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Research Article

Specificity of clinical trials of some osteoporosis medicines

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Abstract

Clinical trials of medicinal products related to the prevention and treatment of osteoporosis cover all activities, operations, methods and means for obtaining summary data and their interpretation in order to reveal the nature of the procedures, as well as certain relationships and dependencies of interest imposed the relevant study. The main objectives of the analysis are to characterize the relationships and dependencies, to measure the significance of these relationships, to model statistically significant relationships and dependencies. An important condition for conducting the statistical analysis is that the data are comparable, i.e. to be based on unambiguously defined features and criteria for their internal content.

Objective: This work covers a documentary analysis of conducted clinical trials of drugs for the treatment of osteoporosis, as well as an analysis of the conducted clinical trials of the drug.

Denosumab.

Methods: Gathering primary empirical information, allowing for: objectification of certain facts; for retrospective study of events and phenomena in a long period; allows to determine the direction of development of the process of clinical trials and processes. The applied statistical analysis covers activities, operations, methods and means for obtaining summary data and for their interpretation in order to reveal the nature of the procedures, as well as certain connections and dependencies.

Results: Studies show that clinical trials of osteoporosis products have the following limitations: gender differentiation – although the disease occurs in both sexes, studies in female patients are more common, patients are required to are in menopause, in some studies it is required as including criteria – the presence of a fracture due to osteoporosis, the age characteristic of patients is on average 45–80 years. All analyzed drugs show a positive effect on the state of bone density and bone structure.

Conclusion: All analyzed medicinal products show a positive effect on the state of bone density and bone structure but the process is irreversible, so early prevention associated with early diagnosis would lead to earlier treatment measures in the early stages of the disease, which in turn, it would lead to long-term savings in indirect and difficult-to-estimate costs for society as a whole.

Keywords

clinical trials, Denosumab, osteoporosis drugs

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PENSOFT

Introduction

Osteoporosis affects 200 million people and in 2000 was defined as the third most socially significant disease in the world (after cardiovascular and oncological diseases), and in 2020 it ranked second (Rachner et al. 2011). Due to it's widespread use worldwide, it is considered a serious risk factor for public health (Reginster and Burlet 2006). Bone resorption is a natural phenomenon and can occur due to old age (Mao and Kamakshi 2014). Osteoporosis affects men and women of all ages, more commonly postmenopausal women (Rosen 2005) and over 50 (Cummings and Melton 2002). Osteoporosis is more common in women than in men: 50% of women (Cummings-Vaughn and Grammack 2011) and 25% of men over the age of 50 have fractures (Seeman et al. 2006). The incidence of osteoporosis varies considerably between races and populations, with the incidence of femoral fractures increasing 2-fold and vertebral fractures 5-fold with age. The European and Mongoloid races are more likely to develop the disease than the African (Cummings-Vaughn and Grammack 2011). The imbalance between bone resorption and formation is due to the prolongation of the life cycle of osteoclasts and the shortening of the cycle of osteoblasts (Gallagher 2008). Bone remodeling in order to maintain optimal endurance consists of 4 cycles lasting several months. The drugs causing osteoporosis are: tranquilizers, hypoglycemics, chemotherapeutics (Mazziotti et al. 2010), excess thyroid hormones (Mao and Kamakshi 2014). Free radicals are responsible for inducing osteoblast apoptosis, inhibiting osteoblastogenesis, and activating osteoclast differentiation. The use of antioxidants has a beneficial effect on bone tissue (Mu et al. 2009). The goals of osteoporosis treatment are to reduce the incidence of new fractures and to address risk factors. Most pharmacological agents used in the prevention and treatment of osteoporosis reduce bone resorption or slow the overall rate of bone metabolism. For the prevention of spinal fractures are used bisphosphonates: Alendronate (Jaroma et al. 2015), Etidronate (Wells et al. 2008), Ibandronate, Rizedronate (Reid et al. 2009), Zoledronate (Maricic 2010), Calcitonin (Knopp et al. 2005), Denosumab (Cummings et al. 2009), parathyroid hormone (Cranney et al. 2006), Teriparatide (Langdahl et al. 2009), Strontium ranelate (Colette et al. 2010).

The aim of the present study is to characterize the specific characteristics of clinical trials in the treatment of osteoporosis.

Materials and methods

To fulfill the stated goal, a comparative analysis of conducted clinical trials of medicinal products for the treatment of osteoporosis and evaluation of the specific characteristics of these studies was performed, as well as a study of the specifics of clinical trials of a specific product of the example of Denosumab.

1. Methods

Documentary method

Procedure for gathering primary empirical information from documents, reflected primarily on other occasions, giving the opportunity to: objectify certain facts; for retrospective study of events and phenomena in a long period; allows to determine the direction of development of the process of clinical trials and processes.

Statistical analysis

It covers all activities, operations, methods and means for obtaining summary data and for their interpretation in order to reveal the nature of the procedures, as well as certain connections and dependencies, the interest in which has required the relevant research. The main objectives of the analysis are to characterize the relationships and dependencies, to measure the significance of these relationships, to model statistically significant relationships and dependencies. An important condition for conducting the statistical analysis is that the data are comparable, i.e. to be based on unambiguously defined features and criteria for their internal content.

2. Materials

a) 5 protocols from conducted clinical trials of products for the treatment of osteoporosis
b) 6 scientific articles describing conducted clinical trials to evaluate the quality, efficacy and safety of products for the treatment of osteoporosis.
c) 16 clinical trials of a specific product for the treatment of osteoporosis – the example of Denosumab.

Results and discussion

Documentary analysis of conducted clinical trials of drugs for the treatment of osteoporosis

For Alendronbate, Ibandronate, Risedronate and Zoledronate (Fig. 1) the data from different clinical trials were analysed.

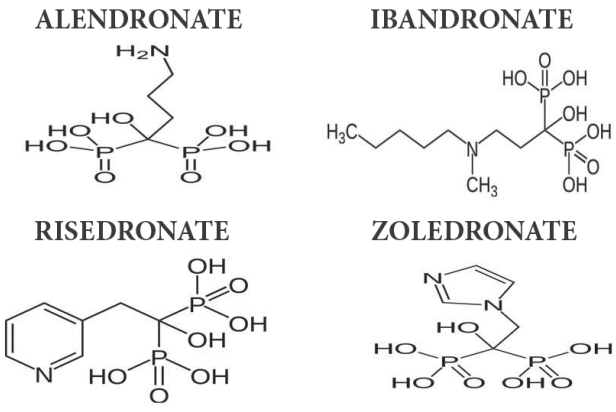

Figure 1. Chemical structures for Alendronbate, Ibandronate, Risedronate and Zoledronate.

Table 1. Clinical trials MOBILE and DIVA for Ibandronate for the treatment of osteoporosis.

	Type of studies: interventional (clinical trial); Distribution: randomized; Intervention model: Parallel assignment Masking: Double; Main goal: Treatment **MOBILE (ClinicalTrials.gov (2018) https://clinicaltrials.gov/ct2/show/NCT00048061)**
Design	Actual registration: 1609 participants Official title: Randomized, double-blind, double-blind, parallel groups, multicenter study comparing the efficacy and safety of monthly oral administration of 100 mg and 150 mg Ibandronate with 2.5 mg daily oral ibandronate in postmenopausal osteoporosis Study start date: April 2002; Actual primary completion date: December 2004 Actual date of completion of the study: December 2004 Inclusion criteria: women aged 55–80 years; postmenopause for > = 5 years
Results	A relative change in BMD is the percentage change from baseline BMD of L2 to L4 vertebrae that are not fractured and not affected by an osteoarthritis process to such an extent that accurate BMD measurement would be considered compromised by the central reading center after 24 months of treatment. It is calculated as the sum of the bone mineral content divided by the sum of the area of all lumbar vertebrae L2–L4 that are not broken and are not affected by osteoarthritis at 24 months. **DIVA (ClinicalTrials.gov (2016) https://clinicaltrials.gov/ct2/show/NCT00048074)**
Design	Actual registration: 1395 participants Official title: A randomized, double-blind study comparing the effect of different intravenous Boniva treatment regimens on lumbar bone mineral density in women with osteoporosis Study start date: June 2002; Actual primary completion date: May 2005 Actual date of completion of the study: May 2005 Eligible ages: 55 to 80 (adults, adults); Gender eligible for study: women
Results	Bone mineral density is measured by single X-ray absorptiometry with X-ray absorption (DXA) of the lumbar spine during screening and at month 12. The change in BMD is defined as the relative difference between the last individual measurement available at 12 months and baseline, using the following formula: Relative change = 100 × (1 year BMI - baseline BMI) / (baseline BMI).

Table 2. Clinical trial SPIMOS-3D for Ibandronate for the treatment of osteoporosis (ClinicalTrials.gov (2009) https://clinicaltrials.gov/ct2/show/NCT00271713 SPIMOS-3D).

Design: Type of study: interventional (clinical trial); Actual registration: 70 participants
Distribution: randomized; Intervention model: Parallel assignment; Masking: Quadruple (participant, caregiver, researcher, outcome evaluator); Main goal: Treatment
Official title: Randomized double-blind placebo-controlled and parallel group study to evaluate the effect of one-year monthly oral Ibandronate 150 mg therapy on bone structural properties in postmenopausal osteoporosis without vertebral fractures
Study start date: March 2006; Actual primary completion date: September 2007
Actual date of completion of the study: September 2007
Inclusion criteria: Age between 60 and 75 years; Menopause > 5 years
Spine (L1–L4) or thigh BMD ≤ -2.0 and > -3.5 SD T-score measured by DXA
3DpQCT is measurable at both skeletal sites, the distal tibia and the radius
Exclusion criteria: BMD of the spine or hip ≤ -3.5 SD T-score measured by DXA; Vertebral fractures; Multiple (> 2) low traumatic peripheral fractures; A disease / disorder known to affect bone metabolism; History of major upper gastrointestinal disease (GI); Diagnosed with malignancy in the previous 10 years; Previous bisphosphonate treatment at any time; Fluoride treatment for osteoporosis (dose greater than 10 mg/day) for the last 12 months or more than 2 years (total duration); Treatment with PTH and similar agents or strontium ranelate or with other drugs that affect bone metabolism in the last 6 months
Chronic systemic corticosteroid treatment; Estrogens, progestins, SERM, anabolic steroids, active analogues/metabolites of vitamin D, calcitonin; Calcineurin inhibitors (eg Cyclosporine, Tacrolimus) or Methotrexate
Total serum calcium < 2.2 mmol/l or > 2.6 mmol/l
Vitamin D deficiency (serum 25-hydroxy vitamin D < 12 ng/ml)
ALT above the triple upper limit of the normal range
Renal impairment (serum creatinine > 210 μmol/l)
Contraindications to ibandronate, calcium or vitamin D.
Results To investigate changes in structural bone properties in vivo using 3DpQCT („Xtreme“ CT, Scanco) in monthly oral Ibandronate therapy for women with postmenopausal osteoporosis. The main structural bone parameters that determine bone strength and predict the risk of fractures earlier and more accurately are measured in vivo by 3DpQCT. To evaluate the tolerability and safety of Ibandronate therapy.

The results from different clinical trials for the treatment of osteoporosis with Ibandronate, Alendronate, Risedronate and Zoledronate are presented in tables as follows:

1. clinical trials MOBILE and DIVA for Ibandronate (Table 1);
2. clinical trial SPIMOS-3D for Ibandronate (Table 2);
3. clinical trial VIBE for Ibandronate (Table 3);
4. clinical trial BONE for Ibandronate (Table 4);
5. clinical trials VERT-1 Multinational (VERT-MN) and VERT-2 VERT-North America (VERT-NA) for Risedronate (Table 5);
6. clinical trial HIP (Hip Intervention Program) for Risedronate (Table 6);
7. clinical trial HORIZON for Zoledronate (Table 7).

Table 3. Clinical trial VIBE for Ibandronate for the treatment of osteoporosis.

	VIBE (Harris et al. 2009)
Design	The Ibandronate Efficacy (VIBE) fracture study compared the incidence of fractures between patients treated with monthly Ibandronate and weekly oral bisphosphonates (BP). This large study included women ≥ 45 years of age, newly prescribed monthly oral Ibandronate or weekly oral alendronate or Risedronate, and no Paget malignancy or bone disease. The primary analysis included patients who adhered to treatment for the first 90 days after the index date. The risks of hip, invertebrate, spinal, and each clinical fracture were compared using Cox proportional hazard models and adjusted for potential confusing factors. Secondary „intent to treat" analysis included all patients who received at least one prescription for AN. Sensitivity analyzes based on the primary assay compared patients receiving Ibandronate with patients receiving weekly Alendronate or Risedronate alone and investigated the effect of excluding patients with potential confusing factors from the assay. Additional sensitivity analyzes change the retention requirement for the first 90 days after the index date. The population from the primary analysis included 7345 Ibandronate per month and 56,837 patients with BP. The incidence of fractures after the 12-month follow-up period was <2% and the risk of fractures did not differ significantly between patients receiving monthly Ibandronate or weekly BP for hip, nonvertebral, or any clinical fracture (corrected relative risk: thigh = 1.06, p = 0.84; = 0.88, p = 0.255; each clinical fracture = 0.82, p = 0.052). Patients with Ibandronate had a significantly lower risk of spinal fracture compared to weekly patients with BP (corrected relative risk 0.36, 95% confidence interval: 0.18–0.75, p = 0.006). In the secondary ‚intention to treat' analysis, the relative risks of fractures did not differ significantly between the treatment groups for each type of fracture. The results of the sensitivity analyzes usually correspond to the primary analysis.
Results	This retrospective cohort study found that patients treated with oral monthly ibandronate or weekly BP (Alendronate and Risedronate) had similar, low risks of hip fracture, nonvertebral fracture, and any clinical fracture. Patients with Ibandronate had a significantly lower relative risk of vertebral fractures than weekly patients with BP; the clinical implications of these findings require further investigation and validation.

Table 4. Clinical trials of Ibandronate and Alendronate for osteoporosis treatment.

	Ibandronate BONE (Delmas et al. 2004)
Design	In a multicenter double-blind fracture prevention study 2,946 postmenopausal women with osteoporosis were randomized to receive placebo or oral Ibandronate administered daily (2.5 mg/day) or periodically (20 mg/ daily for 12 doses every 3 months). The main endpoint is the incidence of new vertebral fractures after 3 years. Secondary baseline measures included changes in bone turnover rate assessed by biochemical markers and an increase in BMD of the spine and hip. Daily and periodic oral Ibandronate significantly reduced the risk of vertebral fractures by 62% and 50%, respectively, and resulted in a significant and sustained reduction in all measured biochemical markers of bone turnover.
Results	Within 3 months, the rate of bone turnover was reduced by approximately 50–60% and this level of suppression was maintained throughout the rest of the study. In summary, oral Ibandronate administered daily or with a dose interval of > 2 months normalizes the rate of bone turnover, provides a significant increase in BMD and a significant reduction in the incidence of vertebral fractures. Intermittent Ibandronate has the potential to become an important alternative to currently licensed bisphosphonates in postmenopausal osteoporosis.
Design	**Alendronate Fracture Intervention Trial (FIT) (Black et al. 2009)** The effect of Alendronate treatment for 3–4 years on the risk of a new fracture was studied among 3658 women with osteoporosis included in the fracture intervention study. This cohort includes women with pre-existing vertebral fractures and with osteoporosis, as defined by a T score less than -2.5 on the femoral neck but without a spinal fracture. All analyzes were specified in advance in the data analysis plan. The degree of reduction in the incidence of Alendronate fractures was similar in both groups.The two groups were pooled to obtain a more accurate assessment of the effect of Alendronate on the relative risk of fracture (95% confidence interval): thigh (0.47, 0.26–0.79), radiographic vertebrae (0.52, 0.42–0.66), clinical vertebral (0.55, 0.36–0.82) and all clinical fractures (0.70, 0.59–0.82). The reduction in the risk of clinical fractures was statistically significant up to 12 months after the study.
Results	The reduction in the risk of fractures during Alendronate risk is evident at the beginning of treatment and is consistent in women with pre-existing vertebral fractures and those without such fractures but with bone mineral density in osteoporosis.

Table 5. Clinical trials of Risedronate for the treatment of osteoporosis.

	Risedronate (Nelson et al. 2003)
Design	Patients had to have two or more predominantly radiographically confirmed vertebral fractures (T4–L4) or one vertebral fracture and low lumbar spine mineral density (L1–L4) [BMD; defined as ≤ 0.83 g/cm^2 (hological instrument) or ≤ 0.94 g / cm2 (lunar instrument)]. Limit values for low BMD of the lumbar spine represent a T-score of -2 (2 SD values below the mean for young adults). In both studies, patients had to be outpatients, no older than 85 years and at least 5 years postmenopausal. Women were excluded from the studies if they had conditions that could interfere with the assessment of spinal bone loss, or if they received drugs that are known to affect bone metabolism. Patients were randomized to receive Risedronate 5 mg/day, Risedronate 2.5 mg/day, or placebo (control). All patients received calcium 1000 mg/day; up to 500 IU/day vitamin D is provided if baseline serum 25-hydroxyvitamin D levels are below 40 nmol/l. Estimates of vertebral fractures Lateral thoracolumbar (T4–L4) radiographs were obtained at baseline and annually during each study and reported in the order in which they were taken. Preliminary (baseline) and incidental (new) vertebral fractures have been diagnosed quantitatively and semi-quantitatively. A new spinal fracture is quantified as a loss of 15% or more in the anterior, posterior or median vertebral height in a vertebra that is normal at baseline and semi-quantitatively as a change from grade 0 (normal) to grade 1), 2 (moderate) or 3 (severe). Discrepancies between quantitative and semi-quantitative methods were resolved by an independent radiologist. Radiologists remain blinded for treatment while performing all assessments of vertebral fractures.
Results	Risedronate 5 mg/day treatment significantly reduced the incidence of new vertebral fractures in subgroups of postmenopausal women at high risk of fractures. These reductions are consistent in the analyzed subgroups and similar to those for the general patient population. A significant reduction in the risk of fractures in response to treatment was evident in the first year, which is an important benefit in patients at high risk of fracture. These findings underscore the importance of early identification of patients at high risk of fracture, rapid intervention, and rapid treatment effect in this patient population.

Table 6. Clinical trial HIP for Risedronate the treatment of osteoporosis.

	Risedronate HIP (Hip Intervention Program) (McClung et al. 2001)
Design	We examined 5445 women aged 70 to 79 years who had osteoporosis (indicated by a T score for femoral neck bone mineral density that was more than 4 SD below the mean peak in young adults [-4] or lower than -3 plus a non-fatal risk factor for a hip fracture, such as poor gait or a tendency to fall) and 3,886 women at least 80 years of age who had at least one non-fatal risk factor for a hip fracture or low bone mineral femoral neck density (T score less than -4 or less than -3 plus thigh axis length 11.1 cm or greater). Women were randomized to receive oral Risedronate (2.5 or 5.0 mg/daily) or placebo for three years. The main endpoint is the appearance of a fracture of the hip joint.
Results	The incidence of hip fractures in all women given Risedronate was 2.8%, compared with 3.9% in those given placebo (relative risk, 0.7; 95% confidence interval, 0.6 to 0.9; P = 0.02). In the group of women with osteoporosis (those aged 70 to 79 years), the incidence of hip fractures among those prescribed risedronate was 1.9%, compared with 3.2% among those prescribed placebo (relative risk, 0.6; 95% confidence interval, 0.4 to 0.9; P = 0.009). In the group of women selected mainly on the basis of non-minor risk factors (those aged at least 80 years), the incidence of hip fractures was 4.2% among those prescribed Risedronate and 5.1% among those prescribed placebo (p = 0.35). Risedronate significantly reduces the risk of hip fracture in elderly women with confirmed osteoporosis, but not in elderly women selected primarily on the basis of risk factors other than low bone mineral density.

Table 7. Clinical trial HORIZON for Zoledronate for the treatment of osteoporosis. HORIZON (ClinicalTrials.gov (2011) https://clinicaltrials.gov/ct2/show/NCT00145327).

Design	Type of study: interventional (clinical trial) Actual registration: 2456 participants Distribution: randomized Intervention model: Parallel assignment Masking: Quadruple (participant, caregiver, researcher, outcome evaluator) Main goal: Treatment Official title: 3-year, double-blind extension of CZOL446H2301 to evaluate the long-term safety and efficacy of zoledronic acid in the treatment of osteoporosis in postmenopausal women receiving calcium and vitamin D Study start date: May 2005 Actual primary completion date: November 2009 Actual date of completion of the study: November 2009 Eligible ages for training: 68 years to 90 years (adults) Gender eligible for study: women Accepts healthy volunteers: No. Criteria Inclusion criteria: Patients who received 3 infusions in the HORIZON-Pivotal Fracture (PFT) study. Exclusion criteria: Poor health of the kidneys, eyes or liver Use of some therapies for osteoporosis in the HORIZON-PFT study (other than the study medicine) Abnormal blood calcium levels Other protocol on / off criteria may be applied.
Results	The results of the HORIZON study showed that Zoledronate, given once a year at a dose of 5 mg in an intravenous infusion, reduced the incidence of vertebral, nonvertebral and femoral fractures. Zoledronate is the only bisphosphonate used in a clinical trial after a new hip fracture – a reduction in the incidence of subsequent fractures has been demonstrated.

For Risedronate data were collected during two similar randomized, double-blind, placebo-controlled studies on the effect of Risedronate on spinal fracture, vertebral efficacy with risedronate therapy (VERT) (Nelson et al. 2003):

1. VERT-1 Multinational (VERT-MN);
2. VERT-2 VERT-North America (VERT-NA).

VERT-NA includes 2,458 postmenopausal women in 110 centers in North America.

VERT-MN includes 1226 postmenopausal women in 80 centers in Europe and Australia.

Analysis of conducted clinical trials of the drug Denosumab

In two placebo-controlled phase III clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 of 4,050) of patients had decreased serum calcium levels (less than 1.88 mmol/l) after administration of Prolia. No reduced serum calcium levels (less than 1.88 mmol/l) were reported in either the two placebo-controlled phase III clinical trials in patients with hormonal ablation and the placebo-controlled phase III clinical trial in men with osteoporosis. Rare cases of severe symptomatic hypocalcaemia have been reported with post-marketing use, mainly in patients at increased risk of hypocalcaemia receiving Prolia, most of whom occurred within the first weeks of treatment. In placebo-controlled phase III clinical trials, the overall incidence of skin infections was similar in the placebo and Denosumab groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 of 4,041] compared to Prolia [1.5%, 59 of 4,050]); in men with osteoporosis (placebo [0.8%, 1 in 120] versus Prolia [0%, 0 in 120]); in patients with breast or prostate cancer receiving hormonal ablation (placebo [1.7%, 14 of 845] versus Denosumab [1.4%, 12 of 860]). Skin infections leading to hospitalization were reported in 0.1% (3 of 4,041) of postmenopausal women with osteoporosis receiving placebo, compared with 0.4% (16 of 4,050) of women receiving

Prolia. These cases are mostly cellulite. In studies of breast and prostate cancer, skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 of 845) and Prolia (0.6%, 5 of 860) groups. Osteonecrosis of the jaw – VFD has been reported rarely in 16 patients in osteoporosis clinical trials and in patients with breast or prostate cancer receiving hormonal ablation, comprising a total of 23,148 patients. Thirteen of these cases of VFD occurred in postmenopausal women with osteoporosis during the extended phase III clinical trial after treatment with Prolia for 10 years. The incidence of VFD was 0.04% at year 3, 0.06% at year 5, and 0.44% at year 10 of Prolia treatment. The risk of VFD increases with the duration of Denosumab exposure. In a placebo-controlled phase III clinical trial in patients with prostate cancer receiving ADT, an imbalance was observed with respect to adverse events for diverticulitis (1.2% denosumab, 0% placebo). The incidence of diverticulitis is comparable between the two treatment groups in postmenopausal women or men with osteoporosis and in women treated with aromatase inhibitors for non-metastatic breast cancer. No Denosumab neutralizing antibodies were observed in clinical trials. Using a sensitive immunoassay, <1% of Denosumab-treated patients up to 5 years of age were positive for nonneutralizing binding antibodies, with no evidence of pharmacokinetic, toxicity or clinical response (European Medicines Agency (undated)).

The efficacy and safety of Denosumab administered every 6 months for a period of 3 years were studied in postmenopausal women (7,808 women aged 60 to 91 years, 23.6% of whom had a predominant vertebral fracture), with baseline Bone mineral density (BMD) Tscores of the lumbar spine or hip joint between -2.5 and -4.0 and an average absolute probability of fracture within 10 years of 18.60% (range: 7.9%–32.4%) for a large osteoporotic fracture and 7.22% (range: 1.4%–14.9%) for a hip fracture. Women with other diseases or who are on treatment that could affect the bones were excluded from this study. Women received daily supplements of calcium (at least 1,000 mg) and vitamin D (at least 400 IU). Denosumab showed a 40% relative reduction (0.5% reduction in absolute risk) of the risk of hip fracture over a period of 3 years ($p < 0.05$). The incidence of hip fractures was 1.2% in the placebo group, compared with 0.7% in the Prolia group at 3 years. In a follow-up analysis in women > 75 years of age, a 62% reduction in relative risk was observed with Denosumab (1.4% reduction in absolute risk, $p < 0.01$). The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by Denousmab for 3 years was steady, regardless of the initial risk of fractures within 10 years. A total of 4,550 women (2,343 on Denosumab and 2,207 on placebo) who missed no more than one dose of the test product in the main study described above and completed the study at the 36-month visit were included. in a 7-year, multinational, multicenter, open-label, extended-arm study to evaluate the longterm safety and efficacy of Denosumab. All women in the extended study were required to receive Prolia 60 mg every 6 months, as well as daily calcium (at least 1 g) and vitamin D (at least 400 IU). A total of 2,626 participants (58% of the women included in the extended study, ie 34% of the women included in the main study) completed the extended study (European Medicines Agency (undated)).

In patients treated with Denosumab for 10 years, BMD increased from baseline in the main study by 21.7% of the lumbar spine, 9.2% of the hip joint, 9.0% of the femoral neck, 13.0% of the trochanter of the femur and 2.8% of the distal 1/3 of the radius. The mean BMD T-score of the lumbar vertebrae at the end of the study was -1.3 in patients treated for 10 years. The incidence of fractures was assessed as a safety endpoint, but fracture prevention efficacy could not be calculated due to the high number of interruptions and the open design of the study. The cumulative incidence of new vertebral and nonvertebral fractures was approximately 6.8% and 13.1%, respectively, in patients treated with denosumab for 10 years (n = 1,278). Patients who did not complete the study for some reason had a higher incidence of fractures during treatment. Thirteen proven cases of osteonecrosis of the jaw (VLD) and two proven cases of atypical femoral fractures occurred during the extended study. The efficacy and safety of Denosumab Prolia administered once every 6 months for a period of 3 years were studied in men with histologically proven non-metastatic prostate cancer receiving ADT (1,468 men aged 48–97 years) who were at increased risk from fractures (defined as >70 years, or <70 years with BMD T-scores of the lumbar spine, hip or femoral neck <-1.0 or history of osteoporotic fracture). All men received a daily supplement of calcium (at least 1,000 mg) and vitamin D (at least 400 IU). Denosumab significantly increased BMD at all clinically measured sites compared to placebo over a 3-year period: by 7.9% in the lumbar spine, by 5.7% in the hip joint, by 4.9% in the femoral neck, by 6.9% of the trochanter of the femur, 6.9% of the distal 1/3 of the radius and 4.7% of the whole body (all $p < 0.0001$). In a prospectively planned exploratory analysis, a significant increase in BMD of the lumbar spine, hip joint, femoral neck and femur trochanter was observed 1 month after the initial dose (European Medicines Agency (undated)).

Denousmab showed a significant reduction in the relative risk of new vertebral fractures: 85% (1.6% reduction in absolute risk) for 1 year, 69% (2.2% reduction in absolute risk) for 2 years and 62% (2.4% reduction in absolute risk) for 3 years (all $p<0.01$). From the clinical trials described in this way, it is clear that there are clinical trials with Denosumab that have also been performed in men. Age differentiation falls within the age range observed in studies of osteoporosis, namely the wide range 31–97, and this range is observed mainly in the study of men. Again, all the studies analyzed were for the treatment of sick patients diagnosed with osteoporosis, and in women the obligatory inclusion criteria is the presence of osteoporosis. The average number of patients included in the study was 6416 patients, and in the studies on the male population the number was lower. The duration of clinical trials is on average 3 years, and longer-term observational studies of up to 10 years are observed (European Medicines Agency (undated)).

Conclusions

Studies have shown that in clinical trials of products for the treatment of osteoporosis, the following limitations are observed:

- Gender differentiation – although the disease occurs in both sexes, studies in female patients are more common.
- It is mandatory for patients to be menopausal.
- In some studies, it is required as a criterion – the presence of a fracture due to osteoporosis.
- The age characteristics of patients are on average 45–80 years, regardless of gender, which coincides with the manifestation of complications of the disease.

All of these limitations should make it difficult to recruit participants in clinical trials of drugs to treat osteoporosis.

All analyzed medicinal products show a positive effect on the condition of bone density and bone structure, but unfortunately the process is irreversible, so early prevention associated with early diagnosis would lead to earlier treatment measures in the early stages of the disease, which in turn would lead to long-term savings of indirect and difficult to estimate costs for society as a whole.

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