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Questo numero di Aggiornamento in Tema di Bisfosfonati è stato stampato in 6.000 copie.

STAMPA

Lineadue, Via Cesare Battisti 380
Marnate (VA)

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EDITORIALE

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BISFOSFONATI E OSTEOGENESI IMPERFETTA

L'osteogenesi imperfetta

Il termine osteogenesi imperfetta raggruppa una serie di patologie ereditarie a trasmissione autosomica dominante, caratterizzate da difetti a carico di uno dei due geni, posti sui cromosomi 7 e 17, responsabili della produzione del collagene tipo I. L'incidenza stimata è di 1 caso ogni 20.000 nati ma, in realtà, la patologia nelle forme meno severe è pesantemente sottodiagnosticata. L'osteogenesi imperfetta, perciò, può avere un'espressione clinica variabile che va da forme praticamente incompatibili con la vita a situazioni al limite della normalità. Gli organi colpiti dalla patologia sono quelli contenenti collagene tipo I (*Tabella 1*), in particolare il tessuto osseo, con conseguente sviluppo di osteoporosi, fratture patologiche e deformità scheletriche.

L'osteogenesi imperfetta in passato era classificata in 4 forme diverse, ma recentemente, grazie agli studi del gruppo del professor FH Glorieux, ne sono state identificate altre 2 contando attualmente un totale di 6 forme (*Tabella 2*).

Terapia dell'osteogenesi imperfetta

Il trattamento dell'osteogenesi imperfetta è finalizzato alla prevenzione delle fratture e alla limitazione delle conseguenze negative sul piano funzionale. L'impossibilità di correggere il difetto genetico, e quindi le alterazioni istologiche ossee, riduce la strategia terapeutica alle sole procedure riabilitative e fisioterapiche (rafforzamento muscolare, stabilizzazione articolare con ausili protesici, ecc.) tese a limitare le cadute e a ripristinare al meglio la funzionalità osteoarticolare danneggiata dalle fratture stesse. Sebbene la maggior parte dei pazienti con OI tipo

Tabella 1. Osteogenesi imperfetta: organi bersaglio e manifestazioni cliniche

Patologia dei tessuti che contengono collagene tipo I	
Osso:	osteopatia, fratture, deformità scheletriche
Denti:	dentinogenesi imperfetta
Sclere:	sottili (bluastre)
Tendini:	fragilità, lassità
Cuore:	valvole sottili con rischio di insufficienza

Tabella 2. Classificazione dell'osteogenesi imperfetta

Classificazione
<p>Tipo I: Forma più frequente e meno grave, caratterizzata da un deficit quantitativo (circa 50%) del collagene, sclere blu, aumentata incidenza di fratture nell'infanzia e nell'età avanzata. Spesso misconosciuta</p> <p>Tipo II: È la forma più grave con morte perinatale</p> <p>Tipo III: Forma severa con bassa statura, gravi deformità scheletriche che condizionano qualità e quantità di vita dei pazienti, sclere blu e dentinogenesi imperfetta</p> <p>Tipo IV: Forma intermedia tra il tipo I e III con statura piuttosto bassa e modeste deformità scheletriche</p> <p>Tipo V: Forma simile al tipo IV da cui si differenzia per la formazione di callo osseo ipertrofico in caso di frattura o di osteotomia</p> <p>Tipo VI: Forma particolare, raramente accompagnata da dentinogenesi e sclere blu e caratterizzata da un accumulo di tessuto osteoide in assenza di patologie del metabolismo minerale</p>

III faccia uso di presidi sanitari quali sedie a rotelle e busti rigidi, subisce ugualmente frequenti fratture, successivamente saldate attraverso l'inserimento intramidollare nelle ossa lunghe (tibia, femore, ecc.) di lunghi chiodi metallici necessari per prevenire ulteriori fratture o incurvamenti del segmento scheletrico (Reing et al. 1995). Nelle forme più severe con deformità scheletriche e bassa statura, l'attesa di vita è fortemente ridotta per insufficienza cardio-respiratoria legata alle innumerevoli fratture vertebrali e alla conseguente comparsa di scoliosi e riduzione dello spazio toracico. In attesa di un'appropriate terapia genica applicabile ai pazienti, sono stati effettuati tentativi terapeutici, purtroppo con risultati modesti o nulli, con sali di fluoro, calcitonina, steroidi anabolizzanti e ormone somatotropo. Prospettive terapeutiche più interessanti sembrano venire offerte dall'utilizzo dei bisfosfonati.

Nelle prime esperienze pubblicate (*Tabella 3*), relative a un numero esiguo di pazienti, è infatti emersa la capacità di questa classe di farmaci di agire positivamente sulla massa ossea, ridurre la sintomatologia dolorosa e migliorare la mobilità determinando così la possibilità di acquisire e mantenere la posizione seduta.

Pamidronato

Il primo studio di discrete dimensioni sull'osteogenesi imperfetta, è stato condotto in Canada dal gruppo del professor Glorieux (*New Engl J Med*, 1998; 339: 947-52). Nello studio, osservazionale e non controllato, sono stati riportati i dati relativi a 30 bambini (3-16 anni di età) trattati con pamidronato ($6,8 \pm 1,1$ mg/kg/anno) a intervalli di 4-6 mesi per 1,3 - 5 anni. Il trattamento aveva prodotto un incremento medio annuale della densità ossea del $41,9 \pm 29\%$ con un calo significativo delle fratture confermato radiologicamente ($- 1,7$ fratture /anno; $p < 0,001$). Il trattamento con pamidronato non aveva modificato il tasso di guarigione delle fratture e il tasso di crescita dei pazienti.

Tabella 3. Bisfosfonati e osteogenesi imperfetta. Prime esperienze pubblicate

Lavoro	N° pazienti	Tipo OI	Età (anni)	Sesso	Trattamento	Durata
B Bembi et al. J Pediatr 1997	3	I	8,5 8,8 4	F F F	Pamidronato ev.	22-29 mesi
EA Landsmeer-Beker et al. Eur J Pediatr 1997	3	III	1 1,7 6	M M M	Olpadronato os	5-7 anni
E Astrom et al. Acta Paediatr 1998	3	III	13 16 20	F F F	Pamidronato ev.	2-5 anni

Tutti i pazienti hanno riportato sostanziale miglioramento del dolore cronico e in 16 pazienti anche della mobilità e della deambulazione.

Neridronato

Neridronato è un aminobisfosfonato di ultima generazione, frutto della ricerca italiana Abiogen, di potenza simile al pamidronato già utilizzato nella cura del morbo di Paget (Atkins et al. 1987; Delmas et al. 1987; McCloskey et al. 1987; Adami et al. in stampa).

Per quanto riguarda l'utilizzo del neridronato nell'osteogenesi imperfetta, sono oggi disponibili i dati relativi al trattamento, sia di soggetti in età pediatrica, sia adulti (Adami et al. Davos 2002; Adami et al. in stampa, Neridronato file registrativo). Il cui protocollo prevede la somministrazione di neridronato (2 mg/kg, fino a un massimo di 100 mg) ogni 3 mesi.

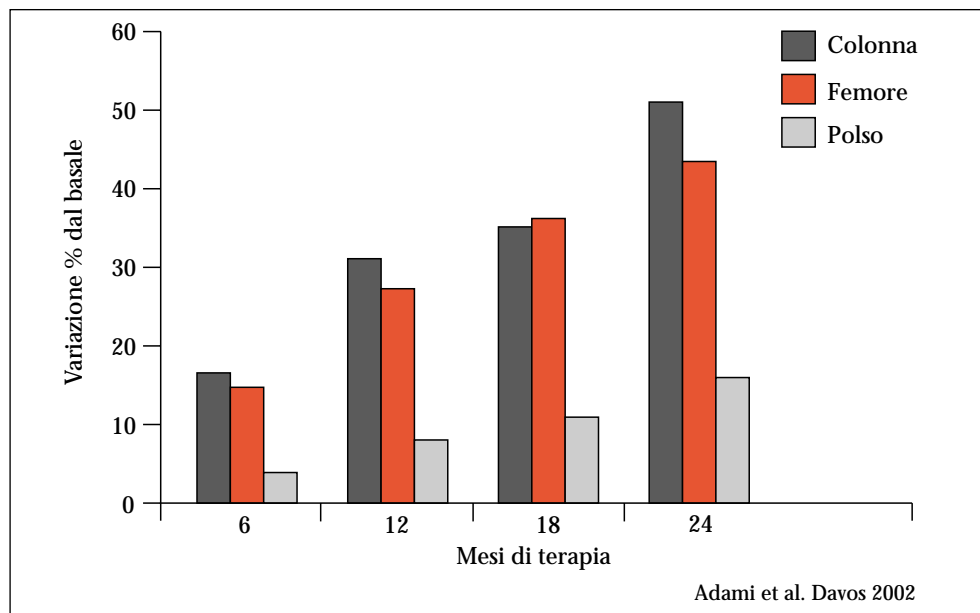
I risultati ottenuti sono relativi a 81 pazienti d'ambo i sessi, 52 di età superiore a 20 anni (range 21-71) e 29 di età inferiore (range 5-17). La gran parte dei pazienti (n= 51) è affetta dalla malattia nella forma più lieve, mentre una minoranza presenta forme di media gravità (Tipo IV=20) e severe (Tipo III=10).

Nel gruppo pediatrico si realizzano i maggiori incrementi di massa ossea, con variazioni significative a livello di tutti i distretti studiati già dopo soli 6 mesi di terapia, che persistono per tutta la durata del trattamento (*Figura 1*). Questi incrementi di massa ossea si accompagnano a un ugualmente significativo aumento dell'area vertebrale proiettata.

Questo dato causa addirittura una sottostima dell'aumento densitometrico lombare ma documenta come il trattamento non incida sull'accrescimento di questi soggetti. D'altra parte il significativo miglioramento anche in q di Z-score (da $-3,29 \pm 1,73$ a $-1,94 \pm 1,78$ dopo 2 anni) dimostra a sua volta che le variazioni densitometriche non possono essere giustificate solo dal normale processo di accrescimento.

Il confronto tra il numero di fratture verificatesi nei 2 anni precedenti l'inizio del trattamento e quello registrato durante i 2 anni di terapia (Neridronato, file registrativo), dimostra un calo significativo di circa il 50% dell'incidenza di frattura (*Figura 2*).

Figura 1. Variazioni densitometriche in corso di terapia con neridronato in soggetti di età inferiore a 20 anni



Per quanto riguarda il trattamento di soggetti adulti, sono disponibili dati relativi a un gruppo di 31 pazienti (età media 35 ± 8 anni; range 21-50 anni) trattati per 2 anni con neridronato (Adami et al. in stampa).

Figura 2. Confronto tra il numero di eventi fratturativi verificatisi nei 2 anni precedenti il trattamento e durante i 2 anni di terapia con neridronato (gruppo pediatrico)

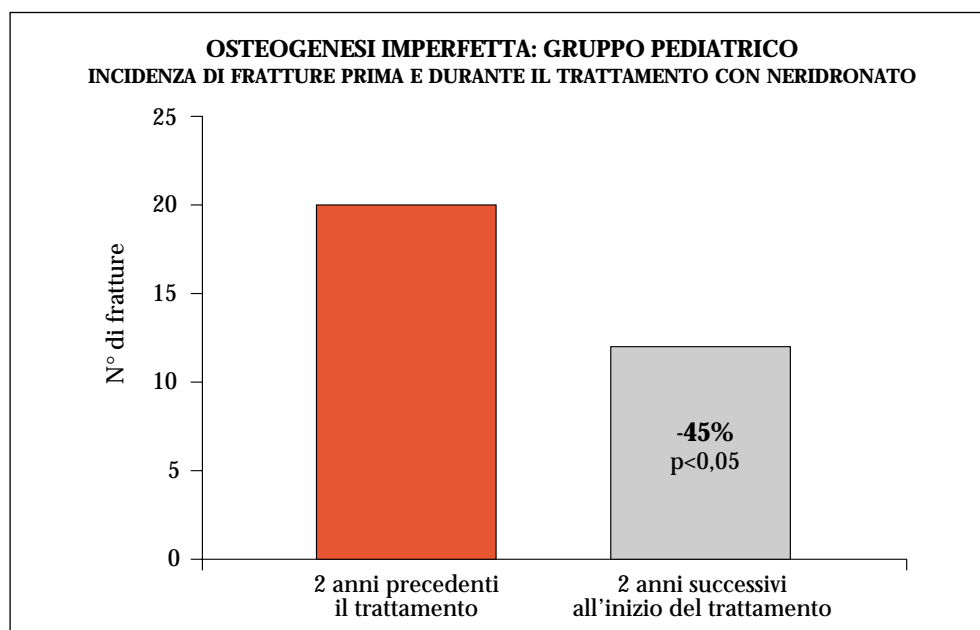
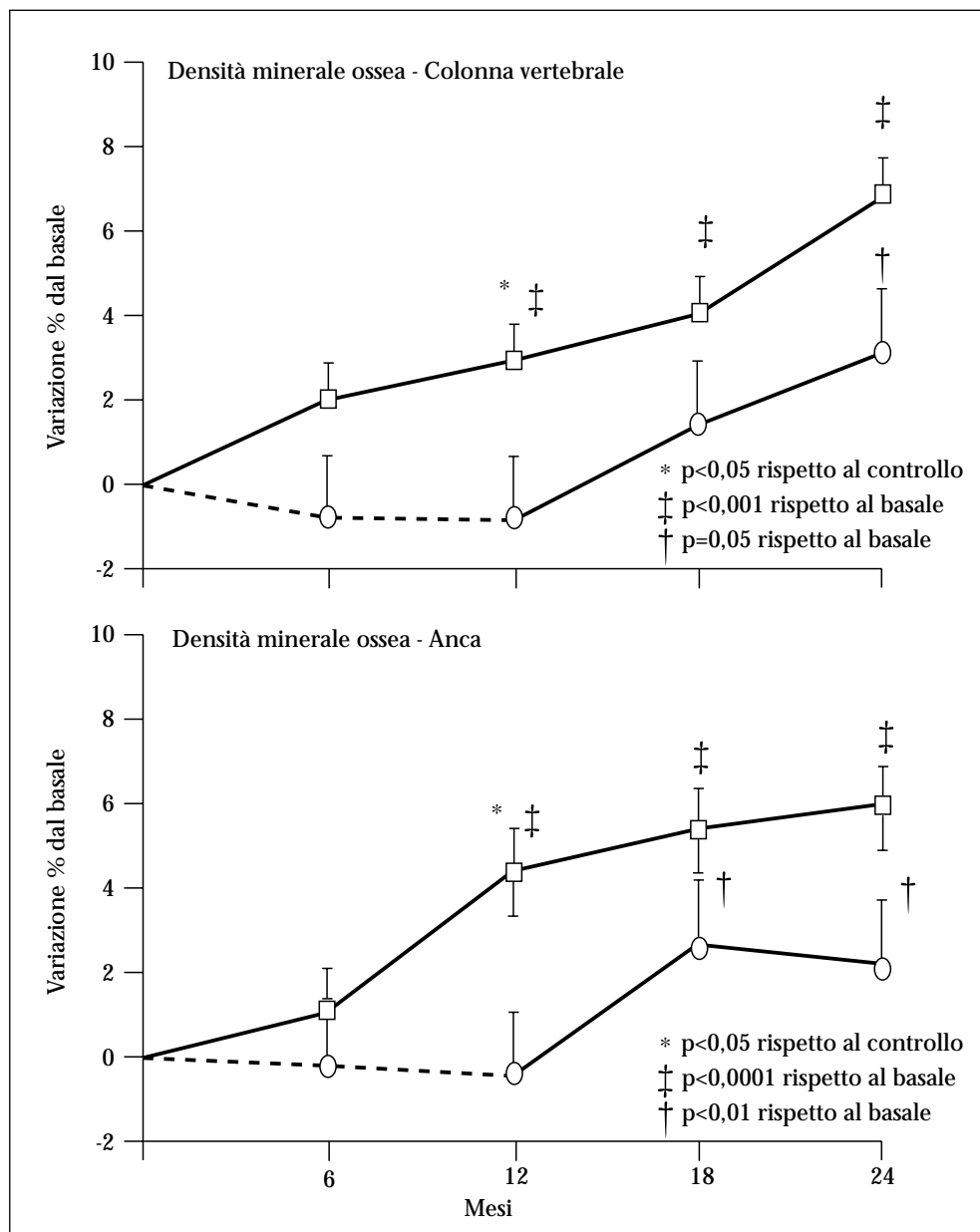


Figura 3. Variazioni densitometriche in soggetti adulti affetti da OI trattati con neridronato per 2 anni, rispetto al gruppo di pazienti di pari età che hanno avviato il trattamento dopo 1 anno di follow-up senza terapia



Nella *Figura 3* sono riportate le variazioni densitometriche, sia lombari, sia femorali dei soggetti trattati rispetto al gruppo di pazienti che, per protocollo, hanno avviato il trattamento farmacologico dopo un anno di follow-up senza terapia. A tale proposito vanno sottolineate alcune importanti osservazioni:
 - nei pazienti che non hanno seguito alcun trattamento non si è verificata alcuna variazione significativa della densità ossea;

- nei pazienti trattati, la massa ossea è aumentata significativamente (sia rispetto al valore iniziale che al gruppo di controllo) del 3-4% in un anno di terapia, con una crescita che si è confermata anche nel secondo anno di trattamento.

In termini di rischio di frattura, l'incidenza registrata durante la terapia (1/77 pazienti per anno) è stata sensibilmente inferiore rispetto a quella verificatasi nei 2 anni prima del trattamento (18/199 pazienti per anno) con una riduzione ai limiti della significatività (RR: 0,14: IC 95% 0,02-1,09).

Il trattamento con neridronato ha determinato, sia nei soggetti pediatrici, sia in quelli adulti, un rilevante miglioramento dei dolori ossei e della mobilità generale senza eventi avversi degni di nota.

In conclusione, i dati ottenuti relativi all'uso dei bisfosfonati nell'osteogenesi imperfetta sono molto positivi. Il neridronato appare la molecola che può vantare maggior supporto scientifico avvalendosi di esperienze in pazienti di tutte le età. Proprio sulla base di questi dati, le autorità sanitarie italiane hanno registrato questa molecola per il trattamento di soggetti con osteogenesi imperfetta.

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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.

Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis

Johnell O, Scheele WH, Lu Y et al.

Department of Orthopaedics, Universitetssjukhuset MAS, Malmo, Sweden

J CLIN ENDOCRINOL METAB 2002; 87(3): 985-92

Both raloxifene (RLX) and alendronate (ALN) can treat and prevent new vertebral fractures, increase bone mineral density (BMD), and decrease biochemical markers of bone turnover in postmenopausal women with osteoporosis. This phase 3, randomized, double-blind 1-yr study assessed the effects of combined RLX and ALN in 331 postmenopausal women with osteoporosis (femoral neck BMD T-score, less than -2). Women (aged ≤ 75 yr; ≥ 2 yr since their last menstrual period) received placebo, RLX 60 mg/die, ALN 10 mg/die, or RLX 60 mg/die and ALN 10 mg/die combined. At baseline, 6 and 12 months, BMD was measured by dual x-ray absorptiometry. The bone turnover markers serum osteocalcin, bone-specific alkaline phosphatase, and urinary N- and C-telopeptide corrected for creatinine were measured. The effects of RLX and ALN were considered to be independent and additive if the interaction effect was not statistically significant ($P > 0.10$) in a two-way ANOVA model. All changes in BMD and bone markers at 12 months were different between placebo and each of the active treatment groups, and between the RLX and RLX+ALN groups ($P < 0.05$). On average, lumbar spine BMD increased by 2.1, 4.3, and 5.3% from baseline with RLX, ALN, and RLX+ALN, respectively. The increase in femoral

COMMENTO EDITORIALE

I risultati di questo studio sono inattesi e di grande interesse. Il fatto che l'aggiunta di raloxifene (RLX) ad alendronato (ALN) produca risultati aggiuntivi sulla massa ossea non può essere spiegato dal semplice sommarsi dell'attività dei due farmaci sugli osteoclasti in quanto l'effetto farmacologico di 10 mg di ALN viene ritenuto già quasi massimale. L'interpretazione di questi risultati è ipotetica. È noto che una severa carenza di estrogeni (sia nella donna che nell'uomo) può iperesprimere l'attivazione del sistema RANK-RANKL e che la risposta densitometrica al RLX è inversamente proporzionale ai livelli basali di estradiolo. È possibile quindi che il sommarsi dell'effetto di ALN e RLX sia il risultato di un particolare potenziamento dell'effetto di ALN in un sottogruppo di donne con livelli di estradiolo particolarmente ridotti.

neck BMD in the RLX+ALN group (3.7%) was greater than the 2.7 and 1.7% increases in the ALN ($P = 0.02$) and RLX ($P < 0.001$) groups, respectively. The changes from baseline to 12 months in bone markers ranged from 7.1 to -16.0% with placebo, -23.8 to -46.5% with RLX, -42.3 to -74.2% with ALN, and -54.1 to -81.0% in the RLX+ALN group. RLX and ALN increased lumbar spine and femoral neck BMD, and decreased osteocalcin and C-telopeptide corrected for creatinine in an additive and independent manner, because the interaction effects were not significant. Although the ALN group had changes in BMD and bone markers that were approximately twice the magnitude as in the RLX group, it is not known how well these changes correlate to the clinical outcome of fracture. RLX+ALN reduced bone turnover more than either drug alone, resulting in greater BMD increment, but whether this difference reflects better fracture risk reduction was not assessed in this study.

Tumor necrosis factor alpha-mediated joint destruction is inhibited by targeting osteoclasts with osteoprotegerin

Redlich K, Hayer S, Maier A et al.

University of Vienna, Vienna, Austria

ARTHRITIS RHEUM 2002; 46(3): 785-92

Objective: To study the effects of osteoclast-targeted therapies, such as osteoprotegerin (OPG) and pamidronate, on joint inflammation and bone destruction using a tumor necrosis factor alpha (TNF α)-transgenic mouse model.

Methods: Mice were placed into 5 groups that received either OPG, pamidronate, a combination of both agents, infliximab as a positive control, or phosphate buffered saline as a negative control. Treatment was initiated at the onset of arthritis, continued over 6 weeks, and thereafter, the clinical, radiologic, and histologic outcomes were assessed.

Results: A significant improvement in clinical symptoms, as assessed by the reduction of paw swelling, was only found in the infliximab group, whereas all other treatment groups failed to show significant improvement. However, when assessing structural damage with radiographic analysis, a significant retardation of joint damage was evident in animals treated with OPG (55% reduction of erosions), pamidronate (50% reduction of erosions) the combination therapy of OPG and pamidronate (64% reduction of erosions), and with infliximab (66% reduction of erosions). Confirming these data, quantitative histologic analysis revealed a significant reduction in the size of bone erosions in all treatment groups (OPG 56%, pamidronate 53%, OPG and

COMMENTO EDITORIALE

In questi ultimi anni si sono accumulati numerosi dati a supporto del razionale per l'uso dei bisfosfonati nella prevenzione delle erosioni ossee in pazienti con artrite reumatoide. Questo uso è stato preconizzato già negli anni 80 dal professor Pasero di Pisa. A quando il primo trial randomizzato e controllato?

pamidronate 81%, and infliximab 46%) compared with the control group. Furthermore, a significant reduction of osteoclast numbers was seen in animals treated with OPG alone or in combination with pamidronate as well as in animals treated with infliximab.

Conclusion: These data suggest that OPG alone or in combination with bisphosphonates is an effective therapeutic tool for the prevention of TNF α -mediated destruction of bone by reducing the number of bone-resorbing cells in the inflammatory tissue.

The effect of bone remodeling inhibition by zoledronic acid in an animal model of cartilage matrix damage

Muehleman C, Green J, Williams JM et al.

Department of Anatomy, Rush Medical College, Chicago, Illinois 60612, USA

OSTEOARTHRITIS CARTILAGE 2002; 10(3): 226-33

Objective: The purpose of this work was to test the effect of inhibition of bone remodeling, through the use of the bisphosphonate, zoledronic acid, on cartilage matrix damage in an animal model of cartilage matrix damage.

Design: New Zealand white rabbits were divided into four groups for treatment purposes: (1) untreated controls; (2) injected into one knee joint with the cartilage matrix degradation enzyme, chymopapain; (3) injected into one knee joint with chymopapain and also given subcutaneous injections of the bisphosphonate, zoledronic acid, three times per week until sacrifice at either day 28 or 56 post-chymopapain-injection; (4) received only the zoledronic acid injections. At sacrifice, the knee joints were examined grossly and histologically, and biochemically for proteoglycan content. Urine samples were analysed, at intervals, for levels of collagen cross-links which are biochemical markers of cartilage and bone.

Results: Animals receiving both intraarticular chymopapain injections and subcutaneous zoledronic acid injections displayed a significantly lower degree of grossly and histologically detectable cartilage degeneration on the tibial articular surfaces (the articular surface displaying the greatest degree of degeneration) than did animals only receiving the chymopapain injections. In addition, urinary levels of collagen cross-links for bone and cartilage were significantly higher in those animals only receiving chymopapain injections.

Conclusions: The bone resorption observed after chymopapain injection into the rabbit knee joint can be inhibited through the use of the bisphosphonate, zoledronic acid. Furthermore, zoledronic acid does

COMMENTO EDITORIALE

Anche questo studio sembra fornire un buon razionale per l'impiego dei bisfosfonati nella prevenzione dell'artrosi. Tra 18 mesi saranno disponibili i risultati di uno studio randomizzato e controllato con risedronato. Sarà l'inizio di una nuova straordinaria era nell'approccio terapeutico dei processi degenerativi articolari?

not increase the level of cartilage degeneration and appears to provide some level of chondroprotection in this model.

A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis
 Maksymowych WP, Jhangri GS, Fitzgerald AA et al.
 University of Alberta, Edmonton, Alberta, Canada
 ARTHRITIS RHEUM 2002; 46 (3): 766-73

Objective: To determine the safety and efficacy of intravenous (IV) pamidronate treatment in ankylosing spondylitis (AS) patients who have had a suboptimal response to nonsteroidal antiinflammatory drugs (NSAIDs).

Methods: Pamidronate at 60 mg was compared with pamidronate at 10 mg rather than placebo in view of the high incidence of transient arthralgias upon first IV exposure to the drug. The drug were given monthly for 6 months in a randomized double-blind, controlled trial. The inclusion criterion was active disease (Bath AS Disease Activity Index [BASDAI] of ≥ 4 or morning stiffness of ≥ 45 minutes) despite stable NSAID therapy. The primary outcome measure was the BASDAI, and secondary outcomes included the Bath AS Functional Index (BASFI), Bath AS Global Index (BASGI), Bath AS Metrology Index (BASMI), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and percentage of patients achieving a reduction of $\geq 25\%$ in the BASDAI. Outcome assessments were done at -2, 0, 12, and 24 weeks, and analysis was by intent to treat.

Results: Eighty-four AS patients (67 men and 17 women; mean age 39.6 years and mean disease duration 15.1 years) were enrolled. Dosage groups were well matched at baseline for demographics, disease activity, and functional indices. At 6 months, the mean BASDAI had decreased by 2.22 (34.5%) in the 60-mg group and by 0.93 (15%) in the 10-mg group ($P = 0.002$). Significantly greater reductions in the 60-mg group were also noted for the BASFI ($P < 0.001$), BASGI ($P = 0.01$), and BASMI ($P = 0.03$). Significantly more patients achieved a reduction of $\geq 25\%$ in the BASDAI in the 60-mg group versus the 10-mg group (63.4% versus 30.2%; $P = 0.004$). Differences in ESR/CRP were not significant (NS). Withdrawals included 9 (20.9%) from the 10-mg group and 3 (7.3%) from the 60-mg group (P NS). Adverse events were confined to transient arthralgias/myalgias after the first IV infusion, occurring in 68.3% and 46.5% of patients in the 60-

COMMENTO EDITORIALE

Si apre un nuovo fronte nell'utilizzo terapeutico dei bisfosfonati? La dose utilizzata in questo studio è piuttosto elevata e il farmaco è disponibile solo per uso ospedaliero. La recente disponibilità sul mercato italiano di neridronato (un bisfosfonato simile per struttura e potenza al pamidronate) potrebbe facilmente consentire qualche studio pilota in pazienti ambulatoriali (le dosi equivalenti da impiegare potrebbero essere neridronato 25 mg 1 fiala i.m. per 4 giorni ogni 6 mesi).

mg and 10-mg groups, respectively (P NS).

Conclusion: Pamidronate has dose-dependent therapeutic properties in AS.

Short-term intravenous therapy with neridronate in Paget's disease

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CLIN EXP RHEUMATOL 2002; 20(1): 55-8

Aims: To describe the effects of two consecutive intravenous infusions of aminohexane bisphosphonate (Neridronate) in patients with active Paget's disease of bone.

Methods: The study population included 83 patients, aged 41 to 85 years, randomized to 4 cumulative doses of Neridronate (25, 50, 100, 200 mg) given over 2 days, with a follow up of 180 days. The baseline serum alkaline phosphatase activity was at least 10% above the upper limit of the laboratory range. The response to treatment was assessed by changes in the serum total alkaline phosphatase (primary end point of the study), bone alkaline phosphatase and N-telopeptide urinary excretion.

Results: All Neridronate doses significantly suppressed the biochemical indices of disease activity. The nadir of total alkaline phosphatase levels ranged from -16 % to -57.5% of pretreatment values in the four groups, with a dose-response relationship that was apparent even between the two highest doses. The proportion of patients still maintaining a partial response (decreases in serum total alkaline phosphatase >25%) at the 6 month follow-up was also related to the dose: 98%, 67%, 57%, 21% in the patients given 200, 100, 50, 25 mg respectively. The proportion of responders in terms of bone alkaline phosphatase and N-telopeptide excretion changes was similar. Bone pain attributed to Paget's disease was significantly reduced. A typical acute phase reaction (fever and/or arthromyalgia) occurred in 16 out of 83 patients.

Conclusions: We conclude that all of the Neridronate doses tested here were well tolerated and effective in decreasing, in a dose-related manner the bone turnover parameters of Paget's disease. The highest dose (200 mg) resulted in the normalization of the markers of disease activity in more than 60% of the patients.

COMMENTO EDITORIALE

Abbiamo a disposizione in Italia un nuovo bisfosfonato per la terapia del morbo di Paget. Il vantaggio maggiore sarà rappresentato dalla possibilità di fare una terapia parenterale a domicilio estremamente semplice. Neridronato 25 mg i.m. al dì per 4-8 giorni dovrebbe determinare la soppressione totale della malattia nel 90% dei casi.

SEZIONE B

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

Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials

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MAYO CLIN PROC 2002; 77(3): 262-70

Risedronate sodium is a pyridinyl bisphosphonate effective for treatment and prevention of postmenopausal and glucocorticoid-induced osteoporosis. Some bisphosphonates have been associated with upper gastrointestinal (GI) tract adverse effects. The objective of this study was to determine the frequency of upper GI tract adverse events associated with risedronate, especially among high-risk patients. The GI tract adverse events reported during 9 multicenter, randomized, double-blind, placebo-controlled studies of risedronate conducted from November 1993 to April 1998 were pooled and evaluated. The evaluation included 10,068 men and women who received placebo (n=5048) or 5 mg of risedronate sodium (n=5020) for up to 3 years (intent-to-treat population). Studies incorporated a comprehensive, prospective evaluation of GI tract adverse events. Adverse event information was collected every 3 months. The treatment groups were similar with respect to baseline GI tract disease and use of concomitant treatments during the studies. At study entry, 61.0% of patients had a history of GI tract disease and 38.7% had

active GI tract disease; 20.5% used antisecretory drugs during the studies. Sixty-three percent used aspirin and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the studies. Upper GI tract adverse events were reported by 29.6% of patients in the placebo group compared with 29.8% in the risedronate group. The risk of experiencing such an event in the risedronate group was 1.01 (95% confidence interval, 0.94-1.09) relative to the placebo group (P=0.77). The rate of upper GI tract adverse events per 100 patient-years was 19.2 in the placebo group compared with 20.0 in the risedronate group (P=0.30). Risedronate-treated patients with active heartburn, esophagitis, other esophageal disorders, or peptic ulcer disease at study entry did not experience worsening of their underlying conditions or an increased frequency of upper GI tract adverse events overall. Concomitant use of NSAIDs, requirement for gastric antisecretory drugs, or the presence of active GI tract disease did not result in a higher frequency of upper GI tract adverse events in the risedronate-treated patients compared with controls. Endoscopy, performed in 349 patients, demonstrated no statistically significant differences across treatment groups. The results of this extensive evaluation indicate that daily treatment with 5 mg of risedronate sodium is not associated with an increased frequency of adverse GI tract effects, even among patients at high risk for these events.

Intravenous zoledronic acid in postmenopausal women with low bone mineral density

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N ENGL J MED 2002; 346(9): 653-61

Background: Bisphosphonates are effective agents for the management of osteoporosis. Their low bioavailability and low potency necessitate frequent administration on an empty stomach, which may reduce compliance. Gastrointestinal intolerance limits maximal dosing. Although intermittent intravenous treatments have been used, the optimal doses and dosing interval have not been systematically explored.

Methods: We studied the effects of five regimens of zoledronic acid, the most potent bisphosphonate, on bone turnover and density in 351 postmenopausal women with low bone mineral density in a one-year, randomized, double-blind, placebo-controlled trial. Women received placebo or intravenous zoledronic acid in doses of 0.25 mg, 0.5 mg, or 1 mg at three-month intervals. In addition, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, six months apart. Lumbar-spine bone mineral density was the primary end point.

Results: There were similar increases in bone mineral density in all the zoledronic acid groups to values for the spine that were 4.3 to 5.1 percent higher than those in the placebo group (P<0.001) and values for the femoral neck that were 3.1 to 3.5 percent higher than those in the placebo group (P<0.001). Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Myalgia and pyrexia occurred more commonly in the zoledronic acid groups, but treatment-related dropout rates were similar to that in the placebo group.

Conclusions: Zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density

as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis.

Bisphosphonates pamidronate and zoledronic acid stimulate osteoprotegerin production by primary human osteoblasts

Viereck V, Emons G, Lauck V et al. Department of Obstetrics and Gynecology, Georg-August-University of Goettingen, Goettingen, D-37075, Germany. viereck@med.uni-goettingen.de BIOCHEM BIOPHYS RES COMMUN 2002; 291 (3): 680-6

Bisphosphonates are potent antiresorptive drugs commonly employed in the treatment of metabolic bone diseases. Despite their frequent use, the mechanisms of bisphosphonates on bone cells have largely remained unclear. Receptor activator of nuclear factor-kappaB ligand (RANKL) is essential for osteoclast formation and activation, whereas osteoprotegerin (OPG) neutralizes RANKL. Various osteotropic drugs have been demonstrated to modulate osteoblastic production of RANKL and OPG. In this study, we assessed the effects of the bisphosphonates pamidronate (PAM) and zoledronic acid (ZOL) on OPG mRNA steady-state levels (by semiquantitative RT-PCR) and protein production (by ELISA) in primary human osteoblasts (hOB). PAM increased OPG mRNA levels and protein secretion by hOB by up to 2- to 3-fold in a dose-dependent fashion with a maximum effect at 10(-6) M (P < 0.001) after 72 h. Similarly, ZOL

enhanced OPG gene expression and protein secretion by hOB in a dose-dependent fashion with a maximum effect at 10(-8) M after 72 h, consistent with the higher biological potency of ZOL. Time course experiments indicated a stimulatory effect of PAM and ZOL on osteoblastic OPG protein secretion by 6-fold, respectively (P < 0.001).

Pretreatment with PAM and ZOL prevented the inhibitory effects of the glucocorticoid dexamethasone on OPG mRNA and protein production. Analysis of cellular markers of osteoblastic differentiation revealed that PAM and ZOL induced type I collagen secretion and alkaline phosphatase activity by 2- and 4-fold, respectively (P < 0.0001 by ANOVA). In conclusion, our data suggest that bisphosphonates modulate OPG production by normal human osteoblasts, which may contribute to the inhibition of osteoclastic bone resorption. Since, OPG production increases with osteoblastic cell maturation, enhancement of OPG by bisphosphonates could be related to their stimulatory effects on osteoblastic differentiation.

A strategy for the management of elderly women with primary hyperparathyroidism: a comparison of etidronate therapy with parathyroidectomy

Horiuchi T, Onouchi T, Inoue J et al. Department of Endocrinology, Tokyo Metropolitan Geriatric Hospital, Tokyo, and Department of Clinical Research, Teikyo University School of Medicine, Chiba, Japan GERONTOLOGY 2002; 48 (2): 103-8

Objective: To evaluate the efficacy of etidronate (EHDP) on lumbar spine bone mineral density (LSBMD) and total bone

mineral density (TBMD) in elderly women with primary hyperparathyroidism (PHPT), we compared changes in LSBMD and TBMD between patients treated by EHDP therapy and parathyroidectomy (PTX). **Subjects and Methods:** Twenty-two PHPT patients were enrolled and randomized into two groups; 9 received EHDP and 13 underwent PTX. All patients were followed up for 1 year by measuring LSBMD, TBMD, serum calcium, inorganic phosphate, parathyroid hormone, 1,25-dihydroxyvitamin D, serum alkaline phosphatase, intact osteocalcin, urinary pyridinoline (U(pyd)) and urinary deoxypyridinoline (U(dpd)). The presence of spinal fractures was evaluated by X-ray photography before and after treatment.

Results: EHDP treatment produced a significant increase in LSBMD of 10% compared with pretreatment levels after 1 year (P < 0.03, compared to baseline), while PTX produced a significant increase in LSBMD of 20% compared to pretreatment levels (P < 0.01). However, TBMD remained unchanged for 1 year after both EHDP administration and PTX. Among biochemical bone turnover markers, EHDP administration resulted in significant decreases in alkaline phosphatase by 78%, U(pyd) by 64% and U(dpd) by 37% after 12 months compared with the pretreatment levels (P < 0.05) and intact osteocalcin by 67% after 6 months (P < 0.05). There were no differences in the fracture rate between the EHDP and PTX groups during 1 year.

Conclusion: EHDP administration results in a somewhat lower increase in LSBMD than that following PTX and suppresses bone formation and resorption in elderly PHPT patients for 1 year. We conclude that PTX is preferable to EHDP

therapy for the management of elderly PHPT patients; however, EHDP administration should also be considered for elderly patients with many complications or who are unfit for surgery.

Pamidronate results in symptom control of hypertrophic pulmonary osteoarthropathy in cystic fibrosis

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CHEST 2002; 121 (4): 1363-4

Hypertrophic pulmonary osteoarthropathy (HPOA) may complicate the advanced lung disease that is associated with cystic fibrosis, resulting in severe joint pain and early-morning stiffness. Symptoms are usually controlled with the administration of nonsteroidal anti-inflammatory drugs, physiotherapy, and, on occasions, oral corticosteroids. This report describes a case of refractory HPOA with complete remission following the administration of IV pamidronate, which is a potent inhibitor of osteoclastic bone resorption. Symptom relief resulted for up to 3 months, but repeated courses of pamidronate have been required to maintain symptom control.

Chronic intravenous aminobisphosphonate therapy increases high-density lipoprotein cholesterol and decreases low-density lipoprotein cholesterol

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J BONE MINER RES 2000; 15 (3): 599-604

Nowadays, bisphosphonates are considered the drugs of choice for the treatment of several bone disorders. Their exact mechanism of action is not clear but recently it has been reported that the aminobisphosphonates inhibit cholesterol biosynthesis and that this might be relevant for their actions on bone osteoclasts. The study includes 87

postmenopausal women with moderate to severe osteoporosis. The patients were randomly assigned to intravenous (iv) infusion of 50 mg of the aminobisphosphonate Neridronate dissolved in 100 ml of saline solution every 2 months for a year (44 patients). The remaining 43 served as controls. At the time of each infusion blood samples were obtained for the evaluation of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), apolipoprotein A-I (Apo A-I), apolipoprotein B (Apo B), and total and bone alkaline phosphatase (AP). Free deoxyypyridinoline (f-DPD) was measured in fasting urine specimens. In the control group no significant changes were observed throughout the study period for any of the biochemical variables. In the Neridronate-treated patients both bone AP and f-DPD excretion fell significantly by 15-20%. In these patients serum total cholesterol and serum triglycerides showed marginal decreases, which were occasionally significant. LDL-C and Apo B fell by 5-6% and these changes were statistically significant at most time points. Apo A-I and HDL-C rose progressively with time. At the 12th month, HDL-C rose 17-18% ($P < 0.0001$) above the baseline values. Similar findings were obtained in four postmenopausal women given high iv doses of

Pamidronate or Alendronate. In conclusion aminobisphosphonates, at least when given iv, induce remarkable and unexpected effects on lipid metabolism with a final profile that might be clinically relevant.

Effect of estrogen replacement plus low-dose alendronate treatment on bone density in surgically postmenopausal women with osteoporosis

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J CLIN ENDOCRINOL METAB 2002; 87 (4): 1502-8

This prospective randomized, double-blind, placebo-controlled, clinical trial was performed to evaluate the effectiveness of estrogens plus low-dose alendronate on bone metabolism. A total of 150 surgically postmenopausal women with osteoporosis were randomized in three groups: group A, micronized E2 (2 mg/die) plus standard-dose alendronate (10 mg/die); group B, micronized E2 plus low-dose alendronate (5 mg/die); and group C, micronized E2 plus placebo (one tablet per day). In all women, bone mineral density (BMD) and serum bone metabolism markers were assessed at admission and every 6 months for 2 yr. After 2 yr, BMD significantly increased compared with baseline in all groups. The percentage BMD change was significantly higher in groups A and B than in group C. The differences in BMD detected between groups A and B were not statistically significant. Since the 6-month follow-up and throughout the study, serum osteocalcin and bone alkaline phosphatase levels and urinary deoxyypyridinoline and pyrilinks-D excretion were

significantly reduced in all groups. Serum bone alkaline phosphatase levels significantly decreased in groups A and B, without difference between them, in comparison with group C. In conclusion, in surgically postmenopausal osteoporotic women treated with estrogen replacement, the addition of alendronate at a low dose of 5 mg daily induces a gain of bone mass not significantly different in comparison with that obtained using a standard dose of 10 mg daily.

Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs

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AM J MED 2002; 112(4): 281-9

Purpose: To estimate how much the improvement in bone mass accounts for the reduction in risk of vertebral fracture that has been observed in randomized trials of antiresorptive treatments for osteoporosis.

Methods: After a systematic search, we conducted a meta-analysis of 12 trials to describe the relation between improvement in spine bone mineral density and reduction in risk of vertebral fracture in postmenopausal women. We also used logistic models to estimate the proportion of the reduction in risk of vertebral fracture observed with alendronate in the Fracture Intervention Trial that was due to improvement in bone mineral density.

Results: Across the 12 trials, a 1% improvement in spine bone mineral density was associated with a 0.03 decrease (95%

confidence interval [CI]: 0.02 to 0.05) in the relative risk (RR) of vertebral fracture. The reductions in risk were greater than predicted from improvement in bone mineral density; for example, the model estimated that treatments predicted to reduce fracture risk by 20% (RR = 0.80), based on improvement in bone mineral density, actually reduce the risk of fracture by about 45% (RR = 0.55). In the Fracture Intervention Trial, improvement in spine bone mineral density explained 16% (95% CI: 11% to 27%) of the reduction in the risk of vertebral fracture with alendronate.

Conclusion: Improvement in spine bone mineral density during treatment with antiresorptive drugs accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture.

AGGIORNAMENTO DELLA LETTERATURA

Numero 2 - Giugno 2002

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

I lavori sono numerati in ordine progressivo.

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19. **Risedronate for the prevention of fractures in postmenopausal osteoporosis**
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- 35. Paget's disease of the spine and its management.**
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- 36. Osteoblast behaviour in the presence of bisphosphonates: ultrastructural and biochemical in vitro studies.**
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CALENDARIO CONGRESSI

16-17 agosto 2002. Buenos Aires, Argentina

Transplant Bone Diseases Meeting 2002

Segreteria Organizzativa: Ana Finocchietto Comunicaciones, Albarello 2625 (B 460EHD) Martinez, Buenos Aires, Argentina
Tel. & Fax 0054 11 4733 9270
e-mail: anafinocom@elsitio.net

12-14 settembre 2002. Ancona, Italia

1° Convegno Nazionale su Osteoporosi Secondarie ed Endocrinopatie

Segreteria Organizzativa: Top Congressi
web: <http://www.topcongressi.com>

19-22 settembre 2002 Malmö, Svezia

2nd European Congress of Andrology

Segreteria Organizzativa: Malmö Kongressbyrå, Ostergården 3, 21125 Malmö, Sweden
Tel. +46 - 40 258550, Fax +46 40 258559
e-mail: info@malmo-congress.com; web: <http://www.malmo-congress.com>

20-24 settembre 2002 San Antonio (TX), USA

24th Annual Meeting of the American Society for Bone and Mineral Research

Segreteria Organizzativa: Tel. +1 202 3671161
Segreteria Scientifica: American Society for Bone & Mineral Research
Tel. +1 202 857 1161, Fax +1 202 223 4579
e-mail: asbmr@dc.sba.com; web: <http://asbmr.org>

26 settembre 2002 Madison, USA

Focus on Rheumatology

Segreteria Organizzativa: Medicalconferences, The Silk Mill House, 196 Huddersfield Road, Meltham, W. Yorks HD7 3AP, United Kingdom
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3-5 ottobre 2002 Chicago (IL), USA

13th Annual Meeting of the North American Menopause Society

Segreteria Scientifica: North American Menopause Society
Tel. +1 440 442 7550, Fax +1 440 442 2660
e-mail: info@menopause.org

24-29 ottobre 2002 New Orleans (LA), USA

66th Annual Scientific Meeting of the American College of Rheumatology

Segreteria Scientifica: American College of Rheumatology, 60 Executive Park South, Suite 150, Atlanta GA 30329 (USA)

Tel. +1 404 633.3777, Fax +1 404 633.1870

27-30 ottobre 2002 Aahrus, Danimarca

Bone Histomorphometry

Segreteria Scientifica: European Calcified Tissues Society, P.O. Box 4, Dursley, GL 11 6YL, UK

Tel. e Fax +44 1454 610255

e-mail: admin@ectsoc.org

31 dicembre 2002 Svezia

29th Scandinavian Congress on 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

e-mail: info@medicalconferences.com