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DRUG THERAPY OF OSTEOPOROSIS

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ABSTRACT

Osteoporosis is a highly prevalent condition characterized by decreases in bone mass and micro architectural alterations. Bone fractures, especially of the hip and vertebrae, are the most burdensome complications of osteoporosis. The gold standard imaging technique of diagnosing Osteoporosis is Digital X-ray Absorptiometry because it shows best predictive value for fracture risk. Lifestyle intervention for osteoporosis includes regular weight-bearing exercise and avoidance of unhealthy behavior, such as cigarette smoking and excess alcohol intake.The drugs used are either those inhibiting bone resorption and those stimulating bone formation and both. Numerous drugs are currently available to treat osteoporosis, such as Bisphosphonates, Strontium ranelate and others and the choice of a specific compound should be guided by efficacy and safety considerations.

KEYWORDS: **Osteoporosis, fractures, Digital X-ray absorptiometry, Bisphosphonates, Strontium ranelate.**

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INTRODUCTION

Osteoporosis is a highly prevalent condition characterized by decreases in bone mass and micro architectural alterations. According to the World Health Organization (WHO), osteoporosis is defined as a bone mineral density (BMD) at the hip and/or the spine at least 2.5 standard deviations below the mean peak bone mass of young healthy adults as determined by dual-energy X-ray absorptiometry (DXA)[1].Mortality associated with osteoporotic fractures ranges from 15 to 30%, a rate similar to breast cancer and stroke[2].Secondary osteoporosis may be the consequence of endocrine and metabolism disorders or certain drugs (e.g., corticosteroids, selective serotonin reuptake inhibitors, anticoagulants and antidiabetic medications)[2].Regardless of the etiology, in all cases of osteoporosis an imbalance exists between bone resorption and formation: the rate of bone formation is often normal, whereas resorption by osteoclasts is increased[3].

Bone density and bone strength

Osteoporosis is "a skeletal disease characterized by compromised bone strength predisposing a person to an increased risk of fracture[4]. Bone mineral density (BMD) correlates very well with fracture risk, with the relative risk of fracture approximately doubling (range 1.6–2.6) for every standard deviation decrease in BMD, depending on the skeletal site measured and the type of fracture[5]. Dual- energy X-ray absorptiometry (DXA) is the method used to diagnose osteoporosis according to criteria established by the World Health Organization[6] Classification of Bone Mineral Density (World Health Organization)[6].

Classification	T- score
Normal	-1.0 or greater
Osteopenia	Between -1.0 and -2.5
Osteoporosis	-2.5 or less
Severe Osteoporosis	-2.5 or less with a fragility fracture

Screening and diagnosis of osteoporosis

The presence of osteoporosis should be ascertained in all women aged ≥ 65 years[7]. Men ≥ 65 years or women aged ≤ 65 years should be screened for the presence of risk factors such as early menopause (≤ 45 years), anorexia, smoking habit or alcohol abuse, chronic use of certain drugs or diseases associated with an increased risk for osteoporosis[2]. DXA is presently considered the gold standard imaging technique for the diagnosis of osteoporosis because it shows the best predictive value for fracture risk[2]. Roughly, 0.5-2% of bone mass is lost every year, whilst anti-osteoporosis therapies allow gaining approximately 1-6% yearly. Since the least significant change of DXA is 2-4%, it is recommended to repeat it not earlier than 1-2 years from the beginning of treatment[2].

Therapeutic measures against osteoporosis

Non pharmacological treatment

Lifestyle intervention for osteoporosis includes regular weight-bearing exercise and avoidance of unhealthy behavior, such as cigarette smoking and excess alcohol intake.Many strategies are available to prevent osteoporosis and its complications, such as supplementation with calcium (500- 1,000 mg daily) and vitamin D, physical activity and multidisciplinary interventions to decrease the risk of falls.[7] The major actions of vitamin D in the context of bone homeostasis include the regulation of calcium metabolism by increasing intestinal absorption and renal reabsorption, and the stimulation of the synthesis of bone proteins such as osteocalcin by osteoblasts[8].

Dose

The daily vitamin D allowance ranges from 1,500 IU (healthy adults) to 2,300 IU (elderly with low calcium intake) .If vitamin D deficiency is detected, a cumulative dose of 300,000-1,000,000 IU over 1-4 weeks isrecommended, followed by a maintenance dose of 800-2.000 IU/day (or weekly/monthly equivalent)[9].

Indications for pharmacological therapy

National Osteoporosis Foundation[10]. Initiate therapy to reduce fracture risk in women with:

1. BMD T-scores below -2.0 by central DXA with no risk factors
2. BMD T-scores below -1.5 by central DXA with one or more risk factors
3. A prior vertebral or hip fracture

Classification of drugs for osteoporosis

Drugs inhibiting resorption[11].

- Bisphosphonates
- Donesumab
- Cinacalcet
- Calcitonin
- Estrogen
- SERMs (selective estrogen receptor modulators)
- Gallium Nitrate

Drugs stimulating formation

- Tripartite
- Calcium
- Calcitriol
- Fluoride

Drugs inhibiting resorption and stimulating bone formation
Strontium Ranelate

Bisphosphonates
First generation (least potent): Mordant, Clodronate, Etidronate
Second generation: Alendronate, Ibadronate,Pamidronate
Third generation: Risedronate, Zolendronate (most potent)

Mechanism of action
These agents were useful due to their inhibitory effect on osteoclast mediated bone resorption.These drugs accelerate apoptosis of osteoclasts and also suppress differentiation of osteoclast precursors to mature osteoclasts (by inhibiting IL-6).This results due to reduction in cholesterol synthesis via inhibition of frankly pyrophosphate synthase by bisphosphonates.

Adverse effects
Esophageal irritation which may lead to ulceration,Zoledronate is associated with Renal toxicity.
First generation bisphosphonates can cause osteomalacia. Osteonecrosis of the Jaw.
Musculoskeletal pain, usually reversible after discontinuation[12,13], ocular inflammation[14], urticaria[15],or mucositis[16] have rarely been reported after use of bisphosphonates.

Dose
Etidronate: 5-7.5mg/kg/day.
Alendronate: 5-10 mg daily or 35-70 mg weekly.
Pamidronate: Only by I.V infusion 60-90 mg over 2-4 hours weekly or monthly.
Risedronate: 35 mg /week orally in the morning with a full glass of water.
Zoledronate: 4 mg diluted in 100 ml saline/ glucose solution and infused I.V over 15 minutes.

Choice of bisphosphonates
Oral – alendronate or risedronate as the initial choice of oral bisphosphonate .Generic alendronateand risedronate are available in many countries, including the United States. Most patients prefer the convenience of the once-weekly regimen.For women with well-controlled gastroesophageal reflux or peptic ulcer disease, initial therapy with either risedronate or alendronate is also acceptable.For women with a history of GI side effects to alendronate (but without esophageal disorders), risedronate can be substituted, as some patients may have fewer GI side effects.
IV – For patients with contraindications or intolerance to oral bisphosphonates, we suggest IV zoledronic acid because it has been shown to prevent fractures in clinical trials. Generic zoledronic acid is available in the United States, United Kingdom, and other countries. Calcium sensing receptors are present on Parathyroid gland that regulate the secretion of PTH. Calcium activates these receptors and decreases PTHsecretion.Hypocalcemia will have the opposite effect that is increased PTH secretion.Cinacalcet is a calcimimetic drug which directly activates calcium sensing receptors on Parathyroid gland.It has been approved for treatment of secondary hyperparathyroidism.

Recombinant human PTH
Recombinant 1-34 fragment of human PTH − rhPTH(1-34)teriparatide − and recombinant human intact PTH − rh- PTH(1-84) − stimulate bone remodeling by inducing an increase in bone formation followed by a slower increase in bone resorption[17]. They strongly increase BMD in the trabecular compartment, whereas their effect appears lower than bisphosphonates in the cortical sites. In osteoporotic women with prevalent vertebral fractures, rh-PTH decreases the incidence of new vertebral fractures by 65% and non-vertebral fractures by 53%[17]. The combined treatment with recombinant PTH and bisphosphonates should not exceed 24 months[18]. Absolute contraindications to teriparatide include primary hyperparathyroidism, Paget's disease of bone, previous radiation therapy of the skeleton and primary or metastatic bone cancer[19].

Current scenario
rh- PTH decreases the incidence of new vertebral fractures by 65% and non-vertebral fractures by 53%[17]. The combined treatment with recombinant PTH and bisphosphonates should not exceed 24 months[18].Absolute contraindications to teriparatide include primary hyperparathyroidism, Paget's disease of bone, previous radiation therapy of the skeleton and primary or metastatic bone cancer[19].

Calcitonin
It inhibits resorption of bone and thus can be used for osteoporosis.It can be administered by nasal route for this indication.

SERMs
Raloxifine is a selective estrogen receptor modulator with estrogen agonistic action on bone and antagonistic action on breast and endometrium. It is the preferred drug for the prevention and treatment of postmenopausal Osteoporosis. Dose: 60-120mg daily

Adverse effects
Major side effect is thromboembolism.

Current scenario
Raloxifene at the dose of 60 to 120 mg daily increases BMD by 2 to 3% at the lumbar spine and femoral neck[20,21]. Based on data from the MORE study, raloxifene reduces the incidence of vertebral fractures by 40 to 50%, with no effect on non-vertebral fractures[22].Raloxifene also reduces the risk of estrogen receptor-positive breast cancer, whilst the impact on cardiovascular risk is controversial[23-26]. Bazedoxifene at the dose of 20 to 40 mg daily decreases bone turnover markers, while increasing BMD of the lumbar spine by 2% and preventing bone loss at the hip[27,28]. In postmenopausal osteoporotic women, bazedoxifene decreases the risk of vertebral fractures by 40% of non-vertebral fracture in high-risk patients[28].

Gallium nitrate

It inhibits bone resorption by depressing ATP-dependent proton pump at the ruffled membrane osteoclasts.It is useful in the management of Paget's disease and hypercalcaemia of malignancy but nephrotoxicity limits its use for this indication.

Dose: Continuous I.V infusion daily for 5 days.

Adverse effects: Nephrotoxicity which limits its use.

Current scenario

Gallium Nitrate is used only as a reserve drug due to its nephrotoxic effect.

Drugs stimulating bone formation

Teriparatide

It is recombinant PTH 1-34. PTH in low and pulsatile dose stimulates bone formation whereas in excess causes resorption of bones. Teriparatide is available for the treatment of Osteoporosis by intermittent subcutaneous administration. Teriparatide stimulates the production of new collagenous bone matrix that must be mineralized.When administered to patients with Osteoporosis in dose of 20 mcg per day subcutaneously for two years it dramatically improves bone density in most bones except distal radius. Teriparatide should be used with caution in patients taking corticosteroids and Thiazide diuretics along with oral calcium supplementation because hypercalcaemia may develop.

Adverse effects

Exacerbation of Nephrolithiasis and elevation of serum uric acid levels.

Current scenario

Teriparatide, human recombinant 1–34 parathyroid hormone, is approved for use in women and men at high risk for fracture. Despite its high cost and the inconvenience of daily subcutaneous injections for a 2-year course of therapy, it is animportant drug for treatment of osteoporosis.Recently it has been observed that combining Teriparatide and Alendronate provides no special benefit. However, giving a bisphosphonate after treatment with Teriparatide may help in preserving bone mass gained earlier. As far as prophylaxis and treatment of Osteoporosisis is concerned, both Calcium and Calcitriol may be used.

Drugs inhibiting resorption and stimulating bone formation

Strontium ranelate

It has a novel mechanism of action as it inhibits bone resorption as well as stimulates bone formation. Strontium is incorporated into hydroxyapatite , replacing calcium. Small increased risk of venous thrombosis, seizures and abnormal cognition have been seen and require further studies.

Adverse effects

The most common side effects of SR therapy are nausea and diarrhea which usually develop at the beginning of the treatment and generally disappear after 3 months of therapy.

Current scenario

It has been introduced as a reserve drug for elderly women more than 75 years of age who have already suffered osteoporotic fracture and are unable to tolerate bisphosphonates. SR increases bone formation markers, reduces bone resorption markers and increases BMD in a progressive and dose-dependentl manner[29,30]. In post- menopausal osteoporotic women during long term treatment (4 years), Strontium ranelate (SR)showed a decreased incidence of vertebral fractures by 33%[31].Incidence of nonvertebral fractures decreased by about 15% and in the oldest women by 31%[32,33].SR is contraindicated in patients with history of cardiovascular disease or uncontrolled hypertension.Patients should also be evaluated for cardiovascular risk before starting treatment with SR and at regular intervals during treatment. Odanacanib is a new drug which has emerged after research on osteoporosis treatment. It is a selective inhibitor of cathepsin K, which is an osteclast-derived protease which degrades bone collagen. This property makes odanacanib an alternative anti-resorptive drug[34].Odanacanib has provided rising BMD gains in osteoporotic women gettingalendronate treatment[34].Another compound, tert-butyl 4-[3-(1H-indole-2-carboxamidobenzoyl]piperazine-1-carboxylate (OA10), inhibits RANKL- mediated osteoclast formation and osteoclastic bone resorption in a dose-dependent manner[35].In the same way, C(25)H(32)N(4)O(4)S(2) (NecroX-7) inhibits osteoclast differentiation by suppressing nuclear factor κB activity. It also suppresses c- Fos expression[36].Sclerostin, is a negative regulator of bone formation and inhibition of which provides another way of treating Osteoporosis. Sclerostin promotes bone anabolism.

SUMMARY

Osteoporosis is a common disorder of low bone strength due to a combination of factors that include low BMD, high bone turnover, altered microarchitecture, geometry, damage accumulation, and mineralization, leading to increased risk of fractures. Bones are living growing tissues that are in a constant state of change with the old tissue being broken down(resorption) and new tissue formed in its place(formation). The fine balance between bone resorption and bone formation is maintained by osteoclast cells which continuously demineralize old tissue and osteoblast cells which continuously form new tissue for growth[37,38]. consequences of fragility fractures are serious-disability, loss of independence, chronic pain, and increased mortality.. BMD testing is the most important clinical tool for diagnosing high risk patients before the first fracture occurs, allowing for timely and appropriate medical intervention to strengthen bones and reduce the risk of fracture.

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