Management of Steroid-Induced Osteoporosis

Edmund K Li

Abstract: Corticosteroid induced bone loss occurs as early as the first six months in patients with rheumatoid arthritis on prednisone at 10 mg daily. For this reason, vitamin D (400-800 IU/day) and calcium (1,000-1,500 mg/day) are recommended in patients on steroids for more than four weeks. In postmenopausal women and elderly men who are to remain on corticosteroid for greater than four to six weeks, bisphosphonates should be used in addition to calcium and vitamin D supplementation. In those with established osteoporosis, the same regimen should be followed. In pre-menopausal women, the decision is less clear because no fractures occurred in this group in four bisphosphonate trials. In addition, the long-term benefit on bone mineral density in pre-menopausal women is not proven. Gonadal hormones are adjunct therapy for patient on corticosteroid therapy. However, there is no evidence of fracture prevention. Similarly, calcitonin is a potentially useful agent in those with bone pain, but its efficacy for fracture prevention remains to be established. Currently, fluoride is not considered appropriate treatment because the effects on bone quality is uncertain. Other agents such as parathyroid hormone, ipriflavone, growth hormone are potential therapeutic options that need more testing. Other measures such as weight-bearing exercises should be encouraged to maintain muscle strength. A bone mineral density measurement of either the lumbar spine or the hip is useful to monitor the efficacy of treatment.

Keywords: Corticosteroid, management, osteoporosis

Introduction

Chronic use of corticosteroid is the most common secondary cause of osteoporosis. Contrary to previous belief apart from the primary or the idiopathic type, it occurs in all racial groups, both genders, and at any age. In a large cross sectional study in which 229 corticosteroid users (mean age 61 years, ≥6 months of prednisone, ≥5 mg/day) were compared with 286 controls not taking corticosteroids, the prevalence of vertebral fracture was 28% in corticosteroid users and 11% had two or more fractures. The risk factors for fractures were age, which was a strong independent predictor than bone mineral density.¹ Corticosteroid induced bone loss can occur early. Available data suggest that vertebral bone loss with corticosteroid can occur as early as in the first 20 weeks in patients with rheumatoid arthritis (RA) on prednisone with a dose of 10 mg daily. Interestingly, upon stopping corticosteroid therapy, the trabecular bone loss can partially be reversed.² While it is true that bone loss in early RA may be due to uncontrolled disease activity and corticosteroid may actually be beneficial, this effect might not offset the detrimental effects of corticosteroids on bone.³

Although the precise dosage of corticosteroid which is safe is not known, long-term low dose prednisone use at 5-mg or greater daily was shown to correlate with an overall increased frequency of adverse effects.⁴ The effects of inhaled corticosteroids on bone density have recently been examined in a large cross-sectional study of 196 asthmatics aged between 20-40 years in whom a significant inverse relationship between cumulative inhaled corticosteroid dose and bone density was seen for both men and women.⁵ In this review, the main treatment modalities currently available for the prevention and treatment of corticosteroid-induced osteoporosis will be discussed, while the major mechanisms by which corticosteroids induce bone loss will not be covered.
MANAGEMENT OF STEROID-INDUCED OSTEOPOROSIS

Prevention and Treatment of Corticosteroid-Induced Osteoporosis

**General Measures**
Preventive measures should begin as soon as corticosteroid treatment is started as it has been shown that bone loss occurs most rapidly in the first six months. Patients should be encouraged to participate in a weight-bearing exercise program and should be given advice regarding the benefit of daily exercises to ensure proximal muscle strengthening. In addition, they should maintain normal body weight, avoid smoking or excess alcohol intake. As far as possible, the lowest doses of corticosteroid should be used. While alternate day steroid therapy has not been shown to cause less bone loss than daily therapy, it is still a preferable option if circumstances allow, to preserve the normal function of the pituitary-adrenal axis.

**Calcium and Vitamin D**
In the management of corticosteroid-induced osteoporosis, appropriate use of vitamin D has always been recommended while calcium prophylaxis alone appears unable to prevent rapid bone loss and is felt to be ineffective. Until recently, the evidence on the efficacy of vitamin D was conflicting. In a recent meta-analysis that identified all randomized controlled trials of patients receiving oral corticosteroids that compared vitamin D plus calcium (or vitamin D alone) with either no therapy or calcium alone, a moderate beneficial effect was seen with vitamin D plus calcium versus no therapy or calcium alone. For this reason, vitamin D plus calcium was recommended to those who are receiving long-term corticosteroids as a minimum.6 However, if this was prophylaxis instituted late in the course of steroid therapy, the beneficial effect of this combination was only modest in a group of premenopausal Chinese SLE women.7 As yet there is no consensus on the appropriate dose or the best formulation of vitamin D. Active metabolites or analogs of vitamin D (calcitriol, alfalcacide 1α-hydroxy D3, or dihydrotachysterol) as well as vitamin D formulations that are not considered to be active can cause hypercalciuria and hypercalcaemia. The American College of Rheumatology (ACR) guidelines on the use of vitamin D included high doses of cholecalciferol (50,000 IU three times weekly), a dosage that is no longer considered appropriate except in specific circumstances such as for individuals who are deficient in serum 25(OH) D.8 Vitamin D is usually prescribed at a dose of 400-800 IU/day. As for calcium intake, premenopausal women and adult men should ingest 1000 mg of calcium/day, and postmenopausal women would need approximately 1500 mg daily.

**Bisphosphonates**
Bisphosphonates are analogues of pyrophosphates. They alter bone remodeling by reducing bone resorption so are considered 'antiresorptive' agents. Substitution of different side chains for hydrogen at certain positions changes the potency of these compounds. The antiresorptive properties increase approximately ten-fold between generations of bisphosphonates. The first-generation bisphosphonates include etidronate and clodronate, which are identified chemically by a short alkyl side chain. Second-generation compounds have amino terminal groups, include alendronate, tiludronate and palmidronate, whereas risendronate, ibandronate and zolendronate are third-generation bisphosphonates which have cyclic side chains. A metaanalysis on the use of bisphosphonates assessing the efficacy for corticosteroid-induced osteoporosis suggests they are effective at preventing and treating the condition at the lumbar spine and to a less extent, femoral neck.9 Vertebral fracture rates were also decreased amongst postmenopausal women but not in men or in premenopausal women.

Based on available evidence, bisphosphonates appear beneficial to postmenopausal women receiving corticosteroids. In premenopausal women, the decision is less straightforward and will depend on a number of other factors including bone mineral density, anticipated dose and duration of corticosteroid treatment.10 Elderly men with low bone mineral density have a fracture risk that approaches that seen in postmenopausal women and may also benefit from treatment.10

**Calcitonin**
Calcitonin is a potent inhibitor of osteoclasts; it also appears to stimulate osteoblasts and to promote enteral calcium absorption. Added benefits include its analgesic effect that is mediated through the release of β-endorphins. Of the available types of calcitonin, which include porcine, human, salmon and eel, salmon calcitonin is the most potent. It can be administered either by subcutaneous injection (100 IU/day) or by nasal spray (200 IU/day). Preliminary conclusions at this time from nine randomized controlled trials with 221 patients suggest calcitonin can preserve bone mass in the first year of corticosteroid treatment at the lumbar spine but not the hip. The protective effect on bone mass may be greater
for those who have been taking steroid for more than three months. There was no consistent effect of different dosages (50-100 IU compared to 200-400 IU). However, subcutaneous calcitonin showed substantially greater prevention of bone loss. Important side effects included nausea and facial flushing, and rhinorrhea when administered by the nasal route. Efficacy of calcitonin for fracture prevention in corticosteroid-induced osteoporosis remains to be established.11

**Sex Hormones**
Exogenous glucocorticoids acutely reduce testosterone levels in men due to a direct suppressive effect on gonadal steroid secretion as well as alteration of hypothalamic GnRH secretion.12,13 A decrease as much as 50% in serum testosterone levels has been reported due to glucocorticoids.12 Replacement with testosterone has been shown to be an effective therapy for corticosteroid-induced osteoporosis in hypogonadal men with asthma with significant improvement in the bone mineral density of the lumbar spine.13

Oestrogens were among the first drugs studied for the treatment of corticosteroid-induced osteoporosis. An early observation in eight women given oestrogen during prednisone treatment for asthma reported an increase in the spine bone density after 12 months.14 Similarly, bone loss in the lumbar spine (but not femoral neck) can be ameliorated amongst postmenopausal women with rheumatoid arthritis on corticosteroid who receive oestrogen replacement.15 A more recent study confirms previous observations with 28 young amenorrheic lupus women proven to have ovarian failure with osteopenia. With hormonal replacement therapy for two years, there was significant improvement of bone mineral density in the lumbar spine and radius, but not the hip.16 Based on current information on the gonadal hormones, and in the absence of availability of large clinical trials and without evidence of fracture prevention, testosterone and oestrogen replacement remain to be considered as an adjunctive treatment for patients on corticosteroid therapy.

**Fluorides**
Fluorides stimulate osteoblast proliferation and formation of bone. In a study consisting of patients with a variety of disorders, some of whom were already receiving corticosteroids and some of whom were commencing steroid treatments, after two years of sodium fluoride (NaF), there was a significant increase in bone density of the lumbar spine in those treated with NaF as compared to those who received placebo.17 Monofluorophosphate plus calcium produced significant increase in bone mineral density of the lumbar spine at two years compared with those on calcium alone, but no data were provided regarding fractures.18 In a recent study of patients with established osteoporosis, sodium fluoride given in addition to cyclic etidronate was shown to be superior to etidronate alone with improvement of bone density in the lumbar spine at two years, but no effect was seen at the hip.19

The trials with fluoride are all small and lack power, so it is not possible to determine whether the increased bone density can actually lead to reduction of fractures. Until more data are available, fluoride at this time is not considered to be appropriate treatment for corticosteroid-induced osteoporosis.

**Summary of the Therapies, Costs and Effectiveness**
Evidence from recent trials suggests that calcium alone is ineffective in preventing bone loss in patients starting corticosteroids. Vitamin D plus calcium is superior to no therapy or calcium alone. There was a trend towards fracture reduction among those treated with vitamin D plus calcium.6 In patients receiving chronic low-dose corticosteroids, this may be sufficient to prevent further bone loss, although there is no data proving such treatment can reduce fracture risk.10 As compared to other classes of osteoporosis therapies, vitamin D is less effective than bisphosphonates, but is similar in efficacy to calcitonin, and probably is less effective than fluorides although there have been very few trials on fluorides.6 The evidence for calcitonin or hormone replacement is limited, but gonadal hormone replacement clearly should be considered if hypogonadism is present.10 Based on available fracture data with bisphosphonates, the estimated numbers of patients that would need to be treated for 12 months to prevent one vertebral fracture (number needed to treat [NNT] for postmenopausal women with the different types of bisphosphonates: etidronate was five, resorionate was eight and alendronate was 26. In men, the NNT from alendronate was 142, and because no fractures occurred in premenopausal women in these bisphosphonate studies, the NNT could not be calculated.10 The low baseline bone mineral density and a high prevalence of vertebral fractures in some of the groups that were studied may explain the low values of NNT with some bisphosphonates.

A recent paper compared the cost-effectiveness of different management strategies for the prevention corticosteroid-induced osteoporosis in postmenopausal female patients with
rheumatoid arthritis. These include (1) screen no one and treat only after an osteoporotic fracture occurs (‘watchful waiting’); (2) screen and treat selectively based on a bone mineral density T score of <-1.0 (‘screen and treat’); and (3) treat empirically without bone mineral density measurement (‘treat all’). The least expensive strategy was ‘watchful waiting’ using etidronate if a fracture occurred, while the most effective strategy, but the most expensive, was to treat all. The incremental cost-effectiveness ratio in US dollars per quality-adjusted life year (QALY) of a strategy of ‘screen and treat’, compared with ‘watchful waiting’ was greater than that of other well-accepted medical interventions. The cost effectiveness ratios were more acceptable when a T score treatment threshold of <-2.5 was used.

Management of the Individual Patient

Only a small proportion of patients who are on chronic long-term corticosteroid treatment are given therapy to prevent bone loss with 14% being treated in a population study and 6.4% in a hospital-based study. This highlights the need for a more uniform approach to patients who are on long-term treatment with steroids. Currently there are guidelines available that are based on assumptions rather than on evidence from randomized controlled trials.

From the current available evidence, what is clear with regard to patients on chronic corticosteroid therapy is that postmenopausal women who have lower bone mineral density and are at greatest risk for fracture would benefit from treatment. The rank order of choice for prophylaxis would be a bisphosphonate, followed by vitamin D (or its metabolites or analogues) and calcium supplements. In most bisphosphonate trials, patients receive supplemental calcium and vitamin D. Older men with low bone mineral density, have a fracture risk that approaches that seen in postmenopausal women, and may also benefit from treatment (non-evidence based). Addition of a bisphosphonate in postmenopausal patients already taking oestrogen replacement may enhance the bone density response. Similarly, addition of hormone replacement therapy to a bisphosphonate in postmenopausal women taking corticosteroids may be appropriate.

In premenopausal women receiving corticosteroid therapy, the decision is less clear. As there was not a single incident of vertebral fracture occurring in four bisphosphonate trials comprising 251 years of patient exposure, the decision to use prophylaxis will depend on patients' bone mineral density and the other risk factors, including their underlying diseases, duration, doses of corticosteroids therapy or other genetic factors. Furthermore, the long-term effect of corticosteroid therapy on bone mineral density in premenopausal women is not definite. Some studies suggest there were minimal bone losses while another suggested otherwise. Two cross sectional studies have shown the relatively low prevalence of osteoporosis of 4-6% amongst premenopausal Chinese women with systemic lupus erythematosus on chronic corticosteroid therapy.

Hence, the treatment strategy needs to be individualized. Whether vitamin D plus calcium supplement with the addition of a bisphosphonate are useful in the primary prevention of corticosteroid-induced osteoporosis and will actually decrease fracture risk in premenopausal women awaits further studies. The efficacy of hormone replacement therapy in premenopausal women starting corticosteroid needs to be further evaluated by clinical trials.

Other Therapeutic Agents

Parathyroid Hormone, Ipriflavone, Growth Hormone

None of the agents that have been discussed reverse the main problem in corticosteroid-induced osteoporosis, the low bone formation rate. Recently, subcutaneous injections of low doses of parathyroid hormone (PTH) have been shown to stimulate bone formation in osteoporotic women and men. A few trials with PTH have shown it to be safe and effective treatment for osteoporosis secondary to corticosteroids.

Ipriflavone may inhibit bone resorption and enhance bone formation with a stimulatory effect on osteoblast proliferation. It has been used in postmenopausal women with established osteoporosis with benefits but there are no data available in patients on corticosteroids.

Growth hormone has been found to affect bone remodeling, causing a transient increase in bone resorption and an increase in bone formation. Studies with exogenous growth hormone in established osteoporosis have demonstrated that the benefits are not sustained during the treatment.

Conclusions

Current evidence suggests that postmenopausal women and probably elderly men on corticosteroids therapy are at the
The greatest risk of bone loss, and for this reason, they should be on prophylaxis in order to avoid the development of fractures. The prophylactic options have previously been discussed and should consist of a bisphosphonate with vitamin D plus calcium supplement, although some would feel when active metabolites of vitamin D are used, calcium may not be required unless the intake of calcium is low.

For premenopausal women, in primary prevention of corticosteroid-induced osteoporosis, treatment with vitamin D and calcium appears to be beneficial up to 12 months. For longer-term treatment efficacy, or in secondary prevention, the data are less clear. Furthermore, there is no evidence to show this treatment can actually reduce fracture risk. The management of this group of patients therefore needs to be individualized, and will depend on the duration of exposure and doses of steroid, as well as the baseline bone mineral density which are determinants of fracture risk.

References