.0001$ between treatments). At the hip, clodronate was associated with a significant increase in total hip BMD of $1.3 \pm 0.3\%$ ($p = 0.018$ vs. baseline) compared with a small decrease of $0.4 \pm 0.3\%$ in the placebo group ($P = 0.027$ for the difference between treatment groups). The mean changes at the spine and hip were similar in all three strata. Incident vertebral fractures were observed in 27 patients at 1 year in the placebo group (9.0%) and in 14 patients receiving clodronate (4.9%) (relative risk 0.54; 95% CI 0.29-1.02; $P = 0.07$). A trend was

observed in all treatment strata. Treatment was well tolerated, with no significant adverse events attributable to clodronate treatment. We conclude that clodronate 800 mg daily is effective in preventing bone loss, and at 1 year, there is a trend consistent with antifracture efficacy in patients with established osteoporosis regardless of causation.

Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial

Adachi JD, Saag KG, Delmas PD et al.
ARTHRITIS RHEUM 2001; 44 (1): 202-11

Objective: To evaluate the continued efficacy and safety of alendronate (ALN) for up to 2 years in patients receiving glucocorticoids.

Methods: This is a 12-month extension of a previously completed 1-year trial of daily ALN, performed to evaluate the effects of ALN over a total of 2 years in 66 men and 142 women continuing to receive at least 7.5 mg of prednisone or equivalent daily. All patients received supplemental calcium and vitamin D. The primary end point was the mean percentage change in lumbar spine bone mineral density (BMD) from baseline to 24 months. Other outcomes included changes in hip and total body BMD, biochemical markers of bone turnover, radiographic joint damage of the hands, and vertebral fracture incidence.

Results: The mean (\pm SEM) lumbar spine BMD increased by $2.8 \pm 0.6\%$, $3.9 \pm 0.7\%$, and $3.7 \pm 0.6\%$, respectively, in the groups that received 5 mg, 10 mg, and 2.5/10 mg of ALN daily ($P < \text{or} = 0.001$) and decreased by $-0.8 \pm 0.6\%$ in the placebo group (P not

significant) over 24 months. In patients receiving any dose of ALN, BMD was increased at the trochanter ($P < \text{or} = 0.05$) and maintained at the femoral neck. Total body BMD was increased in patients receiving 5 or 10 mg ALN ($P < \text{or} = 0.01$). These 2 dose levels of ALN were more effective than placebo at all sites ($P < \text{or} = 0.05$). Bone turnover markers (N-telopeptides of type I collagen and bone-specific alkaline phosphatase) decreased 60% and 25%, respectively, during treatment with ALN ($P < \text{or} = 0.05$). There were fewer patients with new vertebral fractures in the ALN group versus the placebo group (0.7% versus 6.8%; $P = 0.026$). The safety profile was similar between treatment groups.

Conclusion: Alendronate is an effective, well-tolerated therapy for the prevention and treatment of glucocorticoid-induced osteoporosis, with sustained treatment advantages for up to 2 years.

AGGIORNAMENTO DELLA LETTERATURA

Numero 1 - Giugno 2001

Questo aggiornamento della letteratura elenca i lavori riguardanti i bisfosfonati pubblicati negli ultimi mesi sulle più importanti riviste scientifiche internazionali.

I lavori sono in ordine cronologico, numerati in ordine progressivo.

1. **Alendronate-induced hepatocellular lesion de La Serna Higuera C, Perez Villoria A, Rodriguez Gomez S et al.**
GASTROENTEROL HEPATOL, 2001;24(5):244-246
2. **Inhibition of leukotriene function can modulate particulate-induced changes in bone cell differentiation and activity.**
Anderson GI, MacQuarrie R, Osinga C et al.
J BIOMED MATER RES, 2001;58(4):406-14
3. **A slow outward current and a hypoosmolality induced anion conductance in embryonic chicken osteoclasts.**
Krasznai Z, Weidema F, Ypey DL et al.
ACTA BIOL HUNG, 2001;52(1):47-61
4. **New insight into calcinosis of juvenile dermatomyositis: A study of composition and treatment.**
Mukamel M, Horev G, Mimouni M
J PEDIATR, 2001;138(5):763-6
5. **Evidence-based medicine: putting theory into practice.**
Irani M
HOSP MED, 2001;62(3):164-8
6. **Clinical and radiological improvement of periodontal disease in patients with type 2 diabetes mellitus treated with alendronate: a randomized, placebo-controlled trial.**
Rocha M, Nava LE, Vazquez de la Torre C et al.
J PERIODONTOL, 2001;72(2):204-9
7. **Analgesic effect of bisphosphonates in mice.**
Bonabello A, Galmozzi MR, Bruzzese T et al.
PAIN, 2001;91(3):269-75
8. **Managing menopause after breast cancer: balancing risks and benefits.**
Moore HC
CLEVE CLIN J MED, 2001;68(3):243-8
9. **Phosphate ions mediate chondrocyte apoptosis through a plasma membrane transporter mechanism.**
Mansfield K, Teixeira CC, Adams CS et al.
BONE, 2001;28(1):1-8
10. **Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates.**
Dunford JE, Thompson K, Coxon FP et al.
J PHARMACOL EXP THER, 2001;296(2):235-42
11. **Alendronate and naproxen are synergistic for development of gastric ulcers.**
Graham DY, Malaty HM
ARCH INTERN MED, 2001;161(1):107-10
12. **Chemical and biological prerequisites for novel bisphosphonate molecules: Results of comparative preclinical studies.**
Green JR
SEMIN ONCOL, 2001;28(2 Pt 3):4-10
13. **Osteoporosis in men.**
Summers GD
RADIOGRAPHY, 2001;7(2):119-123
14. **The sugar absorption test in the evaluation of the gastrointestinal intolerance to bisphosphonates: Studies with oral pamidronate.**
Twiss IM, Burggraaf J, Schoemaker RC et al.
CLIN PHARMACOL THER, 2001;69(6):431-7
15. **The evolving role of bisphosphonates.**
Theriault RL, Hortobagyi GN
SEMIN ONCOL, 2001;28(3):284-90

16. **Comorbidity in rheumatoid arthritis.**
Mikuls TR, Saag KG
RHEUM DIS CLIN NORTH AM, 2001;27(2):283-303
17. **The bisphosphonate pamidronate is a potent inhibitor of human osteosarcoma cell growth in vitro.**
Sonnemann J, Eckervogt V, Truckenbrod B et al.
ANTICANCER DRUGS, 2001;12(5):459-465
18. **Effect of intramuscular clodronate on bone mass and metabolism in osteoporotic women.**
Gnudi S, Lisi L, Fini M et al.
INT J TISSUE REACT, 2001;23(1):33-7
19. **Systemic treatment of metastatic breast cancer.**
Johnston SR
HOSP MED, 2001;62(5):289-95
20. **Bone mineral density in multiple myeloma patients after intravenous clodronate therapy.**
Tomiska M, Adam Z, Prokes B et al.
ACTA MED AUSTRIACA, 2001;28(2):38-42
21. **Mode of administration-dependent pharmacokinetics of bisphosphonates and bioavailability determination.**
Hoffman A, Stepensky D, Ezra A et al.
INT J PHARM, 2001;220(1-2):1-11
22. **Parathyroid hormone: an anabolic treatment for osteoporosis.**
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CALENDARIO CONGRESSI

5-10 giugno 2001 Madrid (E)

14th Conference of the International Bone and Mineral Society
in Association with the 28th European Symposium on Calcified Tissue

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Tel. +39 91 3612600 - Fax +34 - 91 - 3559208 - Email: ibms2001@tilesa.es

13-16 giugno 2001 Praga (CZ)

EULAR 2001: Annual European Congress of Rheumatology

Segreteria Organizzativa: Medicalconferences, The Silk Mill House, 196 Huddersfield Road, Meltham,
W. Yorks HD7 3AP, United Kingdom - Tel. +44 0 1484 854575, Fax +44 0 1484 859464 Email: info@medicalconferences.com
Segreteria Scientifica - Tel. +41 1 3839690, Fax +41 1 383 9810 - Email: eular@bluewin.ch

5-7 luglio 2001 Torino (I)

Collegio Reumatologi Ospedalieri (CRO)

Segreteria Organizzativa: Planet, C.so Peschiera 165. 10414 Torino. Tel. 011-3825357 - Fax 011-387392

26-31 agosto 2001 Edmonton (CAN)

20th World Congress of the International League of Association for Rheumatology (ILAR)

Segreteria Scientifica: Tel. +1 905 2733080, Fax +1 905 27323611 - Email: healthcarecomm@sympatico.ca
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W. Yorks HD7 3AP, United Kingdom - Tel. +44 0 1484 854575 - Fax +44 0 1484 859464
Email: info@medicalconferences.com

22-25 settembre 2001 Boston, Massachusetts (USA)

Advances in Rheumatology

Segreteria Organizzativa: Medicalconferences, The Silk Mill House, 196 Huddersfield Road, Meltham,
W. Yorks HD7 3AP, United Kingdom - Tel. +44 0 1484 854575 - Fax +44 0 1484 859464
Email: info@medicalconferences.com

3-6 ottobre 2001 Milano (I)

I Congresso Società Italiana dell'Osteoporosi, del Metabolismo Minerale
e delle Malattie Metaboliche dello Scheletro

Segreteria Organizzativa: Centro Italiano Congressi (CIC). C.so Trieste, 42. 00192 Roma.
Tel. 06-8412673 - Fax 06-8412687 - Email: congressi@gruppic.it

11-13 ottobre 2001 Mantova (I)

II Congresso Nazionale SIMFER - SIR

Approccio clinico e riabilitativo in reumatologia
Gestione Interdisciplinare e Superamento della Disabilità nelle Malattie Reumatiche

Segreteria Organizzativa: Euro Conventions, Via Torricella, 14. Piacenza.
Tel. 0523 33.63.39 / 0523 33.57.32 - Fax 0523 33.49.97 <http://www.euroconventions.it/interdisciplinare-2001>

12-16 ottobre 2001 Phoenix, Arizona (USA)

23rd Annual Meeting of the American Society for Bone and Mineral Research - ASBMR 2001

Segreteria Organizzativa: ASBMR, Suite 300, 1200 19th Street, NW, Washington DC 20036, USA.

Tel + 1 202 857 1161 - Fax +1 202 223 4579 - Email: asbmr@dc.sba.com <http://www.asbmr.org>

10-15 novembre 2001 San Francisco, California (USA)

65th Meeting of the American College of Rheumatology

Segreteria Scientifica: American College of Rheumatology, 60 Executive Park South, Suite 150,

Atlanta GA 30329 (USA) - Tel. (404) 633.3777 - Fax 633.1870

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W. Yorks HD7 3AP, United Kingdom - Tel. +44 0 1484 854575 - Fax +44 0 1484 859464

Email: info@medicalconferences.com

11-15 novembre 2001 Roma (I)

96° Congresso Nazionale della Società Italiana di ortopedia e Traumatologia (S.I.O.T.)

Segreteria Organizzativa: O.I.C., Filiale di Roma.

Tel. +39 06 8078912-913 - Fax +06 806693031 - Email: p.turbacci@oic.it

21-24 novembre 2001 Padova (I)

XXXVIII Congresso Nazionale della Società Italiana di Reumatologia

Segreteria Scientifica: Cattedra e Divisione di Reumatologia, Università di Padova,

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4-8 dicembre 2001 Roma (I)

XXIX Congresso Nazionale SIMFER

La riabilitazione per le persone disabili: fisioterapisti, operatori e volontariato per un progetto comune

Segreteria Organizzativa: Compositarch, via C. Felice 101, 00185 Roma.

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