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REVIEW

Effectiveness of Sequential Treatment with Zoledronic Acid Following Discontinuation of Denosumab in Osteoporosis: A Narrative Review

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Abstract: Denosumab is a recently developed anti-osteoporosis agent widely applied in the treatment of osteoporosis in postmenopausal women. As a potent inhibitor of bone resorption, it significantly increases bone mineral density, lowers elevated bone turnover rates, and reduces fracture risk. Because denosumab does not bind to the bone matrix, its effects decrease rapidly after discontinuation, a process commonly known as the "rebound effect." Research has shown that administering zoledronic acid after stopping denosumab can help preserve bone density and reduce the likelihood of vertebral fractures. However, the exact effectiveness of this sequential approach and the factors influencing it, including the duration of prior denosumab treatment, timing, and frequency of zoledronic acid administration, remain insufficiently understood. To address these uncertainties, this review evaluates the effects of sequential zoledronic acid therapy on subsequent changes in bone density, bone turnover markers, fracture risk, and adverse reactions. We also examined in detail the dosage strategies, administration intervals of zoledronic acid, and length of preceding denosumab use across studies, aiming to assist clinicians in designing more evidence-based and clinically relevant sequential treatment protocols.

Keywords: denosumab, zoledronic acid, bone mineral density, bone transformation markers, vertebral fractures

Introduction

Over recent decades, the incidence of osteoporosis has steadily risen, driven by an aging population, longer life expectancy, and widespread unhealthy dietary habits and sedentary lifestyles. Osteoporosis is a chronic skeletal condition characterized by disrupted bone metabolism. Its onset is often silent, and it typically presents as a reduction in both bone mass and structural integrity, resulting in a measurable decline in bone mineral density.[1] According to the World Health Organization (WHO), osteoporosis is defined by a bone density that is 2.5 standard deviations or more below the average of young healthy adults (T-score ≤ -2.5).[2] This decline in bone density sharply increases the risk of both vertebral and non-vertebral fragility fractures,[3] and is strongly associated with elevated morbidity, mortality, healthcare utilization, medical expenses, and deterioration in quality of life.[4–7]

In recent years, notable progress has been made in pharmacological interventions for osteoporosis. These treatments primarily work by increasing bone density and regulating bone remodeling, which helps reduce the likelihood of osteoporotic fractures.[8–10] Among these therapies, monoclonal antibodies that target the receptor activator of nuclear factor kappa-B ligand (RANKL), a key regulator of bone turnover, represent a major advancement. Denosumab (Dmab), a fully human monoclonal antibody against RANKL, is now widely prescribed for postmenopausal women with osteoporosis.[11–14] As a potent anti-resorptive agent, Dmab is administered via subcutaneous injection every six months. It reversibly suppresses the formation, activity, and survival of osteoclasts, which substantially reduces bone resorption.

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Clinical studies have confirmed that Dmab can significantly increase bone density in postmenopausal women with osteoporosis, suppress elevated bone turnover, and reduce fracture risk.[15,16] During the administration of Dmab, it is essential to dynamically monitor changes in blood calcium levels, vitamin D status, bone density, and other relevant indicators. Additionally, potential drug-related adverse reactions, such as allergic reactions, hypotension, and osteonecrosis of the jaw, should be closely observed. The corresponding management flowchart algorithm is presented in Figure 1. Moreover, long-term follow-up data indicate that Dmab continues to lower the incidence of new vertebral, non-vertebral, and hip fractures over treatment durations of up to 10 years.[17–19]

However, unlike bisphosphonates (BPs), Dmab does not bind to the bone matrix, and its effects are reversible. Following Dmab discontinuation, bone turnover markers (BTMs) rise rapidly, surpassing baseline levels within 9 months after the final injection and remaining elevated for approximately 2 years, before gradually returning to baseline around month 30. Consistent with this, bone mineral density (BMD) gained during treatment gradually declines after cessation, typically returning to pretreatment levels by 12 to 24 months.[11,20] This process is commonly referred to as the "rebound effect", likely resulting from increased osteoclastogenesis that drives bone turnover beyond baseline levels.[20–22] During this phase of accelerated turnover, the risk of "rebound bone turnover-related vertebral fractures" increases substantially,by approximately 7%.[23–25] The research revealed that among patients who discontinued Dmab treatment, 60.7% of vertebral fracture cases involved multiple fractures, compared to only 38.7% in the group that discontinued placebo treatment.[26] Furthermore, another study indicated that delayed initiation of Dmab was associated with a fourfold increase in the risk of developing any vertebral fracture.[27,28] In response to these concerns, clinical guidelines published in 2017 clarified that the concept of a "drug holiday" applies only to zoledronic acid (ZOL) and not to Dmab, for which sequential therapy is necessary.[29] To reduce the risk associated with the rebound effect, it is recommended to initiate BPs therapy within 6–9 months of the final Dmab injection,[30–32] with intravenous ZOL being the most extensively studied option.[33–35] As a BP, ZOL also suppresses bone resorption. However, in contrast to Dmab, its effects can persist for years after treatment ends.[36]

At present, reported outcomes on the efficacy of ZOL in maintaining Dmab-induced BMD gains remain inconsistent. Some studies have indicated that most patients maintain stable BMD at one year post-treatment,[33,37,38] while others suggest only partial preservation.[39,40] The variation in outcomes is believed to depend mainly on two clinical factors: the

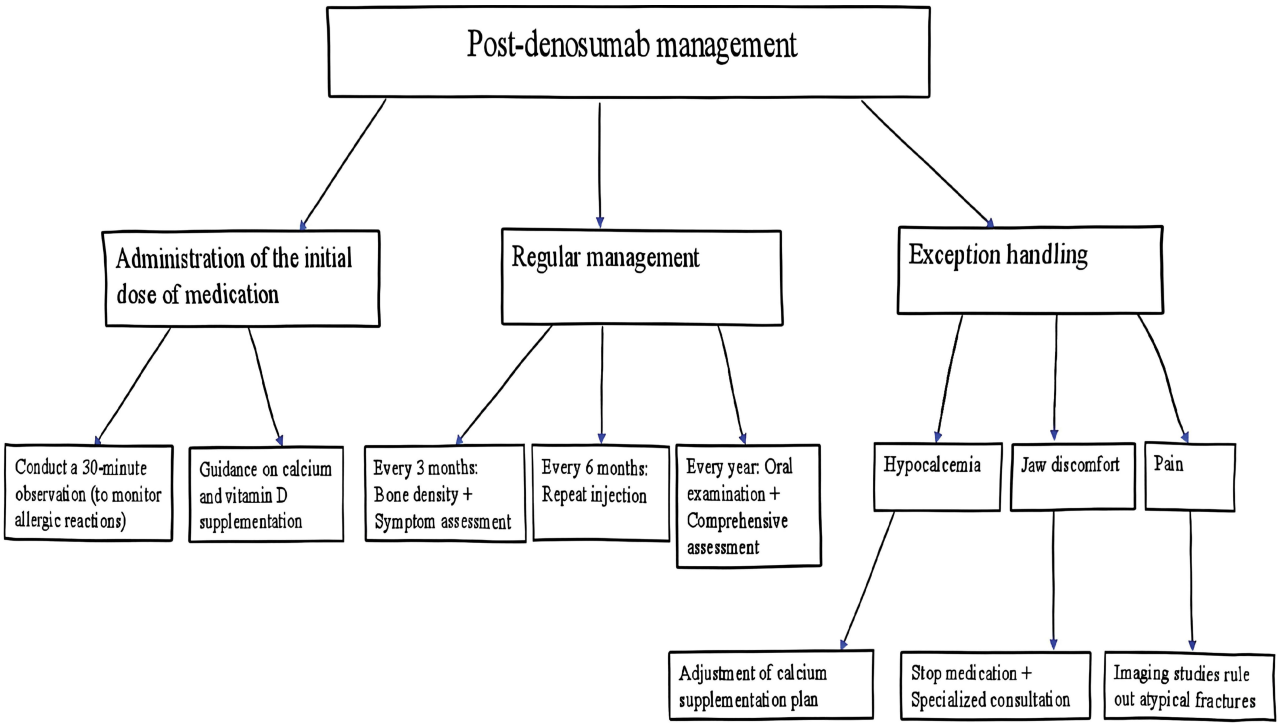

Figure 1 The guide of post-denosumab management.

timing of ZOL infusion and the length of prior Dmab use.[34,40,41] Despite current knowledge, the optimal regimen for ZOL, regarding timing, frequency, and duration, after Dmab discontinuation is still under investigation. Therefore, we collected all relevant studies on the sequential treatment with ZOL after discontinuation of Dmab published up to May 2025 from the PubMed databases and conducted a comprehensive analysis. This review therefore aims to examine the effects of sequential ZOL therapy on subsequent BMD, BTMs, fracture risk, and adverse events. Additionally, it analyzes treatment intervals, ZOL dosing schedules, and duration of preceding Dmab use, with the goal of offering more practical guidance to clinicians. Table 1 provides a list of studies[34,35,39,42–44] on on sequential ZOL treatment following Dmab discontinuation, which will be described in detail later in this review.

The Efficacy of Sequential Zoledronic Acid Treatment After Discontinuation of Denosumab

We compiled and analyzed data on the effects of sequential ZOL on subsequent BMD, BTMs, fracture incidence, and adverse reactions, as presented in Table 2.

The Influence on Bone Mineral Density

Following the discontinuation of Dmab, the BMD gained during treatment gradually declines, a process widely referred to as the "rebound effect." Data from Table 2 suggest that sequential ZOL can partly maintain the BMD improvements achieved during Dmab therapy. In a study by Everts-Graber et al, 120 postmenopausal women with osteoporosis received a 5 mg dose of ZOL sodium 6 months after their final Dmab injection. Their findings showed that BMD decreased by 3.3% at the lumbar spine (following a 6.4% gain from baseline), by 2.2% at the total hip (after a 2.4% increase), and by 1.5% at the femoral neck (following a 2.0% gain). Despite these reductions, the BMD gains retained were 66%(95% CIs:57–75%) at the lumbar spine, 49%(95% CIs:31–67%) at the total hip, and 57%(95% CIs:25–89%) at the femoral neck, indicating that more than half of the improvement was preserved at most sites.[39] Similar results were reported by Horne et al, who found that intravenous ZOL administered after Dmab preserved 73% ((95% CIs:61–85%) of the spinal BMD benefits achieved through the use of Dmab previously, and 87% (95% CIs:77–98%) of the total hip BMD benefits. In contrast, the corresponding spinal and hip bone densities of patients who did not receive treatment only retained 22% ((95% CIs:7–37%) and 8% ((95% CIs: −31-47%), respectively.[50] Kadaru et al compared dual-energy X-ray absorptiometry (DXA) results taken at the end of Dmab treatment with those after the first ZOL infusion. Their findings showed a significant decrease in BMD at the femoral neck, while the lumbar spine and total hip showed a non-significant downward trend. Nevertheless, BMD at all three sites remained above the values recorded before initiating Dmab.[43] Additionally, Everts-Graber et al compared BMD outcomes between women who received ZOL sodium after stopping Dmab and those who received no follow-up treatment. The results showed that patients given sequential ZOL had significantly higher BMD at all measured sites compared to those without subsequent therapy,[34] a finding consistent with results reported by Tutaworn et al.[42] Anastasilakis et al divided postmenopausal women previously treated with Dmab into two groups. One group received a single 5 mg ZOL infusion 6 months after the last Dmab dose, while the other group continued with two additional 60 mg Dmab injections. At 12 months, both groups had increased lumbar spine bone mineral density (LS-BMD) compared with baseline, with no statistically significant difference between them. However, by 24 months, LS-BMD in the ZOL group had returned to baseline, whereas the Dmab group experienced a significant decline from the 12-month value, dropping below baseline levels.[33] In a 3-year follow-up of patients treated with ZOL, 82.6% maintained BMD within the osteopenia range, and only four patients had values below the osteoporosis threshold.[45] At 5 years, 50% of the patients still had BMD in the osteopenia range, suggesting that more than half of postmenopausal women who transitioned from osteoporosis to osteopenia after Dmab treatment could sustain their BMD for up to 5 years with a single ZOL sodium infusion.[47]

The Influence on Bone Turnover Markers

BTMs change rapidly after Dmab is discontinued without follow-up treatment. Within 3–6 months after stopping Dmab, both C-terminal telopeptide of type I collagen (CTX) and type I procollagen N-terminal propeptide (PINP) exceed pretreatment levels, with median peak increases of 63% and 47% from baseline, respectively.[11,20] These elevated levels persist for up to 2

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Table 1 Characteristics of Included Reports (N=16)

Author, Country and Published Year	Study Design	Patients	Intervention Measures	Times	Main Outcome Measures	Conclusions
Makras, Greece, 2021[41]	A multicenter prospective cohort study	47 postmenopausal women	27 women received 6 Dmab injections (≤ 6 group); 20 women received > 6 Dmab injections (> 6 group)	1 year	Changes in LS-BMD	The duration of Dmab treatment significantly affected the efficacy of subsequent ZOL sodium infusion in maintaining BMD gain.Frequent follow-up is recommended for patients treated with Dmab for more than 3 years,as additional therapeutic interventions may be required.
Anastasilakis, Greece, 2019[33]	A prospective cohort study	57 postmenopausal women	30 women received Dmab; 27 women received ZOL	2 years	Changes in LS-BMD between the two groups from 12 to 24 months	In most women with postmenopausal osteoporosis treated with Dmab in whom discontinuation of treatment is considered when a non-osteoporotic BMD is achieved,a single intravenous infusion of ZOL 5 mg given 6 months after the last Dmab injection prevents bone loss for at least two years independently of the rate of bone turnover.
Makras, Greece, 2020[45]	A prospective cohort study	23 patients with osteoporosis	NR	3 years	Changes in LS-BMD	A single i.v. infusion of ZOL 5 mg, given at 6 months after the last injection of Dmab therapy maintains for three years BMD gains in the majority of patients previously treated with Dmab for an approximate period of 2.5 years.
Solling, Denmark, 2020[40]	A randomized study	61 patients with osteoporosis	6M group,n=20; 9M group,n 20; OBS group,n=21	1 year	Changes in LS-BMD 6 months after ZOL and the proportion of patients who failed to maintain BMD	In patients discontinuing Dmab after long-term treatment a single intravenous infusion of ZOL 5 mg given 6 or 9 months after the last Dmab injection or when bone turnover is increased is not sufficient to completely prevent bone loss.
Laroche, France, 2023[46]	A prospective pilot study	13 patients with osteoporosis	Six months after the last dose of Dmab 60 mg,the subsequent injection was performed with a reduced dose of 30 mg, and the month-12 injection was a 15-mg injection.	1 year	Changes in LS-BMD and TH-BMD	Gradual dose reduction of Dmab (30 mg then 15 mg) does not prevent bone loss in the hip and partially maintains the initial gain at the spine.

Anastasilakis, Greece, 2023[47]	A prospective, randomized, controlled clinical trial	19 patients with osteoporosis	NR	5 year	The BMD results of women Followed for an additional 2 years up to a total of 5 years after the ZOL infusion	More than half of the osteoporotic women who became osteopenic with Dmab treatment and stopped it, maintained the BMD gains 5 years after a single ZOL infusion with no additional treatment.
Everts-Graber, Switzerland, 2020[39]	A retrospective observational study	120 women with postmenopausal osteoporosis	NR	8 year	The effect of a single ZOL infusion, administered 6 months after the last Dmab injection, on fracture occurrence and loss of BMD	A single infusion of 5 mg ZOL after a 2 to 5-year Dmab treatment cycle retained more than half of the gained BMD and was not associated with multiple VFx.
Everts-Graber, Switzerland, 2022[48]	A retrospective observational study	282 women with postmenopausal osteoporosis	Short duration of treatment:144 women received 5 ± 2 Dmab injections; medium duration:84 women received 10 ± 2 Dmab injections; long duration:54 women received 15 ± 2 Dmab injections	12-24 months	Changes in BMD and BTMs after discontinuation of Dmab	Rebound-associated bone loss reached a plateau after Dmab treatment durations of 4–6 years, irrespective of the frequency of subsequent ZOL therapy.
Everts-Graber, Switzerland, 2022[49]	A retrospective observational study	151 patients with osteoporosis	1Dmab,1 ZOL,n = 32; 1Dmab,n = 9; 5Dmab,1ZOL,n = 110	1 year	Changes in BMD and BTMs before therapy and 18 months later	A single Dmab injection followed by ZOL led to a remarkable gain of BMD at the LS and TH within a short time.
Anastasilakis, Greece, 2021[35]	A retrospective observational study	42 postmenopausal women with osteoporosis	Early-ZOL(n =27):a single ZOL infusion at 6 months after the last Dmab injection; Late-ZOL(n =15):a single ZOL infusion at 18 months after the last Dmab injection	1 year	Annual changes in LS-BMD, FN-BMD and BTMs (PINP, CTX) at 6 and 12 months following ZOL infusion	There is no clear clinical benefit compared to the early infusion,while any theoretical advantage is counterbalanced from the expected bone loss, especially at the LS,and the risk of rebound-associated fractures.
Everts-Graber, Switzerland, 2021[34]	A retrospective study	219 women with osteoporosis	171 women received ZOL after Dmab discontinuation; 26 women had no subsequent treatment; 22 women received other therapies (other BPs or a SERM)	2 years	Fracture rate, longitudinal BMD changes and BTMs within 2 years after Dmab discontinuation	Compared to no subsequent therapy, ZOL was associated with fewer VFx after Dmab. Further, BMD loss depended on Dmab treatment duration, age, prior BPs therapy and BMD gain under Dmab therapy, whereas BTMs levels were associated with bone loss at the total hip and Dmab treatment duration.

(*Continued*)

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Table 1 (Continued).

Author, Country and Published Year	Study Design	Patients	Intervention Measures	Times	Main Outcome Measures	Conclusions
Horne, NewZealand, 2018[50]	A case series	19 postmenopausal women with osteoporosis	5 women received risedronate; 11 women received ZOL; 3 women not to receive further treatment	1 years	Re-assesses the role of BPs following the use of Dmab	Delaying administration of intravenous BPs when transitioning from short-term Dmab appears to increase the extent to which the gains in BMD are maintained.
Kondo, Japan, 2020[51]	A multicenter retrospective observational study	30 patients with osteoporosis	Performed sequential therapy using ZOL	1 years	To investigate the effects of sequential therapy using ZOL on any adverse events after Dmab discontinuation	Sequential therapy using ZOL could suppress the decrease of BMD,and increase of BTMs,if the period of Dmab administration was less than 3 years.
Tutaworn, USA, 2023[42]	A retrospective study	121 patients with osteoporosis	33 patients received NT; 88 patients received BPs (22 RIS,34 ALN,32 ZOL)	1 years	BMD change after 1 year between groups at the LS,FN, and TH	Subsequent treatment with ALN or ZOL but not NT and RIS mitigates BMD loss after Dmab discontinuation. NT and three BPs treatments:RIS, ALN,ZOL.
Kadaru, USA, 2021[43]	A retrospective case series	12 patients with osteoporosis	12 patients received ZOL after Dmab discontinuation	1 years	Changes in BMD after 1 year	A single dose of ZOL administered approximately 6 months after Dmab leads to some BMD loss, mostly within 1 year of ZOL administration, particularly in patients with osteoporosis at the time of Dmab discontinuation.
Grassi, Italy, 2019[44]	A retrospective study	120 patients with osteoporosis	19 patients have not been treated; 101 patients have been treated with BPs (28 ALN;73 ZOL, single infusion)	NR	The incidence of both clinical and morphometric VFx in treated group and non-treated group	The Dmab withdrawal is associated with an increased risk of clinical but not morphometric VFx. Therapy with ALN or with a single ZOL treatment are partially effective in reducing the increased VFx risk after Dmab withdrawal.

Abbreviations: ZOL, zoledronic acid; Dmab, denosumab; CTX, typelcollagen carboxyterminal peptide; PINP, procollagen type IN-terminalpropetide; BMD, bone mineral density; BTMs, bone transformation markers; BPs, bisphosphonates; LS, lumbar spine; FN, femoral neck; TH, total hip; VFx, vertebral fractures; NT, no subsequent treatment; RIS, risedronate; ALN, alendronate; NR, not reported.

Table 2 The Efficacy of Sequential Zoledronic Acid Treatment After Discontinuation of Denosumab

Author, Country and Published Year	BMD	BTMs	Fracture	Adverse
Makras, Greece, 2021[41]	LS-BMD:compared to baseline, LS-BMD did not change at 12 months in the ≤ 6 group. However, in the > 6 group LS-BMD significantly decreased. The percentage change of LS-BMD of the ≤ 6 group was significantly different compared with the relevant change of the > 6 group. FN-BMD:FN-BMD did not change in the ≤ 6 group but decreased significantly in the > 6 group.	No patient had values above the upper limit of the postmenopausal range for both P1NP and CTX after 12 months post-ZOL infusion.	During the study 1 patient of the > 6 group sustained a clinical VFx, 12 months after ZOL. No other fractures were observed.	Twenty-three (49%) of the 47 patients developed symptoms compatible with a transient acute phase reaction.
Anastasilakis, Greece, 2019[33]	The differences in BMD changes between the two groups 24 and 12 months after discontinuation of Dmab (6 months after the last injection) for the ZOL and Dmab group, respectively, were also statistically significant both at the LS-BMD and the FN-BMD.	High levels of BTMs persisted 18 months after the last Dmab injection in the majority of studied patients.	Three patients sustained clinical VFx, one in the ZOL group (3.7%) and two in the Dmab group (6.7%).	Eighteen (66.7%) of the 27 women in the ZOL group developed symptoms compatible with a transient acute phase reaction that was treated with paracetamol.
Makras, Greece, 2020[45]	Pairwise comparisons of LS-BMD values between study years showed no difference at any time point. Similarly,FN-BMD values did not change significantly at any time point during the 3-year follow-up.	Serum BTMs values changed significantly over time. At the end of the observation period only one patient had serum P1NP levels above the upper limit of normal postmenopausal values (76 ng/mL) while serum CTX values were within the reference range for postmenopausal women (< 1 ng/mL) in all patients.	One woman sustained a low-energy fracture of the right 5th metatarsal.	NR
Sølling, Denmark, 2020[40]	LS-BMD:no significant difference between groups 6 months and 12 months after the initial ZOL treatment or at month 12; FN-BMD:significant difference between groups 6 months after the initial ZOL treatment. No significant difference between groups 12 months after the initial ZOL treatment or at month 12; TH-BMD:no significant difference between groups 6 months and 12 months after the initial ZOL treatment or at month 12.	When comparing changes from baseline to 12 months after baseline,there were no differences between groups for CTX or P1NP; however, p-osteocalcin increased more in the 6-month group.	Four patients suffered a fracture during follow-up.	Nearly 61% experienced flu-like symptoms after the initial treatment with ZOL.No cases of osteonecrosis of the jaw or atypical femoral fracture were observed.

(*Continued*)

Table 2 (Continued).

Author, Country and Published Year	BMD	BTMs	Fracture	Adverse
Anastasilakis, Greece, 2023[47]	7 patients required additional treatment (ZOL or Dmab) during follow-up because LS-BMD T-score decreased below −2.5; 9 patients remained osteopenic at 5 years not requiring retreatment; In all patients who did not receive additional treatment remained also osteopenic at 5years.	NR	None of the patients sustained a new clinical or morphometric vertebral or peripheral fracture during the 5-year follow up period.	NR
Everts-Graber, Switzerland, 2020[39]	BMD decreased by 3.3% at the LS (+6.4% compared to baseline), 2.2% at the TH (+2.4% compared to baseline) and 1.5% at the FN (+2.0% compared to baseline).	The mean CTX concentration was within the normal range for postmenopausal women and the mean P1NP concentration was within the normal range.	Three patients developed symptomatic VFx and four patients developed peripheral fractures. No patients exhibited multiple VFx.	NR
Everts-Graber, Switzerland, 2022[48]	The changes after Dmab discontinuation and subsequent ZOL were significantly different between short and medium Dmab durations,but not between medium and long durations.	Twenty-four women with longer durations from 5 to 9 years had a ≥ 2-fold increases in CTX and/or P1NP measured at 3 months after the first ZOL injection.	10 patients sustained non VFx and 9 suffered VFx. Of the 9 patients with VFx, 4 had multiple VFx:one with medium-duration Dmab treatment (5 years) and 3 with long-term Dmab (7.5, 8 and 8.5 years of Dmab therapy, respectively).	NR
Everts-Graber, Switzerland, 2022[49]	Compared to patients without subsequent BPs therapy after the Dmab injection, patients with subsequent ZOL demonstrated a significant increase in BMD at the LS,TH and FN. Compared with patients with subsequent BPs therapy after the five Dmab injections (2.5 years), patients with subsequent ZOL demonstrated a significant increase in BMD at the LS,TH and FN.	This decrease in P1NP concentration was significant.	Neither VFx or peripheral fractures were recorded.	NR
Anastasilakis, Greece, 2021[35]	There was a significant difference in the percent changes in LS-BMD between the late-ZOL (−3.5%) and early-ZOL (+ 1.7%) group. On the contrary,no statistical difference was found between the percent changes in FN- BMD in the late-ZOL (−1.6%) and early-ZOL (+ 0.1%).	P1NP and CTX gradually increased in the early-ZOL group, while profoundly decreased and remained suppressed in the late-ZOL infusion.	No clinical fracture was recorded, and no radiological fracture from the late-ZOL group. only one patient from the early-ZOL group sustained one new VFx.	No serious adverse event was observed. 60% of patients from late-ZOL and 66.7% from early-ZOL group developed symptoms compatible with a transient acute phase reaction that was treated with paracetamol.

Everts-Graber, Switzerland, 2021[34]	Patients who received either ZOL or BPs/SERM after Dmab discontinuation demonstrated a significantly lower decrease of BMD at all sites compared to patients who received no treatment. When analysing only treated patients, no difference was found between patients with ZOL and those with other BPs or SERM.	The levels of CTX and P1NP did not different according to the subsequent therapy received after Dmab discontinuation.	No subsequent treatment:3 VFx and 1 Non-VFx; ZOL:3 VFx and 3 Non-VFx; Other therapy (BPs or SERM):2 VFx.	NR
Horne, NewZealand, 2018[50]	In the ZOL group,LS-BMD was17.3% above baseline at trial-end, and still 12.3% above baseline a year later, a 73% retention of the treatment benefit.The comparable BMD figures for the TH were 10.7 and 9.2% above baseline, a 87% retention of treatment effect. In contrast, those not receiving treatment after the conclusion of the FRAME trial lost 80–90% of the BMD gained on-trial in the following 12 months. Women treated with RIS showed an intermediate response.	In the ZOL group, mean PINP 6 months post-FRAME was 23 ± 4 ug/L and at 12 months it was 47 ± 8 ug/L, suggesting that repeat ZOL dosing is needed at 1 year to maintain the BMD gains.	NR	NR
Kondo, Japan, 2020[51]	Compared to pre-Dmab administration, there was a significant increase in BMD change rate at LS and FN at the start of ZOL administration,at 6 months after ZOL administration,and at 12 months after ZOL administration.	Compared with at the start of Dmab administration, a significant decrease was observed at the average serum P1NP levels at the start of ZOL administration,6 months after ZOL administration and 12 months after ZOL administration.	Neither clinical VFx nor X-ray morphological new VFx occurred in any of the 30 patients evaluated for fractures at 6 months and 12 months after ZOL administration.	During the Dmab administration,there was no clinically significant adverse events.
Tutaworn, USA, 2023[42]	The absolute LS-BMD significantly decreased in the no treatment group and in the RIS group. Patients who received either ALN or ZOL after Dmab discontinuation demonstrated a smaller absolute BMD change. Absolute FN and TH BMD were significantly decreased in the no treatment group.	NR	A total of 7 female patients sustained VFx (n=5). Multiple VFx (more than 1 level) occurred in 4 out of 5 instances of VFx in the no treatment group.	NR

(*Continued*)

Table 2 (Continued).

Author, Country and Published Year	BMD	BTMs	Fracture	Adverse
Kadaru, USA, 2021[43]	A significant decline in BMD at the femoral neck. A non-significant downward trend was seen at the LS and TH. However,the BMD at all 3 sites remained higher than the BMD measured prior to initiation of Dmab.	NR	1 patient sustained a distal radial fracture upon a fall.	NR
Grassi, Italy, 2019[44]	No statistically significant difference between treated and non-treated group, however non treated patients seems to present a more pronounced worsening of TH and FN BMD.	NR	10 patients (8.3%) experienced a VFx, which occurred in 4 patients (21.1%) from not-treated group, but, importantly,even in 6 patients (5.9%) from treated group.	NR

Abbreviations: LS-BMD, lumbar spine bone mineral density; FN-BMD, femoral neck bone mineral density; TH-BMD, total hip bone mineral density; SERM, selective estrogen receptor modulator.

years before gradually declining to pretreatment values by around 24 months. As shown in Table 2, sequential ZOL appears to lessen the rebound in BTMs to some degree. Studies report that when 5 mg of ZOL is given 6 months after the final Dmab injection, serum CTX and P1NP levels rise but remain below the upper limit of the postmenopausal range.[39] In a study by Anastasilakis et al, BTMs in the ZOL group rose slightly in the first year and then stabilized. At 24 months, only 7.4% of patients had PINP levels above the postmenopausal reference range, and no patients had elevated CTX levels. In contrast, patients who remained on Dmab showed significant increases in both CTX and PINP by month 15 (9 months after their last injection), with levels significantly higher than those in the ZOL group. By month 24, only 6.6% of patients in the Dmab group had serum PINP within the premenopausal range, while 40% had CTX values within that range. These results suggest that although a single ZOL infusion can suppress the rebound in BTMs, it does not fully maintain BTMs levels within the reference range (either premenopausal or postmenopausal) 2 years after stopping Dmab.[33] An extended follow-up of the same study found that, at 3 years after ZOL treatment, only one patient had a serum P1NP value above the postmenopausal reference range, and none had elevated CTX levels. This suggests that ZOL can effectively restrain the rebound in BTMs following Dmab discontinuation and may provide lasting control.[45] Additionally, variation in BTMs levels was found to be associated with the duration of prior Dmab treatment.[31] This finding aligns with the results reported by Everts-Graber et al, who observed that most patients with long-term Dmab use (5 to 9 years) experienced a ≥2-fold rise in CTX and/or PINP levels within 3 months of their first ZOL infusion. These patients required ongoing treatment with ZOL (≥2 infusions), in contrast to those with shorter Dmab exposure (≤5 years).[48] However, other studies reported that serum CTX and P1NP levels increased significantly within 12 months after a single ZOL injection, regardless of whether prior Dmab treatment duration was ≤6 months or >6 months, yet these values remained within the postmenopausal reference range.[41] In studies focusing on a single ZOL infusion following one course of Dmab, the average P1NP level before treatment was 53 ng/mL((95% CIs:28–78%), which declined to 36 ng/mL((95% CIs:22–49%) at 18 months, suggesting a significant reduction in P1NP concentration.[49]

The Impact on the Risk of Fractures and Other Adverse Reactions

The "rebound phenomenon" following Dmab discontinuation appears to be linked with an increased risk of clinical vertebral fractures (VFx). Several case reports and case series have documented VFx in patients who stopped Dmab, with most cases reported in women,[52] though VFx in men[53] and hip fractures[54] have also been described. A population-based cohort study of 2594 patients showed a gradual rise in fracture risk corresponding to the time elapsed since the last Dmab injection.[55] The cumulative fracture risk was 27.3 per 1000 within 4 weeks after discontinuation, increased to 32.2 per 1000 during weeks 4 to 16, and reached 42.4 per 1000 beyond 16 weeks. Evidence indicates that the risk of both clinical and multiple VFx increases significantly in patients who stop Dmab without follow-up BPs therapy. In contrast, BPs offer protection against VFx. Among the studies collected on sequential treatment with ZOL following the discontinuation of Dmab, a total of 5 prospective cohort studies[33,40,41,45,47] and 9 retrospective observational studies[34,35,39,42–44,48,49,51] assessed the risk of fractures, as presented in Table 2. In a 2-year cohort study on sequential ZOL treatment, three patients developed clinical VFx, one in the ZOL group (3.7%) and two in the Dmab group (6.7%).[33] During a 3-year follow-up, no major non-vertebral fragility fractures were reported in the ZOL group, and only one patient sustained a metatarsal fracture.[45] The follow-up was extended to 5 years, and no additional clinical or radiological VFx were observed in the ZOL group.[47] However, in retrospective observational studies,Everts-Graber et al found that the incidence of VFx was lower in patients who received ZOL compared to those who received no follow-up treatment, with no significant difference between the ZOL group and those treated with other agents such as selective estrogen receptor modulators (SERMs) or different BPs.[34] A retrospective study by Kadaru et al showed that the incidence of VFx was 5.5% in patients who received BPs after Dmab, significantly lower than the 21.1% observed in the untreated group. Notably, all cases of multiple VFx occurred in patients who did not receive follow-up treatment.[43] This result aligns with findings from Tutaworn, Solling, and others,[39–42] who reported no cases of multiple VFx in patients following sequential ZOL treatment. However, Everts-Graber et al observed a different pattern when analyzing patients by the number of prior Dmab injections. Among those who received ZOL after Dmab discontinuation, 9 patients developed VFx, including 4 cases involving multiple vertebrae. Of these, 1 patient had mid-term Dmab exposure (5 years), while the other 3 had undergone long-term treatment (7.5, 8, and 8.5 years).[48] These findings suggest that the duration of Dmab use may influence the effectiveness of subsequent therapy and highlight a need for further investigation. Importantly, no cases of

osteonecrosis of the jaw or atypical femoral fractures were reported among patients who received sequential ZOL. About half of the patients experienced symptoms resembling a transient acute-phase reaction, which were effectively relieved with symptomatic treatment using paracetamol.

The Related Factors Influencing the Efficacy of Sequential Zoledronic Acid Treatment After Discontinuation of Denosumab

One prevailing theory is that the "rebound phenomenon" observed after stopping Dmab may be caused by the reactivation of osteoclast precursors that remained dormant during treatment.[56] Considering this rebound effect, long-term Dmab use is generally advised. However, there are specific situations in which discontinuation becomes necessary. These include the development of adverse drug reactions, cases where prolonged treatment has already raised bone density to a level where further reduction in fracture risk is unlikely,[57] or when bone density reaches the upper half of the osteopenia range and the patient has a long life expectancy ahead. For patients who discontinue Dmab, follow-up anti-resorptive therapy should be initiated within the first year, along with close monitoring, as the majority of bone loss tends to occur within the initial 12 months post-discontinuation. Current evidence suggests that although sequential ZOL cannot fully preserve the BMD gains achieved with Dmab, it can retain more than half of the BMD increase at the lumbar spine, total hip, and femoral neck.[34,39,42,43,50] Additionally, sequential treatment with ZOL appears to reduce the extent of rebound in BTMs to some degree.[33,39,45] Still, variations exist among studies regarding the degree and duration of BMD preservation. These inconsistencies imply that certain underlying factors may influence the patient's response to ZOL. To better understand these influences, we summarized the Dmab and ZOL treatment details from the included studies, as shown in Table 3.

The Duration of Denosumab Use Before Sequential Zoledronic Acid Treatment

Makras et al divided postmenopausal women into two groups based on the number of prior Dmab infusions and administered a single ZOL infusion 6 months after the final Dmab dose. After one year, no significant changes in LS-BMD or femoral neck bone mineral density (FN-BMD) were observed in the ≤6 group (≤6 denosumab injections). In contrast, the >6 group (>6 injections) showed significant reductions in both LS-BMD and FN-BMD. These results suggest that the duration of Dmab therapy has a significant impact on the effectiveness of subsequent ZOL in maintaining BMD.[41] Everts-Graber et al used more detailed groupings based on the number of Dmab injections: the "short-term" group (5±2 injections), the "medium-term" group (10±2), and the "long-term" group (15±2). Their findings showed that after Dmab discontinuation and sequential ZOL treatment, changes in BMD at the lumbar spine, total hip, and femoral neck differed significantly between the short-term and medium-term groups, with greater bone loss seen in the medium-term group. However, no significant difference in bone loss was found between the medium-term and long-term groups. The authors proposed that after 4–6 years of Dmab treatment, rebound-related bone loss may reach a plateau, regardless of how frequently ZOL is given afterward.[48] Additionally, compared with patients who underwent short-term Dmab treatment (≤5 years), most individuals with longer treatment durations (5 to 9 years) required two or more ZOL infusions following Dmab discontinuation. The same study found that within 12 months after stopping Dmab, there were no significant differences in LS-BMD, total hip BMD(TH-BMD), or FN-BMD between women who received a single ZOL infusion and those who received two.[48] In another study examining the effect of a single ZOL infusion following one Dmab injection, patients who received ZOL showed significant increases in LS-BMD, TH-BMD, and FN-BMD compared to those who received no BPs after Dmab. Furthermore, patients who had received only one Dmab injection before ZOL showed greater BMD increases at all measured sites than those who received five Dmab injections followed by ZOL.[49] These findings suggest that the severity of the rebound phenomenon is closely linked to the duration of Dmab treatment. Long-term suppression of osteoclast differentiation by Dmab may lead to an expansion of the osteoclast precursor pool. Once Dmab is stopped, these precursors differentiate in a synchronized manner, triggering a sharp rise in BTMs and eventually resulting in the loss of BMD gains achieved during treatment.[34] Therefore, a single 5 mg infusion of ZOL may not be sufficient to counter the bone resorption triggered by extended Dmab use.

Table 3 Related Factors Affecting Curative Effect

Author,Country and Published Year	Patients	BMI(kg/m^2)	Dmab Duration	ZOL Dose/Route/Number	Interval from Last dmab	Follow-Up Length
Makras,Greece,2021[41]	47 postmenopausal women	≤ 6 injections:28.9 ± 3.85 > 6 injections:24.00 ± 5.11	≤ 6 injections:2.2 ± 0.79 years > 6 injections:4.2 ± 0.6 years	ZOL 5 mg/Intravenous infusion/A single	6 months	1 year
Anastasilakis, Greece,2019[33]	57 postmenopausal women	Dmab groups:27.5 ± 0.7 ZOL groups:29.4 ± 0.7	Dmab groups:2.0 ± 0.2years ZOL groups:2.4 ± 0.2 years	ZOL 5 mg/Intravenous infusion/A single	6.5 ± 0.1 months	2 years
Makras,Greece,2020[45]	23 patients	29.5 ± 0.8	2.4 ± 0.2 years	ZOL 5 mg/Intravenous infusion/A single	6.5 ± 0.1 months	3 years
Solling, Denmark,2020[40]	61 patients with osteopenia	6-month group:24.0 ± 4.2 9-month group:24.4 ± 4.6 observation group:24.3 ± 2.9	4.6 ± 1.6 years	Intravenous infusion /5 mg/Once, only one patient used it twice	6 or 9 months or when bone turnover had increased	1 year
Anastasilakis, Greece,2023[47]	19 postmenopausal women	29.7 ± 0.8	2.4 ± 0.2 years	ZOL 5 mg/Intravenous infusion/A single;7 required additional treatment (ZOL or Dmab) during follow-up	6.5 ± 0.1 months	5 year
Everts-Graber, Switzerland, 2022[48]	282 women with postmenopausal osteoporosis	Short Dmab:23 Medium Dmab:22 Long Dmab:22	Short Dmab:5 ± 2 injections Medium Dmab:10 ± 2 injections Long Dmab:15 ± 2 injections	ZOL 5 mg/Intravenous infusion/A single; Twenty-four women received a second ZOL dose 6 months after the first one.	6 months	0.5–1 year
Everts-Graber, Switzerland, 2022[49]	151 patients with osteoporosis	1x Dmab, 1x ZOL:22 1x Dmab:24 5x Dmab,1x ZOL:23	1x Dmab,1x ZOL:1 injection 5x Dmab,1x ZOL:5 injections	ZOL 5 mg/Intravenous infusion/A single	6 months	1 year
Anastasilakis, Greece,2021[35]	42 postmenopausal women with osteoporosis	Early-ZOL:29.4 ± 0.7 Late-ZOL:28.2 ± 0.9	Early-ZOL:2.4 ± 0.2years Late-ZOL:2.8 ± 0.2years	ZOL 5 mg/Intravenous infusion/A single	6 months or18 months	1 year
Everts-Graber, Switzerland, 2021[34]	219 women with osteoporosis	No subsequent treatment (n = 26):24 ± 4.1 ZOL (n = 171):24 ± 3.8 Other therapy (BPs or SERM) (n = 22):23 ± 3.7	No subsequent treatment: mean 5 injections ZOL:mean 5 injections Other therapy (BPs or SERM): mean 5 injections	ZOL 5 mg/Intravenous infusion/A single	6-7 months	2 years
Horne, NewZealand,2018[50]	19 postmenopausal women with osteoporosis	RIS:weight (kg) 66.4 ± 12.6, height (cm)158 ± 1 ZOL:weight (kg)55.9 ± 6.6, height(cm)160 ± 3 No treatment:weight (kg)60.4 ± 8.9,height (cm)161 ± 8	2 years	ZOL 5 mg/Intravenous infusion/A single	6.4–11.8months(median 8months)	1 years
Kondo,Japan,2020[51]	30 patients with osteoporosis	NR	mean 3.1 injections	ZOL 5 mg/Intravenous infusion/A single	9.3months(range 6.1–16.5months)	1 years

(*Continued*)

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Table 3 (Continued).

Author,Country and Published Year	Patients	BMI(kg/m^2)	Dmab Duration	ZOL Dose/Route/Number	Interval from Last dmab	Follow-Up Length
Tutaworn,USA,2023[42]	121 patients with osteoporosis	No treatment (n=33):22.3 ± 2.8 Risedronate (n=22):22.7 ± 2.9 Alendronate (n=34):24.3 ± 4.9 ZOL (n=32):23.2 ± 3.0	No treatment (n=33):4.6 ± 1.6 Risedronate (n=22):5.2 ± 2.4 Alendronate (n=34):6.5 ± 2.8 ZOL (n=32):5.3 ± 2.6	ZOL 5 mg/Intravenous infusion/A single	6.4 ± 1.0 months	1 years
Kadaru,USA,2021[43]	12 patients with osteoporosis	21.9 ± 4.5	5.3 ± 1.2	ZOL 5 mg/Intravenous infusion/A single	6.7 ± 1 months	1 years
Grassi,Italy,2019[44]	120 patients with osteoporosis	Treated (n=101):24.0 ± 3.9 Non-Treated (n=19):24.5 ± 3.9	Treated (n=101):6.6 ± 2.6 Non-Treated (n=19):3.6 ± 1.8	ZOL 5 mg/Intravenous infusion/A single	1-2 months	NR

Furthermore, related studies have shown that compared with placebo, patients treated with Dmab for 2–3 years exhibited a continued increase in matrix mineralization between years 2–3 and year 5, but no further increase was observed beyond the fifth year.[58] This suggests that by year 5 of Dmab treatment, additional minerals had been incorporated into the bone matrix, contributing to a reduction in bone remodeling. However, when Dmab was discontinued and followed by ZOL infusion, the resulting changes in BTMs were sufficient to preserve the newly added mineral content in patients treated for 2–3 years, but not enough to fully retain the higher mineral loads in patients treated for more than 5 years. As a result, patients in the former group maintained bone density, while those in the latter experienced BMD loss.[58] This finding was supported by other studies.[41,48] Makras et al further confirmed that patients who received more than 6 Dmab injections experienced a significant decrease in LS-BMD compared to those who had 6 or fewer injections. A negative correlation was found between the duration of Dmab use and percentage change in LS-BMD.[41] Similarly, Everts-Graber et al observed that patients who received 10±2 Dmab injections had greater BMD loss after transitioning to ZOL than those with 5±2 injections. Interestingly, those who received ≥15±2 injections did not show further bone loss, suggesting that rebound-related BMD decline may level off after 4–6 years of Dmab treatment.[48] Additionally, one study found that patients who received a single Dmab injection followed by ZOL had greater increases in LS-BMD, TH-BMD, and FN-BMD than those who received five Dmab injections before switching to ZOL.[49] This indirectly suggests that the duration of Dmab therapy can influence the effectiveness of subsequent ZOL treatment. The results also imply that if ZOL is administered at a time when a large number of bone multicellular units (BMUs) are active, it can achieve sufficient and sustained suppression of bone turnover.

The Time Points for Sequential Zoledronic Acid Treatment

Beyond the timing of the final Dmab injection, the timing of the subsequent ZOL infusion is also a key clinical consideration. Anastasilakis et al compared ZOL infusions administered 6 months and 18 months after the last Dmab dose over a one-year period. The study showed that delayed ZOL infusion at 18 months led to a notable overall decline in BMD, particularly at the lumbar spine.[35] Solling et al conducted a more detailed subgroup analysis by administering ZOL at 6 months, 9 months, or at the time when BTMs were elevated. Although all groups experienced BMD loss, there were no significant differences in the average percentage changes in LS-BMD, TH-BMD, and FN-BMD across the different time points. However, the 6-month group generally had a slower rate of bone loss, while BMD reduction, especially at the hip, was more pronounced when ZOL infusion was delayed beyond 6 months.[40] Earlier hypotheses suggested that the suppression of bone remodeling by the last Dmab injection could limit the number of active bone resorption surfaces available for intravenous BPs like ZOL to bind, potentially reducing their effectiveness. Based on this, it was proposed that administering ZOL when a greater number of BMUs were active, indicated by elevated BTMs, could lead to more effective and lasting inhibition of bone turnover.[59] However, findings from two randomized trials showed that ZOL effectively suppressed bone turnover regardless of whether it was administered before or after the onset of the rebound phenomenon, with similar reductions in BTMs in both cases.[33,40] Still, the 6-month group consistently showed a slower rate of BMD loss, while delays beyond 6 months were associated with more substantial reductions in BMD, particularly at the hip.[40] Additionally, when ZOL was administered to patients experiencing rebound high bone turnover following Dmab discontinuation, its suppressive effect on BTMs lasted for at least 12 months, similar to the pattern observed in postmenopausal osteoporotic women receiving annual ZOL infusions.[60] This suggests that administering ZOL during periods of abundant bone binding sites, such as when activated BMUs rebound fully, does not offer additional benefit for improving BMD. Current studies support the view that a 6-month interval between the last Dmab injection and the ZOL infusion is optimal, regardless of BTMs levels.[61] This conclusion aligns with the findings of Anastasilakis et al, who reported that ZOL administered 6 months after the final Dmab dose effectively limited bone loss in many patients, making it a safer and more practical clinical choice.[35] Makras et al further proposed that the severity of the patient's disease might influence both the response to Dmab and the rebound risk. More advanced disease often requires longer treatment durations, and upon discontinuation, BMD tends to decline more significantly, often returning closer to baseline.[41] In a prospective pilot study, Laroche et al investigated whether gradually tapering the Dmab dose could help prevent bone loss. After a final 60 mg injection, the dose was reduced to 30 mg at 6 months and to 15 mg at 12 months. One year after the last 15 mg dose, the initial LS-BMD gain was maintained at approximately 39%. However, BMD loss at the hip offset the initial gain. These findings indicate that while tapering the Dmab dose does not prevent hip bone loss, it can help preserve part of the

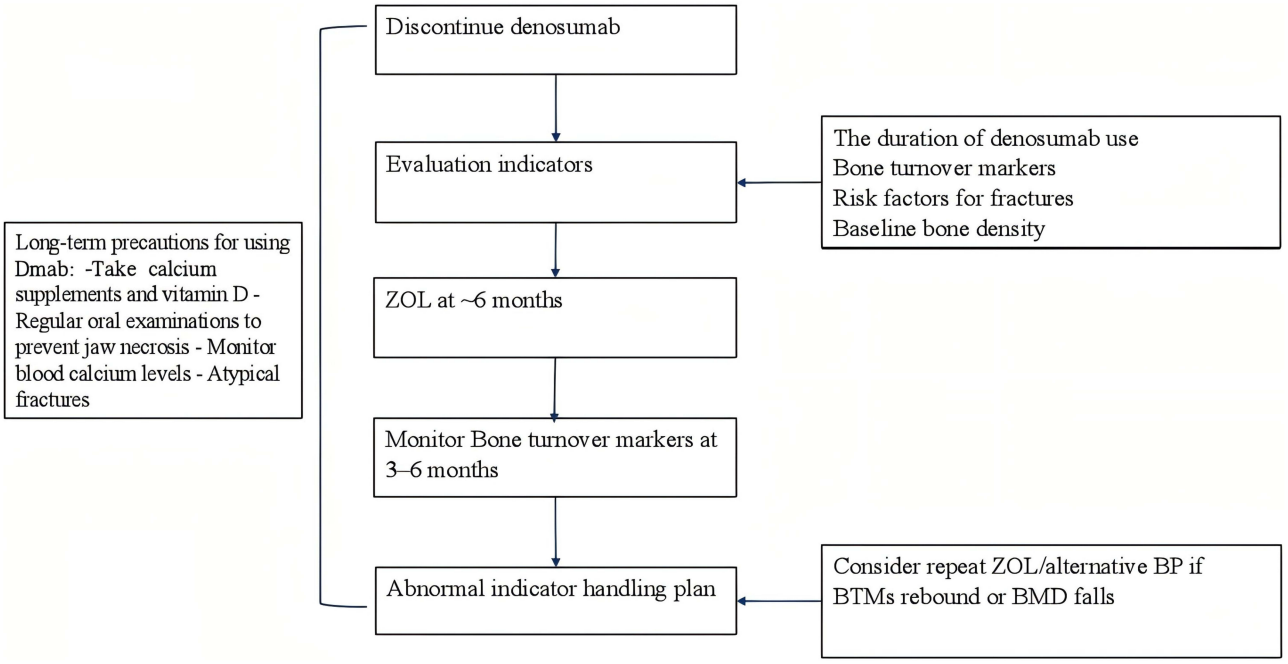

Figure 2 A clinical pathway figure of sequential treatment of zoledronic acid after denosumab discontinuation.
Abbreviations: ZOL, zoledronic acid; Dmab, denosumab; BMD, bone mineral density; BTMs, bone transformation markers; BP, bisphosphonate.

initial spinal BMD increase.[46] Currently, ZOL alone cannot fully retain the BMD gains following Dmab discontinuation. On the other hand, gradual dose reduction of Dmab retains around 40% of spinal BMD gain. This opens up the possibility that a combination strategy, ZOL paired with low-dose Dmab, may warrant further investigation.

Conclusion

Over the past few decades, as the population has gradually aged, the incidence of osteoporosis has steadily increased. The loss of bone strength raises the risk of brittle fractures in both spinal and non-spinal regions, accompanied by high mortality, greater healthcare service usage, rising medical costs, and a decline in quality of life. Dmab effectively suppresses BTMs, increases BMD, lowers fracture risk, and demonstrates a favorable safety profile. However, in certain cases, discontinuation of Dmab may be required. These include the occurrence of adverse effects, achievement of a BMD level at which further fracture risk reduction is unlikely, attainment of a high bone mass status following treatment with Dmab in patients with a long remaining life expectancy, and financial constraints. Nonetheless, stopping Dmab can result in a rapid loss of BMD and has been linked to multiple VFx in a subset of patients. This condition is referred to as the "rebound phenomenon." To reduce the likelihood of this outcome, sequential administration of ZOL following Dmab discontinuation is recommended. This approach can partially preserve the BMD gains achieved with Dmab, dampen the rebound increase in BTMs, and offer some protection against VFx. Currently,there is no established consensus regarding the optimal timing for initiating ZOL following discontinuation of Dmab. Further validation through large-scale,rigorously designed randomized controlled trials is warranted. Nevertheless, based on existing evidence, we propose that it is important to monitor markers of bone metabolism, BMD, serum calcium, vitamin D, and other relevant parameters,within 3 to 6 months after ZOL administration. If BTMs rebound or BMD declines, further intervention with another dose of ZOL or alternative bone-protective agents (such as teriparatide) should be considered. The clinical pathway is illustrated in Figure 2.

Although our review is the first to focus on the sequential use of BPs following Dmab discontinuation, it has certain limitations and presents challenges that call for further investigation. First, most studies examining ZOL after stopping Dmab are small-scale observational studies, often with limited participant numbers and variability in race, background, and age. Consequently, future research should include larger, regionally diverse, population-based randomized controlled trials to better analyze these observations. Second, existing studies offer limited data on the duration of Dmab use before

discontinuation and on the optimal timing for initiating sequential ZOL. The grouping in these studies tends to be broad. Future investigations should widen the study scope, refine group classifications, and examine potential factors influencing patient response to ZOL, to increase both clinical applicability and therapeutic relevance of this regimen. Additionally, although ZOL has shown effects in maintaining BMD and reducing BTMs rebound, few studies have assessed parameters such as bone trabecular score(BTS), serum calcium, phosphorus, and vitamin D levels. Lastly, inconsistencies in measurement timing, indicator accuracy, and intervention timing across studies may also influence clinical outcomes. Despite these limitations, the findings and shortcomings outlined in this review may help guide the design of future clinical trials.

In conclusion, in most postmenopausal osteoporosis patients treated with Dmab, discontinuation of the drug leads to a "rebound phenomenon", resulting in BMD loss and, in some cases, multiple fractures. Intravenous infusion of ZOL after the final Dmab injection can retain more than half of the BMD gain and has not been shown to be significantly associated with multiple VFx. However, the effectiveness of this sequential approach can be influenced by several factors, including the timing of the ZOL infusion, the duration of prior Dmab treatment, and the patient's disease status. Therefore, patients transitioning from Dmab to ZOL should be managed with an individualized plan that includes regular assessment of BMD, monitoring of BTMs, and a comprehensive evaluation of clinical risk factors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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