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Glucocorticoid – Induced Osteoporosis: Considerations in Ophthalmology

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Ophthalmologists occasionally take the initiative and responsibility for prescribing systemic corticosteroids to patients with vision-threatening ocular inflammatory disorders. Examples of such disorders include idiopathic orbital inflammatory syndrome, scleritis, uveitis, giant cell arteritis, and optic neuritis. Preoccupation with the goal of preserving vision, coupled with the tendency for some cases to relapse during attempted steroid tapering (gradual dose reduction), can lead to prolonged corticosteroid use without adequate attention to bone preservation strategies.

It is well known that prolonged use of corticosteroids has a 100% chance of adverse reactions,[1] including: severe bone mineral loss, insulin resistance, myopathy, behavioral disorders, easy bruising, rise in blood pressure, cataract, and glaucoma.[2] Additionally, cyclosporine A, which may be used in combination with corticosteroids to obtain control of ocular inflammation, can also cause bone loss by inducing high intensity bone remodeling and resorption exceeding formation in animal models, indicating an increase of osteoclast activity.[3,4]

Osteoporosis means “porous bone”. The Consensus Development Conference held in conjunction with the fourth International Symposium on Osteoporosis defined osteoporosis as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture”. Osteoporosis is a serious public health concern that affects almost 28 million people in the United States, and the overall cost of acute and

long-term health care associated with it will approach $14 billion annually, or more than $38 million per day by 2015.

The incidence of atraumatic fractures in patients who receive supraphysiologic corticosteroid therapy is 30 to 50%.[5,6] The chronic use of corticosteroids is associated with a lower bone mineral density (BMD) and a higher risk of bone fractures in a dose-response relationship. Most of the BMD loss occurs during the first twelve months, peaking at six months.[7]

Corticosteroids cause bone loss primarily by suppressing bone formation. If bone resorption is simultaneously increased—due to other medications, the underlying disease for which corticosteroids are prescribed, or concomitant conditions such as estrogen deficiency—then bone loss is further accelerated. Dosages of corticosteroids >5 mg /day are associated with accelerated bone loss in elderly men and women.[8] It has been estimated that 800 mcg/day of beclomethasone, budesonide or fluticasone can cause bone loss.[9,10] It is also known that changes to dosage does not prevent bone loss.[11]

Corticosteroids suppress Insulin-like Growth Factor-1 (IGF-1) primarily by inhibiting its production (transcription reduction in liver/tissues) and decreasing its bioavailability. They also reduce local IGF-1 production in tissues like the growth plate and bone.[12] Recombinant IGF-1 can prevent devastating effects of steroids on bone. But, this therapy has certain disadvantages: it is expensive; there are significant potential adverse effects (dermatologic and cardiac); and IGF therapy must be delivered by subcutaneous injections.

Corticosteroids also can induce androgen deficiency by pharmacological suppression of adrenal function,[13] and androgen deficiency increases bone resorption. This is evident in postmenopausal women[14] and in hypogonadal males.[13] The adrenal glands are an important source of circulating androgens. In addition, high doses of corticosteroids decrease testicular responsiveness to gonadotropins, and thereby reduce serum testosterone even in normal males.

Strategies to prevent corticosteroids induced bone loss

BMD testing is the most reliable tool to assess fracture risk. Routine radiography used to be the only non-invasive method to evaluate BMD. Currently, the most reliable method to assess BMD is dual energy x-ray absorptiometry (DEXA). It has proven to be a reliable indicator of risk for developing osteoporotic fracture, and an efficient tool to assess response to treatment. Two measures are of importance when interpreting DEXA results. Both measures are statistically compared in standard deviations (SD) from a normal distribution or along a “bell curve”. They are the individual’s T-score and Z-score.

The T-score compares the patient's BMD to the mean score of a healthy adult. The Z-score compares the patient's BMD to the mean score of an age-matched control. The World Health Organization has established the following criteria for osteoporosis preventive and therapeutic decisions[15]:

• Normal: a value for BMD greater than -1 SD of a healthy young adult mean value.
• Osteopenia: a value for BMD more than -1 SD but less than -2.5 SD below that of a healthy young adult mean value.
• Osteoporosis: a BMD value -2.5 SD or greater below that of a healthy young adult mean value.
• Individuals who have sustained one or more low-impact fractures are considered to have osteoporosis regardless of their BMD score.

It is important for a physician not only to recognize the risk of osteoporosis induced by anti-inflammatory therapy but also to explain this to patients. The consequences of profound bone loss and fractures can be devastating from the standpoint of patient's well-being, health care costs, and legal issues.

Here, we discuss medications used to prevent glucocorticoid-induced bone loss.

Bisphosphonates

Bisphosphonates have been in clinical use since 1988. They are effective in preventing bone mineral density (BMD) loss.[16] Their mechanism of action is the inhibition of osteoclastic bone resorption once the drug binds to the bone surface. Potential side effects include gastritis and/or esophagitis,[17] myalgia,[18] and altered hepatic function.[18] Since bone resorption is essential for fracture healing and the repair of microscopic fatigue cracks in bone, inappropriately high doses of bisphosphonates may interfere with fracture repair and lead to the accumulation and propagation of fatigue cracks, thereby weakening bone. Bisphosphonates may also abolish the skeleton's adaptive capacity;[19] however, in general, they are well tolerated.

Several studies have shown that treatment with calcium and multivitamins plus alendronate (Fosamax) or risedronate (Actonel) prevents corticosteroid-induced bone loss in the spine and hip, whereas treatment with calcium and multivitamins plus placebo does not.[20-22] Research has also shown that patients who have recently started corticosteroid therapy require higher doses of bisphosphonates than those who have been treated for a longer period. Additionally, patients treated for less than four months or women with estrogen deficiency require 10 mg of alendronate daily, as opposed to 5 mg, to achieve significant improvement in bone mineral density (BMD). A placebo-controlled trial of risedronate (Actonel) reached similar conclusions. The effects of both drugs are dose

dependent. Weekly dosing regimens are now available: 70 mg of alendronate or 35 mg of risedronate.

It is important to note that bisphosphonates may cause a wide range of ocular inflammatory diseases and should be used with caution in these patients

Human parathyroid hormone and Hormone Replacement Therapy (HRT)

Postmenopausal women receiving chronic corticosteroid therapy are only partially protected from bone loss by hormone replacement therapy (HRT) alone. Additionally, clinicians must be aware of the potential adverse effects of long-term HRT, including an increased risk of breast cancer, stroke, and myocardial infarction.[23,24] One study demonstrated that treatment with human parathyroid hormone significantly increased bone mass in the lumbar spine and hip in postmenopausal women with corticosteroid-induced osteoporosis who were already receiving HRT. However, the maximal effect of this anabolic agent on hip BMD occurred after six months.[23] Human parathyroid hormone must be administered via daily subcutaneous injections, which may be inconvenient for patients. Teriparatide (Forteo), a synthetic form of parathyroid hormone, is now FDA-approved and available for patients with severe osteoporosis.

Selective estrogen receptor modulators

Raloxifene (Evista) was initially developed as a breast cancer preventive agent. It increases bone mineral density (BMD) in the spine and hip, although less effectively than bisphosphonates or estrogen. The drug acts on estrogen receptors and exhibits estrogen-agonist effects on bone and lipid metabolism. Raloxifene (Evista) alone does not prevent corticosteroid-induced bone loss.[25,26]

Calcitonin

Salmon calcitonin (SCT), administered as a nasal spray, can prevent bone mineral density (BMD) loss by inhibiting osteoclastic activity. Luengo et al. reported that in patients with corticosteroid-dependent asthma, intranasal SCT increased spinal BMD during the first year of treatment and maintained bone mass during the second year.[27,28] Adachi and colleagues evaluated intranasal SCT in patients with polymyalgia rheumatica, with or without temporal arteritis, receiving chronic high-dose corticosteroid therapy.[29] SCT prevented bone loss in the lumbar spine as measured by dual-energy X-ray absorptiometry.

Both studies used 200 mcg of SCT with daily calcium supplementation (800–1000 mg), but were limited by small sample sizes. There is a lack of large-scale studies providing robust data on the efficacy of SCT in patients receiving chronic glucocorticoid therapy.[30] SCT may

be considered in pregnant women requiring long-term glucocorticoids, as bisphosphonates are contraindicated in this population.[31,32]

Vitamin D

Patients over 60 years of age and those with chronic diseases tend to have low vitamin D levels. Chronic corticosteroid use may increase vitamin D catabolism and reduce serum levels by approximately 5–10%.[33] Vitamin D and its metabolites (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) have been reported in one study to increase bone mineral density (BMD) in corticosteroid-treated patients; however, other studies have failed to confirm these benefits.[33]–[35] In general, vitamin D supplementation does not improve bone density in patients without vitamin D deficiency.[36] Vitamin D deficiency is common in regions with limited sunlight exposure, particularly in northern climates during winter. Nevertheless, vitamin D supplementation should be included as part of chronic glucocorticoid therapy.

Systemic Illness causing bone loss

Cushing's disease causes severe bone loss, but osteopenia can reverse completely after cure of Cushing's.[37] Hyperparathyroidism is another well-known cause of bone loss. Successful surgical treatment results in improvement of bone density, with an 8 to 12% increase in bone mass observed during the first 2 to 4 years following surgery.[38] Gastrointestinal diseases associated with bone loss include celiac sprue, cystic fibrosis, chronic liver disease and inflammatory bowel disease. Osteopenia is explained by glucocorticoid use in many patients with inflammatory bowel disease. But it appears that inflammatory bowel disease may cause osteoporosis even in the absence of such therapy,[39] with a 40% increase in fracture rate reported by some authiors.[40]

A new dawn for osteoporosis drug development

Similar to other areas of medicine, biologic response modifying agents have transformed and advanced the treatment of osteoporosis.[41,42] Several classes of these medications are discussed below.

- RANKL inhibitor (denosumab)

The cytokine receptor activator of nuclear factor-κB ligand (RANKL), produced by osteocytes, is essential for osteoclast differentiation. Inhibition of RANKL prevents osteoclast formation, thereby reducing bone resorption and increasing bone density.

Denosumab is a fully human monoclonal antibody targeting RANKL, approved by the FDA for the treatment of men and women at high risk for fracture, defined as those with a history

of osteoporotic fracture and/or multiple risk factors. It is indicated for patients who have failed or are intolerant to other osteoporosis therapies, for postmenopausal women with osteoporosis at high risk for fracture, for increasing bone mass in men with osteoporosis at high risk for fracture, and for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture.

- Sclerostin inhibitor (romosozumab)

Romosozumab is a fully human monoclonal antibody that targets sclerostin. It is currently FDA-approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as those with a history of osteoporotic fracture, multiple risk factors for fracture, or an inadequate response or intolerance to other available osteoporosis therapies.

Benjamin Leder and colleagues present the findings of the LIDA trial, which evaluated 3 months of romosozumab treatment (the most potent anabolic agent) followed by 9 months of denosumab, compared with 12 months of continuous romosozumab in postmenopausal women at high risk of fracture. At 12 months, the percent change in total hip BMD in the 3-month romosozumab group was non-inferior to that observed in the 12-month romosozumab group.

In summary

• Check axial BMD early, preferably in lateral and PA spine
• Assure 1000-1500 mg Ca and 800 units vitamin D in tablets daily
• Then check serum PTH and 25-OH vitamin D
• Refer to a specialist if there are multiple osteoporosis risk factors
• Prescribe a bisphosphonate as first line treatment, or PTH if the patient has had a fragility fracture or if the T-score is below – 2.5 SD
• Consider nasal spray calcitonin if T-score is borderline low, or if the patient is pregnant
• If androgen therapy would be safe: check serum testosterone in men over 60, and in men taking high-dose of corticosteroids
• Other medications resulting in bone loss include anti-convulsants, heparin and supraphysiologic doses of levothyroxine (i.e. those used to treat thyroid tumors)
• Remember that risk factors, such as smoking, alcohol abuse and sedentary lifestyle contribute to increased rate of bone loss.

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