

BISFOSFONATI

GRUPPO ITALIANO PER LO STUDIO DEI BISFOSFONATI

IN QUESTO NUMERO

Valutazione comparativa dei trial di prevenzione delle fratture nell'osteoporosi post-menopausale

Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women

Alendronate for the treatment of osteoporosis in men

Decrease in carotid intima-media thickness after 1-year therapy with etidronate for osteopenia associated with type 2 diabetes

Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate

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EDITORIALE

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VALUTAZIONE COMPARATIVA DEI TRIAL DI PREVENZIONE DELLE FRATTURE NELL'OSTEOPOROSI POST-MENOPAUSALE

In questi ultimi anni sono stati conclusi i primi trial per la terapia dell'osteoporosi finalizzati a verificare l'efficacia di farmaci per la prevenzione delle fratture osteoporotiche.

I farmaci testati sono stati due bisfosfonati, alendronato e risedronato, oltre al SERM raloxifene e alla calcitonina spray nasale. Si ricorda che in Italia è molto diffuso l'uso di clodronato i.m., nonostante l'assenza di studi di efficacia sulle fratture.

Gli studi su tutti questi farmaci hanno comportato impegni economici ragguardevoli e, per tale ragione, difficilmente saranno ripetuti raffrontando direttamente i vari principi attivi. Il confronto in termini di efficacia non può quindi basarsi che sui dati sinora acquisiti.

Queste analisi comparative hanno ovvie limitazioni per la diversità delle casistiche, le caratteristiche cliniche delle pazienti, i fattori di rischio concomitanti, il trattamento del gruppo placebo, gli obiettivi, i criteri di inclusione ed esclusione, il protocollo clinico e strumentale per il follow-up e persino per le caratteristiche dei ricercatori.

Dimensioni degli studi

Nella *Tabella 1* vengono riportate le dimensioni dei singoli trial. Il numero di pazienti è sempre stato adeguato agli obiettivi prefissati, anche se ci sono evidenti differenze. Si ricorda che i pazienti in trattamento attivo negli studi sino ad ora disponibili con clodronato i.m. sono complessivamente 86^(1,2): si tratta pertanto di studi di piccole dimensioni finalizzati solo a individuare la dose ottimale per successivi trial adeguati.

Lo studio FIT (*Fracture Intervention Trial*) è stato il primo trial, diventando il punto di riferimento per tutti gli altri. Questo studio, per esempio, ha dimostrato che una pregressa frattura vertebrale costituisce un elevato fattore di rischio per ulteriori successive fratture vertebrali. Così, selezionando esclusivamente pazienti con pregresse fratture, è possibile avere un considerevole numero di "eventi" e ridurre proporzionalmente la numerosità della popolazione nel calcolo del "potere statistico" (*Tabella 2*).

Gli studi più recenti si sono anche avvantaggiati di una più precisa definizione del rapporto tra valori basali di BMD e rischio di frattura. Nello studio FIT è stata scelta una soglia di BMD pari a un T score di -1,8, un valore rivelatosi troppo elevato e associato a un basso numero di "eventi" con prevalenza di fratture associate a traumi rilevanti.

Tabella 1. Dimensioni dei differenti studi

Trial	Numerosità della casistica		Durata (anni)
	Placebo	Trattamento attivo	
Alendronato - FIT1 ⁽³⁾	1005	1022	3
Alendronato - FIT2 ⁽⁴⁾	2218	2214	4
Risedronato-VERT Nord America ⁽⁵⁾	820	821 (5 mg)	3
Risedronato-VERT Europa, Australia ⁽⁶⁾	408	408 (5 mg)	3
Risedronato-HIP ⁽⁷⁾			3
Gruppo 1, T score <-4	1821	3624	
Gruppo 2, T score <-3, + rischi cadute	1313	2573	
Raloxifene-MORE ⁽⁸⁾			3
Gruppo 1 (pregressi crolli vertebrali)	1522	3002	
Gruppo 2 (T score <-2,5)	770	1534	
Calcitonina-PROOF ⁽⁹⁾	311	316 (200 UI)	5

Il solo studio il cui obiettivo primario era rappresentato dalla frattura del femore è stato condotto con risedronato (studio HIP): in questo studio è stato osservato che nei soggetti con rischio di caduta, il rischio di fratture del femore è elevato, pur tuttavia non può essere ridotto dalla terapia con un bisfosfonato. Questi dati rappresentano degli elementi che potranno essere rilevanti in futuri trial.

Tabella 2. Caratteristiche delle pazienti studiate

Trial	Età (media anni)	Fratture vertebrali pregresse	Densità minerale Colonna (media, g/cm ²)	Densità minerale Collo femorale (media, g/cm ²)
Alendronato-FIT1	71	+	0,790	0,565
Alendronato-FIT2	68	-	0,841	0,592
Risedronato-VERT-NA	69	+	0,831	0,597
Risedronato-VERT-EA	71	+ (>1)	0,781	0,574
Risedronato-HIP1	74	+/-	-	0,538
Risedronato-HIP2	83	+/-	-	-
Raloxifene-MORE1	65	90% -	0,771	0,584
Raloxifene-MORE2	68	90% +	0,746	0,567
Calcitonina (200 UI)-PROOF	69	79% +	0,850	-

Tabella 3. Supplementazione calcica-vitaminica D/trattamento del gruppo placebo

Trial	Calcio (mg)	Vitamina D (UI)
Alendronato	500 (solo se apporto dietetico <1 g)	250
Risedronato	1000	500 (solo se livelli basali di 250HD <40 nmol/l)
Raloxifene	500	400-600
Calcitonina	1000	400

In tutti gli studi era prevista la supplementazione con calcio e vitamina D. La non omogeneità di questi valori, e le differenze soprattutto relative all'apporto di calcio (*Tabella 3*), sono state dovute anche al fatto che la FDA americana ha tardato a emanare linee guida dove fosse chiaramente indicato il giusto dosaggio giornaliero da somministrare ai pazienti arruolati nei vari studi. È stato successivamente definito un apporto di calcio per tutti i pazienti di 1000 mg/die.

Un apporto più elevato di calcio può ridurre il numero globale di "eventi" fratturativi e, quindi, il potere statistico dello studio.

In tutti gli studi, i pazienti del gruppo placebo hanno mostrato qualche aumento della BMD lombare e una stabilità della BMD femorale. Ciò sembra in relazione alla supplementazione calcica e all'assistenza "non-farmacologica" assicurata di solito ai pazienti che partecipano a trial clinici. Per "compensare" queste differenze è necessario calcolare il delta medio della BMD tra i pazienti in trattamento attivo e quelli in placebo (*Tabella 4*).

Gli aumenti densitometrici conseguiti con la terapia con alendronato sono stati sempre superiori a quelli osservati con gli altri farmaci. Va ricordato che il dosaggio medio di alendronato durante il FIT era di 7 mg. Con i 10 mg/die raccomandati oggi, le variazioni densitometriche dopo 3 anni⁽¹⁰⁾ sono di circa 9% e 5%, rispettivamente, per colonna e femore. Il raffronto con risedronato, anche per quanto attiene le variazioni di marker di turnover, dimostra che per il trattamento dell'osteoporosi il rapporto di potenza alendronato/risedronato è sicuramente superiore allo 1:2 delle dosi commercializzate.

Le variazioni densitometriche osservate con raloxifene, invece, sono state inferiori. Va tuttavia ricordato che "per protocollo", i pazienti che nel corso dello studio perdevano più del 10% di massa ossea interrompevano la partecipazione al trial. Alla conclusione dello studio è stato osservato che questi pazienti erano due volte superiori nel gruppo placebo. Ciò dovrebbe aver comportato una sottovalutazione degli effetti densitometrici di raloxifene di circa lo 0,7%.

La calcitonina spray nasale non ha determinato variazioni densitometriche significative per nessuno dei dosaggi giornalieri studiati (100, 200 e 400 U/die).

In quasi tutti gli studi l'obiettivo primario era sempre l'incidenza di fratture vertebrali (pazienti con una nuova frattura) mentre l'incidenza di fratture non-vertebrali rappresentava un end-point secondario o di *safety*. L'unico studio il cui end-point primario era rappresentato dall'incidenza di fratture del femore è stato condotto con risedronato (studio HIP).

Tabella 4. Variazione % della densità minerale nel gruppo in trattamento attivo rispetto a placebo

	I anno	II anno	III anno
Collo femorale			
Alendronato-FIT1 5/10 mg	+1,9 (5 mg)	+2,9 (5 mg)	+4,1 (10 mg)
Alendronato-FIT2 5/10 mg	+1,7 (5 mg)	+2,8 (5 mg)	+4,1 (10 mg)
Risedronato-VERT-NA 5 mg	+1,7	+1,9	+2,8
Risedronato-VERT-EA 5 mg	+0,9	+1,8	+3,1
Risedronato-HIP 2,5 mg			+2,1
Risedronato-HIP 5 mg			+3,4
Raloxifene-MORE 60 mg	+1,2	+1,9	+2,1
Raloxifene-MORE 120 mg	+1,3	+2,2	+2,4
Calcitonina-PROOF 200 UI	ns	ns	ns
Colonna lombare			
Alendronato-FIT1 5/10 mg	+3,9	+4,9	+6,2
Alendronato-FIT2 5/10 mg	+3,6	+4,8	+6,0
Risedronato-VERT-NA 5 mg	+3,1	+4,3	+4,3
Risedronato-VERT-EA 5 mg	+4,0	+5,5	+5,9
Raloxifene-MORE 60 mg	+1,9	+2,5	+2,6
Raloxifene-MORE 120 mg	+2,1	+2,7	+2,7
Calcitonina-PROOF 200 UI	+1,2	+1,0	ns
ns = statisticamente non significativo			

La dimostrazione di un effetto protettivo sul rischio di fratture di femore è disponibile per alendronato (sia in soggetti con precedente frattura che in soggetti non fratturati ma osteoporotici alla densitometria) e per risedronato (Tabella 5).

L'alendronato è l'unico composto per il quale esista una costante evidenza di efficacia per le fratture del femore e non-vertebrali in genere, anche se limitatamente a pazienti con presenza di osteoporosi densitometrica⁽¹¹⁾.

Raloxifene non ha alcun effetto protettivo sul femore ma ciò potrebbe dipendere, almeno in parte, dal fatto che lo studio era stato disegnato per le fratture vertebrali. Inoltre, "per protocollo" era previsto che i pazienti che andavano incontro a un'esagerata perdita di massa ossea uscissero dallo studio. Ciò comportava una selezione graduale dei pazienti con conseguente aumento, alla conclusione del trial, di casi più osteoporotici nel gruppo raloxifene rispetto a quello placebo.

Nello studio PROOF con calcitonina, la scarsità del campione studiato esclude la possibilità di valutare un eventuale effetto protettivo sulle fratture del femore.

La riduzione del rischio di fratture vertebrali ottenuta dopo 4 anni di calcitonina è assai modesta (circa del 30%) e ai limiti della significatività. Alendronato,

Tabella 5. Percentuali di pazienti con nuove fratture femorali e rischio relativo (RR)

	Periodo (anni)	Placebo	Farmaco	RR	p
Alendronato-FIT1	0-3	2,2%	1,1%	0,50	<0,05
Alendronato-FIT2	0-4	1,1%	0,9%		ns
T score collo femorale <-2,5		2,2%	1,0%	0,44	<0,05
Risedronato-VERT-NA	0-3	2,4%	1,9%		ns
Risedronato-VERT-EA	0-3	3,4%	2,7%		ns
Risedronato-HIP1	0-3	3,3%	1,9%	0,61	<0,05
Con pregressa frattura vertebrale		6,0%	2,3%	0,42	<0,05
Senza pregressa frattura vertebrale		1,6%	1,1%		ns
Risedronato-HIP2	0-3	5,1%	4,6%		ns
T score collo femorale <-2,5		10,7%	7,6%		ns
Raloxifene-MORE	0-3	0,7%	0,8%		ns
Calcitonina (200UI)-PROOF	0-5	3%	2%		ns
ns = statisticamente non significativo					

risedronato e raloxifene riducono il rischio di frattura vertebrale in maniera molto simile. I criteri di definizione della frattura vertebrale e il tipo di analisi statistica utilizzata non sono stati tuttavia uniformi. Per quanto riguarda la definizione della frattura vertebrale, il criterio utilizzato per alendronato e raloxifene appare più severo di quello utilizzato per risedronato. Ciò si riflette in un'apparente maggiore incidenza di eventi negli studi di risedronato (Tabella 6).

Nei trial con alendronato e raloxifene è stata utilizzata l'analisi *by intention-to-treat*. Per risedronato e calcitonina, a causa del largo numero di pazienti che non hanno portato a termine lo studio, il calcolo del rischio relativo è stato fatto sulla base della valutazione secondo metodica Kaplan-Meier. Con questo metodo per ogni singola valutazione nel tempo sono considerati solo i pazienti ancora in trattamento (non, quindi, i *drop-out*) e che non abbiano già subito eventi fratturativi. I risultati dei due metodi non sono in realtà facilmente confrontabili anche se ugualmente rigorosi.

Sicurezza dei farmaci

Tutte le terapie qui indicate possono essere globalmente considerate ben tollerate. L'alendronato nelle valutazioni post-marketing, ma non in corso dei trial clinici, è stato gravato da intolleranza gastro-esofagea in circa il 5% dei casi. La discrepanza tra i dati dei trial clinici e quelli di sorveglianza post-marketing può essere giustificata dal fatto che nei trial erano rigorosamente escluse pazienti con problemi a carico delle prime vie digestive, esclusione chiaramente non possibile nell'utilizzo generale, laddove è anche possibile immaginare una minor osservanza per le norme di assunzione del farmaco.

Tabella 6. Percentuali di pazienti con nuove fratture vertebrali (criterio morfometrico) e rischio relativo (RR)

	Rx dopo anni	Criterio	Placebo	Farmaco	RR	p
Alendronato-FIT1	3	↓h>20% e ≥4 mm	15%	8%	0,53	<0,05
Alendronato-FIT2	4	↓h>20% e ≥4 mm	3,8%	2,1%	0,55	<0,05
Risedronato- VERT-NA	1	↓h>15%	6,4%	2,4%	0,35	<0,05
	3	met. Kaplan-Meier	16,3%	11,3%	0,59	<0,05
Risedronato- VERT-EA	1	↓h>15%	13%	5,6%	0,39	<0,05
	3	met. Kaplan-Meier	29%	18,1%	0,51	<0,05
Raloxifene (60 mg)-MORE1	3	↓h>20% e ≥4 mm	4,5%	2,3%	0,5	<0,05
Raloxifene (60 mg)-MORE 2	3	↓h>20% e ≥4 mm	21,2%	14,7%	0,7	<0,05
Calcitonina (200 UI)-PROOF	1	↓h>20% e ≥4 mm	6%	3%		ns
	3	met. Kaplan-Meier	21%	13%		ns
	5		26%	18%	0,67	<0,05

ns = statisticamente non significativo

Alcuni studi controllati sembrerebbero suggerire una miglior tollerabilità gastroesofagea di risedronato rispetto ad alendronato. Rimane da stabilire se ciò sia legato a qualche intrinseca proprietà dei due farmaci o semplicemente alla validità del rapporto di potenza. Come abbiamo infatti visto è probabile che 5 mg di risedronato abbiano un'attività farmacologica inferiore a 10 mg di alendronato. La terapia con raloxifene si associa ad alcuni effetti collaterali minori (vampate e crampi agli arti inferiori) del tutto attesi e prevedibili per il suo meccanismo d'azione. Il problema più rilevante appare legato al rischio di trombosi venosa. Il rischio assoluto è, tuttavia, modesto specie se si evita di trattare le pazienti più a rischio per questa complicanza.

Conclusioni

- Una sicura documentazione di efficacia nel ridurre il rischio di fratture vertebrali in pazienti affette da osteoporosi post-menopausale esiste per alendronato, raloxifene e risedronato, mentre appare incerta per calcitonina spray nasale ed è del tutto assente per clodronato.
- Solo alcuni farmaci sono stati in grado di ridurre il rischio di fratture del femore; il beneficio è evidente in particolare nelle pazienti con precedente frattura vertebrale. L'effetto sulle fratture non-vertebrali e cliniche appare ben documentato solo con la terapia con alendronato.

- Gli incrementi densitometrici indotti dai vari farmaci sono molto variabili. Gli incrementi maggiori sono stati ottenuti con alendronato che, alla dose di 10 mg, è anche il farmaco più potente nel ridurre il turnover osseo. La relazione tra variazioni densitometriche e riduzione del rischio di frattura vertebrale appare lineare sino a incrementi a livello lombare del 2-3% tendendo al plateau per ulteriori incrementi. Questo può spiegare la capacità della terapia con raloxifene di ridurre il rischio di frattura malgrado incrementi densitometrici modesti. La relazione tra variazioni densitometriche femorali e rischio di fratture cliniche (o sintomatiche) è diretta, perciò tanto maggiori saranno gli effetti sulla massa ossea, tanto maggiore risulterà l'efficacia di prevenzione delle fratture.
- Il profilo di tollerabilità dei farmaci registrati per la terapia dell'osteoporosi è globalmente buono.

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ERRATA CORRIGE

Di seguito riportiamo l'elenco corretto, precedentemente pubblicato su "Aggiornamento in tema di Bisfosfonati" Vol. 1 - N° 2 settembre 2000 pag. 16. Ce ne scusiamo con gli Autori.

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ABSTRACT

SEZIONE A

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

Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women

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GASTROENTEROLOGY 2000; 119(3): 631-8

Background & Aims: Bisphosphonates are effective treatment for osteoporosis, but upper gastrointestinal injury associated with some compounds has caused concern. This study compared the incidence of gastric ulcers after treatment with risedronate, a pyridinyl bisphosphonate, and alendronate, a primary amino bisphosphonate. Esophageal and gastroduodenal injury assessed by endoscopy scores was a secondary endpoint

Methods: Healthy, postmenopausal women (n = 515) received 5 mg risedronate (n = 255) or 10 mg alendronate (n = 260) for 2 weeks. At baseline and on days 8 and 15, subjects underwent endoscopy and evaluator-blinded assessment of the esophageal, gastric, and duodenal mucosa.

Results: Gastric ulcers were observed during the treatment period in 9 of 221 (4.1%) evaluable subjects in the risedronate group compared with 30 of 227 (13.2%) in the alendronate group (P < 0.001). Mean gastric endoscopy scores for the risedronate group were lower than those for the alendronate group at days 8 and 15 (P ≤ 0.001). Mean esophageal and duodenal endoscopy scores were similar in the 2 groups at days 8 and 15. Esophageal ulcers were noted in 3 evaluable subjects in the alendronate group, compared with none in the risedronate group, and duodenal ulcers were noted in 1 evaluable subject in the alendronate group and 2 in the risedronate group.

Conclusions: At doses used for the treatment of osteoporosis, risedronate was associated with a significantly

COMMENTO

Questo studio sembra dimostrare una maggiore tollerabilità gastrica di risedronato rispetto ad alendronato. Vanno, tuttavia, tenuti presenti alcuni punti:

1. Le erosioni gastriche sono molto "volatili" e di scarsa rilevanza clinica. In questo studio la mancanza di un gruppo di controllo rende incerta l'interpretazione dei risultati, tenendo anche conto che lo stesso Autore, in un altro studio, ha dimostrato che la terapia con alendronato si associa a una incidenza di erosioni gastriche pari a quella rilevata nei pazienti trattati con placebo (Lanza FL et al. *Am J Gastroenterol* 1998; 93: 753-757).
2. Le lesioni a carico dell'esofago sono quelle tipicamente associate alla terapia con alendronato. L'incidenza di questo tipo di lesioni era bassa e sovrapponibile con i due bisfosfonati.
3. Il rapporto di potenza tra i due farmaci sembra essere diverso da quello implementato in questo studio (alendronato 10 mg uguale a risedronato 5 mg). Le variazioni densitometriche lombari medie rispetto a placebo in pazienti trattati per 3 anni con alendronato 10 mg o con risedronato 5 mg sono state dell'8,8% e del 4,3%, rispettivamente. Sarebbe quindi opportuno raffrontare la tollerabilità gastro-intestinale dei due farmaci utilizzando dosi equivalenti, per esempio alendronato 10 mg vs risedronato 8-10 mg (Leder, Kronenberg. *Gastroenterology* 2000; 115: 866-871).

lower incidence of gastric ulcers than alendronate. These findings confirm that bisphosphonates differ in their potential to damage the gastroesophageal mucosa.

Alendronate for the treatment of osteoporosis in men

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N ENGL J MED 2000, 31; 343(9): 604-10

Background: Despite its association with disability, death, and increased medical costs, osteoporosis in men has been relatively neglected as a subject of study. There have been no large, controlled trials of treatment in men.

Methods: In a two-year double-blind trial, we studied the effect of 10 mg of alendronate or placebo, given daily, on bone mineral density in 241 men (age, 31 to 87 years; mean, 63) with osteoporosis. Approximately one third had low serum free testosterone concentrations at base line; the rest had normal concentrations. Men with other secondary causes of osteoporosis were excluded. All the men received calcium and vitamin D supplements. The main outcome measures were the percent changes in lumbar-spine, hip, and total-body bone mineral density.

Results: The men who received alendronate had a mean (\pm SE) increase in bone mineral density of 7.1 ± 0.3 percent at the lumbar spine, 2.5 ± 0.4 percent at the femoral neck, and 2.0 ± 0.2 percent for the total body ($P < 0.001$ for all comparisons with base line). In contrast, men who received placebo had an increase in lumbar-spine bone mineral density of 1.8 ± 0.5 percent ($P < 0.001$ for the comparison with base line) and no significant changes in femoral-neck or total-body bone mineral density. The increase in bone mineral density in the alendronate group was greater than that in the placebo group at all measurement sites ($P < 0.001$). The incidence of vertebral fractures was lower in the alendronate group than in the placebo group (0.8 percent vs. 7.1 percent, $P = 0.02$). Men in the placebo group had a 2.4-mm decrease in height, as compared with a decrease of 0.6 mm in the alendronate group ($P = 0.02$). Alendronate was generally well tolerated.

Conclusions: In men with osteoporosis, alendronate significantly increases spine, hip, and total-body bone mineral density and helps prevent vertebral fractures and decreases in height.

Decrease in carotid intima-media thickness after 1-year therapy with etidronate for osteopenia associated with type 2 diabetes

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J CLIN ENDOCRINOL METAB 2000; 85(8): 2793-6

It has been suggested that bisphosphonates may have

COMMENTO

Lo studio di Orwoll è l'unico di adeguate dimensioni condotto in pazienti maschi con osteoporosi. Sorprendentemente i benefici densitometrici sono pari o superiori a quelli osservati in donne dopo la menopausa. Malgrado le dimensioni relativamente modeste dello studio, è stato possibile evidenziare un effetto significativo sull'incidenza di fratture.

COMMENTO

Questo lavoro incoraggia ulteriori ricerche utilizzando anche altri bisfosfonati. Sarà di notevole interesse valutare il tasso di sopravvivenza e di morbilità cardiovascolare tra trattati e controlli nei grandi trial clinici con alendronato e risedronato.

some antiatherogenic actions in experimental animals or in vitro, but their effects on the atherogenic process in humans has not been reported. In the present study the effect of etidronate treatment on carotid arterial intima-media thickness was prospectively examined in 57 subjects with type 2 diabetes associated with osteopenia. After 1 yr of therapy with cyclical etidronate (200 mg/day for 2 weeks every 3 months), intima-media thickness showed a decrease (mean \pm SE, 0.038 ± 0.011 mm), which was significantly different from a change in 57 control subjects (0.023 ± 0.015 mm; $P < 0.005$). Cardiovascular parameters were not changed after etidronate treatment. These findings suggest that etidronate in clinical dosage may have an antiatherogenic action, at least in type 2 diabetes, although its mechanisms remain to be elucidated.

Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate

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J CLIN ENDOCRINOL METAB 2000; 85(6): 2129-34

Treatment of osteoporosis with PTH causes a marked increase in vertebral bone mineral density (BMD). However, this effect is rapidly reversed when the treatment is stopped. The purpose of the present study was to determine whether the bisphosphonate alendronate could preserve or enhance bone density in patients previously treated with PTH. Sixty-six postmenopausal osteoporotic women were treated for 1 yr with 50, 75, or 100 microg recombinant human PTH-(1-84) or placebo, and then were given 10 mg alendronate daily for an additional year. BMD was measured in the femoral neck, lumbar spine, and whole body. Markers of bone turnover included skeletal alkaline phosphatase, osteocalcin, and N-telopeptide. During the first year, changes in BMD (mean \pm SD) in women receiving PTH (all doses combined) were $7.1 \pm 5.6\%$ (spine), $0.3 \pm 6.2\%$ (femoral neck), and $-2.3 \pm 3.3\%$ (total body). After switching to alendronate for 1 yr in women who previously had received PTH, mean changes in BMD were $13.4 \pm 6.4\%$ (spine), $4.4 \pm 7.2\%$ (femoral neck), and $2.6 \pm 3.1\%$ (whole body). In the subgroup of patients who had received the highest dose of PTH, the mean increase in vertebral BMD was $14.6 \pm 7.9\%$. All markers of bone turnover increased during treatment with PTH and decreased to below baseline after 1 yr of alendronate. In conclusion, sequential treatment of osteoporosis with PTH and alendronate results in an increase in vertebral bone density that is considerably more than has been reported with alendronate or estrogens alone. This combination of drugs may be a useful approach to maximizing bone density in women with vertebral osteoporosis.

COMMENTO

L'associazione tra un efficace inibitore del turnover osseo con uno stimolatore della neoformazione ossea non è più una ipotesi avveniristica.

I risultati di questo studio aprono interessanti prospettive per la terapia delle forme più severe di osteoporosi.

SEZIONE B

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

Gastric damage in the rat with nitrogen-containing bisphosphonates depends on pH

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ALIMENT PHARMACOL THER 2000; 14(9): 1215-1223

Background: The use of nitrogen-containing bisphosphonates (N-BPs) has been reported to be associated with gastrointestinal intolerance. The fasted, indomethacin-treated rat provides a model for assessing the gastrointestinal effects of these compounds. AIMS: The aims of this study were to elucidate the effect of pH on N-BP-induced gastric damage, and to evaluate the structure-activity relationship between N-BP anti-resorptive and gastric effects.

Methods: Fasted rats were dosed concomitantly with indomethacin (40 mg/kg, subcutaneously) and an N-BP (pamidronate, alendronate, or risedronate at 150 or 300 mg/kg, orally), with the N-BP dosing solutions adjusted to pH 2, 4 or 7. The aminopentane and aminohexane N-BPs (150, 225 or 300 mg/kg, orally) were only tested at pH 4 only.

Results: Nitrogen-containing bisphosphonate-induced gastric damage was pH-dependent, with increased damage at increasing pH.

Conclusions: Gastric damage

potential did not correlate with bone anti-resorptive effects, and the more potent anti-resorptive N-BPs were not necessarily more damaging to the stomach.

Effects of bisphosphonate on matrix metalloproteinase enzymes in human periodontal ligament cells

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J PERIODONTOL 2000; 71(7): 1158-66

Background: The host response is a critical component in the pathogenesis of periodontitis. In fact, the clinical benefits associated with regulating the host response have been demonstrated in studies using several different classes of drugs. Bisphosphonates are one host-modulating class of drugs that has demonstrated this ability. These drugs are clinically effective at reducing bone resorption and have shown the ability to inhibit host degradative enzymes, specifically the matrix metalloproteinases (MMPs). Therefore, the purpose of this study was to investigate the regulatory effects of a bisphosphonate, tiludronate, on MMP levels and activity in human periodontal cells.

Methods: MMP-1 and MMP-3 were assessed in cultured human periodontal ligament cells treated with a bisphosphonate, tiludronate. Reverse transcription-polymerase chain reaction was used to identify mRNA levels for both enzymes, and also for tissue inhibitors (TIMP-1). Enzyme immunoassay (EIA) and immunocytochemistry were used to assess MMP proteins in these cell cultures. Enzyme activity was assessed using FITC-conjugated substrates and quantitated using spectrophotofluorometry.

Results: Tiludronate significantly inhibited both MMP-1 and MMP-3 activity in a concentration-dependent manner. A maximal reduction in activity of 35% was achieved for each of the enzymes at a 10⁻⁴ M concentration.

Tiludronate did not have a significant effect on the mRNA levels for MMP-1, MMP-3, or TIMP-1. Similarly, there were no effects noted for either MMP-1 or MMP-3 on the protein level.

Conclusions: This study demonstrates an inhibitory effect of tiludronate on the activity of both MMP-1 and MMP-3. These effects appear to occur without altering either mRNA or protein levels for these enzymes, supporting a possible mechanism of action that involves the ability of bisphosphonates to chelate cations from the MMPs. Furthermore, these results support the continued investigation of these drugs as potential therapeutic agents in periodontal disease.

Primary hyperparathyroidism: pathophysiology and impact on bone

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CMAJ 2000; 25; 163(2): 184-7

Primary hyperparathyroidism has been associated with bone loss, especially at cortical skeletal sites. Results from studies evaluating the mineral density of cancellous bone have been more difficult to interpret. Most densitometry studies support the concept that the parathyroid hormone appears to be catabolic at cortical sites and may have anabolic effects at cancellous bone sites. Studies completed to date, however, have been limited by design, definitions of fracture and inadequate control groups. Primary hyperparathyroidism is

now increasingly being detected during the asymptomatic phase. The need for parathyroidectomy has been questioned in such patients because there may be no disease progression in the absence of surgery. Medical management of primary hyperparathyroidism has to date been limited to estrogen replacement therapy in postmenopausal women. Identification of the calcium receptor has improved our understanding of calcium homeostasis, and significant reductions in calcium receptor levels have been detected in parathyroid adenomas. Thus, a new class of therapeutics may include the calcimimetic agents. Bisphosphonates are also currently being evaluated with regard to their impact on fracture prevention and their beneficial effects on bone mineral density.

Bisphosphonates in the management of prostate carcinoma metastatic to the skeleton

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CANCER 2000; 88(12 SUPPL): 3047-53*

Background: Prostate carcinoma metastasizes frequently to the skeleton, causing significant morbidity, particularly severe bone pain. Metastatic lesions typically are osteosclerotic, but there is experimental, histologic, and biochemical evidence of increased bone resorption. Furthermore, bone resorption rates appear to correlate with bone pain. These observations provide the rationale for the use of bisphosphonates in the management of patients with prostate carcinoma and skeletal metastases.

Methods: The authors reviewed

the literature and current findings on the use of bisphosphonates in the management of patients with prostate carcinoma metastatic to the skeleton.

Results: Compared with the large number of studies with bisphosphonates in predominantly osteolytic bone disease, there have been relatively few (mostly uncontrolled) studies in patients with prostate carcinoma. Apart from the lack of appropriate experimental models, the osteoblastic nature of the metastases and the low incidence of objectively assessed endpoints of treatment (e.g., hypercalcemia, pathologic fractures) have delayed developments. Available data, however, strongly suggest that potent bisphosphonates are efficacious in reducing skeletal morbidity in patients with prostate carcinoma.

Conclusions: For the optimal management of patients with skeletal metastases from prostate carcinoma with bisphosphonates their mode of administration, the dose and duration of treatment need to be evaluated. Better understanding of the cellular and molecular mechanisms underlying bone metastases can lead to the design of improved treatment protocols with potent bisphosphonates.

Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases

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CANCER RES 2000; 60(11): 2949-54*

The molecular mechanisms by which tumor cells metastasize to bone are likely to involve

invasion, cell adhesion to bone, and the release of soluble mediators from tumor cells that stimulate osteoclast-mediated bone resorption.

Bisphosphonates (BPs) are powerful inhibitors of the osteoclast activity and are, therefore, used in the treatment of patients with osteolytic metastases. However, an added beneficial effect of BPs may be direct antitumor activity. We previously reported that BPs inhibit breast and prostate carcinoma cell adhesion to bone (Boissier et al., *Cancer Res.*, 57: 3890-3894, 1997). Here, we provided evidence that BP pretreatment of breast and prostate carcinoma cells inhibited tumor cell invasion in a dose-dependent manner. The order of potency for four BPs in inhibiting tumor cell invasion was: zoledronate > ibandronate > NE-10244 (active pyridinium analogue of risedronate) > clodronate. In addition, NE-58051 (the inactive pyridylpropylidene analogue of risedronate) had no inhibitory effect, whereas NE-10790 (a phosphonocarboxylate analogue of risedronate in which one of the phosphonate groups is substituted by a carboxyl group) inhibited tumor cell invasion to an extent similar to that observed with NE-10244, indicating that the inhibitory activity of BPs on tumor cells involved the R2 chain of the molecule. BPs did not induce apoptosis in tumor cells, nor did they inhibit tumor cell migration at concentrations that did inhibit tumor cell invasion. However, although BPs did not interfere with the production of matrix metalloproteinases (MMPs) by tumor cells, they inhibited their proteolytic activity. The inhibitory effect of BPs on MMP activity was completely reversed in the

presence of an excess of zinc. In addition, NE-10790 did not inhibit MMP activity, suggesting that phosphonate groups of BPs are responsible for the chelation of zinc and the subsequent inhibition of MMP activity. In conclusion, our results provide evidence for a direct cellular effect of BPs in preventing tumor cell invasion and an inhibitory effect of BPs on the proteolytic activity of MMPs through zinc chelation. These results suggest, therefore, that BPs may be useful agents for the prophylactic treatment of patients with cancers that are known to preferentially metastasize to bone.

Treatment of bone diseases with bisphosphonates, excluding osteoporosis

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CURR OPIN RHEUMATOL 2000; 12(4): 331-5

The main biologic action of bisphosphonates consists of the inhibition of osteoclastic bone resorption, and, at least, for the drugs introduced after etidronate, without any significant inhibition of bone mineralization. Bisphosphonates therefore play a major role in conditions that are characterized, at least partly, by an increased bone resorption. Primary and secondary osteoporosis by far constitute the most widespread indications for bisphosphonates, mostly because recent published trials have demonstrated their ability to prevent fractures. Potentially crippling conditions such as symptomatic Paget disease of bone remain a major therapeutic challenge for bisphosphonates, but the

prevention of the major complications such as sarcoma has still to be proven. The availability of more potent bisphosphonates, less toxic for bones, has certainly widened the therapeutic interventions to asymptomatic patients, bearing in mind the various potential troublesome complications. Fibrous dysplasia resembles, in certain aspects, Paget disease; it is therefore not surprising that bisphosphonate therapy has been proposed in this indication. With the aging of world populations, more and more cancers will be diagnosed. For those with a bone metastatic propensity or malignant hematologic condition, such as multiple myeloma, the most recent generation of more potent bisphosphonates may bring more comfort to crippled patients and even, hopefully, have a direct antitumoral activity, if used synergistically with the armamentarium already available to the clinician. New indications for bisphosphonates include osteogenesis imperfecta both in children and adults. In the future, they might be used in the prevention of erosions in rheumatoid arthritis and of loosening of joint prostheses, as well as possibly in osteoarthritis. Now that the fear of theoretically freezing bone remodeling has been reasonably dismissed, potential uses for bisphosphonates might be considered nearly infinite.

Intravenous pamidronate in juvenile osteoporosis

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ARCH DIS CHILD 2000; 83(2): 143-5

Aims: To investigate the use of the aminobisphosphonate,

disodium pamidronate, in children with vertebral osteoporosis.

Methods: Five children (aged 10-15 years) with vertebral osteoporosis who developed compression fractures in the thoracic and/or lumbar spine as a consequence of five different conditions, received treatment with intravenous disodium pamidronate in doses ranging from 0.5 to 12 mg/kg/y.

Results: Each child had rapid pain relief following the first treatment, followed by large increments in lumbar spine bone density over one year; the change in bone density standard deviation score ranged from 0.5 to 2.5 with percentage increments of 26% to 54%.

Conclusions: Intravenous pamidronate appears to be a useful therapeutic option in childhood osteoporosis, but its use in children must still be regarded as experimental and therefore closely monitored.

Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women

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AM J CLIN NUTR 2000; 72(3): 745-50

Background: Supplementation with calcium and vitamin D reduces bone loss and prevents fractures in elderly people, but it is not known whether any lasting benefit remains if the supplements are discontinued.

Objective: The objective was to determine whether gains in bone mineral density (BMD) induced by calcium and vitamin D supplementation persist after

supplement withdrawal.

Design: Two-hundred ninety-five healthy, elderly men and women (aged ≥ 68 y) who had completed a 3-y randomized, placebo-controlled trial of calcium and vitamin D supplementation were followed for an additional 2 y during which no study supplements were given. BMD was measured by dual-energy X-ray absorptiometry, and biochemical variables related to calcium metabolism and bone turnover were measured. Results: In the 128 men, supplement-induced increases in spinal and femoral neck BMD were lost within 2 y of supplement discontinuation, but small benefits in total-body BMD remained. In the 167 women, there were no lasting benefits in total-body BMD or at any bone site. Consistent with the observations on BMD, the bone turnover rates in both men and women (as measured by serum osteocalcin concentrations) returned to their original higher concentrations within the same 2-y period.

Conclusion: Discontinued calcium and vitamin D supplementation has limited cumulative effect on bone mass in men and women aged ≥ 68 y.

Polymorphisms in the vitamin D receptor gene and bone mass, bone turnover and osteoporotic fractures

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 EUR J CLIN INVEST 2000 JUL; 30(7): 608-17

Background: Vitamin D is essential for normal bone metabolism. Polymorphisms in exon 2, intron 8 and exon 9 of the vitamin D receptor (VDR)

gene have previously been found to be associated with bone mass and bone turnover.

Material and Methods: We examined the effect of these polymorphisms, separately and in combination, on bone mineral density (BMD), bone turnover, and the prevalence of osteoporotic fractures in 192 osteoporotic patients and 207 normal controls. The four polymorphisms were determined by RFLP using Fok I (T2-C), Bsm I (intron 8), Apa I (intron 8) and Taq I (T1055-C) after PCR.

Results: We did not find any association between the Fok I polymorphism and bone mass, bone turnover or prevalence of osteoporotic fractures. We found that BB + Bb-genotypes were more frequent in patients with osteoporotic fractures ($\chi^2 = 3.50, P = 0.06$). Furthermore, BMD of the intertrochanteric region ($P < 0.0001$, ANOVA) as well as the total hip ($P < 0.01$, ANOVA) were higher in individuals with the bb-genotype. The Apa I and the Taq I polymorphisms were not distributed differently among osteoporotic patients and normal controls. Apa I was not associated with differences in BMD. BMD of the intertrochanteric region was higher in individuals with the TT-genotype compared with individuals with the Tt- or tt-genotypes ($P < 0.01$, ANOVA), while no differences could be demonstrated in BMD of the lumbar spine, femoral neck, trochanter or Wards triangle. Combining the genotypes generally reflected the differences caused by the Bsm I polymorphism.

Conclusion: We have found that the B-allele of the Bsm I polymorphism in the 3' untranslated region of the VDR was associated with low BMD at the hip, and tended to be associated with osteoporotic

fractures. The translation initiation polymorphism in the VDR does not affect BMD and is not associated with osteoporotic fractures in men or women.

Intramuscular clodronate in nonresponders to oral alendronate therapy for osteoporosis

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J RHEUMATOL 2000; 27(8): 1980-3

Objective: Oral alendronate is effective in increasing bone mineral density (BMD) and in reducing fracture incidence. However, a large proportion of patients under treatment do not show significant changes in BMD, or even bone loss. Incorrect administration, low intestinal absorption, and poor compliance are among factors that may account for this effect. In this subgroup of patients we evaluated whether intramuscular (im) clodronate increased the number of responders.

Methods: Using an open case-control design we studied 60 postmenopausal osteoporotic women (mean age 58.9 years \pm 4.8 SD) after one year of therapy with oral alendronate who had an increase in BMD that was lower than the in vivo densitometry measurement error (2%). Subjects were divided into 2 groups: the first continued alendronate treatment (AL group); the second began weekly im injections of clodronate 100 mg (CL group). BMD measurements were performed at the right femoral neck by the same operator, using dual energy x-ray absorptiometry. **Results:** After 12 months of therapy the prevalence of responders (increase in BMD $> 2\%$) was 40% in the AL group and 66% in the CL group

(prevalence rate ratio=1.65; 95% CI 1.25-2.04). The treatment group was the only variable that showed a significant correlation with being a responder (beta=1.13; p=0.03), as analyzed by multiple logistic regression to account for the effect of confounding factors. In the CL group the difference in the mean value of BMD between time T0 and time T+12 was greater than in the AL group, but did not reach statistical significance. The mean percentage variation of BMD was significantly greater in the CL group (+3.21%) compared to the AL group (+0.98%) (P <0.001, t test) (f value = 8.4; P <0.01, by multiple linear regression analysis using the same covariates).

Conclusion: Treatment with weekly intramuscular injection of clodronate in nonresponders to oral alendronate showed a higher number of subjects with a significant increase in BMD, compared to continuation of therapy with alendronate.

Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome.

A randomized, double blind, placebo controlled study

Varenna M, Zucchi F, Ghiringhelli D et al. Department of Rheumatology, Istituto Ortopedico Gaetano Pini, Milano, Italy J RHEUMATOL 2000; 27(6): 1477-83

Objective: To evaluate the efficacy of intravenous (i.v.) clodronate in patients with reflex sympathetic dystrophy syndrome (RSDS) and to assess the urinary excretion of type I collagen crosslinked N-telopeptide (NTx) before and after the treatment.

Methods: Thirty-two patients with RSDS were randomized to receive either i.v. clodronate 300 mg daily for 10 consecutive days or placebo. Forty days later, the

placebo treated patients received the clodronate treatment.

Outcome measures included as a primary endpoint the visual analog scale of pain (VAS, range 0-100); secondary endpoints were a clinical global assessment (CGA, range 0-3) and an efficacy verbal score (EVS, range 0-3). Clinical and biochemical assessments were performed before the treatment, 40 (T40), 90 (T90), and 180 (T180) days later.

Results: At T40 the 15 patients randomized to clodronate treatment showed significant decreases of VAS and CGA (P = 0.002, P = 0.001, respectively). Compared with the placebo group (17 patients), significant differences were found in all clinical variables (VAS: P = 0.001; CGA: P = 0.001; EVS: P <0.0001). A further clinical improvement was observed throughout the study. Pooling the results of all 32 patients after clodronate treatment, at T180 the overall percentage decrease of VAS was 93.2±15.6%, with 30 patients significantly improved or asymptomatic. Significant inverse correlations between baseline NTx values and decreases of VAS were found at T90 (p = 0.03) and T180 (P = 0.01). No adverse events related to treatment occurred.

Conclusion: A 10 day i.v. clodronate course is better than placebo and effective in the treatment of RSDS. NTx seems to be a predictive factor for clodronate efficacy.

Efficacy of Pamidronate for Osteoporosis in Patients with Cystic Fibrosis following Lung Transplantation

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AM J RESPIR CRIT CARE MED 2000; 162(3): 941-946

Lung transplantation with its attendant life-long immunosuppression contributes to bone loss and its sequelae, fractures and kyphosis, in patients with lung disease, many of whom already suffer from severe osteoporosis. Patients with cystic fibrosis (CF) are one of the most severely affected groups. We conducted a controlled, randomized, nonblinded trial of pamidronate (30 mg intravenously every 3 mo) with vitamin D (800 IU/d) and calcium (1 g/d) (n=16) compared with vitamin D and calcium alone (n=18, the control subjects) for 2 yr in 34 patients after lung transplant to improve bone mineral density (BMD). The treatment groups were similar in age, sex, baseline T-scores, renal function, hospitalization rates, immunosuppressant levels, change in lung function, and body mass index (BMI) over the study period. The patients treated with pamidronate gained 8.8±2.5% and 8.2 ± 3.8% in spine and femur BMD after 2 yr in comparison to control subjects, who gained, on average (±SD), 2.6±3.2 and 0.3±2.2%, respectively (P ≤0.015 for both). Seven and six fractures occurred in the control and pamidronate groups, respectively (P >0.2). Measures of bone resorption were highest immediately after lung transplant and improved with both pamidronate and time. Measures of bone formation were very poor after lung transplant, but recovered in the first post-lung transplant year irrespective of therapy. We conclude that pamidronate was more effective than control in improving bone mineral density after lung transplantation in

patients with CF and appears to be one of the most promising agents studied to date for posttransplant osteoporosis.

Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome

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J Pediatr 2000; 137(3): 403-409

Objectives: An open trial of pamidronate treatment was undertaken in 5 children and 4 young adults with polyostotic fibrous dysplasia associated with McCune Albright syndrome to assess clinical response, bone turnover, and cardiovascular status over a 2-year period. Study design: Pamidronate was administered by intravenous infusion 1 mg/kg/d for 3 days every 6 months for 2 years. Bone turnover was measured at 0, 6, 12, 18, and 24 months with bone mineral density, and cardiac output was assessed by echocardiography at 0, 12, and 24 months.

Results: All subjects reported marked reduction in bone pain and sustained increased mobility. The fracture rate decreased in most. Orthopedic insertion of intramedullary rods was successful with maintenance of rod position. Mean osteocalcin levels fell from 35.5±5.6 mug/L to 28.4±4.1 mug/L (P <0.03). Other bone turnover marker changes were not significant. The mean bone mineral density at lumbar spine increased from 0.5 ±0.08 to 0.67 ±0.03 g/cm(2) (P <.002) in children and 1.16 ± 0.6 to 1.33 ±0.08 g/cm(2) in adults (P <.005). Other changes in bone mineral density were not

significant. Cardiac output did not change significantly.

Conclusions: Pamidronate treatment is an effective therapeutic modality for children with polyostotic fibrous dysplasia, with a good short-term safety profile. Failure to demonstrate major biochemical or bone densitometry improvements is due to the nature of the fibrous dysplasia and intercurrent microfracture.

Bone mineral density in lung-transplant recipients before and after graft: prevention of lumbar spine post-transplantation-accelerated bone loss by pamidronate

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J HEART LUNG TRANSPLANT 2000; (8): 736-43

Lung-transplant recipients are at risk of osteoporosis. They may have low bone mass even before posttransplantation immunosuppressive therapy. We studied bone mineral density (BMD) before and after lung transplantation and compared the efficacy of antiresorptive therapies to calcium and vitamin D supplementation. Areal BMD was assessed in 42 patients awaiting lung transplantation and measured again after surgery at 6 (n = 29), and at 12 months (n = 20). Nineteen patients received antiresorptive therapy (30 mg pamidronate IV every 3 months (n = 14), or hormonal replacement therapy (n = 5)), and 10 patients received only calcium and vitamin D supplements. Mean age- and gender-adjusted lumbar spine (LS) and femoral neck (FN) BMD was significantly decreased prior to transplantation (- 0.6 ± 0.2, P < 0.01, and - 1.5 ± 0.2 standard deviation, P < 0.001,

respectively). At that time, 29% were osteoporotic (T-score < - 2.5 below the peak bone mass), while 55% were below - 1.0 T-score. Antiresorptive therapy decreased the rate of LS bone loss during the first 6 months and led to a significant increase of BMD at 1 year, with LS changes of + 0.2 ± 0.1 vs - 0.4±0.1 Z-score in the calcium-vitamin D group (P<0.002), and + 0.2 ± 0.1 vs - 0.04 ± 0.1 for FN (NS). One out of 20 patients experienced clinically evident fractures during antiresorptive therapy, and 3 out of 12 in the calcium-vitamin D group. A significant proportion of patients awaiting lung transplantation was osteoporotic or osteopenic. Antiresorptive therapy (pamidronate or hormone-replacement therapy (HRT)) prevented accelerated LS bone loss after graft.

Prevention of osteoporosis in heart transplant recipients: A comparison of calcitriol with calcitonin and pamidronate

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CALCIF TISSUE INT 2000; 67(2): 116-21

Bone loss and osteoporotic fractures are common in cardiac transplant recipients. To compare two prophylactic medical regimens after heart transplantation, 26 consecutive heart transplant recipients were randomized to receive either continuous oral calcitriol (0.5 &mgr;g/day) combined with nasal salmon calcitonin (200 U/day) for the first 3 months (group A) or intermittent intravenous pamidronate (0.5 mg/kg body weight) every third month (group B). Bone mineral density (BMD) and biochemical indices of bone turnover were measured at baseline and 3, 6, 12, and 18 months after

transplantation. The mean pretransplant BMD, measured by dual energy X-ray absorptiometry (DXA) was significantly lower in the patients compared with age-matched healthy controls. During the first year of treatment, rates of bone loss at the lumbar spine and femoral neck were slightly but significantly slower in the patients treated with pamidronate, but there was no longer a significant difference between the two groups after 18 months of heart transplantation. Irrespective of the mode of osteoporosis prevention, osteocalcin levels increased whereas urinary deoxyypyridinoline decreased after transplantation, and significant bone loss was observed in both treatment groups. We found no relationship between initial BMD, markers of bone turnover, cumulative glucocorticoid dose, or cyclosporine levels and the rate of bone loss after cardiac transplantation. In summary, we found that the rapid and severe bone loss following heart transplantation could be attenuated by two preventative measures, pamidronate or calcitriol with calcitonin.

Effectiveness of local delivery of alendronate in reducing alveolar bone loss following periodontal surgery in rats

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Background: Mucoperiosteal flaps are used to access bone and root surfaces for debridement, pocket elimination, management of periodontal defects, and in

regenerative procedures, as well as in implant surgery. Many reports show that periodontal surgery stimulates osteoclast activity with varying amounts of alveolar bone loss. Alendronate given intravenously significantly reduced alveolar bone loss in mucoperiosteal flap procedures. In the present study, we explored the effectiveness of different concentrations of alendronate, delivered at the surgical site at the time of surgery, in distant delivery in reducing alveolar bone loss.

Methods: Following elevation of a mucoperiosteal flap next to molars of the rat mandible, a gelatin sponge soaked with different concentrations of alendronate (0, 1, 5, 20, or 40 mg/ml; experiment A) was applied to exposed bone on the experimental side. In the second group (experiment B), alendronate (0, 50, 200, or 400 microg) was topically delivered in the cheek submucosa on the left side (distant to the surgical site) in a small cut into which the gelatin sponge soaked with the drug was placed.

Results: Topical application of 200 microg and 400 microg doses of alendronate at the time of surgery was significantly effective ($P < 0.001$) in reducing bone loss. Generally, the percentage of sections with mild bone loss (V1, V2) increased with an increase in the dose of alendronate, while the percentage of sections with severe bone loss (H1, H2) decreased with an increase in alendronate dose. Topical application of 400 microg of alendronate had a systemic effect.

Conclusions: This study implies that topical delivery of alendronate at the time of surgery reduces bone loss in periodontal procedures involving mucoperiosteal flap

surgery. The most effective dose is 200 microg for topical delivery at the surgical site and 400 microg for distant sites.

Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study

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J BONE MINER RES 2000; 15(6): 1006-13

Long-term use of high-dose corticosteroids often results in bone loss, which may lead to osteoporosis-related fractures. This was a multicenter, double-blind study in which 290 ambulatory men and women receiving high-dose oral corticosteroid therapy (prednisone ≥ 7.5 mg/day or equivalent) for 6 or more months were randomized to receive placebo, risedronate 2.5 mg/day, or risedronate 5 mg/day for 12 months. All patients received calcium 1 g and vitamin D 400 IU daily. The primary endpoint was lumbar spine bone mineral density (BMD) at month 12. Additional measurements included BMD at the femoral neck and trochanter and the incidence of vertebral fractures. Overall, there were statistically significant treatment effects on BMD at 12 months at the lumbar spine ($P < 0.001$), femoral neck ($P = 0.004$), and trochanter ($P = 0.010$). Risedronate 5 mg increased BMD at 12 months by a mean (SEM) of 2.9% (0.49%) at the lumbar spine, 1.8% (0.46%) at the femoral neck, and 2.4% (0.54%) at the trochanter, whereas BMD was maintained

only in the control group. Although not powered to show fracture efficacy, we observed a reduction in the incidence of vertebral fractures of 70% in the combined risedronate treatment groups, relative to placebo ($P=0.042$). Risedronate was well tolerated, had a good safety profile, and was not associated with gastrointestinal adverse events. We conclude that risedronate increases BMD and potentially reduces the incidence of vertebral fractures in patients with corticosteroid-induced osteoporosis.

Short-term administration of the bisphosphonate ibandronate increases bone volume and prevents hyperparathyroid bone changes in mild experimental renal failure

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CLIN NEPHROL 2000;54(1):45-53*

Background: Bisphosphonates (BP) are potent antiresorptive agents that have been used successfully in several bone diseases associated with hyperresorption. Hyperresorption, hypercalcemia, and osteoporosis are frequent findings in patients with renal failure or after renal transplantation. The present study was carried out to determine the effects of a new BP, ibandronate, on bone in a state of normal vs. moderately impaired renal function. **Material and Methods:** Forty 90-day-old female rats were either 2/3 nephrectomized (Nx, $n = 20$) or sham-operated (Sham, $n = 20$). Half of the Nx and Sham rats received either ibandronate (1.25 microg/rat s.c.) or vehicle once weekly for three weeks. Before euthanasia, blood drawings were performed and 24-

hr urine was collected. Femurs were analyzed by bone histomorphometry. **Results:** Serum creatinine, parathyroid hormone, and osteocalcin levels were equally higher in Nx rats given ibandronate or vehicle than in Sham rats. There was no difference in serum calcium, phosphorus, alkaline phosphatase, and urinary creatinine among the groups. Ibandronate-treated rats had lower urinary calcium and deoxypyridinoline crosslink levels than their Sham counterparts. Ibandronate-treated rats had higher bone volume than vehicle-treated animals. Ibandronate prevented the increase in erosion depth and bone turnover in Nx rats. **Conclusions:** BPs such as ibandronate represent potentially useful tools in the treatment of certain facets of renal bone disease. Indications for BP therapy may include treatment of osteoporosis, hypercalcemia, and/or extraosseous calcifications. Optimal dose and frequency of BP administration need to be determined in these patients.

Alendronate increases lumbar spine bone mineral density in patients with Crohn's disease

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Background & Aims: Low bone mineral density (BMD) is a common complication of Crohn's disease and may lead to increased morbidity and mortality because of fractures. We investigated the effect of treatment with the bisphosphonate alendronate on

bone mass and markers of bone remodeling in patients with Crohn's disease. **Methods:** A 12-month double-blind, randomized, placebo-controlled trial examined the effect of a 10-mg daily dose of alendronate. Thirty-two patients with a bone mass T score of -1 of the hip or lumbar spine were studied. The main outcome measure was the difference in the mean percent change in BMD of the lumbar spine measured by dual-energy X-ray absorptiometry. Secondary outcome measures included changes in BMD of the hip and total body and biochemical markers of bone turnover (S-osteocalcin, urine pyridinoline, and urine deoxypyridinoline excretion). **Results:** Mean (\pm SEM) BMD of the lumbar spine showed an increase of $4.6\% \pm 1.2\%$ in the alendronate group compared with a decrease of $0.9\% \pm 1.0\%$ in patients receiving placebo ($P < 0.01$). BMD of the hip increased by $3.3\% \pm 1.5\%$ in the alendronate group compared with a smaller increase of $0.7\% \pm 1.1\%$ in the placebo group ($P = 0.08$). Biochemical markers of bone turnover decreased significantly in the alendronate group ($P < 0.001$). Alendronate was well tolerated, and there was no difference in adverse events among treatment groups. **Conclusions:** Treatment with alendronate, 10 mg daily, significantly increased BMD in patients with Crohn's disease and was safe and well tolerated.

Effects of two intermittent alendronate regimens in the prevention or treatment of postmenopausal osteoporosis

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BONE 2000; 27(1): 119-22*

ABSTRACT

In clinical practice, a large proportion of patients have bone mass values for which a therapeutic intervention is considered necessary, but the accepted aim might be the sole preservation or marginal increases of the actual bone mass. These goals might be achieved with lower or intermittent doses of a powerful agent for the purpose of fewer side effects and improved compliance. The aim of this study was to assess the effects of two intermittent alendronate regimens in the treatment of postmenopausal osteoporosis. One hundred twenty-four postmenopausal women (age range 52-75 years, at least 7 years since last menopause) with a bone mineral density (BMD) at either the femoral neck or lumbar spine of 2 SD below the

mean values of young healthy individuals, and without a history of previous osteoporotic fracture, were randomly assigned either to calcium/vitamin D supplements, alone or associated with two different intermittent oral alendronate regimens: 20 mg once a week (weekly alendronate group) or 10 mg daily (orally) for 1 month out of 3 (cyclical alendronate group). After 1 year, in both groups given intermittent alendronate, we observed significant increases in BMD at both the spine ($+2.2 \pm 2.6$ and $+2.5 \pm 2.9$) and femoral neck ($+1.6 \pm 4.8$ and $+1.5 \pm 2.2$) for the weekly and cyclical regimens, respectively. This was associated with a significant diminution of both serum bone-specific alkaline phosphatase and urinary N-telopeptides of collagen type I excretion. In the patients in the

control group BMD decreased significantly at the lumbar spine, with a slight decline of serum bone-specific alkaline phosphatase. Compliance with treatment and drug tolerability were good in both alendronate groups. In conclusion, intermittent alendronate administration at cumulative doses (and costs) three times lower than those currently recommended for osteoporosis treatment is very well accepted, and is able to significantly increase BMD at the spine and femoral neck and to decrease the markers of bone turnover. These regimens can be clinically useful in the long-term treatment of postmenopausal osteoporosis without prevalent osteoporotic fractures, particularly in women with lower compliance for continuous administration.

AGGIORNAMENTO DELLA LETTERATURA

Numero 3 - Dicembre 2000

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.

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4. **Management of osteoporosis in primary biliary cirrhosis.**
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6. **Palliation of bone metastases: a survey of patterns of practice among Canadian radiation oncologists.**
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17. **Recognition and management of hungry bone syndrome-a case report.**
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19-20 gennaio 2001 **Roma, Italia**

Moderne Opzioni nella Prevenzione e nel Trattamento dell'Osteoporosi

Segreteria: Fondazione Internazionale Menarini, Piazza del Carmine, 4 - 20121 Milano
Tel. +39 - 02-874 932 Fax +39 - 02-804 739 e-mail: milan@fondazione-menarini.it

6 febbraio 2001 **Edimburgo (GB)**

Evening Teach-IN Session on Rheumatology

Segreteria: Lee Ross, Royal College of Physicians of Edinburgh, 9 Queen Street,
Edinburgh EH2 1JQ, United Kingdom
Tel. +44 - 131-225 7324 Fax +44 - 131-220 4393 e-mail: l.ross@rcpe.ac.uk

9-11 marzo 2001 **Firenze, Italia**

3° Congresso Nazionale GIBIS

Segreteria: A.I.C. - Asti Incentives & Congresses, Via Rigattieri, 10 - 56126 Pisa
Tel. +39 - 050 - 598808; +39 - 050 - 541402 Fax +39 - 050 - 598688
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14 marzo 2001 **Aberdeen (GB)**

Osteoporosis and Other Bone Diseases

Segreteria: Royal College of Physicians of Edinburgh, 9 Queen Street,
Edinburgh EH2 1JQ, United Kingdom
Tel. +44 - 131- 225 7324 Fax +44 - 131- 220 4393

22 marzo 2001 **Edimburgo (GB)**

Rheumatology 2001

Segreteria: Royal College of Physicians of Edinburgh, 9 Queen Street,
Edinburgh EH2 1JQ, United Kingdom
Tel. +44 - 131- 225 7324 Fax +44 - 131- 220 4393

24-28 marzo 2001 **Barcellona, Spagna**

6th International Conference on Systemic Lupus Erythematosus

Segreteria: Viajes Iberia Congresos Diagonal, 523 4 2 - 08029 Barcelona, Spain
Tel. +34-93-495 5306 Fax +34-93-405 1390 e-mail: congresos@v-iberia.com

19-21 aprile 2001 **Mantova, Italia**

2nd International Congress Glucocorticoid Induced Osteoporosis

Segreteria: Symposium, Via Gozzano, 14 - 10073 Ciriè (TO)
Tel. +39 - 011 - 9211467 Fax +39 - 011 - 9224992

1-4 giugno 2001 **Stresa Lago Maggiore (NO), Italia**

VI Workshop on Osteobiology

Segreteria: Aristeia, Salita di Santa Caterina, 4/7 - 16123 Genova
Tel. +39 - 010 - 583224 Fax +39 - 010 - 5531544

5-10 giugno 2001 Madrid, Spagna

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

Segreteria: Tel. +44 – (0)1453 549929 Fax +44 – (0)1453 548919;
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13-16 giugno 2001 Praga, Repubblica Ceca

EULAR 2001 – Annual European Congress of Rheumatology

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