ORIGINAL ARTICLE

Fracture risk following intermission of osteoporosis therapy

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Abstract

Summary Given the widespread practice of recommending drug holidays, we reviewed the impact of medication discontinuation of two common anti-osteoporosis therapies (bisphosphonates and denosumab). Trial evidence suggests the risk of new clinical fractures, and vertebral fracture increases when osteoporosis treatment with bisphosphonates or denosumab is stopped.

Introduction The aim of this paper was to review the available literature to assess what evidence exists to inform clinical decision-making with regard to drug holidays following treatment with bisphosphonates (BiP) or denosumab.

Methods Systematic review.

Results Differing pharmacokinetics lead to varying outcomes on stopping therapy. Prospective and retrospective analyses report that the risk of new clinical fractures was 20–40% higher in subjects who stopped BiP treatment, and vertebral fracture risk was approximately doubled. Rapid bone loss has been well described following denosumab discontinuation with an incidence of multiple vertebral fractures around 5%. Studies have not identified risk factors for fracture after stopping treatment other than those that provide an indication for treatment (e.g. prior fracture and low BMD). Studies that considered long-term continuation did not identify increased fracture risk, and reported only very low rates of adverse skeletal events such as atypical femoral fracture.

Conclusions The view that patients on long-term treatment with bisphosphonates or denosumab should always be offered a drug holiday is not supported by the existing evidence. Different pharmacokinetic properties for different therapies require different strategies to manage drug intermission. In contrast, long-term treatment with anti-resorptives is not associated with increased risk of fragility fractures and skeletal adverse events remain rare.

Keywords Atypical fracture · Bisphosphonates · Denosumab · Drug holiday

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Introduction

The burden of osteoporotic fracture is very high, with an estimated 8.9 million fractures annually [1]. Many anti-osteoporosis medications (AOMs) are available, with the oral bisphosphonates (BP) being among the most widely prescribed. The efficacy of these is well established, with fracture reduction of the order of 50% possible [2]. These effects on fracture risk are offset by poor adherence to AOM, as with other therapy for long-term conditions, estimated at about 35% at 1 year [3], although other studies suggest higher persistence for secondary fracture prevention [4]. Adherence with AOM has been further challenged in recent years with widespread publicity about rare risks associated with long-term bisphosphonate use, namely atypical femoral fracture (AFF) and osteonecrosis of the jaw [5]. The recognition of these rare side events has led to the common practice of 'drug holidays' whereby patients who have been on BiP for 3–5 years are considered for their suitability for a rest from treatment, typically for 1–2 years [5–9]. Patients may be aware, through media communication, of adverse events that have been linked to long-term bisphosphonate use, and may appropriately wish to be involved about decisions regarding their osteoporosis management; patient preference, after appropriate counselling, is an important element of the osteoporosis consultation. More temperate guidance has recently been published to assist physicians in the form of guidelines from the American Society of Bone and Mineral Research and UK National Osteoporosis Guideline Group [10, 11]. However, there is a growing concern that 'drug holidays' are becoming the norm in many countries, and even in high-risk patients who might derive more benefit than harm from ongoing therapy, cessation of treatment is being offered [5], for example in the UK, particularly since NICE guidelines recommended stopping treatment at 3 years [12].

The aim of this work was to review the available literature to assess what evidence exists to inform clinical decision-making, and to identify any clinical indicators that might inform a decision regarding whether to continue or discontinue therapy. With the advent of widespread denosumab use, we included a review of evidence for the effects of stopping this therapy. This piece of work follows on from a previous editorial [5] and formed the introduction for an International Osteoporosis Foundation (IOF) project that aimed to identify surrogate markers that predict outcomes upon intermission of therapy and to develop a new algorithm based on a patient's risk profile. The four key questions we sought answers for in the available literature were as follows: Does fracture risk increase upon treatment discontinuation? Conversely, does fracture rate decrease or remain stable upon treatment continuation? Are there patient or treatment characteristics that are associated with increase fracture risk upon discontinuation? Finally, do adverse events increase with long-term exposure?

Methods

A single reviewer searched Pubmed; EMBASE; Cochrane Library; NHS Evidence; Epistemonikos and NIH records on ClinicalTrials.gov. using the following PICO criteria:

> Participants - Post-menopausal women on osteoporosis medication for ≥1 year;
> Intervention - Medications for osteoporosis with focus on denosumab, or bisphosphonates/diphosphonates specifically alendronate/alendronic acid, risedronate/risedronic acid, ibandronate/ibandronic acid and zoledronate/zoledronic acid;
> Comparison - Medication continuation versus discontinuation. Hormone replacement therapy was excluded from this systematic review;
> Outcomes - Bone turnover markers; bone mineral density (BMD); fracture; osteonecrosis of the jaw; atypical femoral fracture.

Exclusion criteria were other metabolic bone diseases, non-English language guidelines, recommendations, systematic reviews, overviews and clinical opinions. However, non-English language primary research articles with English abstracts were included if relevant. We considered RCTs and observational studies and used the following search terms: (osteoporosis OR osteopenia) AND (denosumab OR bisphosphonates [specifically alendronate/alendronic acid, risedronate/risedronic acid, ibandronate/ibandronic acid and zoledronate/zoledronic acid] OR oral treatments). We considered studies reported over the period 2011–2016, though other key literatures (e.g. results from the FLEX study) were reviewed as part of this work and specifically recent studies that consider the effects of denosumab discontinuation will be discussed. Current conference abstracts (2017–2018) were considered for inclusion only if they provided essential new information to what was published in peer-reviewed form (Table 1).

Results

Effects of treatment discontinuation versus continuation on fracture risk (RCT data)

We identified 38 articles that reported the findings of clinical trials [14–51]. The breakdown of studies is as shown in Fig. 1. A large number of systematic reviews (16) were identified as addressing treatments, specifically bisphosphonates (namely alendronate, risedronate, ibandronate, zoledronate) or denosumab, for post-menopausal osteoporosis or osteoporosis in general. Hence, a considerable number of review papers were also identified, although the number of source trials

Table 1 Key findings of available RCT data

Medication	Study	Outcomes recorded	Key findings	Reference
Alendronate	FLEX	BMD; fracture	2–2.5% difference in BMD in groups receiving 5 or 8 years therapy; clinical vertebral fractures higher in the 5-year group	[38, 39]
Risedronate	VERT	BTM; BMD	Difference between 2 and 7 years therapy	[25]
Risedronate	VERT-NA	BTM: BMD; fracture	One year after discontinuation of 3 year's treatment with risedronate, BMD decreased at the lumbar spine and hip and BTM returned to control group levels. Risk of new morphometric vertebral fractures remained lower in previous risedronate patients vs previous control patients.	[13]
Zoledronate	HORIZON (6 vs. 3 years therapy)	BTM; BMD; fracture	In participants receiving 3 years vs. 6 years therapy, differences seen in BTM (start to return to normal but remain below baseline in the 3-year group); FN BMD trended downwards in the 3-year group; morphometric vertebral fracture higher in the 3-year group	[15]
Zoledronate	HORIZON (9 vs. 6 year therapy)	BTM; BMD; fracture	Small non-significant differences in BTM, BMD and fracture between the two groups	[17]
Ibandronate		BTM; BMD	Discontinuation of 3 BiPs (Alendronate, risedronate, ibandronate) all resulted in reduction in hip BMD and rise in BTM	[51]
Denosumab	FREEDOM	BMD; vertebral fracture	10-year treatment associated with lower vertebral and non-vertebral fracture rates than virtual placebo cohort; if not followed by BiP therapy, denosumab withdrawal associated with bone loss and vertebral fracture	[40–47]

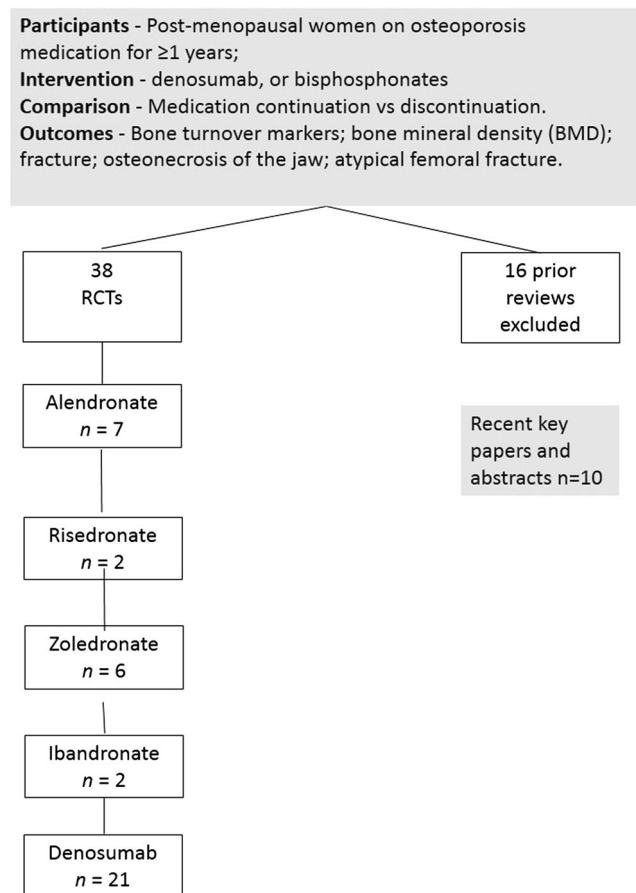*BTM*, bone turnover marker; *BMD*, bone mineral density; *BiP*, bisphosphonate

Fig. 1 Overview of studies reporting the findings of randomised controlled trials included

was much less. Of the clinical trials identified for this review, the majority were extension studies of randomised controlled trials (RCTs). Some of the best data come from studies of bisphosphonates; articles reported studies including the Fracture Interventional Trial Long Term Extension (FLEX) [30, 31, 38, 39] and the Vertebral Efficacy with Risedronate Therapy (VERT) extension studies [25]. Finally, the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly–Pivotal Fracture Trial (HORIZON-PFT) extension studies have reported effect of discontinuation of bisphosphonates in some detail [15–17, 23, 24].

Randomised controlled trials of osteoporosis treatment discontinuation have been undertaken. Black and colleagues compared the effects of 3 versus 6 years zoledronic acid in the HORIZON Pivotal Study [15], and found that, whilst femoral neck bone mineral density (BMD) remained constant in women randomised to 6 years of intravenous BiP, it decreased slightly in those randomised to placebo after 3 years (between treatment difference 1.04%; $p = 0.0009$) with similar effects at other sites. Biochemical markers tended to rise in those allocated to placebo but remained below pre-treatment levels, and new morphometric vertebral fractures increased about twofold after zoledronate was stopped at 3 years as compared with women maintained 6 years on therapy (OR 0.51 for 6 versus 3 years; $p = 0.035$). However, no rise in risk of non-vertebral fractures was observed among those who went on placebo after 3 years compared with those who continued therapy for 6 years, although firm conclusions cannot be drawn due to limited power in this sample. A randomised second extension

provided data regarding 9 years versus 6 years of treatment [17]. From year 6 to 9, the mean change in total hip BMD was − 1.31% versus − 0.54% in those randomised to placebo after 6 years of treatment compared with those who continued to receive infusions (difference, 0.78%; 95% confidence interval [CI], − 0.37%, 1.93%; $p = 0.183$). Bone turnover markers showed small, non-significant increases in those who discontinued after 6 years compared with those who continued for 9 years. The number of fractures was low and did not significantly differ by treatment. There was a small increase in cardiac arrhythmias (combined serious and non-serious) in the continued treatment group but no significant imbalance in other safety parameters. The results suggest almost all patients who have received six annual zoledronate infusions can stop medication for up to 3 years without apparent adverse consequences.

The implications of discontinuing alendronate treatment were considered in the FLEX study [38, 39]. This study randomised postmenopausal women aged 61 to 86 years previously treated with 4 to 5 years of alendronate therapy to 5 more years of alendronate or placebo. Among the women who had prior alendronate therapy in FIT, further therapy with alendronate (5 and 10 mg groups combined) for 3 years compared with placebo-maintained BMD at the hip (2.0% difference; 95% CI, 1.6–2.5%) further increased BMD at the spine (2.5% difference; 95% CI, 1.9–3.1%). When comparing fracture-risk outcomes after 5 years, clinically recognised vertebral fractures were significantly more common among those discontinuing alendronate, but the cumulative risk for non-vertebral fractures and morphometric vertebral fractures was similar [39]. Given, however, that alendronate did not decrease the risk of non-vertebral fracture in the overall study population (but only those with low BMD at baseline), it is not surprising that stopping treatment had no effect on the fracture outcome. Eastell et al. undertook an analysis of women who had participated in the VERT-MN study and who had received either 2 or 7 years of risedronate [25]. They report that 1 year of risedronate discontinuation resulted in increases of NTX/Cr levels towards baseline and decreases in femoral trochanter and total hip BMD. No fracture data were reported. In other work considering change in bone turnover markers on discontinuing bisphosphonate study, persistent reduction in bone turnover 2 years after stopping alendronate, risedronate and ibandronate was demonstrated [51].

Denosumab has been shown to be effective in improving BMD and reducing fracture among women who received up to 10 years of treatment [26, 35, 47]; in the long-term treatment group, BMD increased from FREEDOM baseline by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck and 2.7% at the one-third radius. The yearly incidence of new vertebral fractures (ranging from 0.90 to 1.86%) and non-vertebral fractures (ranging from 0.84 to 2.55%) remained low during the extension, similar to rates

observed in the denosumab group during the first 3 years of the FREEDOM study, and lower than rates projected for a virtual long-term placebo cohort [46]. However, several studies have suggested that denosumab withdrawal is associated with adverse outcomes, including accelerated bone loss and vertebral fractures [40–46]. In a first analysis of 797 subjects withdrawing from the study drug (placebo or denosumab) during the original FREEDOM study, 42% versus 28% of placebo- and denosumab-treated subjects, respectively, initiated another therapy (mostly bisphosphonates). Following discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab), resulting in a fracture rate per 100 subject-years of 13.5 for placebo and 9.7 for denosumab (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.49–1.38), and for vertebral fractures of 9.3 and 5.6 for off placebo and off denosumab, respectively, adjusted for age and total hip BMD T-score at baseline [22]. However, a more recent analysis of subjects stopping denosumab during FREEDOM and its extension indicates an increased risk of new or worsening vertebral fractures, though fracture risk never exceeded that in the placebo group (see below).

Risk factors for fractures upon treatment discontinuation

A number of studies have considered whether certain risk factors are associated with increased risk of fracture after discontinuation of treatment. Cosman and colleagues considered this issue with zoledronate treatment [23] and reported that after 3 years of treatment, those women who might benefit from continued treatment with regard to lower subsequent fracture risk were those who had a total hip T-score below − 2.5 or an incident fracture during the first 3 years of treatment. Other investigators have considered the factors associated with outcome after stopping alendronate treatment. For example, Schwartz and colleagues considered which groups of women might benefit from continued alendronate therapy and reported that continuing alendronate for 10 years instead of stopping after 5 years reduces non-vertebral fracture risk in women without prevalent vertebral fracture whose femoral neck T-scores, achieved after 5 years of alendronate therapy, are − 2.5 or less [48]. Conversely, in another analysis of the FLEX data, Bauer and colleagues [49] reported a clinical fracture incidence near 30% in the 5 years of receiving placebo after receiving 5 years of alendronate among subjects with hip T-scores below − 2.5, whereas this risk was lower than 10% in those with T-scores at − 1.5 or better. McNabb et al. used the FLEX data to model likely outcomes on alendronate discontinuation [30]. They reported that using their tool in women with a total hip T-score greater than − 1.9 at the time of alendronate discontinuation would have less than a 20% probability of BMD dropping to below − 2.5 over 5 years of

follow-up. However, in a separate analysis [31], the same group used the same data and reported that 5-year bone losses of > 5% were experienced by 29% subjects at the total hip, 11% at the femoral neck and 1.3% at the lumbar spine. Whilst several risk factors such as age and BMI were associated with greater bone loss, no models based on these risk factors predicted bone loss rates, reinforcing the need for caution and monitoring when considering drug intermission. In another analysis of the FLEX data, Bauer and colleagues [49] reported that whilst 1-year changes in hip DXA, NTX and BAP were not related to subsequent fracture risk, older age and lower hip T-score at the time of discontinuation were significantly related to increased fracture risk (lowest tertile of baseline femoral neck DXA versus other 2 tertiles relative hazard ratio, 2.17 [95% CI, 1.38–3.41]; total hip DXA relative hazard ratio, 1.87 [95% CI, 1.20–2.92]). Hence, it appears that the main predictors of fracture on treatment discontinuation are BMD and prior fracture, i.e. similar to determinants of fracture prediction in treatment-naïve patients.

In the FREEDOM extension trial, the risk of multiple vertebral fractures upon discontinuation after 3 years of denosumab was more than threefold higher among those with a prevalent vertebral fracture (incidence 5.9%, compared with 4.1% off placebo in this high-risk group). The risk also increased with the duration off therapy, the gain in hip BMD on therapy and the loss of hip BMD off therapy [50], possibly reflecting association between fracture risk and BMD. The overriding conclusion is that these studies have not identified risk factors for fracture after stopping treatment other than those that provide an indication for treatment (e.g. prior fracture and low BMD).

Observational studies

A recent observational study [52] that utilised 4 Kaiser Permanente integrated health system regions and included 39,502 women aged ≥ 45 years with ≥ 3 years exposure to BP compared women on a drug holiday to those with persistent BiP use. Compared to the persistent-user group, there was a slight reduction in overall osteoporosis-related fracture risk (HR, 0.92; 95% CI, 0.84–0.99) and no difference in hip fracture risk (HR, 0.95; 95% CI, 0.83–1.10) for the BP holiday group. A slight reduction in risk of vertebral fracture was also observed (HR, 0.83; 95% CI, 0.74–0.95). Furthermore, compared to the persistent-user group, the BiP holiday group was at decreased risk for osteoporosis-related fractures (HR, 0.71; 95% CI, 0.65–0.79), vertebral fractures (HR, 0.68; 95% CI, 0.59–0.78) and hip fractures (HR, 0.59; 95% CI, 0.50–0.70). This seemingly unexpected result may reflect a decision by clinicians and their patients to continue therapy in those at higher risk of fracture. By contrast, an analysis of Medicare data covering 160,369 women who had been established on BP for 3 years with high refill compliance reached a different conclusion. Overall, during a median follow-up of 2.7 years, those whose treatment was interrupted—suggesting implementation of a drug holiday—exhibited a significantly increased risk of hip fractures (adjusted HR of 1.22; 95% CI, 1.11–1.34). The risk gradually increased with longer drug holidays and was 1.8-fold increased after a drug holiday of 4 years, compared with continued use [53].

Some observational studies also inform about additional risk factors for fractures upon treatment discontinuation. For example, Strom and colleagues reported that, using the Swedish Prescribed Drug Register, time on BiP treatment was inversely associated with the incidence of hospitalised fractures during post-treatment follow-up [54]. In their study, adjusted regression results showed that patients persisting with therapy for > 12 months had 60% lower fracture risk the first 6 months after treatment discontinuation (RR 0.40, $p = 0.001$) compared with patients who had discontinued treatment within the first year. Of note, patient characteristics, including prevalent fractures and co-morbidities, and post-treatment mortality were comparable across persistence durations, with no evidence of a healthy adherer effect. In another analysis by Xu et al., of 208 patients, significant predictors of BMD decline during the BiP holiday including lower body mass index at the start of the holiday and change in body weight during the holiday [55]. BMD decline was more pronounced in former risedronate compared with former alendronate users. BMD trends were similar in patients who sustained a fracture during the holiday versus those who did not sustain [56, 57].

Risks observed in long-term exposure to anti-resorptives: atypical femoral fracture

The relationship between adverse events and treatment continuation and cessation has been considered in trials and other study designs. In HORIZON, significantly more women receiving 6 years of zoledronate treatment had transient rises in creatinine than those receiving 3 years of treatment [16] (0.65% vs. 2.94%); there were non-significant differences in rates of AF and stroke in the two groups, but hypertension rates were lower in women receiving extended therapy. Adverse event profiles were not different between women who continued or discontinued risedronate [25], whilst histomorphometric studies of alendronate suggest that prolonged reduction in bone turnover is unlikely to be associated with adverse effects on bone material properties [27]. Black and colleagues performed secondary analyses using the results of three large, randomised BiP trials: the Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT) [58] (Table 2). A total of 284 records for hip or femur fractures among 14,195 women were

Table 2 Summary of risk of atypical femoral fracture in BiP users, relative to placebo from an analysis by Black et al. [58]

Study population (drug used vs. placebo)	Study	Relative hazard atypical fracture in active treated group, with 95% CI
Alendronate	FIT	1.03 (0.06–16.46)
Zoledronate	HORIZON	1.50 (0.25–9)
Alendronate	FLEX	1.33 (0.12–14.67)

reviewed and 2 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient-years. As compared with placebo, the relative hazard was 1.03 (95% confidence interval [CI], 0.06 to 16.46) for alendronate use in the FIT trial, 1.50 (95% CI, 0.25 to 9.00) for zoledronic acid use in the HORIZON-PFT trial and 1.33 (95% CI, 0.12 to 14.67) for continued alendronate use in the FLEX trial. Hence, in this analysis, the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare, even among women who had been treated with BiPs for as long as 10 years, but the study was underpowered for definitive conclusions. However, it is important to note that without reviewing radiographs, it may be hard to definitely classify a femoral fracture as typical or atypical.

Schilcher and colleagues reviewed radiographs of Swedish women who sustained a hip fracture in 2008, identifying 59 atypical femoral fractures [59]. Data on medications and coexisting conditions were obtained from national registries. The relative and absolute risk of atypical fractures associated with BiP use was estimated by means of a nationwide cohort analysis. The 59 case patients were also compared with 263 control patients who had ordinary subtrochanteric or shaft fractures. In this study, the age-adjusted relative risk of atypical fracture was 47.3 (95% confidence interval [CI], 25.6 to 87.3) in the cohort analysis. The increase in absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7). A total of 78% of the case patients and 10% of the controls had received BiPs, corresponding to a multivariable-adjusted odds ratio of 33.3 (95% CI, 14.3 to 77.8). The duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6). Importantly after drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38). In a follow-up paper of 172 patients with atypical femoral fractures, the age-adjusted relative risk (RR) of atypical fracture associated with BiP use was 55 (95% CI, 39–79) in women and 54 (95% CI, 15–192) in men [60]. In BiP users, women had a threefold higher risk than men (RR = 3.1; 95% CI, 1.1–8.4). Alendronate users had higher risk than risedronate users (RR = 1.9; 95% CI, 1.1–3.3). The RR after 4 years or more of use reached 126 (95% CI, 55–288), with a corresponding absolute risk of 11 (95% CI, 7–14) fractures per

10,000 person-years of use. The risk decreased by 70% per year since last use. These data are complementary to previously reported figures that suggest the incidence of atypical femoral fracture appears related to the duration of exposure. This observation receives some support from preliminary reports from the Southern California Osteoporosis Cohort Study (SOCS) where the risk of radiology adjudicated AFFs declined by 44% in the first year after discontinuation compared to women who continued to use BiPs (HR, 0.56; 95% CI, 0.38–0.82). After 4 years or more, the AFF risk was found to be reduced by 78% (HR, 0.22; 95% CI, 0.08–0.59) compared to current users. The rate of AFFs among current users was reported as 4.6 per 10,000 patient-years [61].

Dell using radiographic review of claims data found a rate of AFF of 2/100,000 after 2 years of exposure and 78/100,000 after 8 years of exposure [62]. Finally a recent systematic review [63] included 23 studies on atypical femoral fractures: 14 on epidemiology and 11 on treatment outcomes (two articles reported on both aspects). The review showed that the incidence of atypical femoral fractures is low (3.0–9.8 per 100,000 person-years) but relative risk increased with longer duration of BiP use, especially after more than 3 years; it also suggested that female sex and Asian ethnicity may be risk factors for the condition, in addition to reporting postoperative outcomes (often poor). The high mortality following these fractures has also been reported [64].

What about osteonecrosis of the jaw with long-term bisphosphonates?

Osteonecrosis of the jaw (ONJ) is a very rare clinical event that was first reported in connection with bisphosphonate use in 2003 [65]. The incidence of ONJ is rare and increases with exposure; an inflexion point of 4 years has been suggested [65]. The AAOMS using data from Lo [66] estimated 210/100,000 patient-years. The American Society for Bone and Mineral Research (ASBMR) estimated ONJ incidence as between 1 in 10,000–100,000 patient-treatment years [67]. Most of the reported cases have been in association with the use of zoledronate or pamidronate used intravenously to control metastatic bone disease [65–69]. The risk of ONJ in association with the use of oral BiPs is very much less and was reviewed by Masoodi in 2009, who concluded that the use of oral BiPs did not increase the risk of ONJ in osteoporosis patients [70]. Furthermore, no cases of ONJ were reported in over 3000 patients participating in clinical studies of effectiveness of alendronate and zoledronate [39, 69]. More recent studies have suggested that pre-existing dental disease and prior dental extraction are the strongest risk factors [71, 72]. Danish national health data also suggest a low incidence rate of surgically treated ONJ of 2.5 (95% CI, 2.1 to 3.1) per 10,000 patient-years for users of oral BiPs, albeit a higher risk in users with 5 years of exposure or more. The risk was higher in

patient with rheumatoid disorders or diabetes [73]. Denosumab therapy has also been associated with ONJ. The incidence of adverse and serious adverse events did not increase over time in the denosumab extension study; through extension year 5, eight events of osteonecrosis of the jaw and two events of atypical femoral fracture were confirmed [35]. Very recently, 10-year data have been published for denosumab therapy [47]. Serious adverse event rates were generally stable over time, varying between 11.5 and 14.4 per 100 participant-years, against a backdrop of 10.9 to 11.7 per 100 participant-years in placebo. One atypical femoral fracture occurred in each group during the extension. Seven cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the crossover group.

Discussion

This review served to consider the amount and quality of information relating to effects of discontinuing or continuing BiPs or denosumab therapy in osteoporotic women. In recent publications, the effect of discontinuation of denosumab on BMD and vertebral fractures has been highlighted [40–46], and it is now recognised that in some patients, this is associated with multiple vertebral fractures, although identification of those at risk is problematic (other than previous fracture). In general, the risks associated with interrupting osteoporosis therapy, including with BiPs, are poorly appreciated, particularly because a large proportion of treated subjects may remain at high fracture risk even after 5 years of therapy, and there is a need to highlight this among patients and primary care physicians. Interrupting treatment may be justified, in the case of BiPs, given certain treatment goals have been met, but the decision should always be taken in consultation with the patient, after considering the full spectrum of clinical risk factors which determines the risk of recurring fragility fractures [11].

These observations have led to a number of position papers and guidelines [9–12, 14], which generally reinforce the importance of continuing therapy among women who remain at high risk of fracture, as intermission of therapy, even those with residual effects on bone turnover after intermission, such as BiPs, will be followed by an increase in fracture incidence in those subjects. Despite these recommendations, more than one in every two patients stop therapy after 2 years and most physicians would stop therapy regardless of risk evaluation after 3 to 5 years. When considering long-term therapy though, one has to balance benefits and risks. With the exception of denosumab, the number of patients in RCTs carried through to 10 years or longer is very small. A particular concern of patients and physicians alike is the apparent association of osteoporosis treatment with atypical femoral fractures and ONJ. However, this risk remains less than 1 in 1000 subjects treated even for 10 years according to most long-term extensions of RCTs and observational studies. Although the long-term benefits remain difficult to exactly evaluate in the absence of large placebo-controlled extension studies, assuming a long-term reduction of fracture risk in the order of 30% with anti-resorptive therapy, as suggested by the available evidence, particularly among high-risk subjects, would result in a benefit:risk ratio (fractures prevented:adverse skeletal event) of at least 100:1. Observational data suggest that patients treated with oral bisphosphonates in excess of 10 dose years maintain a low incidence of both hip fractures and fractures of the subtrochanteric femur and femoral shaft [74].

Whilst many observational studies were reviewed as part of this exercise, in general, they were unable to add significantly to the evidence base, as they lead to variable, and sometimes contradicting observations regarding fracture risk after treatment with bisphosphonates are discontinued. Some of these studies considered factors associated with BiP treatment failure; these included smoking, baseline alkaline phosphatase, spinal deformity and baseline lumbar spine BMD [75]. Of note, observational data are always vulnerable to confounding by indication; women who chose to remain on treatment, and who are encouraged by physicians to do so, differ in many ways related to fracture risk to those who do not, and it is difficult to disentangle competing risks. Based on the most recent studies from the USA [53], which are observational and which have not yet been published in peer-reviewed form, a drug holiday for 1 year in 10,000 women should avoid two AFFs but would be associated with 25 additional hip fractures due to the much higher rate of hip fractures over AFFs. As discussed above, this would also come accompanied by additional non-hip major osteoporotic fractures. Hence, this supports the concept that a drug holiday, even with BiPs, should be considered only in patients at low risk of fracture.

In conclusion, the available evidence from prospective and retrospective analyses indicates that treatment cessation is often associated with an increase in fracture risk. From the randomised trial data available, it appears that the strongest predictors of outcome after interrupting therapy are age and BMD at discontinuation. Women whose hip T-score is below − 2.5 or even in the osteopenic range after 3 years have prevalent fragility fractures, are older, were poorly compliant with therapy, are at highest risk for new fractures and should therefore receive continued therapy for osteoporosis. The difference in pharmacokinetics between the BiPs and denosumab in a very important distinction that must be clearly communicated to primary care physicians and patients commenced on this therapy. An important limitation of this review is the lack of clinical trial data from which we can infer best practice; further studies to inform algorithm development are now warranted, particularly in subgroups where available data are very limited, such as male osteoporosis, steroid-induced osteoporosis and populations of different ethnicities.

Compliance with ethical standards

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