Alternatives to Estrogen in Postmenopausal Osteoporosis

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Osteoporosis is characterized by a decrease in bone mass and deterioration in skeletal microarchitecture, which lead to increased fragility and susceptibility to fractures. In treating established osteoporosis, the objective is to prevent further skeletal deterioration, and to increase bone mass and/or improve bone microarchitecture to reduce the risk of vertebral and/or peripheral fractures. One of the major determinants of skeletal weakness is bone loss that occurs after menopause.

Estrogens, calcium and vitamin D supplementations, calcitonin, and early-generation bisphosphonates were considered effective and well-tolerated agents for maintaining bone mineral density (BMD) of trabecular and cortical bone at premenopausal levels by counteracting the exacerbated activity of osteoclasts induced by the sharp postmenopausal decrease in circulating endogenous estrogens. Also, new medications have been developed with the goal of meeting a better risk-to-benefit ratio. These include selective estrogen receptor modulators [SERMs], second- and third-generation bisphosphonates, parathyroid peptide, strontium [Sr] ranelate, and others.

Raloxifene

It is one of the selective estrogen receptor modulators (SERMs); compounds that produce estrogen agonism in one or more desired target tissues (e.g. bone, liver) together with estrogen antagonism and/or minimal agonism in reproductive tissues, such as the breast or uterus.

On a molecular basis, raloxifene activates the gene encoding transforming growth factor beta (TGF beta3), which, together with other growth factors and cytokines, induces production of osteoblasts and inhibits the activity of osteoclasts and shortens their life span. The general pattern of bone remodeling is similarly affected by both raloxifene hydrochloride and conjugated equine estrogens.

From a cost-utility analysis of a Swedish database, it appears that raloxifene can be targeted cost-effectively to postmenopausal women with osteopenia with a risk for hip fracture (relative risk 2.6) and to women aged 65 or older or at high risk (relative risk 3.0) for hip fracture.

Thirteen cases of breast cancer were confirmed among the 5129 women assigned to raloxifene vs. 27 among the 2576 women assigned to placebo (RR = 0.24, 95% CI = 0.13-0.44; $P < .001$).

Raloxifene decreased the risk of estrogen receptor-positive breast cancer by 90% (RR = 0.10, 95% CI = 0.04-0.24), but not estrogen receptor-negative invasive breast cancer (RR = 0.88, 95% CI = 0.26-3.0].

Raloxifene also significantly reduced the risk of cardiovascular events in a subset of women with increased cardiovascular risk.

Cautions

- Risk factors for venous thrombo-embolism. (Discontinue in case of prolonged immobilization).
- History of estrogen-induced hypertriglyceridemia
- History of severe vasomotor symptoms
- Breast cancer

Contraindications

- History of venous thrombo-embolism
- Undiagnosed uterine bleeding
- Hepatic impairment or cholestasis
- Severe renal impairment
- Endometrial cancer

Side effects

- Venous thrombo-embolism
- Leg cramps
- Hot flashes
- Thrombophlebitis
- Influenza like symptoms
- Peripheral Edema
- Rarely Rashes, Gastro-intestinal disturbances, hypertension, and headache (including migraine).

Dose

60-120 mg/day.

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Market names and prices

Evista (14 tabs = 84 LE)

Bisphosphonates

Etidronate

Its inferior anti-resorption efficacy and low potential for inducing bone mineralization compared with newer molecules have minimized its popularity.

Alendronate and risedronate sodium are considered the drugs of choice, but disodium etidronate may be considered if these drugs are unsuitable or not tolerated.

Cautions

- Avoid food for at least 2 hours before and after oral treatment particularly calcium containing products e.g. milk. Also avoid iron and mineral supplements and antacid.
- Reduce dose in mild renal impairment

Contraindications

Moderate to severe renal impairment

Side effects

- Nausea, diarrhea, constipation, and abdominal pain.
- Transient hyperphosphatemia.
- Headache, parasthesia, peripheral neuropathy.
- Blood disorders including leucopenia, agranulocytosis, and pancytopenia.
- Rarely skin reaction including angiooedema, urticaria, and pruritis.

Market names and Prices

Didronel PMO tablets, disodium etidronate 400mg x1x 14 and calcium carbonate 1.25 g x1x76 days.

Alendronate

The cornerstone of the development of alendronate for osteoporosis was the Fracture Intervention Trial (FIT), a 3-year randomized, controlled trial investigating the effects of alendronate on the risk of fractures in 2027 women with prevalent vertebral fractures and in 4432 women with low femoral BMD but no prevalent fractures. The dose of alendronate (initially 5 mg daily) was increased to 10 mg daily at 24 months. In the fracture arm of the study, 8% of women in the alendronate group had 1 or more new morphometric vertebral fractures compared with 15% in the placebo group (RR = 0.53, 95% CI = 0.41-0.68). For clinically apparent vertebral fractures, the relative hazard was 0.45 (95% CI = 0.27-0.72). In this arm of the study, a significant reduction in the risk of any clinical fracture (RR = 0.72, 95% CI = 0.58-0.90), hip fracture (RR = 0.49, 95% CI = 0.23-0.99), and wrist fracture (RR 0.49, 95% CI 0.23-0.99) was also reported for alendronate users.

Esophageal erosion and ulcerative esophagitis were reported in association with the use of oral alendronate. However, particular recommendations for alendronate intake (swallowing alendronate with 180-240 ml water on arising in the morning, and remaining upright for at least 30 minutes after swallowing the tablet and until the first food of the day has been ingested) reduce the risk of esophagitis.

Cautions

- Upper gastro-intestinal disorders. (Dysphagia, symptomatic oesophagial disease, gastritis, duodenitis, ad ulcer).
- Renal impairment.
- Correct disturbances of calcium and mineral metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting.
- Exclude other causes of osteoporosis.

Contraindications

- Abnormalities of esophagus and other factors which delay emptying (e.g. stricture or achalasia).
- Hypocalcaemia.
- Pregnancy or breast-feeding.

Side effects

- Oesophagial reactions.
- Abdominal pain and distension.
- Diarrhea or constipation, Flatulence
- Musculoskeletal pain, headache; rarely rash, erythema, photosensitivity, uveitis, transient decrease in serum phosphate.
- Nausea, vomiting, peptic ulceration and hyper-sensitivity reactions (including urticaria and angioedema) also reported
- Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported.

Dose

- Treatment of postmenopausal osteoporosis, 70 mg once weekly
- Prevention of postmenopausal osteoporosis, 5 mg daily

Market names and prices

- ***Fosamax*** 10mg 1x1, (14 tabs, 82.5 L.E.).

- ***Fosamax*** 70mg once weekly, (2 tabs 95 L.E.).
- ***Alendene*** 5mg 1x1 (7 tab, 24 L.E.).
- ***Bonapex*** 5mg 1x1 (30 tab, 57 L.E.).
- ***Bonapex*** 10mg 1x1(30 tab, 84L.E.).
- ***Osteomax*** 5mg 1x1 (30 tab, 45L.E.).
- ***Alendomax*** 10mg 1x1 (14 tab, 39.20 L.E.)
- ***Alendomax*** 40 mg 1x1 (7 tab, 40 L.E.)
- ***Osteomepha***-10 1x1 (7 tab, 19.60 L.E.)
- ***Osteonate*** 1x1 (10 tab, 28 L.E.)
- ***Alendex*** 1x1 (10 tab, 24 L.E.)

Risedronate

In women with a mean lumbar spine T-score of </= -2, risedronate (5 mg/day) has been shown to increase BMD after 24 months, by 4% at the lumbar spine, 1.3% at the femoral neck, and 2.7% at the femoral trochanter. All these changes were significantly different from the evolution observed in the placebo group. The evidence for an antifracture efficacy of risedronate came from 3 randomized controlled clinical trials. In 2458 postmenopausal women who had at least 1 prevalent vertebral fracture, treatment with 5 mg/day of risedronate, compared with placebo, decreased the cumulative incidence of new vertebral fractures by 41% (RR = 0.59, 95% CI = 0.43-0.82) over 3 years.

In another study, 1226 postmenopausal women with 2 or more prevalent vertebral fractures were also exposed to the same protocol (risedronate 5 mg/day vs placebo) for 3 years. In this cohort, risedronate reduced the risk of new vertebral fractures by 49% (RR = 0.51, 95% CI = 0.36-0.73) after 3 years.

The risk for clinically important gastric irritation with risedronate was reported to be similar to that associated with alendronate and, in any case, very low even at the highest available doses. However, the prolonged use of risedronate in women with established osteoporosis has been linked with a statistically significant increase in the occurrence of pulmonary cancer (3.9/1000 patient-years of exposure and 1.9/1000 patient-years of exposure for 2.5 and 5 mg/day, respectively, compared with 1.2/1000 patient-years of exposure with placebo, based on the results of 10 phase 3 studies involving approximately 30000 patient-years of exposure).

Cautions

- Oesophageal abnormalities and other factors which delay transit or emptying (e.g. stricture or achalasia.
- Renal impairment (manufacturer advises avoid if creatinine clearance is less than 30mL/minute).

Contraindications

- Hypocalcaemia.
- Pregnancy and breast-feeding.

Side effects

- Gastro-intestinal effects (including dyspepsia, nausea, diarrhea, constipation, oesophageal stricture, and duodenitis).
- Headache.
- Musculoskeletal pain; rarely glossitis, oedema, weight loss, apnoea, bronchitis, sinusitis, rash, nocturia, amblyopia, cornea! Lesion, dry eye, tinnitus, iritis

Dose

Treatment and prevention of osteoporosis in post-menopausal women, 5 mg daily.

Market names and prices

- ***Actonel 5***mg 1x1, (14 tabs, 80 L.E.).
- ***Actonel*** 35 mg once weekly, (2 tabs 110 L.E.).

Tibolone

Tibolone combines estrogenic and progestogenic activity with weak androgenic activity. It is indicated for the treatment of vasomotor symptoms of the menopause and osteoporosis prophylaxis.

Cautions

- Renal impairment.
- History of liver disease.
- Epilepsy, migraine
- Diabetes mellitus, hyper-cholesterolaemia.
- Withdraw if signs of thromboembolic disease, abnormal liver function tests or cholestatic jaundice ز

Contraindications

- Hormone-dependent tumors.
- History of cardiovascular or cerebro-vascular disease (e.g. thrombophlebitis, thromboembolism), uninvestigated vaginal bleeding.
- Severe liver disease.
- Pregnancy, breast-feeding.

Side-effects

- Weight changes, oedema.
- Dizziness.
- Seborrhoeic dermatitis.
- Vaginal bleeding.
- Headache.
- Abdominal pain, gastro-intestinal distur-bances.

- Increased facial hair.
- Depression, arthralgia, myalgia, migraine, visual disturbances.
- Liver-function changes.
- Rash and pruritus are also reported.

Dose

- 2.5 mg daily
- ***Note:*** Unsuitable for use in the premenopause (unless being treated with gonadotrophin-releasing hormone analogue) and as (or with) an oral contraceptive; also unsuitable for use within 12 months of last menstrual period (may cause irregular bleeding); induce withdrawal bleed with progestogen if transferring from another form of HRT

Market names and prices

*Livial 2.5*mg 1x1, (28 tabs, 55 L.E.).

Calcitonin

Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homoeostasis. Calcitonin (salmon) (salcatonin, synthetic or recombinant salmon calcitonin) is used to lower the plasma-calcium concentration in some patients with hypercalcaemia (notably when associated with malignant disease). In the treatment of severe Paget's disease of bone it is used mainly for relief of pain but it is also effective in relieving some of the neurological complications, for example deaf-ness. Calcitonin can also be used in the prevention and treatment of postmenopausal osteoporosis in patients who do not.

Cautions

- History of allergy (skin test advised);
- Renal impairment.
- Heart failure.
- Children—use for short periods only and monitor bone growth.
- Pregnancy, breast-feeding.

Side effects

- Nausea, vomiting, diarrhea,
- Flushing, dizziness, tingling of hands, unpleasant taste.
- Rash, abdominal pain.
- Allergic reactions including anaphylaxis reported.
- Inflammatory reactions at injection site.
- Nasal spray may cause local irritation and ulceration, rhinitis, sinusitis, epistaxis

Dose

- By subcutaneous or intramuscular injection, 100 units daily with dietary calcium and vitamin D supplements
- Intranasal, 200 units (1 spray) into one nostril daily, with dietary calcium and vitamin D supplements.

Market names and prices

- ***Calcitonin `100***, (5 amp, 198.05 L.E.).
- ***Calcitonin `50***, (5 amp, 113.45 L.E.).
- ***Miacalcic `100***, (5 amp, 127.5 L.E.).
- ***Miacalcic `50***, (5 amp, 70 L.E.).
- ***Miacalcic `50 nasal spray***,.
- ***Miacalcic `100 nasal spray***.
- ***Miacalcic `200 nasal spray***. (150 L.E.).
- ***Cibacalcin 0.5***(1 amp, 39 L.E.)
- ***Cibacalcin 0.25***(1 amp, 19 L.E.)

Vitamin D

Vitamin D deficiency causes osteomalacia rather than osteoporosis but is used to increase calcium deposition in the bones of elderly malnourished patients.

The term Vitamin D is used for a range of compounds, which possess the property of preventing or curing rickets. They include ergocalciferol (calciferol, vitamin D2), colecalciferol (vitamin D3), dihydrotachysterol, alfacalcidol (lα-hydroxycholecalciferol), and calcitriol (1, 25 dihydroxycholecalciferol).

Simple vitamin D deficiency can be prevented by taking an oral supplement of only 10 rnicrograms (400 units) of ergocalciferol (calciferol, vitamin D2) daily. Vitamin D deficiency is not uncommon in Asians consuming unleavened bread and in the elderly living alone and can be prevented by taking an oral supplement of 20 micrograms (800 units) of ergocalciferol daily. Since there is no plain tablet of this strength available calcium and ergocalciferol tablets can be given (although the calcium is unnecessary).

The newer vitamin D derivatives, alfacalcidol and calcitriol, have a shorter duration of action, and therefore have the advantage that problems associated with hypercalcaemia due to excessive dosage are shorter lasting and easier to treat.

Vitamin D requires hydroxylation by the kidney to its active form therefore the hydroxylated derivatives alfacalcidol or calcitriol should be prescribed if patients with severe renal impairment require vitamin D therapy. Calcitriol is also licensed for the management of postmenopausal osteoporosis.

Important: All patients receiving pharmacological doses of vitamin D should have the plasma-calcium concentration checked at

intervals (initially weekly) and whenever nausea or vomiting is present.

Ergocalcfirol

Cautions

Monitor plasma calcium in patients receiving high doses and in renal impairment.

Contraindications

- Hypercalcaemia.
- Metastatic calcification.

Side effects

- Symptoms of overdose include anorexia, lassitude, nausea and vomiting, diarrhea, weight loss, polyuria, sweating, headache, thirst, vertigo.
- Raised calcium and phosphate level in plasma and urine.

Dose

See notes above.

Alfacalcidol (1α Hydroxycholecalciferol)

Cautions

See under Ergocalciferol.

Contraindications

See under Ergocalciferol.

Side effects

See under Ergocalciferol.

Dose

- By mouth or by intravenous injection over 30 seconds, adult and child over 20kg, initially
- 1 microgram daily (elderly 500 nanograms), adjusted to avoid hypercalcaemia; maintenance, usually 0.25-1 microgram daily.

Calcitriol (1.25-Dihydroxycholecalciferol)

Cautions

See under Ergocalciferol monitor.
Plasma calcium and creatinine during dosage titration

Side effects and Contraindications

See under Ergocalciferol.

Colecalciferol (Cholecalciferol, vitamin D3)

Indications

Alternative to ergocalciferol in calciferol tablets and injection.

Cautions

See under Ergocalciferol.

Contraindications

See under Ergocalciferol.

Side-effects

See under Ergocalciferol.

Dihydrotachysterol

Indications

Alternative to ergocalciferol in calciferol tablets and injection.

Cautions

See under Ergocalciferol.

Contraindications

See under Ergocalciferol.

Side-effects

See under Ergocalciferol.

Market names and prices

- ***One-alpha 0.25*** (30 tab, 24 L.E.).
- ***One-alpha 1*** (30 tab, 48 L.E.)
- ***One-alpha 1*** (drops 1x1, 186.50 L.E.).
- ***One-alpha 1*** (10 amp, 1x1 115 L.E.).
- ***Sterogyl 15 (H) 1*** (1 amp, 1x1 11 L.E.).
- ***Devarol*** (10 amp, 1x1, 7 L.E.).
- ***Devarol S*** (3 amp, weekly, 2 L.E.).
- ***Vitamin-D3 natural*** (drops, 4x2, 9 L.E.)
- ***Vi-De 3*** (drops, 4x2, 18 L.E.)
- ***Vidrop*** (drops, 4x2, 5 L.E.)
- ***Rocatrol*** (100 cap.).
- ***Rocatrol*** (100 cap).
- ***A.T.10*** (drops, 25 L.E.)

Calcium

Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy, and lactation, due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended daily amount (RDA) reduces the rate of bone loss. If the actual dietary intake is less than the RDA, a supplement of as much as 40 mmol is appropriate.

In hypocalcaemic tetany an initial intravenous injection of 10 ml (2.25 mmol) of calcium gluconate injection 10% should be followed by the continuous infusion of about 40 ml (9 mmol) daily, but plasma calcium should be monitored. This regimen can also be used immediately to temporarily reduce the toxic effects of hyperkalaemia.

Cautions

Renal impairment, sarcoidosis, interactions: Appendix 1 (calcium salts).

Contraindications

Conditions associated with hypercalcaemia and hypercalciuria (e.g. some forms of malignant disease).

Side effects

Mild gastro-intestinal disturbances; bradycardia, arrhythmias, and irritation after intravenous injection.

Dose

By mouth, daily in divided doses, see notes above.

By slow intravenous injection, acute hypocalcaemia, calcium gluconate 1-2 g (Ca2+2.25 - 4.5 mmol).

Market names and prices

- ***Ca leucovorin*** (1 vial, 1x1, 30 L.E.).
- ***Hi-cal*** (syrup, 1x1, 5 L.E.)
- ***Calci-Top*** (syrup, 1x1, 6.5 L.E.)
- ***Calcium Sandoz*** (syrup, 1x1, 4.65 L.E.)
- ***Calcium Sandoz*** (5 amp, 1x1 37.50 L.E.).
- ***Calcium Natural*** (syrup, 1x1, 7.00 L.E.)
- ***Bone Density*** (20 tab, 1x1, 19.50 L.E.).
- ***Os-Cal 500*** (30 tab, 1x1, 27.50 L.E.).
- ***Novo Calcium*** (30 tab, 1x1, 22.50 L.E.).
- ***Calcichew*** (20 tab, 1x1, 18.50 L.E.).
- ***Sandoz Ca- D3*** (12 tab, 1x1, 11.00 L.E.).
- ***Calcimate*** (120 cap, 1x1, 2.00 L.E.).
- ***Calci-D*** (20 tabs, 1x2, 14.00 L.E.).

Parathyroid Hormone

The role of PTH in the human is mainly to modulate the physiologic function of bone and kidney in order to restore mineral ion homeostasis. In vivo, the skeletal action of PTH is mainly to stimulate release of calcium from the bones by stimulating osteoclastic bone resorption.The activity of PTH on mature osteoclasts is mediated by the osteoblasts through direct cellular contact and/or local humoral mechanisms, and the hormone appears to increase the number of osteoclasts, by promoting the differentiation and/or fusion of the precursors. PTH also exerts a direct inhibitory effect on osteoblasts.

In fact, the effects of PTH on bone formation seem to be more difficult to fully elucidate than the well-known stimulating action on bone resorption.

The effect of PTH to prevent osteoporosis was evaluated in women with estrogen deficiency caused by treatment of endometriosis with gonadotropin-releasing hormone analogues. PTH(1-34) (40 mcg or 500 u/day) was given subcutaneously for 6 months to a group of women (n = 20) receiving nafarelin acetate. The effect on BMD was compared with that in a randomly assigned control group for which the only intervention was to maintain an approximate calcium intake of 1200 mg/day. Lumbar BMD was preserved in PTH-treated women when measured in the anteroposterior projection and significantly increased in the lateral projection, whereas these parameters both decreased significantly in the control group, whatever the type of projection used. BMD of the femoral neck decreased slightly and similarly in the 2 groups and radial BMD did not change in the 2 groups.

Strontium Ranelate (Sr)

Animals and humans consume varying amounts of Sr, depending on their source of food and water, leading to the presence of small physiologic amounts of Sr in soft tissues, blood, and bones.

On the basis of in vitro studies, Sr ranelate appears to have a particular profile characterized by an inhibition of bone resorption and a stimulation of bone formation.

Sr ranelate was administered to 160 postmenopausal women in a 24-month double-blind, placebo-controlled, prospective, randomized study. Daily oral doses of 125 mg, 500 mg, or 1 g of Sr ranelate were compared with placebo. All patients received 500 mg of elemental calcium daily. The main characteristics of the study population were as follows: age 54 years; duration of menopause 3 years, mean lumbar BMD (as measured by DXA) 0.931 g/cm^2.

At the conclusion of the study, the percent variation of lumbar-adjusted BMD from baseline was significantly different in the group receiving 1 g/day of Sr as compared with placebo: +1.41% vs -0.98%, respectively [95% CI = 0.010-4.776]. Increase in total hip and neck measured BMD averaged 3.2% and 2.5%, respectively.

Further reading

British National Formulary. The Royal Pharmaceutical Society of Great Britain, London. 2005.