Review

Safety issues with bisphosphonate therapy for osteoporosis

Ernest Suresh1, Michael Pazianas2 and Bo Abrahamsen3,4

Abstract

Randomized controlled trials have demonstrated the efficacy of bisphosphonates (BP) in improving BMD and reducing fracture risk. Various safety issues that were not noted in clinical trials have, however, now emerged with post-marketing surveillance and increasing clinical experience. The risk of atypical femoral fracture could increase with long-term use of BP, although absolute risk is very small, particularly when balanced against benefits. A drug holiday should be considered after 5 years of treatment for patients at low risk of fracture, although there is no official recommendation regarding this to guide clinicians. Osteonecrosis of the jaw from low-dose BP used for osteoporosis is very rare, and mainly a complication with high-dose i.v. BP used in oncology. The risk of atrial fibrillation too is negligible, and a definite link cannot be established between BP and oesophageal cancer. BP should be avoided in patients with severe renal impairment and during pregnancy and lactation because of limited safety data. Further epidemiological and clinical data are required to establish safety of BP in long-term users (>5 years) and provide evidence-based management.

Key words: bisphosphonates, osteoporosis, safety, osteonecrosis of jaw, atrial fibrillation, oesophageal cancer, atypical femoral fracture, drug holiday, renal impairment, pregnancy.

Introduction

Bisphosphonates (BP) are potent inhibitors of osteoclast-mediated bone resorption. Several large, randomized controlled trials among post-menopausal women have demonstrated their efficacy in improving BMD and reducing risk of osteoporotic vertebral, non-vertebral and hip fractures [1–8]. Additionally, alendronate and risedronate have been shown to reduce vertebral fractures in patients with glucocorticoid-induced osteoporosis (although not in primary analysis of study data) [9, 10], and alendronate and zoledronate to reduce vertebral fractures in men [11, 12]. There is also evidence for improvement in morbidity and mortality and reduced overall health care costs with BP therapy [13–16]. It is therefore not surprising that BP are the most commonly prescribed drugs for patients at risk of fragility fractures, with several millions of prescriptions written every year.

At the time when the first BP, alendronate, was approved in 1995, the only notable adverse effect mentioned in the product monograph was upper gastrointestinal intolerance. Recently, however, various other safety issues have triggered widespread debate and received extensive media coverage. Pathologies such as osteonecrosis of the jaw (ONJ), atrial fibrillation, oesophageal cancer and atypical femoral fracture (AFF) have been associated with BP exposure.

This review aims to provide an evidence-based update on these safety issues and discuss current thinking on long-term use of BP and need for drug holidays. Safety issues that are relevant to specific groups of patients such as women of childbearing age and those with age-related decline in renal function are also discussed.

Sources and selection criteria

We searched PubMed up to January 2013 for relevant articles using the search terms osteoporosis and bisphosphonates. Emphasis was placed on peer reviewed original papers, meta-analyses and systematic reviews.
We also reviewed guidelines from professional societies. Citations of these papers were used to get additional references. All relevant keyword variations were used to acquire specific information on safety issues with BP. We only considered articles published in English.

Safety issues that triggered widespread debate

ONJ: should patients receiving BP for osteoporosis be concerned?

ONJ, first reported among BP-exposed patients in 2003 [17–19], is a painful and destructive complication that leads to significant morbidity. The three elements that define BP-related ONJ include (i) presence of exposed and necrotic bone in the maxillofacial region that does not heal within 8 weeks, (ii) any past exposure to BP and (iii) negative history for prior radiation therapy to the craniofacial region [20]. Pathogenesis remains elusive. Low bone turnover and infection have been implicated, and a prominent role for macrophages has been suggested [21]. Reduced angiogenesis has been proposed as a contributor as well [22]. ONJ has also been reported in BP-naïve individuals [23], with other antiresorptives such as denosumab (mainly in the context of higher doses used for cancer) [24], and in patients treated with anti-angiogenic drugs such as bevacizumab [25] and sunitinib [26].

Risk of developing ONJ is proportional to the duration of therapy and cumulative dose, and also influenced by the route of administration and potency of the BP in question [17–20, 27–31]. Thus, more than 95% of cases reported in the literature have occurred in patients with metastatic bone disease receiving long-term, high-dose, i.v. BP, in whom the estimated incidence is 1–12% at 36 months of exposure (the oncology dose is about 10–12 times the dose used for osteoporosis) [20, 31]. Other risk factors include invasive dental procedures, pre-existing dental disease, poorly fitting dental appliances, use of tobacco or alcohol and concomitant therapy with corticosteroids or chemotherapeutic drugs [20].

ONJ in patients receiving low-dose BP for osteoporosis is very rare, with estimated incidence rate of less than 1:100,000 patient-years [20]. Importantly, not a single case of ONJ was reported in clinical trials of osteoporosis that included more than 60,000 patient-years of exposure to nitrogen-containing BP [32]. Likewise, blinded adjudication of HORIZON-pivotal fracture trial that randomized 7765 postmenopausal patients with osteoporosis to receive either zolendronate or placebo only identified two patients with ONJ, one in each arm [6]. Systematic reviews of controlled trials too have found insufficient evidence to confirm a causal link between low-dose BP used for osteoporosis and ONJ [33, 34].

The task force of American Society of Bone Mineral and Research (ASBMR) and American Dental Association (ADA) have provided recommendations for diagnosis, prevention and management of ONJ [20, 35]. Key recommendations (relevant to physicians managing osteoporosis) include the following:

(i) It is not necessary for patients to undergo dental evaluation or complete any dental treatments prior to initiation of BP therapy for osteoporosis (this has however been recommended as a precautionary measure for oncology patients, despite lack of evidence in support of this strategy).

(ii) All patients should see a dentist on a regular basis, maintain good oral hygiene and seek dental advice if they experience symptoms of ONJ such as pain or swelling in the mouth, soft tissue ulceration, paraesthesia or loosening of teeth.

(iii) Should the need to perform an invasive dental procedure arise after therapy is initiated, there is no evidence that discontinuation of BP will improve dental outcome.

Discontinuation of BP treatment once ONJ is diagnosed has been a matter of debate [21]. However, if systemic conditions permit, modification or cessation of oral BP therapy should be done in consultation with the treating physician and patient [36]. Some [37], but not all [38], reports have described healing of ONJ with teriparatide, possibly mediated through its effects on stimulating bone remodelling and removing damaged bone.

BP and atrial fibrillation: is there any link?

A possible link between BP and atrial fibrillation (AF) was first reported by HORIZON-pivotal fracture trial that was published in 2007 [6]. Serious AF (defined as life threatening or resulting in hospitalization or disability), unexpectedly occurred more often among those randomized to zolendronate than among those randomized to placebo (1.3% vs 0.5%, $P < 0.001$). However, there was no difference in overall number of AF events between the two groups. Hypocalcaemia was proposed as a possible mechanism, but seemed unlikely because administration of zolendronate had little or no effect on serum calcium. Because most AF events occurred more than 30 days after infusion, it was postulated that BP-induced release of pro-inflammatory cytokines may cause atrial remodelling, fibrosis and subsequent development of AF [39], but this theory has not been proved either. Why BP should only increase risk of serious AF rather than AF per se was also not clear.

Subsequent post hoc analysis of Fracture Intervention Trial (FIT) found non-significant trend towards increased risk of serious AF (not total number of AF events) among patients randomized to alendronate compared with those randomized to placebo [1.5% vs 1%, relative risk (RR) 1.51, 95% CI 0.97–2.40] [40], while that of HORIZON-recurrent fracture trial (zolendronate) [41] and VERT (Vertebral Fracture with Risedronate Therapy) [42] found no difference in the rate of AF between patients randomized to BP and placebo.

Population studies also yielded conflicting results. One American case–control study reported that ever use of alendronate (compared with never use) was associated
with increased risk of serious AF [43], while a similar but larger study from Denmark did not find any evidence for increased risk of AF with etidronate or alendronate [44]. Other large population studies, using databases from USA, UK and Denmark, were also unable to find an association [45–48]. Of these, two studies reported an increased risk of AF with shorter duration of exposure to BP, but this was not seen with persistent use [46, 48]. One meta-analysis of seven non-experimental studies concluded that BP exposure was not associated with increased risk of AF [49], but other meta-analyses that also included controlled trials showed discordant results, ranging from no increased risk of AF [50] to non-significant trend towards increased risk of AF [51] or an increased risk of only serious AF [52, 53].

These conflicting results were possibly due to confounding factors because osteoporosis mainly affects those who are at increased risk of cardiovascular events, such as postmenopausal women and the elderly [53]. One large national cohort study indeed suggested that BP are targeted preferentially to patients who are already at increased risk of developing AF, and that BP may not increase this risk further [48]. There are also common risk factors for osteoporosis and AF, such as old age, hyperthyroidism, smoking and alcohol [55]. Interestingly, one population study that used a self-controlled case series method (to control for confounding factors) reported that long-term risk of AF was not increased with alendronate or risedronate [46]. In this design, only cases (patients who were exposed to BP and with diagnosis of AF) were studied, with no control group. The observation time of each case was divided into risk period (period during or after exposure to BP) and control period (period before exposure to BP), and incidence of AF in risk period relative to incidence in control period was calculated. Because this was intra-person comparison, confounding due to variation between individuals in risk factors for AF was removed.

Thus, available evidence does not support the need to avoid BP in patients who are at increased risk of developing AF. Concerned patients can be reassured that absolute risk of AF is negligible, and that benefits of fracture reduction with BP far outweigh the risk of AF [56].

Oesophageal cancer: do BP increase risk?

The association between oral nitrogen-containing BP and oesophagitis had long been known, but concerns about possible link with oesophageal cancer were first raised in 2009 [57]. The author referred to previous histological studies that had demonstrated crystalline material similar to ground alendronate tablets in patients with erosive oesophagitis and persistent mucosal abnormalities, suggesting a potential for carcinogenic effects [58, 59]. The usefulness of these data were limited, however, because the mean lag time between exposure to drug and diagnosis of oesophageal cancer in these patients was only 1.3–2.1 years, which was not consistent with the natural history for development of oesophageal cancer [60]. Also, patients receiving BP were more likely to undergo endoscopy for complaints of indigestion, and hence, cancer was more likely to be detected (4.1% of alendronate users vs 1.7% of non-users underwent endoscopy in one national cohort study, $P = 0.001$) [61].

Several large observational studies have since been conducted, but results have been controversial. One case-control study that used data from the United Kingdom General Practice Research Database (UKGPRD) concluded that the risk of oesophageal cancer was increased with oral BP (RR 2.24, 95% CI 1.47–3.43 for BP exposure $\geq 3$ years), but there was no association with gastric or colorectal cancers [62]. One cohort study too reported an excess risk of oesophageal cancer, but the association was not felt to be causal, as there was no dose response (risk was higher with lower dose of BP than with higher dose) or time relationship (risk at $\leq 2$ years was higher than risk at $> 5$ years) [63].

In contrast, none of the other studies found any association between BP and oesophageal cancer [61, 64–69]. Interestingly, one cohort study that used data from the same UKGPRD did not find an association with either oesophageal (RR 1.01, 95% CI 0.48, 2.12 for BP exposure $\geq 3$ years) or gastric cancers [64]. Another register-based observational study showed reduced risk for oesophageal, but not gastric, cancer [68]. One recent series of nested case-control studies using two large primary care databases in the UK also found no association between BP and oesophageal cancer, but increased risk of gastric cancer was noted with short-term use of alendronate [69]. One meta-analysis of seven epidemiological studies too concluded that there was no evidence for increased risk of oesophageal cancer with BP, with pooled RR of 1.23 (95% CI 0.79, 1.92) for cohort studies and pooled RR of 1.24 (95% CI 0.98, 1.57) for case-control studies [70]. These discrepant results could probably be explained on the basis of differences in the types of patients who were studied (those who were exposed to BP vs those who had already developed oesophageal cancer) and the length of follow-up (mean of 4.5 years vs 7.6 years) [71]. Also, inaccurate coding could be a problem with register-based studies (gastric cancer being coded as oesophageal cancer or vice versa). Thus, the ratio of oesophageal to gastric cancers could be altered, even if the combined incidence rate were unchanged.

Summing up, a definite link between the use of oral BP and oesophageal cancer cannot be established with certainty at present because of inconsistency in available data. It would be prudent, however, to avoid oral BP in patients with delayed oesophageal emptying and balance the benefits and potential risks of BP therapy on an individual basis in patients with known pre-malignant conditions such as Barrett’s oesophagus (parenteral treatments would be preferable in such patients).

BP and AFF: what have we learnt so far?

AFFs (see Fig. 1 for a radiographic example), first reported in 2005 [72], are characterized by the features
listed in Table 1. Pathogenesis could be related to long-term suppression of bone turnover. In health, bone remodelling helps to remove microcracks and microdamage, but because of inhibition of osteoclasts by BP, repair of microcracks and microdamage may be impaired, and accumulation of microcracks may eventually lead to atypical fractures. Animal studies have shown that microcracks are more likely to develop in BP-treated bone [73], but there is no direct evidence linking (i) BP to microcrack formation or (ii) microcrack formation to atypical fractures. Furthermore, they also occur in BP-naive individuals [74]. Hence, a causal relationship is yet to be proved.

Because of the rarity of this condition, current evidence linking BP with AFF only comes from observational studies and case series [76–83]. Some key studies that showed a positive association are summarized in Table 2. Based on the results of these studies, one could conclude that there appears to be an increased risk of AFF with longer duration of BP therapy. Absolute risk, however, seems very small, particularly when balanced against the reduction in risk of typical fractures.

By contrast, secondary analysis of data from FIT, FLEX and HORIZON that included more than 51,000 patient-years of follow-up for up to 10 years revealed that occurrence of AFF was similar among placebo- and BP-treated women, with estimated incidence of AFF with BP of 2.3 per 10,000 patient-years [84]. However, (i) very few women received more than 5 years of BP treatment, (ii) only radiographic reports were reviewed and (iii) the study was underpowered to draw definite conclusions. One retrospective study reported that rate of AFF meeting ASBMR major criteria was not increased in BP-treated patients, with relative risk of only two [85]. This study was criticized because many fractures in both groups were incorrectly classified as atypical, resulting in attenuation of relative risk [86]. Other studies that could not find an association [87–89] were published before the working definition for AFF was introduced, compared one class of anti-resorptives with another, could not exclude the possibility that risk might increase with long-term use of BP or could not differentiate typical from atypical fractures because of lack of access to radiographs.

From a practical perspective, clinicians should be aware of the patient on BP who complains of persistent thigh pain or has evidence of stress fracture in the femur. If evidence of stress fracture is found in one femur, the contralateral side should be imaged because of the high frequency of bilateral involvement [90].

Table 1 Major and minor features of AFF proposed by ASBMR

<table>
<thead>
<tr>
<th>Major features</th>
<th>Additional minor features that may be present</th>
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<tr>
<td>Subtrochanteric location (below the lesser trochanter), or anywhere along the diaphysis (above the distal metaphysis)</td>
<td>Prodomal dull or aching hip, thigh or groin pain, with history often dating back several months</td>
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<td>because these are the sites that are subject to maximal tensile loading (unlike typical hip fractures that occur at intertrochanteric level or neck of femur).</td>
<td>Bilateral fractures</td>
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<tr>
<td>Minimal or no preceding trauma</td>
<td>Presence of co-morbid conditions such as RA, diabetes mellitus, vitamin D deficiency, and concomitant therapy with corticosteroids, proton pump inhibitors or other anti-resorptive agents</td>
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<tr>
<td>Transverse or slightly oblique (&lt;30°) fracture line</td>
<td>Discrete cortical thickening on the lateral side of the femur (periosteal reaction as in stress fractures) may be present</td>
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<td>Non-comminuted</td>
<td>Delayed healing of fracture, sometimes taking several years.</td>
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<td>Complete fracture (extending through both cortices) with medial spike, or incomplete (involving only lateral cortex).</td>
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*The Task force of ASBMR has been reconvened and a revised definition is expected shortly. All major features should be present to satisfy case definition for atypical fracture. Adapted from J Bone Miner Res 2010;25:2267–94 with permission of the American Society for Bone and Mineral Research.
So, should all patients on long-term BP be offered a drug holiday? Drug holiday (temporary discontinuation of BP after a certain duration) has been proposed because of concerns about occurrence of AFF with long-term continuous suppression of bone turnover, and also because anti-fracture efficacy may persist for an unknown length of time following discontinuation of BP. The idea is to maintain the benefits while reducing risk.

Three long-term, prospective extension trials (Table 3) [91–93] have addressed this, but it should be noted that change in hip BMD was used as the primary outcome measure in these studies, and that none of them was powered to demonstrate a difference in fracture risk [94]. Analysis of results of these studies indicates that

(i) Hip and spine BMD decline following discontinuation of BP, but still remain above pre-treatment levels from 10 years earlier.

(ii) There is no difference in the rates of non-vertebral fractures between those continuing alendronate for 10 years and those discontinuing after 5 years.

(iii) In patients who continue BP, there is a reduced risk of vertebral fractures (clinically recognized fractures in FLEX and morphometric fractures in HORIZON-PFT).

(iv) Other studies have shown that hip fracture risk too might be increased following discontinuation of BP (in non-compliant patients) [95, 96].

(v) Following discontinuation, bone loss is most rapid with risedronate (possibly because skeletal half-life of risedronate is shorter than that of other BPs). Hence, drug holiday is advisable only for patients who have been on alendronate or zoledronate (there is currently no information about fracture risk upon discontinuing ibandronate).

Can we identify beforehand those patients who might benefit from continuing BP beyond 5 years? Post hoc analysis of FLEX suggests that among patients without prevalent vertebral fractures, the risk of non-vertebral fractures is reduced only in those patients with femoral neck T-score < −2.5, and not in those with T-score > −2.0 [97].

### Table 2: Some key trials that demonstrated increased risk of AFF with BP treatment

<table>
<thead>
<tr>
<th>Study design</th>
<th>Results</th>
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<tbody>
<tr>
<td>Park-Wyllie et al. [76]</td>
<td>Population based nested case–control study&lt;br&gt;Women &gt;68 years who initiated BP between 2002 and 2008 were included.&lt;br&gt;Cases were those who were hospitalized with subtrochanteric or femoral shaft fracture.&lt;br&gt;Each case was matched with five controls with no fracture.</td>
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<tr>
<td>Schilcher et al. [77]</td>
<td>Women who sustained femoral fracture in 2008 were included (n = 12 777). Review of radiographs identified 59 patients with atypical fracture.&lt;br&gt;Data on BP use obtained from national registries.</td>
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<tr>
<td>Meier et al. [78]</td>
<td>Total of 477 patients, aged ≥ 50 years, hospitalized with subtrochanteric or femoral shaft fracture were included.</td>
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<tr>
<td>Nieves et al. [79]</td>
<td>Studied epidemiology of femoral fractures from 1996 to 2006, using National Hospital discharge survey and Medical claims database in USA</td>
</tr>
<tr>
<td>Wang and Bhattacharyya [80]</td>
<td>Studied epidemiology of hip fractures from 1996 to 2007, using Nationwide Inpatient Sample and Medical Expenditure Panel Survey in USA</td>
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</table>
Can BP be given to patients with renal impairment?

Safety issues relevant to specific groups of patients

TABLE 3 Long-term extension trials that followed up patients who discontinued BP

<table>
<thead>
<tr>
<th>Study design</th>
<th>Change in BMD</th>
<th>Difference in fracture risk</th>
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<tr>
<td>FLEX [91]</td>
<td>Compared with continuing alendronate, switching to placebo resulted in decline in BMD at hip (~2.4%) and spine (~3.7%). Mean BMD still remained above pre-treatment levels from 10 years earlier.</td>
<td>Those who continued alendronate for 10 years had fewer clinical vertebral fractures (5.3% vs 2.4%), but there was no difference in rate of morphometric (radiographic or asymptomatic) fractures. No difference in risk of non-vertebral fractures between the two groups.</td>
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<td>HORIZON-PFT extension [92]</td>
<td>Hip BMD remained constant in Z6 group, but dropped slightly in Z3P3 group (although still above pre-treatment levels).</td>
<td>Morphometric vertebral fracture rates were lower in Z6 compared with Z3P3 (3.0% vs 6.2%). There was no difference in rate of non-vertebral, clinical vertebral or hip fractures between the two groups. Incidence of morphometric fractures was 46% lower in the former risedronate group (relative risk 0.54) compared with former placebo group.</td>
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<tr>
<td>VERT extension [93]</td>
<td>Hip and spine BMD declined in both groups, but remained above pre-treatment levels in risedronate group.</td>
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Although the Food and Drug Administration (FDA) in the USA did not make any clear recommendations, an expert panel [13] has recently suggested that treatment should be continued beyond 5 years for high-risk patients (those with T score $\leq -2.5$ at hip, previous hip or spine fracture, or ongoing glucocorticoid therapy), and that a drug holiday be considered for moderate-risk patients (patients with T score of $>-2.5$ at hip, with no previous spine or hip fracture). The duration for which drug holiday should be advised is not known, simply because the length of time for which patients are protected from fracture following discontinuation of BP is not known. A drug holiday should probably be considered for 2–3 years (but terminated earlier if the patient sustains fragility fracture in the interim). One suggested approach [13], despite lack of supportive data, is to test BMD and measure bone turnover markers (BTM) about 2 years after discontinuation (decreasing BMD or increasing BTM would suggest need to reintroduce therapy). Rising BTM could be an early indicator for reintroduction of treatment and occur well before any decline in BMD.

Safety issues relevant to specific groups of patients

Can BP be given to patients with renal impairment?

Safety of BP in the presence of renal impairment is relevant because about 50% of the absorbed BP is taken up by the skeleton and the remainder excreted unchanged by kidneys. Renal impairment can, therefore, lead to significant accumulation of BP; BP are unlikely to be beneficial in patients who already have low bone turnover as a consequence of severe renal osteodystrophy with adynamic bone. It is possible that BP could aggravate the condition, which is difficult to diagnose without bone biopsy. Both renal function and BMD decline with age. One large survey among patients with osteoporosis found that 85% of women and 58% of men had creatinine clearance (CrCl) of $<60$ ml/min. The prevalence of renal impairment increased with age, and about 54% of women and 37% of men older than 80 years had severe renal impairment, with CrCl of $<35$ ml/min [98].

In clinical trials, BP have been shown to have an excellent safety profile down to CrCl of 30 ml/min, but there is lack of prospective safety data among patients with more severe degrees of renal impairment. Hence, the manufacturer’s recommendation is to prescribe BP in the usual dose for patients with CrCl $\geq 30$ ml/min, but avoid in patients with CrCl $<30$ ml/min (or $<35$ ml/min for alendronate or zoledronate).

Limited data are, nevertheless, available for safety and efficacy of BP in patients with CrCl of $<30$ ml/min because patients with renal impairment have typically been excluded from clinical trials on the basis of elevated serum creatinine rather than reduced CrCl. Because elevated creatinine is not sensitive for renal impairment, some patients with normal creatinine who were recruited to these trials had CrCl in the range for renal impairment. This formed the basis for post hoc analysis of almost 9000 patients with age-related decline in renal function from nine randomized, double-blind, placebo-controlled trials of risedronate, of which about 7% were categorized as having severe renal impairment ($\text{CrCl} \geq 15$ to $<30$ ml/min) [99]. No patient had end-stage renal failure...
Table 4 Use of BP in patients with CKD

<table>
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<th>GFR, ml/min/1.73 m²</th>
<th>Guidance for prescribing BP</th>
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<tr>
<td>45-59 (CKD stage III A) [104]</td>
<td>Dose of BP is the same as in non-renal patients, but ensure that patient is vitamin D replete.</td>
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<td>30-44 (CKD stage III B)</td>
<td>Dose of BP is the same as in non-renal patients, but one expert opinion [104] recommends checking PTH and 25(OH) vitamin D level first. If PTH is high and 25(OH) vitamin D is &lt; 30 ng/ml, then start standard vitamin D (ergocalciferol or cholecalciferol) in therapeutic dose. Accept PTH level up to 100 ng/l (normal range 10–55 ng/l). If PTH remains &gt; 100 ng/l despite trial of standard vitamin D in therapeutic dose for at least 3 months, change to calcitriol or alfalcalfodil (because it might imply problem with vitamin D activation in kidneys). If PTH remains &gt; 100 ng/l despite calcitriol or alfalcalfodil, suspect tertiary hyperparathyroidism. Refer to nephrologist. If PTH level drops to &lt; 100 ng/l following standard vitamin D, calcitriol or alfalcalfodil, then it is appropriate to commence BP.</td>
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<tr>
<td>15-29 (CKD stage IV)</td>
<td>There are no prospective safety data on use of BP. BP are especially not appropriate for CKD patients with already low bone turnover. Bone biopsy may be required in some patients. If osteoporosis is the cause of fracture (and not renal osteodystrophy), one expert opinion suggests trying risedronate in half the usual dose (2.5 mg daily or 35 mg every 2 weeks) for up to 3 years [102]. This recommendation is based on post hoc data (see text) and also the fact that 50% of the absorbed drug is excreted by kidneys.</td>
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<td>&lt;15, or patients on dialysis (CKD stage V)</td>
<td>Avoid BP. Bone biopsy may be required to distinguish from other forms of metabolic bone diseases (renal osteodystrophy) that are associated with CKD.</td>
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GFR: glomerular filtration rate.

(simply because someone with normal creatinine cannot have CrCl < 15 ml/min) [100] or intrinsic renal disease.

Results of this analysis suggested that there was no difference in overall adverse events between patients randomized to receive 5 mg/day of risedronate or placebo for up to 3 years, irrespective of renal function. Risedronate was also effective in reducing the incidence of vertebral fractures across all groups. Likewise, post hoc analysis of alendronate data from FIT showed that efficacy and frequency of adverse events were similar among patients with eGFR ≥ 45 ml/min and those with eGFR < 45 ml/min [101]. In the absence of long-term prospective data, however, no firm recommendations can be made for use of BP in patients with CrCl < 30 ml/min at this point in time (see Table 4 for expert opinion on use of lower dose of risedronate in patients with CrCl of 15–29 ml/min) [102]. There are essentially no data for use of BP in stage V chronic kidney disease (CKD) (CrCl < 15 ml/min), apart from one small randomized placebo-controlled trial of 31 haemodialysis patients [103]. Hip BMD remained stable after 6 months in patients who were treated with 40 mg/week of alendronate for 6 weeks, while there was a reduction in BMD in patients who were treated with placebo (P = 0.05). Alendronate, administered for a limited duration, thus appears to be tolerated in dialysis patients, but in the absence of data from larger studies, BP cannot be recommended for patients with end-stage renal disease, either. A bone biopsy should certainly be considered in these patients in order to differentiate from renal osteodystrophy. Table 4 provides a summary of practical guidance for use of BP in patients with CKD.

Can BP be used in women of childbearing age?

Use of BP in women of childbearing age is not likely to be common because absolute risk of fracture is very small in this age group. Accordingly, many clinicians will prefer lifestyle advice and sequential dual-energy absorptiometry (DXA) scan in pre-menopausal women who have low BMD but no low-energy fractures. The main concerns with using BP in a woman of childbearing age are [105]: (i) BP cross the placenta because of their small molecular weight; (ii) skeletal half-life of BP is very long and measured in years, and therefore, there is potential for exposure to the fetus even long after therapy is discontinued; (iii) BP are possibly teratogenic and (iv) there is a risk of hypocalcaemia (in mother as well as newborn).

Although animal studies in pregnant rats, conducted with BP doses much larger than that used in humans, have demonstrated severe retardation of bone growth, prolonged labour (possibly consequent to hypocalcaemia) and fetal underdevelopment [106, 107], there are numerous reports of successful pregnancies among women who had been exposed to BP before or during pregnancy [108-111]. Barring a small number of women who were exposed to BP during the second and third trimesters for malignant hypercalcaemia, most were exposed before conception or during the first 3 months of pregnancy.
Abortions and lower birth weight have been reported in a small number of women who received BP, but they were attributed to other medical conditions or concomitant therapy like corticosteroids. Transient hypocalcaemia in the newborn has also been reported, but this usually resolved within the first few days after birth. In one series of 10 patients who were treated with BP during pregnancy, two congenital malformations were reported, one with ventricular septal defect (clodronate) and another with kidney and cardiac malformation (alendronate) [112]. In the only reported patient who received BP during breast feeding, pamidronate was undetectable in breast milk for up to 48 h after infusion, and the baby was healthy and grew normally [113]. There are also reports of patients

<table>
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<th>Problem</th>
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<td>Gastrointestinal (GI) intolerance</td>
<td>Incidence of upper GI adverse events were similar between BP and placebo in clinical trials, but post-marketing reports have noted oesophagitis, oesophageal and gastric erosions and ulceration, and rarely, strictures, perforation and bleeding, with oral BP. Local irritation of upper GI mucosa is thought to underlie these side effects. To minimize the risk of GI side effects, all oral BP should be taken on an empty stomach with 6-8 ounces of plain water at least 30 min before the first food, beverage or medication. Patients must stay upright for at least 30 min (60 min in the case of ibandronate, because BMD gains are reduced if this fasting interval is reduced to 30 min) [116]. BP should be avoided in patients with delayed oesophageal emptying. One head-to-head trial did not note any significant difference in upper GI adverse effects between alendronate and risedronate [117]. GI side effects were noted with i.v. BP as well, in clinical trials, but were no different from placebo. Although not demonstrated in clinical trials, GI side effects have been noted to be less with weekly or monthly BP, compared with daily BP, in post-marketing reports.</td>
</tr>
<tr>
<td>Acute phase reaction (APR)</td>
<td>APR (low-grade fever, arthralgia, myalgia, bone pain and fatigue) is the most common adverse effect of i.v. BP and is mediated by TNF-α and IL-6. In one study, the frequency of APR was 42% in the zolendronate group and 12% in the placebo group [118]. APR was mild to moderate in 90% of patients, began within 24 h of infusion and lasted for a median of 3 days. This reaction was usually seen after the first infusion of BP, and became less common with subsequent infusions. Paracetamol has been shown to reduce the severity of symptoms by more than half (hence, prophylactic use is advisable with the first dose of zolendronate) [119]. APR has also been reported with weekly alendronate or risedronate, but overall frequency was low (5.6%), and the reactions were less severe [120].</td>
</tr>
<tr>
<td>Inflammatory eye reactions</td>
<td>Uveitis, conjunctivitis, episcleritis and scleritis have been reported with both oral and i.v. BP [121–123]. One register-based cohort study estimated that the risk of inflammatory eye reaction requiring topical eye steroid was no different between BP and no-BP users, and that patients with rheumatic or pulmonary disease were at increased risk [124]. Clinicians should, however, be vigilant of the patient who complains of ocular pain or visual loss, and in the absence of underlying condition that may have caused ocular inflammation, consider discontinuing BP, especially for patients who develop scleritis.</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Rapid infusion of i.v. BP has been reported to cause transient rises in creatinine and in rare cases acute renal failure due to acute tubular necrosis [125, 126]. There were no long-term effects on renal function. Hence, it would be prudent to administer zolendronate slowly over 15 min, check renal function before each dose, ensure adequate hydration and avoid concomitant use of nephrotoxic drugs. Oral BP have, thus far, not been reported to cause renal toxicity.</td>
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<tr>
<td>Hypocalcaemia</td>
<td>Although BP inhibit osteoclasts, most patients do not become hypocalcaemic because of compensatory PTH secretion, but any pre-existing hypocalcaemia or osteomalacia should be treated before commencing BP. All patients should receive adequate calcium and vitamin D intake. I.v. BP usually causes transient hypocalcaemia but has been reported to cause severe symptomatic hypocalcaemia as well [127], especially in patients with pre-existing vitamin D deficiency, hypomagnesaemia, renal impairment or post-surgical hypoparathyroidism. Hence, i.v. BP should only be administered in those who are vitamin D replete. Pronounced compensatory increase in PTH level in the first few days after i.v. infusion is common, and may occasionally surprise clinicians.</td>
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<tr>
<td>Hepatotoxicity</td>
<td>Hepatotoxicity that resolved after drug withdrawal has been reported with alendronate [128]. Zolendronate has also been reported to cause hepatotoxicity in a patient with Paget’s disease and pre-existing non-alcoholic fatty liver disease [129].</td>
</tr>
</tbody>
</table>
who breast fed after receiving BP prior to conception, but no adverse events were reported, apart from transient hypocalcaemia [114].

If BP needs to be used in women who have not completed their families, benefits and risks should be balanced on an individual basis. Interestingly, one recent study found that following cessation of treatment, alendronate could be detected in the urine for up to 19 months, whereas risedronate could not be detected after 5 months [115]. Hence, experts have suggested that if BP treatment is required in women of childbearing age, risedronate should perhaps be preferred and treatment discontinued about 6–12 months before planned conception. It is important to monitor serum calcium, both in the mother and newborn.

Miscellaneous safety issues

Some rare adverse effects and those that are definitely linked with use of BP are summarized in Table 5.

Conclusion/the way forward

Several unanswered questions remain (Table 6). Because most randomized, controlled trials (i) only lasted up to 3 years, (ii) excluded patients with co-morbidity and (iii) did not recruit sufficient numbers of patients to study rare side effects, several safety issues have come to light only with increasing clinical experience or from post-marketing surveillance. Even in the future, it may not be feasible or ethical to design placebo controlled trials to answer these questions. Some suggestions offered by the task force of the ASBMR include conduct of additional large-scale and rigorous observational studies to study the epidemiology and risk factors for development of rare adverse events like atypical fractures, oesophageal cancer or atrial fibrillation, increased surveillance, creation of specific diagnostic and procedural codes, establishment of international registries and development of animal models [75].

It should be emphasized that if risk of further fracture is considered high on the basis of previous fragility fracture, T-score < –2.5 or results of FRAX (fracture risk assessment) [130], then treatment with BP should not be withheld, especially considering the impact of these fractures on morbidity, mortality, quality of life and costs [13]. As an example, the number needed to harm (be statistically associated with one AFF) was 667 in one study, whereas numbers needed to treat (NNT) with BP for 3 years have been estimated to be 91 for hip fractures and 14–21 for vertebral fractures [131]. Even with BP treatment for 10 years, it has been estimated that age-adjusted incidence rate for AFF is only 1.1 per 1000 patient-years [132]. By contrast, the overall rate of non-vertebral fractures was 37 per 1000 patient-years [133], and that of vertebral fractures was 62.7 per 1000 patient-years [1], respectively, in the placebo arm of two separate clinical trials. Hence, patients in whom BP is indicated should be reassured that the benefits of fracture reduction with treatment far outweigh its risks.

Rheumatology key messages

- Treatment with BP should not be withheld from patients at high risk of fracture.
- Benefits of fracture reduction with BP therapy far outweigh its risks.
- Safety of BP therapy beyond 10 years has not been established.

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