Letters to the Editor

Markers of bone resorption in bisphosphonate therapy of Paget's disease

Sirs,

Bone turnover markers are used in diagnosis but particularly in the therapeutic monitoring of Paget's disease (1, 2). In recent years the evaluation of serum and urine N (NTx) and C (CTx) telopeptides of type I collagen has assumed particular importance. NTx released into the bloodstream and eliminated by the kidney without further metabolism are sensitive indicators of bone mass variation; CTx β isomerized fragments expressing the historical memory of the bone could be utilized as an index of bone resorption.

We studied 10 patients with Paget's disease – 4 women (age 60-72 yr.; average age: 68) and 6 men (age 64 - 78 yr.; average age: 76) – who were treated with Risendronate, in order to evaluate the utility of some of the parameters of bone resorption (sCTx, uNTx and sNTx) in the management of therapy. All subjects provided written informed consent before enrolling in the study.

The diagnosis of Paget's disease was made according to clinical-rheumatological tests: tAP> 270 U/L, x-rays of the involved bone areas, and three-phase bone scintigraphy. All patients had poliostotic Paget's disease and normal liver and renal function and were treated with oral Risendronate (30 mg/day) for 2 months. The drug was taken with water in the morning on an empty stomach, the patients then waiting more than 60 minutes before ingesting any food or drink other than water.

The bone turnover markers were evaluated on morning samples obtained between 8:00 and 9:00 a.m. after an overnight fast, before and 30 days after therapy. Urine parameters were evaluated on the first voided urine of the morning and results were expressed as urinary creatinine excretion to reduce the variability due to diuresis. All samples were divided into aliquots and stored at -20°C for a maximum of 30 days until assayed. Statistical analysis was performed using Student's t-test. Laboratory methods and the mean values of bone resorption markers before and after therapy are reported in Table I.

Regarding bone formation markers, the mean total serum alkaline phosphatase (tAP) levels were 419.50±259.25U/Lat baseline and 191.33 ± 38.94 U/Lafter therapy; mean serum levels of bone alkaline phosphatase (bAP) were 69.75 ± 38.43 ng/ml at baseline and 36.50 ± 29.82 ng/ml after therapy; one patient with symptomatic Paget's disease (documented by radiography and bone scintigraphy) showed high levels of bAP despite a normal tAP.

Before starting therapy, resorption parameters were above the normal range in all the patients examined; one month after the end of treatment sCTx, uNTX and sNTx were significantly reduced. In particular, sCTx returned to the normal range in all patients and showed the highest statistical significance (Table I). After beginning therapy, a significant reduction in the markers both of resorption (within 4-6 weeks) and of neoformation (within 2-3 months) was demonstrated.

Table I. Values of the parameters examined before and after therapy.

Biochemical markers	Baseline (mean ± SD)	30 days after therapy (mean ± SD)	p
uNTX	236.25 ± 141.13	75.50 ± 80.31	0.09
sNTX	42.59 ± 12.15	21.00 ± 14.02	0.05
sCTX	7776.00 ± 2929.39	1772.50 ± 1553.58	0.01

uNTx: urine cross linked N telopeptides of type I collagen (nM Bone Collagen Equivalent/mM Creatinine); normal value: male 5-65, female 3-51; competitive inhibition enzyme linked immunosorbent assay; CVwithin run 4.5% (osteomark Ostex International Inc., Seattle, USA).
sNTx: serum cross linked N telopeptides of type I collagen (nMBone Collagen Equivalent/L); normal value: male 5.4 - 24; female 6.2 - 19; competitive inhibition enzyme linked immunosorbent assay; CVwithin run 4.6% (osteomark Ostex International Inc., Seattle, USA).
sCTx: serum cross linked C telopeptides of type I collagen (pmol/L); normal value: male 1100-3700, premenopausal female 1300-3400, menopausal female 1800-5400; one-step ELISAwith monoclonal antibodies; CVwithin run 5.2% (Nordic Bioscience Diagnostics Denmark).

Some authors (3-7) have demonstrated that sCTx is a highly sensitive biological marker to assess the efficacy of anti-resorptive therapy, and it has become the most widely used laboratory parameter in clinical practice. Alvarez (3) investigated the individual biological variability of the markers of bone turnover in patients with stable and non-symptomatic Paget's disease. Over a period of one year the markers of bone resorption showed a very low variability: in particular, the sCTx showed the lower within-subject variability. Recently the development of a new method of evaluating sCTX has permitted a further reduction in individual variation. Furthermore, some authors (8, 9) have standardized the method of obtaining samples of serum in which the sCTx shows the lowest biological variation.

Our study shows that sCTX is a sensitive marker of bone resorption in the management of bisphosphonate therapy in Paget's disease.

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Infliximab induced lupus in patients with rheumatoid arthritis

Sirs,

Treatment of rheumatoid arthritis (RA) with either etanercept or infliximab has been associated with the development of antinuclear antibodies (1) and anti- ds DNAantibodies of the IgM class (2), although clinical drug-induced lupus (DIL) has been occasionally reported (3,4). We describe here two patients with seropositive rheumatoid arthritis who developed clinical and serological signs of lupus while treated with infliximab.

Patient 1 was a 61-year-old woman with a 10-year history of inadequately controlled RAdespite consecutive and combined treatment with MTX, azathioprine, hydroxychloroquine, sulfasalazine, cyclosporine and low doses corticosteoids. On September 2001, while on prednisone and MTX, she started treatment with infliximab at a dosage of 3 mg/kg on days 1, 14 and 45. After the second infusion, she presented significant improvement, with a reduction in the number of tender and swollen joints (from 12 to 5 and from 8 to 2, respectively), a decreased duration of morning stiffness, and decreased ESR and serum CRP levels.

Ten days after the third infusion, she developed fever up to 38°C, myalgias, severe arthralgias and a symmetric rash on her legs and arms, with erythematous squamous lesions along with an increase in the ESR. A biopsy of the skin lesions was consistent with discoid lupus. The titer of immunofluorescent anti-nuclear antibodies (FANA) increased from 1/80 before starting infliximab to 1/5160. Anti-dsDNA and anti-histone antibodies, which had been normal before therapy increased to 25 and 22 units/dl respectively (normal range – up to 15 for anti DNA, and 20 for antihistone). Infliximab was stopped, the dosage of prednisone was increased up to 20 mg/d and plaquenil was administered. A complete resolution of the clinical symptoms was observed within 3 weeks.

Patient 2 was a 54-year-old patient with seropositive rheumatoid arthritis for the last 3 years, resistant to treatment with methotrexate, sulfasalazine and plaquenil. On August 2001 she started treatment with infliximab at a dosage of 3 mg/kg. An impressive response was observed after the second infusion, with complete resolution of arthritis, morning stiffness and normalization of the ESR from 65 to 20 mm/h. Two weeks after the 5th infusion (22 weeks after the initiation of infliximab), she experienced fever, myalgias, and severe exacerbation of the polyarthritis. Anti-nuclear antibodies, which were previously negative, turned positive with a titer of 1/320. Anti-histone was found to be increased (78 U/ml; upper normal limit 25 U/ml). Anti-dsDNA and complement levels remained normal. Infliximab was stopped and treatment with prednisone initiated at a dosage of 15 mg/d, with complete resolution of the fever and arthralgia within 1 week. Although it may be speculated that the occurrence of fever and arthritis was a mere exacerbation of RA, the fact that the patient primarily responded to infliximab and only after the 5th infusion developed fever and arthritis along with the occurrence of ANA and anti-histone, supports a lupus-like phenomenon.

Although treatment with infliximab and etanercept has been associated with the development of FANAand anti-dsDNA(2), clinical manifestation of DIL is rare. A review of the literature concerning anti-TNFα induced lupus reveals 9 cases related to etanercept and 5 cases provoked by infliximab (Table I) (2-11). All of the patients except one were women, with a mean age of 53 (range 38-72) for etanercept and 51 for infliximab (range 36-69). The first signs suggestive of lupus were noted from 4 days to 14 months (mean time 5 months) after the initiation of etanercept, while infliximab-induced symptoms occurred between the 2nd and 5th infusions. Aconsistent symptom of etanercept-related DIL was rash, including discoid lupus, subcutaneous lupus and photosensitive eruption. Arthritis and fever were common manifestations. The clinical features of infliximab-induced lupus were less consistent, but included immune hepatitis, arthritis and skin manifestations. All of the cases resolved, either spontaneously after stopping the drug or following a short course of low-dose corticosteroids.

Although many patients on infliximab or etanercept may develop autoantibodies, clinical manifestations are rare. However, some cases may evolve into true drug-induced SLE, which can be underdiagnosed in RA patients due to the overlapping symptoms. Alertness to this rare but important switch in autoimmunity, as well as further investigations of these phenomena are necessary to clarify their prevalence and pathogenesis.

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Table I. Clinical characteristics of etanercept-induced lupus.

Patient	Age/gender	Treatment and duration	Clinical manifestations	Serological abnormalities	Time to resolution after stopping E
1 (5)	54/W	E/3 months	Subcutaneous lupus	ANA, anti-dsDNA	6 m, topical steroids, E continued
2 (6)	51/W	E/7 months	Photosensitive rash, Raynaud's, synovitis	ANA, anti-dsDNA, nucleosome	1 month, topical steroids
3 (3)	72/W	E/14 months	Fever, polysynovitis	ANA, anti-ds DNA, Histone	4 weeks
4 (3)	47/W	E/3 months	Rash (discoid lupus)	ANA, anti-dsDNA	6 weeks
5 (3)	50/W	E/5 months	Diffuse rash, malar rash, pleuritis	ANA, anti-ds DNA, RNP, Sm, histone, low C3	2 weeks
6 (3)	39/W	E/6 weeks	Facial erythema, arthritis, edema, HT	Anti-histone	2 weeks
7 (7)	78/W	E/4 days	Discoid lupus	None	2 weeks
8 (8)	38/W	E/3months	Scaling erythema myalgia	ANAanti-dsDNAcardiolipin low C4	1 month
9 (8)	50/W	E/4 months	Scaling erythema	ANA	1 month
10 (2)	37/W	I/4th infusion	Fever, rash, synovitis pleuropericarditis	ANA, anti- dsDNA(IgG, IgM)	8 weeks
11 (4)	51/W	I/2th infusion	Synovitis	ANA, anti-histone, dsDNA	NK
12 (9)	36/W	I/ 3thinfusion	Synovitis, hepatitis	ANA, anti- dsDNA	3 weeks, steroids
13 (10)	69/W	I/5th infusion	Fever, synovitis, rash, myalgia	ANA, anti-dsDNA, Low C3, C4	8 weeks, prednisone
14 (8)	54/M	I/4th infusion	Photosensitivity, malar rash	ANA, anti-dsDNA	2 months
15*	61/w	I/3th infusion	Synovitis, myalgias, rash	ANA, anti-dsDNA, anti-histone	3 weeks, steroids
16*	51/w	I/5th infusion	Synovitis	ANA, anti-histone	2 weeks, steroids

HT: hypertension; ANA: anti-nuclear factor; E: etanercept; I: infliximab. * Our patients.