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Anabolic treatment of osteoporosis in 2020

This report is based on a webinar presented by Dr Lipschitz on the 17th of November 2020.

Speaker

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Learning objectives

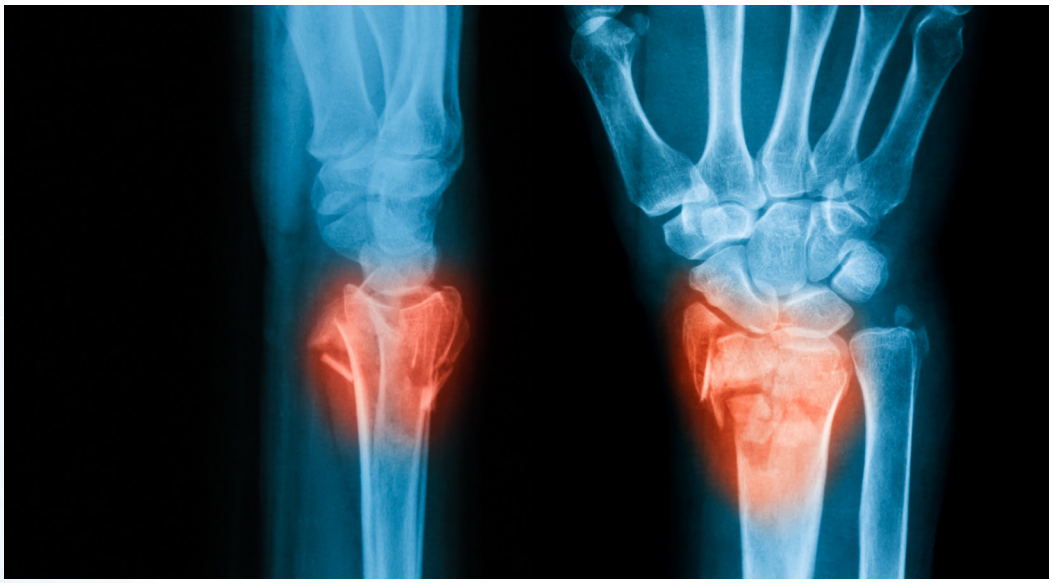
You will learn:

- Indications for differentiating fracture risk
- To identify and individualise long-term osteoporosis treatment strategies
- The criteria for use of anabolic therapy for the treatment of osteoporosis
- Evidence of the efficacy of teriparatide, and its use in patients with prior treatments for osteoporosis
- Efficacy data on the new anabolic agents, abaloparatide and romosozumab.

Introduction

The normal bone remodelling cycle is a very active process. Osteoclasts initiate resorption and over an approximately two-week period they resolve bone. Osteoblasts then fill the remodelled cavity so that on balance, the bone has been replaced with neither gain nor loss. In postmenopausal osteoporosis there is increased remodelling and drugs such as the bisphosphonates act to suppress this osteoclast activity. All anabolic agents work on modelling; they can stimulate osteoblast deposition of bone but they can also stimulate osteoclasts so that there is increased bone resorption. New anabolic agents actually uncouple bone remodelling, so that the osteoclast is suppressed and the osteoblast is stimulated (Figure 1).[1]

This review considers how anabolic agents work in terms of the objectives of osteoporosis therapy: to improve bone strength, to reduce the risk of fracture and to prevent rapid bone loss (less common).



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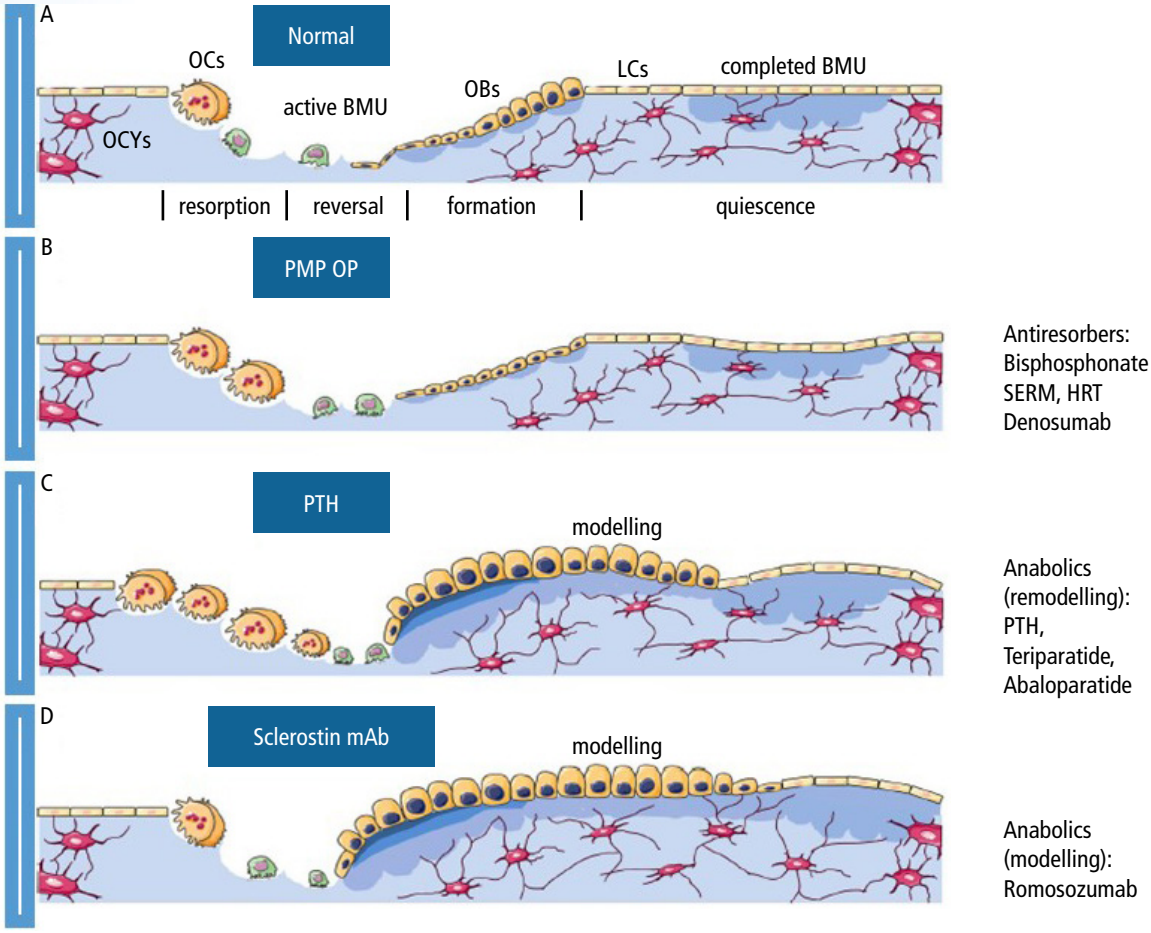

SERM: selective oestrogen receptor modulators; HRT: hormone replacement therapy; PTH: parathyroid hormone; PMP OP: postmenopausal osteoporosis; mAb: monoclonal antibody

Panel A: Osteoclasts resorbing bone with osteoblasts replacing bone to a similar amount as was present prior to the initiation of resorption. Osteocytes are a network of cells within the substance of bone that are responsible for detecting stress and interacting with bone cells.
Panel B: Overactive osteoclasts in postmenopausal osteoporosis and the inability of osteoblasts to fill in the resorption. Antiresorbers reduce the activity of osteoclasts and hence restore a more physiological balance.
Panel C: Remodelling-based anabolic therapies stimulate both osteoclasts and osteoblasts; 90% of the new bone formed is within the resorption space, the remaining 10% on adjacent bone. This effect on quiescent bone is called modelling.
Panel D: Effects of sclerostin monoclonal antibody anabolic therapy that suppresses osteoclasts and stimulates osteoblasts, both within the resorption space and on previously quiescent bone. Of the bone formation with sclerostin monoclonal antibodies, 90% is modelling-based.

Figure 1. Schematic of bone remodelling and modelling activities under physiological conditions, in osteoporosis and during anabolic treatment.[2,3]

Differentiating fracture risk

Recent guidelines differentiate fracture risk to help individualise and identify long-term treatment strategies (Figure 2).[2,3]

VERY HIGH RISK	HIGH RISK	LOW RISK
If one or more of the below is true	If any of the below is true	If all of the below are true
• Fx within past 12 months • Multiple Fxs • Fx while on OPTx • Fx while on medication harmful to bone • Very low T-score <–3.0 • FRAX probability >30% MOF, >4.5 hip	Age: postmenopausal • Prior Fx or • T-score ≤-2.5 or • T-score –1.0 to –2.5 and FRAX probability ≥20% or ≥3% hip	Age: postmenopausal • No prior Fx • T-score >–1.0 and FRAX probability <20% MOF and <3% hip

Figure 2. Indications for differentiating fracture risk[2,3]

Focus on very high-risk patients

Patients at very high risk for fractures are those who have had:

- A fracture within the past year
- Multiple fractures
- A fracture while on osteoporosis treatment
- A fracture while on medication harmful to bone (glucocorticoids or anti-cancer medications).

Based on this differentiation, most guidelines recommend anabolic agents as the preferred first line of treatment, followed by denosumab (Figure 3).[2,3] Despite the fact that clinicians know that patients who have recently had a fracture are likely to have another fracture, a care gap in osteoporosis remains problematic in that these patients are not being assessed and not being treated. The 'Capture the Fracture' initiative of the International Osteoporosis Foundation stresses the special role of all doctors coming into first contact with patients, be they general practitioners, orthopaedic surgeons, or physicians. A recent fracture is a red-light warning and these patients need to be investigated for secondary causes. An assessment of falls and increased efforts to reduce the risk of falling must be included when considering treatment options.

Despite the fact that clinicians know that patients who have recently had a fracture are likely to have another fracture, a care gap in osteoporosis remains problematic in that these patients are not being assessed and not being treated

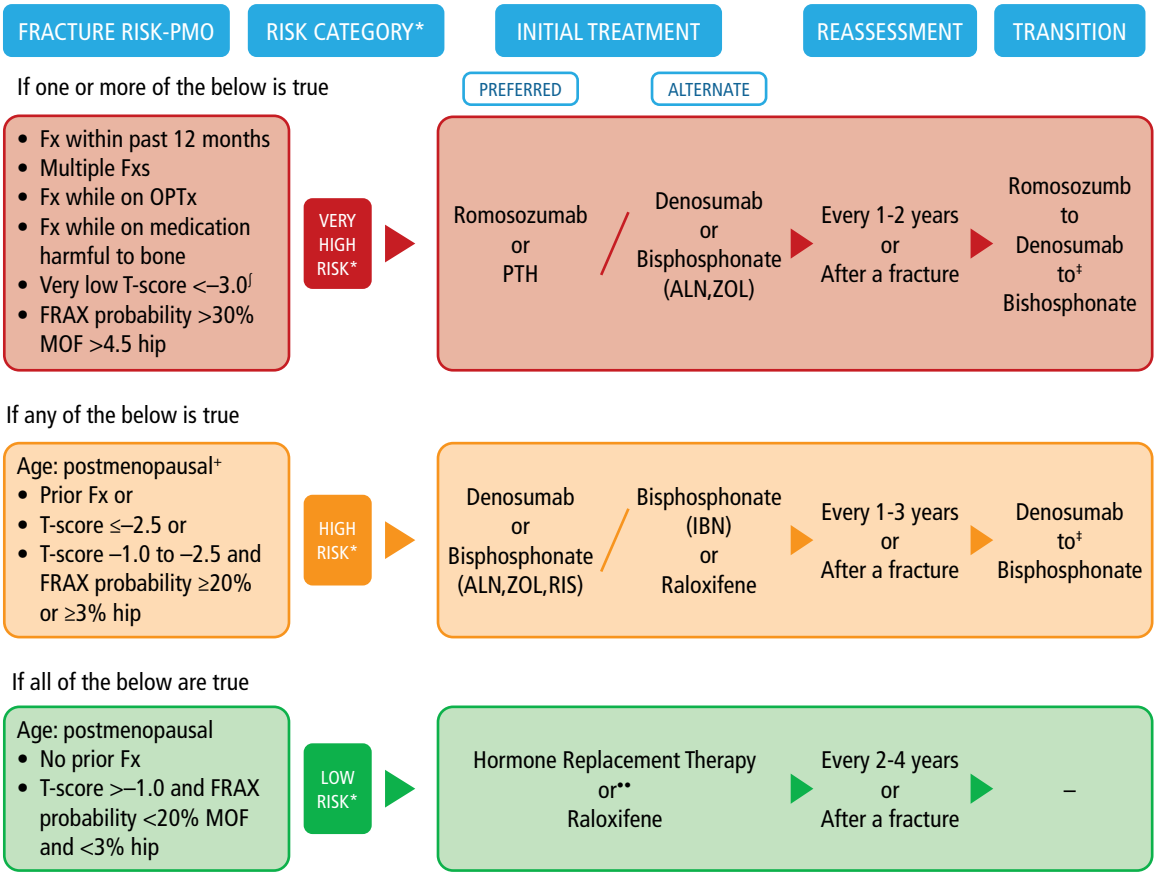

Figure 3. Fracture risk categorisation and treatment strategies

ALN, alendronate; BMD, bone mineral density; FRAX, Fracture Risk Assessment Tool; Fx, fracture; IBN, ibandronate; MOF, major osteoporotic fracture; OP, osteoporosis; PTH, parathyroid hormone analogues (abaloparatide, teriparatide); RIS, risedronate; Tx, treatment; ZOL, zoledronic acid
*Regional and local guidelines may override certain of these criteria based on differences in FRAX data and cost-effectiveness thresholds. [†]If FRAX not available, major determinants of risk should include age, BMD, fracture and medication harmful to bone. [‡]Applicable if decision is made to discontinue denosumab. [••]IOF-ESCEO defers to local guidelines for definitions of low risk but offers treatment guidance, whereas ENDO offers low risk definition but no treatment recommendation. [f]ENDO requires both risk factors to be met for very high risk categorisation.

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What are the criteria for use of anabolic therapy for osteoporosis treatment?

The National Osteoporosis Foundation of South Africa (NOFSA) guidelines, which are in need of updating, recommend that male or female patients ≥65 years, with a T-score of <-2.5, and ≥2 fragility fractures or multiple fragility fractures, satisfy criteria for anabolic therapy as a first-line treatment.

Anabolic therapy is recommended as second-line treatment when bone-specific treatment has failed, either because of a new fracture or because of unacceptable rates of bone loss following appropriate and compliant antiresorptive therapy. Anabolic therapy is also recommended for patients on chronic

glucocorticoid therapy because the risk of fracture is so high in these patients; this includes any patient taking the equivalent of ≥5mg prednisone daily if their T-score is <-3.5 without a fracture, or <-2.5 with one fracture.

Teriparatide

Teriparatide is a form of parathyroid hormone (PTH). Its use is paradoxical because if there is continuous release of PTH, as would occur in primary hyperparathyroidism, this results in activation of osteoclasts giving rise to massive bone resorption, osteoporosis and hypercalcaemia. In contrast, intermittent treatment with PTH does not result in the massive stimulation of the osteoclast, mediated by the receptor activator of NF-κB ligand (RANKL), but does stimulate the osteoblasts; although there is some increase in bone resorption, there is a greater increase in bone formation. This anabolic effect results in an increase in total bone volume, the periosteal diameter, and cortical thickness. The endocortical diameter decreases and that makes the bone stronger (Figure 4).[4]

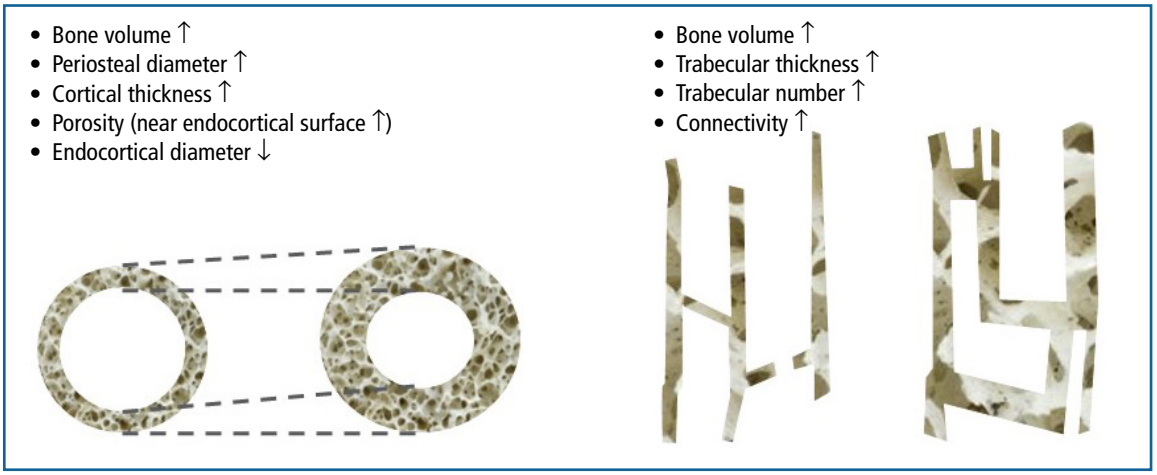


Figure 4. Changes in cortical geometry and trabecular architecture with PTH treatment[4]

The VERO study

Recently, the Vertebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) study comparing teriparatide to risedronate at 24 months of treatment included postmenopausal women over the age of 45 years, all of whom had severe osteoporosis by definition with either two moderately severe or one severe vertebral fracture. Importantly, patients who previously used osteoporosis medication were included in the study (>70% of cohort). The findings from this study are very pertinent (Figure 5), showing that teriparatide worked after bisphosphonate therapy and also in a smaller percentage of patients who were on glucocorticoid therapy.[5]

A subgroup analysis of the VERO study showed that in patients receiving teriparatide, there was an approximate 50% reduction in risk irrespective of the number of vertebral fractures that occurred. The benefit seems to be more robust in patients with severe fractures (Figure 6).

Side effects of teriparatide include extreme pain, which is twice as common, and dizziness, also about twice as common, compared to risedronate. Hypercalcaemia can occur, which in clinical practice is not really important, but rather a signal to stop the calcium supplement.

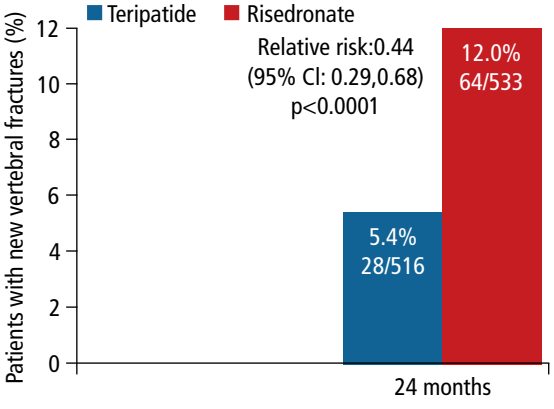
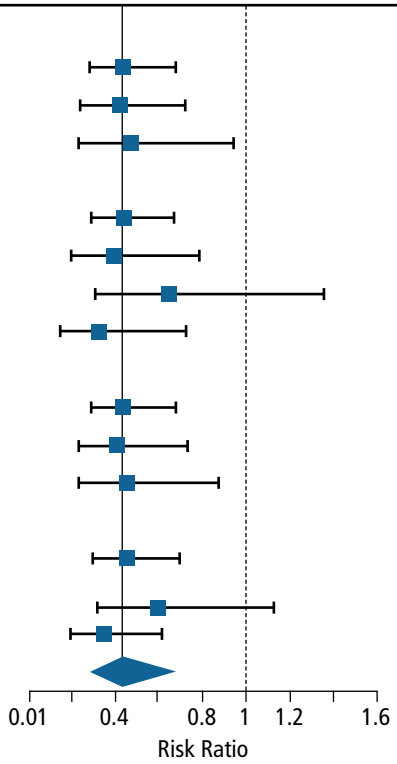


Figure 5. VERO primary endpoint: Incidence of new vertebral fractures - teriparatide vs risedronate in severe osteoporosis

Subgroup	Teriparatide n/N (%)	Risedronate n/N (%)	Interaction p-value	Risk Ratio [95% CI]
Lowest BMD T-score				
overall			0.86	0.45 [0.29, 0.69]
<–2.5	17/270 (6.3)	42/297 (14.1)		0.43 [0.25, 0.73]
≥–2.5	11/246 (4.5)	22/236 (9.3)		0.47 [0.23, 0.94]
Age (teriles), years				
overall			0.44	0.44 [0.29, 0.67]
<68.7	10/184 (5.4)	28/202 (13.9)		0.40 [0.20, 0.79]
≥68.7 and <76.8	10/152 (6.6)	18 /192 (9.4)		0.65 [0.31, 1.36]
≥ 76.8	8/180 (4.4)	18/139 (12.9)		0.33 [0.15, 0.73]
Recent bisphosponate use				
overall			0.85	0.44 [0.29, 0.68]
no	16/309 (5.2)	39/324 (12.0)		0.42 [0.24, 0.74]
yes	12/207 (5.8)	25/209 (12.0)		0.46 [0.24, 0.88]
Recent clinical VFx				
overall			0.22	0.46 [0.30, 0.68]
no	14/319 (4.4)	25/341 (7.3)		0.60 [0.32, 1.13]
yes	14/197 (7.1)	39 /192 (20.3)		0.35 [0.20, 0.62]
Overall VERO population	28/516 (5.4)	64/533 (12.0)		0.44 [0.29, 0.68]



Subgroup	Teriparatide n/N (%)	Risedronate n/N (%)	Interaction p-value	Risk Ratio [95% CI]
Prevalent VFx (number)				
overall			0.81	0.42 [0.27, 0.66]
1	7/180 (3.9)	16/191 (8.4)		0.46 [0.19, 1.08]
2	4/132 (3.0)	14/135 (10.4)		0.28 [0.09, 0.81]
3	5/86 (5.8)	10/82 (12.2)		0.50 [0.18, 1.38]
>3	12/118 (10.2)	24/125 (19.2)		0.49 [0.26, 0.93]
Prevalent VFx (severity)				
overall			0.18	0.26 [0.0.9, 0.73]
SQ2	1/59 (1.7)	7/57 (12.3)		0.14 [0.02, 1.07]
SQ3	27/457 (5.9)	57/476 (12.0)		0.48 [0.31, 0.74]
Prior on-vertebral fracture				
overall			0.13	0.39 [0.25, 0.61]
no	20/355 (5.6)	38/385 (9.9)		0.55 [0.33, 0.92]
yes	8/161 (5.0)	26/148 (17.6)		0.27 [0.13, 0.58
Glucocorticiod use				
overall			0.76	0.40 [0.20, 0.79]
no	25/466 (5.4)	57/491 (11.6)		0.45 [0.29, 0.70]
yes	3/50 (6.0)	7/42 (16.7)		0.36 [0.10, 1.30]
Prior osteoporosis drugs**				
overall			0.97	0.42 [0.19, 0.92]
BP	14/280 (5.0)	34/281 (12.1)		0.42 [0.23, 0.76]
non-BP	1/23 (4.3)	3/25 (12.0)		0.39 [0.04, 3.45]
treatment-naive	113/213 (6.1)	27/227 (11.9)		0.46 [0.25, 0.87]
Overall Vero population	28/516 (5.4)	64/533 (12.0)		0.44 [0.29, 0.68]

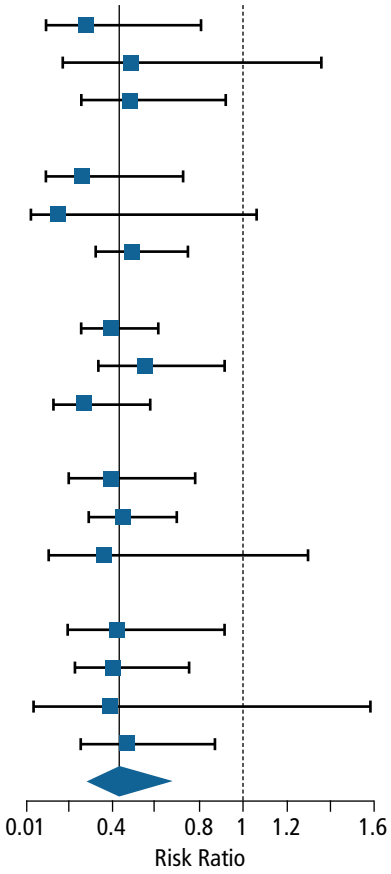


Figure 6. Risk ratio for new vertebral fractures

Teriparatide and bisphosphonates

It is important to note that previous bisphosphonate therapy does not preclude the use of teriparatide and certainly does not dampen the response to teriparatide in terms of fracture reduction. There are no data to support the combined use of teriparatide with a bisphosphonate or any other antiresorptive agent, although the VERO results confirm the efficacy of using teriparatide following a bisphosphonate in contrast to initial concerns. In the very high-risk patient, it is preferable to initiate treatment with teriparatide or an anabolic drug. It is essential, after using teriparatide or denosumab, to follow on with bisphosphonate therapy or all gains will otherwise be rapidly lost.

Who should not be treated with teriparatide?

There are certain patients who should not use teriparatide, particularly the paediatric population, those with Paget's disease, those who have undergone radiation, and those with bone metastases or a history of skeletal metastases, and metabolic bone diseases other than osteoporosis. Teriparatide should also not be used in patients with pre-existing hypercalcaemia or in the context of pregnancy and lactation.

New anabolic agents

The new anabolic agents are not yet available in South Africa.

In the very high-risk patient, it is preferable to initiate treatment with teriparatide or an anabolic drug

Abaloparatide

Abaloparatide is a novel analogue of human PTH-related protein (PTHrP). Increases in bone density are more robust with abaloparatide than with teriparatide as demonstrated in the pivotal Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) study in which both agents were compared to placebo. Considering that the cohort was of postmenopausal women over the age of 65 years with extremely low T-scores and perhaps fractures, the ethical use of placebo is questionable. After 18 months of treatment, the placebo group and the abaloparatide group were continued on alendronate.

New vertebral fractures were reduced by 86% in the group receiving abaloparatide and by 80% in the teriparatide group, with no significant difference between the two. Non-vertebral fracture reduction was significant with abaloparatide and not significant with teriparatide, contrary to data from the VERO study that show a significant reduction with teriparatide. Once again, there were no significant differences between the two drugs in terms of non-vertebral fracture. Hypercalcaemia is half as likely to occur in abaloparatide-treated patients compared to teriparatide-treated patients. Abaloparatide has been registered for use in the USA but not in Europe.

Romosozumab

Sclerostin is a protein released by the osteocytes, generally in response to oestrogen deficiency, lack of skeletal loading, and glucocorticoids. Sclerostin binds to its inhibitor and this stimulates the osteoclast and suppresses the osteoblast. Romosozumab is monoclonal antibody against sclerostin, which blocks the stimulation of the osteoclast to decrease bone resorption and stimulates the activation of the osteoblast to increase bone formation (Figure 7); bone formation markers increase and bone resorption markers decrease. Romosozumab is given as an injection every two weeks (Table 1).

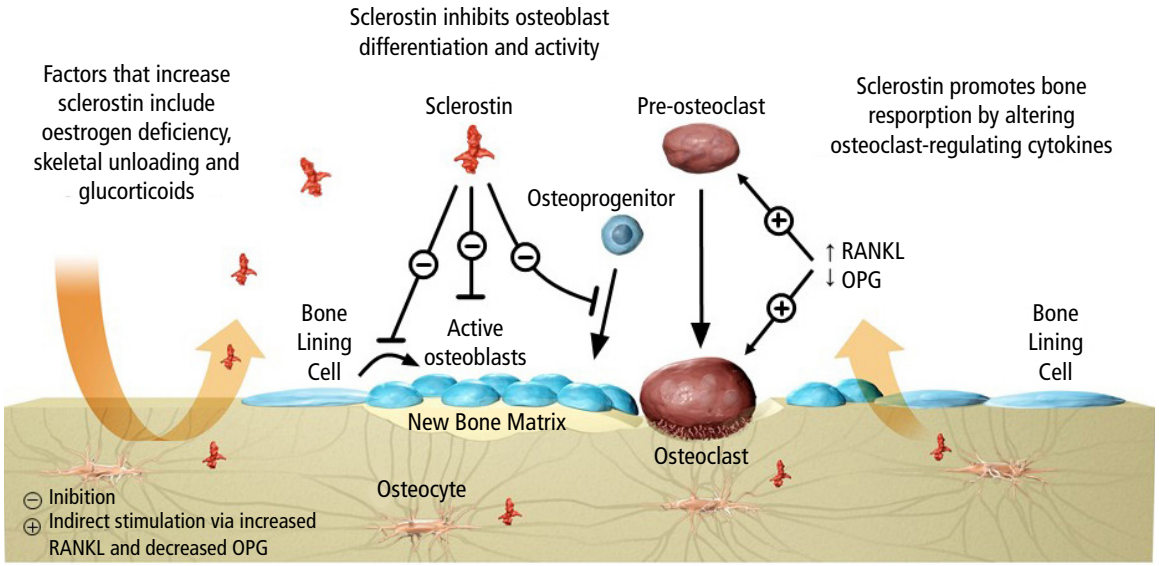


Figure 7. Sclerostin, primarily secreted by osteocytes, inhibits bone formation and increases bone resorption[6-8]

Table 1. Romosozumab summary

- Sclerostin was discovered when investigating the cause of high bone mass in individuals with genetic sclerostin deficiency (sclerosteosis)[9-11]
- Sclerostin inhibits bone formation and increases bone resorption[10,12]
- Romosozumab is a bone-forming agent and sclerostin antibody that binds and inhibits sclerostin[13]
- Romosozumab exerts a dual effect on bone, increasing bone formation and decreasing bone resorption.[14]

The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) study[15] compared romosozumab with alendronate in over 4 000 patients, including South Africans, who were postmenopausal women aged 55-90 years with a low bone mineral density (BMD) and fractures (either one moderate or one severe fracture, or two mild vertebral fractures), or who had a better BMD with more than two moderate and one severe vertebral fracture or a hip fracture. Treated with either romosozumab or alendronate for 12 months, all patients received open-label alendronate for the following two years.

The incidence of new vertebral fractures at 12 and 24 months is depicted in Figure 8. With romosozumab, non-vertebral fractures were reduced by approximately 20% and hip fractures were reduced by approximately 40% (Figure 9). The incidence of cardiac ischaemic events was significantly higher in the romosozumab group.

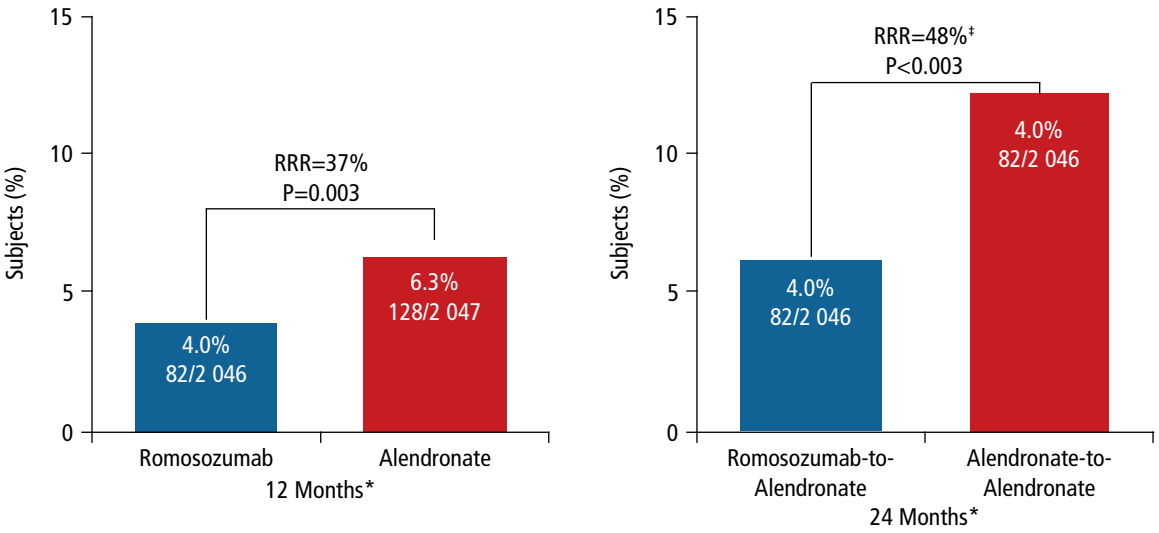


Figure 8. ARCH study: Incidence of new vertebral fracture over 24 months[15]

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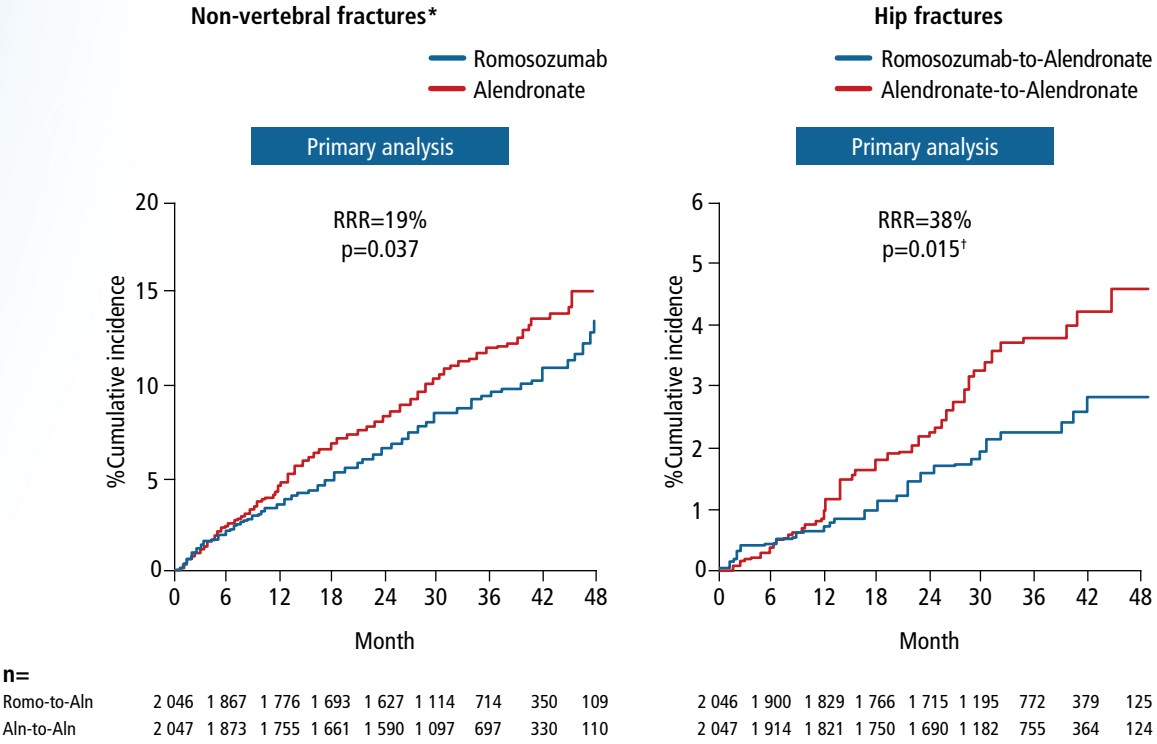

n=									
Romo-to-Aln	2 046	1 867	1 776	1 693	1 627	1 114	714	350	109
Aln-to-Aln	2 047	1 873	1 755	1 661	1 590	1 097	697	330	110

Romo-to-Aln	2 046	1 900	1 829	1 766	1 715	1 195	772	379	125
Aln-to-Aln	2 047	1 914	1 821	1 750	1 690	1 182	755	364	124

Aln, alendronate; Romo, romosozumab; RRR, relative risk reduction
*Secondary endpoint. †Not adjusted for multiplicity. n=number of subjects at risk for event at time of interest.

Figure 9. ARCH study: Incidence of non-vertebral and hip fractures at primary analysis[15]

Key learnings

- Substantially reducing very high risk of fracture will likely require a combination of strategies to strengthen the skeleton and reduce the frequency and effects of falls by increasing muscle strength and balance
- There is very strong evidence that pharmacological therapy reduces fracture risk in patients with a very low BMD or after a recent fracture
- Anabolic therapy appears to be more effective in reducing fracture risk
- Anabolic drugs can be used first-line in high-risk patients or introduced in patients on antiresorptive therapy when indicated (i.e. where there is treatment failure)
- The risk of the disease is far greater than the risk of the drug:
  - Choose the most appropriate agent
  - Continue therapy for as long as is necessary; always follow anabolic therapy with antiresorptive therapy
  - Osteoporosis is a chronic disease/risk, so long-term treatment is required.

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References

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1. Baron R, Hesse E. Update on bone anabolics in osteoporosis treatment: Rationale, current status, and perspectives. *J Clin Endocrinol Metab* 2012; **97**: 311-325.
2. Camacho PM, Petak SM, Diab DL, *et al*. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2020 update. *Endocr Pract* 2020; **26**(Suppl 1): 1-46.
3. Shoback D, Rosen CJ, Black DM, *et al*. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society guideline update. *J Clin Endocrinol Metab* 2019; **104**(5): 1595-1622.
4. Allen MR, Burr DB. Parathyroid hormone and bone biomechanics. *Clin Rev Bone Miner Metab* 2006; **4**: 259-268.
5. Geusens P, Marin F, Kendler DL, *et al*. Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: The VERO Trial. *J Bone Miner Res* 2018; **33**(5): 783-794.
6. Wijenayaka AR, Kogawa M, Lim HP, *et al*. Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. *PLoS One* 2011; **6**(10): e25900.
7. Taylor S, Ominsky MS, Hu R, *et al*. Time-dependent cellular and transcriptional changes in the osteoblast lineage associated with sclerostin antibody treatment in ovariectomized rats. *Bone* 2016; **84**: 148-159.
8. Nioi P, Taylor S, Hu R, *et al.* Transcriptional profiling of laser capture microdissected subpopulations of the osteoblast lineage provides insight Into the early response to sclerostin antibody in rats. *J Bone Miner Res* 2015; **30**(8): 1457-1467.
9. Brunkow ME, Gardner JC, Van Ness J, *et al*. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet* 2001; **68**: 577-589.
10. Gardner JC, Van Bezooijen RL, Mervis B, *et al*. Bone mineral density in sclerosteosis; affected individuals and gene carriers. *J Clin Endocrinol Metab* 2005; **90**: 6392-6395.
11. Li X, Ominsky MS, Niu QT, *et al*. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. *J Bone Miner Res* 2008; **23**: 860-869.
12. Winkler DG, Sutherland MK, Geoghegan JC, *et al*. Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. *EMBO J* 2003; **22**: 6267-6276.
13. McClung MR, Grauer A, Boonen S, *et al*. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014; **370**: 412-420.
14. Cosman F, Crittenden DB, Adachi JD, *et al*. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016; **375**: 1532-1543.
15. Saag KG, Petersen J, Brandi ML, *et al*. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; **377**: 1417-1427.

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