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Original article

Treatment strategies in osteoporosis - an analysis of practice guidelines

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Abstract. The goal of this paper is to present the sequential therapies used in the treatment of osteoporosis, according to the new practice guidelines.Various specialized e-platforms have been searched (PubMed, Scopus, Web of Science), as well as forums specializing in the treatment of osteoporosis, American Association of Clinical Endocrinologists (AACE/ACE), National Osteoporosis Foundation (NOF) ACR (American College of Rheumatology) and ISCD (International Society for Clinical Densitometry) and the new osteoporosis treatment guidelines have been analysed.The therapeutic agents used in the treatment of osteoporosis have antiresorptive action or osteoforming action. The studies performed until the present did not show the superiority of associating the two types of medication as compared to each of them considered separately. When bisphosphonates are contraindicated, there is intolerance or the obtained results are minimum, human, anti-RANKL (denosumab) monoclonal antibodies may be administered, which inactivate the osteoclasts and their development. The hormone replacement therapy, as well as the selective estrogen receptor modulators (raloxifene), has very limited indications due to the severe adverse reactions (thromboembolism, endometrium cancer, breast cancer, cardiovascular diseases). At present, numerous preparations having antiresorptive action or osteoforming action are being studied: sclerostin inhibitors (romosozumab), Cathepsin K inhibitors (odanacatib), integrin inhibitors (proteins involved in osteoclasts' adhesion), new parathormone derivates. The new administration methods of the existing preparations are equally possible future approaches of the osteoporosis treatment.

Key words: osteoporosis, monoclonal antibodies, fracture, sequential therapy

Introduction

Osteoporosis has been more frequently encountered over the last years due to the population's aging. The disease fragilizes the bones and exposes the people to an enhanced fracture risk. Osteoporosis has a slow development over several years and is most often asymptomatic and undiagnosed until a fragility fracture occurs.

Osteoporosis is a systemic skeletal disease, characterized by the decrease of bone mass and bone tissue micro architectural deterioration, resulting into an increased bone fragility (1). According to the World Health Organization (WHO), it is defined as bone mineral density (BMD) with 2.5 standard deviations below the maximum value (woman, 20 years, healthy) measured by DXA- *Dual energy x-ray absorptiometry (2)*. Osteoporosis represents a growing

health and economic issue in the United States and Europe. Many individuals, male and female, suffer from pain, disabilities and diminished quality of life as a result of this disease (3). A revised definition of osteoporosis includes the BMC associated with fracture risk risks. A fracture risk score, named FRAX (The fracture risk assessment), is calculated in order to assess the likelihood of fracture after 10 years. Basically, the osteoporosis diagnosis is established by the presence of the osteoporotic fracture regardless of BMC, or only by measuring the BMD at L1-L4 / NF (femoral collum) and total hip and or 1/3 distal non-dominant radius– *Dual energy x-ray absorptiometry (DXA)(4*,5,6,7,8,9*).*

The specialized fore in the treatment of osteoporosis, American Association of Clinical Endocrinologists (AACE/ACE), National Osteoporosis Foundation (NOF), ACR (American College of Rheumatology) and ISCD (International Society for Clinical Densitometry) established the BMD-DXA calculation indications (10,11,12,13).

Osteoporosis therapy

The recommendations of AACE/ACE, NOF for the pharmacologic therapy are to initiate the therapy in the patients with osteopenia and fracture history, OP, T-score ≤ - 2.5 at lumbar level, femoral collum, total hip or 1/3 distal radius in the absence of fracture, OP, age > 40 years with osteopenia and likelihood after 10 years > 30% for a major OP fracture or > 3% for the hip fracture according to FRAX (10,11,12,13).

NOF recommendations about the non-pharmacologic therapy of osteoporosis:

- ◦ Adequate intake of Calcium and vitamin D
  - • Calcium, 1200mg/day in women > 51 years and men > 71 years
    - decreases the bone mass loss and fracture risk
  - • Vitamin D 800 UI/day vs. 1000-2000 UI/day for adults > 50 years
    - Level of 25HO Vitamin D 20ng/ml vs 30ng/ml
- ◦ Regular physical exercise
  - • Aerobic, resistance exercises increase spine BMD
  - • Walking increases hip BMD
- ◦ Stop smoking
  - • Decrease of coffee and alcohol consumption

Treatment Initiation Criteria

1) Patients with osteoporosis–T-score lower than or equal to -2.5 DS, at spine or hip

2) Patients with fragility fracture (hip, vertebra, humerus, pelvis, forearm) and T-score lower than or equal to -2 DS

3) Patients with T-score lower than or equal to -2 DS under chronic cortisone therapy (over 5 mg prednisolone/day or equivalent corticosteroids for more than 3 months)

4) Patients with severe osteoporosis for some drugs. In order to prescribe PTH-derived peptides, a T-score lower than or equal to -2.5 DS is required in the spine or hip and at least one moderate-severe vertebral fragility fracture.

FDA (Food and Drug Administration), Metabolic and Endocrine Drugs Division published the Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis *(14,Table2).*

Table 1. Indications for the calculation of BMD-DXA

Purpose	Category	NOF	AACE	ACR	ISCD
diagnosis	♀ ≥ 65 years	Yes	Yes	Yes	Yes
	♀ + FR	Yes>50	Yes	Yes	Yes
	♂ + FR	Yes>50	No	Yes	Yes
	♂ ≥ 70 years	Yes	No	No	Yes
monitoring		Yes	Yes	Yes	Yes

Table 2. FDA-approved doses

Medicament	Postmenopausal OP	
	Prevention	Treatment
Alendronate	5 mg/day po 35 mg/week po	10 mg po 70 mg/week po
Ibandronate	2.5 mg/day po 150 mg/month po	2.5 mg/day po 150 mg/month po 3 mg/3 months iv
Risedronate	5 mg/day po 35 mg/week po 150 mg/month po	5 mg/day po 35 mg/week po 150 mg/month po
Zoledronic acid	5 mg iv after 2 years	5 mg iv annually
Denosumab	-	60 mg/6 months sc
Teriparatide	-	20 mg/day sc
Raloxifene	60 mg/day po	60 mg/day po
Calcitonin	-	20 u/day intranasal/100 u /2

Sequential therapy

In both sexes, *bisphosphonates* are antifracture agents within the **first intention therapy.** Denosumab, the newest antiresorptive agent, shows evidence of vertebral, non-vertebral and hip fracture risk reduction ***(recommendation A).*** In postmenopausal women, *Raloxifene* may also be used as first intention therapy. Alendronate, Risedronate, Ibandronate and Zoledronate have a proven effect in the reduction of vertebral fracture risk ***(recommendation A)*** and non-vertebral in postmenopausal osteoporosis (*recommendation A-B*). Raloxifene has a proven effect only on vertebral fractures ***(recommendation A)***. Alendronate, Risedronate and Zolendronate have indications in men's osteoporosis ***(recommendation A-C)***.

The parathyroid hormone and teriparatide are indicated in individual cases, non-responsive to the antiresorptive treatment and patients with increased fracture risk and in the treatment of cortisone osteoporosis (15,Table 3,Table 4).

Bisphosphonates are included in the first intention therapy of postmenopausal osteoporosis. They are the natural equivalent of pyrophosphate. The action mechanism consists in the increase of osteoclasts' apoptosis, thus reducing bone remodelling by > 70%,

Table 3. Sequential therapy

First therapeutic line	Second therapeutic line	Third therapeutic line
Diphosphonates		
Denosumab	Bisphosphonates	
Diphosphonates Denosumab	Teriparatide	Bisphosphonates Denosumab
Raloxifene	Bisphosphonates Denosumab Teriparatide	Bisphosphonates Denosumab
Teriparatide	Bisphosphonates Denosumab	

Table 4. Therapeutic recommendations (professional societies guidelines-NOF, AACE, ACE, ES, ACP)

1. Clinical history 2. Fracture risk	FIRST-LINE THERAPY • Alendronate, Risendronate (oral bisphosphonates) • Zoledronic acid (IV bisphosphonate) Denosumab (RANKL, monoclonal Ac; for those having fracture risk) • Teriparatides (PTH) ("first line" for those who cannot use oral therapy and high fracture risk)
3. Patient's history	ALTERNATE THERAPY IN POSTMENOPAUSAL OSTEOPOROSIS FOR THOSE NEEDING JUST SPINAL EFFICACY Ibandronate (oral and IV bisphosphonate) Raloxifene (SERM; especially in women with enhanced invasive breast cancer)
4. Therapeutic agent risk/benefit	OTHER THERAPIES Abaloparatides (PTHrP)(new recommendation, similar to teriparatides) Calcitonin (last therapy line for osteoporosis) Bazedoxifene/conjugated estrogen (DUAVEE for short-term prevention of postmenopausal osteoporosis) Estrogen (at present it is no longer indicated for the prevention or treatment of osteoporosis) Other SERMs have medical approvals in other geographical areas, but not in the United States as well

they reduce the bone loss rate, maintain or increase BMD. Bisphosphonates increased BMD within the spine and hip, reduce bone turnover markers and reduce fracture risk (Zolendronic acid > Risendronate > Ibandronate > Alendronate). They produce side effects represented by GI intolerance (po) and flu-like symptoms (iv), ON (osteonecrosis) of mandible and atypical fracture, hypocalcaemia, renal dysfunction. They are considered as first-line treatment of osteoporosis. Randomized trials proved the reduction of hip fracture risk with Alendronate and Risendronate (16,17). Moreover, Alendronate and Risendronate reduce the fracture risk in men (18,19) and the patients with osteoporosis induced by cortisone therapy (20,21). The optimum duration of bisphosphonates treatment has not been accurately established (22,23,Table 5).

Strontium ranelate is recommended in the case of postmenopausal osteoporosis, in the patients with fracture risk, but has contraindications for other therapeutic options. The action mechanism consists in the substitution of bone tissue calcium with divalent strontium ions. It also causes the uncoupling of resorption formation with the OB function stimulation, simultaneously with the OC inhibition (22). Teriparatide is a recombinant human parathyroid hormone with anabolic bone activity. Teriparatide was approved by the FDA and the European Medicines Agency as the first anabolic therapeutic agent for the postmenopausal women with severe osteoporosis. Subsequently, it received an additional approval for the treatment of osteoporosis in men and for the treatment of osteoporosis associated with the glucocorticoid therapy in men and women with fracture risk. It acts by reducing osteoblasts' apoptosis, reduces sclerostin, increases osteoblasts' activity, also achieving RANKL down regulation (24). Raloxifene is a selective estrogen receptors' modulator approved for the treatment of postmenopausal osteoporosis, which efficiently reduces the risk of vertebral fracture. (16,17) It is associated with an enhanced risk of thromboembolism and reduces the invasive breast cancer risk. (16) Bazedoxifene is a selective estrogen receptors' modulator recently approved for human use in the United States of America. Calcitonin is peptide hormone (32AA) secreted by the

Table 5. Bisphosphonates doses

Bisphosphonates	Prophylactic dose	Treatment	CrCI Recommendation
Alendronate	5 mg PO /day or 35 mg PO /week	10 mg PO / day or 70 mg PO / week	≥ 35 mL/min
Risendronate (IR)	5 mg PO / day or 35 mg PO / week	10 mg PO / day or 70 mg PO / week or 150 mg PO/month	≥ 30 mL/min
Zolendronic acid	5 mg IV / 2 years	5 mg IV annually	≥ 35 mL/min
Ibandronate	2.5 mg PO/ day or 150mg PO/month	2.5 mg PO/ day or 150mg PO/month or 3 mg IV at 3 months	≥ 30 mL/min
CrCl = creatinine clearance, IR = immediate release, IV = intravenous, PO = oral			

thyroid gland parafollicular cells as a response to hypercalcemia, which interacts with RGs and RGq on the osteoclast, inhibiting bone resorption. It was proven that it decreases the occurrence of vertebral compression fractures. (16,17) Calcitonin is not considered as a first-line treatment for osteoporosis because more effective drugs are available (16,25). The increases of cancer rates associated with the use of calcitonin have also been reported (26). Denosumab is a human IgG2 anti-RANKL monoclonal antibody, it inhibits osteoclast-mediated bone resorption, decreases the number of osteoclasts. It has been proven that Denosumab decreases the hip, vertebral and non-vertebral fracture risk compared with the low doses of Calcium and Vitamin D. It represents an optimum treatment option in the people who had no improvement further to bisphosphonates treatment. It also represents a therapeutic alternative to the patients with various stages of renal insufficiency. The treatment's effect is not maintained after it is stopped: it is continued with bisphosphonates (27). The administration of estrogens in the postmenopausal osteoporosis reduces bone turnover and decreases the hip, vertebral and non-vertebral fracture risk. Despite that, the estroprogestative treatment is exceptionally administered as antiresorptive medication. The estroprogestative therapy increased the occurrence of mammary cancer, ischemic cardiopathy, strokes and embolisms. Tibolone, a derived preparation (having estrogenic, progestative and androgenic action) might be used in the osteoporosis therapy. Its use was limited by the studies that proved the increase of strokes' occurrence (28,29,30).

Future Therapies (sclerostin, cathepsin K inhibitors)

Numerous preparations having antiresorptive or osteoforming potential are currently being studied. Sclerostin inhibitors (Romosozumab). Sclerostin inhibits bone formation and its inhibition increases bone mass. Romosozumab is an anti-sclerostin monoclonal antibody. Its administration increases DMO within the spine, femoral collum and total hip. It reduces the vertebral fracture risk. Cathepsin K inhibitors. Cathepsin K is a protease involved in the osteoclastic resorption. This enzyme's inhibitors (e.g. Odancatib) reduce bone resorption and increase BMD, reduce the risk of vertebral and non-vertebral fractures. The safety profile has not been established, there is data suggesting the increase of the risk of stroke. Integrin inhibitors (proteins involved in OC adhesion), new parathormone derivatives or new administration methods of the existing preparations are also possible future approaches of osteoporosis (31).

Conclusions

The sequential therapy in osteoporosis is supported by therapy guidelines and preferred to simultaneous therapy. If a patient still has a high-fracture risk after 3-5 years of therapy with bisphosphonate, the switchover to Denosumab might enhance BMD and reduce the fracture risk. If or when a treatment target has been reached with the Denosumab therapy, a bisphosphonate may be used after the interruption,

with re-assessment after two years. The continuation with bisphosphonate is justified in order to prevent bone mass loss and to hopefully maintain the protection against fractures. A bisphosphonate must be used when estrogen is interrupted, especially in the patients meeting the criteria for osteoporosis therapy, in order to prevent the return of BMD to the pre-treatment levels and, perhaps, the rapid loss of fracture protection. The switchover from teriparatide or abaloparatide to bisphosphonate or from teriparatide to denosumab is associated with progressive BMD increase. Instead, the switchover from bisphosphonates, and Denosumab in particular, to teriparatide, results into a transitory loss of cortical bone mass, the proximal femur included. Continuing with Bisphosphonates or denosumab for 6-12 months since starting Teriparatide seems a better option than the simple change of therapies. There should be no hesitation in using PTH-like drugs in the patients previously treated with bisphosphonates, especially when the vertebral fracture risk is high, despite the somewhat smaller anabolic responses and BMD that result when compared to the therapy start in native patients. Further to the therapy with an anti-modelling drug, Remosozumab improves the protection against fractures, rendering that sequential therapy a very attractive regime for the patients with severe osteoporosis or very high fracture risk.It is well known that Romosozumab is effective in the patients previously treated with an anti-modelling agent, but studies are required (32). The duration of the anti-osteoporotic treatment is unknown. Biphosphonates decrease the fracture risk after 5 years of oral administration or 3 years of intravenous administration. Teriparatides are recommended for 2 years. With Denosumab the therapeutic pause is not recommended. Teriparatide or Raloxifene may be used during the bisphosphonates therapeutic pause for those incurring a high risk.

Conflict of Interest

The authors declare that they have no competing interests.

Authors' Contributions

All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

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