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How effective is risedronate in preventing bone loss in patients on high-dose steroids?

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SUMMARY

Oral bisphosphonates have proven to be an effective strategy for the prevention and treatment of glucocorticoid-induced osteoporosis; however, information on the efficacy of these agents in patients receiving high-dose glucocorticoid therapy is scarce. In this Practice Point commentary, we discuss the 6-month, randomized, placebo-controlled study of Mok *et al.*, which evaluated the efficacy of 5 mg oral risedronate daily for the prevention of bone loss at the spine and hip in patients receiving high-dose prednisolone therapy (>0.5 mg/kg/day). Risedronate prevented bone loss at the spine and attenuated, but did not prevent, bone loss at the hip. We compare and contrast the findings of Mok *et al.* with previously published studies of bisphosphonate therapy in glucocorticoid-induced osteoporosis, taking into account the pathophysiology of this condition, and highlight gaps in our knowledge and in current patient care.

KEYWORDS bisphosphonates, BMD, glucocorticoid, osteoporosis, risedronate

COMMENTARY

Around 1–3% of all adults are currently on long-term glucocorticoid therapy.[1] Nonetheless, this breakthrough in the management of inflammatory disorders—first introduced in the late 1940s by Dr Philip Showalter Hench—comes at the expense of major morbidities. These morbidities include glucocorticoid-induced osteoporosis (GIO), the most common cause of iatrogenic osteoporosis.[1] Patients receiving glucocorticoids experience accelerated bone loss, which is more substantial at trabecular sites than at cortical sites. Bone loss is most pronounced early in the course of treatment, as well as in steroid-naive patients and in individuals who are administered high doses. Up to 50% of patients on chronic glucocorticoid therapy experience debilitating osteoporotic fractures, which occur at higher BMD thresholds than those observed in non-glucocorticoid-treated individuals.

Administration of calcium, vitamin D and oral bisphosphonates represents the established strategy for prevention and treatment of GIO.[2] Daily doses of alendronate (10 mg) or risedronate (5 mg), given with calcium and/or vitamin D, increase BMD by 1–5% at the spine and by 1–2% at the femoral neck, and markedly reduce the incidence of morphometric vertebral fractures.[2] Fracture reduction is, however, largely assessed on the basis of secondary outcomes. Furthermore, most trials to date were conducted in individuals who received only modest steroid doses (i.e. <20 mg prednisone daily).

Mok *et al.*[3] have now performed a double-blind, randomized, placebo-controlled trial of 120 patients receiving high-dose steroid therapy (>0.5 mg/kg/day of oral prednisolone or its equivalent for at least 6 weeks). Participants received either 5 mg oral risedronate or placebo daily for a period of 6 months. In addition, all participants received 1 g elemental calcium daily. Two-thirds of the patients were corticosteroid-naive at study entry. BMD at the lumbar spine increased by 0.7% ± 0.3% from baseline in the risedronate-treated group ($P = 0.03$) but was reduced in the placebo group (–0.7% ± 0.4%). By contrast, BMD was stable at the femoral neck and decreased at the hip in the risedronate group, although less so than in the placebo group (between-group difference $P = 0.38$). The mean increment in spine BMD with risedronate was smaller than that observed in most studies, but similar to that previously reported in subgroup analyses of trials that included steroid-naive patients.[2] The relatively small treatment effect in the risedronate group might, therefore, be attributed to the large dose of glucocorticoid used, its recent initiation, and the short study duration. Other possibilities not explored by the authors, that might have affected

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the response to treatment, include the effect of menopausal status and renal function.

Several mechanisms are known to cause bone loss in GIO.[2] Inhibition of intestinal calcium absorption, and of renal tubular calcium reabsorption, render calcium and vitamin D supplementation an essential part of the therapeutic regimen; however, they are not a substitute for bisphosphonate therapy. Sambrook *et al.*[4] demonstrated that although calcium plus 30,000 IU of vitamin D weekly was as efficacious as 0.50–0.75 μg of calcitriol daily for prevention of bone loss at the spine and femoral neck and in total body, administration of calcium and 10 mg alendronate daily was superior to both. The lack of response to risedronate at cortical sites in the study of Mok *et al.* might, therefore, reflect the fact that the participants did not receive vitamin D supplementation.

Glucocorticoids are known to increase bone resorption; however, impaired osteoblast differentiation and maturation, in conjunction with enhanced osteoblast apoptosis, represents the central mechanism for the pathogenesis of GIO. This fact provides the rationale for the use of anabolic therapies.[2] The efficacy of 20 μg of teriparatide daily was compared with that of 10 mg alendronate daily in a randomized, controlled trial in patients receiving 7.5 mg prednisone daily.[5] The median duration of steroid therapy at baseline was 1.2–1.5 years. Patients administered teriparatide experienced more-substantial increments in BMD at the spine and hip, as well as fewer vertebral fractures, than patients treated with alendronate. The discontinuation rate in this study was 30% in both groups, which indicates a need for regimens that improve treatment adherence. Indeed, less than a quarter of patients treated with glucocorticoids receive appropriate therapy to prevent bone loss.[1]

This observation suggests that yearly, rather than daily, administration of bisphosphonates could be an attractive option for patients at risk of GIO. The efficacy of a yearly infusion of 5 mg of zoledronate was compared with that of 5 mg of risedronate daily.[6] After 1 year of treatment, zoledronate increased spine BMD more than did risedronate in both the treatment trial (4.1% versus 2.7%, $P = 0.001$) and the prevention trial (2.6% versus 0.6%, $P < 0.0001$), with markedly improved BMD increments also observed with zoledronate at other skeletal sites. Treatment with potent bisphosphonates, such as zoledronate, has been implicated in the development of osteonecrosis of the jaw. As steroid therapy is also a risk factor for osteonecrosis of the jaw, this possibility is an important consideration for glucocorticoid-treated patients receiving bisphosphonates. Nonetheless, osteonecrosis of the jaw has so far been reported unequivocally in only 4 patients administered bisphosphonate therapy to prevent steroid-induced bone loss.[7]

To conclude, high-dose glucocorticoid therapy causes substantial bone loss early in the treatment course, particularly at the spine. The majority of patients, however, receive chronic therapy with lower doses of glucocorticoids. Although such patients are at the greatest risk for fractures, they often remain untreated. Calcium, vitamin D, and an oral bisphosphonate is the standard treatment in such cases; however, teriparatide is also an attractive option. Trials of the currently available treatment regimens are urgently needed, as are novel agents that minimize adverse events, improve patient adherence, and reduce fractures with high efficacy.

Competing interests
A Arabi declared an association with the following company: Sanofi-Aventis; G El-Hajj Fuleihan declared associations with the following companies: Eli Lilly, Merck Sharp & Dohme, Novartis, and Sanofi-Aventis. See the article online for full details of the relationships.

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PRACTICE POINT
Administration of calcium, vitamin D, and oral alendronate or risedronate is an approved strategy to prevent steroid-induced bone loss; however, the optimal bisphosphonate regimen and dose for patients receiving high-dose glucocorticoid therapy is unclear

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