Glucocorticoid Induced Osteoporosis: Update on Treatment Guidelines

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Abstract: Glucocorticoid induced osteoporosis (GIOP) is the commonest cause of iatrogenic osteoporosis. Recommendations in prevention and treatment of GIOP are reviewed with update on new treatment. Evidence on efficacy of various treatment options including bisphosphonates, parathyroid hormone, hormonal replacement therapy, raloxifene and calcitonin will be discussed.

Keywords: Bisphosphonates, Glucocorticoid induced osteoporosis, Parathyroid hormone

Introduction

Glucocorticoid induced osteoporosis (GIOP) is the commonest type of iatrogenic osteoporosis and a frequent cause of secondary osteoporosis. Patients with rheumatic disease are very often subject to long term glucocorticoid (GC) treatment. Individual taking GC for more than 3 months is at risk of GIOP, which corresponds to approximately 0.5% of the population. Observational data has suggested that 30% of the patients taking long-term GC for more than 3 years have evidence of osteoporotic fracture. This elevation of risk is seen already within 3 months of GC therapy initiation and is associated with increased bone loss especially in the first year. Higher regular GC dose (≥7.5 mg/day), longer duration of therapy (≥6 months) and continuous GC usage were associated with increase fracture risk.

Pathogenesis of GIOP

Glucocorticoid inhibits osteoblast proliferation and stimulates apoptosis of osteoblasts and mature osteocytes. It stimulates osteoclastic proliferation by suppressing synthesis of osteoprotegerin and stimulating production of the receptor activator of nuclear factor kappa-B (RANK). Glucocorticoid also decreases intestinal calcium absorption and increases renal calcium excretion. Moreover, it decreases sex hormones secretion and increases secretion of parathyroid hormone.

Fracture Risk

A study from the UK general practitioner research database comparing 244,235 patients on GC with control revealed that the relative risk of vertebral, hip and forearm fractures for GC users was 2.6, 1.6 and 1.1 respectively. Besides, the fracture risk was dose dependent. There was a 55% increased rate of clinical vertebral fractures even for patients receiving prednisolone less than 2.5 mg daily. For patients receiving prednisolone of more than 7.5 mg daily, there was a 4-fold increased risk of clinical vertebral fractures.

Bone mineral density (BMD) is an important predictor of fracture. However, it is known that the fracture risk in majority of current GC users is underestimated by using BMD alone, especially in those receiving high daily dose. Data showed that there are different fracture thresholds in postmenopausal osteoporosis (PMO) as compared to that of GIOP. Despite a relatively higher lumbar T-score (-1.2), there was an increase in incidence of vertebral fractures in GIOP (16%) versus PMO (5-13%) (T-score -2.4 to -2.8). The differences occurred despite a higher average age and a higher prevalence of incident vertebral fractures in the PMO arm.
Clinical Guidelines

In 2001, the American College of Rheumatology (ACR) published recommendations on the prevention and treatment of GIOP. Besides general measures, calcium and vitamin D supplements are recommended for patients who are about to start on prednisolone 5 mg daily or more. Dual-energy X-ray absorptiometry (DEXA) evaluation is recommended before considering bisphosphonates for patients who are on GC for more than 6 months. Bisphosphonate is recommended if the T-score is less than -1. The Royal College of Physicians of also defined their guidelines in 2003 recommending bisphosphonate if T-score is less than -1.5.

General Measures

Life style advice related to diet (calcium, protein and vitamin D intake), exercise, fall prevention, cessation of smoking and moderation of alcohol intake should be given to all patients who are on or about to start on GCs.

Calcium and Vitamin D

The ACR Task Force on Osteoporosis recommends patients taking GCs to maintain a calcium intake of 1000 to 1500 mg per day and vitamin D intake of 800 IU per day through either diet or supplements. The efficacy of calcium and vitamin D supplement has been evaluated. A total of 65 patients with rheumatoid arthritis receiving prednisolone at a mean dose of 5.6 mg per day were randomized to calcium carbonate (1000 mg of elemental calcium daily) plus vitamin D3 (500 IU daily) or placebo. Bone mineral density (BMD) over lumbar spine increased by 0.7% per year in the treatment group but decreased by 2% in the placebo group. BMD over trochanter increased by 0.8% per year in treatment group but decreased by 0.9% in placebo group.

A meta-analysis of 33 randomized, controlled, double-blinded trials from 1985 to 2003 comparing native vitamin D versus its hydroxylated analogs showed that alfacalcidol, calcitriol, both native vitamin D and vitamin D analogs were able to improve the BMD in general and over the lumbar spine compared with placebo. However, the inter-treatment difference was not significant.

Animal Proteins

A study by Yale University in 1992 found that 70% of the fracture rate in women at fifty years and older was associated with animal protein consumption. Another study by University of California found that women with the highest ratio of animal to plant protein intake had higher incidence of bone fracture than women with the lowest ratio. Therefore, the recommendation is to reduce animal protein intake.

Bisphosphonates

Bisphosphonates are the standard therapy for the prevention and treatment of GIOP. It promotes osteoclastic apoptosis and prolongs the lifespan of osteoblasts. An early study involving 477 patients with GIOP comparing alendronate 5 mg daily, 10 mg daily or placebo showed that the mean BMD of lumbar spine increased by 2.1% and 2.9% over 48 weeks in patients receiving 5 mg and 10 mg of alendronate daily respectively, but decreased by 0.4% in the placebo group. Femoral neck, trochanter and total body BMD also increased significantly in the alendronate groups. Those receiving alendronate had fewer new vertebral fractures compared with placebo group (2.3% versus 3.7%).

A multi-center, double blind randomized study with 290 GC treated patients assigned to placebo, risedronate 2.5 mg daily or risedronate 5 mg daily showed statistically significant treatment effects on BMD at 12 months at the lumbar spine (p<0.001), femoral neck (p=0.004) and trochanter (p=0.01). Risedronate 5 mg daily increased BMD at 12 months by 2.9% over lumbar spine, 1.8% over femoral neck and 2.4% over trochanter. BMD was maintained in the control group. A 70% reduction in the incidence of vertebral fractures in the combined risedronate treatment groups was observed compared to placebo (p=0.042).

A study comparing intermittent intravenous ibandronate and alfacalcidol in GIOP showed a significant better improvement of lumbar spine BMD over 36 months in the ibandronate group (13.3% versus 2.6%, p<0.001). The femoral neck BMD also increased significantly in the ibandronate group (5.2% versus 1.9%, p<0.001). Fewer new vertebral fractures were detected in the ibandronate group (8.6% versus 22.8%, p=0.043).
The multi-center, randomized, double blind "HORIZON" study with 833 patients randomized to receive either zoledronic acid 5 mg intravenous infusion or daily oral 5 mg risedronate for 1 year. Zoledronic acid was found to be non-inferior and superior to risedronate in increasing lumbar spine BMD in both the treatment (4.06% versus 2.71%) and prevention (2.6% versus 0.64%) subgroups at 12 months.14

Strontium

Strontium increases deposition of osteoblasts and reduces the resorption of bone by osteoclasts. Two major phase III clinical studies "SOTI" and "TROPOS" showed that strontium is a strong anti-osteoporotic agent. It showed significant reduction in vertebral fractures (41%) and hip fractures (36%) in PMO patients compared with placebo. Sustained efficacy was observed in 5 years. However, there has yet been no data to support its use in GIOP.15

Parathyroid Hormone Peptides

Teriparatide is human recombinant parathyroid hormone (PTH) amino acids 1-34. It is administrated subcutaneously at 40 g daily and is able to stimulate bone formation at the tissue and cellular levels. Randomized controlled clinical trial comparing daily subcutaneous PTH and placebo in GIOP showed a greater increase in BMD in the lumbar spine in women treated with PTH compared to placebo at 12 months, as measured by quantitative CT (25% versus 2%, p<0.001) or DEXA (11% versus 1%, p<0.001).16

An international randomized controlled trial showed that the lumbar spine BMD increased more in the teriparatide group than in the alendronate group (8.2% versus 3.9%, p<0.001) at 18 months. The difference was significant from 6 months onwards. BMD also increased more at the hip at 12 months in the teriparatide group (3.8% versus 2.4%), with also fewer vertebral fractures (1 versus 10) but no difference in non-vertebral fractures (5.6% versus 3.7%). Adverse event rates were equivalent in both groups. There were more nausea and insomnia in the teriparatide group but more rash in the alendronate group.17

Hormone Replacement

Estrogen was once thought to be capable in reducing or reversing bone loss in the hypo-estrogenemic women treated with GCs. Retrospective study had showed a significant gain in BMD in women treated with estrogen but continuous bone loss in those not on estrogen in GIOP.18 However, estrogen shows no benefit in premenopausal women. Its use is also not recommended in PMO women in view of the increased risk of breast cancer, stroke and venous thromboembolism.

A randomized placebo-controlled trial comparing testosterone, nandrolone and placebo in men on long term steroid showed that spinal BMD, fat mass and muscle strength were increased in the testosterone group compared with the placebo group.19 However, there is no data on the reduction of fracture risk. Testosterone replacement should be considered in men taking high dose GC who were hypogonadal.

Raloxifene

The anti-fracture efficacy of raloxifene was shown in the Multiple Outcomes of Raloxifene Evaluation (MORE) study in PMO women with osteoporosis. Raloxifene 60 mg daily significantly reduced the 1-year risk of new clinical vertebral fractures by 68% in the total study population and by 66% in women with prevalent vertebral fracture. However, there is no data on reducing vertebral fracture risk to support the use of raloxifene in GIOP. A local study comparing the use of raloxifene and placebo in 114 PMO women treated with GCs showed that at 12 months, spinal BMD increased more in the raloxifene group than in the placebo group (1.2% versus -0.9%).20 Hip BMD was also increased more in the raloxifene group (1% versus -0.8%). Three new fractures developed in the placebo group but none was reported in the raloxifene treated patients. Raloxifene was well tolerated and could be considered for patients intolerant to bisphosphonates.

Calcitonin

Calcitonin reduces vertebral fractures when taken by PMO women for at least 1 year. It has been used in men with osteoporosis who have normal levels of the male sex hormone
or whose osteoporosis do not improve with testosterone treatment. A 2-year randomized prospective study in 44 GC treated patients found that the BMD in the calcitonin group increased by 2.7% in the first year but decreased by 2.8% in the placebo group. However, a meta-analysis of 9 trials comparing calcitonin to placebo for the treatment of GIOP reported no efficacy of calcitonin on femoral neck BMD, vertebral and non-vertebral fractures. Calcitonin has not been found to reduce the risk of fractures in GC treated patients. It is not considered as first line therapy for the treatment or prevention of GIOP but can be considered in patients who cannot tolerate bisphosphonates.

New ACR Guidelines

Based on the promising results from new studies, the new ACR guidelines published in 2010 recommended the use of zoledronic acid and teriparatide besides alendronate and risedronate in GIOP. Fracture Risk Assessment in Osteoporosis (FRAX) should be used to assess the individual risk of fracture in this group of patients. Patients are classified into different fracture risk categories. Management recommendations are dependent on the risk stratification, dosage and the anticipated duration of GC therapy. For elderly patients at high-risk of GIOP, treatment should be initiated even for GC therapy less than 5 mg daily for less than 1 month.

Conclusion

GIOP is the most common form of iatrogenic osteoporosis. The risk is associated with both the dosage and duration of therapy. Postmenopausal women are at particularly high risk. Besides lifestyle modification like smoking cessation, regular weight bearing exercise, patients on long-term steroid should have adequate calcium (1000-1500 mg/day) and vitamin D (800 IU/day) intake. Bisphosphonates are considered as the first line therapy for both prevention and treatment of GIOP with evidence demonstrated by alendronate, risedronate and zoledronic acid respectively. Recent study demonstrated the efficacy of parathyroid hormone but at a much higher cost. Other options including raloxifene and strontium warrant further trials to look into their efficacy (Table 1).

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<th>Table 1. Effects of different drugs on BMD improvement and vertebral fracture reduction in GIOP</th>
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<td><strong>Spine BMD improvement</strong></td>
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<td>Calcium and vitamin D</td>
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