

THERAPY OF ENDOCRINE DISEASE

Denosumab vs bisphosphonates for the treatment of postmenopausal osteoporosis

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Abstract

The most widely used medications for the treatment of osteoporosis are currently bisphosphonates (BPs) and denosumab (Dmab). Both are antiresorptives, thus targeting the osteoclast and inhibiting bone resorption. Dmab achieves greater suppression of bone turnover and greater increases of bone mineral density (BMD) at all skeletal sites, both in naïve and pretreated patients. No superiority on fracture risk reduction has been documented so far. In long-term administration, BPs reach a plateau in BMD response after 2–3 years, especially at the hip, while BMD increases progressively for as long as Dmab is administered. Both BPs and Dmab are generally considered safe, although they have been correlated to rare adverse events, such as osteonecrosis of the jaw and atypical femoral fractures. Dmab should be preferred in patients with impaired renal function. BPs are embedded in the bone, from which they are slowly released during bone remodeling, therefore continuing to act for years after their discontinuation. In contrast, Dmab discontinuation fully and rapidly reverses its effects on bone markers and BMD and increases the risk for fractures; therefore, Dmab discontinuation should be discouraged, especially in previously treatment-naïve patients, regardless of the conventional fracture risk. In case of discontinuation, other treatment, mainly BPs, should immediately follow, although the optimal sequential treatment strategy is yet to be defined. Combination of teriparatide with Dmab or zoledronic acid, but not alendronate, provides increased BMD gains at all sites. In conclusion, both BPs and Dmab are safe and efficient therapeutic options although their particularities should be carefully considered in an individual basis.

*European Journal of
Endocrinology*
(2018) **179**, R31–R45

Invited Author's profile

Athanasios Anastasilakis is a consultant of Endocrinology at 424 General Military Hospital in Thessaloniki, Northern Greece where he conducts several clinically oriented research projects alongside a busy clinical schedule. He has published extensively in the areas of thyroid, metabolism, gestational diabetes and especially metabolic bone diseases, which represent his main area of focus and expertise.



Introduction

Osteoporosis is the most common skeletal disease. It is caused by an imbalance in bone turnover, namely a relatively increased rate of bone resorption by the osteoclasts that exceeds the rate of bone formation by the osteoblasts, resulting in gradual loss of bone mass and attenuation of bone strength, therefore predisposing to low-energy fractures. Postmenopausal osteoporosis is the most common form of osteoporosis, affecting a significant proportion of postmenopausal women and advancing with aging (1). Given that life expectancy for women in Western countries is currently over 80 years and continues to rise, the projections of women at risk of osteoporotic fractures in the next decades and the respective economic burden to the health care systems are expected to continuously grow (1). Therefore, the need for antiosteoporotic agents that can be administered for prolonged periods with both efficacy and safety is more than important.

A common and effective treatment strategy in osteoporosis is to target the osteoclast, thus reducing bone resorption rate. Antiresorptives are currently the cornerstone of osteoporosis treatment. Bisphosphonates (BPs) have been serving well for several decades as the main representative of this category. During the last decade, denosumab (Dmab), a monoclonal antibody that binds the receptor activator of nuclear factor κ -B ligand (RANKL), thus inhibiting the formation and activity of osteoclasts, has introduced a new category of more sophisticated, biological agents targeting the osteoclast and initiated a new era in our attempt to treat the disease. Dmab has gradually gained ground over BPs in the osteoporosis market year by year, despite its considerably higher cost.

In this review, we summarize the particularities of these two most commonly used antiosteoporotic treatment modalities and the differences between them.

Bisphosphonates

The BPs are synthetic compounds discovered during the search for pyrophosphate analogs, in an attempt to take advantage of the inhibitory effect of pyrophosphates on calcification (2). The oxygen atom that provides the P-O-P binding of pyrophosphate is replaced by a carbon resulting in the formation of BPs, which resist biological degradation, have a retained activity, and therefore, are suitable for clinical use (2). The additional side chains

of the BPs, namely R1 and R2, enhance their affinity for calcium crystals (R1) and their potency and mechanism of action (R2), while differences in these chains result in several chemical molecules with different biological effects (2). The cornerstone of BPs' action is their ability to bind to hydroxyapatite at the surface of bone and especially within the resorption lacunae where they could be internalized by the active osteoclasts and inhibit the intracellular mevalonate pathway; this effect eventually leads to either inactivation or increased apoptosis of the osteoclasts and inhibition of bone resorption (Fig. 1).

Efficacy

Following BPs' administration, a new reduced bone turnover equilibrium is reached after 3–6 months of treatment with oral BPs and faster with iv ones. This lower turnover state remains throughout the treatment period (3), and eventually leads to bone mineral density (BMD) improvement and decreased fracture risk (2). The potency of BPs is directly related with the level of bone remodeling inhibition, and greater gains in BMD are expected among patients with high baseline bone remodeling rates; however, a consistent finding in all long-term trials is a plateau effect in BMD response after 2–3 years of treatment, especially at the hip (4, 5). A potential explanation for this is probably the new equilibrium established between the new bone formed through the modeling process irrespective of BPs treatment and the bone removed by the not fully suppressed bone remodeling (6).

All currently approved BPs for the treatment of postmenopausal osteoporosis are nitrogen containing (N-BPs) and include alendronate (ALN), risedronate (RIS), ibandronate (IBN) and zoledronic acid (ZOL). They all adequately suppress bone remodeling, although probably at slightly different levels (Table 1).

ALN is a potent antiresorptive agent that increases BMD at both trabecular and cortical skeletal sites. When treatment is continued beyond 5 years, femoral neck (FN) BMD is maintained, while lumbar spine (LS) BMD continues to increase up to 10 years (7). The risk of vertebral fractures (VFs) is reduced significantly with daily ALN 10mg (8, 9) along with an overall 23% reduction of the risk of non-vertebral fractures (non-VFs) and a 53% reduction of hip fractures (9). The collective once-weekly dose of 70mg, currently used in every day practice, has the same pharmacodynamics profile with the daily treatment and concomitantly improves patients' adherence (10). In the FLEX (Fracture Intervention Trial Long-term Extension) study (4), the 5-year extension of the pivotal

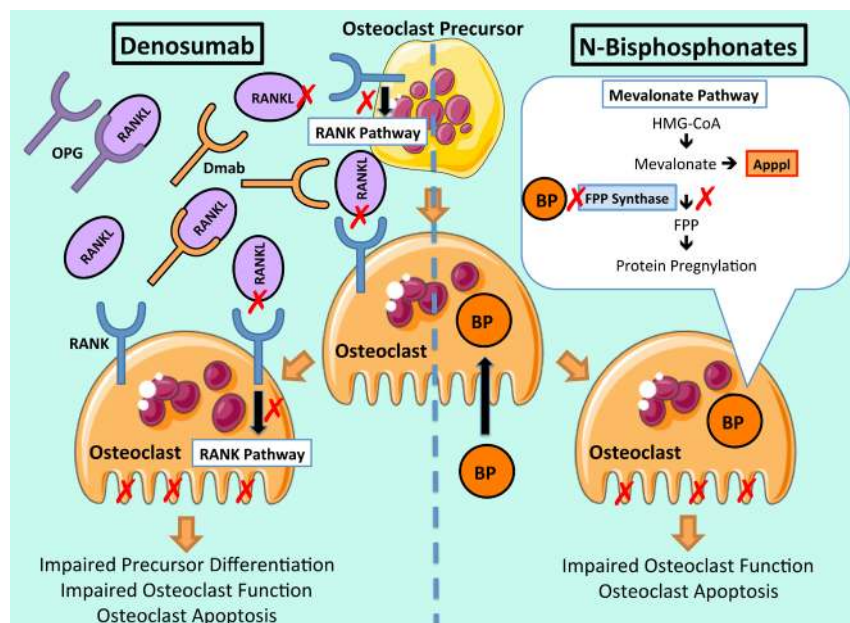


Figure 1

A summary of the different mechanisms of action of Dmab and N-BPs. Denosumab acts similarly to OPG, which is the natural decoy receptor of RANKL; Dmab binds RANKL, thereby deterring RANKL binding on its receptor, RANK, on the surface of osteoclasts, but also on osteoclast precursors. Subsequently, RANK signaling pathway is not activated, resulting in impaired osteoclast precursor differentiation, impaired osteoclast function and possibly osteoclast apoptosis. All these effects lead to the inhibition of bone resorption. N-BPs act on osteoclasts, but not on their precursors. N-BPs are internalized into the osteoclasts possibly through endocytosis. Subsequently, N-BPs inhibit the FPP synthase, a key enzyme of the mevalonate signaling pathway. This leads to impaired intracellular protein prenylation and accumulation of cytotoxic intermediate products, including Apppl, thereby impaired osteoclast function and possibly osteoclast apoptosis. Thus, bone resorption is inhibited. Apppl, triphosphoric acid 1-adenosin-5'-yl ester 3-(3-methylbut-3-enyl) ester; FPP, farnesyl diphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; N-BPs, nitrogen containing bisphosphonates; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor κ -B; RANKL, RANK ligand.

Fracture Intervention Trial (11), a significantly lower risk of 55% was found solely for the clinical VFs among patients receiving ALN for 10 years compared to those who stopped ALN after the first 5 years. A more recent *post hoc* analysis of the FLEX study identified a subgroup of patients who may benefit from the continuation of ALN up to 10 years: postmenopausal women with a FN BMD within the osteoporotic range, and no VFs can exhibit a significant reduction in the risk of non-VFs (12).

RIS increases significantly BMD at all skeletal sites, although at a lesser magnitude compared with ALN, a finding possibly attributed to the difference in bone turnover inhibition or even to the difference in approved doses (70 vs 35 mg/week) between the two BPs (13, 14). Similarly with ALN, the inconvenient daily RIS dose has long been replaced with the administration of the cumulative dose either in a weekly or monthly basis (15). After treating postmenopausal women with RIS for a mean

period of 5 years, the risk of VFs is reduced by 36–39% (16), along with an overall reduction of the risk of non-VFs by 20% and of hip fractures by 26%. Long-term studies up to 7 years are available, however, with a small number of participants and probably not representative of the core study population (17). In specific, RIS resulted in a relative risk (RR) reduction of 59% for radiographic VFs within years 4–5 of treatment where a placebo arm was available (18), whereas in the additional 2-year extension, patients previously on placebo, who received RIS for only 2 years, exhibited a significant reduction in VFs incidence during years 6–7, similar with the corresponding unchanged incidence of the 7-year RIS group (19).

IBN is another commonly used N-BP. IBN studies suggest that both dose and dosing intervals are important factors regarding the response to treatment (2). Daily oral IBN (2.5 mg) administered for 3 years significantly reduced the risk of new morphometric VFs by 62% vs placebo, but

Table 1 Schematic synopsis of the advantages/disadvantages of denosumab vs bisphosphonates for the treatment of postmenopausal osteoporosis.

	Denosumab	Bisphosphonates			
		Alendronate	Risedronate	Ibandronate	Zoledronic acid
Efficacy					
Bone markers	↓↓↓	↓↓	↓	↓	↓↓
BMD	↑↑↑	↑↑	↑	↑	↑↑
VFx	↓↓	↓↓	↓↓	↓↓	↓↓
Non-VFx	↓↓	↓↓	↓↓	↓	↓↓
Treatment duration	Up to 10 years	Up to 10 years	Up to 7 years	Up to 5 years	Up to 9 years
Residual effect (1 year after discontinuation)					
Bone markers	↑↑↑	↓	Return to baseline	Return to baseline	↓↓
BMD	↓↓↓	–	↓	↓	–
VFx	Return to baseline	↓↓	↓	Return to baseline	↓↓
Non-VFx	Return to baseline*	Return to baseline	Return to baseline	Return to baseline	Return to baseline
Safety–adverse effects					
ONJ	+	+	+	+	+
AFF	+	+	+	+	+
Other	+*	–	–	–	+**
Cost (annual)	++	+	+	+	+

(↑), increased; (↓), decreased; (–), unchanged; (+), possibility; (*), multiple VFX in a minority of patients following discontinuation of Denosumab; (**), atrial fibrillation in a very small proportion of patients receiving Zoledronic acid.

AFF, atypical femoral fractures; BMD, bone mineral density; non-VFX, non-vertebral fracture; ONJ, osteonecrosis of the jaw; VFX, vertebral fracture.

no reduction of hip fractures was found in the registration study, a finding that differentiates IBN from ALN, RIS and ZOL. A significant 69% reduction in the risk of non-VFs was only found among patients with a FN BMD <–3.0 in *post hoc* analyses (20). However, higher cumulative doses administered either once monthly orally (150 mg) or iv every 3 months (3 mg) significantly increased BMD and reduced the risk of non-VFs by 38% (21, 22, 23). IBN long-term trials lasted up to 5 consecutive years of treatment (5, 24). Unfortunately, solid conclusions cannot be drawn from the IBN extension studies, as fractures were analyzed as adverse events (AEs) rather than study endpoints, and there were no placebo arms (17).

ZOL is the most potent N-BP, and it is administered as an iv infusion of 5 mg once a year for the treatment of osteoporosis. Besides an increase of BMD at all skeletal sites ranging from 5.1 to 6.7%, ZOL significantly reduced the incidence of VFs by 70% already from the first year of treatment and the incidence of non-VFs by 25% and hip fractures by 41% at the 3-year core HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) study (25). Similar to the FLEX study, the ZOL extension trial randomized the patients of the HORIZON trial to either continue treatment for another 3 years or switch to placebo for the next 3 years (26). Among the patients who received ZOL for six consecutive years, a significantly lower risk of only morphometric VFs was found. A subsequent *post hoc* analysis found that patients with a total hip (TH) or FN BMD ≤–2.5 and/or

an incident morphometric VF during the first 3 years of treatment would benefit from the continuation of ZOL for 6 years (27). A second extension trial that compared 6 vs 9 consecutive years of ZOL treatment concluded that almost all patients can stop ZOL after six infusions, at least for the next 3 years, with apparent maintenance of benefits (28).

Safety

Besides the early recognition of AEs, such as upper gastrointestinal irritation and nephrotoxicity, there have been concerns regarding the long-term suppression of bone remodeling (2, 29), although the ability of the skeleton to renew itself is preserved even after several years of N-BP treatment (30, 31). These safety concerns include two rare but clinically serious AEs, namely osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). The pathogenesis of ONJ is still unclear and its incidence among patients treated with BPs for osteoporosis is estimated between 1/10,000 and 1/100,000 patient-years, a figure marginally higher than that of the general population (29, 32). Up to now, there are no data regarding the incidence of ONJ after cessation of BP treatment. The absolute risk for AFF among patients treated with BP for osteoporosis ranges between 3.2 and 50 cases/100,000 patient-years, which is doubled with prolonged BP use (>3 years, median duration, 7 years), and declines following discontinuation (29, 33).

Finally and regarding cardiovascular safety, a significantly higher incidence of serious AEs of atrial fibrillation (1.5 vs 0.3%, $P < 0.001$) was reported in the ZOL core study (25), although the overall rates of atrial fibrillation did not differ significantly between the treatment group and the placebo. Furthermore, these findings were not replicated in other studies (34). The association between oral BP use and atrial fibrillation is considered weak (35).

Residual effect

The major difference of BPs, probably with all the other medications used for chronic diseases, is that they could continue to act for years following their discontinuation. In specific, as they are embedded in bone at the site of their initial binding, they remain in a pharmacologically inactive state for a long time and can potentially be released whenever their burial site is again subjected to remodeling; interestingly, the half-time of their elimination from the skeleton can be up to 8–10 years (36), and this slow release is definitely the reason for both beneficial and adverse effects, although it may substantially vary between subjects and molecules.

Regarding ALN, retention within the skeleton is probably the reason for the marginal fluctuation of LS BMD even after the discontinuation of treatment in the majority of patients, while FN BMD decreases modestly during 1–2 years following treatment's cessation and stabilizes thereafter (7). This is probably the case for the lack of an increased risk of non-VFs or morphometric VFs in all the extension trials of ALN (4, 37, 38). Similarly to ALN, a residual BMD effect has also been reported with ZOL: a net loss of only 0.8% in the FN and a 1.2% gain in the LS were observed following discontinuation (26). The residual benefits of ZOL in BMD probably account for the observed preservation of lower fracture risk for clinical VFs, non-VFs and hip fractures at least for 3 years following ZOL discontinuation (26). No studies have been specifically designed to investigate prospectively and in a double-blinded placebo-controlled manner the residual effects on BMD and fracture risk following the discontinuation of IBN or RIS. However, from a pharmacokinetics and pathophysiological point of view and from previously reported data (39, 40, 41), a modest BMD decrease after cessation of IBN (39, 40), and a slight decrease or maintenance of BMD, although with a stable VF fracture risk, following discontinuation of RIS (39, 40, 41) seems rational at least for the following years. In a recent, rather small, cohort of patients receiving various

BPs as first-line treatment, drug holidays resulted in increase of the risk of clinical fractures (42).

Denosumab

Dmab is a fully human monoclonal IgG2 antibody that binds and inhibits RANKL with high specificity and affinity (43). RANKL is essential for the activation of its receptor, RANK, on the surface of osteoclasts and their precursors, which promotes their differentiation, function and survival (44). Osteoprotegerin (OPG), a soluble receptor of RANKL that binds it, thus intercepting RANK activation, is the natural antagonist of RANKL (Fig. 1). Imbalance of the RANKL/OPG ratio is associated with osteoporosis and other metabolic bone diseases (45). Dmab administration results in suppression of bone resorption (46), which is considerably longer than that of previously tested recombinant OPG or RANK molecules (47, 48).

Efficacy

Following Dmab injection, bone resorption markers are reduced rapidly (within the first 12h) and profoundly (>80% from baseline), reaching a nadir at about 1 month and remaining suppressed for the subsequent 6 months, and then gradually begin to rise, while bone formation markers decrease by 55–75% at 2–3 months following injection (47, 49). As with any other potent antiresorptive agent for example the BPs, the decrease of bone remodeling results in transient reduction of serum calcium levels, causing an increase of serum parathyroid hormone (PTH), especially during the first 1–2 months (47, 50). Based on its pharmacokinetics, Dmab at the approved dose of 60mg is administered subcutaneously every 6 months. This intermittent way of administration renders the agent appealing, especially for older patients with polypharmacy, inability to remain in an upright position for long or impaired memory, and it increases the persistence to treatment (51).

Following the phase 1 (47) and 2 (49) studies, which proved the efficacy of Dmab in humans in terms of BMD increase at all sites and bone turnover markers (BTM) suppression, the phase 3 pivotal FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial (52) proved its anti-fracture efficacy at all skeletal sites tested. At 36 months of treatment, a reduced RR for VFs by 68%, non-VFs by 20% and hip fractures by 40% compared with placebo was found. BMD increased progressively, reaching an

overall increase of 9.2% at the LS and 6.0% at the TH compared to placebo.

The FREEDOM trial was extended to follow patients receiving Dmab for up to 10 years (53). About one-third of the patients (33.6%) completed the extension study. Prolonged reduction of bone remodeling did not result in increased fragility. In the opposite, fracture rates remained consistently low throughout the study, similar to rates observed in the active treatment group during the first 3 years and lower than that in a virtual long-term placebo cohort. At the completion of 10 years of Dmab, the cumulative BMD increase from baseline reached 21.7% at the LS, 9.2% at TH, 9.0% at FN and 2.7% at the one-third radius, suggesting a gradual increase of BMD for as long as the treatment is continued without reaching a plateau. A favoring bone formation imbalance between the modeling-based bone accrual and the minimal bone removal through an almost completely suppressed bone remodeling has been proposed to be responsible for this continuous BMD increase with Dmab treatment (6, 53).

The majority of patients participating in the FREEDOM trial were treatment naïve and those who were not should have been off-treatment for at least 12 months (52). In studies evaluating patients previously treated with other agents, most commonly BPs, the increases in BMD with Dmab were more modest compared to treatment-naïve patients treated with Dmab, although still significant, despite the similar reduction of BTM (30, 54, 55, 56). Up to date, there are no data regarding the anti-fracture efficacy of Dmab in patients transitioning from other agents.

Safety

In general, the information accumulated from the up to 10 years of continuous administration of Dmab in clinical trials and the more than 7 years of post-marketing surveillance suggests an acceptable safety profile.

Despite the initial concerns related to suboptimal tissue specificity (increased risk of serious infections, malignancies, cellulitis, eczema, pancreatitis, urinary tract infections, etc.) (57) data from both the clinical trials (53) and everyday clinical practice (58) do not suggest an increased incidence of such AEs neither short term nor long term.

Regarding AEs related to bone remodeling suppression (hypocalcemia, AFF, impaired fracture healing and ONJ), data are also reassuring. By the end of FREEDOM extension, two out of the nine subtrochanteric or diaphyseal femoral fractures were adjudicated as atypical ones, while 13 positively adjudicated cases of ONJ were

also reported (53). In earlier announced post-marketing safety surveillance data, four adjudicated cases of AFFs, all among patients with previous use of BPs, and 32 adjudicated cases of ONJ were reported (58). Risk factors included at least one of the following: prior glucocorticoid and/or BP use, chemotherapy, invasive dental procedures and older age. In the same report, eight cases of severe symptomatic hypocalcemia were included; most events occurred within 30 days of Dmab administration and responded to calcium/vitamin D, while seven out of eight patients had chronic kidney disease. Finally, there were five reports of medically confirmed anaphylaxis, most of which occurred the first day of the first Dmab dose (58).

An advantage of Dmab over other antiosteoporotic medications is that it is relatively safe in patients with impaired renal function. Furthermore, it is effective across a broad range of subjects with estimated glomerular filtration rate (GFR) as low as 15 mL/min (59), and its effect on fracture risk reduction is not associated with the level of renal function; however, there is an elevated risk of hypocalcemia in patients with severe renal deficiency or on dialysis (60, 61). Therefore, early and closer monitoring of serum Ca is warranted in patients with renal failure treated with Dmab.

Residual effect

Dmab discontinuation seems to fully and rapidly reverse its effects on BTM and BMD. In fact, upon discontinuation, a rebound of bone turnover is observed; BTM rise above baseline at 3 months and remain elevated until reaching again baseline levels approximately 30 months after the last dose. BMD gains are also lost and BMD values reach original baseline values after 1–2 years off-treatment (62, 63, 64, 65). Of interest, although lost during a washout period of just 1 year, the BMD gains achieved after 4 years of Dmab treatment may be completely restored in just another year of Dmab re-institution (63). The magnitude of BMD decrease may be linked to the duration of Dmab treatment (66).

Regarding the sustainability of its anti-fracture efficacy, Dmab discontinuation seems to be associated with increased fragility manifested as multiple clinical VFs in a subset of patients, even if they are considered at 'low risk' in terms of absence of previous fractures and BMD values within the osteopenic or even normal range at the time of discontinuation (67). Such events have been reported in about 10% of the treated patients (64, 65). In patients who discontinued Dmab during the FREEDOM study or its extension, despite the very short

off-treatment mean follow-up period (0.2–0.5 years e.g. 2–6 months) that could underestimate the risk (68), VF rate increased from 1.2 per 100 patient-years during the treatment period to 7.1, a value similar to placebo-treated subjects, while the risk for multiple VFs was significantly higher among those who discontinued Dmab compared with placebo (69). A proposed mechanism for this effect is the upregulation of osteoclast formation and activity (70). The location of the fractures is typically osteoporotic, located at the lower thoracic and the upper lumbar spine (67), while factors predisposing patients to a higher risk are prevalent VFs (67, 69), lack of other osteoporotic treatment before Dmab initiation (67), administration of Dmab for longer periods (67) and greater hip BMD loss following discontinuation (69). The suggested preventive role of prior exposure to BPs (67, 71) has been recently questioned (72); however, the latter study should be cautiously interpreted as it had several methodological limitations (73). It is of clinical significance that fractures as such were described 2–10 months after the last Dmab injection effect was depleted, highlighting the importance of not omitting or delaying Dmab doses (67, 74). Given all the above, it has become clear that Dmab should not be stopped without considering alternative treatment (75).

Studies directly comparing Dmab to BPs

In treatment-naïve patients, there is only one head-to-head comparison study between Dmab and ALN in which the former achieved greater BTM reduction and higher increases in both LS and TH BMD after 12 months

of treatment (76). There are several studies comparing Dmab with practically all commercially available BPs in patients previously treated with BPs (30, 55, 56, 77, 78). Given the short duration (12 months) and the relatively small number of patients included in all these studies, comparisons referred to BMD and BTM changes as a surrogate marker of each agent's efficacy. In brief, Dmab was superior to ALN (30), RIS (56), IBN (55) and ZOL (77, 78) in terms of BMD accrual and BTM suppression (Table 2). Similarly, in an 1-year, head-to-head, non-randomized study in patients previously treated with teriparatide (TPTD), Dmab increased LS, TH and FN BMD and decreased BTMs more than oral BPs (ALN, RIS and minodronate) (79). In accordance with all the above, in an exploratory analysis, Dmab achieved greater BMD accrual both in LS and TH at 12, 24 and 36 months compared to ALN, RIS, IBN (per os or iv) and ZOL (80). A proposed explanation for the superior effects of Dmab on cortical sites is that, as BPs are mainly attached to bone surfaces with active bone remodeling, they are more likely to be sequestered in trabecular rather than cortical bone, as the former skeletal sites harbor around 80% of total bone remodeling (6). Therefore, BPs may not inhibit cortical bone remodeling at a level comparable with Dmab, due to their difference in the accessibility of bone cortex (81). Notably, there are no data comparing fracture risk reduction between Dmab and BPs, at least as a primary or a secondary end point.

Regarding adherence, compliance and persistence to treatment, a comparison between Dmab and once-weekly ALN favored the former in terms of treatment preference and satisfaction (82).

Table 2 The effect of switching from BPs to denosumab or continuing on the same or other BP on BMD and BTM in women with postmenopausal osteoporosis, as derived from randomized controlled trials.

Study	Comparison (duration)	Number [†] (Dmab vs BP)	LS BMD change % (Dmab vs BP)	TH BMD change % (Dmab vs BP)	FN BMD change % (Dmab vs BP)	Radius BMD change % (Dmab vs BP)	Suppression of BTMs
(30)	From ALN to Dmab or ALN (1 year)	253 vs 251	3.0 vs 1.9*	1.9 vs 1.1*	1.4 vs 0.4* (approx)	0.8 vs 0.1* (approx)	Greater with Dmab
(55)	From oral BPs to Dmab or IBN (1 year)	417 vs 416	4.1 vs 2.0*	2.3 vs 1.1*	1.7 vs 0.7*	NA	Greater with Dmab
(56)	From ALN to Dmab or RIS (1 year)	435 vs 435	3.4 vs 1.1*	2.0 vs 0.5*	1.4 vs 0.0*	NA	Greater with Dmab
(77)	From ZOL to Dmab or ZOL (1 year)	34 vs 30	4.5 vs 4.4	NA	NA	NA	Greater with Dmab
(78)	From oral BPs to Dmab or ZOL (1 year)	321 vs 322	3.2 vs 1.1*	1.9 vs 0.6*	1.2 vs -0.1*	0.6 vs 0.0*	Greater with Dmab

[†]At the stage of randomization; *Statistically significant between groups.

ALN, alendronate; approx, approximately; BMD, bone mineral density; BTM, bone turnover markers; BPs, bisphosphonates; Dmab, denosumab; FN, femoral neck; IBN, ibandronate; LS, lumbar spine; NA, not available; RIS, risedronate; TH, total hip; ZOL, zoledronic acid.

Sequential treatment

There is uncertainty about the long-term effectiveness and safety of existing antiosteoporotic medications, partly owing to the fact that clinical trials are not *a priori* specifically designed for their extensions, and the extensions are usually open label and have high withdrawal rates, thereby being underpowered and prone to selection bias. Given that osteoporosis is a chronic disease, when the administered medication reaches its maximum adequately studied duration, a sequential antiosteoporotic treatment is often considered. Additionally, sequential treatment is needed when a patient experiences an AE or when better compliance and persistence to treatment is required or when a less costly regimen is desirable. In this section, clinical evidence regarding BPs and Dmab on-treatment sequence will be summarized, with a special focus on randomized controlled trials (RCTs).

Transitioning from BPs to Dmab

Dmab is a reasonable sequential treatment when drug holiday is not considered safe following 3–5 years on BPs (hip BMD T-score remains <-2.5 , or there is still high fracture risk score, or in patients with previous major osteoporotic fracture, or patients who experience one or more new low-energy fracture while on-treatment, or in osteoporosis secondary to chronic diseases or medications (e.g. glucocorticoids)) (29, 83). RCTs investigating the efficacy of Dmab in women previously on BPs are summarized in Table 2. It is of interest that Dmab administration results in similarly suppressed BTMs, despite the lower baseline levels in patients pretreated with BPs compared to treatment-naïve patients (54, 84, 85). BMD increases with Dmab were similar between responders and non-responders to previous BP treatment (84).

Transitioning from Dmab to BPs

Contrary to BPs which, as already mentioned, are retained in the skeleton for long and therefore, at least partly preserve their benefits after their discontinuation (86, 87), Dmab discontinuation is highly recommended to be immediately followed by another antiosteoporotic medication regardless of the fracture risk (75). Although optimal post-Dmab treatment is currently unknown, BPs, either orally or intravenously are proposed by most experts (75). ALN administered for 1 year following 1 year of Dmab treatment maintained BMD at LS, TH and FN

(82). A single infusion of ZOL in a few patients previously treated for 7 years with Dmab partially prevented bone loss at the LS but not the TH (88) while in another study, in patients treated for 2.5 years with Dmab, a single ZOL infusion maintained around 60% of the BMD gains at the LS and TH achieved with Dmab during the following 2.5 years (89). Somewhat better results were reported in patients treated for 1 year with Dmab after 1 year on romosozumab or placebo (90). ZOL infused around 2 months after the depletion of Dmab effect achieved 73% retention of the BMD gains at the LS and 87% retention of the gains at the TH. Authors proposed that delaying administration of iv BPs might increase their skeletal uptake resulting in improved retention of the bone accrual achieved with Dmab (90). In the DATA follow-up study, BMD increases achieved after 4 years of Dmab treatment were maintained only in patients that continued Dmab or were promptly switched to BPs (91). However, all the above studies were small and of short duration, therefore, definite conclusions cannot be drawn. Thus, the optimal strategy to handle bone loss after Dmab discontinuation remains currently unknown (75).

Osteoanabolic medications before, after or in combination with BPs or Dmab

Sequential treatment

Although the use of PTH analogs, for example, TPTD is common in non-responders to antiresorptives, this might not be the optimal sequence of antiosteoporotic treatment, as it could result in a transient loss of hip BMD and strength (92). More specifically, hip BMD declines below baseline for at least 12 months after switching from ALN, or RIS, or Dmab to TPTD (31, 93, 94, 95, 96). However, it remains unknown whether this BMD decline is translated in higher fracture risk when TPTD follows BP or Dmab treatment or it is due to an increase in cortical bone dimensions ensuing from increased endosteal and periosteal bone accretion during TPTD treatment, which will ultimately improve cortical bone strength (97). In support of the latter, in a network meta-analysis TPTD had the highest hip and non-vertebral fracture risk reduction among antiosteoporotic medications (98). In contrast, LS BMD, does not decline with BPs (31, 95), while the decrease is minor and/or transient with Dmab (96). Based on these considerations, until more data elucidate the effect on fracture risk, sequential use of TPTD should be carefully considered in high-risk patients previously treated with BPs or Dmab.

On the other hand, BMD gains achieved with PTH analogs (TPTD, abaloparatide) are maintained or further increased at all sites when treatment with either BPs (79, 99, 100, 101) or Dmab (79, 96) follows. The effects seem to be greater with Dmab (79).

The greater to-date BMD gains with a sequence of antiosteoporotic medications were achieved with 1-year treatment with the anti-sclerostin antibody romosozumab followed by 1-year of Dmab (LS: 17.6%; TH: 8.8%; FN: 6.6%) (102). Dmab further increased BMD at all sites (LS: 4.3%; TH: 2.0%; FN: 1.4%) during year 2 of the study (102). In contrast, postmenopausal women treated with ALN after 1-year of romosozumab maintained the BMD gains at LS, TH and FN BMD which were achieved during the first year of treatment without further increases (103). In comparison with the romosozumab-ALN sequence, overall BMD gains with an 18-month abaloparatide treatment followed by 6-month ALN were 12.8% at LS, 5.5% at TH and 4.5% at FN (104). Finally, an RCT comparing the 1-year effect of romosozumab vs TPTD in high-risk women previously treated with BPs for at least 3 years, showed greater BMD increases at LS, TH and FN with romosozumab (94).

Combination treatment

The addition of TPTD in patients on ongoing ALN treatment results in greater increases on LS, TH and FN BMD (105, 106). However, TPTD-ALN coadministration achieves smaller LS BMD gains than TPTD monotherapy and smaller TH gains than ALN monotherapy (106). This seems to be different, especially for hip BMD, when ALN is added on ongoing TPTD treatment, possibly because TPTD has already provided its anabolic effect (107). In contrast with ALN, TPTD combination with ZOL achieved greater and faster BMD gains at the LS, TH and FN than TPTD or ZOL monotherapy (108). Clinical fractures in the combination group were lower than ZOL, but did not differ from TPTD.

The combination of TPTD with Dmab provided additive effects on LS, TH, FN and distal radius BMD, already from the first year of treatment (109) compared with Dmab or TPTD monotherapy, and this continued during the second year (110). More specifically, the BMD changes for the combination, Dmab or TPTD monotherapy, respectively, were 12.9, 8.3 and 9.5% at the LS, 6.3, 3.2 and 2.0% at the TH, 6.8, 4.1 and 2.8% at the FN and 2.2, 2.1 and -1.7% at distal radius (110). Similar BMD trends at the LS and TH, although not statistically significant, were observed in another

open-label study (111). The combination of TPTD and Dmab was also superior of either monotherapy in improving bone microarchitecture and estimated strength, especially in cortical bone (112).

In a short-term head-to-head RCT, a single high-dose (40 µg) of TPTD continued to affect bone resorption after 8 weeks in women treated with ALN, but not with Dmab (113). Although these findings may imply that Dmab, in contrast with ALN, inhibits the ability of high-dose TPTD to acutely increase bone resorption thereby providing a more potent anabolic stimulus, further comparative studies are needed with BMD or fractures as endpoints.

It should be highlighted that combination treatments are not approved in most countries.

Comparison of cost-effectiveness

The annual cost of BPs and especially of the generic ones is considerably lower than Dmab across the world. There are limited comparative data on cost-effectiveness of BPs vs Dmab on the treatment of postmenopausal osteoporosis. Dmab was reported to be more cost-effective than oral BPs in Belgium (114) and ALN in Japan (115). In United States, Dmab was reported to be more cost-effective than branded but not generic BPs, with the exception of high-risk subgroups (e.g. >75 years), in which Dmab was more cost-effective than generic BPs (116). In contrast, in a recent meta-analysis, the most cost-effective initial therapy for postmenopausal osteoporosis was generic ALN or generic ZOL (117). Dmab showed benefits in VF reduction over ALN at incremental cost of \$46,000 per fracture prevented (117).

Conclusions

Both BPs and Dmab are potent antiresorptives and significantly reduce the risk of fractures in postmenopausal women. Dmab seems to achieve larger suppression of BTM and greater increases of BMD than BPs regardless of previous treatment. No evidence of greater fracture risk reduction with Dmab compared to BPs has been documented so far. BPs reach a plateau in BMD response after 2–3 years of continuous administration. Long-term Dmab administration results in progressive BMD increase at all skeletal sites and consistently low fracture rates. BPs remain in the skeleton for long after their administration and continue to act for years following

their discontinuation, thus allowing the consideration of a 'drug holiday'. On the opposite, Dmab discontinuation without subsequent treatment option is currently discouraged, especially in previously treatment-naïve patients, because of the rapid increase of BTM, the loss of BMD gains and the ensuing increased risk of fractures, specifically this of multiple, clinical VFs among high-risk subjects. Therefore, in case of Dmab discontinuation, treatment with BPs should immediately follow; the optimal BP and the sufficient duration of sequential treatment is not known up to date. The rates of ONJ and AFF are very low with both BPs and Dmab in the treatment of postmenopausal osteoporosis. Dmab seems safe and effective in patients with severe renal impairment, however, the risk of severe hypocalcemia should be considered. Sequential treatment with BPs or Dmab is important to maintain or even increase bone mass and possibly improve mineralization in patients previously treated with osteoanabolic medications. Although not currently approved by the vast majority of health systems around the world, coadministration of TPTD with Dmab or ZOL, but not ALN, provides more rapid BMD gains at all skeletal sites.

Suggested treatment strategy

In ambulatory patients with normal renal function, it is probably better to start treatment with a BP for 5 years and reconsider. Dmab instead is an excellent choice in cases of upper gastrointestinal problems, BP treatment failure or even in subjects needing continuation of osteoporosis treatment after some years under BPs. In patients with very low BMD, patients with renal impairment, and elderly subjects with polypharmacy it seems better to initiate treatment with Dmab. In any case, the informed patient's preference should be taken into consideration in the design of treatment strategy, as it will significantly affect the adherence to treatment.

Declaration of interest

Athanasios D Anastasilakis has received lecture fees from Amgen, Eli-Lilly, ELPEN, ITF Hellas, Rafarm, VIANEX. Stergios A Polyzos has received a lecture fee from AMGEN. Polyzois Makras has received lecture fees and research grants from Amgen; lecture fees from Glaxo, Lilly, Pfizer, Leo, Genesis, ELPEN, VIANEX.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

Osteoclast and osteoclast precursor in Fig. 1 were downloaded from Servier Medical Art, supported by Servier, which is licensed under a Creative Commons Attribution 3.0 Unported License.

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Received 19 January 2018

Revised version received 10 April 2018

Accepted 23 April 2018