REVIEW ARTICLE

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Tolerability of Different Dosing Regimens of Bisphosphonates for the Treatment of Osteoporosis and Malignant Bone Disease

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Abstract

Bisphosphonates are the primary pharmacological agents used for the management of osteoporosis and hypercalcaemia of malignant bone disease. The efficacy of these agents in these two conditions has been demonstrated in many well designed trials published over the past 2 decades. The variety of bisphosphonates currently available to us provides a wide range of tolerability and dosing profiles thus necessitating a thorough comparison of the most recent oral and intravenous bisphosphonates to differentiate the clinical context in which they should be used. Despite the fact that bisphosphonates are generally well accepted, their tolerability is dependent on complications which encompass gastrointestinal (GI) and renal toxicity. Other adverse events include osteonecrosis of the jaw, arthralgias, flu-like symptoms and uveitis. Studies have shown that various dosing regimens are able to modulate these rates of toxicity. To maximise tolerability, the direction of future therapy will likely fall into a pattern of decreasing the frequency of administration of bisphosphonates, whether it is oral or intravenous formulations, thus improving patient adherence.

To review the literature on different dosing regimens of various bisphosphonates and their associated tolerability, we searched MEDLINE for articles from 1975 to 2006. Oral bisphosphonates, in particular alendronate and risedronate, have been systematically evaluated with regards to GI toxicity. Overall tolerability with these oral formulations has found GI toxicity to be the

primary adverse event of interest. Both alendronate and risedronate have been found to have similar rates of GI toxicity when compared with placebo. Mounting evidence has developed validating the use of intravenous ibandronate and zoledronic acid for the purpose of treating hypercalcaemia secondary to malignancy. Unique to all other bisphosphonates, ibandronate also has an oral form which has a similar GI-toxicity profile to placebo. In addition, no significant differences in renal toxicity have been observed between those receiving intravenous ibandronate compared with placebo. Because of its potency and mode of administration, zoledronic acid has been widely accepted for the treatment of hypercalcaemia secondary to malignancy. However, a decrease in renal function, albeit rare, remains a significant complication of zoledronic acid; therefore, regular renal monitoring is recommended.

The effect of osteoporosis on health status in the North American population is significant. The lifetime risk of a fracture of the hip, vertebra or wrist in a Caucasian woman is approximately 40–50%.[1] Furthermore, mortality associated with hip fractures alone approaches 12–20% in the first year after fracture.[2] Currently, the first-line agents for the treatment of osteoporosis are bisphosphonates, drugs that have been shown to increase bone mineral density and decrease the risk of fracture. Malignancy-induced fractures, spinal cord compression and hypercalcaemia are prevalent secondary manifestations of solid malignancies, which are also responsive to these agents.[3] The broad application of bisphosphonates also includes ankylosing spondylitis and Paget's disease.[4-6] The high prevalence of osteoporosis and solid malignancies emphasizes the variety of applications of bisphosphonates and the importance of evaluating the limitations and strengths of each one of these medications in their respective clinical context.

Several bisphosphonates play a significant role in the management of osteoporosis and hypercalcaemia of malignancy. Oral alendronate and risedronate are bisphosphonates that are currently used in the management of osteoporosis, whereas ibandronate and zoledronic acid are administered intravenously and are more recent additions to the playing field. The effectiveness of these medications is dependent upon a number of factors, which should be integrated into the decision-making process. In the case of osteoporosis, age, disease severity reflected by bone mineral density and the presence of fractures, underlying metabolic bone disease, gastro-oesophageal reflux disease or underlying oesophageal disease in general, renal disease, lack of response to a previous bisphosphonate therapy, planned future pregnancy and previous fracture are some factors that must be considered. Tolerability and dosing regimens are also important factors to consider when treating patients. Both of these variables are features that are unique to different bisphosphonates and each play an important role in directing treatment towards a specific clinical context.[2,7-11]

Alendronate and risedronate have clearly circumscribed tolerability features whereas tolerability features of ibandronate and zoledronic acid are still being defined. Primary factors that influence tolerability include gastrointestinal (GI) and renal toxicity in the case of oral and intravenous bisphosphonates, respectively. Oral bisphosphonates can still contribute to renal toxicity but not to the extent of intravenous bisphosphonates.[7] More recently, extra-renal and extra-GI complications associated with bisphosphonates have come to light including osteonecrosis of the jaw, arthralgias, flu-like symptoms and uveitis.[12,13]

The pivotal characteristics of instituting oral therapy include frequency and dose, which are applied in principle on an inverse relationship with respect to each other. Similarly, an increase in cumulative dose per unit time is associated with a decrease in tolerability when not addressing efficacy. Tolerability has been found to be similar amongst daily and weekly dosing of alendronate while maintaining a similar cumulative weekly dose.[14] With the knowledge that patients prefer intermittent dosing com-

pared with daily dosing and given that the regimens have proven similar efficacy, intermittent dosing clearly plays a superior role in the context of patient perception of tolerability and potential adherence to therapy.[15] The necessary precautions when taking an oral bisphosphonate alter the adherence when using either a daily or intermittent dose. Patients themselves describe having a significant preference for intermittent treatment.[5]

Malignancy-induced bone disease can be treated with intravenous bisphosphonates, such as ibandronate and zoledronic acid, which have greater potency than first- or second-generation bisphosphonates. The importance of treating malignancy-induced hypercalcaemia is multifactorial since treatments may help to manage symptoms such as fatigue, nausea and coma while simultaneously alleviating bone pain.

Given that tolerability and variations in dosing regimens are key features used by physicians to determine which bisphosphonate should be used to treat a patient in various clinical circumstances and also in determining the effectiveness of bisphosphonates, a review of the relevant studies was conducted. The focus of this review is the newer more potent bisphosphonates, namely alendronate, risedronate, ibandronate and zoledronic acid.

1. Literature Search Methodology

A systematic search for relevant articles pertaining to the tolerability and dosing of bisphosphonates was carried out using MEDLINE. Key search terms in the title included 'alendronate', 'risedronate', 'ibandronate', or 'zoledronic acid' (zoledronate). In line with the focus of this review, etidronate, clodronate or pamidronate were not specifically looked at in this analysis. This was an exhaustive search that examined all articles published between 1975 and 2006 containing the name of the bisphosphonate in the title and encompassed relevant clinical trials. Supplementary search terms in the title also included tolerability, adverse events and toxicity (renal or GI in nature). The search also looked at terms relevant to dosing including oral or intravenous modalities.

2. Alendronate

Studies covering the tolerability profile of alendronate are summarised in table I.

Classically, alendronate has been evaluated in several dosing regimens of progressive intensity, thus necessitating the study of drug tolerability. One avenue of evaluating tolerability is to identify factors that have the ability to alter patient adherence. Tolerability is tightly linked with adherence in the case of alendronate. Approximately one-quarter of individuals taking alendronate on a daily basis described a decrease in their quality of life and tolerability resulting in a decrease in adherence.[5] The main reason for lack of adherence is having to wait 30 minutes before eating.[5] It is for this reason that alendronate adherence is significantly higher in the weekly alendronate group (51.7%) than in the daily alendronate group (37.7%).[27] Although it is possible that adherence may improve in light of the fact the medication is only taken once a week with the necessary precautions, once weekly dosing may also be negatively affected by memory lapses compared with a daily intake of the medication. However, this hypothesis has not been validated in the context of alendronate.

Decreased adherence evident with once-daily dosing is also a result of GI adverse effects, the other most common concern relevant to alendronate.[5] Although, increasing daily dose of alendronate or increasing the frequency of dosing may lead to increases in the incidence of GI adverse effects, there does not appear to be a difference in the incidence of serious adverse events of GI origin.[14,15] Conflicting results with regard to GI tolerability have been reported. When compared with placebo, GI adverse effects were noted, however, they were not severe enough to result in a significant difference in discontinuations compared with placebo.[10,19] Bone et al.[14] and Sambrook et al.[24] describe differences in the rates of GI events related to different dosing regimens while Simon et al.[15] and Schnitzer et al.[25] showed that daily, bi-weekly and weekly dosing (with the same weekly cumulative dose) had similar adverse effect profiles.

A number of studies have been conducted to investigate the incidence of GI adverse effects with alendronate. Bone et al.[14] described a clear differ-

Table I. The tolerability profile of oral alendronate (ALE)

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	GI toxicity
Black et al. (1996)[16]	r, db, pc (36 months)	ALE: n = 1022; PLA: n = 1005	ALE 10mg daily	Vertebral fractures	There was no significant difference in rates of discontinuation in both groups	40% in the PLA group and 41.3% in the treatment group described GI adverse effects
Bone et al. (2004)[14]	r, db, pc, mc (3 years)	ALE variable dosing: n = 199; ALE low dose: n = 202; ALE moderate dose: n = 196; PLA: n = 197	ALE 20 mg/day for years 1–2, then 5 mg/day for year 3; ALE 5 mg/day; ALE 10 mg/day	Mean percentage in change of BMD	Skeletal safety. PLA group had 6.2% new vertebral fractures compared with 3.2% in the ALE group	The safety profiles were similar amongst all three groups. One or two women in each group withdrew because of upper GI events
Cummings et al. (1998)[17]	r, db, pc (48 months)	ALE: n = 2214; PLA: n = 2218	ALE 5 mg/day for the first 2 years followed by 10 mg/day throughout the rest of the study	BMD, fracture	Other adverse events not discussed	ALE did not increase the risk of GI adverse events
Eisman et al. (2004)[18]	r, db, pc, mc, int (12 weeks)	ALE: n = 225; PLA: n = 225	ALE 70mg weekly	Clinical and laboratory adverse events	NA	Upper GI adverse events occurred in the ALE group 9.8% and the PLA group 9.4%. Patients who discontinued due to a drug-related event: 2.7% in the ALE group; 2.2% in PLA
Ensrud et al. (2004)[19]	r, db, pc (3 years)	ALE high dose: n = 333; ALE moderate dose: n = 329; PLA: n = 437	ALE 10 mg/day; ALE 5 mg/day	BMD, safety	10.4% in the ALE 5mg and 10mg groups combined and 11.4% in PLA discontinued due to adverse experiences ($p = 0.621$). There was no difference in adverse experiences in hospital or rates of death	35.7% reported GI adverse events compared with 29.8% taking PLA. There were no significant differences between the two groups with regard to abdominal pain, acid reflux, oesophagitis, oesophageal ulcer and gastric or duodenal ulcer
Greenspan et al. (2002)[10]	r, db, pc, mc (2 years)	A total of 327 individuals who met inclusion and exclusion criteria were enrolled in this study. Patients were then randomised	ALE 10 mg/day	BMD, adverse outcomes	Reporting any clinical adverse event was the same in both groups at 93%	The presence of GI toxicity was 33% in the ALE group and 35% in the PLA group. There was no significant difference in the two groups

Continued next page

Table I. Contd

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	GI toxicity
Greenspan et al. (2003)[20]	r, db, pc, fd (3 years)	PLA: n = 93; HRT: n = 93; ALE: n = 93; HRT and ALE: n = 94	ALE 10 mg/day; HRT estrogen 0.625 mg/day	BMD	Other adverse events were evaluated and none seemed to be significant including hypertension, hospitalisations and clinical fractures	There was no significant difference in rates of oesophagitis, indigestion, heartburn or dysphagia compared with PLA. In the ALE group, rates of oesophagitis, heartburn and dysphagia were 26%, 18% and 3%, respectively. There was no significant difference from the PLA group
Kushida et al. (2004)[21]	r, db, ac, dd (3 years)	ALE: n = 90; ALF: n = 80	ALE 5 mg/day	Vertebral fracture, BMD	There was no significant difference in rates of all clinical adverse events: 22.2% in the ALE group	The incidence of GI events did not differ significantly between the two groups: ALE 14.4%
Pols et al. (1999)[22]	r, db, pc, mc (12 months)	ALE: n = 950; PLA: n = 958	ALE 10 mg/day	BMD	Overall incidence of adverse events was 67.1% in the ALE group and 69.7% in the PLA group	There was no significant difference in rates of GI events between the two groups: 21.3% ALE and 19.3% PLA
Quandt et al. (2005)[23]	r, db, pc, mc (4.5 years follow-up)	ALE: n = 1878; PLA: n = 1859	ALE 5mg for 2 years then 10mg for 3.8 years	Risk of vertebral fracture	Vertebral fractures: ALE: 16/10 000 person years; PLA: 40/10 000 person years	One weakness of this study is that it does not account for adverse events, including those of a GI nature
Sambrook et al. (2004)[24]	r, db, dd, mc, int (12 months follow-up)	ALE: n = 246; RAL: n = 241[a]	ALE 70mg once weekly; RAL 60 mg/day	BMD	Any adverse event in the ALE group 62.6%. Discontinuation due to an adverse event was 15.4%	Drug-related GI adverse event occurred in 15.4% of the ALE group. Drug-related upper GI event 9.3%
Schnitzer et al. (2000)[25]	r, db, pc (12 months)	ALE weekly: n = 519; ALE bi-weekly: n = 369; ALE daily: n = 370	ALE 70mg weekly; ALE 35mg every 3.5 days; ALE 10 mg/day	BMD, GI adverse events	There was no significant difference in rates of adverse events across different treatment groups	There was no significant difference in rates of GI adverse events across the three treatment modalities. There was a trend towards lower GI events in the once weekly dosing group

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Table I. Contd

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	GI toxicity
Simon et al. (2002)[15]	r, op, co (4 weeks followed by 1 week washout, then 4 weeks)	n = 287 randomised to treatment; n = 142 weekly to daily; n = 145 daily to weekly	ALE 70mg weekly for 4 weeks followed by washout of 1 week, then 10 mg/day for 4 weeks	Patient preference for mode of treatment: 86.4% of individuals preferred the weekly dosing compared with 9.2% who preferred the daily dosing	Clinical adverse events were reported in 30.7% with once weekly ALE and 30% with once daily ALE with no significant difference over the course of 9 weeks	Diarrhoea: 3.2%, 0.7%; nausea: 2.9%, 1.8%; heartburn: 1.8%, 1.4%; dyspepsia: 1.1%, 1.8%; epigastric discomfort: 0.7%, 1.4% for once weekly and once daily, respectively
Turbi et al. (2004)[26]	pr, op, nr, mc, ob, ac (12 months)	ALE: n = 426; RAL: n = 476	ALE 10 mg/day; RAL 60 mg/day	Compliance, discontinuation	Relative risk 1.4-fold higher for discontinuation in the ALE than the RAL group	Most common adverse events were GI disorders. 9.9% in the ALE group and 3.4% in the RAL group, p < 0.001

a ALE for the purpose of this review is being evaluated independently.

ac = active comparator; **ALF** = alfacalcidiol; **BMD** = bone mineral density; **co** = crossover; **db** = double-blind; **dd** = double-dummy; **fd** = factorial design; **GI** = gastrointestinal; **HRT** = hormone replacement therapy; **int** = international; **mc** = multicentre; **nr** = nonrandomised; **ob** = observational; **op** = open-label; **pc** = placebo-controlled; **PLA** = placebo; **pr** = prospective; **r** = randomised; **RAL** = raloxifene.

ence in the rates of GI adverse events related to different dosing regimens, whereas Simon et al.[15] did not. Ensrud et al.[19] also evaluated rates of upper GI adverse events between the lower dose (5 mg/day) and higher dose (10 mg/day). Unfortunately, analyses of a direct comparison of the number of GI adverse events that occurred in each of the two groups were not carried out but instead a combined population of 5mg and 10mg was compared with placebo. Unlike the study by Bone et al.,[14] which compared tolerability across step-up dosing of alendronate, the study by Greenspan et al.[10] compared alendronate with placebo in a way similar to Ensrud et al.[19] Neither study found a significant difference in rates of GI events or GI events requiring discontinuation between the alendronate group and placebo. The primary difference between the study of Ensrud et al.[19] and the study of Greenspan et al.[10] was the dosing regimens, the former using a combination of 5mg and 10mg daily and the latter using a daily dose of 10mg.

Schnitzer et al.[25] found that daily, bi-weekly and weekly dosing (with the same weekly cumulative dose) had similar adverse effect profiles.[25] Sambrook et al.[24] evaluated the number of GI adverse events in a study comparing alendronate and raloxifene. In relation to alendronate, the study found that adverse events did occur in a significant number of individuals resulting in an increased number of discontinuations. The observed rate of GI adverse events by Ensrud et al.[19] was 35.7%. Similar conclusions can also be drawn from another pivotal study by Turbi et al.[26] who, like Sambrook et al.,[24] described a comparison between raloxifene and alendronate. Focusing on the alendronate arm, approximately 10% of individuals receiving alendronate at 10 mg/day had a GI adverse event during a 12-month follow-up period. Such a finding lies in contrast to Sambrook et al.[24] who found a higher incidence of GI adverse events in the 70 mg/week group.

Since bisphosphonates may be used concomitantly with NSAIDs, interactions between NSAIDs and alendronate have been studied particularly because both have the ability to cause GI adverse events. Both drugs are capable of damaging the gastric mucosa. However, the two drug classes affect different regions of the gastric mucosa with

bisphosphonates being associated with oesophageal mucosal ulcerations and erosions, and NSAIDs commonly being associated with gastric ulcers.[28] Graham and Malaty[28] showed that there is synergism between alendronate with NSAIDs in causing GI adverse events, which was observed when 500 mg/day of naproxen was combined with 10 mg/day of alendronate. The study concluded by suggesting that bisphosphonates be used with caution in the context of NSAID use. Future research is needed to investigate the rate of upper GI adverse events when bisphosphonates are used in combination with celecoxib or diclofenac/misoprostol as these agents are used on a more common basis.

Based on this brief summary of studies that evaluated the tolerability of alendronate, several conclusions can be made. Alendronate has a better GI adverse effect profile and improved compliance when administered once weekly compared with daily administration. Finally, alendronate, when used in combination with NSAIDs, has a synergistic effect on rates of GI adverse events and thus this combination should be used with caution.

3. Risedronate in Contrast to Alendronate

Studies covering the tolerability profile of risedronate are summarised in table II.

Similar to alendronate, the primary precaution with regards to implementing therapy with risedronate is the consideration of GI toxicity. Hooper et al.[32] conducted a study to identify adverse events in general and GI adverse events in particular in their assessment of risedronate. With a follow-up of 24 months, the prevalence of GI adverse events was 16%, 21% and 19% in the placebo and 2.5mg and 5mg daily risedronate groups, respectively.[32] When comparing these results to alendronate as observed in the study by Greenspan et al.[10] where the prevalence of GI adverse events was approximately 30%, one might conclude that risedronate is associated with fewer adverse events. However, the studies have different structures and inclusion and exclusion criteria, making a comparison between studies difficult to interpret.

Just as Bone et al.[14] conducted a study of different doses of alendronate, Brown et al.[1] carried out a comprehensive study evaluating daily, weekly and high-dose weekly risedronate. Their results showed a similar prevalence of GI adverse events amongst all three treatment groups. Despite the fact that there was a high prevalence of NSAID and aspirin (acetylsalicylic acid) use amongst the population being evaluated, the rate of GI adverse events was similar to previous studies with a 12-month follow-up with severe or moderate events occurring only in a third of the study population. A placebo arm was most likely not used in this study, as the standard of therapy at the time would be risedronate. It should also be noted that an unforeseen adverse event observed in this study population was arthralgia.

Upper GI adverse events are consistently described as complications related to bisphosphonate use. Adami et al.[7] examined the use of risedronate in combination with NSAIDs and its association with GI adverse events. Unlike the conclusion made by Graham and Malaty[28] who suggested that caution be used when combining alendronate with an NSAID, a similar conclusion was not reached with risedronate. Doses of 5 mg/day, 15 mg/day and 35 or 50 mg/week were not found to be associated with an increased rate of GI events even in individuals at risk for these events, such as those patients using an NSAID. This result was consistent across different doses of risedronate. One weakness that Adami et al.[7] point out is that the patients who participated in their study primarily had osteoarthritis whereas bisphosphonates are primarily used for osteoporosis. The differences between these two diseases, osteoarthritis and osteoporosis, may confound these results.[36]

There is a paucity of available data when comparing the GI adverse effects associated with risedronate compared with alendronate. Rosen et al.[35] evaluated both medications in a head-to-head trial and found there to be no significant difference in adverse events in general, upper GI adverse events specifically or rates of discontinuation between these two drugs when using the standard weekly dose. The only aspect of this trial that remains undetermined is the presence of a placebo arm for direct comparison of the incidence of adverse events in both treatment groups. Since previous placebo-controlled risedronate trials have shown no difference in rates of adverse events, one

Table II. The tolerability profile of oral risedronate (RIS)

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	GI toxicity
Adami et al. (2005)[29]	r, db, pc (2 years)	PLA: n = 622; RIS: n = 628. 77% were regular NSAID users	RIS 5 mg/day; RIS 15mg daily; RIS 35 mg/ week or 50 mg/week	Upper GI events	Only GI events were discussed	The rate of upper GI events was not significantly different among each of the treatment groups. Secondly, the rate of GI events was not significantly different amongst those with pre-existing GI disease
Boonen et al. (2004)[30]	Pooled analysis of data r, db, pc (3 years)	RIS: n = 704; PLA: n = 688; all >80 years of age	RIS 5 mg/day	Cumulative incidence of new vertebral fractures	Withdrew due to adverse event PLA: 20.3%, RIS = 20.6% (p = 0.947)	Any upper GI event PLA 26.5% vs RIS 28.8%; dyspepsia PLA 6.8% vs RIS 6.8%
Brown et al. (2002)[1]	r, db, ac (2 years)	RIS daily dose: n = 480; RIS weekly moderate dose: n = 485; RIS weekly high dose: n = 491	RIS 5 mg/day; RIS 35 mg/week; RIS 50 mg/ week	BMD in the lumbar spine and the femoral neck	The individuals who reported adverse events were similar in numbers between the three groups. Most common adverse events were arthralgia and constipation	The incidence of GI events was not significantly different among the three groups. Moderate or severe GI events occurred in the same level in all three groups. 4.8%, 4.5% and 4.3% in the 5mg, 35mg, and 50mg group, respectively
Henderson et al. (2006)[31]	r, db, pc (12 months)	Population with Crohn's disease and ulcerative colitis: RIS: n = 23; PLA: n = 25	RIS 5 mg/day	BMD	Amongst the RIS and PLA group there was no significant difference in rates of emesis, arthralgia and flu-like symptoms	Diarrhoea: n = 12 RIS; and n = 17 in the PLA group. Abdominal pain: n = 2 RIS; and n = 3 in the PLA group
Hooper et al. (2005)[32]	r, dm, pc, pg (24 months)	PLA: n = 125; low-dose RIS: n = 127; moderate-dose RIS: n = 129	RIS 2.5 mg/day or 5 mg/day	BMD; tolerability	Vertebral and non-vertebral fractures were monitored as adverse events and there was no significant difference across groups	Upper GI events were reported 16% in the PLA group, 21% in the RIS 2.5mg group and 19% in the 5mg group. Majority of upper GI events were mild and did not lead to discontinuation. The incidence of GI events in individuals with pre-existing GI disease or NSAID use was similar across groups
Leung et al. (2005)[33]	r, db, pc, mc (12 months)	RIS: n = 31; PLA: n = 34	RIS 5 mg/day	BMD	No serious adverse events. Five patients discontinued the study: one due to stroke; two migration; two GI upset	Two GI upsets: one in the RIS group and one in the PLA group

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Table II. Contd

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	GI toxicity
Miller et al. (2005)[34]	Combined data from nine r, db, pc trials (3 years)	PLA: n = 4500; RIS: n = 4496; all of which had renal impairment – mild, moderate or severe	RIS 5 mg/day	Renal event; BMD; vertebral fractures	The overall incidence of adverse events secondary to renal deterioration was similar in both the RIS and PLA group. There was no significant change in serum creatinine from the baseline for both the treatment and PLA group	GI adverse events were not addressed in this study
Rosen et al. (2005)[35]	r, db, ac (12 months)	ALE: n = 520; RIS: n = 533	ALE 70 mg/week; RIS 35 mg/week	BMD in hip and spine	Significant adverse event: ALE 6.4%; RIS 6.3%	Upper GI adverse events 22.5% in ALE; 20.1% in RIS. Most common upper GI event was dyspepsia 8.2% vs 7.8% in ALE vs RIS

ac = active comparator; **ALE** = alendronate; **BMD** = bone mineral density; **db** = double-blind; **dm** = double-masked; **GI** = gastrointestinal; **mc** = multicentre; **pc** = placebo-controlled; **pg** = parallel-group; **PLA** = placebo; **r** = randomised.

may make the assumption that the addition of placebo arm to the study of Rosen et al.[35] would be redundant. More important is the fact the standard of therapy is treatment with bisphosphonate in this osteoporotic population. However, Rosen et al.[35] did find that arthralgias, back pain, headache and upper respiratory tract adverse events were prevalent in >5% of the risedronate treatment arm. Arthralgias were also found by Brown et al.[1] suggesting that this may be a significant adverse event to consider. Concordantly, there is some evidence of arthralgia-like symptoms occurring secondary to alendronate use.[37] Of the trials presented in the section on alendronate, none discussed articular events. It is difficult to reconcile these events based on the pharmacodynamics of risedronate and alendronate, suggesting further studies are necessary.

Boonen et al.[30] utilised a pooled analysis from three randomised, double-blind, placebo-controlled trials to evaluate the tolerability of daily risedronate. They evaluated a population of individuals ≥80 years of age using a study that was much simpler in design to the others previously described. Like previous studies, results showed no significant difference in rates of adverse events in the treatment group compared with placebo.[30]

Classically, oral bisphosphonates are known to cause upper GI toxicity but risedronate has also been evaluated in the context of renal toxicity. The rationale behind bisphosphonates playing a role in renal toxicity is through decreased glomerular filtration leading to accumulation of bisphosphonates in the renal tubule.[34,38,39] One study revealed no significant differences in rates of renal toxicity between the risedronate (5 mg/day) group compared with the placebo, with baseline renal dysfunction being the same between the two groups.[34] Across mild, moderate and severe age-related renal dysfunction, risedronate had no significant effect on rates of adverse events or specific renal adverse events.[34] In the group with severe renal dysfunction, it is difficult to perceive the effect of medication as the level of dysfunction is already at a maximum. Evidence based on renal dysfunction in dissuading treatment is not clear. When considering renal dysfunction secondary to an independent disease process, one should still be cautious when using risedronate.

Risedronate has a consistent safety profile across several dimensions. There is no evidence that age has an effect on altering tolerability across different dosages. Unlike alendronate, risedronate has not demonstrated definite synergism with NSAIDs contributing to GI toxicity. The evidence for the different profiles of interaction with NSAIDs is not strong and caution should be used when implementing therapy with either of these two bisphosphonates in an individual using an NSAID. Finally, after accounting for underlying renal dysfunction, risedronate does not appear to have any effect on renal toxicity. Based on the evaluation of alendronate, compliance with risedronate at once-weekly dosing is likely to be superior. One weakness in the evaluation of these two bisphosphonates is that extra-GI adverse events were not evaluated in detail with the purpose of drawing comparisons between different dosing regimens for both alendronate and risedronate.

4. Oral Ibandronate in Contrast to Alendronate and Risedronate

Studies covering the tolerability profile of oral ibandronate are summarised in table III.

Ibandronate was developed in both an oral and intravenous form making it unique when compared with alendronate, risedronate and zoledronic acid. Ibandronate is not only used in the treatment of osteoporosis but it also plays a significant role in the management of hypercalcaemia of malignancy secondary to metastatic bone disease. Both formulations of ibandronate are well tolerated, have adverse event profiles comparable with placebo and are associated with no significant renal toxicity.[50]

McClung et al.[48] conducted a study of daily oral ibandronate with the objective of establishing an optimal tolerable dose. Like alendronate and risedronate, ibandronate did not have a significant influence on adverse events across varying dosages compared with placebo. Similar to risedronate, ibandronate did not cause a rise in serum creatinine level, and liver enzyme levels were not affected by the stepwise dose increments inherent to this study.

Studies evaluating ibandronate have examined its intermittent treatment with wide dosing intervals for the treatment of osteoporosis, such a unique attribute that is not available with alendronate or risedronate. Intermittent treatment with ibandronate has proven efficacy yet the tolerability may differ from a daily dose schedule. Delmas et al.[45] compared tolerability between daily, intermittent and placebo groups. Both treatment regimens were well tolerated with a similar occurrence of adverse events and neither was associated with increased GI adverse events.[45] The adverse effects of the study described by Delmas et al.[45] are reported in detail in the study by Chesnut et al.[43] Although the levels of any adverse event were high in all three groups (approximately 90%), there were no statistically significant differences in the rates of upper GI adverse events. Although the rate of dyspepsia appeared slightly higher in the ibandronate 2.5mg group (11%) compared with placebo and intermittent ibandronate at 20mg (9% and 9%, respectively), differences between groups did not reach significance ($p > 0.08$).[43] A further subgroup analysis between individuals with and without pre-existing GI disease found no significant effect of both doses of ibandronate on rates of GI adverse events, results which are comparable to those found with alendronate and risedronate.[1,18,43] Increasing the dosing interval to weekly or monthly does not seem to change rates of GI adverse events when comparing daily dosing for alendronate, risedronate or ibandronate.[1,18,43]

It has been shown that monthly oral ibandronate is well tolerated and has high efficacy in postmenopausal women treated for osteoporosis. Reginster et al.[51] drew this conclusion when they carried out a double-blind, placebo-controlled phase I study where oral ibandronate 50, 100 and 150mg was given once a month for a total of 3 months. The rationale for this study was to show good tolerability and efficacy of this monthly treatment schedule and to explore the potential for improving compliance and adherence to therapy due to the lower frequency of dosing.[51] The primary endpoints were adverse events such as flu-like symptoms and abnormal laboratory findings of both haematological and biochemical nature. With regards to safety, there were no significant differences in the occurrence of adverse events between the three groups. No serious adverse events or events causing death were evident. The number of GI adverse events occurring within 3 days of administration was not significantly differ-

Table III. Tolerability profile of ibandronate (IBA)

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	Renal toxicity	GI toxicity
Body et al. (2003)[40]	r, db, pc (2 years)	IBA: n = 154; PLA: n = 158	IV IBA 6mg every 3–4 weeks	Skeletal-related event	Two serious adverse events related to treatment: bone pain; lung oedema	IBA 6mg 6%; PLA 12%	Not addressed as mode of treatment is IV
Body et al. (2004)[41,42]	r, db, pc (96 weeks)	IBA: n = 287; PLA: n = 277	Oral IBA 50mg daily	Skeletal-related event	Hypocalcaemia IBA 9.4; PLA 5.1%	IBA 50mg 5.2%; PLA 4.7%	GI events were not assessed
Chesnut et al. (2004)[43]	r, db, pc, pg (3 years)	IBA daily: n = 977; IBA intermittent: n = 977; PLA: n = 975	Oral IBA 2.5mg daily; IBA intermittent (20mg every other day for 12 doses every 3 months)	Vertebral fractures	Drug-related adverse events: daily IBA 19.8%; intermittent IBA 18.5%; PLA 17.9%	Renal events not discussed	Duodenal ulcer 0.9%, 0.1% and 0.1% in daily, intermittent and PLA groups, respectively. Dyspepsia was 9.1%, 11.4% and 9.0%, respectively
De Cock et al. (2005)[44]	Global economic modelling study	NA	Oral IBA; ZOL; PAM	Healthcare cost and quality-adjusted life year; skeletal-related events; bone pain	Discontinuation rates due to adverse events: oral IBA 2%; PAM 2%; ZOL 4%	Renal events not discussed	GI events not discussed

Continued next page

Table III. Contd

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	Renal toxicity	GI toxicity
Delmas et al. (2004)[45]	r, db, pc (3 years)	IBA daily: n = 224; IBA intermittent: n = 229; PLA: n = 224	Oral IBA daily 2.5mg; IBA intermittent 20mg alternating days of 12 doses every 3 months	Biochemical markers; lumbar spine and total hip BMD; safety	Similar adverse events in the treatment and PLA groups	Renal events not discussed	There was no increase in GI events in the treatment group as compared with PLA
Diel et al. (2004)[46]	r, db, pc (96 weeks)	IBA 2mg: n = 154; IBA 6mg: n = 154; PLA: n = 158	IV IBA 2mg or 6mg monthly	Incidence of adverse events; quality of life; bone pain	Flu-like symptoms: IBA 2mg 6.5%; 6mg 6.6%; PLA 1.9%. Arthralgias: 2mg 13.1%; 6mg 11.2%; PLA 7.6%	Renal events were not discussed	GI events were not discussed
Felsenberg et al. (2005)[47]	r, db, pc (3 years)	IBA: n = 977; PLA: n = 975	Oral IBA 2.5mg daily	Vertebral fracture	Drug-related adverse events were similar in the treatment and PLA group. IBA 19.8%; PLA 17.9%	Renal events not discussed	GI events not directly addressed

Continued next page

Table III. Contd

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	Renal toxicity	GI toxicity
McClung et al. (2004)[48]	r,db, pc (24 months)	IBA 0.5mg: n = 162; 1mg: n = 166; 2.5mg: n = 163; PLA: n = 162	Oral IBA once daily at staged dosing	BMD	Discontinuation was 9%, 5%, 5% and 7% in the PLA, IBA 0.5, 1 and 2.5mg groups, respectively	Renal function remained stable throughout the study	Dyspepsia 14, 16, 14 and 15 events in the PLA, IBA 0.5, 1 and 2.5mg groups, respectively
Mancini et al. (2004)[41]	op, pilot (6 weeks)	IBA: n = 18	IV IBA 4mg daily for 4 days	Bone pain; opioid consumption; quality of life	One patient experienced flu-like symptoms; one patient with a transient increase in bone pain	Renal events were not noticed	No GI effects were noted
Miller et al. (2005)[49]	r, db, ni	IBA daily: n = 395; 50/50[a]: n = 396; monthly: n = 396; monthly high dose: n = 396	Oral IBA 2.5mg daily; 50mg/50mg monthly; 100mg monthly; 150mg monthly	BMD; biochemical markers	Adverse events were slightly higher in the monthly arms	Renal events not discussed	Any upper GI adverse event. Daily: 18%; 50/50: 20.2%; monthly: 21.7%; high dose monthly: 19.6%

a Single doses of 50mg on consecutive days monthly.

BMD = bone mineral density; **db** = double-blind; **GI** = gastrointestinal; **IV** = intravenous; **NA** = not applicable; **ni** = noninferiority; **op** = open-label; **PAM** = pamidronate; **pc** = placebo-controlled; **pg** = parellel-group; **PLA** = placebo; **r** = randomised; **ZOL** = zoledronic acid.

ent among treatment groups and placebo. A slightly higher occurrence of GI adverse events occurred in the 100mg and 150mg arms during the entire study duration, although the majority of these events were mild.[51] This study by Reginster et al.[51] is unique in that dosing was compared at one maximal interval rather than comparing across intervals, which is seen commonly in alendronate and risedronate trials. The results are also novel in that high doses of ibandronate did not appear to elicit any more frequent adverse GI adverse events in comparison to lower doses at the same intermittent interval. This leads us to believe that efficacy can be maximised within the constraints of high levels of tolerability evident at higher doses without causing more frequent adverse events.

Felsenberg et al.[47] evaluated the effects of oral ibandronate in the context of reducing vertebral fractures in a placebo-controlled study where the treatment group received ibandronate 2.5mg daily, a study bringing us back to the standard basic comparison evident in early trials of alendronate and risedronate where daily dosing is compared with placebo. The presence of any adverse event was consistent with Chesnut et al.[43] at approximately 90% and was not significantly different between the placebo arm and the treatment arm. The incidence of GI adverse events was also comparable between the two groups. Oral ibandronate has also been used for the treatment of skeletal metastases. A trial conducted by Body et al.[52] investigated the use of ibandronate for the purposes of preventing bone pain and improving quality of life in women affected by breast cancer. Ibandronate was given as a daily dose of 50mg with a contralateral placebo arm over 96 weeks. Adverse events occurred in both the ibandronate and placebo arms (26.6% and 17.7% of patients, respectively, yielding a significant result), the ibandronate group having more adverse events as a result of a greater incidence of hypocalcaemia.

5. Intravenous Ibandronate

The infusion of ibandronate to treat hypocalcaemia due to malignancy takes 1–4 hours and can vary in dose based on clinical context.[9] Adverse effects may occur early after treatment but are seldom, if ever, serious. An acute-phase reaction can occur with ibandronate and may manifest as flu-like symptoms.[53]

Intravenous bisphosphonates can also be used in the context of postmenopausal osteoporosis. Stakkestad et al.[54] conducted a study examining ibandronate at doses of 0.5mg, 1mg and 2mg given by intravenous infusion every 3 months compared with placebo. Results revealed that ibandronate was well tolerated. Seventy-five percent of individuals in the placebo group had at least one adverse event compared with 82–84% in the treatment group. Myalgias also occurred with significantly increased frequency in the treatment groups at 14%, 12% and 22% for the 0.5mg, 1.0mg and 2.0mg group, respectively, compared with 7% in the placebo group. Although myalgia is considered an adverse event, it was self-limited and usually occurred only with the first injection. Similar to the oral formulation of ibandronate, renal toxicity was not evident with the intravenous infusion. In comparison to alendronate, risedronate and oral ibandronate, the tolerability profile of intravenous ibandronate appears to be good. Combined with its low frequency of administration, this method of administration allows the physician to monitor adherence.

Similar to the study by Stakkestad et al.,[54] the effects of intravenous ibandronate have been evaluated by Thiebaud et al.[55] across different dosing profiles of 0.25mg, 0.5mg, 1mg, 2mg and placebo. Adverse events were comparable across all dosing regimens; however, the placebo group had significantly fewer adverse events. With regards to GI adverse events, similar findings were evident. The most common causes of withdrawal were headache, back pain, arthralgia and upper respiratory infections.[56]

With the advent of ibandronate in an intravenous formulation, a concern of renal toxicity has developed. In a small study, Jackson[57] evaluated the incidence of renal adverse events using 6mg intravenous ibandronate over 1–2 hours every 3–4 weeks to manage breast cancer metastatic to bone. Renal adverse events occurred in 4% of study participants in the ibandronate group and 4.5% in the placebo group, with the differences between groups not being statistically significant. The possibility of renal toxicity being dose dependent was tested by Mancini et al.,[41] who evaluated a 4mg dose of intravenous

ibandronate over 2 hours for 4 consecutive days. Despite the relatively high doses in the study, no significant events of renal toxicity or GI toxicity were observed, although flu-like symptoms (fever, myalgias and malaise) were evident in one patient for approximately 48 hours.

The rapid infusion of ibandronate has been examined in several studies, which led to its final formulation of 6mg intravenous infusion over 15 minutes.[58] However, initial studies investigated the role of ibandronate for the treatment of metastatic disease, beginning with a trial that successfully infused 4mg over 1 hour every 4 weeks, with no change in serum creatinine levels.[58,59] In a further analysis evaluating the presently used dosage of ibandronate, there was no significant change in serum creatinine levels.[58,60] Various doses were applied to monitor renal adverse effects and results revealed they rarely occurred.

Intermittent dosing has been used to maximise tolerability; however, the question remains as to whether it is the chronicity of treatment or magnitude of dose that contributes to renal toxicity or systemic toxicity in general.

6. Zoledronic Acid and a Contrast with Ibandronate

Studies covering the tolerability profile of zoledronic acid are summarised in table IV.

Like ibandronate, the tolerability of zoledronic acid has been evaluated for the purpose of treating hypercalcaemia associated with malignancy.[53] In individuals with pre-existing risk factors for the deterioration of renal function including aging, multiple myeloma, diabetes mellitus and hypertension, zoledronic acid should be used with caution.[70-72]

Zoledronic acid is a new generation, highly potent, nitrogen-containing bisphosphonate.[71] The recommended treatment for hypercalcaemia with zoledronic acid is 4mg intravenous infusion over 15–30 minutes every 3–4 weeks. Significant adverse effects that have come to light include renal failure and, more recently, osteonecrosis of the jaw.[73]

Renal toxicity associated with zoledronic acid use has been evaluated in detail. A study by Munier et al.[62] utilising the pharmacovigilance system created in 1973, based on a network of 31 regional centres in France, attempted to identify cases of renal toxicity in individuals with different types of metastatic cancer during treatment. Four patients were identified with *de novo* renal toxicity, two of which resulted in fatalities. Three additional patients experienced acute deterioration (one was not accounted for in the final analysis) from a baseline of chronic renal failure. After discontinuation of zoledronic acid, three patients had complete recovery whereas one only had partial recovery.[62] Based on the renal event outcomes in this study, regular renal monitoring is recommended.

The rate of administration and dose plays an important role in predicting a future renal adverse event. In phase III trials, the 8mg infusion group had to be decreased to 4mg infusion because of renal impairment.[74] Based on this study, the recommended infusion is 4mg intravenous infusion every 3–4 weeks.

In studies where zoledronic acid was compared with placebo in patients with solid tumours other than breast and prostate, the most commonly occurring adverse events were bone pain, nausea, anaemia and vomiting.[66] Incidences of nausea, vomiting and dyspnoea were significantly higher in the zoledronic acid group versus placebo.[65] Renal adverse events were also evaluated in detail by examining the incidence that each population reached creatinine levels that were two times normal. There was no significant difference in the treatment versus non-treatment group (10.9% vs 6.7%).[65]

Zoledronic acid has also been evaluated in the setting of treating bone-related metastases in breast carcinoma, where it has been compared with pamidronate.[64] The most common adverse events in both groups were bone pain, nausea, fatigue, emesis and fever, although the incidence of the most commonly reported adverse events was similar between groups. Comparing the osteolytic and non-osteolytic subgroups, there was no significant difference in adverse events.[64] The incidence of a standardised increase in creatinine level (two times baseline) was 7.7% in the zoledronic acid group treated with 4mg and 6.0% in the pamidronate group. A larger percentage of the zoledronic acid group treated with 8mg (11.9%) had increased rates of elevated creatinine leading to the recommenda-

Table IV. Tolerability profile of intravenous (IV) zoledronic acid (ZOL)

Study (year)	Study design (duration)	Sample size	Intervention	Outcomes	Other manifestations of toxicity	Renal toxicity	GI toxicity
Kohno et al. (2005)[61]	r, db, pc (1 year)	ZOL: n = 114; PLA: n = 114	ZOL 4mg every 4 weeks	Skeletal-related event	Nausea ZOL 4mg 50%; PLA 53.1%	There was no evidence of any renal events when treated with ZOL	Emesis ZOL 4mg: 32.5%; PLA: 38.9%
Munier et al. (2005)[62]	cs (retrospective study drawing cases from a cohort)	Pharmacovigilance system – 7 cases identified in cohort	ZOL	Renal adverse event	Only outcome assessed was renal adverse events	Four patients with *de novo* renal impairment; three patients with exacerbation of renal failure	Not addressed – unlikely considering modality of treatment via IV
Polascik et al. (2005)[63]	pr, sa, mc (1 year)	ZOL: n = 221	ZOL 4mg every 3 weeks	BMD; skeletal-related event	Arthralgia 20.4%; nausea 14%; fatigue 14%	Three patients had renal insufficiency	Not addressed
Rosen et al. (2003)[64]	r, ac (12 months)	ZOL low dose: n = 378; high dose: n = 364; PAM: n = 388	ZOL: 4mg every 3 weeks; 8mg; PAM: 90mg every 4 weeks	Skeletal-related event	Nausea: ZOL 4mg 48%; 8mg 48%; PAM 46%	4mg: 7.7%; 8mg: 11.9%	Emesis: ZOL 4mg 32%; 8mg 33%; PAM 31%
Rosen et al. (2003)[65]	r, pc (9 months)	ZOL low dose: n = 254; high dose: n = 265; PLA: n = 247	ZOL: 4mg; 8mg every 3 weeks	Skeletal-related event	Nausea: ZOL 4mg 46%; 8mg 40%; PLA 34%	Hazard ratio for 4mg group: 1.57; p = 0.228	Emesis: ZOL 4mg 36%; 8mg 31%; PLA 29%
Rosen et al. (2004)[66]	r, pc (21 months)	ZOL low dose: n = 257; high dose: n = 266; PLA: n = 250	ZOL: 4mg; 8mg every 3 weeks	Skeletal-related event	Nausea: ZOL 4mg 48.8%; 8mg 42.3%; PLA 36.4%	Renal safety with 4mg and 8mg was comparable to PLA	Emesis: ZOL 4mg 37.8%; 8mg 33.2%; PLA 30.4%
Saad (2005)[67]	r, pc (15 months)	ZOL low dose: n = 214; high dose: n = 218; PLA: n = 208	ZOL: 4mg; 8mg every 3 weeks	Skeletal-related event; renal adverse	Nausea: ZOL 4mg 36%; PLA 37%	4mg 1.5%; 8mg 2.1%	Emesis: ZOL 4mg 20%; PLA 21%
Vogel et al. (2004)[68]	op, pr, mc (6 months)	ZOL stratified according to: myeloma: n = 129; breast: n = 355; prostate: n = 154	ZOL 4mg every 3–4 weeks	Quality of life; adverse events; serum creatinine	Nausea: 0–6 months of treatment 17%; 6–24 months 15%; >24 months 14.5%. Total 17%	Renal event: myeloma 7.8%; breast 6.2%; prostate 6.5%	Not addressed
Wardley et al. (2005)[69]	r, op, co (9 months)	ZOL infusion at baseline: in hospital: n = 45; community: n = 56	ZOL 4mg every 3 weeks	Brief pain inventory; adverse events	Nausea in all patients 24%	Renal function was normal for a majority of patients throughout the study. Creatinine only rose in 3%	Emesis 17% in all patients

ac = active comparator; **BMD** = bone mineral density; **co** = crossover; **cs** = case series; **db** = double-blind; **mc** = multicentre; **op** = open-label; **PAM** = pamidroninc acid; **pc** = placebo-controlled; **PLA** = placebo; **pr** = prospective; **r** = randomised; **sa** = single arm.

tion that an 8mg dose of zoledronic acid is too high.[64]

Using zoledronic acid to treat osteoporosis, dosing schedules that were implemented in a placebo-controlled trial included 0.25mg, 0.5mg and 1mg given at 3-month intervals for 1 year. Another group received 4mg once a year for 1 year and 2mg given every 6 months for 1 year thereafter.[75] The most common adverse events were myalgias (10–20%), pyrexia (9–20%), arthralgias (8–25%), influenza-like illness (2–16%) and nausea (5–13%), although the incidence of myalgias and arthralgias was similar between zoledronic acid in comparison with ibandronate.[75,76]

One of the more recent evaluations of zoledronic acid involved its comparison with a standard of therapy, in this case risedronate, for the treatment of Paget's disease.[6] Although the number of adverse events was similar in both groups, the zoledronic acid group experienced almost twice the number events of the risedronate group in the first 3 days. These were primarily influenza-like symptoms that are known to be associated with intravenous bisphosphonates and ended, in most cases, within 4 days. Similar results have also been found with intravenous infusions of ibandronate, where the occurrence of renal and GI events was similar in both groups. Higher rates of hypocalcaemia were observed in the zoledronic acid group compared with the risedronate group, but only a quarter of these (2 of 8) were actually symptomatic.[6]

Kohno et al.[61] found the administration of a 4mg zoledronic acid infusion of 15 minutes every 4 weeks for 1 year to be well tolerated. The most common adverse effects were pyrexia, nausea, fatigue, nasopharyngitis, vomiting and bone pain as well as increased evidence of myalgias or arthralgias occurring in the acute setting of the administration of zoledronic acid. These findings are consistent with those that have been previously reported; both zoledronic acid and intravenous ibandronate are triggers for myalgias and arthralgias in the few days following administration.

Zoledronic acid has also been administered at high doses of 4mg infused over 15 minutes every 3 weeks over a 9-month period to treat breast cancer patients with bone metastases.[69] Unlike previous trials, myalgias and arthralgias developed in a larger number of individuals, in this case 21%, although an influenza-type illness associated with the infusion surpassed myalgias and arthralgias in frequency. Due to the high dosages and frequency of administration in this study, one would expect higher incidence of adverse events. However, despite the increased frequency of dosing at every 3 weeks with the study by Wardley et al.,[69] comparison to the study by Kohno at al.[61] yielded no significant differences.

7. Osteonecrosis of the Jaw

Another adverse effect of bisphosphonates includes osteonecrosis of the jaw, often after procedures such as tooth extractions.[77,78] Although the pathophysiology of osteonecrosis of the jaw and its relationship to bisphosphonates is not known, it has been seen to primarily occur after several months of intravenous infusions of zoledronic acid or pamidronate. Recent statistics suggest that 217 patients treated with intravenous bisphosphonates have been affected with osteonecrosis of the jaw.[79] Wooltorton[79] suggested that possible additional risk factors include the use of corticosteroids, chemotherapy and radiation therapy. Comorbid conditions such as poor dental hygiene, dental disease and infection including osteomyelitis are also known risk factors as are anaemia and coagulopathies.[79]

Osteonecrosis of the jaw is rarely described in patients treated with oral bisphosphonates, although it has been reported in an osteoporotic individual being treated with alendronate.[78] More commonly, osteonecrosis of the jaw is seen with zoledronic acid in those with malignancy. For example, Durie et al.[12] revealed that osteonecrosis of the jaw occurred in 10% of individuals treated with zoledronic acid after 36 months and 4% of individuals treated with pamidronate after 36 months. These results were taken from an internet-based survey and thus conclusions should be interpreted with caution. The effect of intravenous ibandronate has not been assessed in the context of jaw osteonecrosis.

Ruggiero et al.[80] evaluated 63 cases of osteonecrosis of the jaw, all of whom had received bisphosphonate. Thirty-one percent of the cases were treated with zoledronic acid and 57% were treated with pamidronate and the remaining 12% was treated with oral alendronate. Individuals with

breast cancer and multiple myeloma made up a predominant component of the population accounting for 32% and 44% of the study group, respectively. Osteoporosis accounted for 13% of the population. This study supports the observation that osteonecrosis of the jaw is primarily associated with high-dose intravenous bisphosphonates.[80] Risk factors for osteonecrosis of the jaw must be considered and balanced with the benefit for starting an individual on a bisphosphonate to treat either malignancy-induced bone disease or osteoporosis.

In a separate study of 252 patients with a diagnosis of a solid tumour, osteonecrosis of the jaw was found to be prevalent in 6.7% of patients being treated with zoledronic acid, pamidronate and intravenous ibandronate.[81] As expected, rates of osteonecrosis of the jaw increased with prolonged duration of therapy with the intravenous bisphosphonate. Of those affected by osteonecrosis of the jaw, all had undergone dental procedures in the preceding year. The potential mode of action is that zoledronic acid is thought to have antiangiogenic properties.[82]

8. Conclusion

Alendronate, risedronate, ibandronate and zoledronic acid play distinctive roles in the management of osteoporosis and malignancy-induced bone disease. The adverse events associated with taking oral alendronate and risedronate are minimal, making their daily or weekly use tolerable and thus acceptable. However, with intravenous zoledronic acid tolerability may be compromised as a result of renal toxicity – even if it occurs infrequently. Myalgias and arthralgias in the acute setting also appear to play a significant role in defining the tolerability of intravenous bisphosphonates. In response to individuals who are intolerant of intravenous bisphosphonates, one can make the switch to oral bisphosphonate if the clinical context of treatment is maintained. In comparison to setting up and administering an infusion site where a patient must be present for a predefined period of time, oral treatment may appear more tolerable. Even so, treatment efficacy in specific indications and adherence to therapy of intravenous ibandronate and zoledronic acid make them valuable additions to our therapeutic armamentarium. Validating this conclusion is the relative low levels of adverse events, despite being potent antiresorptive agents.

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References

1. Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002; 71 (2): 103-11
2. Kherani RB, Papaioannou A, Adachi JD. Long-term tolerability of the bisphosphonates in postmenopausal osteoporosis: a comparative review. Drug Saf 2002; 25 (11): 781-90
3. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27 (3): 165-76
4. Cairns AP, Wright SA, Taggart AJ, et al. An open study of pulse pamidronate treatment in severe ankylosing spondylitis, and its effect on biochemical markers of bone turnover. Ann Rheum Dis 2005; 64 (2): 338-9
5. Mersfelder T, Armitstead JA, Ivey MF, et al. A medication use evaluation of alendronate: compliance with administration guidelines. Pharm Pract Manag Q 1999; 18 (4): 50-8
6. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005; 353 (9): 898-908
7. Adami S, Felsenberg D, Christiansen C, et al. Efficacy and safety of ibandronate given by intravenous injection once every 3 months. Bone 2004; 34 (5): 881-9
8. Atula S, Powles T, Paterson A, et al. Extended safety profile of oral clodronate after long-term use in primary breast cancer patients. Drug Saf 2003; 26 (9): 661-71
9. Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. Oncologist 2004; 9 Suppl. 4: 28-37
10. Greenspan S, Field-Munves E, Tonino R, et al. Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. Mayo Clin Proc 2002; 77 (10): 1044-52
11. Ho AY, Kung AW. Efficacy and tolerability of alendronate once weekly in Asian postmenopausal osteoporotic women. Ann Pharmacother 2005; 39 (9): 1428-33
12. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005; 353 (1): 99-102
13. Fietta P, Manganelli P, Lodigiani L. Clodronate induced uveitis. Ann Rheum Dis 2003; 62 (4): 378
14. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004; 350 (12): 1189-99
15. Simon JA, Lewiecki EM, Smith ME, et al. Patient preference for once-weekly alendronate 70mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clin Ther 2002; 24 (11): 1871-86
16. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing

vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348 (9041): 1535-41
17. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; 280 (24): 2077-82
18. Eisman JA, Rizzoli R, Roman-Ivorra J, et al. Upper gastrointestinal and overall tolerability of alendronate once weekly in patients with osteoporosis: results of a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 2004; 20 (5): 699-705
19. Ensrud KE, Barrett-Connor EL, Schwartz A, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res 2004; 19 (8): 1259-69
20. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA 2003; 289 (19): 2525-33
21. Kushida K, Shiraki M, Nakamura T, et al. Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. J Bone Miner Metab 2004; 22 (5): 462-8
22. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999; 9 (5): 461-8
23. Quandt SA, Thompson DE, Schneider DL, et al. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. Mayo Clin Proc 2005; 80 (3): 343-9
24. Sambrook PN, Geusens P, Ribot C, et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. J Intern Med 2004; 255 (4): 503-11
25. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70mg once-weekly and alendronate 10mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. Aging (Milano) 2000; 12 (1): 1-12
26. Turbi C, Herrero-Beaumont G, Acebes JC, et al. Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: An open-label, prospective, nonrandomized, observational study. Clin Ther 2004; 26 (2): 245-56
27. Bartl R, Gotte S, Hadji P, et al. Adherence with daily and weekly administration of oral bisphosphonates for osteoporosis treatment [in German]. Dtsch Med Wochenschr 2006; 131 (22): 1257-62
28. Graham DY, Malaty HM. Alendronate and naproxen are synergistic for development of gastric ulcers. Arch Intern Med 2001; 161 (1): 107-10
29. Adami S, Pavelka K, Cline GA, et al. Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2005; 80 (10): 1278-85
30. Boonen S, McClung MR, Eastell R, et al. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the use of antiresorptive agents in the old and oldest old. J Am Geriatr Soc 2004; 52 (11): 1832-9
31. Henderson S, Hoffman N, Prince R. A double-blind placebo-controlled study of the effects of the bisphosphonate risedronate on bone mass in patients with inflammatory bowel disease. Am J Gastroenterol 2006; 101 (1): 119-23
32. Hooper MJ, Ebeling PR, Roberts AP, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric 2005; 8 (3): 251-62
33. Leung JY, Ho AY, Ip TP, et al. The efficacy and tolerability of risedronate on bone mineral density and bone turnover markers in osteoporotic Chinese women: a randomized placebo-controlled study. Bone 2005; 36 (2): 358-64
34. Miller PD, Roux C, Boonen S, et al. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res 2005; 20 (12): 2105-15
35. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70mg compared with once-weekly risedronate 35mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005; 20 (1): 141-51
36. Drees P, Decking J, Breijawi N, et al. [Osteoporosis and osteoarthritis-is there really an inverse relation?]. Z Orthop Ihre Grenzgeb 2005; 143 (2): 161-9
37. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. Arch Intern Med 2005; 165 (3): 346-7
38. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. Bone 1996; 18 (2): 75-85
39. Troehler U, Bonjour JP, Fleisch H. Renal secretion of diphosphonates in rats. Kidney Int 1975; 8 (1): 6-13
40. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003; 14 (9): 1399-405
41. Mancini I, Dumon JC, Body JJ. Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. J Clin Oncol 2004; 22 (17): 3587-92
42. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. Pain 2004; 111 (3): 306-12
43. Chesnut CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004; 19 (8): 1241-9
44. De Cock E, Hutton J, Canney P, et al. Cost-effectiveness of oral ibandronate compared with intravenous (i.v.) zoledronic acid or i.v. generic pamidronate in breast cancer patients with metastatic bone disease undergoing i.v. chemotherapy. Support Care Cancer 2005; 13 (12): 975-86
45. Delmas PD, Recker RR, Chesnut CH, et al. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. Osteoporos Int 2004; 15 (10): 792-8
46. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004; 40 (11): 1704-12
47. Felsenberg D, Miller P, Armbrecht G, et al. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. Bone 2005; 37 (5): 651-4
48. McClung MR, Wasnich RD, Recker R, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. J Bone Miner Res 2004; 19 (1): 11-8
49. Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year

results from the MOBILE study. J Bone Miner Res 2005; 20 (8): 1315-22

50. Tripathy D, Lichinitzer M, Lazarev A, et al. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. Ann Oncol 2004; 15 (5): 743-50
51. Reginster JY, Wilson KM, Dumont E, et al. Monthly oral ibandronate is well tolerated and efficacious in postmenopausal women: results from the monthly oral pilot study. J Clin Endocrinol Metab 2005; 90 (9): 5018-24
52. Body JJ, Bartl R, Burckhardt P, et al. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. J Clin Oncol 1998; 16 (12): 3890-9
53. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. Drug Saf 1999; 21 (5): 389-406
54. Stakkestad JA, Benevolenskaya LI, Stepan JJ, et al. Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. Ann Rheum Dis 2003; 62 (10): 969-75
55. Thiebaud D, Portmann L, Jaeger P, et al. Oral versus intravenous AHPrBP (APD) in the treatment of hypercalcemia of malignancy. Bone 1986; 7 (4): 247-53
56. Thiebaud D, Burckhardt P, Kriegbaum H, et al. Three monthly intravenous injections of ibandronate in the treatment of postmenopausal osteoporosis. Am J Med 1997; 103 (4): 298-307
57. Jackson GH. Renal safety of ibandronate. Oncologist 2005; 10 Suppl. 1: 14-8
58. Pecherstorfer M, Diel IJ. Rapid administration of ibandronate does not affect renal functioning: evidence from clinical studies in metastatic bone disease and hypercalcaemia of malignancy. Support Care Cancer 2004; 12 (12): 877-81
59. Wuster C, Schoter KH, Thiebaud D, et al. Methylpentylaminopropylidenebisphosphonate (BM 21.0955): a new potent and safe bisphosphonate for the treatment of cancer-associated hypercalcemia. Bone Miner 1993; 22 (2): 77-85
60. Heidenreich A. Bisphosphonates in the management of metastatic prostate cancer. Oncology 2003; 65 Suppl. 1: 5-11
61. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol 2005; 23 (15): 3314-21
62. Munier A, Gras V, Andrejak M, et al. Zoledronic Acid and renal toxicity: data from French adverse effect reporting database. Ann Pharmacother 2005; 39 (7-8): 1194-7
63. Polascik TJ, Given RW, Metzger C, et al. Open-label trial evaluating the safety and efficacy of zoledronic acid in preventing bone loss in patients with hormone-sensitive prostate cancer and bone metastases. Urology 2005; 66 (5): 1054-9
64. Rosen LS, Gordon DH, Dugan W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004; 100 (1): 36-43
65. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial-the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol 2003; 21 (16): 3150-7
66. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004; 100 (12): 2613-21
67. Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. Clin Prostate Cancer 2005; 4 (1): 31-7
68. Vogel CL, Yanagihara RH, Wood AJ, et al. Safety and pain palliation of zoledronic acid in patients with breast cancer, prostate cancer, or multiple myeloma who previously received bisphosphonate therapy. Oncologist 2004; 9 (6): 687-95
69. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. Br J Cancer 2005; 92 (10): 1869-76
70. Balla J. The issue of renal safety of zoledronic acid from a nephrologist's point of view. Oncologist 2005; 10 (5): 306-8
71. Berenson J, Hirschberg R. Safety and convenience of a 15-minute infusion of zoledronic acid. Oncologist 2004; 9 (3): 319-29
72. Hillner BE, Ingle JN, Berenson JR, et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel. J Clin Oncol 2000; 18 (6): 1378-91
73. Lugassy G. "Safety and convenience of a 15-minute infusion of zoledronic acid": not so safe. Oncologist 2005; 10 (5): 309-10
74. van Beek ER, Cohen LH, Leroy IM, et al. Differentiating the mechanisms of antiresorptive action of nitrogen containing bisphosphonates. Bone 2003; 33 (5): 805-11
75. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. Clin Ther 2003; 25 (11): 2669-708
76. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002; 359 (9321): 1929-36
77. Pogrel MA. Bisphosphonates and bone necrosis. J Oral Maxillofac Surg 2004; 62 (3): 391-2
78. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005; 353 (1): 99-102
79. Wooltorton E. Patients receiving intravenous bisphosphonates should avoid invasive dental procedures. CMAJ 2005; 172 (13): 1684
80. Ruggiero SL, Mehrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004; 62 (5): 527-34
81. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005; 23 (34): 8580-7
82. Wood J, Bonjean K, Ruetz S, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002; 302 (3): 1055-61

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