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REVIEW

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The next step after anti-osteoporotic drug discontinuation: an up-to-date review of sequential treatment

Núria Guañabens[1] · María Jesús Moro-Álvarez[2] · Enrique Casado[3] · Josep Blanch-Rubió[4] · Carlos Gómez-Alonso[5] · Guillermo Martínez Díaz-Guerra[6] · Javier del Pino-Montes[7] · Carmen Valero Díaz de Lamadrid[8] · Pilar Peris[1] · Manuel Muñoz-Torres[9,10] · SEIOMM Working Group

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Abstract

Several antiresorptive drugs, like bisphosphonates and denosumab, are currently available for the treatment of osteoporosis due to their evidenced efficacy in reducing fracture risk at mid-term. Osteoanabolic therapies, like teriparatide, whose treatment duration is limited to 2 years, have also shown efficacy in the reduction of fracture risk. However, depending on the severity of osteoporosis and the presence of other associated risk factors for fracture, some patients may require long-term treatment to preserve optimal bone strength and minimize bone fracture risk. Given the limited duration of some treatments, the fact that most of the antiresorptive drugs have not been assessed beyond 10 years, and the known long-term safety issues of these drugs, including atypical femoral fractures or osteonecrosis of the jaw, the long-term management of these patients may require an approach based on drug discontinuation and/or switching. In this regard, interest in sequential osteoporosis therapy, wherein drugs are initiated and discontinued over time, has grown in recent years, although the establishment of an optimal and individualized order of therapies remains controversial. This review reports the currently available clinical evidence on the discontinuation effects of different anti-osteoporotic drugs, as well as the clinical outcomes of the different sequential treatment regimens. The objective of this article is to present up-to-date practical knowledge on this area in order to provide guidance to the clinicians involved in the management of patients with osteoporosis.

Keywords Osteoporosis · Drug discontinuation · Sequential treatment · Parathyroid hormone · Bisphosphonates · Denosumab

✉ Núria Guañabens
nguanabens@ub.edu

[1] Metabolic Bone Diseases Unit, Department of Rheumatology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), University of Barcelona, Barcelona, Spain

[2] Bone Metabolism, Internal Medicine, University Hospital Infanta Leonor, Madrid, Spain

[3] Rheumatology Department, Parc Taulí University Hospital, Autonomous University of Barcelona, Sabadell, Spain

[4] Rheumatology Service, Hospital del Mar, Barcelona, Spain

[5] Bone and Mineral Metabolism Unit, Central University Hospital of Asturias (HUCA), University of Oviedo, Oviedo, Spain

[6] Endocrinology Service, University Hospital 12 de Octubre, Complutense University, Madrid, Spain

[7] University Hospital of Salamanca/University of Salamanca, Salamanca, Spain

[8] University Hospital Marqués de Valdecilla, Research Institute Marqués de Valdecilla (IDIVAL), University of Cantabria, Santander, Spain

[9] Endocrinology and Nutrition Unit, Hospital Universitario San Cecilio de Granada, Department of Medicine, University of Granada, Granada, Spain

[10] Instituto de Investigación Biosanitaria (Ibs.GRANADA), CIBERFES, Instituto de Salud Carlos III, Granada, Spain

Introduction

Osteoporosis is a chronic disease characterized by a loss of bone strength and a subsequent increase of fracture risk. Anti-fracture efficacy of anti-osteoporotic drugs is mainly related to a progressive increase in bone mineral density (BMD) and/or a bone microarchitecture improvement [1]. Depending on the osteoporosis severity or associated risk factors, a long-term treatment may be required to achieve or maintain an optimal bone strength.

Anti-osteoporotic drugs (anabolic agents and anti-resorptives) approved by the European Medicines Agency (EMA) are listed in Table 1. They vary by their mechanism of action, effects on remodeling, administration route, efficacy, safety, and adherence [2, 3]. Since some anti-osteoporotic drugs have a limited treatment duration (i.e., 2 years in the case of teriparatide) [4] and there is a concern about side effects related to long-term use (e.g., bisphosphonates or denosumab) [5], discontinuation and/or switching may be required in some patients. Thus, a sequential strategy, wherein drugs are initiated and discontinued over the course of treatment, appears to be necessary for treating patients with osteoporosis.

In this review, we report the current evidence regarding the effect of anti-osteoporotic drugs discontinuation, as well as the clinical outcome of different sequential treatment regimens.

Mechanisms of action of the available anti-osteoporotic drugs

Understanding the different mechanism of action of anti-osteoporotic drugs is crucial to settle an appropriate timing in the introduction or discontinuation of a determined drug in a specific patient, in order to achieve the greater therapeutic advantage [6, 7].

Antiresorptive drugs

Estrogen replacement therapy

Estrogens play a major role in regulating bone turnover. During puberty they control the completion of bone growth, whereas decreasing estrogen levels during menopause are associated with an imbalance between formation and resorption, causing loss of bone mass and an increased risk of fracture. Hence, estrogen reduction is the etiological link in postmenopausal osteoporosis [8]. Estrogens act by activating specific nuclear estrogen receptors (ERα and ERβ) distributed in different cells and tissues. ERα is the predominant estrogen receptor in bone, and its stimulation regulates osteoclastogenesis by inhibiting the receptor activator of nuclear factor-kappa B ligand (RANKL) production and upregulating osteoprotegerin synthesis [9].

Estrogen replacement therapy reduces bone remodeling, the risk of vertebral, nonvertebral, and hip fractures and increases BMD, offering the best risk-benefit profile when administered at the time of menopause transition or afterwards (e.g., 5–10 years since menopause) [10, 11]. However, its use is limited due to adverse events (breast cancer, endometrial cancer, deep vein thrombosis [DVT], and stroke) that are associated with estrogen's pleiotropic effects [12, 13].

Selective estrogen receptor modulators (SERMs)

Selective estrogen receptor modulators (SERMs) are a group of structurally diverse compounds that have differential agonist/antagonist activities on estrogen receptors [14]. The main goal of SERM therapy in osteoporosis is to obtain the beneficial effects of estrogens on bone and minimize their adverse effects on breast and endometrium. Raloxifene and bazedoxifene currently have an approved indication for the treatment of postmenopausal osteoporosis due to their proven effects in bone remodeling reduction, bone mass increase or maintenance, and vertebral fracture risk reduction. However, they have not been shown to reduce the risk of hip or nonvertebral fractures, or avoid the risk of DVT [15, 16]. Therefore, these drugs are suitably indicated for relatively young patients, whose fracture risk is mainly vertebral and DVT risk is minimal. As the patient ages and the risk of nonvertebral and hip fracture increases, it is convenient to substitute them for another drug, keeping in mind that discontinuation of SERM therapy is associated with increased remodeling, as well as early bone loss [17] and perhaps a non-demonstrated subsequent increase in fracture risk.

On the other hand, the combination of bazedoxifene and conjugated estrogens has demonstrated to maintain the positive effects on bone mass and bone remodeling while minimizing climacteric symptoms, showing an adequate safety profile regarding both gynecological aspects and cardiovascular risk factors [18–20].

Bisphosphonates

Bisphosphonates are inorganic pyrophosphate analogs that have evolved through different generations of drugs. Nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid) are the current first-line drugs for the treatment of patients with osteoporosis [21]. Several dosing options are currently available, including oral (alendronate 10 mg daily, 70 mg weekly [effervescent, in solution or tablets enriched with vitamin D]; risedronate 5 mg daily, 35 mg weekly or 75 mg

Table 1 Summary of approved drugs for osteoporosis by the European Medicines Agency

	Rationale	Cellular mechanisms of action	Effects on BMD/remodeling/histology	Effects on fractures	Limitations	Adverse/beneficial effects
Bisphosphonates Alendronate Risedronate Ibandronate Zoledronic acid	Chemical antiresorptive agents	Osteoclast inhibition (FPPS inhibition) ↓ Resorption	Increased BMD++↓ BTMs+++↓ Dynamic parameters and stability of the static parameters	↓ Vertebral Fx (all) ↓ Nonvertebral Fx ↓ Hip Fx (except ibandronate)	- Advanced chronic kidney failure (ClCr <30mL/min) - Bone accumulation - Gastrointestinal tolerance	Excess ↓ remodeling: - Osteonecrosis of the jaw - Atypical femoral Fx In oral, risk of esophagitis ↓ Risk of cancer of the colon/breast ↓ Mortality
SERMs Raloxifene Bazedoxifene	Selective etiological treatment of PM-OP (activation of ERα and inhibition of ERβ)	Osteoblast effects (↑ OPG; ↓ RANKL) Osteoclast effects (↓ osteoclastogenesis)	Increased BMD+↓ BTMs+↓ Dynamic parameters and preservation of static parameters	↓ Vertebral Fx	- Women only - Increase of climacteric signs and symptoms	↑ DVT/PE ↓ Risk of breast cancer ER+(↓ 70%)
PTH Teriparatide	Bone formation hormonal stimulation	Osteoblast effects (↑ osteoblastogenesis) (↓ apoptosis) Osteocyte effects (↓ sclerostin)	Increased (trabecular and cortical) BMD +++↑ Remodeling+++(1st F; 2nd R) Early cortical porosity Microarchitecture recovery, ↑ dynamic and static parameters ↑ Bone modeling	↓ Vertebral Fx ↓ Nonvertebral Fx	- Not in children or risk of sarcoma - Transient effect (limited to 2 years) - Caution if history of malignancy or bone radiation therapy	Hypercalcemia Urolithiasis Leg cramps Headache Accelerated bone loss when treatment is discontinued
Denosumab	Selective molecular biological therapy (Monoclonal Ab)	Osteoclast inhibition (RANKL inhibition)	Increased (trabecular and cortical) BMD +++↓ BTMs+++↓ Dynamic parameters and preservation of static parameters ↓ Cortical porosity	↓ Vertebral Fx ↓ Nonvertebral Fx ↓ Hip Fx	- "Rebound" effect if discontinuation	Hypocalcemia if CKF Excess ↓ remodeling: - Osteonecrosis of the jaw - Atypical femoral Fx Cellulitis

Note: Estrogens are currently not approved by the EMA for osteoporosis treatment. They are prescribed to treat the symptoms (such as hot flushes) in women who have been through the menopause

↓ reduction; ↑ increase; + degree of effect (+ mild, ++ moderate, +++ severe), *BTMs* bone turnover markers, *PM-OP* postmenopausal osteoporosis, *Fx* fracture, *CV* cardiovascular, *DVT/PE* deep vein thrombosis/pulmonary embolism, *CKF* chronic kidney failure, *ERα* estrogen receptor α, ERβ estrogen receptor β, *ER+* positive estrogen receptor, *ClCr* creatinine clearance, *BMD* bone mineral density, *PTH* parathyroid hormone, *SERMs* selective estrogen receptor modulators, *Ab* antibody, *OPG* osteoprotegerin, *FPPS* farnesyl pyrophosphate synthase, *F* formation, *R* resorption, *RANKL* receptor activator of nuclear factor-kappa B ligand

bimonthly; ibandronate 150 mg monthly) and intravenous presentations (ibandronate 3 mg quarterly; zoledronic acid 5 mg annually) [22].

Bisphosphonates reduce bone remodeling (mainly affecting resorption and coupled bone formation), increase bone mass (not reestablishing microarchitecture) and reduce the risk of fractures (all types [alendronate, risedronate, zoledronic acid] and vertebral [ibandronate]) (Table 1) [23–28].

The underlying molecular mechanism of bisphosphonates is based on their extraordinary affinity for hydroxyapatite, which favors their uptake by osteoclasts within the bone remodeling units. There, nitrogen-containing bisphosphonates inhibit the farnesyl pyrophosphate synthase enzyme (FPPS) (Table 1), which causes downstream instability of several osteoclast structural proteins and the induction of apoptosis [21]. The differential effects of bisphosphonates depend on their affinity for hydroxyapatite, which determines their diffusion and reuse, and the degree of FPPS inhibition [21]. Their ability to strongly bind to hydroxyapatite favors their long-term retention on the bone surface. This, together with their capacity to accumulate within bone tissue, implies a residual effect once their administration is discontinued. As a result, the remodeling increase and bone loss associated with treatment discontinuation is much lower than with other drugs [29]. However, long-term suppression of the remodeling process, together with other mechanisms, has been related to the development of atypical fractures due to tissue fatigue (Table 1) [30].

Therefore, bisphosphonates may be the only therapeutic group for which "drug holidays" may be considered *stricto sensu* [31].

Regarding the association of exposure to bisphosphonates (and other antiresorptive drugs such as denosumab) with osteonecrosis of the jaw, this process appears to be much less relevant in the treatment of osteoporosis (incidence 0.01–0.025%) than in the treatment of cancer (incidence 1–5%), and increases with treatment duration [32]). However, treatment discontinuation is frequent in patients with osteoporosis who will undergo dental interventions [33, 34].

Bisphosphonates are the most suitable treatment in patients previously treated with estrogens or SERMs, when their age-related adverse events or fracture risk increases or when the patient refuses to continue with hormonal treatment (see chapter 3.1) (Table 1). In addition, bisphosphonates may be indicated after anabolic agents and should be started after denosumab discontinuation [35].

Denosumab

Denosumab is a human monoclonal antibody that strongly inhibits osteoclastic activity by reversibly blocking RANKL [36]. Denosumab is evenly distributed throughout the skeleton, as its uptake by bone tissue does not depend on bone turnover [37] (Table 1). In several clinical trials, denosumab has shown a higher increase of BMD in all skeletal sites evaluated when compared to different bisphosphonates, as well as an additional increase of BMD when administered after discontinuation of bisphosphonates [7, 38–40]. However, unlike bisphosphonates, denosumab is associated with a substantial increase in bone turnover and loss of bone mass within a few months of discontinuation, as discussed in the "Different effects of drug discontinuation: Implications for treatment sequence" section below. Occasionally, this "rebound" phenomenon is related to the development of spontaneous fractures (mainly vertebral) [41, 42]. Although the cause for this effect is not clearly established, several hypotheses have been proposed, such as the possible existence of an increased "sleeping pool" of osteoclast precursors during the treatment period with denosumab that become activated after its discontinuation, and/or that the RANKL/OPG ratio ensues increased after the drug is cleared from the circulation, leading to a rapid rebound in the circulation [42]. Interestingly, a recent study that evaluated postmenopausal women who developed vertebral fractures after discontinuing denosumab, reported a significant decrease in the expression of microRNAs that negatively regulate osteoclast formation and activity. These findings were associated with increases in the mRNA of their target genes RANK (13-fold) and cathepsin K (2.6-fold) in serum, as well as in the markers of bone turnover. These results indicate an upregulation of osteoclastogenesis and osteoclast activity as a critical contributor to increasing vertebral fragility following the discontinuation of denosumab treatment [43].

Anabolic agents

Parathyroid hormone and protein related to parathyroid hormone

Anabolic drugs include the parathyroid hormone (PTH 1-34 [teriparatide] and PTH 1-84 [not currently available in the market for osteoporosis treatment]) and the protein related to PTH (PTHrP [abaloparatide]). The latter has been recently approved by the Food and Drug Administration (FDA) but has not received approval by the EMA. PTH and PTHrP inhibit sclerostin secretion by osteocytes, stimulate osteoblastogenesis and reduce osteoblast apoptosis upon PTH receptor binding [44] (Table 1). This effect is greater and earlier than the increase in RANKL secretion by osteoblasts, also caused by PTH, that involves activation of osteoclasts and bone resorption. This mechanism explains the net increase in trabecular bone mass associated with PTH treatment, in particular in the lumbar spine, with

improvement in microarchitecture parameters, and an increase in bone strength and cortical porosity. Despite this latter effect, treatment with teriparatide is associated with reduction of fracture risk in patients with severe osteoporosis [7, 44, 45]. However, this drug can only be used for upto 2 years, with fast loss of bone mass occurring after discontinuation. Hence, antiresorptive treatment must be administered after the discontinuation of teriparatide [6, 7, 45], as discussed in the following sections.

Romosozumab

The humanized monoclonal antibody romosozumab binds to and inhibits sclerostin, rapidly increasing bone formation and reducing bone resorption both in animals and humans. In phase 3 studies, romosozumab has shown marked increases in bone mass and reductions in the risk of fracture. Its effects are particularly rapid in the first 3 months, persisting upto 12 months, albeit more slowly [46]. The positive effects of romosozumab on the trabecular and cortical bone arise through several mechanisms mediated by the inhibition of sclerostin, an extracellular inhibitor of the Wnt signaling pathway that not only regulates the bone forming process but also bone resorption by up regulating RANKL synthesis [47, 48]. Thus, in the first few months of treatment, an increase is seen in cortical formation by modeling in the periosteum and endocortical surface. At 12 months, histomorphometry shows that bone turnover of trabecular bone is reduced [49]. While the use of romosozumab has recently been approved for treating high risk fracture patients in Japan, it remains to be approved by the FDA and EMA until the cardiovascular safety concerns raised by an increase in cardiovascular risk when compared to alendronate are ruled out [7, 50].

Effects of drug discontinuation: implications for treatment sequence

Effects of hormone replacement therapy discontinuation

Estrogen withdrawal is followed by rapid bone loss and the reduction in the risk of hip fracture induced by estrogen treatment dissipates over time [51, 52]. It has been demonstrated that alendronate prevents bone loss after withdrawal of hormone replacement therapy [53] and presumably, denosumab has similar effects, although those positive effects have not been proven until now. A recent analysis of the Women's Health Initiative trial found no evidence for increased fracture risk 5 years after discontinuation of hormone therapy, which calls into question the need for further treatment [54]. However, in patients at risk of fracture who stop estrogen therapy, it seems advisable to start treatment with another antiresorptive drug.

Effects of bisphosphonate discontinuation

Randomized studies with bisphosphonates lasting 3–5 years have shown their efficacy in reducing the risk of vertebral (40–70%), hip (20–50%) and nonvertebral (15–40%) fractures [37]. After treatment discontinuation, the sustained low levels of bone turnover markers (BTMs) may be an indicator of bisphosphonate-associated residual effects on BMD, which may persist for 1–3 years, depending on the bisphosphonate used [29].

The efficacy and safety of longer treatment courses with bisphosphonate is a matter of debate. Patients with postmenopausal osteoporosis treated with alendronate for 4 to 5 years in the Fracture Intervention Trial (FIT) were randomized to continue with alendronate or placebo for 5 years (Fracture Intervention Trial Long-term Extension [FLEX] study) [55]. After completing the extension period, patients treated with alendronate had less BMD loss at all sites and fewer clinical vertebral fractures (RR = 0.45, 95% CI: 0.24–0.85) vs. those in the placebo group. However, there were no significant differences in morphometric vertebral fractures or nonvertebral fractures [55]. In the extension study of the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON) study, patients treated with zoledronic acid for 3 years were randomized to continue with zoledronic acid or placebo for another 3 years [56]. Patients in the zoledronic acid group had lower BMD loss and fewer morphometric vertebral fractures (RR = 0.51, 95% CI: 0.26–0.95; $p = 0.035$), but there were no differences between groups in nonvertebral or hip fractures. In contrast, a recent observational study showed that an oral bisphosphonate "drug holidays" greater than 2 years is associated with a significant increased risk of hip fractures [57].

Long-term studies have shown that 10 years of treatment with alendronate or 6 years with zoledronic acid prevent BMD loss and reduce the risk of vertebral fractures vs. treatment for 5 and 3 years, respectively [55, 56]. Patients obtaining a greater benefit from long-term treatment are those at high risk [55, 56]. The concept of a high-risk patient in this situation has not been fully defined, but appears to include patients with hip or femoral neck T-scores lower than −2.0 or −2.5 (at discontinuation), or those with prevalent vertebral fractures and/or incident fractures during the pivotal studies. The risk-benefit ratio of bisphosphonates treatment beyond 10 years has not been adequately investigated and there is no scientific evidence for this issue. A recent fragility fracture in a long-term treated patient with a bisphosphonate could indicate

therapeutic failure, and another pharmacologic agent such as teriparatide or denosumab should be considered.

Effects of denosumab discontinuation

Unlike bisphosphonates, the effects of denosumab are rapidly reversible and its discontinuation has been associated with a reduction in the obtained BMD gain. In 2011, Bone et al. found that the BMD increase after two years of treatment with denosumab was rapidly lost upon drug discontinuation, and that after approximately one year, the values had returned to baseline in the lumbar spine and femur. BMD reduction was associated with a marked, fast increase in BTMs. Thus, after discontinuation, the values of C-telopeptide-cross-linked Type I collagen (sCTX) increased at 3 months (9 months after the last dose) and reached their maximum value at 6 months, returning to baseline values at 2 years. The values of procollagen type I N-terminal propeptide (PINP) followed a similar evolution of later onset, at 6 months [58]. This bone turnover rebound raised the possibility of an imminent increase in fracture risk associated with impairment in bone microarchitecture. Initial analysis of a group of patients discontinuing the treatment during the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial did not show an excess fracture risk. However, the post-treatment period was very short (median 0.8 years per patient) [59]. In this regard, several clinical cases of multiple vertebral fractures after discontinuing denosumab have been reported, most between 8 and 16 months after the last dose of the drug [60–62], which led to a positioning article of the European Calcified Tissue Society (ECTS) [42]. Here, authors suggest that a re-evaluation should be performed after 5 years of denosumab treatment. Patients with high fracture risk should either continue denosumab treatment for upto 10 years or be switched to an alternative treatment, especially bisphosphonates. If the risk is low, denosumab may be discontinued after 5 years, but, again, bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.

The results of the *post-hoc* analysis of the FREEDOM study and its extension have been recently published, analyzing the effects of discontinuing denosumab in a large group of patients [63]. The vertebral fracture rate was reduced during ongoing denosumab treatment when compared with placebo. However, after denosumab discontinuation, the overall vertebral fracture rate increased and was similar to that observed in the placebo group (Fig. 1a). In addition, the rate of multiple vertebral fractures was slightly higher after denosumab discontinuation in contrast to placebo (4.2 [2.8–5.7] vs. 3.2 [1.4–5.1] per 100 participant-years) (Fig. 1b). Furthermore, in women who had at least one vertebral fracture after discontinuing denosumab, the incidence of multiple vertebral fractures was 60.7% and 23% had >4 vertebral fractures. In the group with vertebral fractures after discontinuing placebo, 38.7% developed multiple vertebral fractures and only 6.4% had >4 fractures. The new nonvertebral fracture rate was similar in both groups. Prior vertebral fracture was the main risk factor for developing multiple vertebral fractures after discontinuing treatment (OR 3.9; CI 2.1–7.2) [63]. Recently, it has been suggested that women under 65 years have a higher number of spontaneous vertebral fractures and in a shorter period than women over 65 years [64].

Some studies have suggested that previous treatment with bisphosphonates could prevent the transient increase in the resorption marker sCTX [65] and the development of fractures after denosumab discontinuation. However, the

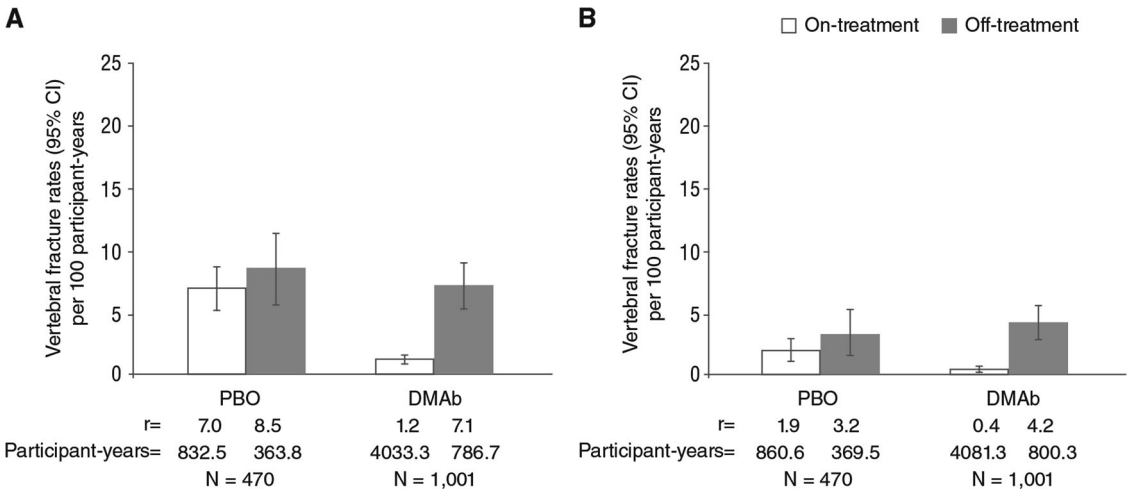

Fig. 1 Vertebral fracture rates (**a**, any; **b**, multiple fractures) in participants treated with placebo or denosumab (FREEDOM study) and denosumab (Extension). White bar: before treatment discontinuation; gray bar: after treatment discontinuation. Source: Cummings et al. [63]. DMAb denosumab, PBO placebo, r rate per 100 participant-years

protective effect of bisphosphonates has not been confirmed in all studies [63, 66]. There has also been speculation about whether treatment duration could modify the risk, since patients treated for less than 2 years with denosumab could have a lower risk [41]. Although this has not been confirmed, no case of multiple vertebral fractures has been described in patients after a single dose of denosumab.

The effects of denosumab discontinuation have also been explored in women with early hormone receptor positive (HR+) breast cancer receiving aromatase inhibitors (AI) in a prospective, double-blind, placebo-controlled trial including 3,425 postmenopausal women treated with denosumab 60 mg subcutaneous every 6 months or placebo [67]. Denosumab discontinuation was associated with a higher risk of clinical vertebral fractures (HR 2.44 [1.12,5.32]) and multiple clinical vertebral fractures (HR 3.52 [0.98,12.64]) after a median off-treatment follow-up of 36 months. This increased risk of rebound-associated fractures was not observed in patients who ended AI treatment within 6 months after stopping denosumab. Therefore, in women with HR + breast cancer who discontinue denosumab, it would be advisable to stop AI therapy within 6 months since the last dose of denosumab.

The optimum treatment after discontinuation of denosumab is not well known. It has been suggested that a potent antiresorptive drug could prevent the adverse consequences associated with its discontinuation. Preliminary results may indicate that a single dose of 5 mg of zoledronic acid, 6 months after the last dose of denosumab, provides only partial protection against BMD loss when bone turnover is still suppressed [68]. In a recent editorial article, Chapurlat proposed a 9-month period between the last dose of denosumab and zoledronic acid administration to allow for bone turnover reactivation and increased drug uptake [69]. In the DAPS study, postmenopausal women who transitioned from denosumab (only treated for 1 year) to alendronate remained stable after one year of treatment [70]. Thus, the administration of zoledronic acid with more than one dose or when BTMs are into the normal range, or alendronate for 1 or more years may be the optimum sequence. However, the most effective treatment should be explored [68]. In order to clarify the uncertainty regarding denosumab discontinuation, randomized clinical trials are currently underway to evaluate the effect of different zoledronic acid regimens [71, 72].

Effects of teriparatide and other anabolic agent discontinuation

In the Parathyroid Hormone and Alendronate (PaTH) randomized trial, treatment with 100 µg/d of PTH 1-84 for 12 months was followed by a second year of placebo or alendronate. During year 2, women receiving placebo significantly lost areal BMD at the spine as evaluated by dual energy X-ray absorptiometry (DXA; −1.7%), as well as trabecular BMD as measured by quantitative computerized tomography (QCT; −10%) [73]. In another study, treatment with teriparatide for a median of 21 months was associated with a significant BMD increase at different sites and a reduction of vertebral (65%) and all nonvertebral fracture risk when compared to placebo (53%) [74], but its discontinuation involved a reduction of BMD in the lumbar spine and proximal femur during the following 12 months, which was more marked in postmenopausal women (7.1%) than in men (4.1%) [35]. Although the anti-fracture effect is likely to disappear, an observational study reported some residual effect on vertebral fractures during the first 18 months of follow-up [75]. In this regard, it is important to remark that several studies in which PTH was administered in a sequential schedule followed by different antiresorptive agents have shown that the initial BMD gain can be sustained or increased (discussed in the section below) [45, 73, 76–78].

Regarding the new anabolic agents abaloparatide and romosozumab, recent studies have shown that their effects are reversible and that the greatest benefits are obtained using sequential treatment with antiresorptive agents [79, 80]. However, due to the novelty of these agents, published data on the effects of their discontinuation is limited at the time of this writing.

Different treatment sequences of anabolic and antiresorptive agents

Anabolics followed by antiresorptive agents

As mentioned above, progressive loss of BMD occurs after discontinuing treatment with PTH [35]. However, the subsequent administration of an antiresorptive agent can prevent this effect, as shown in the following studies of different treatment sequences:

Teriparatide followed by raloxifene

The European Study of Forsteo (EUROFORS) was the first randomized clinical trial comparing three different sequential treatment approaches (anabolic [teriparatide], antiresorptive [raloxifene], or no active treatment [calcium and vitamin D]) after 1 year of treatment with teriparatide in severe postmenopausal osteoporosis [81]. Sequential treatment with raloxifene after 1 year of teriparatide maintained the gain obtained in lumbar BMD and caused a significant additional increase in the hip BMD (femoral neck and total hip). In contrast, a partial loss (−2.5%) in the lumbar BMD was seen in the second year in the group receiving only

calcium and vitamin D. The group receiving teriparatide for 2 years had a progressive lumbar and femoral BMD increase [81].

A similar clinical trial performed in 380 patients with postmenopausal osteoporosis reported that sequential treatment with raloxifene started immediately after 1 year of teriparatide prevents rapid spine BMD loss and causes a BMD increase in the femoral neck, even higher than that seen during treatment with teriparatide. This positive effect of raloxifene persisted for one year after teriparatide discontinuation [76].

PTH 1-84 followed by bisphosphonates

In the PaTH trial, a 12% increase in lumbar spine BMD was observed by DXA in patients receiving PTH 1-84 for one year followed by alendronate for another year, in contrast to the placebo group (4%). Hip and femoral neck BMD changes were more pronounced in the alendronate (4% for both hip and femoral neck BMD) vs. the placebo group (0% and 1%, respectively). Furthermore, measurements of volumetric trabecular BMD showed an increase over 24 months, which was significantly higher in alendronate than in placebo treated patients (31% vs. 14%, for lumbar spine BMD; 13% vs. 4%, for hip BMD). Regarding the bone formation (PINP) and bone resorption (sCTX) BTMs, the increases seen during 12 months of treatment with PTH were followed by a significant reduction at 24 months. In the placebo group, BTMs returned to baseline levels, while in the case of PTH followed by alendronate, PINP and sCTX levels decreased below baseline levels. Taken together, the results of the PaTH study confirmed that spine and hip BMD gains are higher if treatment with PTH in monotherapy is followed by alendronate. Therefore, if treatment with PTH is not followed by an antiresorptive agent, most of the BMD gain is lost [73].

Teriparatide followed by denosumab

In the open-label DATA-Switch study, an extension of the Denosumab And Teriparatide Administration Study (DATA) [82], 27 women with postmenopausal osteoporosis, who were originally randomized to treatment with teriparatide for 24 months, were switched to 2 years of denosumab. During treatment with denosumab, a continued BMD increase was observed: + 8.6% in lumbar spine, +5.6% in femoral neck, +4.7% in total hip, and +2.3% in distal radius [77] (Fig. 2). Overall, transition from teriparatide to denosumab resulted in a marked increase in the lumbar and hip BMD, upto 18.3% and 6.6%, respectively (total 4-year increase), with greater gains than those obtained with the transition from denosumab to teriparatide, particularly at the hip (described in the next section) [77]. In addition, switching from teriparatide to denosumab was associated with an increase in the lumbar Trabecular Bone Score (TBS) of +5.1% at 48 months [83]. TBS is obtained from a commercially available software that uses data derived from lumbar spine DXA images to generate a gray-level textural index. TBS has been associated with vertebral, hip, and major osteoporotic fracture risk in postmenopausal women and can be used in the FRAX algorithm to estimate the probability of fracture risk [84].

Despite its reduced sample size and open-label nature, the DATA-Switch study is relevant as it suggests that the sequence of teriparatide and denosumab administration is appropriate to increase bone mass. However, no conclusions can be drawn regarding the efficacy of this approach in fracture risk. In fact, there are no randomized studies that have analyzed the impact on fracture rates of antiresorptive agents after teriparatide. Open-label follow-up studies after the Fracture Prevention Trial (FPT) have shown that the risk reduction persists for vertebral [75] and nonvertebral fractures in women with osteoporosis initially randomized to teriparatide [85]. In this setting, after discontinuation of teriparatide, approximately 60% of patients received medications for osteoporosis, mainly bisphosphonates [85]. Similar results were seen in the observational, prospective European Forsteo Observational Study (EFOS), including 1576 women with severe osteoporosis treated with teriparatide for 18 months and followed for a total of 36 months. 63% of patients received bisphosphonates in the post-teriparatide period and the vertebral and nonvertebral fracture rate remained significantly lower compared to the baseline period of 0–6 months [86].

Antiresorptives followed by anabolic agents

Few studies have analyzed the value of this sequential therapy, for which it has been suggested that the anabolic response to teriparatide could depend on the type of antiresorptive agent previously used [87, 88]. The randomized, prospective study EUROFORS analyzed the value of teriparatide after different antiresorptive treatment regimens (alendronate, risedronate, etidronate and non- bisphosphonates) in 245 postmenopausal women with osteoporosis. All groups showed an increase in lumbar spine BMD at 6, 12, 18, and 24 months of treatment with teriparatide. However, in the alendronate group there was a slight reduction in total hip (−1.2%) and femoral neck BMD (−2%) [89] at 6 months, with subsequent recovery of values at 24 months. Ettinger et al. performed a prospective, non-randomized study in 59 postmenopausal women to establish the effect of teriparatide after 18–36 months of treatment with alendronate or raloxifene [90]. These authors found a slight hip BMD reduction at 6 months of treatment with teriparatide in those previously treated with

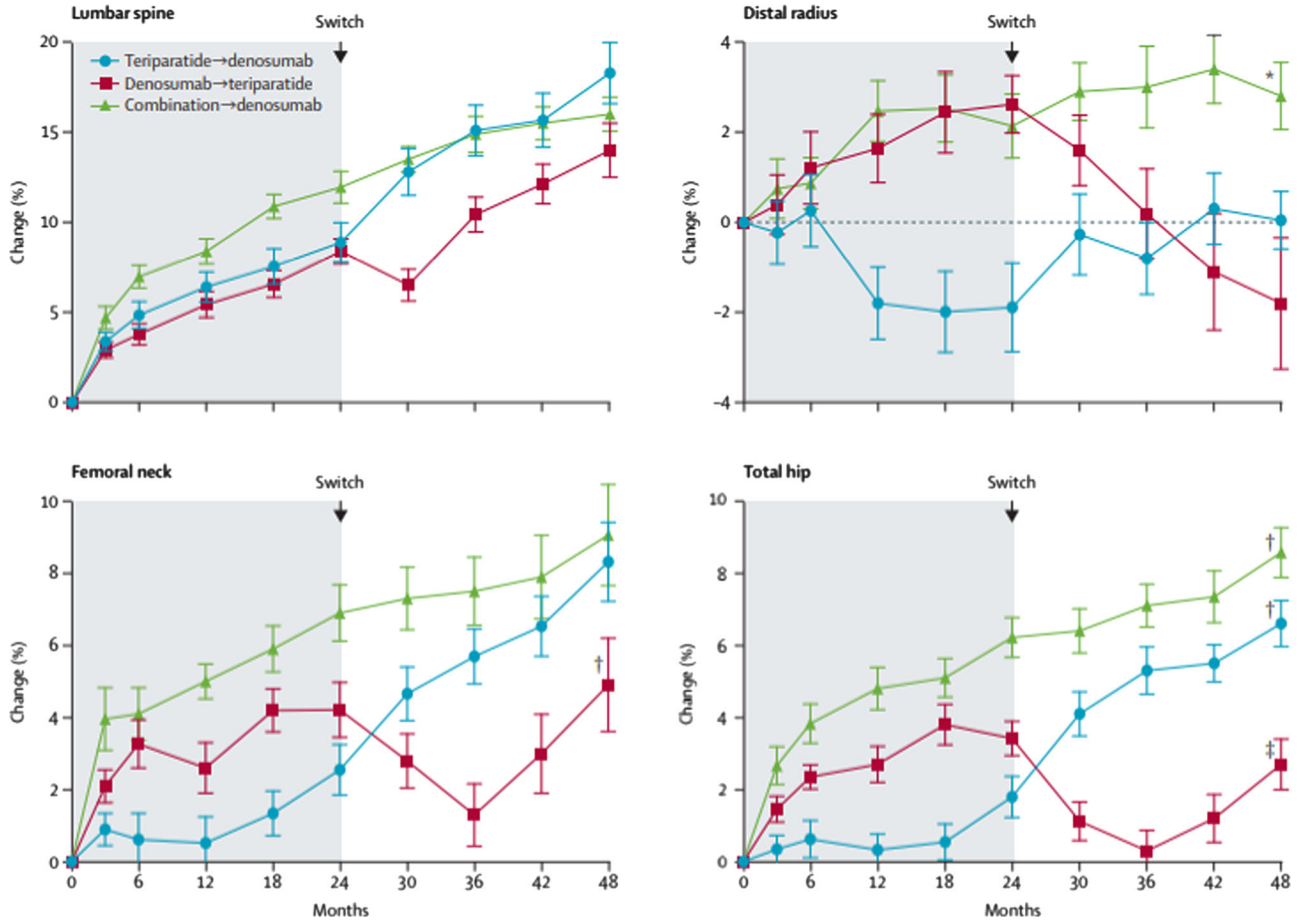

Fig. 2 . BMD mean percent change (SEM; error bars) from baseline to 48 months in the lumbar spine, distal radius, femoral neck, and total hip in the DATA-Switch study design, an extension of the DATA study. Women originally randomized to the teriparatide, denosumab or combination group in the DATA study received denosumab, teriparatide or denosumab for 24 additional months, respectively. Source: Leder et al. [77]. *$p < 0.01$ vs. both other groups. †$p < 0.05$ vs. both other groups. ‡$p < 0.0005$ versus both other groups. SEM standard error of the mean

alendronate, but not in those receiving raloxifene (alendronate −1.8% vs. RLX +0.5%). Another prospective, non-randomized study in 669 patients with teriparatide showed a smaller increase in lumbar spine BMD in those previously receiving alendronate vs. risedronate (3.6 vs. 5.1%), together with a transient reduction in total hip BMD at 6 months in both groups [91]. In spite of the aforementioned studies, the recent VERtebral fracture treatment comparisons in Osteoporotic women (VERO) study has shown that vertebral and clinical fracture risk reduction associated with teriparatide treatment was not affected by previous bisphosphonate use [92].

In the DATA-Switch study, discussed above, increases in spine BMD in the denosumab to teriparatide group were lower than in the teriparatide to denosumab group (+4.8% and +1.2%) with an initial 6-month decline. In addition, a transient marked reduction was seen in total hip and femoral neck BMD, together with a progressive loss in distal radius BMD (−1.8%) when denosumab treatment was followed by teriparatide [77] (Fig. 2). The analysis of the changes by high-resolution peripheral QCT (HR-pQCT) showed that the denosumab to teriparatide sequence is associated with reductions of total and cortical volumetric BMD, as well as cortical thickness and estimated strength by finite element analysis, while these parameters increased with the other teriparatide to denosumab treatment sequence [93].

When assessing BTMs, most studies describe an increase in bone turnover when antiresorptives are followed by PTH treatment. This increase appears to be higher than described in a combination regimen and depends on the type of antiresorptive agent used (higher with raloxifene and risedronate than with alendronate) [94]. In the DATA-Switch study, women receiving teriparatide after denosumab experienced a marked increase in bone remodeling at 6 months (values of 275% in osteocalcin and 183% in sCTX levels), which may reflect the stimulatory effect of teriparatide on the pool of quiescent osteoclast precursors [77].

Interestingly, it has been described in several case reports and in short series of patients, that teriparatide may improve fracture healing, particularly if it is an immediate treatment, in bisphosphonate-associated atypical femur fractures [95].

Future insights in sequential treatment: role of abaloparatide and romosozumab

Abaloparatide

As mentioned above, abaloparatide is a novel synthetic analog of the PTHrP that has strong anabolic activity, but induces less bone resorption and infrequent hypercalcemia compared to teriparatide [96]. Abaloparatide has been shown to induce a marked BMD increase and reduce the incidence of vertebral and nonvertebral fractures [97].

After abaloparatide is discontinued, as with teriparatide, the beneficial effect on BMD will dissipate over time. Therefore, in the ACTIVE study extension, the ability of antiresorptive agents to improve or maintain the benefit previously obtained with 18-month of abaloparatide treatment was evaluated [98]. A total of 1139 women who had completed the study with placebo or with abaloparatide continued for another 6 months with oral alendronate [98]. In the abaloparatide to alendronate group, new morphometric vertebral fractures decreased by 87%, nonvertebral fractures by 52%, major osteoporotic fractures by 58%, and clinical fractures by 45% vs. the placebo to alendronate group [98]. The study also showed that a sequential treatment with abaloparatide and alendronate results in an increased BMD at the lumbar spine, total hip and femoral neck [98]. There were no differences in safety end points between groups during the ACTIVE study extension and the only adverse event reported in more than 4% of the population was arthralgia, with a similar incidence between groups [98]. Thus, treatment with abaloparatide followed by alendronate for at least 6 months seems to be an effective and safe sequential treatment approach to reduce the fracture risk in postmenopausal women.

Romosozumab

Romosozumab is a humanized monoclonal antibody against sclerostin that increases bone formation and reduces bone resorption, improving BMD and bone strength in patients with postmenopausal osteoporosis. In this setting, romosozumab reduces the risk of vertebral and clinical fractures when compared with placebo at 12 months [99].

A phase 2 randomized clinical study showed that the 2-year administration of romosozumab to women with low BMD caused a BMD gain that persisted for another year with denosumab (60 mg sc/6 months). The observed BMD increase is highest during the first few months of treatment and lower during the second year, with BMD returning to baseline levels when no antiresorptive agent is administered after ending romosozumab treatment. Therefore, it may be advisable after romosozumab treatment to continue with an antiresorptive agent to maintain the benefit of the former. No relevant adverse effects were seen in this study except for those related to parenteral administration, which were mild [80].

FRAME is a 2-year, double-blind, randomized, international phase 3 pivotal study, including more than 7,000 postmenopausal women over 55 years of age with densitometric osteoporosis at the hip [99]. Patients were randomized to receive romosozumab sc (210 mg/monthy) or placebo for one year. Afterward, in an open-label phase for another year, patients received denosumab (60 mg every 6 months) [100]. At 24 months, after the transition to denosumab, the reduction of vertebral fractures in the romosozumab to denosumab group was 75% vs. the placebo to denosumab group [100]. There were no differences at 12 and 24 months in the nonvertebral fracture rate [99, 100]. This result was considered by the authors to be secondary to the low frequency of nonvertebral fractures in the Latin American population of this study, a geographic region with high enrollment [100].

Another sequential therapy based on the administration of romosozumab followed by an antiresorptive agent has been assessed. The Alendronate for Osteoporosis (ARCH trial) included over 4000 women with postmenopausal osteoporosis and fractures and compared the effect of romosozumab vs. alendronate for 1 year, followed by an open-label extension with oral alendronate for 12 additional months [50]. A higher reduction in fracture risk was seen in patients treated with romosozumab followed by alendronate when compared with the alendronate group [50]. However, a higher rate of cardiovascular events was found in the romosozumab group when compared with the alendronate group. These cardiovascular concerns are under analysis [50].

In summary, romosozumab has beneficial effects on bone mass and on the prevention of fractures in women with postmenopausal osteoporosis. The BMD gain returns to baseline values after treatment discontinuation, but this loss is prevented with the switch to an antiresorptive treatment (alendronate or denosumab) for at least another year [50, 80, 100]. The best strategy has yet to be established.

Conclusions and key messages

- Bisphosphonates are the only anti-osteoporotic drugs for which “drug holidays” may be considered, due to their

bone tissue accumulation and their residual anti-fracture effect.

- Patients at high risk of fracture (i.e., hip or femoral neck T-score <−2,5 or those with incident fractures) can benefit from a longer therapy with bisphosphonates (10 years instead of 5 years of alendronate and 6 years instead of 3 years of zoledronic acid).
- Estrogen and SERM discontinuation is associated with increased bone turnover and early bone loss.
- Patients treated with estrogens or SERMs with potential age-related adverse events or high age-related fracture risk should be switched to bisphosphonates and, presumably, to denosumab.
- Unlike bisphosphonates, denosumab discontinuation has an immediate "rebound effect", with a substantial increase in bone turnover and bone loss, that in some cases leads to the development of spontaneous fractures (mainly multiple vertebral). This "rebound effect" has been described only in patients who have previously received 2 or more doses.
- After 5 years of denosumab treatment, fracture risk should be assessed. Patients at high risk may continue denosumab for up to 10 years or switch to an alternative treatment. Patients at low fracture risk may discontinue denosumab, but bisphosphonates should be initiated. The administration of alendronate for 1 or more years or a more intensive treatment regimen with zoledronic acid may be the optimum sequence.
- Teriparatide discontinuation is also associated with bone loss. Thus, an antiresorptive agent should be administered, mainly oral or intravenous bisphosphonates, upon discontinuation. In patients at high fracture risk, denosumab may be more effective. Raloxifene may be an option in women when bisphosphonates are contraindicated.
- New anabolic agents such as abaloparatide or romosozumab, also have reversible bone effects. The administration of an antiresorptive drug after their discontinuation seems to be indicated, although data is limited at present.
- Anabolic therapy after antiresorptives can be associated with an initial decrease in femoral BMD. However, there is no reduction in fracture risk effectiveness with this sequential regimen, particularly when teriparatide is given after oral bisphosphonate therapy.

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Compliance with ethical standards

Conflict of interest Dr. N.G. has received fees for lectures and participation in advisory boards from Amgen, Eli Lilly, Alexion, and UCB. Dr. E.C. has received fees for lectures and/or participation in advisory boards from Amgen, Lilly, UCB and Rubió. Dr. J.B.-R. has received advisory fees from Amgen and Gebro Pharma. Dr. C.G.-A. has received fees for lectures and participation in advisory boards from Amgen, Eli Lilly, Faes, Gebro, and UCB. Dr. G.M.D.-G. holds a research grant from Amgen and Shire, has received advisory fees from Amgen, UCB, Eli Lilly, and Shire and speaker honoraria from Amgen and Eli Lilly. Dr. J.d.P.-M. has received advisory and conference fees, as well as congress grants from Amgen, UCB, and FAES and conference fees from Eli Lilly and Gebro. Dr. P.P. has received lecture fees from Amgen, Eli Lilly, Alexion, and Kyowa Kirin. Dr. M.M.-T. has received fees for lectures and advisory boards from Amgen, UCB, Eli Lilly, Alexion, Shire, and Kyowa Kirin.

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