Gonadotropin-releasing Hormone Agonists, Aromatase Inhibitors, Antiepileptic Drugs and Risk of Osteoporosis

a report by
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Osteoporosis is an important clinical and public health problem because of its association with fracture, which is associated with increased mortality and morbidity. Preventative strategies against osteoporotic fractures include the identification of patients at high risk of fracture. Various risk factors such as underlying diseases and certain drugs can increase the risk of fractures; for example, prior and current use of oral corticosteroids is strongly associated with an increased risk of fracture. However, other medications such as hormonal-deprivation therapies (gonadotropin-releasing hormone [GnRH] agonists and aromatase inhibitors [AIs]) and antiepileptic drugs (AEDs) could be involved and should be assessed to ensure the optimal care of patients at risk of osteoporosis.

Gonadotropin-releasing Hormone Agonists
GnRH agonists are widely used for the treatment of hormone-dependent cancers (such as prostate and breast cancers) and other benign conditions (such as endometriosis).

Use of Gonadotropin-releasing Hormone Agonists in Prostate Cancer
Inducing hypogonadism in men with prostate cancer using GnRH agonists increases the risk of osteoporosis. The role of androgens in maintaining bone health appears to be mediated indirectly through their conversion to oestrogens, although testosterone may be an important factor in bone formation. Shahinian et al. evaluated the relationship between the use of GnRH agonists or orchiectomy and the risk of fracture in 50,613 men over 66 years of age with prostate cancer who had survived for five years after their diagnosis. Men treated with GnRH agonists or orchiectomy sustained more fractures than those who were not treated (19.6 versus 12.6%; p ≤ 0.001).1 The risk of fracture was correlated with the duration of therapy, and patients treated with at least nine doses of GnRH agonists during the first year were more likely to suffer a fragility fracture than others.1

Accelerated bone loss similar to that seen in women undergoing bilateral oophorectomy has been demonstrated in men with hypogonadism who undergo orchiectomy or who receive GnRH agonists. Mittan et al. showed a 3.3% decrease in bone mineral density (BMD) at the hip and a 5.3% decrease in BMD at the distal radius after 12 months of treatment with GnRH agonists.2 The rate of bone loss varied from 2 to 8% in the spine and from 1.8 to 6.5% in the hip in the first year after commencing therapy; these rates increased with time. Bone loss is maximal in the first year after initiation of androgen-deprivation therapy (ADT), indicating that early initiation of preventative therapy could be indicated. This bone loss is associated with increased levels of urinary cross-linked N telopeptide of type 1 collagen (NTX), a marker of bone resorption, at both six and 12 months.2

Bisphosphonates (pamidronate, zoledronic acid) have been studied in men with prostate carcinoma to assess their ability to inhibit hypogonadal-induced bone loss. Smith et al. reported on the effects of intravenous zoledronic acid 4mg administered at three-month intervals in a randomised, placebo-controlled trial of 106 men 71 years of age with prostate carcinoma who were receiving ADT either alone or in combination with antiandrogens. Zoledronic acid significantly increased BMD at all skeletal sites, from 1.2 to 5.3%.3 In a randomised trial conducted in 40 men receiving a GnRH agonist, a single treatment with zoledronic acid significantly increased BMD and suppressed serum N-telopeptide levels over 12 months.4

Diamond and colleagues5 recommend evaluating BMD in all patients with prostate cancer treated with GnRH agonists, ensuring adequate vitamin D status and calcium intake; they also recommend use of bisphosphonates in patients with osteoporosis (defined by a T score ≤ -2.5) and/or fracture.

Use of Gonadotropin-releasing Hormone Agonists in Endometriosis
In severe endometriosis, prolonged GnRH agonist therapy induces a rapid and severe decrease of BMD. Hormonal add-back therapy can be used to prevent this bone loss. In a study of 78 patients with endometriosis receiving GnRH agonists, use of oestradiol 2mg and promegestone 0.5mg per day is an effective and safe add-back therapy that can be proposed for prolonged leuprorelin treatment over six months in severe endometriosis.6

Aromatase Inhibitors
AIs are increasingly being used as adjuvant therapy in post-menopausal women with oestrogen-receptor-positive breast cancer. After menopause, extraglandular sites are the main source of oestrogen. Oestrogen deprivation in post-menopausal women is best achieved by inhibition of the enzyme aromatase, which mediates the peripheral conversion of androgenic precursors of adrenal origin (testosterone and androstenedione) to oestriol and oestrone in adipose, liver, muscle and brain tissues. However, the profound suppression of biologically available oestrogens has a deleterious impact on bone health. Bisphosphonates and calcium are recommended in patients on AIs for the prevention of osteoporosis.7

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Osteoporosis

The role of androgens in maintaining bone health appears to be mediated indirectly through their conversion to oestrogens, although testosterone may be an important factor in bone formation.

Clinical Data

In a prospective sub-study of the ATAC trial conducted in 197 women who underwent serial BMD measurements over the course of five years, a significant decrease was noted in BMD of the lumbar spine and hip in the tamoxifen group (median decrease of 6.1 and 7.2%, respectively) compared with the tamoxifen group (median increase of 2.8 and 0.7%, respectively). The rate of bone loss was slower in years two to five compared with baseline to two years. Bone sub-protocols of large AI studies show that bone loss is similar with the three AIs during the first two years of treatment.

Management

Given the evidence of increased bone loss and fractures in women treated with adjuvant treatment for breast cancer, it is necessary to prevent bone loss, or treat it early to prevent further bone loss.

Various randomised trials support the use of bisphosphonates to prevent bone loss in patients receiving antiaromatase treatment. In a three-year randomised trial comparing tamoxifen and goserelin ± zoledronic acid (4mg administered intravenously every six months) versus anastrozole and goserelin ± zoledronic acid, zoledronic acid significantly inhibited bone loss in pre-menopausal women with oestrogen-receptor-positive breast cancer, maintaining baseline BMD at the end of three years; in comparison, those receiving anastrozole or tamoxifen (20mg/day) alone had significant bone loss at the lumbar spine (-17.4 and -11.6%, respectively; p<0.0001), and similar results were observed at the hip.

Bruksy et al. studied the benefit of zoledronic acid in preventing bone loss associated with letrozole in 602 post-menopausal women who were randomly assigned to start receiving zoledronic acid (4mg every six months) at the same time as starting letrozole (up-front group), or to a group in which zoledronic acid was delayed until the T score decreased to less than -2 or a non-traumatic fracture occurred. At one-year follow-up, BMD was higher at the lumbar spine (+4.4%) and hip (3.3%) in women who received zoledronic acid at the same time as receiving letrozole.

Data from studies of oral bisphosphonates are emerging. In the Study of Anastrozole with the Bisphosphonate Risedronate (SABRE) in 234 post-menopausal women with hormone-receptor-positive early breast cancer, 12-month results indicate that oral risedronate reduces bone marker levels and prevents bone loss in patients receiving anastrozole who are at moderate to high risk of fragility fractures. This bone loss was prevented at the hip and increased at the spine in women treated simultaneously with anastrozole and risedronate.

Concurrent use of raloxifene and AIs is not recommended based on the adverse effect of combining tamoxifen with anastrozole in the ATAC trial.

Bone density should be measured at the beginning of AI therapy. The American Association of Clinical Oncology suggests that women with osteoporosis – defined by a T score lower than -2.5 – should receive calcium, vitamin D and a bisphosphonate. For women with T scores between -1.5 and -2.5, a bisphosphonate may be considered based on individual risk. Any patient initiating or receiving an AI with a T score >2.5 and no fracture factors should be monitored every one to two years for change in risk status or BMD loss.

Antiepileptic Drugs

The risk of fractures in patients with epilepsy is two to six times higher than in the general population. A large proportion of these fractures occur in relation to seizures (35%), but fractures may also be caused by falls without seizures. People with epilepsy have an increased risk of falling secondary to either seizures or the side effects of AEDs (sedation, dizziness and ataxia). Use of AEDs may also have a direct effect on bone.
Mechanisms of Action
A potential mechanism of action of AEDs is hepatic induction of the P-450 cytochrome (CYP450). Phenytoin, carbamazepine and phenobarbital induce CYP450, leading to increased catabolism of vitamin D and decreased calcium absorption, leading to secondary hyperparathyroidism. However, there appear to be multiple mechanisms of AED-induced bone loss, and all types of AED are potentially implicated, including valproate, a cytochrome P450 enzyme inhibitor. Other mechanisms of action have been suggested, such as resistance to parathyroid hormone, inhibition of calciitonin secretion, direct effect of AEDs on osteoblasts and impaired calcium absorption.

There are limited data regarding the newer AEDs. Pre-menopausal women treated with lamotrigine did not have significant reductions in BMD or changes in bone turnover markers.

Clinical Data
In a Swedish case-control study, the risk of fractures was higher in patients receiving AED polytherapy compared with patients receiving AED monotherapy. In a case-control study using data from the General Practice Research Database (GPRD), the risk of fracture increased with cumulative duration of exposure, with the strongest association for over 12 years of use (adjusted OR 4.15, 95% CI 2.71–6.34). In this study, there was no difference between patients receiving AEDs that induce the hepatic cytochrome P-450 system and those receiving AEDs that do not induce it. This finding confirms the results of a Danish case-control study including 124,655 fractures, which concluded that use of the hepatic inducers does not explain all of the observed increase in fracture risk.

This increased risk of fracture is associated with a modest decrease in BMD. In a meta-analysis of 12 studies of the BMD of treated patients, BMD Z scores were significantly decreased at the spine (-0.38±0.06%) and hip (-0.56±0.06%). These results suggest that fracture risk may be explained by factors other than AED use alone.

Management
Although there are no consensus guidelines, adult patients receiving long-term AEDs, particularly if they have other risk factors for bone disease, require screening for osteoporosis and measurement of serum calcium, phosphate, alkaline phosphatase and vitamin D. Preventative measures include optimal control of seizures and supplementation with calcium and vitamin D, with the precise role of anti-osteoporotic treatments such as bisphosphonates being unclear.

In addition to oral glucocorticoids, the most common form of medications that cause osteoporosis, other medications should be assessed in patients at risk of fracture.

However, as AEDs induce vitamin D dysfunction, patients will require higher doses of vitamin D, and the efficacy of vitamin D supplementation should be monitored. Despite these data, a survey of neurologists revealed that only 28% screen patients taking AEDs for osteoporosis and only 7% prescribe calcium and vitamin D.

Conclusion
In addition to oral glucocorticoids, the most common form of medications that cause osteoporosis, other medications should be assessed in patients at risk of fracture. There is strong evidence that GnRH agonists, AIs and AEDs increase fracture risk. Healthcare providers should screen all patients initiating these medications for bone mass and risk factors for osteoporosis. Because these agents can rapidly reduce bone mass, appropriate preventative therapy is recommended.