Official Journal of the Irish Medical Organisation

Ir Med J; March 2022; Vol 115; No. 3; P567

March 16th, 2022

Treatment Challenges When Stopping Denosumab

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Abstract

Introduction

Denosumab is commonly used to treat osteoporosis. However, discontinuation results in rebound bone loss and increased vertebral fracture risk. We report a clinical case series, illustrating the dilemma in deciding the best treatment should denosumab be stopped.

Cases

In eight patients aged 56-89 years, zolendronic acid after stopping denosumab resulted in BTM rises and BMD decline.

- In a 68-year-old, two years of oral bisphosphonate after three years of denosumab resulted in elevated bone turnover markers (BTM) and decline in bone mineral density (BMD), necessitating a switch to zoledronic acid.
- In a 79-year-old, two annual doses of zolendronic acid after three years of denosumab failed to suppress high BTM, with BMD dropping and denosumab being restarted.
- In a 60-year-old, on stopping denosumab after 10 years of oral bisphosphonate, BMD remained stable despite no further therapy.

Conclusion

Drug holidays are not an option with denosumab, with a risk of bone loss even on transitioning to bisphosphonates. Risk is greater with longer duration of treatment[6] and may be mitigated by prior bisphosphonate use. Standard dose zoledronic acid does not prevent bone loss in a significant proportion of patients. BTM may help in monitoring treatment and need for further bisphosphonates.

Introduction

Osteoporosis is prevalent in Ireland where it affects an estimated 300,000 people[1]. Denosumab is the most potent antiresorptive used in the treatment of osteoporosis and is commonly prescribed by Irish general practitioners (GPs)[2]. It is a monoclonal antibody that blocks the action of the RANKL, resulting in a reduction in the number and activity of osteoclasts and profound inhibition of bone resorption[3]. While bisphosphonates are the mainstay of therapy, denosumab can be administered every six months as a subcutaneous injection and is often favoured by doctors due to better compliance and avoidance of gastro-intestinal malabsorption or side-effects[4]. It can also be used in renal impairment (eGFR <30 ml/min) where bisphosphonates are contraindicated.[3]

Denosumab compares favourably with bisphosphonates, with similar anti-fracture efficacy to zoledronic acid[5]. In the FREEDOM trial (n=5928)[3], which included osteoporotic patients aged 60-90 years, treatment with denosumab for three years resulted in a reduction by 68% in vertebral, 40% in hip and 27% in non-vertebral fractures. Furthermore, anti-fracture efficacy was maintained for 10 years, with sustained rises in BMD[3].

The paradigm of drug holidays does not apply to denosumab with its anti-resorptive effect wearing off after about six months, in contrast to bisphosphonates which have a long skeletal half-life[6]. Indeed, the earliest study of denosumab discontinuation in a phase two randomised controlled trial of 28 patients identified a rapid rise in bone turnover and loss of BMD at the hip and spine[7]. This is now known to occur within one month of missing a dose[8] and loss of all treatment gains has been reported after 12-24 months[7].

A post-hoc analysis of the FREEDOM and its extension trial found that vertebral fracture risk on stopping denosumab increased five-fold and was equivalent to those on placebo[9]. Concerningly, early and multiple vertebral fractures were identified, consistent with numerous case reports[10]. Vertebral fracture risk likely results from a greater rise in bone turnover in the spine, which has more trabecular bone compared with other sites. However, studies also show a decline in hip BMD and increased risk of non-vertebral fractures[10].

Vertebral fracture risk after stopping denosumab is greater in those with prior vertebral fracture[9], lower spine BMD[11] and with longer duration of use[8], though it is also reported after only two treatment doses[10]. BTM in the rebound period have been found to predict bone loss at the lumbar spine[12] as well as vertebral and multiple vertebral fractures[13]. Longer therapy is also associated with attenuation of its antiresorptive effect, which appears to predict rebound bone loss[8]. A counter-regulatory mechanism and activation of pre-osteoclasts after therapy cessation could be a factor[8,10]. Consistent with this hypothesis is the finding that bone turnover on stopping denosumab can be higher than at baseline, before treatment initiation[10,11]. Some case reports suggest that prior bisphosphonate use before denosumab therapy may lower fracture risk which could be explained by their residual anti-resorptive effects[16,10.]

Current evidence has established that drug holidays are not compatible with denosumab. Indeed, recent guidelines recommend against drug holidays and advise alternative treatments should denosumab be stopped[12]. However, efficacy and safety of denosumab beyond ten years is lacking[3] and the optimal treatment after stopping is unclear[12]. In fact, there is a paucity of studies and only two randomised trials (n<120)[16,14] that address bisphosphonate use in this context, though none provide definitive answers. We report on clinical cases at our Bone Health Unit where patients were transitioned from denosumab therapy and discuss treatment challenges. We also detail the change in BMD and BTM in eight patients switched from denosumab to intravenous bisphosphonates (see table 4).

*All Dual Energy X-ray Absorptiometry (DXA) scans were performed using a Hologic Horizon A scanner. BTM were non-fasting and taken in the morning. C-telopeptide (CTX) was measured using a Roche assay with results in ng/ml. The range for CTX are post-menopausal (0.016-1.008ng/ml) and pre-menopausal (0.016-0.573ng/ml). CTX results less than the mean pre-menopausal range (i.e. <0.295ng/ml) or a reduction of 25% from baseline are indicative of a treatment response[15]. Estimated glomerular filtration rate (eGFR) was calculated with the MDRD formula, using serum creatinine assessed at the time of BTM measurement.

*Hyperparathyroidsm and myeloma were excluded in all patients with BMD loss on stopping denosumab and no new medications that cause bone loss were started.

Case 1

A 68-year-old lady who was on long-term treatment for osteoporosis was referred to our clinic. Therapy included strontium ranelate for 10 years (started in 2005 after a DXA diagnosis of osteoporosis) followed by denosumab for three years. Medical history included hypertension, hyperlipidaemia and monoclonal gammopathy of undetermined significance. In 2017, after three years of denosumab, a DXA revealed a T- score of -2.1 in spine and -1.7 in total hip and she was switched to alendronate (70 mg weekly), starting six months after her last injection. Despite two years of oral bisphosphonate, bone density in 2019 declined significantly at the spine (T- score drop to -3.1) and total hip (T- score drop to -2.1) with a concomitant rise in CTX to 0.28, measured 21 months after her last dose of denosumab (see table 1). Her therapy was then switched to zoledronic acid. In summary, there was a failure of oral bisphosphonates to prevent BMD loss.

Table 1: Change in BMD (T- scores) and BTM on transitioning from denosumab to an oral bisphosphonate.

Year	2015 -2017		2017- 2019	2020
Treatment	Denosumab		Alendronate	Zoledronate
eGFR (ml/min)	77		79	70
CTX (ng/ml)	0.05		0.28	0.10
Spine T score (BMD g/cm^2)	-2.4 (0.78)	-2.1 (0.82)	-3.1 (0.71)	-
Total hip T score (BMD g/cm^2)	-2.0 (0.70)	-1.7 (0.73)	-2.1 (0.69)	-
Femoral neck T score	-2.8 (0.54)	-2.6 (0.56)	-2.5 (0.57)	-

Case 2

A 79-year-old lady with severe osteoporosis and multiple vertebral fractures was started on denosumab in 2016, after prior treatment with teriparatide and strontium. Medical history included hypertension and hyperlipidaemia. In mid-2017, her treatment was switched to intravenous zoledronate, administered six months after her last dose of denosumab. Despite two annual infusions of zoledronate (4mg) BTM remained high and T- scores declined substantially from -2.0 at the spine and -2.2 at the total hip in 2016, to -3.1 and -2.6 respectively in 2019. (See table 2). Denosumab was re-started, to be continued indefinitely. In summary, there was a failure of zolendronic acid to prevent BMD loss.

Table 2: Change in BMD (T- scores) and BTM on transitioning from denosumab to zoledronic acid.

Year	2013-2014	2014-2017	2017	2018	2019
Treatment	Teriparatide	Denosumab	Zoledronic acid		
eGFR (ml/min)	70	75		78	70
CTX (ng/ml)	0.44	0.06	-	0.73	0.40
Spine T score (BMD, g/cm^2)	-3.9 (0.62)	-2.0 (0.83)	-	-	-3.1 (0.71)
Total hip T score (BMD, g/cm^2)	-2.4 (0.67)	-2.2 (0.68)	-	-	-2.6 (0.62)
Femoral neck T score (BMD, g/cm^2)	-2.8 (0.54)	-2.2 (0.61)	-	-	-2.3 (0.59)

Case 3

A 60-year-old lady with osteoporosis and a history of bilateral wrist fractures attended our clinic for guidance on further management. Background history included hypothyroidism, depression and mild gastro-oesophageal reflux disease. Treatment for osteoporosis included risedronate for ten years until 2016, followed by denosumab for 18 months which the patient stopped in 2017 due to musculoskeletal pain. Despite no follow up treatments, BMD remained relatively stable with only modest change in BTM (see table 3). In summary, prior bisphopshonate use was associated with stable BMD.

Table 3: Change in BMD (T- scores) and BTM on stopping denosumab with no follow up therapy.

Year	2006-2016	2016-2017	2017	2019
Treatment	Risedronate	Denosumab	No treatment	
eGFR (ml/min)	79	83	84	80
CTX (ng/ml)	0.23	0.05	0.35	0.27
Spine T score (BMD, g/cm^2)	-2.1 (0.82)	-1.7 (0.86)	-	-1.9 (0.84)
Total hip T score (BMD, g/cm^2)	-2.3 (0.67)	-2.0 (0.70)	-	-1.9 (0.71)
Femoral neck T score (BMD, g/cm^2)	-2.7 (0.55)	-2.6 (0.56)	-	-2.7 (0.55)

Table 4: Clinical case series: change in BMD and BTM on transitioning from denosumab to zoledronic acid.

Change in BMD and BTM on transitioning from denosumab to zoledronic acid									
Age (yrs)	Sex	Denosumab therapy (yrs)	Duration of zoledronic acid (yrs)	Time to therapy[b] (yrs)	CTX 1	CTX 2	BMD change *%		Time to DXA[c] (yrs)
							Spine	Total hip	
56	F	3[a]	3	7	0.02	0.37	-3.9%	-1.8%	1.3
69	F	3[a]	2	6	0.09	0.38	-9.6%	-6.5%	1.8
85	F	3.5	3	6	0.08	0.73	-14.3%	-7.7%	2.3
58	F	4[a]	3	8	0.04	0.44	-11.4%	-6.9%	1.5
79	M	4 [a]	4	7	0.08	0.47	-8.5%	-2.6%	2.8
79	F	5[a]	3	9	0.04	0.48	-15.6%	-5.7%	1.9
89	F	5.5	2	6	0.07	0.63	-13.9%	-7.8%	2.6
64	F	6	1	8	0.05	0.71	-12.5%	-8.0%	1.5

F = female, M = male, CTX1 = CTX on denosumab therapy, CTX2 = CTX on bisphosphonate therapy.

[a] Oral bisphosphonate therapy prior to starting denosumab

[b] Time in months since the last denosumab injection

[c] Interval between final dose of denosumab and follow-up DXA

Discussion

To date, there are only two randomised trials of zoledronic post denosumab. Anastasilkis e*t al*[16] found that one dose of zoledronic acid (5mg) in 57 patients (on denosumab for 2.0-2.4 years) resulted in stable BMD at 24 months. In contrast, Sølling *et al*[8] looked at 61 patients who received zoledronate (5 mg) at either six or nine months after their last denosumab injection or when their BTM began to rise. Duration of denosumab therapy was longer (mean 4.6 years) and patients were older. However, regardless of regimen there were rises in BTM and loss in BMD in 30-47% at spine and in 5-25% at the hip. While BMD was similar at 12 months in all three regimens, there was early bone loss and two new vertebral fractures in patients receiving zoledronic acid at nine months and 50% who were treated at six months had a major rise in BTM. Overall, mean drop in T score was 0.25 to 0.50[8] and nearly half of patients required retreatment due to elevated BTM in the first year. However, in 58 patients with follow up at two years, BMD was stable between 12-24 months.[14]

Our cases also emphasise the dilemma posed in deciding on the most appropriate treatment post denosumab. We identified that even in patients with a short duration of denosumab therapy (two to three years), neither standard dose oral nor intravenous bisphosphonates were effective at preventing loss in BMD. A sustained rise in BTM after three years of zoledronic acid was identified in one patient (case 2), who was subsequently restarted on denosumab. Furthermore, in all patients there was a rise in BTM despite bisphosphonate treatment. BTM were non fasting which is a limitation, and we also acknowledge that the correlation between BTM and bone loss in individuals is only moderate.

However, changes in BTM may be more predictive.[15] Two patients with significant bone loss on transitioning to bisphosphonates had prior treatment with strontium, which has predominantly antiresorptive effects and lowers CTX. However, inhibitory effects on bone resorption appear to wear off early after strontium discontinuation which could be a factor.[17] Our cases also suggest that prior bisphosphonate therapy and shorter duration of denosumab use may reduce the extent of bone loss. Indeed, in one patient on denosumab therapy less than two years, prior long-term bisphosphonate use (10 years) appeared to mitigate against any major rise in BTM and bone loss.

Studies on bisphosphonate use post denosumab are limited and have varied by timing and dose of treatment, as well as duration of prior denosumab therapy. One study of female patients (n=115)[18], identified that BMD was maintained in most patients treated with oral alendronate for one year after 12 months of denosumab. However, loss of BMD occurred in 21.7% in the femoral neck and 15.9% in the spine. Treatment of five patients with risedronate for one year after two years of denosumab also resulted in a partial (61%) preservation of BMD[19].

Most studies have used zoledronic acid after stopping denosumab though apart from the two aforementioned trials, there is limited observational data. Horne et al[20] found that in 11 females, one dose of zoledronic acid (5mg) after two years of denosumab maintained 87% of BMD gains at the hip and 73% at the spine at 12 months. However, further BMD loss was identified at two years with BMD retention dropping to 59.0% at the spine and 71.9% at the hip[20]. One dose of zoledronic acid also failed to preserve BMD gains in six women who had received denosumab for seven years[21] and in 22 females who had two years of denosumab (33% loss of spine BMD)[22]. Furthermore, only 50-70% of BMD gains were maintained at one year in 120 women who received a single dose of zoledronic acid (5 mg) six months after their last denosumab injection[23]. However, patients were only on denosumab for a mean of 2.5 years and vertebral fractures occurred with an incidence of 1.1 per 100 patient years.

Consistent with our cases, studies show that standard treatment with bisphosphonates after denosumab does not prevent bone loss in a significant proportion of patients. Duration of denosumab therapy appears to be an important determinant of bisphosphonate response, with failure to maintain BMD more likely when treatment is given for more than two years[8,12]. Oral bisphosphonates might be cautiously considered in those with a short duration of therapy (<2.0- 2.5 years) and with lower risk of rebound fracture (T score >-2.5 and no prior vertebral fractures). However, such patients could be monitored with BTM (initially at three months) to assess treatment response and the need to switch to more potent therapy such as zoledronic acid, an approach suggested by Anastasilakis et al.[10] and by the European Calcified Tissue Society in a recent position statement.[12] In practise, patients are often on denosumab due to contraindications, intolerance or failure of oral bisphosphonates. In these patients and those at higher risk of bone loss and fracture (i.e. prior vertebral fracture, denosumab therapy for more than two to three years), treatment with zoledronic acid within seven months of the last denosumab injection may be the best option. Close monitoring with BTM will identify patients who may benefit from additional treatment with zoledronic acid [8,10,12]. Such a regimen still constitutes a much lower dose than given to some cancer patients who are free of skeletal metastases[24].

In patients with a life expectancy of less than ten years, it seems reasonable to remain on denosumab indefinitely. While data on safety and efficacy beyond this timeframe is lacking, the decision for longer treatment needs to be carefully balanced against the risk of fracture on transitioning to bisphosphonates (e.g. low T scores, recent fractures, falls). Reassuringly, atypical fracture risk is lower with denosumab than bisphosphonates[3].

Finally, despite bisphosphonates being considered a first line treatment, studies point to a high rate of denosumab use in 'treatment naive patients'. In a sample of 1146 Irish patients prescribed denosumab by GPs between 2012-2017, over half had no prior bone therapy[2]. There was also a persistence rate in Irish patients of only 53.8% at two years, similar to the results of a large systematic review.[2] However, only 6% who stopped were started on alternative treatments[2], albeit at a time when the effects of rebound bone loss were less known. The Covid-19 pandemic has also resulted in delays in denosumab administration, with guidelines recommending the option of oral bisphosphonates as a 'stop gap'[25]. This may only partly mitigate against bone loss, though there is rapid recovery of BMD on restarting denosumab[2].

In conclusion, doctors and patients need to be aware that drug holidays are not an option with denosumab. If starting therapy, patients should be counselled on the risk of bone loss if later transitioning to bisphosphonates, given that no optimal treatment regime is established. For patients on denosumab for more than two and a half years, follow up treatment with zoledronic acid may be the best option.[12] BTM may aid in determining an individualised approach to care in patients where denosumab is stopped. Denosumab therapy beyond ten years may also be the best option for some patients, with due vigilance for potential adverse effects. More studies are needed to guide future management of patients treated with denosumab.

Declaration of Conflicts of Interest:
The authors confirm that they have no conflicts of interest to declare.

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