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Switching of oral bisphosphonates to denosumab in chronic glucocorticoid users: A 12-month randomized controlled trial ☆

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ABSTRACT

Objectives: To evaluate the effect of switching from oral bisphosphonates to denosumab on bone mineral density (BMD) in long-term glucocorticoid users.
Methods: Adult patients who were receiving long-term prednisolone (≥2.5 mg/day for ≥1 year) and oral bisphosphonates (≥2 years) were recruited. Participants were randomized to either continue oral bisphosphonates or switch to denosumab (60 mg subcutaneously every 6 months) for 12 months. Serial BMD (lumbar spine, hip) and bone turnover markers (serum osteocalcin, P1NP, β-CTX) were measured.
Results: 42 women were recruited (age 54.7 ± 12.9 years; 21 shifted to denosumab and 21 continued on bisphosphonates). The duration of prednisolone therapy was 101 ± 66.3 months and the daily dose was 4.4 ± 2.1 mg. Baseline demographic data, osteoporosis risk factors, and BMD at various sites were similar between the two groups of patients. At month 12, BMD of the spine and hip increased by +3.4 ± 0.9% ($p = 0.002$) and +1.4 ± 0.6% ($p = 0.03$), respectively, in the denosumab group; whereas the corresponding change was +1.5 ± 0.4% ($p = 0.001$) and +0.80 ± 0.5% ($p = 0.12$) in the bisphosphonate group. The spinal BMD at month 12 was significantly higher in the denosumab than bisphosphonate group after adjustment for baseline BMD and β-CTX values, and other confounding factors ($p = 0.01$). Bone turnover markers (β-CTX and P1NP) were more strongly suppressed by denosumab than the bisphosphonates. Minor infections were more common in denosumab-treated patients while other adverse events occurred at similar frequencies between the two groups.
Conclusions: In patients receiving long-term glucocorticoids, switching from oral bisphosphonates to denosumab resulted in greater gain of the spinal BMD and suppression of bone turnover markers after 12 months of therapy. The results have to be confirmed by a larger clinical trial with fracture as endpoint.

Introduction

Glucocorticoid (GC) is the main stay of treatment of many rheumatic diseases but is also an important cause of secondary osteoporosis. The long-term use of GCs increases the risk of fragility fracture at a much higher bone mineral density (BMD) than postmenopausal osteoporosis, indicating an additional deleterious effect of GC on bone quality [1]. More than one-third of postmenopausal women receiving GC therapy developed asymptomatic vertebral fractures [1–3]. A study in general practice reported an increased relative risk of vertebral and hip fractures in chronic GC users [4], with fracture risk proportional to the daily dose of GC. Another study also confirmed that intermittent use of high-dose GC and the cumulative GC dose was associated with an augmented risk of osteoporotic fracture [5].

The American College of Rheumatology recommends pharmacological treatment in postmenopausal women or older men (>50 years) receiving GC therapy for more than 3 months unless the fracture risk in 10 years is low (<10%) and the daily prednisone dose is less than 7.5 mg [6]. In premenopausal women and younger men receiving GCs with a history of fragility fracture, treatment with bisphosphonates or teriparatide should also be considered [6]. For premenopausal women and younger men without a history of fracture, the American Society of Bone and Mineral Research recommends to consider pharmacological treatment when BMD Z scores are below −2.0 or a significant drop of BMD occurs after GC therapy [7].

In addition to the negative effects on calcium homeostasis, GCs inhibit the production, survival and differentiation of the osteoblasts through their antagonism to Wnt signaling [8–11]. GCs also enhance the survival and activity of the osteoclasts by increasing the expression of the RANK ligand (RANKL) [12]. The anti-resorptive agents, such as the bisphosphonates, are the first-line treatment for GC induced osteoporosis (GIOP) [13–15]. However, a drawback of the oral bisphosphonates is their low compliance rates. Although there are no specific data in

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chronic GC users, evidence in postmenopausal women suggests that adherence to the oral bisphosphonates is unsatisfactory, which may lead to a compromise of their efficacy [16–19]. Therefore, alternative treatment options have to be explored in GC users.

Denosumab is a fully humanized monoclonal antibody that targets the RANKL and prevents its binding and activation of the RANK receptors on the osteoclasts, leading to diminished survival and functions of the osteoclasts [20]. A randomized controlled trial (RCT) has confirmed the efficacy of denosumab (60 mg subcutaneous injection every 6 months) in reducing vertebral and non-vertebral fractures in postmenopausal women [21]. However, there is little information regarding the use of denosumab in GIOP. This prompts the current study to examine the effects of switching from oral bisphosphonates to denosumab on BMD and bone turnover in patients receiving long-term GCs.

Patients and methods

Study population

Patients who were receiving long-term GC therapy in the out-patient rheumatology clinics of Tuen Mun Hospital were invited to participate in this study. Inclusion criteria were: (1) Adults (≥18 years of age) with various rheumatic diseases requiring long-term prednisolone treatment (≥1 year). Pre-menopausal women should have no plan for pregnancy within 2 years of study entry and agree to practice contraception during the study period; (2) a daily dose of prednisolone of ≥2.5 mg within 3 months of study entry; (3) having received oral bisphosphonates with the recommended doses for ≥2 years; (4) BMD change since therapy with the oral bisphosphonates that met one of the following criteria: (i) failure of lumbar spine, femoral neck or total hip BMD values to increase by 2%; (ii) BMD of the lumbar spine, femoral neck or total hip BMD remaining osteoporotic, i.e. T scores < −2.5 or Z scores < −2.0; or (iii) development of new vertebral or fragility non-vertebral fractures (after a fall from a standing height or less). Exclusion criteria were: (1) Patients with previous use of denosumab or teriparatide; (2) premenopausal women who planned for pregnancy within 2 years of study entry or those who did not agree for contraception during the study period; (3) patients with known bone disorders such as osteomalacia, renal osteodystrophy, and hyperparathyroidism; (4) patients with unexplained hypocalcemia; (5) patients with serum creatinine level of ≥200 μmol/L.

The protocol was approved by the Research and Ethics Committee of our hospital and registered in the US ClinicalTrials.gov (number NCT01465568). Written consent was obtained from all the participants. Severe adverse events were reported to our Research and Ethics Committee.

Randomization and treatment protocol

This is a 12-month parallel-group open randomized controlled study. At study entry, all participants were continued on elemental calcium (1000 mg/day) and calcitriol (0.25 μg/day), and were randomized by computer-generated blocks in a 1:1 ratio to receive one of the two treatment arms: (1) Discontinuation of existing oral bisphosphonate, with replacement by denosumab (60 mg) subcutaneously every 6 months for 2 doses; or (2) continuation of the same oral bisphosphonate. Other medications for the treatment of the underlying medical disorders were continued as usual.

Clinical assessment and follow-up

Demographic data and information on risk factors of osteoporosis were collected at baseline. BMD at various sites (lumbar spine, total hip, femoral neck) and markers of bone turnover (serum osteocalcin, procollagen type I N-terminal propeptide [P1NP] and C-terminal cross-linked telopeptide collagen degradation product of type I collagen [β-CTX]) were measured at baseline, month 6, and month 12. Plain radiographs of the thoracic and lumbar spine at baseline were taken for pre-existing vertebral fractures and repeat examinations at month 12 were performed for new fractures.

Participants were followed up at 3-month intervals with special attention to adverse events. In case of serious adverse events thought to be related to denosumab or bisphosphonates, these medications would be discontinued and patients would be withdrawn from the study.

Clinical outcomes

The primary endpoint of the study was the difference in BMD of the lumbar spine between the two groups of patients at month 12. Secondary outcomes included the following: differences in the BMD of the hip and femoral neck, changes in bone turnover markers from baseline, new fractures (vertebral and non-vertebral) and adverse events between the two groups.

BMD and vertebral fracture assessment

BMD at various body sites (lumbar spine [L2-4], non-dominant hip, femoral neck and trochanter and whole body) was measured by the dual energy X-ray absorptiometry (DXA) technique using a Delphi™ densitometer (Hologic, Bedford, USA). For patients with avascular bone necrosis of the hip or joint replacement, the BMD of the other hip was used. The reference ranges for the T scores were derived from the third National Health and Nutrition Examination Survey (NHANES III) database (hip) and the device manufacturer's dataset (lumbar spine) [22]. The technician who was responsible for measuring BMD was blinded for the details of the study.

The radiographs of the thoracic and lumbar vertebrae were examined for deformities by visual inspection. Baseline vertebral fracture was defined when there was a loss of at least 25% of the vertebral height. Incident/new vertebral fractures at month 12 were diagnosed when there were distinct alterations in the morphology of the vertebral bodies that resulted in a loss of at least 25% of vertebral height in previously normal vertebrae or worsening of previously deformed vertebrae.

Assay of bone turnover markers

Markers of bone resorption (serum β-CTX) and bone formation (serum osteocalcin and P1NP) were studied. Serum β-CTX was assayed by electrochemiluminescence (Roche Diagnostics, GmbH, Mannheim, Germany) using a commercially available kit. Serum osteocalcin and P1NP were also studied by electrochemiluminescence using commercial kits (Roche Diagnostics, GmbH, Mannheim, Germany). All blood samples were collected at 9 am in the morning, with fasting for at least 8 h.

Sample size calculation and statistical analysis

Assuming that the mean baseline BMD at the spine of the participants is 0.87 g/cm^2 (estimated from our RCT of raloxifene in GIOP [23]), with a SD of 0.085 g/cm^2, and there was an expected increase of 8% after 12 months of denosumab treatment (but expected change in less than 2% in the group with continuation of the bisphosphonates), a sample size of 21 in each arm was required to detect the difference between the two groups at month 12, with an α error of 5% and a power of 80%.

Data analyses and statistical methods

Between-group (denosumab and bisphosphonates) comparison of data at baseline was performed by the independent Student's t-test for continuous variables and by Chi-square test for categorical variables (Fisher's exact test was used when the frequency of any cell of the contingency table was ≤5). BMD at month 12 between the denosumab and bisphosphonate groups was compared with the adjustment of the