Rheumatic diseases, glucocorticoid treatment and bone mass: Recent developments

M. Mazzantini[1], N.E. Lane[2]

[1]Rheumatology Section, Department of Internal Medicine, University of Pisa, Pisa, Italy; [2]Division of Rheumatology, University of California San Francisco, San Francisco Hospital, San Francisco, California, USA.

Please address correspondence to:
Dr. Maurizio Mazzantini, Rheumatology Section, Department of Internal Medicine, University of Pisa, Via Roma no. 67, Pisa 56126, Italy.

Key words: Osteoporosis, glucocorticoids, prevention, treatment, rheumatic diseases.

ABSTRACT
Recent research has made striking advances, adding to our understanding of the aethiopathogenesis of several forms of secondary osteoporosis, including those associated with rheumatic diseases and glucocorticoid treatment. Furthermore, in the last 3 years new drugs have been shown to prevent glucocorticoid-induced bone loss. Guidelines that are suitable for clinical practice have been published. Knowledge of those new opportunities and strategies, which are briefly reviewed in this article, will reduce the risk of osteoporotic fractures in rheumatic and non-rheumatic patients.

The deleterious effect on bone of glucocorticoids (GC) has long been recognized. Today GC-induced osteoporosis still represents the most common secondary form of osteoporosis. GC are widely used in the rheumatic diseases and have been considered to be the principal aetiologic factor underlying the bone loss observed in rheumatic patients. Over the last decade, however, marked advances have been made in our knowledge of the negative impact that some rheumatic diseases can exert on bone mass. There have been three crucial steps in this understanding:

1. The application of densitometry measurements which quantitate bone mass with high precision and accuracy, such as double energy x-ray absorptiometry (DEXA).
2. The use of urinary and serum markers of bone turnover, whose assessment gives information about the uncoupling between osteoblasts and osteoclasts which can occur in physiologic (i.e., menopausal status) and pathologic conditions and as a response to GC treatment.
3. The understanding that several cytokines and inflammatory mediators induce the recruitment, differentiation and activation of osteoclasts, including interleukin (IL)-1, tumor necrosis factor (TNF)- and TNF- , IL-6, IL-11 and IL-17.

On the basis of biological, densitometric, and biochemical studies, osteoporosis has been finally recognized as a common complication of rheumatoid arthritis (RA) independently of GC use; a 2-fold increase in the risk of osteoporosis [defined as a bone mineral density (BMD) that is 2.5 standard deviations (SD) or more below the mean value in young healthy adults] and in the risk of hip and vertebral fractures has been consistently reported in RA with respect to the normal population. It is now well documented that bone loss in RA is mainly due to increased bone resorption with normal or reduced bone formation, and that this uncoupling parallels disease activity. Furthermore, densitometric surveys have recently shown that systemic lupus erythematosus (SLE) and ankylosing spondylitis patients are also at higher risk of osteoporosis than the normal population. SLE patients have a 5-fold greater probability of sustaining a fracture than normal subjects, and both the prevalence and extent of this bone mass reduction seem to be similar to that seen in RA. GC are believed to play a significant role in the induction of osteoporosis in SLE, but some evidence suggests that disease-dependent mechanisms can lead to bone loss.

In the last 3 years great advances have been made in the field that encompasses rheumatic diseases, GC treatment and bone loss. The present supplement will offer a comprehensive review of present knowledge in this field, of which this chapter will provide a brief overview.

One of the most important recent discoveries has concerned the mechanism underlying the regulation of osteoclastogenesis and bone resorption. Osteoclast differentiating factor (ODF) is a newly discovered member of the TNF family that induces the differentiation and maturation of osteoclast precursor cells into osteoclasts (1, 2). ODF is also known as

TNF-related activation-induced cytokine (TRANCE), receptor activator of nuclear factor kB (RANK) ligand, or osteoprotegerin (OPG) ligand, and is expressed as a transmembrane ligand on osteoblasts/stromal cells. It binds to RANK, a transmembrane receptor expressed on hemopoietic osteoclast precursor cells. The interaction between the RANK ligand and RANK results in osteoclast maturation and bone resorption. This is regulated by OPG, a soluble decoy glycoprotein synthesized by early osteoblasts, which is also referred to as osteoclastogenesis inhibitory factor (OCIF). OPG binds to the RANK ligand and blocks its interaction with RANK, thus inhibiting osteoclast development. What is of special interest in rheumatology is that it has been reported that activated T-cells also express the RANK ligand: the resulting imbalance between OPG and the excess RANK ligand could play an important role in the induction of excessive bone resorption in chronic arthritis, such as RA. In fact, a protective role of OPG against bone loss in adjuvant arthritis has been reported (3,4). This finding clearly opens up new perspectives for the possible treatment of diseases characterized by increased bone resorption.

Much has also been learned about the pathogenesis of GC-induced osteoporosis. It is now evident that the primary mechanism behind this form of bone loss is the suppression of osteoblastogenesis and osteoclastogenesis and the increased apoptosis of osteoblasts and osteocytes. With our increasing knowledge of the clinical and diagnostic features of GC-induced bone loss and with the availability of effective new therapies, various guidelines have been recently published (5-7). In the period 1997-2000 the bisphosphonates etidronate (8), alendronate (9) and risedronate (10-12) have been shown to be effective in the prevention and treatment of GC-induced osteoporosis at both the lumbar spine and femoral neck. They also showed a trend for a reduction in the vertebral fracture incidence in postmenopausal women. Bisphosphonates are currently the recommended first line therapy for the prevention and treatment of GC-induced osteoporosis. The finding that etidronate,

alendronate and pamidronate prevent the apoptosis of murine osteocytic cells and osteoblasts induced by TNF- and dexamethasone *in vitro*, and that alendronate suppresses the apoptosis of cancellous bone osteocytes and osteoblasts *in vivo* in mice following prednisolone administration are of great interest (13).

In the near future new drugs could become available that will suppress the effect of GC on bone and reverse bone loss. Human parathyroid hormone (hPTH) fragment 1-34 given intermittently prevents osteoblast and osteocyte apoptosis in animal models, prolongs the lifespan of these cells and increases bone formation (14). Furthermore, intermittent hPTH can reverse the inhibitory effect of GC on the synthesis of insulin-like growth factor I (IGF-I) and can prevent the imbalances in the RANK/RANK ligand/OPG equilibrium which have been documented in the early phases of GC treatment (15). It has been shown that a 12-month period of hPTH (1-34) therapy in postmenopausal, estrogen-replete women on chronic GC treatment results in an 11% increase of the lumbar spine BMD, measured by DEXA. Quantitative computerized tomography, which measures the lumbar spine trabecular bone, showed a 35% increase. On the other hand, total hip and femoral neck BMD remained unchanged the first year, but increased 5% over baseline 12 months after hPTH treatment was stopped (16, 17). hPTH may therefore represent a powerful therapy for reversing GC-induced trabecular bone loss. The association of hPTH with strong inhibitors of bone resorption, such as the newer bisphosphonates alendronate and risedronate, could result in a greater effect on bone accrual.

Finally, a new agent, the selective estrogen receptor modulator raloxifene, has been shown to significantly reduce the risk of vertebral fractures in postmenopausal osteoporosis (18). Raloxifene has not been tested so far in the prevention and treatment of GC-induced osteoporosis, but it already represents an alternative to estrogen replacement therapy in postmenopausal women on long-term GC who refuse or cannot take estrogen. We now possess strategies capable of significantly limiting bone loss and frac-

tures in rheumatic patients taking GC. If used, these strategies could in the future substantially reduce the social and economic burden of osteoporotic fractures. However, clinicians must keep these options clearly in mind and should consider offering every patient who is beginning long-term GC treatment the preventive measures now available. Data in the literature show that at present only a small percentage of patients starting long-term therapy with GC also receive sound advice for the prevention of osteoporosis (19, 20). Perhaps the importance of the precautionary measures recommended in all of the available guidelines (such as early vertebral and hip bone mass measurement, risk factor assessment, optimization of calcium intake, evaluation of vitamin D status, etc.) has not been adequately appreciated by the physicians who prescribe GC. Hopefully, in the near future – during the Bone and Joint Decade – the general approach to the prevention and treatment of GC-induced osteoporosis will change.

References

1. LACEY DL, TIMMS E, TAN HL *et al.*: Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998; 93: 165-76.
2. HOFBAUER LC, KHOSLA S, DUNSTAN CR, LACEY DL, BOYLE WJ, RIGGS BL: The roles of osteoprotegerin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res* 2000; 15: 2-12.
3. GOLDRING SR, GRAVALLESE EM: Mechanism of bone loss in inflammatory arthritis: Diagnosis and therapeutic implications. *Arthritis Rheum* 2000; 2: 33-7.
4. KONG YY, FEIGE U, SAROSI L *et al.*: Activated T-cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* 1999; 402: 304-9.
5. EASTELL R, REID DM, COMPSTON J *et al.*: A UK consensus group on management of glucocorticoid-induced osteoporosis: An update. *J Intern Med* 1998; 244: 271-92.
6. AMERICAN COLLEGE OF RHEUMATOLOGY TASK FORCE ON OSTEOPOROSIS GUIDELINES: Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum* 1996; 39: 1791-801.
7. ADACHI JD, OLSZYNSKI WP, HANLEY DA *et al.*: Management of corticosteroid-induced osteoporosis. *Semin Arthritis Rheum* 2000; 29: 228-51.
8. ADACHI JD, BENSEN WG, BROWN J *et al.*: Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *New Engl J Med* 1997; 337: 382-7.
9. SAAG KG, EMKEY R, SCHNITZER TJ *et al.*:

Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med* 1998; 339: 292-9.

10. COHEN S, LEVY RM, KELLER M *et al.*: Risedronate therapy prevents corticosteroid-induced osteoporosis. *Arthritis Rheum* 1999; 42: 2309-18.

11. REID DM, HIGHES RA, LAAN RF *et al.*: 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. *J Bone Miner Res* 2000: 15: 1006-13.

12. EASTELL R, DEVOGELAER JP, PEEL NF *et al.*: Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. *Osteoporosis Int* 2000; 11: 331-7.

13. PLOTKIN LI, WEINSTEIN RS, PARFITT AM, ROBERSON PK, MANOLAGAS SC, BELLIDO T: Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. *J Clin Invest* 1999; 104: 1363-74.

14. JILKA RL, WEINSTEIN RS, BELLIDO T *et al.*: Increased bone formation by prevention of osteoblast apoptosis with PTH. *J Clin Invest* 1999; 104: 439-46.

15. HOFBAUER LC, GORI F, RIGGS BL *et al.*: Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: Potential paracrine mechanisms of glucocorticoid-induced osteoporosis. *Endocrinology* 1999; 140: 4382-9.

16. LANE NE, SANCHEZ S, MODIN GW *et al.*: Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. *J Clin Invest* 1998; 102: 1627-33.

17. LANE NE, SANCHEZ S, MODIN GW *et al.*: Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis. *J Bone Miner Res* 2000; 15: 944-51.

18. ETTINGER B, BLACK DM, MITLACK BH *et al.*: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. *JAMA* 1999; 282: 637-45.

19. BUCKLEY LM, MARQUEZ M, FEEZOR R, RUFFIN DM, BENSON LL: Prevention of corticosteroid-induced osteoporosis: Results of a patient survey. *Arthritis Rheum* 1999; 42: 1736-9.

20. AAGARD EM, LIN P, MODIN GW, LANE NE: Prevention of glucocorticoid-induced osteoporosis: Provider practice at an urban county hospital . *Am J Med* 1999; 107: 456-60.