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Review Article

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS

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ABSTRACT

Introduction: The optimal duration of osteoporosis treatment is controversial. As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.
Methods: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab and provide advice on management.
Results: Data from phase 2 and 3 clinical trials underscore a rapid decrease of bone mineral density (BMD) and a steep increase in bone turnover markers (BTMs) after discontinuation of denosumab. Clinical case series report multiple vertebral fractures after discontinuation of denosumab and a renewed analysis of FREEDOM and FREEDOM Extension Trial suggests, albeit does not prove, that the risk of multiple vertebral fractures may be increased when denosumab is stopped due to a rebound increase in bone resorption.
Conclusion: There appears to be an increased risk of multiple vertebral fractures after discontinuation of denosumab although strong evidence for such an effect and for measures to prevent the occurring bone loss is lacking. Clinicians and patients should be aware of this potential risk. Based on available data, a re-evaluation should be performed after 5 years of denosumab treatment. Patients considered at high fracture risk should either continue denosumab therapy for up to 10 years or be switched to an alternative treatment. For patients at low risk, a decision to discontinue denosumab could be made after 5 years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover. However, since the optimal bisphosphonate regimen post-denosumab is currently unknown continuation of denosumab can also be considered until results from ongoing trials become available. Based on current data, denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

Contents

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1. Introduction

The optimal duration of osteoporosis treatment remains controversial. Ever since bisphosphonates were introduced in clinical practice some 40 years ago there have been discussions on how long these drugs can be used safely for the therapy of osteoporosis [1]. It is well recognised that the antiresorptive effect after stopping treatment with bisphosphonates persists for months or years due to their high affinity for binding hydroxyapatite. Alendronate and zoledronic acid are known to have a more sustained effect on bone mineral density (BMD) and bone turnover markers (BTMs) than risedronate presumably because of their greater binding affinity to hydroxyapatite [2]. There is evidence that treatment of women with postmenopausal osteoporosis with alendronate for as long as 10 years and zoledronic acid for 6 years is not associated with increased fracture risk, but even leads to a further decrease in clinical vertebral fractures in patients continuing alendronate [3], and morphometric vertebral fractures in patients continuing zoledronic acid [4] compared to individuals who went on with placebo after 5 years of alendronate and 3 years of zoledronic acid. Nevertheless, due to their long-term retention in the skeleton, there has been concern that prolonged use of bisphosphonates and a sustained suppression of bone turnover might lead to so-called 'frozen' or 'brittle' bone. Although this has not been demonstrated some rare but serious potential side-effects of long-term bisphosphonate use such as atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ) make a reassessment of the benefit-to-risk ratio after several years of treatment imperative. The American Society for Bone and Mineral Research (ASBMR) Task Force suggests that after 3 years of treatment with intravenous zoledronic acid or 5 years with oral bisphosphonates a treatment break often referred to as 'drug holiday' should be considered, unless there are characteristics indicative of high fracture risk as for example, older age, low hip T-score or high fracture risk score, previous major osteoporotic fractures, or fractures on therapy [5]. Similar recommendations have been issued by the UK National Osteoporosis Guideline Group (NOGG) [6] and by the European Menopause and Andropause Society (EMAS) [7]. This concept of a treatment break does not apply to drugs other than bisphosphonates, since for drugs without skeletal retention the fracture risk is expected to increase after drug discontinuation. For example, after teriparatide discontinuation BMD progressively declines [8], so that the risk of fracture maybe increasing later on [9], and reversibility of drug effect as measured by BMD and BTMs has been shown for postmenopausal estrogen therapy and estrogen receptor modulators [10,11].

Denosumab is a fully human monoclonal antibody with high affinity and specificity for human receptor activator of NF-κB ligand (RANKL) which neutralizes the activity of human RANKL, thereby inhibiting osteoclast formation, function and survival. There is ample data demonstrating that denosumab decreases bone resorption and increases bone mass and strength in both trabecular and cortical bone, with the pivotal randomized, double-blind, placebo-controlled, phase 3 Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 months (FREEDOM) trial in women with postmenopausal osteoporosis showing that denosumab treatment reduced the incidence of new vertebral fractures, nonvertebral fractures, and hip fractures when compared to placebo [12]. The long-term efficacy and safety of denosumab has been evaluated in the FREEDOM Extension Trial with results published for up to 10 years of denosumab exposure, demonstrating a continuing increase in BMD, a sustained reduction of BTMs, a low fracture incidence (similar to rates observed during the FREEDOM trial) and a consistent safety profile [13]. Notably, adverse events such as serious infections, cellulitis and eczema showed no evidence of increased frequency through 10 years of denosumab exposure and the rates of bone related adverse events such as atypical femur fractures (AFF) remained low, with 13 cases of osteonecrosis of the jaw (ONJ) reported to date [13].

Despite the fact that the concept of a treatment break does not apply to drugs without skeletal retention, we notice in clinical practice that after 5 years of denosumab treatment many patients are now being taken off the drug [14]. Also, patients are often advised by dentists that medication should be stopped temporarily before a dental procedure to avoid the risk of ONJ. Recently, there has been concern that discontinuation of denosumab will lead to an increased risk of multiple vertebral fractures associated with rapid bone loss when treatment is stopped. Here, we performed a systematic review to assemble relevant evidence on the clinical consequences following withdrawal of denosumab treatment for osteoporosis and on options to prevent bone loss afterwards. Based on available data and expert opinion we provide advice for physicians on how long to continue denosumab treatment in the setting of osteoporosis and how to deal with patients who discontinue the drug. The treatment duration with denosumab in other settings (oncology conditions, Paget's disease, fibrous dysplasia, avascular necrosis, bone marrow oedema) is beyond the scope of this paper.

2. Methods

The systematic review was performed under the auspices of the European Calcified Tissues Society (ECTS) Professional Practice Committee. We searched electronic databases (PubMed/MEDLINE) and ClinicalTrials.gov using MeSH terms "Denosumab" and "Osteoporosis" up to May 31st 2017. The review included randomized controlled trials as well as observational studies which investigated the effect of denosumab discontinuation on bone mineral density (BMD), bone turnover markers (BMTs), bone histomorphometry and clinical or morphometric vertebral and/or non-vertebral fractures in postmenopausal women with osteopenia or osteoporosis. We also included studies investigating the effects of pre- or post-treatment with bisphosphonates on the decrease in BMD and/or increase in BTMs. Studies conducted in oncology patients or in those with other metabolic bone disease, such as Paget's disease of bone, or in patients in receipt of glucocorticoid treatment were excluded. In view of sparse data concerning fracture incidence after denosumab discontinuation, we also included patient case series and searched for abstracts form the annual meetings of ASBMR, ECTS, EULAR, ACR, IOF, ESCEO and Endocrine Society in the years 2015 and 2016 using the same terms.

Two independent researchers (ET and MCZ) reviewed all eligible studies. The following data were recorded: number of participants, duration of denosumab treatment (months), duration of denosumab discontinuation (months), effect of denosumab discontinuation on lumbar

spine and femoral neck/total hip BMD, BTMs, and vertebral and non-vertebral fractures as well as effects of pre- and post-treatment with oral and intravenous bisphosphonates on BMD and BTMs. ET and MCZ prepared the initial draft, which was circulated to all other named authors- members of the ECTS Professional Practice Committee or the ECTS Board-for comments and approval.

3. Results

As part of the search for the systematic review we identified 901 abstracts on PubMed, 71 clinical trials on ClinicalTrials.gov and 25 abstracts of past annual meetings of the societies mentioned in the Methods Sections using the terms stated in the Methods Section. After eliminating publications which did not describe effects of discontinuation of denosumab or duplicates we retained 24 relevant contributions (Fig.1).

3.1. Reversibility of treatment effects with denosumab

The results of these studies related to BMD, BTMs, bone biopsies and fractures after denosumab cessation are summarized in Table 1. An observational retrospective study looking into the frequency of discontinuation of injectable osteoporosis therapies in US patients reported that by 24 months 64% of patients receiving denosumab had discontinued treatment [15]. In a phase 2 multidose trial and an extension of a phase 3 osteoporosis prevention study a rapid reversal of BMD accrual gained during the treatment period was noted [16,17] (Fig.2). A small observational study involving 82 patients on long-term therapy with denosumab also showed reversal of the drug's effect on BMD within 12 months after 8 years of treatment [14], and case-series of denosumab-treated patients presented in abstract form reported a similar effect after 10 years of treatment [18,19]. In contrast, within 1 year of retreatment with denosumab, BMD increased again at all sites as shown by a phase 2 clinical trial [20].

The figures show percentage change from month 0 in Lumbar spine (A), Total Hip (B) and 1/3 Radius (C) in patients treated with denosumab between months 0–24 compared with months 25–48 when patients were taken off-treatment. From Bone HG, Bolognese MA, Yuen CK et al. [17], permission acquired.

In addition to the BMD decline seen after denosumab discontinuation, a rapid increase in BTM concentrations to above pretreatment baseline levels has been observed. In an extension of a phase 3 osteoporosis prevention study, BTMs increased above baseline within 3 months (sCTXI) or 6 months (PINP) after denosumab discontinuation (9 to 12 months after the last denosumab injection) and returned to baseline by 48 months [17] (Fig. 3). Similar results were reported in the phase 2 multidose trial [16], whereas in patients who were retreated after discontinuation, the BTM concentrations decreased to values below baseline within 6 months of retreatment [20].

The figures show percentage change from month 0 in sCTXI (A) and PINP (B) in patients treated with denosumab between months 0–24 compared with months 25–48 when patents were taken off-treatment. From Bone HG, Bolognese MA, Yuen CK et al. [17], permission acquired.

The changes observed in BTMs are mirrored by alterations in bone turnover at the tissue level as evaluated by bone histology and quantitative histomorphometric analysis. In a study of fifteen patients who had discontinued osteoporosis treatment with denosumab for a mean time of 25 months, bone histomorphometry showed bone remodeling results indistinguishable from those of untreated postmenopausal women [21]. A small study presented in abstract form evaluated microarchitecture changes by HR-pQCT and reported that cessation of denosumab for ≥12 months reverses the benefits achieved in microstructure [22].

It has been postulated that, in the case of BTMs, the rebound effect is more prominent as the duration of denosumab treatment increases [23], although this has not been proven by the extension trials that have been performed to date. There is some evidence that reversal of changes in BMD may be related to the duration of denosumab therapy. For example in the study of Bone et al. [17], BMD values returned to baseline one year following cessation of treatment in women that had been treated with denosumab for two years. In contrast, women who discontinued denosumab after 10 years of treatment experienced a rapid BMD loss at the total hip, the magnitude of which even exceeded BMD gains achieved during treatment, as reported in a small series of patients recently presented in abstract form [18]. Possible explanations for the 'rebound effect hypothesis' could be that an increased pool of osteoclast precursors which were dormant during the treatment period with denosumab become activated after its discontinuation, and/or that a high RANK ligand/osteoprotegerin ratio ensues after denosumab is cleared from circulation leading to a rapid rebound in remodeling rates [24]. A recent small case-control study also reported an upregulation of markers of osteoclast formation and activity in patients who sustained vertebral fractures after denosumab discontinuation [25]. This is very different from the effect of bisphosphonates which remain

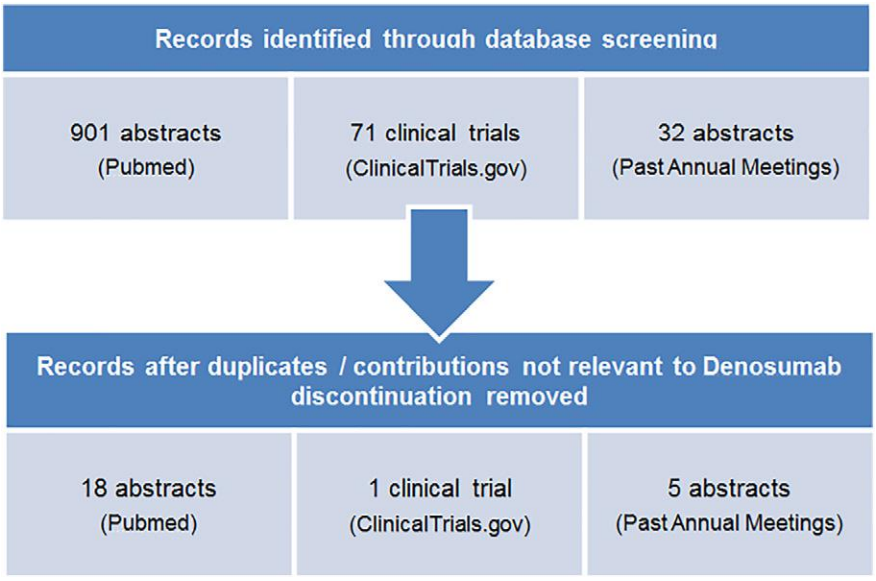

Fig. 1. Flowchart of records included in the systematic review.

Table 1
Effects of Denosumab Treatment Discontinuation on Bone Turnover Markers, Bone Mineral Density and Fracture Risk.

Design	Phase	No	Duration of Treatment (months)	Duration of Discontinuation (months)[c]	↑BTMs	↓BMD LS	↓BMD Hip	↑Vertebral Fx or ↑ multiple vertebral Fx	↑ Non-vertebral Fx	Reference
Open-label single arm in postmenopausal women with osteopenia/osteoporosis	2	200	24	24	+	+	+	N/A	N/A	[16]
Randomized blinded placebo controlled in postmenopausal women with osteopenia	3	256	24	24	+	+	+	–	–	[17]
Observational follow-up study after 8 years of denosumab treatment in patients with osteoporosis	N/A	82	96	12	N/A	–	+	N/A	N/A	[14]
Observational follow-up study after 10 years of denosumab treatment in women with osteoporosis	N/A	9[a]	120	12	+	N/A	+	+	–	[18]
Observational follow-up study after 7 to 10 years of denosumab treatment in women with osteoporosis	N/A	38	84–120	10–14	+	+	+	+	+	[19]
RCT blinded placebo controlled in postmenopausal women with osteopenia/osteoporosis	2	307	24	24	+	+	+	–	–	[20]
Retrospective analysis of participants of FREEDOM trial [12]	N/A	797	12–30	24	N/A	N/A	N/A	–	–	[27]
Case report	N/A	1	36	2	+	N/A	N/A	+	–	[28]
Case series	N/A	3	30–36	4–10	N/A	N/A	N/A	+	–	[29]
Case report	N/A	1	36	6	+	+	+	+	–	[30]
Case series	N/A	9	12–48	3–10	N/A	N/A	N/A	+	–	[31]
Case series	N/A	2	12–24	6–8	N/A	N/A	N/A	+	–	[32]
Case series	N/A	24[b]	12–30	2–10	N/A	N/A	N/A	+	-	[33]
Retrospective analysis based on administrative claims data	N/A	7.855	N/A	>6	N/A	N/A	N/A	+	+	[34]
Retrospective analysis of participants of FREEDOM and FREEDOM Extension trials [12,13]	N/A	1.001	>12	>7	N/A	N/A	N/A	+	–	[35]

Abbreviations: BMD LS, Bone Mineral Density at Lumbar Spine; BMD Hip, Bone Mineral Density at Total Hip/Femoral Neck; BTMs, Bone Turnover Markers; n/a, not applicable; N/A, not available; No, Number of patients; vertebral Fx; vertebral fractures; non-vertebral Fx, non-vertebral fractures.
[a] Patients from the FREEDOM and FREEDOM Extension Trials.
[b] 11 new patients, remaining patients already described [28–32].
[c] Duration of discontinuation in months is calculated from the time point the next injection of denosumab would be due.

in the skeleton long after their discontinuation and which also decrease the survival of osteoclasts, as evidenced by the reduction in circulating osteoclast precursors with long-term oral bisphosphonate therapy [26].

Since the rapid decline in BMD with high bone turnover upon stopping denosumab can negatively influence bone microarchitecture [22], especially of the trabecular bone, an increased fracture risk might be expected. No increase in fracture incidence after treatment discontinuation was reported in the 256 low risk patients in the denosumab bone loss prevention study, where a similar percentage of patients coming off denosumab or placebo (3%) sustained clinical fractures [17]. In 2013, Brown et al. reported fracture incidence in 797 patients who discontinued denosumab or placebo in the Phase 3 FREEDOM trial [27]. The average duration on therapy before patients discontinued was less than two years (about 3.4 doses). Clinical fractures occurred after stopping therapy in 9% and 7% of patients who had received placebo or denosumab, respectively. The rate of vertebral fractures was not higher in patients after stopping denosumab (5.6 per 100 patient-years) compared to the previous placebo group (9.3 per 100 patient-years). Thus, the data looked reassuring with respect to fracture incidence after stopping denosumab. However, this was a post-hoc analysis and the median off-treatment interval in the study by Brown et al. was short, median 0.8 years per subject. Also, 42% and 28% of placebo- and denosumab-treated subjects, respectively, had started other osteoporosis treatments during follow-up. Recently, several case reports have been published in which multiple (≥2) vertebral fractures occurred within 2 to 10 months after denosumab cessation [28–33] (Table 1). In an observational study using administrative claims data in 7855 older women, fracture risk was evaluated after denosumab discontinuation (defined as the absence of denosumab claim within 6 months +8 weeks following a previous claim) and results were

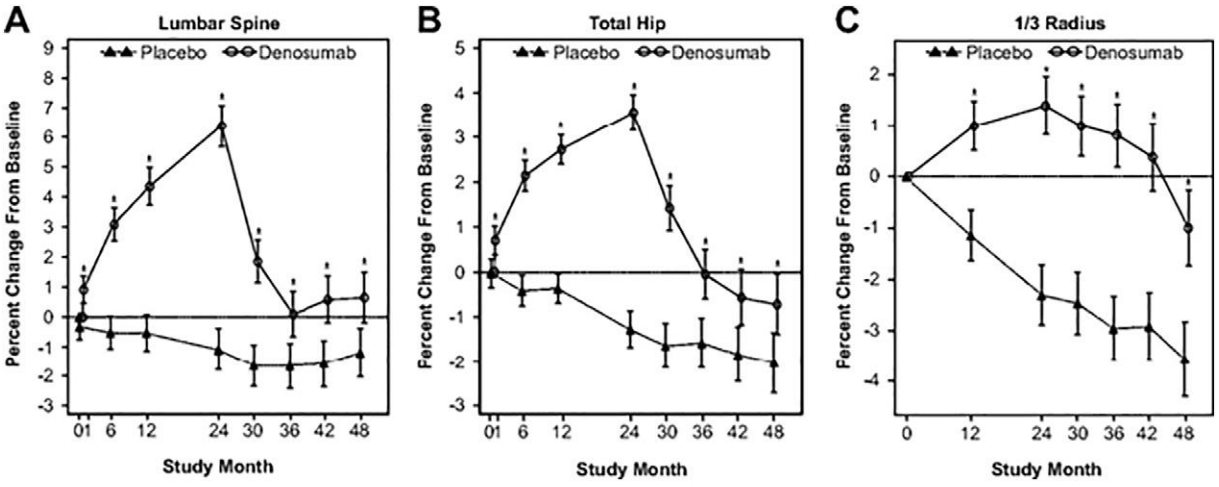

Fig. 2. Effects of stopping denosumab on bone mineral density.

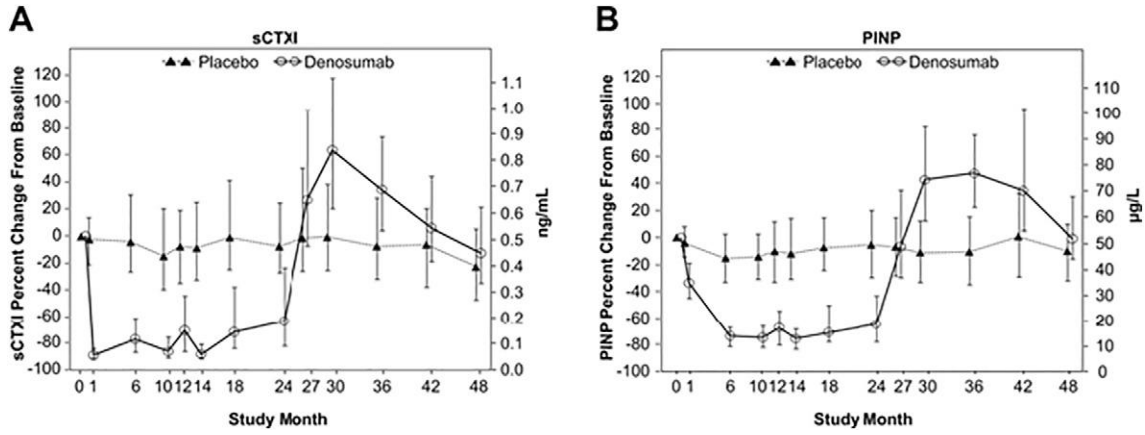

Fig. 3. Effects of stopping denosumab on bone turnover.

presented recently in abstract form Vertebral fracture incidence rates increased after denosumab discontinuation for 6–12 months (3.09/100 patient-years during the off-treatment period vs 2.07/100 patient-years during the treatment period), but remained lower than the baseline rates observed during the early treatment period [34]. A renewed analysis of data in patients discontinuing denosumab in the FREEDOM and FREEDOM Extension Trial was presented by Brown et al. at the 38th Annual Meeting of the ASBMR [35]. The authors reported that 5.6% of subjects who discontinued denosumab during FREEDOM or Extension Trial sustained new vertebral fractures, which was not different from patients discontinuing placebo (6.2%). However, among subjects with off-treatment new vertebral fractures, 60.7% of those that discontinued denosumab and 34.5% of those who discontinued placebo sustained multiple vertebral fractures. Prior vertebral fractures before or during treatment were the strongest predictor of off-treatment new fractures. Drawbacks of this study are that no systematic spine radiographs were taken in all subjects and not all subjects were evaluated as this was not a preplanned study and fracture data of patients receiving denosumab for three years (FREEDOM) or seven years (FREEDOM Extension) are not presented separately. However, combined with the case reports and clinical case series of patients who were not included in the FREEDOM and FREEDOM Extension studies these analyses suggest, albeit do not prove, that after discontinuation of denosumab the rebound increase in bone turnover associated with the steep decline in BMD may lead to an increased risk of multiple vertebral fractures.

3.2. Effects of pre- and post-treatment with bisphosphonates on changes in BMD and BTMs after denosumab discontinuation

In a small retrospective observational study of 37 patients who had either been pre-treated with bisphosphonates before being switched to denosumab or not, pre-treatment with bisphosphonates was associated with lower serum CTX levels after denosumab discontinuation [36]. A study in postmenopausal women transitioning to alendronate after a 12-month treatment period with denosumab showed that BMD remained stabilized and BTMs increased only slightly [37]. In a series of six women with postmenopausal osteoporosis who had been treated with denosumab for 7 years, a single infusion of zoledronic acid prevented 50% of BMD loss at the spine but failed to prevent BMD loss at the femur [38]. In the DATA-Follow-up study it was shown that the large gains in BMD by denosumab were maintained in those who received prompt antiresorptive therapy (including oral and intravenous bisphosphonates), but not in those left untreated [39]. In a recent observational study ($n = 82$) bone loss after stopping denosumab after 8 years was attenuated in the small number of patients ($n = 17$) who started osteoporosis medication, including alendronate ($n = 7$), denosumab ($n = 5$), risedronate ($n = 4$) ibandronate ($n = 2$) and teriparatide ($n = 2$) [14]. A very recent small study by Lehmann and Aeberli [40] showed that 22 subjects who received a single dose of zoledronic acid after 5 injections of denosumab lost about 38% of BMD gained at the spine, 43% at the total hip and 26% at the total neck, so not losing all BMD gained. It should be noted that 13 out of 22 patients were pre-treated with bisphosphonates. A study addressing the question of whether a single infusion of zoledronic acid can prevent the increase in bone turnover and decrease BMD after discontinuation of denosumab is currently ongoing (NCT02499237).

4. Discussion

4.1. Consequence for management of patients on denosumab

4.1.1. Denosumab treatment duration in patients with low and high risk for fracture

Since osteoporosis is a chronic condition, continued treatment is a prerequisite in many patients to sustain therapeutical benefits as is the case with other chronic diseases. However, as in any chronic disease, it is important to define targets to achieve the therapeutical goal. In the setting of cardiovascular diseases, blood pressure, blood glucose and lipid concentrations constitute well-defined targets to decrease the incidence of stroke or myocardial infarction. In the setting of osteoporosis targets are less well defined but BMD or fracture risk are logical therapeutic targets [41]. Especially in the case of patients with high fracture risk, treatment with drugs without skeletal retention and in particular with denosumab should not be terminated without considering substitution with an alternative agent because gains in BMD will be lost rapidly. Based on the biological mechanism of action of denosumab it was stated early on that continued therapy is required to maintain treatment effects [17]. Since denosumab treatment for 10 years is associated with a continuing gain in BMD, persistently low BTMs, a low fracture incidence and acceptable tolerance and safety [13], a case for a long-term treatment with denosumab up to 10 years can indeed be made in those patients that are still considered at high risk for fracture after 5 years [42], e.g. who still have low BMD as defined by T-score <−2.0 [43], or by T-score <−2.5 [5] or with multiple vertebral fractures or a high fracture risk score [5]. Whether it is still beneficial to continue denosumab beyond 10 years is not known since the risk of rare side effects such as AFF and ONJ may increase while there is no data on fracture incidence beyond 10 years. Another alternative, when reimbursed, could be teriparatide, especially in case of fractures under denosumab. A point to be considered is that when denosumab is followed by teriparatide, a temporal decrease of BMD can be expected, especially at cortical sites, like the hip and radius, as shown in the DATA-Switch study [44], possibly because of initial increases in the remodeling space, However, there is yet no data showing that this temporal decrease in BMD will lead to an increased fracture risk.

In patients considered at low risk of fracture after 5 years of treatment, discontinuation of denosumab is an option but a follow-up treatment with bisphosphonates should be considered as discussed below.

4.1.2. What to do after discontinuation of denosumab

It seems quite clear that there is a rebound increase in bone turnover increases and a fall in BMD following cessation of denosumab. In some patients, this may be accompanied by an increased risk of multiple vertebral fractures, although there is no evidence at present to suggest that the risk of single vertebral fractures or non-vertebral fractures is increased after stopping denosumab other than to be expected after stopping an effective osteoporosis treatment. Although there is uncertainty as to the risk of multiple vertebral fractures we believe that it is important that patients and physicians should be advised against discontinuing denosumab without evaluation and consideration of an alternative therapy, especially in those patients considered at high fracture risk. If, after 5 years of treatment with denosumab, BMD levels have increased to such a degree that they are no longer within the osteoporotic range [5], cessation of denosumab treatment may be considered. In both situations, after stopping denosumab, we recommend to consider treatment with bisphosphonates in order to reduce or prevent the rebound increase in bone turnover. At present, the optimal bisphosphonate regimen is unknown, but information from small case-series may indicate that a single infusion of zoledronic acid may not be effective in preventing bone loss following denosumab when bone turnover is still suppressed [38].Therefore, if future studies show that zoledronic acid is more effective in preventing BMD loss if given when bone turnover increases, consideration may be given to start intravenous bisphosphonates when BTMs start to rise or to consider oral bisphosphonates. It is acknowledged however that BTMs are not routinely used in many clinics, e.g., due to lack of standardization and costs. Another option in the low risk patient group after 5 years would be to continue denosumab for up to 10 years until the outcome of ongoing clinical trials on the optimal regimen of post-treatment with bisphosphonates becomes available. In case of previous intolerance for bisphosphonates, a selective estrogen receptor modulator could be considered for follow-up when there are no contra-indications but there are no data available to support this policy.

Further prospective studies are also needed to examine the effect of discontinuing denosumab in patients who have been previously treated with bisphosphonates. Data from the small retrospective observational study by Uebelhart et al. suggests that the increased bone turnover after denosumab discontinuation may be prevented in those previously treated with bisphosphonates [36].

As a scientific organization promoting research to improve bone health, the ECTS believes that the presentation by Brown et al. coupled with the case reports/series makes it imperative that, pending new studies, the public (patients, physicians, nurses, dentists and health authorities) should be made aware of the potential risks after denosumab discontinuation. In clinical practice we notice that after 5 years of denosumab many patients are now being taken off the drug in analogy with the advice concerning long term use of bisphosphonates, with physicians not realizing that the effects of discontinuation of these drugs are very different. Also, patients are often advised by dentists that medication should be stopped temporarily before a dental procedure to avoid the risk of ONJ. ECTS suggests that patients should be instructed very clearly when starting denosumab that, in case they want to or need to stop treatment, this should always be discussed with their treating physician. For some patients the risk may be deemed acceptable, but for other patients this may carry a potential risk of experiencing multiple vertebral fractures. Also, the period advised for re-evaluation of fracture risk of 2–3 years after cessation of bisphosphonates is most likely too long after stopping denosumab. A period of 1–1.5 year after the last injection seems more appropriate, especially when no alternative antiresorptive therapy is initiated, and patients should also be instructed to report to their treating physicians when they experience new or worsening back pain or after new fractures. In case a dentist or dental surgeon wants to stop treatment before an invasive dental procedure, the patient should preferably be referred to the treating physician for risk assessment and sometimes interdisciplinary consultation will be needed.

5. Summary and conclusion

In contrast to the discontinuation of bisphosphonates, withdrawing other bone active drugs results in rapid loss of their effects on BMD and BTMs. BMD gains achieved with estrogens, SERMs, denosumab or teriparatide therapy are lost over 1–2 years. With regards to denosumab, markers of bone turnover rebound to values well above baseline for 1–2 years after stopping therapy corresponding to the interval of rapid decrease of the significant gains in BMD. Concern has been raised early on that this pattern of high bone turnover and rapid bone loss could be associated with a rebound in the risk of fracture during the immediate post-treatment interval. Six recent case reports and series of patients who experienced multiple and/or severe vertebral fractures within a few months after stopping denosumab have brought this theoretical concern into the clinical arena. There is very limited information from clinical trials about fracture risk upon stopping denosumab therapy, and recently Brown and colleagues reported no increase in vertebral fracture incidence in 1001 patients who discontinued denosumab or placebo in the FREEDOM and FREEDOM Extension trials [35]. However, among subjects with off-treatment new vertebral fractures, there was an excess of multiple vertebral fractures in those that discontinued denosumab compared to those that discontinued placebo. There is also a lack of information on how the duration of denosumab treatment and previous treatment with bisphosphonates affect the rebound in BMD, bone turnover and fracture risk. Although the current data do not prove a rebound increase in multiple vertebral fracture risk after stopping denosumab, there is enough concern for such an effect to advise not to stop the treatment without considering alternative treatment. Regarding long-term treatment we suggest to perform a re-evaluation after five years of denosumab treatment. In those patients who are still considered at high fracture risk e.g. who still have low BMD as defined by T-score <−2.0) [43] or by T-score <−2.5 [5] or with multiple vertebral fractures or a high fracture risk score [5], it is advisable to continue treatment with denosumab for up to 10 years and consolidate with a single infusion of zoledronic acid, although this may not completely prevent bone loss when given at a moment when bone turnover is still low, or one or more years of oral bisphosphonates. Ongoing studies will give more insight in the most optimal post denosumab bisphosphonate treatment regimen. In high risk patients that wish to stop denosumab after 5 years an additional 5 years of oral or 3 years of intravenous bisphosphonates should be considered, or, when reimbursed, teriparatide, although a temporal decrease of BMD, especially at cortical sites, can be expected when denosumab is followed by teriparatide but it is not known if this is associated with an increased fracture risk. When fracture risk after 5 years of treatment with denosumab is deemed to be low and BMD has increased (T-score >−2.0) [43] or T-score >−2.5 [5], cessation of denosumab treatment may be possible, also with the recommendation to consider follow-up with a course of bisphosphonate therapy to reduce or prevent the rebound increase in bone turnover. As the optimal follow-up bisphosphonate treatment regimen is currently unknown, continuing denosumab for up to 10 years can also be considered in this low risk group, until the outcome of ongoing clinical trials become available. With this position statement we want to increase awareness among patients, physicians, nurses, dentists and health authorities that, in contrast to long-term use of bisphosphonates, at this moment no treatment break should be advised in patients who have started denosumab without considering follow-up treatment.

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