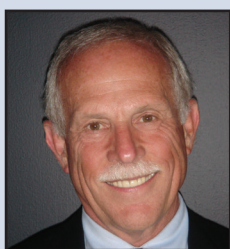


BISPHOSPHONATES: OPTIMISING OSTEOPOROSIS PROTECTION

**Best practice from the 2018 National Osteoporosis
Foundation of South Africa (NOFSA) Congress**



Dr Michael McClung

MD, FACP

Director, Oregon

Osteoporosis Center,

Portland, OR

Professorial Fellow,

Institute of Health and

Ageing, Australian

Catholic University,

Melbourne

Introduction

Osteoporosis is a disorder that damages skeletal architecture and weakens the skeleton. A combination of low bone mass and damaged microarchitecture increases the risk of osteoporotic fragility fractures (most importantly of the hip and spine), resulting in substantial morbidity, mortality and societal cost. Objectives of osteoporosis therapies in postmenopausal and older women are to improve bone strength, thereby reducing risk of fracture and, less commonly, to prevent rapid bone loss. Osteoporosis therapies take advantage of, and modulate, the bone remodelling cycle. Anti-remodelling drugs (anti-resorptive agents) that reduce bone remodelling include oestrogen receptor modulators, bisphosphonates (BPs) and denosumab. Remodelling stimulators (anabolic agents), the parathyroid hormone analogues, can be used for a short time to induce new bone formation.^{1,2}

BPs are the agents most extensively studied and prescribed in clinical practice for more than 20 years. BPs provide effective protection from fractures (vertebral 40-70%, hip 40-60%, non-vertebral 20-40%), are generally well tolerated and have a favourable safety profile.² The recently revised National Osteoporosis Foundation of South Africa (NOFSA) 2017 guideline for the diagnosis and management of osteoporosis recommends the use of a bisphosphonate or denosumab (not routinely available in South Africa) as first-line therapy in DXA-confirmed osteoporosis (T-score ≤ -2.5).³ The 17th NOFSA Congress (16-18 March 2018, Cape Town) hosted Dr Michael McClung (USA), who shared his clinical experience in the use of BPs for the treatment of osteoporosis.

KEY MESSAGES

- The revised NOFSA 2017 guideline recommends the use of a BP or denosumab as first-line therapy in DXA-confirmed osteoporosis
- BPs used in South Africa are risedronate, alendronate, ibandronate and zoledronic acid
- Binding affinity for the bone mineral matrix varies between BPs, as does potency in inhibiting the farnesyl pyrophosphate synthase (FPPS) enzyme
- The 'off effect' of BP withdrawal on bone remodelling varies between agents
- Oral BPs are poorly absorbed (<1%) into the circulation and are rapidly excreted through the kidney
- There are no head-to-head studies evaluating fracture risk reduction between BPs
- Upper gastrointestinal intolerance is associated with oral BP therapy
- Persistence on oral BP therapy is improved with less frequent dosing.

This report was made possible by an unrestricted educational grant from Cipla. The content of the report is independent of the sponsor.

Cipla

Mechanism of action of BPs

The mechanism of action by which BPs inhibit osteoclastic activity is reliant on binding affinity and intracellular enzyme inhibition. Once on the surface of the bone, BPs are preferentially deposited at sites of active bone remodelling where they bind to the matrix of the resorption pit and are absorbed by active osteoclasts. Binding affinity varies between BPs; agents with high affinity bind more tightly and persist in the skeleton for a longer time. Intracellularly, BPs inhibit the

FPPS enzyme in the HMG-CoA reductase pathway, interfering with osteoclast activity. All BPs used in clinical practice are nitrogen-containing, as this substantially increases reduction of osteoclastic resorption. Alendronate and ibandronate are simpler molecules with a straight N-containing side-chain; whereas riseridronate and zoledronic acid have a cyclic side-chain stabilising the position of the nitrogen molecule, imparting a greater potency in osteoclast inhibition (Table 1).⁴

Table 1. A classification of the bisphosphonates based on mechanism of action⁴

Structure	'Simple' non-N BPs	Alkyl-amino BPs	Heterocyclic N BPs
Mechanism of action	Act via ATP-BP metabolites	Inhibition of FPPS	Inhibition of FPPS
Inhibition of osteoclast resorption	Low potency	Intermediate potency	High potency
Molecules	• Etidronate • Clodronate • Tiludronate	• Pamidronate • Alendronate • Ibandronate	• Risedronate • Zoledronic acid

Pharmacokinetics of BPs

Oral BPs are poorly absorbed from the gastrointestinal (GI) tract into circulation (<1%) even under ideal conditions (empty stomach with a large glass of tap water 30 minutes before other medications, food or drink). Within 24 hours of the dose, about half of the absorbed dose is redistributed to the bone and the remainder is quickly excreted through the kidney, with very little exposure to tissue other than the skeleton and no active metabolites in circulation.⁵

In terms of duration of attachment to

the skeleton, risedronate binds less tightly to hydroxyapatite than ibandronate, alendronate or zoledronic acid (Figure 1).⁶ Variation in binding affinity is also reflected in total cumulative urinary excretion over time: 70% of alendronate is lost over two years, whereas 85% of risedronate is excreted within only 28 days.^{5,7-10} In terms of *in vitro* FPPS inhibition, zoledronic acid is the most potent, risedronate the second most and alendronate the least potent (Figure 2).¹¹

**EARN FREE
CPD POINTS**

Join our CPD community at
www.denovomedica.com
and start to earn today!

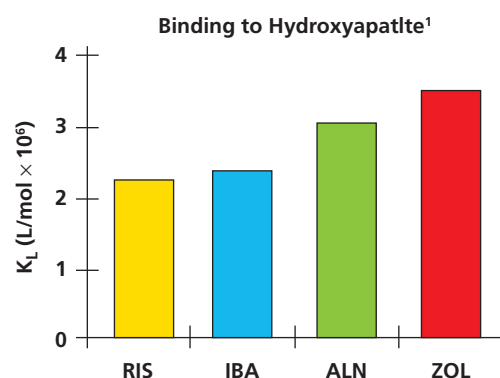


Figure 1. BP binding affinity for bone in vitro
Adapted from Nancollas GH, et al. *Bone* 2006; **38**: 617-627

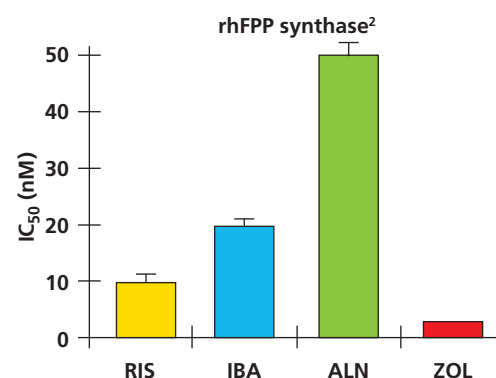


Figure 2. BP inhibition of FPPS in vitro
Adapted from Dunford JE, et al. *J Pharmacol Exp Ther* 2001; **296**: 235-42

Withdrawal of BPs

Upon withdrawal of BPs, the ‘off effect’ on bone remodelling differs between BPs. Using markers of bone resorption, the VERT-NA Extension study showed that discontinuation after three years of risedronate treatment resulted in the loss of the full effect of bone turnover inhibition within one year.¹² This is in marked contrast to alendronate and especially zoledronic acid. A single-dose IV infusion of zoledronic acid provides substantial inhibition of bone turnover for as long as three years.¹³ In the Extension of HORIZON PFT, indices of bone remodelling remained well below baseline for three years in patients who had received annual doses of zoledronic acid for three

years.¹⁴ This has implications for how long a BP ‘holiday’ should be. A shorter drug holiday is recommended for risedronate than for alendronate or zoledronic acid. Importantly, the VERT-NA Extension study indicated that during the year off risedronate therapy, patients were still protected from vertebral fracture. During three years on risedronate therapy there was a 41% decreased risk of vertebral fracture vs placebo;¹⁵ during the year off therapy, vertebral fracture risk reduction was 47%.¹² This important distinction from denosumab was emphasised by Dr McClung, as rapid loss of vertebral fracture protection occurs within months of discontinuing denosumab therapy.

“The speed with which risedronate reduces non-vertebral fracture risk is very impressive.”

Clinical consequences of differences among BPs

Each BP has its own ‘pharmacological signature’ of binding affinity and potency. Due to the lack of head-to-head studies documenting fracture risk reduction, it is difficult to determine if these differences translate into important clinical outcomes. There are several possible clinical consequences of these differences:

- Skeletal retention of drug (amount and duration of binding)
- Speed of onset of effect on inhibition

of bone remodelling

- Speed of reversal of effect (offset)
- Potency in degree of bone turnover suppression
- Differences in BP uptake in trabecular and cortical bone (drugs that bind very tightly don’t diffuse through to the cortical bone)
- Types of anti-fracture effects (vertebral vs non-vertebral)
- Safety and tolerability.⁴

Fracture risk reduction with BPs

There are no head-to-head studies evaluating fracture risk reduction with BPs. Dr McClung emphasises that one cannot and should not attempt to compare efficacy across studies because patient populations are different and even definitions (e.g. non-vertebral fracture) differ between studies. Alendronate, risedronate and zoledronic acid have been shown to substantially reduce risk of vertebral, hip

and other fractures in clinical trial settings of postmenopausal women with osteoporosis. Ibandronate has only been shown to reduce the risk of vertebral fracture. In a large clinical phase III study, there was no significant effect on non-vertebral and hip fracture, although the study design was inadequate for confidence that ibandronate reduces non-vertebral and hip fracture risk (Table 2).

Table 2. BP studies evaluating fracture risk reduction

Note: Not possible to compare efficacy across trials

	Vertebral	Non-vertebral	Hip
Alendronate ^{16,22}	48%	26%	53%
Risedronate ^{15,17,18}	41-65%	39%	40-60%
Ibandronate ¹⁹	62%	Not significant	Not significant
Zoledronic acid ²⁰	70%	25%	41%

Fracture risk with risedronate therapy

Long-term fracture risk reduction with risedronate was examined in the VERT-MN trial. Patients were assigned risedronate 5mg once daily or placebo for five years, after which everybody received risedronate for years six and seven. Patients continuing risedronate therapy maintained the same low rate of vertebral fracture during years six and seven, despite growing older and therefore having an increased fracture risk during the treatment period.²¹

For Dr McClung, ‘the speed with which risedronate reduces non-vertebral fracture risk is very impressive’. Post-hoc analyses of pooled clinical trial data from more than 6000 patients showed a significant reduction in non-vertebral fracture within the first six months of risedronate therapy (59%) compared to alendronate therapy (36%).^{16,23} The REAL retrospective observational study assessed cohorts of women receiving risedronate (n=12 215) or alendronate (n=21 615) and followed the incidence of hip fracture over one year. Cumulative incidence over time shows fewer patients with hip fracture on risedronate therapy. This is not a randomised trial so a definite conclusion that risedronate is more effective than

alendronate for hip fracture reduction cannot be made. However, the authors did attempt to adjust for various contributors of fracture risk (bone density, prior fracture, age, body weight) that could be identified and no explanation for the difference in hip fracture reduction was observed.²⁴

The FACT study randomly assigned treatment-naïve patients to receive clinically approved doses of alendronate 70mg weekly or risedronate 35mg weekly.²⁴ The difference in approved doses is a likely explanation as to why, in this study, risedronate is a less potent inhibitor of bone turnover than is alendronate. Dr McClung hazards the guess that if the same doses of the two agents were used, there would be little difference in the inhibition of bone turnover or trochanter bone mineral density (BMD). He pointed out that the greater BMD increase observed with alendronate in this study does not necessarily translate into greater protection from fractures, for in the Phase III alendronate study, the risk of vertebral fracture was the same in the groups of patients receiving 5 or 10mg once daily, despite greater increases in BMD with the larger dose.²⁵

Risks and concerns

Several adverse events have been associated with BP therapy, especially upper GI intolerance with the oral agents. Remaining in an upright position for 30 minutes after taking an oral BP is advised. Various clinical studies indicate that frequency of upper GI adverse events is no different between oral BP and placebo groups, “...however, there is a very strong perception in the clinical community and in patients that as soon as you take your first dose, the next hiccup that you get is clearly related to the drug.” The background incidence of GI distress among osteoporotic women older than 70 is

high.²

Atypical fracture of the femur (AFF) has an incidence of 1/1000 patients after 8-10 years of alendronate and is clearly related to the duration of oral BP therapy. In Australia, where risedronate is the most commonly used BP, the majority of AFF fractures were still observed in patients on alendronate therapy.²⁶ Acute phase reaction with influenza-like symptoms is seemingly exclusively associated with very high IV doses of BP. Concerns about atrial fibrillation with IV dosing are, in the opinion of Dr McClung, not valid or true.²

**EARN FREE
CPD POINTS**

Join our CPD community at
www.denovomedica.com
and start to earn today!

Adherence to BP therapy

Persistence on oral BP therapy is suboptimal. Reduced fracture rates are observed only in patients with proper persistence and compliance (adherence >80%) on long-term BP therapy.^{27,28} Less frequent, more convenient dosing is associated with better adherence to therapy. Surveys have

indicated preference for weekly over daily dosing and monthly over weekly dosing of oral BPs.^{29,30} A preference for three-monthly IV ibandronate and six-monthly denosumab over weekly oral alendronate is evident in the real-world setting.^{31,32}

Risedronate once-a-month dosing

A study to evaluate the efficacy of risedronate 150mg once-a-month vs risedronate 5mg once daily (as per FDA registration requirements) over two years had a primary endpoint of mean change in lumbar spine BMD at 12 months from

baseline. Once-a-month risedronate was determined to be non-inferior to the daily regimen in respect of BMD and markers of bone turnover, with similar tolerability to daily dosing.^{33,34}

“Risedronate is the only drug that protects from non-vertebral and hip fracture with a monthly dosing option”

Conclusion

For Dr McClung, risedronate is the BP of choice for first-line therapy in the treatment of osteoporosis. The high potency of risedronate offers substantial protection from important fractures, with a rapid onset of action and persistent effect. Low

binding affinity of risedronate results in a relatively rapid off-effect with faster clearance after stopping, allowing for a short drug holiday while the patient is still protected from fracture. Risedronate is well-tolerated with convenient dosing options.

References

- Seeman E, Tsalamandris C, Bass S, *et al.* Present and future osteoporosis therapy. *Bone* 1995; **17**(2 Suppl): 23S-29S.
- McClung M, Harris ST, Miller PD, *et al.* Bisphosphonate therapy for osteoporosis: benefits, risks and drug holiday. *Am J Med* 2013; **126**(1): 13-20.
- Hough S, Amod A, Ascott-Evans BH, *et al.* South African Clinical Guideline for the Diagnosis and Management of Osteoporosis 2017. http://osteoporosis.org.za/wp-content/uploads/2017/06/NOFSA-Guidelines-2017_protected.pdf
- Russell RG, Watts NB, Ebetino FH, *et al.* Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporosis Int* 2008; **19**(6): 733-759.
- Chen T, Berenson J, Vescio R, *et al.* Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002; **42**(11): 1228-1236.
- Nancollas GH, Tang R, Phipps RJ, *et al.* Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. *Bone* 2006; **38**(5): 617-627.
- Conrad KA, Lee SM. Clodronate kinetics and dynamics. *Clin Pharmacol Ther* 1981; **30**(1): 114-120.
- Mitchell DY, Barr WH, Eusebio RA, *et al.* Risedronate pharmacokinetics and intra- and inter-subject variability upon single-dose intravenous and oral administration. *Pharm Res* 2001; **18**(2): 166-170.
- Cocquyt V, Kline WF, Gertz BJ, *et al.* Pharmacokinetics of intravenous alendronate. *J Clin Pharmacol* 1999; **39**(4): 385-393.
- Gertz BJ, Holland SD, Kline WF, *et al.* Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther* 1995; **58**(3): 288-298.
- Dunford JE, Thompson K, Coxon FP, *et al.* Structure-activity relationships for inhibition of farnesyl diphosphate synthase *in vitro* and inhibition of bone resorption *in vivo* by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001; **296**(2): 235-242.
- Watts NB, Chines A, Olszynski WP, *et al.* Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporosis Int* 2008; **19**(3): 365-372.
- Brown JE, Ellis SP, Lester JE, *et al.* Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. *Clin Cancer Res* 2007; **13**(18 Pt 1): 5406-5410.
- Black DM, Reid IR, Boonen S, *et al.* The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012; **27**(2): 243-254.
- Harris ST, Watts NB, Genant KD, *et al.* Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. *JAMA* 1999; **282**(14): 1344-1352.
- Black DM, Thompson DE, Bauer DC, *et al.* Fracture risk reduction with alendronate in women with osteoporosis:

EARN FREE CPD POINTS

Are you a member of Southern Africa's leading digital Continuing Professional Development website earning FREE CPD points with access to best practice content?

Only a few clicks and you can register to start earning today

Visit

www.denovomedia.com

For all Southern African healthcare professionals

Find us at



DeNovo Medica



@deNovoMedica

denovo
Medica

- the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab* 2000; **85**(11): 4118-4124.
17. Reginster J, Minne HW, Sorensen OH, *et al.* Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporosis Int* 2000; **11**(1): 83-91.
18. McClung MR, Geusens P, Miller PD, *et al.* Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001; **344**(5): 333-340.
19. Chestnut 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): 1241-1249.
20. Black DM, Delmas PD, Eastell R, *et al.* Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; **356**(18): 1809-1822.
21. Mellstrom DD, Sorensen OH, Goemaere S, *et al.* Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int* 2004; **75**(6): 462-468.
22. 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): 1535-1541.
23. Harrington JT, Ste-Marie LG, Brandi ML, *et al.* Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. *Calcif Tissue Int* 2004; **74**(2): 129-135.
24. Silverman SL, Watts NB, Delmas PD, *et al.* Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. *Osteoporosis Int* 2007; **18**(1): 25-34.
25. Rosen CJ, Hochberg MC, Bonnick SL, *et al.* Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 2005; **20**(1): 141-151.
26. Liberman UA, Weiss SR, Broll J, *et al.* Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995; **333**(22): 1437-1443.
27. Silverman SL, Gold DT and Cramer JA. Reduced fracture rates observed only in patients with proper persistence and compliance with bisphosphonate therapies. *South Med J* 2007; **100**(12): 1214-1218.
28. Cramer JA, Silverman S. Persistence with bisphosphonate treatment for osteoporosis: find the root of the problem. *Am J Med* 2006; **119**(4 Suppl 1): S12-S17.
29. Simon JA, Lewiecki EM, Smith ME, *et al.* Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. *Clin Ther* 2002; **24**(11): 1871-1886.
30. Reginster JY, Adami S, Lakatos P, *et al.* Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Ann Rheum Dis* 2006; **65**(5): 654-661.
31. Hadji P, Kauka A, Ziller M, *et al.* Effects of zoledronic acid on bone mineral density in premenopausal women receiving neoadjuvant or adjuvant therapies for HR+ breast cancer: the ProBONE II study. *Osteoporosis Int* 2014; **25**(4): 1369-1378.
32. Fremantle N, Satram-Hoang S, Tang ET, *et al.* Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporosis Int* 2012; **23**(1): 317-326.
33. Delmas PD, McClung MR, Zanchetta JR, *et al.* Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. *Bone* 2008; **42**(1): 36-42.
34. McClung MR, Zanchetta JR, Racewicz A, *et al.* Efficacy and safety of risedronate 150-mg once a month in the treatment of postmenopausal osteoporosis: 2-year data. *Osteoporosis Int* 2013; **24**(1): 293-299.

Disclaimer

The views and opinions expressed in the article are those of the presenters and do not necessarily reflect those of the publisher or its sponsor. In all clinical instances, medical practitioners are referred to the product insert documentation as approved by relevant control authorities.

Published by

deNovo Medica

Reg: 2012/216456/07

70 Arlington Street, Evergreen, Cape Town, 7550
Tel: (021) 976 0485 | info@denovomedia.com