

Should denosumab treatment for osteoporosis be continued indefinitely?

Jane A. Noble, Malachi J. McKenna and Rachel K. Crowley 

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Abstract: Denosumab was approved for the treatment of postmenopausal osteoporosis in 2010, based on the FREEDOM study, which indicated a benefit in terms of increased bone mineral density and reduced risk of major osteoporotic fracture. In the initial clinical studies it was noted that discontinuation of denosumab can lead to a rebound of bone turnover markers and loss of accrued bone mineral density. An increased risk of fractures (multiple vertebral fractures in particular) associated with discontinuation was noted after approval and marketing of denosumab. For many patients experiencing gain in bone mineral density and fracture prevention while taking denosumab, there is no reason to stop therapy. However, discontinuation of denosumab may happen due to non-adherence; potential lack of efficacy in an individual; where reimbursement for therapy is limited to those with bone mineral density in the osteoporosis range, when assessment reveals this has been exceeded; or patient or physician concern regarding side effects. This review paper aims to discuss these concerns and to summarize the data available to date regarding sequential osteoporosis therapy following denosumab cessation to reduce the risk of multiple vertebral fracture.

Keywords: atypical femoral fracture, denosumab, denosumab cessation, multiple vertebral fractures, osteonecrosis, osteoporosis

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Introduction

Denosumab was first approved by the European and US Regulatory authorities in 2010. The first approved monoclonal antibody for osteoporosis, it binds to and inhibits the receptor activator of nuclear factor- κ B ligand (RANKL) leading to reduced bone resorption.¹ Denosumab is recommended by the Endocrine Society and others as a first line treatment option for post-menopausal women at high risk for osteoporotic fractures.^{2–4} Denosumab is also recommended for treatment of osteoporosis in men and in glucocorticoid-induced osteoporosis.³ Denosumab is used for several oncological indications including bone metastases, women with low bone mass receiving adjuvant aromatase inhibitor therapy for breast cancer and men receiving androgen deprivation therapy for non-metastatic prostate cancer.^{5,6} It is also employed in the treatment of Paget's disease of the

bone and fibrous dysplasia.⁵ The current paper presents an overview of the safety concerns regarding prolonged exposure to denosumab for the treatment of osteoporosis, the consequences of cessation and the putative harm-reducing strategy of sequential osteoporosis therapy for patients in whom cessation is medically indicated or patient determined. Six-monthly subcutaneous administration of denosumab increased bone mineral density at the lumbar spine, total hip and distal third radius site compared with both placebo and alendronate.⁷ During the initial 36 month FREEDOM trial, it was also shown to reduce the risk of new radiographic vertebral fracture, hip fracture and non-vertebral fracture when compared with placebo.⁸ At the time of its approval there was no pre-specified treatment duration and the deleterious rebound effect of denosumab withdrawal on fracture incidence was not fully anticipated.

Correspondence to:
Rachel K. Crowley
Department of
Endocrinology, St Vincent's
University Hospital, Elm
Park, Dublin, 4, Ireland
School of Medicine
and Medical Science,
University College Dublin,
Belfield, Dublin, Ireland
rcrowley@svhg.ie

Jane A. Noble
Department of
Endocrinology, St Vincent's
University Hospital, Dublin,
Ireland

Malachi J. McKenna
St Vincent's Private
Hospital, Dublin, Ireland
School of Medicine
and Medical Science,
University College Dublin,
Belfield, Dublin, Ireland



Long-term efficacy of denosumab

The long-term efficacy of denosumab was assessed in the FREEDOM extension study published in 2017.⁹ This study reported progressive increases in bone mineral density (BMD) at lumbar spine, total hip and femoral neck with up to 10 years of denosumab therapy, unique amongst all current osteoporosis therapies. Prolonged therapy was associated with low fracture rates, estimated relative risk for new vertebral fracture at 0.62 [95% confidence interval (CI) 0.47–0.80] and for non-vertebral fracture at 0.54 (95% CI 0.43–0.68) compared with a virtual twin simulation placebo arm.⁹ Using the same data set, Ferrari *et al.*¹⁰ reported on the positive relationship between on-treatment BMD and current fracture risk; they showed that the incidence of non-vertebral fracture decreased significantly as a function of T-score of the total hip achieved during treatment. The relationship plateaued at T-score between –2.0 and –1.5; 95% of participants attained T-score \geq –2.5 by year 10 of denosumab treatment. Further work by the same authors compared the non-vertebral fracture rate in years 1–3 of denosumab use with that of more prolonged use up to 10 years.¹¹ Treatment with denosumab beyond year 3 resulted in significantly lower rates of fracture with the lower risk becoming evident at year 4, and with the low risk being maintained (but not progressively declining) in up to 10 years of treatment. Analysis of these data compared the observed *versus* the estimated incidence of major osteoporotic fracture using the fracture risk assessment tool (FRAX), reporting a more modest but still significant reduction in relative risk of major osteoporotic fracture at spine, shoulder, wrist and hip for patients receiving denosumab.¹² Of note denosumab has been shown to have greater efficacy in those who have a higher probability of fracture based on their FRAX estimate of risk.¹³

Safety of denosumab

The initial safety data regarding denosumab came from the FREEDOM trial; no significant differences were found regarding total incidence of adverse events, serious adverse events or discontinuation of study because of adverse events.⁸ There was no increase in incidence of delayed fracture healing or hypocalcaemia in participants receiving denosumab rather than placebo; these had been noted as theoretical concerns due to the mechanism of action of denosumab and thus

analysed as specific safety endpoints. Eczema was reported in significantly more participants receiving denosumab than placebo, as was flatulence and cellulitis requiring hospitalisation. The results of FREEDOM indicated that some low frequency adverse events were numerically more common in patients receiving denosumab rather than placebo, including infection and malignancy.

Watts *et al.*¹⁴ in 2012 performed a detailed analysis of FREEDOM specifically regarding incidence of adverse events related to infection. Though the rate of serious adverse events of skin infection (cellulitis and erysipelas) occurred in significantly more participants receiving denosumab (15) compared with placebo (three) (0.4% *versus* <0.1%), the numbers were small and there was no association with timing or duration of exposure to denosumab; so the authors concluded that there was no causative link. Numerically, more participants in the denosumab arm experienced serious adverse events of infections involving the gastrointestinal system, renal and urinary system, ear and endocarditis – but these differences did not reach statistical significance. Importantly, the rate of infection-related mortality did not differ between the denosumab and placebo groups. Watts *et al.*¹⁵ in 2017 examined the rate of these and other low frequency adverse events in the first 3 years of the FREEDOM extension study, examining incidence rates following commencement of denosumab in the cross-over arm participants and those receiving long-term denosumab in FREEDOM (exposure of 4–6 years continuously). This study concluded there was no increasing trend amongst events which had displayed imbalances in FREEDOM, specifically the five most frequently reported adverse events of back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia and cystitis as well as other adverse events of interest including malignancy, eczema/dermatitis, pancreatitis, endocarditis, delayed fracture healing and serious adverse events infections, opportunistic infections, and cellulitis or erysipelas. A 2014 meta-analysis by Zhou *et al.*¹⁶ found that the adverse event of infection was significantly increased in participants receiving denosumab compared with placebo (relative risk 1.23, 95% CI 1.00–1.52). The meta-analysis also reported a significantly reduced risk of vertebral fractures when comparing the two cohorts. The authors further investigated the incidence of infection in participants receiving denosumab compared with bisphosphonates and did

not find a significant difference, concluding denosumab to be as safe as bisphosphonates for the treatment of osteoporosis. In 2020 Diker-Cohen *et al.*¹⁷ published a systematic review and meta-analysis concluding that the serious adverse event of infection is increased in participants receiving denosumab in osteoporosis dose, with relative risk related to ear, nose and throat infections of 2.66 (95% CI 1.20–5.91) and to gastrointestinal origin of 1.43 (95% CI 1.02–2.01). Reassuringly, the relative risk for any infection was 1.03 (95% CI 0.99–1.06) and for infection related mortality was 0.50 (95% CI 0.20–1.23).

Regarding malignancy, concerns were initially raised based on the immunomodulatory role of RANKL and thus potential involvement in malignancy risk *via* an effect on immune surveillance. The data from FREEDOM and the extension study revealed no difference in malignancy rate in those receiving placebo compared with those receiving denosumab. The 2014 meta-analysis discussed above also reported a lack of significant difference in rate of incidence of malignancy in denosumab compared with placebo.¹⁶ A further 2020 meta-analysis by Rosenberg *et al.*¹⁸ showed there was no difference in rate of malignancy or malignancy related mortality.

Denosumab and osteonecrosis of the jaw

Denosumab has been associated with the development of osteonecrosis of the jaw (ONJ), the first case reports of which were published in 2010.^{19,20} ONJ is defined as: (1) exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider; (2) with history of exposure to an antiresorptive agent; and (3) no history of radiation therapy to the craniofacial region.²¹ Within the world of dentistry the guidance regarding the withholding of antiresorptive treatment (bisphosphonates and denosumab) for invasive dental procedures is unclear; guidelines are contentious and self-admittedly non-evidence based.²² When denosumab was a new medication guidelines tended to group it together with the advice for bisphosphonates. For example, the 2011 report of the American Dental Association Council on Scientific Affairs advised to continue bisphosphonates/denosumab during elective dentoalveolar surgery and advised against withholding antiresorptives due to a lack of evidence for prevention

of antiresorptive-associated ONJ.²³ This is similar to the advice of the International Task Force on ONJ in 2015.²¹ The 2014 American Association of Oral and Maxillofacial Surgeons' position paper recommends a 2–3 month antiresorptive drug holiday preceding and following invasive dental procedure in particular for patients with prolonged exposure to antiresorptives.²⁴ Although this position paper refers to antiresorptives generally it is worth emphasising that the concept of a “drug holiday” within the field of osteoporosis therapies pertains only to bisphosphonates and not to denosumab.²⁵ The Scottish Dental Clinical Effectiveness Programme 2017 offers specific guidance for denosumab users advising delaying elective procedures until the month prior to the next scheduled administration, and further delaying the next dose until the extraction socket/soft tissues have healed.²⁶ Consensus guidelines now emphasize the importance of preventive dentistry, recommending the identification and treatment of dental issues prior to initiation of antiresorptive therapy where possible.^{21,22}

The majority of ONJ associated with denosumab use occurs in patients taking high dose (120 mg every 4 weeks) for oncology treatment where the incidence is 1–15%.²¹ The incidence of ONJ in patients treated with the osteoporotic treatment dose of denosumab (60 mg 6-monthly) is 0.001–0.01% compared with <0.001% in the general population.²¹ There were no cases of ONJ reported in the original safety data from the initial 3 year FREEDOM study.⁸ By year 5 of the FREEDOM extension study, five adjudicated cases of ONJ were noted in the long-term denosumab group and three cases had occurred in the crossover group.²⁷ Combining the two arms (cross-over and long-term denosumab) the cumulative exposure-adjusted incidence of ONJ for the extension study years 1–5 was 4.2 per 10,000 participant-years. In 2017, Bone *et al.*⁹ published updated figures from the extension study with combined data from up to 10 years of denosumab exposure, reporting the cumulative exposure adjusted incidence as 5.2 per 10,000 participant-years. In 2014 Amgen advised prescribers that post-marketing studies of denosumab had found it to be associated with ONJ when used for the treatment of osteoporosis. Currently available European prescribing information for denosumab for the treatment of osteoporosis states that the risk of ONJ may increase with duration of therapy: 0.04% at 3 years, 0.06%

at 5 years and 0.44% at 10 years (available at https://www.ema.europa.eu/en/documents/product-information/prolia-epar-product-information_en.pdf accessed February 2021). Watts *et al.*²⁸ provided an analysis of the 13 positively adjudicated cases of ONJ which occurred in patients participating in FREEDOM and the extension study. The main risk factor for ONJ was undergoing an invasive oral procedure and event (OPE) including dental implant, tooth extraction, natural tooth loss, scaling/root planing, or jaw surgery. The overall rate of ONJ was low; the incidence rate of ONJ was 0.68% in those undergoing OPE compared with 0.05% in those who did not. Of these 13 patients, eight patients received at least one further dose of denosumab following ONJ onset, two did not because they had reached the end of study participation, and the remaining three patients did not despite being eligible for further doses. ONJ resolved in seven of the eight patients who continued to receive denosumab after onset of ONJ; healing of the lesion in the remaining patient was noted at the end of the study. The authors conclude that there is little evidence to support changes to normal dental procedures and there are no data to suggest a benefit in withholding denosumab or altering dose timing to facilitate procedures occurring between doses. The relationship between denosumab exposure and ONJ remains somewhat unclear due to the small number of cases. There is no evidence to support delaying doses to promote healing of established ONJ.

Denosumab and atypical femoral fracture (AFF)

The American Society for Bone and Mineral Research (ASBMR) has defined criteria for AFF as a fracture originating along the lateral femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare as an absolute necessity for diagnosis.²⁹ Four of the following must be met: (1) no or minimal trauma, (2) a predominantly transverse fracture line originating from the lateral cortex, (3) involvement of the lateral cortex only for incomplete AFFs, while complete AFFs extend through both cortices and may have a medial spike, (4) no or minimal comminution and (5) localized periosteal or endosteal thickening of the lateral cortex present at the fracture site, called “flaring” or “beaking” (if with a fracture line). AFFs were first described in patients receiving bisphosphonates in 2005;³⁰

since then many further articles have reported an increased frequency of AFF in such patients and the presence of a direct relationship between duration of exposure and risk of developing AFF.³¹ The first case report linking denosumab use and the development of AFF was published in late 2013.³² Whilst cases of AFF following brief prior bisphosphonate exposure have been reported,³³ the majority of patients diagnosed with AFF whilst receiving denosumab also have a history of extensive bisphosphonate exposure.³⁴

During the FREEDOM extension study (4550 participants followed over 7–10 years) there were just two atypical subtrochanteric or diaphyseal femoral fractures,⁹ one occurring in the long-term denosumab group after 7 years of exposure and one in the crossover group in year 3 of denosumab therapy. A recent systematic review by the European Calcified Tissue Society (ECTS) on the topic of AFF reported a total of 31 AFFs in 22 patients receiving denosumab based on 14 case reports and the data from two clinical trials.³⁵ Eleven of these patients were treated with the 60 mg dose for osteoporosis, with the other patients receiving higher oncological doses. Interestingly, AFF occurred in only four bisphosphonate-naïve patients receiving treatment with denosumab for osteoporosis. Two of these patients were participants in the FREEDOM trial; one achieved fracture healing within 6 months of stopping denosumab and another continued denosumab but there is no information available regarding fracture healing.³⁵ Another patient was a participant in a trial assessing denosumab in the treatment of glucocorticoid-induced osteoporosis and had received glucocorticoids for over 30 years. Another patient had a medially located fracture not visible on X-ray (only seen on magnetic resonance imaging) that did not meet the criteria for AFF according to the ASBMR Task Force.²⁹ The ECTS maintain that the absolute risk of AFF associated with denosumab use is low based on the data analysed in the systematic review. Given the limited evidence for AFF associated with denosumab use (in the absence of other risk factors), no conclusion about the relationship between therapy duration (or even treatment itself) and risk of AFF can be made. Therefore there is no evidence that denosumab therapy should be discontinued to avert AFF. Furthermore due to a lack of randomized studies, it is not possible to assess the effect of denosumab on fracture healing after AFF. It is worth noting that in the ECTS

systematic review, there were two patients who developed a second complete AFF on denosumab and a third patient with bilateral recurrent incomplete AFFs on denosumab, despite use of teriparatide.³⁵ Thus the ECTS suggest ceasing denosumab therapy after a unilateral AFF to prevent worsening of the initial fracture and reduce the risk of developing a contralateral fracture. The risk of denosumab rebound effect, rapid decline in BMD, and potential for multiple VFs must be weighed against the risk of contralateral AFF.

ECTS recommendations regarding denosumab use following diagnosis of AFF include:

- Follow with a short course of bisphosphonate or selective oestrogen receptor modulator (SERM) for surgically treated bilateral AFF or unilateral AFF without sign of contralateral incomplete AFF.
- Denosumab could be continued or initiated in patients at high risk of fragility fracture with bilateral surgically managed AFFs.
- Denosumab could be stopped without follow-up therapy in patients at low risk of fragility fractures without history of vertebral fractures (VFs), particularly in those who have only had one or two six-monthly injections of 60 mg.
- Consider a SERM or teriparatide in patients at high risk of fragility fracture, with the caveat of accelerated loss of BMD when switching from denosumab to teriparatide.

Further evidence of the low risk of both AFF and ONJ is presented by Ferrari *et al.*,³⁶ who published an estimate of fractures prevented relative to skeletal adverse events observed with up to 10 years of denosumab use. The group modelled a hypothetical placebo group and calculated the fractures prevented with denosumab treatment and related these to the number of cases of AFF and ONJ observed in the FREEDOM trial and its extension study (five per 100,000 subject-years and 35 per 100,000 subject-years respectively). The skeletal benefit/harm ratio was 281 for AFF and 40 for ONJ,³⁶ indicating a favourable outcome of denosumab use long-term.

Early detection of incomplete atypical AFF using dual energy X-ray absorptiometry (DXA) systems is a means to early identification of AFF because default length of the femur field visualizes the subtrochanteric region.^{37,38} Focal thickening of the

periosteal surface and endosteal surface of the lateral femur cortex can be identified. The default length of the femur image at the time of DXA can be extended to view the entire length of the femur.^{39,40} DXA manufacturers have added a feature to DXA protocols that allows rapid imaging of the entire femur length, with low radiation exposure and near X-ray quality imaging. The Official Positions of the International Society of Clinical Densitometry recommends: consider bilateral full length femur imaging for detecting abnormalities in the spectrum of AFF in patients who are receiving bisphosphonates or denosumab therapy or discontinued it within the last year, with a cumulative exposure of 3 or more years, especially those on glucocorticoid therapy.⁴¹

Discontinuing denosumab

It has been recognized for some time that discontinuing therapy with denosumab results in a rapid reversal of its inhibition of bone remodelling, as manifested by an increase in bone turnover markers as soon as the effect of denosumab lapses, that is followed by decline in BMD. This was recognized as early as 2008 when Miller *et al.*¹ reported on the complete reversibility of BMD gains following cessation of denosumab therapy, but they did not show an increase in fracture risk in these patients, who were followed for 12–24 months post discontinuation. Similarly Bone *et al.*⁴² completed follow-up of patients for up to 30 months after last injection of denosumab or placebo with similar findings to Miller *et al.*¹ regarding BMD and bone turnover markers; they showed equal frequency of clinical fractures in both placebo and denosumab discontinuers (4%).⁴² Despite these findings, concern remained that at least in theory there may be an increase in fracture risk following denosumab discontinuation. Further work by Brown *et al.*⁴³ in 2013 attempted to characterize this risk, following the treatment groups from FREEDOM for up to 24 months following cessation, but again concluded that there was no apparent excess of fracture risk. This study assessed both vertebral and non-vertebral major osteoporotic fractures occurring more than 7 months following the last treatment dose in patients who received 2–5 treatment doses. It is worth noting that 28% of the denosumab-discontinuing patients began an alternative osteoporosis treatment (predominantly bisphosphonates), compared with 42% of the patients who discontinued placebo, which may have mitigated the risk of subsequent

fracture. The median follow-up from treatment cessation was 8 months (shorter than the known duration of the rebound phenomenon) and importantly the study did not analyse multiple VFs as a separate entity.⁴³

Some physicians had stopped denosumab therapy citing attainment of a BMD above the osteoporosis range, concern re side effects or perceived lack of efficacy for these decisions.^{44,45} The “drug holiday” guidance used for patients on bisphosphonate therapy appears to have been applied erroneously to patients on denosumab in some cases. Other groups of patients delayed or ceased administration upon the advice of their dentist or of their own volition. In 2015, case reports indicated an increased rate of new VFs upon discontinuation of denosumab.^{46,47} Aubrey-Rozier *et al.*⁴⁸ in 2016 published a case series of three patients who experienced VF within 10–16 months of stopping denosumab therapy, each patient having received 5–6 doses of denosumab. In two of the cases the patient’s general practitioner stopped denosumab because the patient’s BMD had increased significantly to within the osteopenic range. The third patient stopped denosumab herself without consulting a physician. These three cases and six new cases were reported in 2017 by Lamy *et al.*⁴⁷ All patients were managed in general practice, seven commenced denosumab for a diagnosis of osteoporosis with two patients included who commenced denosumab for bone preservation during aromatase inhibitor treatment. The patients had received 2–8 doses of denosumab and the time from last dose to fracture was 9–16 months. Anastasilakis *et al.* in 2017⁴⁶ reported a systematic review of 24 reported patients with VF following denosumab discontinuation (including the nine cases discussed above),⁴⁶ the mean time on denosumab treatment was 2.9 years and mean time from discontinuation to VF was 11.2 months. The most common reasons for discontinuing denosumab were attaining BMD within the osteopenic or normal BMD ranges, treatment duration (rationale for this not explained) or the completion of treatment with aromatase inhibitors. It was unclear from these case reports whether these patients who stopped denosumab had merely reverted to their baseline risk of a VF, or whether the cessation of denosumab itself had conferred an excess risk.

The publication of a post hoc analysis of FREEDOM and the extension trial in 2018 confirmed that the rate of VF following discontinuation of denosumab

rapidly increased from a low rate on therapy to the incidence seen in the untreated population.⁴⁹ Cummings *et al.*⁴⁹ analysed the data of 1001 participants who received at least two doses of denosumab and subsequently discontinued therapy but stayed in the study for at least 7 months following the last dose of denosumab. They compared the rate of VF, multiple VF and non-vertebral fracture in the denosumab discontinuers with the same data in 470 equivalent participants who had discontinued placebo in the FREEDOM trial. The VF rate increased from 1.2 per 100 participant-years during the on-treatment years to 7.1 in the denosumab discontinuers; this estimate is similar to the rate of 7.0 in the on-placebo years that increased to 8.5 during the post-placebo years. This increase back to baseline (placebo) is in keeping with the loss of protection of an effective therapy that does not have a sustained post-treatment effect. Interestingly, among the cohort with at least one off-treatment VF, the proportion of denosumab discontinuers with multiple VFs was significantly higher at 60.7% compared with 38.7% of placebo discontinuers. The risk of multiple VFs was 3.4% for denosumab discontinuers compared with 2.2% for placebo discontinuers. This increase in risk of multiple VFs beyond that seen in placebo discontinuers appears more in keeping with the concept of a rebound phenomenon rather than purely the loss of an effective therapy. The risk of sustaining multiple VFs was increased in those with a history of prior VF with an odds ratio of 3.9 (95% CI 2.1–7.1). Multiple VFs were also more common in those with greater gain in hip BMD, greater loss of hip BMD off therapy and longer duration off therapy. There was no significant difference in the rate of non-VFs detected. The argument has been made that the duration of follow-up (only a minority were observed beyond 7 months post last denosumab dose) was insufficient to capture all of the VFs because the biological rebound persists longer than this and thus the rate of VF at 16 months of follow-up has been estimated by other investigators as being up to 15%.⁵⁰

In 2020 Tripto-Shkolnik *et al.*⁵¹ published a retrospective data retrieval analysis comparing incident (clinically evident) fractures within 1 year of denosumab discontinuation in real world patients who had received at least two consecutive doses of denosumab before ceasing to incident fractures in persistent denosumab users.⁵¹ The data were obtained from the data-base of a major healthcare provider in Israel and the study participants were predominantly female (>90%) with a mean age of

72. This analysis reported that although the rate of VF overall was low, there was a significant difference in incidence of multiple VFs: 0.8% of discontinuers diagnosed with multiple VFs compared with just 0.1% of persistent users ($p=0.006$) with a relative risk of 14.6 (95% CI 3.3–65.3). Furthermore, the relative risk of major osteoporotic fracture – namely, VF (single and multiple), hip and non-hip non-VFs – was significantly higher in denosumab discontinuers with relative risks of 3.2, 4.7, 5.3 and 2.2 respectively. Similar to the findings of the post hoc analysis of FREEDOM,⁴⁹ history of a prior VF was again identified as a risk factor for multiple VFs following denosumab discontinuation (relative risk 2.3, 95% CI 0.7–7.4). Interestingly, the rate of major osteoporotic fracture occurring in denosumab discontinuers was higher in those with previous bisphosphonate exposure than in those without prior bisphosphonate exposure (relative risk 1.67, 95% CI 0.8–3.48), although this did not reach statistical significance. This study also identified new associations between cerebrovascular disease and chronic kidney disease (estimated glomerular filtration rate lower than 60 mL/min per 1.73 m²) as risk factors significantly associated with increased fracture risk following denosumab discontinuation. There were some limitations; the authors reported a much lower incidence of VF than that described in the *post hoc* analysis of the FREEDOM study; as they mentioned, FREEDOM was a prospective study that included both solely radiologically detected fractures and clinically evident fractures whereas their study included only clinically evident fractures (it is thought only one-third of VFs are clinically evident).

The effect of delayed denosumab injections rather than discontinuation on fracture risk was reported by Lyu *et al.*⁵² The authors used observational data in a hypothetical trial format, analysing the effect of on-time (within 4 weeks of date due), short delay (4–16 weeks overdue) and long delay >16 weeks on fracture incidence. The incidence of fracture at any site over the 6 months following the missed dose was 27.3 per 1000 patients for on-time delivery, 32.2 in 1000 for short delay, and 42.4 for long delay. Patients who delayed their dose of denosumab by more than 4 months had a 3.91-fold increased risk of VF.

There is an emerging body of evidence that the duration of denosumab treatment may be an important determinant of the extent of rebound

phenomenon^{5,53} and time to VF following discontinuation.⁵⁴ Gonzalez-Rodriguez *et al.*⁵⁴ in 2020 reported a case series of 15 patients who sustained VF following withdrawal of denosumab and aromatase inhibitors for early stage breast cancer finding that VF developed earlier in patients with longer exposure or osteoporosis prior to commencing denosumab. Longer duration of treatment was also identified as being associated with a higher number of VFs in another study.⁴⁶ Duration of denosumab exposure may also have an effect on the response to sequential treatment, with shorter duration leading to better preservation of BMD with sequential bisphosphonate therapy, but this is yet to be fully ascertained in large, prospective studies.⁵

Why stop denosumab?

There are very few clinical reasons to stop denosumab therapy. Potential reasons include:

- Achieving a treatment goal “treat-to-target approach”;
- Treatment failure as evidenced by fracture or inadequate response on BMD re-assessment;
- A drug related adverse event such as hypersensitivity or hypocalcaemia;
- Concerns about potential long-term risks (ONJ and AFF);
- Cost or lack of government/insurance coverage;
- Patient factors.

Treat-to-target

Some physicians advocate for a treat-to-target approach to management of osteoporosis. Usually this target is a particular BMD which when reached indicates that the patient is at an acceptably low risk of fracture. There are multiple facets to this approach: selecting the therapy most likely to bring about improvement in BMD towards the target within a particular time-line; stopping the therapy when the target is reached; maintaining this target BMD. Whilst this approach is discussed by the Endocrine Society in its guidance from 2019, they caution that current therapies may not be potent enough to achieve or maintain the gains in BMD required.² The treat-to-target approach is advocated in the more recent position statement from the ECTS;⁵ however, they acknowledge that the assignment of fracture risk based on BMD alone is limited. Furthermore, as discussed below the evidence base supporting the guidance for

sequential therapy to maintain BMD and reduce rebound fracture risk following denosumab cessation is weak. Nonetheless, even without consensus denosumab reimbursement parameters differ across healthcare jurisdictions, in some cases mandating cessation of denosumab once target BMD is reached.

Treatment failure

There is uncertainty as to what defines treatment failure in osteoporosis. No currently available therapy completely eliminates the risk of sustaining a fracture, thus deciding to cease or switch away from denosumab due to the occurrence of an on-treatment fracture may not always be justified. A 2018 study by Kendler *et al.*⁵⁵ assessed this issue based on the incidence rate of subsequent fracture in participants who sustained an “on-treatment fracture” whilst receiving either denosumab or placebo in FREEDOM or the extension study. The adjusted hazard ratio for subsequent fracture for the participants receiving denosumab compared with placebo was 0.59 (95% CI 0.43–0.81). This study offers evidence that sustaining a single fracture on denosumab is not necessarily indicative of treatment failure or inadequate response. The Endocrine Society suggests that treatment failure may be indicated by two or more on-treatment fractures, or BMD loss greater than the least significant change over 2 years or bone turnover marker suppression less than the least significant change.²

Concerns regarding adverse events

Given the concern about possible association of denosumab with ONJ and AFF, some physicians are keen to minimize the time younger patients, in particular, are exposed to denosumab in an attempt to optimize the harm:benefit ratio. In the early days following approval of denosumab, the risk of abruptly stopping denosumab may not have been completely understood and there was a lack of advice on duration of treatment, likely leading to inappropriate cessation of treatment. Tripto-Shkolnik *et al.*⁵⁶ published a case series of nine patients who discontinued denosumab and subsequently developed VF; the reasons for discontinuation included “drug holiday”. In 2017 McClung *et al.*⁴⁴ published the results of a small observational study assessing osteoporosis management strategies adopted at the discretion of a patient’s personal physician

following participation in a phase II clinical trial involving up to 8 years of denosumab treatment. Of the 82 patients who enrolled in the study, most (79%) were not prescribed further osteoporosis medication following completion of the trial phase. The most common reason, noted in 52% of these patients, was a decision by a physician that medication was no longer required.

Patient factors

In common with therapeutics employed in many chronic diseases, unscheduled discontinuation occurs secondary to compliance/persistence issues. Studies of persistence with denosumab therapy have reported widely variant estimates of 24 month persistence, ranging from 28.3% to 98.7%.⁵⁷ In 2019 Borek *et al.*⁵⁷ published the results of a retrospective non-interventional observational study of persistence and compliance with denosumab in a real-world patient cohort of 1158 patients diagnosed with osteoporosis attending a suburban USA community based specialist osteoporosis clinic. They analysed persistence by means of Kaplan–Meier survival analysis at 36 months. Persistence was 76.9% at 12 months, 67.3% at 18 months, 59.6% at 24 months, 54.1% at 30 months and 50.7% at 36 months. Four hundred and thirty-two patients discontinued denosumab; the reason for discontinuation was recorded for 91.6% (396 patients). Almost half (49.7%) of patients discontinued for an individual patient decision including the sub-categories of de-prioritisation of therapy/forgetfulness (18.7%), drug related costs (13.6%) and perceived side effect (13.1%). The percentage that ceased therapy due to clinical issues was 19.7%, including 6.6% who were advised to discontinue by their provider and 3.8% who had their dosing rescheduled due to dental procedure. The only baseline characteristic predictor of non-persistence was age greater than or equal to 75 years (odds ratio 0.68, $p=0.003$). Higher persistence was associated with recent osteoporosis therapy (odds ratio 1.43, $p=0.005$) and prior VF (odds ratio 1.54, $p=0.05$) at baseline. Briot *et al.*⁵⁸ in 2021 have reported a 24 month study of persistence with denosumab for the treatment of postmenopausal osteoporosis in France, reporting that 86% of participants were persistent at 12 months and 72% at 24 months. Of those who discontinued denosumab the most common reason was patient request (45%).

Mitigating the risk of discontinuing denosumab

Regardless of the underlying reason for denosumab discontinuation, whether it is a clinical decision or a patient factor, it is clear that many patients will ultimately discontinue therapy. It is important that evidence-based guidance is developed in order to minimize the risk of harm when discontinuing denosumab. An evidence gap exists regarding subsequent management; to date the potential strategies to reduce the rebound effect of stopping denosumab have not been conclusively adjudicated but suggested therapies include oral or intravenous bisphosphonates before or after denosumab with or without reference to bone turnover markers, or SERM after denosumab.

Guidance to date

In 2017 the ECTS published a systematic review of the literature regarding discontinuation of denosumab and offered advice on how to manage such patients.⁴⁵ They recommended a re-evaluation of denosumab prescription after 5 years and that those considered high risk for fracture (e.g. who still have low BMD as defined by T-score worse than -2.0 or with multiple VFs or a high fracture risk score) could continue on denosumab up to 10 years. In patients considered at low risk of fracture at 5 years, the authors endorsed discontinuation of denosumab as an option but with need to consider follow-up treatment with bisphosphonate. At the time of publishing this guidance, and indeed now, the optimum regimen of bisphosphonate treatment following discontinuation of denosumab remains unclear. The guidance offered by the ECTS included the option of continuing denosumab up to 10 years even in the low risk group pending the outcome of trials to ascertain optimum bisphosphonate prescription following discontinuation. The alternative of post-discontinuation treatment with SERM was also included for patients with previous bisphosphonate intolerance. It is worth noting that the antiresorptive efficacy of SERMs is lower than that of bisphosphonates. Since the publication of this guidance, Gonzalez-Rodriguez *et al.*⁵⁹ concluded that raloxifene had no efficacy for reducing risk of spontaneous VF following denosumab discontinuation. Teriparatide was also included in the discussion section of the guideline as a further potential alternative; but the DATA-Switch study demonstrated that teriparatide therapy after denosumab is associated with decreases in BMD,

particularly at cortical sites,⁴⁵ and is not recommended. Furthermore, the ECTS guidance states that should a dentist or dental surgeon wish to alter or halt denosumab treatment due to invasive procedure that this should be discussed with the patient's physician and interdisciplinary consultation may be required.

The Swiss Association against Osteoporosis released a position statement in 2017.⁶⁰ The position statement recommended continuing denosumab up to 10 years in patients at high fracture risk, defined as: hip, spine or multiple fractures before or during therapy; femoral neck T-score <-2.5 if age <65 years, <-2.0 SD if age >65 years and/or frequent falls; continuing hormone ablative therapy (e.g. aromatase inhibition, androgen deprivation therapy); secondary osteoporosis; and continuing glucocorticoid therapy. In patients with good treatment response (low fracture risk, increase of BMD to within age-adjusted range, cessation of aromatase inhibition) they advised mandatory sequential treatment with bisphosphonates (or SERM if bisphosphonate intolerant) for 12–24 months post discontinuation of denosumab. They emphasized the importance of this particularly in older women with prevalent VFs and in women without a history of long-term bisphosphonate use prior to denosumab.

The Endocrine Society 2019 suggests that in postmenopausal women with osteoporosis who are prescribed denosumab the fracture risk should be reassessed after 5–10 years.² The guidance is that women who remain at high risk of fracture should continue denosumab or receive other osteoporosis treatment. The high-risk group is defined as patients who have a prior spine or hip fracture, or a BMD T-score of -2.5 or below at either the hip or spine, or a 10-year hip fracture risk $>3\%$, or a risk of major osteoporotic fracture $>20\%$. According to the guideline, denosumab could then be stopped in low to moderate risk patients (i.e. those who do not meet these criteria) but they recommend against delaying or stopping denosumab without subsequent antiresorptive (bisphosphonate, hormone therapy or SERM) administered in order to prevent rebound increase in bone turnover, rapid BMD loss and increased risk of fracture. The advice for follow-up of these patients is a reassessment of fracture risk every 1–3 years. If bone loss is noted, fracture occurs or the patient becomes high risk, then the guideline recommends consideration of restarting therapy.

ECTS 2020

The ECTS have updated their guidance in a position paper published in October 2020.⁵ They reference the “treat to target” approach to osteoporosis treatment, BMD being the sole discussed marker of fracture risk. It is acknowledged that a BMD-only based concept has not been universally accepted and it is prudent to consider other risk factors such as prevalent fractures and continued glucocorticoid or aromatase inhibitor use. The ECTS thus state that in patients with high fracture risk, long-term treatment is supported by safety and efficacy data up to 10 years. The Society advise that pending longer term data the decision to extend denosumab treatment beyond 10 years should be decided in individual cases (for example those with limited life expectancy, significant renal impairment or an explicit patient wish). Mindful of the increased risk of unscheduled treatment cessation with longer treatment duration they recommend to thoroughly assess the indication to start denosumab before commencing, particularly in younger patients where the longer duration may predispose to unscheduled discontinuation. The guidelines also comment on the issue of dentist-initiated treatment interruption, advising that it is preferable to wait for 5 months after last administration before undergoing a procedure and to withhold further treatment until the lesion is healed. Regarding treatment cessation and sequential therapy after denosumab, the ECTS recommend that denosumab may be ceased once the patient is no longer considered at high risk of fragility fracture but that it is then necessary to prescribe a potent antiresorptive, particularly a bisphosphonate. Oral bisphosphonate can be considered in patients reaching this threshold prior to exceeding 2.5 years of denosumab therapy, but if opting for an oral bisphosphonate the advice is to perform a DXA at the time the next denosumab dose is due and to measure bone turnover markers 3 months later to monitor efficacy and adherence, aiming for a level below the mean found in healthy premenopausal women. If there is an adequate response, then they recommend to continue for 1–2 years and reassess with repeat DXA and decide about continuation or discontinuation of bisphosphonate as per the guidance of Kanis *et al.*⁶¹ Intravenous zoledronate is recommended when there is gastric intolerance of oral bisphosphonate, inadequate response to therapy, or in patients with a long duration of denosumab exposure (longer than 2.5 years). As discussed, the

optimal timing of the infusion is yet to be clarified but the ECTS recommend the pragmatic approach of beginning treatment 6 months after the last denosumab injection, and monitoring the bone turnover markers at 3 and 6 months; if bone remodelling is increased, then a second infusion could be considered. The subsequent duration of zoledronate treatment is also yet to be optimally assessed. For patients who have received denosumab for over 2.5 years, the option is also provided to continue denosumab up to 10 years. Despite these guidelines the evidence behind the sequential therapy recommendations is limited and summarized below.

Bisphosphonates before denosumab

Some studies have suggested that a history of bisphosphonate exposure prior to denosumab initiation is protective against rapid loss of BMD and incident VF after discontinuation of denosumab. Uebelhart *et al.*⁶² in 2017 reported the results of a retrospective study of bone resorption marker C-terminal telopeptide of type I collagen (CTX) following denosumab discontinuation. They showed that those with prior bisphosphonate exposure were more likely to have CTX levels remaining in the pre-menopausal range 12–18 months after the last denosumab injection. The authors hypothesized that prior bisphosphonate exposure could blunt or suppress bone turnover, but they noted they had not assessed BMD. Tripto-Shkolnik *et al.*⁵⁶ in 2018 described a series of nine patients (identified retrospectively by phone survey of physicians) who suffered multiple VFs following denosumab discontinuation despite prolonged prior exposure to bisphosphonates, concluding that prior bisphosphonate exposure was not protective. However, the conclusions of this case series have been questioned due to the unusual case identification method, unclear interval between bisphosphonate exposure and denosumab initiation, as well as unclear underlying aetiology of osteoporosis in some cases.⁶³ In 2020 Sølling *et al.*⁶⁴ reported the results of a 2 year randomized study investigating the effect of differences in timing of zoledronate infusion following denosumab discontinuation. The authors found no difference in BMD or bone turnover markers at any time point for those who had previous bisphosphonate exposure compared with those who did not have a history of bisphosphonate use. The majority of participants in the study had received treatment with alendronate

prior to commencing denosumab (nine of 59 participants had received bisphosphonates other than alendronate). The duration of prior exposure was just 0.6 ± 0.7 years, with patients who had received more than 3 years of alendronate being excluded from participating in the study, therefore the findings may not apply to those from other jurisdictions who may have a longer history of alendronate exposure. The short duration of alendronate exposure is explained by the research setting; in Denmark denosumab is reimbursed only for patients who have contraindications against or are intolerant of alendronate.

Bisphosphonates after denosumab

Although it is currently recommended to transition to another antiresorptive after discontinuing denosumab^{2,4} there is a lack of robust evidence supporting this recommendation. Several groups have recently completed studies in an attempt to build the evidence base to support the current consensus guidelines. These groups have sought to clarify optimal timing, route of administration and duration of efficacy.

In their 2017 study of women completing the Denosumab and Teriparatide Administration (DATA) study and its extension DATA-Switch, Leder *et al.*⁶⁵ reported maintenance of the teriparatide and denosumab-induced gains in BMD in patients who received prompt antiresorptive therapy (denosumab, oral bisphosphonates or intravenous zoledronate) but not in those who were untreated.

Lehmann and Aeberli⁶⁶ in 2017 reported 22 cases of women with postmenopausal osteoporosis who were commenced on denosumab, all receiving five injections before discontinuing denosumab and receiving a single dose of zoledronate 6 months later. Thirteen of the participants had prior bisphosphonate exposure whereas nine did not. None of the patients experienced a new VF (up to 24 months after discontinuation of denosumab). The authors reported prominent loss of BMD at the lumbar spine, total hip and femoral neck (change BMD % of -3.8 , -1.7 and -0.6). There was no difference in BMD loss between the participants with prior bisphosphonate exposure and those without.

Reid *et al.*⁶⁷ in 2017 reported a case series of six patients with postmenopausal osteoporosis who

participated in FREEDOM receiving continuous denosumab for 7 years followed by a single infusion of zoledronate 6 months after the last dose of denosumab. BMD increased significantly at the spine and hip following denosumab compared with baseline. BMD was re-measured at 18–23 months post zoledronate infusion and had decreased significantly at the spine and hip. Spine but not hip BMD remained significantly above the pre-denosumab baseline, indicating that this single infusion provided partial protection at the spine only.

Horne *et al.*⁶⁸ in 2018 published an *ad hoc* case series of participants from the FRAME trial. In FRAME, women with a diagnosis of osteoporosis were randomized to romosozumab or placebo for 1 year followed by 2 years of denosumab. In this study the participants were then offered either intravenous or oral bisphosphonate. The participants who declined bisphosphonate retained 22% [95% confidence interval (CI): 7–37%] of spine BMD gained and 8% (CI: -31 to 47%) of total hip BMD gained at 12 months following completion of denosumab. Those who opted for zoledronate retained 73% (CI: 61–85%) of the treatment effect at the spine and 87% (CI: 77–98%) at the hip. The time from last denosumab dose to zoledronate infusion was 191–353 days (median 241). Amongst those who opted for zoledronate the retention of BMD gains at completion of the study was similar in the cohort of patients who had initially received romosozumab compared with those who had received placebo. The participants who received risenedronate had a response intermediate to that of no treatment and zoledronate, with 41% retention at the spine (CI: 11–72%), 64% at the hip (CI: 14–114%). No clinical fractures occurred in the 12 month period. In 2019, the same group reported minimal further BMD loss in a cohort of nine patients from the above study who were treated with zoledronate following denosumab discontinuation with no further intervention up to 24 months.⁶⁹

In 2019 Anastasilakis *et al.*⁷⁰ published the results of the AfterDmab trial, an open-label randomized controlled study of zoledronate *versus* continued denosumab in previously treatment-naïve postmenopausal women who had attained osteopenia on denosumab. The participants were randomized 1:1 to receive either a single infusion of zoledronate 6 months after the last denosumab injection or to continue denosumab for two

further doses. Each participant was then followed for 2 years post randomization. The mean duration of prior denosumab therapy was 2.0 years for the denosumab arm and 2.4 years for the zoledronate arm; 57 patients received treatment, three discontinued, one participant in each arm experienced a clinical VF and one withdrew consent. Lumbar spine BMD increased $1.7\% \pm 1.1\%$ at 12 months but returned to baseline in the zoledronate group at 24 months ($0.1\% \pm 1.2\%$). Lumbar spine BMD also increased at 12 months in the denosumab group ($2.1\% \pm 1.0\%$) but decreased significantly in the denosumab group at 24 months compared with baseline ($-4.8\% \pm 0.7\%$). The between-group difference in lumbar spine BMD from 12 to 24 months was also significant; this was also true for the change in femoral neck BMD. Participants who received zoledronate experienced a small but significant rise in CTX and procollagen type I N-terminal propeptide (PINP) in the first 12 months, which then stabilized. Both bone turnover markers increased significantly at month 15 in the denosumab arm (9 months post last injection). There was no association found between BMD and both baseline and 12 month bone turnover markers. Three patients experienced a VF: one in the zoledronate arm had a VF at 12 months; two in the denosumab arm had a VF at 9 and 12 months following last injection. A further participant in the denosumab arm was diagnosed with VF on X-ray at 24 months. These findings suggest that zoledronate prevents full rebound of bone turnover markers and that following cessation of denosumab BMD falls to a lower level than at baseline. This paper was followed up by the publication by Makras *et al.*⁷¹ in 2020 that comprised a 1-year single arm observational extension of this study. There was no significant change in lumbar spine BMD at year 3, compared with year 2 or to baseline, in the zoledronate group. There was no change in femoral neck BMD or in CTX, but there was a decrease in PINP. Four of the 23 participants in the study had reverted to BMD within the osteoporotic range by year 3.

Sølling *et al.*⁶⁴ in 2020 reported the findings of a 2-year randomized controlled trial of denosumab discontinuation followed by zoledronate infusion in a group with a history of denosumab use longer than 2 years and with most recent BMD indicating osteopenia. The participants were randomized into three groups based on the timing of zoledronate infusion: the first received an infusion of

zoledronic acid 6 months after the last denosumab injection; the second group received an infusion at 9 months; and the third when CTX increased above $1.26 \mu\text{g/L}$. There was a significant decrease in lumbar spine and total hip BMD across all groups at 6 or 12 months after zoledronate infusion but there was no significant between-group difference. Two patients in the 9-month group had a VF. They concluded that treatment with single dose zoledronate did not fully prevent loss of BMD in patients discontinuing denosumab and that timing of the infusion did not influence loss of BMD. They recommended that the best option was to administer zoledronate at 6 months after cessation of denosumab and that repeat zoledronate at about 3–6 months would be needed in those with a subsequent increase in CTX, pending outcomes from future trials.

Everts-Graber *et al.*⁷² reported the results of an 8 year observational study assessing the effect of a single infusion of zoledronate on BMD and VF rate 6 months after last denosumab administration in a cohort of 120 patients with postmenopausal osteoporosis following 2–5 years of denosumab therapy. The indication for ceasing denosumab was attaining osteopenia (or almost osteopenia)-range BMD; the majority of patients received denosumab for equal to or less than 3 years in total. The decrease in BMD at a median of 29 months after last denosumab injection was significant across all sites. The percentage of retained BMD gain was 66% at the lumbar spine, 49% at the total hip, 57% at the femoral neck (CIs 57–75%, 31–67% and 25–89% respectively). There was no difference in change in lumbar spine BMD following denosumab discontinuation between patients who had received prior bisphosphonate therapy and those who had not, nor between those with and without prevalent VFs. Three patients developed symptomatic single VFs 1–3 years after the last denosumab injection, (mean off-treatment interval 26.9 months). No patient developed multiple fractures. Two of these patients had a history of VF prior to commencing denosumab. The three patients who experienced VF did not have a greater than average loss of BMD. The incidence of VF overall was 1.1 per 100 patient-years. Interestingly, 11 patients who discontinued denosumab without subsequent zoledronate infusion remained in the study; two of the patients sustained multiple VFs.

Ebina *et al.*⁷³ in 2020 reported the results of a multicentre retrospective study of patients with

post-menopausal osteoporosis who commenced denosumab following either oral bisphosphonate (49.1%) or teriparatide (50.9%) and then discontinued denosumab after an average of 2.6 doses. Denosumab was discontinued for a variety of reasons. The participants commenced either raloxifene ($n=13$), weekly or monthly bisphosphonate ($n=40$), or zoledronate ($n=11$) at a mean interval of 7.2 months following last denosumab administration. The participants underwent BMD assessment at final denosumab injection and again 1.5 years after final denosumab injection. Spinal X-rays were obtained at final denosumab injection and at unscheduled times if participants became symptomatic of VF. The change in lumbar spine BMD was +0.7% for those receiving follow-up oral bisphosphonate (alendronate, ibandronate, risedronate) and +1.9% for those receiving zoledronate. Those receiving raloxifene experienced a significant decrease in lumbar spine BMD from their baseline and also a significant decrease compared to participants receiving zoledronate. Similar results were seen for BMD at the femoral neck. Of those who received raloxifene 23.1% experienced clinical VF, compared with 3.4% of those receiving oral bisphosphonates and 0.0% of those receiving zoledronate. No patient experienced multiple VFs; three of the four patients who suffered VF had received bisphosphonates before denosumab. Overall, participants who received a bisphosphonate (oral or intravenous) experienced greater preservation of BMD gains and fewer VFs than those receiving raloxifene.

Kendler *et al.*⁷⁴ in 2020 published the results of a post hoc analysis of the Denosumab Adherence Preference Satisfaction (DAPS) study. DAPS was a randomized crossover open labelled study of treatment naïve post-menopausal women with low BMD (-2.0 to -4.0) where the participants received 12 months of denosumab or alendronate before crossing over.⁷⁵ This sub-analysis examined the cohort randomized to denosumab/alendronate. With denosumab treatment, change in BMD from baseline to month 12 was +5.4% at lumbar spine, +3.1% at total hip, and +2.7% at femoral neck. After changing to alendronate for month 12 to month 24 the mean percentage change between 12 and 24 months was +0.5% at lumbar spine, +0.5% at total hip and -0.2% at femoral neck; 84.1% maintained or gained BMD at the lumbar spine, 92.4% maintained or gained at the total hip and 78.3% at the femoral neck. Subjects who lost BMD with alendronate in year

2 had shown a greater change in BMD in year 1, but the majority still remained above their pre-treatment baseline. There were no VF events during the study. Bone turnover markers were assessed, CTX was suppressed by 12 months of denosumab with a percentage change of -69.1% ; this suppression was partially lost with alendronate as evidenced by a median percentage change of -64.7% at month 18 and -54.8% at month 24. Median percentage change of PINP was -67.7% , -57.0% and -53.1% for the same time points. This study presented positive data to suggest a role for alendronate. This is particularly important for those countries where denosumab therapy is widely prescribed in primary care and where access to bone turnover marker monitoring and to infusion facilities post denosumab discontinuation is limited. It is important to note that the short duration of denosumab therapy prior to switching is atypical when compared with real world practice.

Kondo *et al.* in 2020⁷⁶ reported a retrospective observational study of the effect of sequential therapy with zoledronate following less than 3 years of denosumab treatment with an average number of administrations of 3.3 doses. BMD data and fracture incidence was available for 18 participants at time of commencing denosumab, time of zoledronate infusion, 6 months post zoledronate and 12 months post zoledronate. The time from last denosumab treatment to zoledronate was 277.8 days (from 182 to 495 days). No new vertebral or non-vertebral fractures were noted, BMD was increased at every time point when compared with the BMD prior to commencing denosumab.

Teriparatide with/after denosumab

Although monotherapy with teriparatide after denosumab is not advised, the combination of synchronous denosumab with teriparatide has been evaluated in recent trials and appears to be promising (in terms of BMD gained, but the effect on fracture risk has not been assessed).⁷⁷ The combination period should also be followed by a potent antiresorptive. The 2021 results of the DATA-HD extension study (short duration combination teriparatide/denosumab followed by a single dose of 5 mg intravenous zoledronate 24–35 weeks after the last denosumab dose) provide evidence of prolonged protection of BMD gains with sequential bisphosphonate.⁷⁸

Covid-19-related disruption to denosumab

The coronavirus pandemic and associated social distancing requirements has led to significant curtailment of outpatient services and also hesitancy amongst some patients to attend health care centres. Several organizations in the field of osteoporosis have issued guidance on fracture risk mitigation strategies for patients who are unable or are unwilling to attend for their denosumab injections as planned.⁷⁹ The recommendation for most is to transition to an oral bisphosphonate when delays of >4 weeks cannot be avoided. Patients have been offered training in self-administration of the injection.

Conclusions

The optimal duration of denosumab is unknown. Although there is a lack of published evidence for benefit in denosumab use beyond 10 years, the continued benefit seen and low risk of adverse events in FREEDOM and the Extension study at 10 years is reassuring.^{8,9} Denosumab has a good safety profile. The potential deleterious effects of prolonged denosumab use have perhaps been overstated. ONJ and AFF are rare; the relationship with duration of denosumab treatment is unclear, but the number of cases thus far is too low to estimate the risk associated with prolonged treatment. Though the risk remains low it is not negligible, and the lack of data past the 10 years point still leaves prescribers uncertain regarding the harm:benefit ratio of more prolonged administration. Though denosumab has an established and progressive benefit in terms of increasing BMD and maintaining a reduced fracture risk, even long-term use cannot restore normal trabecular bone architecture. Thus for the moment at least, some form of treatment of osteoporosis is required lifelong. Perhaps in light of the low risk of these and other adverse events coupled with the limited evidence to support sequential therapies, the best advice is to continue denosumab indefinitely, especially in high fracture risk patients, at least whilst longer term data on the safety and efficacy of administration beyond 10 years is gathered.

Notwithstanding the lack of evidence beyond 10 years of use, there are very few clinical reasons to stop denosumab. Denosumab is an effective antiresorptive with clear benefits in reduced risk of fracture for patients whilst on treatment, and there evidently is an increased risk of multiple VF and perhaps other major osteoporotic fractures⁵¹

following its discontinuation. In studies of denosumab-discontinuers, patient factors predominate. Physicians have a duty to educate their patients on the possible risk of discontinuing denosumab and measures to prevent unscheduled breaks should be instituted, such as automatic call back. In addition specialty prescribers must communicate such information to primary care teams, who may not be as up-to-date as physicians who specialize in treating bone disease. Delayed denosumab administration is very common in patients on long-term therapy; up to 50% of such patients experience at least one significant delay (>4 months) in their therapy.⁵² This is important because the risk of VF appears to increase steeply when delays exceed 12 weeks. The COVID-19 pandemic has disrupted many aspects of healthcare, not least osteoporosis care, delays to denosumab administration, and the strategies advised by major organisations involved may shed more light on the optimal sequential therapy following denosumab discontinuation.

If denosumab must be discontinued for clinical reasons, the guidance for most indicates a course of bisphosphonate or SERM for consolidation. Bisphosphonates are the preferred option based on available evidence. Evidence for use of SERMs is lacking (the evidence presented by Gonzalez-Rodriguez *et al.*⁵⁹ and Ebina *et al.*⁷³ argues against SERM as an alternative), although further randomized controlled studies including SERMs are ongoing.⁵ The studies discussed in this review indicate that bisphosphonate treatment after denosumab is at least partially effective for maintaining BMD, in particular spinal BMD. Furthermore bisphosphonates appear to protect against the development of multiple VFs. There remain limitations in the evidence governing the optimum timing, route and duration of sequential bisphosphonate in addition to the potential role of bone turnover markers and how best to monitor individual patient response. For now, the strongest evidence, with which the current authors concur, is from Sølling *et al.*,⁶⁴ who recommend an infusion of zoledronate at 6 months after cessation of denosumab, followed by serial monitoring of bone turnover markers and advising a second infusion even within the next 6 months if bone resorption marker increases. The current authors argue that osteoporosis is a chronic condition requiring chronic treatment and that denosumab represents a viable safe and effective treatment indefinitely for most patients.

Author contributions

JAN was responsible for data collection, data interpretation, analysis and drafting of the article and revisions.

MJM, formal analysis, drafting the article, writing-review, critical revisions of the article and final approval of the version for publication.

RKC, conception of the work, project administration, supervision, critical revisions of the article and final approval of the version for publication.

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ORCID iD

Rachel K. Crowley  <https://orcid.org/0000-0003-1472-4117>

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