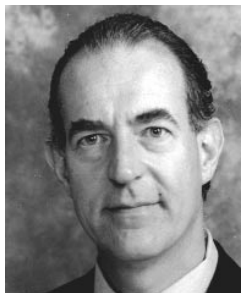
Editorial

Current Consensus Recommendations for Rheumatoid Arthritis Therapy: A Blind Spot for Osteoporosis Prevention and Treatment



In response to new developments in therapy for rheumatoid arthritis (RA), there have been recent international consensus publications recommending guidelines for the treatment of RA[1,2]. Two symposia in 2000, in Chicago in February and Nice in June, came to similar conclusions[1,2]. The general goal of treatment was explained as elimination of synovitis and disease activity, or control to the fullest extent possible in order to diminish symptoms and prevent articular damage. Recommendations were made for all patients (with few exceptions) to begin treatment promptly after initial diagnosis of RA with a disease modifying antirheumatic drug (DMARD) or a biologic agent[1]. An algorithm for optimizing DMARD use alone or in combination was also published[3].

The American College of Rheumatology[4] and Homik, *et al* in the Cochrane Database Systematic Review 2000[5] provided an update for the prevention and treatment of glucocorticoid induced osteoporosis. The consensus recommendations presented in Chicago[1] recommend that corticosteroids not be used in RA without biological agents and mentions "unacceptable levels of toxicity," but does not describe effects on bone other than erosions. Neither consensus document[1,2] provided direction for the prevention or treatment of an important adverse outcome in RA (whether glucocorticoids have been prescribed or not): loss of bone and alteration of bone structure, which leads to fracture and severe morbidity in many patients. The authors' vision for the recommended management of RA apparently did not encompass managing bone quantity and quality.

EXTENT OF OSTEOPOROSIS IN PATIENTS WITH RA

Osteoporosis is the principal bone abnormality of RA. It is associated with rapid remodeling, which results in degradation of the mechanical properties of the skeleton in juxtaarticular bone, in the diaphyses of long bones, in the pelvis, and at the base of the skull. It affects both cortical and cancellous bone, characterized by a loss of bone volume and strength, with increased bone formation and resorption rates[6,7].

Clinical evidence of this high remodeling rate includes the rapid appearance of radiographic periarticular osteopenia and increased scintigraphic technetium uptakes. In the first year after RA diagnosis, a loss of 2.5% to 5% of bone mineral density (BMD) of the vertebrae and proximal femur has been documented by dual energy x-ray absorptiometry. For patients with active disease over 2 years, mean BMD loss at each site was between 5.5% and 10%[8,9].

Most female patients with longstanding disease have radiographic evidence of cortical thinning and decreased cancellous density, findings that require a minimum 30% loss of bone substance to be detectable. In male patients, a recent study showed that active arthritis, and not low testosterone, was the principal cause of bone loss in men with RA[10]. Moreover, active RA was, at least in theory, the most important modifiable risk factor for osteoporosis in these men.

It is well known that corticosteroid use exacerbates bone loss in the axial skeleton, but severe, typical abnormality occurs commonly in patients with severe RA who have never received corticosteroids[11].

In juvenile rheumatoid arthritis (JRA), analysis of biomechanical markers of bone turnover in children who have not received corticosteroids has revealed a low bone turnover resulting in osteopenia. These children had normal serum calcium, parathyroid hormone, and vitamin D levels[12-14].

CONSEQUENCES OF OSTEOPOROSIS IN RA

Several negative clinical consequences occur in patients with RA as a result of alteration in bone remodeling.

The risk of fracture of the proximal and distal femur is significantly increased among patients with RA[15,16]. Three-fold increased risk of hip fractures has been noted and hip fracture is associated with a 26% twelve-month mortality rate[17]. The management of these fractures is complicated by poor implant fixation in weak cancellous bone, leading to a high rate of failure of fracture fixation[18].

Stress fractures (insufficiency fractures) are common, although frequently undiagnosed, in patients with RA, partic-

See First do no harm — a bone of contention in RA, *page 1818*

ularly in the distal fibula and tibia. Potential angulation and malunion of these fractures can exacerbate a preexisting impairment of hindfoot and ankle function. Other sites of stress fracture are numerous, including femoral neck, metatarsal, pubic ramus, and sternum[19,20].

Progressive bone deformation is another consequence of osteoporosis in severely affected patients. In addition to protrusion of the acetabulum, a well recognized deformity of the hip affected by severe RA, patients may manifest basilar invagination of the skull, an analogous example, as well as loss of glenoid bone stock in the shoulder, resulting in a characteristic medial migration of the humeral head[21]. Valgus deformity of the knee and proximal migration of the forearm relative to the humerus following remodeling of the humeroulnar joint are also related to intraarticular bone loss in RA, which is responsible for these characteristic deformities.

Thus, osteoporosis is responsible for fracture, and probably for other modes of increased morbidity in RA.

PREVENTION AND TREATMENT OF OSTEOPOROSIS IN RA

Medication for the prevention and treatment of osteoporosis in patients with RA has now been shown experimentally and clinically to be effective in increasing BMD[22,23]. In a double blind placebo controlled study, Eggelmeijer, *et al* showed that a 20 mg pamidronate infusion was associated with a rapid and sustained decrease in urinary calcium- and hydroxyproline-creatinine ratios to a maximum of 29% and 64% of initial values, respectively; changes over time in these variables were significant, indicating effective suppression of bone resorption[24].

Comparing the effect of oral alendronate and calcium to calcium alone on BMD, Yilmaz, *et al* reported that patients who received calcium alone had decreases in their mean BMD after 6 month followup; patients with alendronate and calcium had increased their mean BMD during the same period in all regions, with a significant increase of 5% in BMD in the lumbar spine[25].

In a prospective double masked and placebo controlled study exploring the effects of oral risedronate on BMD in postmenopausal women with glucocorticoid treated RA, Eastell, *et al* found that a 2 year daily 2.5 mg risedronate administration prevents bone loss at the lumbar spine and femoral trochanter (+1.4%, +0.4% increased BMD, respectively), while significant bone loss was observed in placebo patients[26].

The effect of intranasal salmon calcitonin was investigated in a randomized double blind placebo controlled study that evaluated BMD in the forearm and spine. Over 12 months, the control group lost bone at a rate of 2%/year at the spine and 4.8%/year at the distal third of the radius, whereas the group receiving nasal calcitonin gained 1% in BMD at the lumbar spine and experienced no bone loss at the distal third of the radius[27].

Vitamin D (calcitriol, alfacalcidol) possesses immunoregulatory effects and protects osteoblasts against tumor necrosis factor-α induced cell death[28]. Although its use is recommended for patients undergoing glucocorticoid treatment (to increase intestinal calcium absorption and reduce renal calcium excretion and sensitivity of bone to parathyroid hormone (PTH) as well), its main application in RA has been to preserve bone mass, not to increase it[4,29].

Intermittent subcutaneous PTH has recently shown not only an anabolic effect on bone but also large and significant reductions in the incidence of new vertebral and extravertebral fractures. In a randomized controlled trial[30], Body, *et al* found 12.2%, 4.0%, and 4.8% mean increases in BMD for the lumbar spine, the total hip, and the femoral neck, respectively, after 14 months of PTH treatment in postmenopausal women with osteoporosis. These increases were significantly higher than those obtained for the control patients treated with alendronate sodium. However, no study has been done yet in the RA population or in glucocorticoid treated patients.

A review of therapeutic approaches for preventing bone loss in inflammatory arthritis has been published recently by Rehman and Lane[31]. Cellular immune response suppression, anticytokine therapy, improvement of the receptor activator of nuclear factor κB-osteoprotegerin ratio, osteoclast-bone interaction blocking, osteoclast function inhibition, and osteoblast function activation are therapeutic interventions that are currently or soon will be available to alter the inflammation induced bone loss in RA.

The necessity of prevention and treatment of osteoporosis in RA is greatest for women, who may be severely affected and require treatment even premenopausally. Osteoporosis prevention is also of great concern in patients with JRA. The importance of development of a high peak bone mass in youth to prevent osteoporosis in later life is well recognized.

It would not be reasonable to commence an osteoporosis prophylaxis program for every patient diagnosed with RA. The incidence of this condition is about 1–3%, but only a minority of patients will develop erosive or destructive disease or osteoporosis related fracture. Clearly, a woman with long-standing severe disease and low bone mass should be treated. On the other hand, a young man with only one episode of synovitis, normal BMD, and no ongoing disease should probably not receive prophylaxis. The question is to define a threshold for prophylaxis and treatment. Although BMD does not accurately predict fracture in an individual patient[32-34], it does identify the level of fracture risk. Bone densitometry can assist in establishing baseline BMD[34]. Risk factors for fracture in RA have not yet been well established. Table 1 summarizes studies that provide information useful to define these risk factors.

We propose that since abnormalities in bone remodeling causing osteoporosis are common in RA and lead to an important component of the morbidity of the disease, and since

Table 1. Risk factors for fracture in patients with RA

Risk Factors	Study	Reference
Longstanding RA	Retrospective study of 32 elbow fractures	Ikavalko, 2001[35]
Low body mass index History of total joint arthroplasty	Retrospective study of 21 limbs of female patients with fracture	Miyamoto, 1995[36]
Functional impairment Low body mass index	Matched controlled study of 300 patients with fracture of proximal femur	Cooper, 1995[37]
Aging Female sex Osteopenia Longstanding severe polyarticular RA	Retrospective study of 95 patients with femoral fractures (33 intertrochanteric, 52 neck, 12 supracondylar)	Bogoch, 1993[38], Bogoch, 1991[39], Bogoch, 1988[40]
Years taking prednisone Prior diagnosis of osteoporosis Disability Aging Lack of physical activity Female sex Longstanding RA Impaired grip strength Low body mass index	Cross sectional study of 1110 patients. Odds ratio (osteoporosis) = 1.68 (95% CI 1.30–2.17)	Michel, 1993[41]
Corticosteroids in women (> 5 mg/day prednisone) Prior diagnosis of osteoporosis	Cross sectional study of 395 patients. Relative risk (osteoporosis) = 6.3	Michel, 1991[42]
Aging Impaired ambulation Thinness	Cohort study of 388 women with RA Multivariate analyses	Hooyman, 1984[16]

effective prophylaxis is now available, guidelines for the management of RA should address this issue.

BRIGITTE M. JOLLES, MD,
Hôpital Orthopédique de la Suisse Romande, CHUV, University of Lausanne, Lausanne, Switzerland;
EARL R. BOGOCH, MD, MSc, FRCSC,
Professor, The Mobility Program, Department of Surgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

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Address reprint requests to Prof. E.R. Bogoch, 55 Queen Street East, Suite 800, Toronto, Ontario M5C 1R6, Canada.

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