Published in final edited form as:

Arthritis Rheum. 2011 February ; 63(2): 325–328. doi:10.1002/art.30135.

Should bisphosphonates be used for long-term treatment of glucocorticoid-induced osteoporosis?

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Skeletal mass is a reflection of the relative activities of bone synthesizing osteoblasts and resorbing osteoclasts. When the activity of the latter supersedes that of the former, bone loss occurs, which if profound, eventuates into osteoporosis (1). While their clinical manifestations may be similar, the causes of osteoporosis are many, the most common attending menopause. Estrogen-deficiency typically prompts a high turnover form of osteoporosis in which both formation and resorption are accelerated but the relative activity of the osteoclast is greater than that of the osteoblast (2–3). Thus, suppression of the osteoclast using hormone replacement was standard of care for decades. With the realization that estrogens increase risk of breast cancer and cardiovascular complications in older women, bisphosphonates have become the most common treatment for post-menopausal osteoporosis. Given the absolute increase in osteoclast activity in estrogen-deficient osteoporosis, the effectiveness of bisphosphonates is not surprising. Alendronate, for example, maintains bone mass and reduces fracture risk of post-menopausal, osteoporotic women for as long as a decade with minimal complications in the great majority of patients (4).

The most common secondary form of osteoporosis is that induced by glucocorticoids, but its skeletal dynamics are distinctly different than those attending estrogen deprivation. Whereas bone formation is enhanced following the menopause, inhibition of the osteoblast by glucocorticoids is a major cause of progressive bone loss (5–8). The dynamics of bone resorption, under the influence of glucocorticoids are, however, more complex. Upon initiation of therapy, resorption is accelerated. The fact that low dose glucocorticoids given to normal women immediately suppresses bone degradation as determined by urinary excretion of free deoxypyridinoline (9), suggests the early acceleration of resorption attending treatment of afflicted patients may represent persistence of the effects of osteoclast-activating inflammatory cytokines (10–12). It is during this early stage that the combination of reduced formation and accelerated resorption yields the most profound bone loss in the natural history of glucocorticoid-induced osteoporosis (GIO) (13–14). The misconception that glucocorticoids accelerate osteoclast activity, regardless of duration of administration, forms the theoretical basis for the recommendations of the American College of Rheumatology (15), Royal College of Physicians (16) and essentially all international guidelines, that bisphosphonates be routinely administered for prevention and treatment of GIO. In fact, with chronic, therapeutic exposure to the steroids, resorption turns from

accelerated to diminished, likely due to direct suppression of the osteoclast via inhibited calpain 6 (6,8,17–18). Supporting this contention, prolonged glucocorticoid treatment dampens expression of the key osteoclastogenic transcription factor, NFATc1 (19). In contrast to high turnover post-menopausal osteoporosis, chronic GIO is, therefore, a low turnover form of the disease in which both formation and resorption are suppressed but the former is more so than the latter. Importantly, the efficacy of bisphosphonates in preventing bone loss is substantially greater in states of high as compared to low turnover (20).

Clearly, bisphosphonate therapy, for at least 24 months, is moderately successful in preventing loss of bone and reducing vertebral fractures in glucocorticoid treated patients (21–23). The impact of long-term administration of bisphosphonates on the steroid-exposed skeleton is, however, unknown. Furthermore, pharmacology raises caution about their long-term use in the context of glucocorticoids. Bisphosphonates bind bone mineral with high affinity and remain within the skeleton until mobilized by osteoclasts which they inactivate, forming the basis of their skeleton-sparing properties (24). Thus, one may expect persistence of bisphosphonates in bone for years, particularly in face of low turnover osteoporosis, in which osteoclast function is diminished (25).

Clinical assessment of fracture risk typically reflects densitometric measurement of bone mass. This analysis, however, does not consider another critical component of skeletal integrity, namely bone quality which is the relationship of bone mass to biomechanical strength(26). Hence, impaired bone quality is manifest by an increased pre-disposition to fracture at a given bone mineral density (BMD).

Skeletal remodeling is the key event regulating bone mass and likely, bone quality (26). This ever-occurring process is characterized by tethering of the activities of bone resorption and formation. Remodeling is initiated by osteoclast activity. In consequence, arrested bone resorption dampens formation. Glucocorticoids suppress osteoblasts directly (6) and probably by inhibiting remodeling (17).

Perhaps the most important function of remodeling, however, is to replace effete bone with new (26). Thus, arrested remodeling, exemplified by the adynamic form of renal osteodystrophy, diminishes bone quality, and disassociates bone mass from structural stability (26–27). Long-established GIO reflects not only diminished bone mass, but also impaired bone quality (28).

Bisphosphonates also compromise bone quality (26,29–30). Reflecting their anti-remodeling effects, skeletal microdamage is substantially increased in bisphosphonate-treated animals and the drugs reduce bone toughness. In most individuals with post-menopausal osteoporosis, these negative effects appear to be compensated for by increased bone mass, at least for the first decade of use (4).

Given its skeletal dynamics, treatment of GIO is complex. Anti-resorptive therapy, alone, is logical within the first year or two of glucocorticoid administration wherein osteoclast activity is accelerated and increased bone mass appears to compensate for altered bone quality. In the chronic, long term, low turnover phase of the disease, the steroids continue to suppress bone formation but also directly inhibit the osteoclast, often resulting in a virtual cessation of remodeling. Recent information suggests caution regarding bisphosphonates in face of more prolonged glucocorticoid administration. Specifically, a number of bisphosphonate-treated patients who developed osteonecrosis of the jaw were exposed to systemic steroids (31). Furthermore, investigators have reported atypical, poorly healing, fractures, particularly of the femoral shaft, of bisphosphonate-treated patients (32). Interestingly, bone biopsies of these individuals often demonstrate suppressed remodeling and a number were receiving glucocorticoids (33–35).

Caution about the prolonged use of bisphosphonates is complemented by the greater success on bone mineral density and preventing vertebral fractures of the bone anabolic drug, teriparatide, which accelerates remodeling, in GIO patients (22). In this randomized, double-blind trial, teriparatide or alendronate was administered to glucocorticoid-treated patients, most of whom were post-menopausal women with rheumatic disease. In contrast to the suppressive effects of alendronate, those receiving teriparatide experienced accelerated bone remodeling. In a 36 month continuation study, the anabolic effects of teriparatide persisted, reflected by BMD, decreased occurrence of vertebral fractures, and slight, but significantly sustained markers of bone formation (36–37). As demonstrated in a recent post-hoc analysis, glucocorticoid dose affects these responses (38).

The use of teriparatide in GIO is compromised, however, by cost, absence of long-term data due to restricted duration of administration and potential plateauing of anabolic action. Thus, from a public health perspective, anti-resorptive strategies are presently necessary. Early clinical trials indicate that 12 months of treatment with denosumab, a humanized monoclonal antibody targeting the osteoclast-stimulating cytokine RANK ligand, effectively reduces GIO in patients with rheumatoid arthritis (39). On the other hand, denosumab suppresses bone remodeling more profoundly than do bisphosphonates (40). Therefore, prolonged administration of denosumab to glucocorticoid-treated patients also deserves vigilance. Further comparative effectiveness studies, ideally sufficiently large and long enough to fully understand fracture risk at both vertebral and non-vertebral sites, are urgently needed to better discern the benefits of anti-resorptive and anabolic agents in long term management of GIO.

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