

WHICH IS THE BEST ANTIRESORPTIVE TREATMENT AFTER FINISHING TERIPARATIDE?

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Abstract Anabolic drugs are the treatment of choice for osteoporotic patients with very high risk of fractures. Post anabolic treatment with an antiresorptive drug maintains the bone mineral density (BMD) gained. The recommendations regarding the ideal antiresorptive drug are not precise. The aim of this paper is to compare the usefulness of zoledronate and denosumab in a group of 28 women with very high risk of fractures. All of them completed at least one year of treatment with teriparatide and latter 14 received zoledronate and 14 denosumab for another year. We retrospectively review their biochemical and densitometric changes. Both treatment groups experienced a reduction in bone turnover markers of the same magnitude at the end of the second year. In Lumbar Spine BMD increase of $3.96 \pm 8.56\%$ Median (Me) 2.54 $p = 0.21$ in zoledronate group and $3.55 \pm 5.36\%$ (Me 5.14) $p = 0.07$ in denosumab group. Femoral Neck BMD changed $-0.09 \pm 6.50\%$ (Me 0.29) $p = 0.85$ in zoledronate group, and $-3.41 \pm 5.08\%$ (Me 5.35) $p = 0.59$ in denosumab group, with no difference between both groups. In Total Hip BMD an increase of $0.55 \pm 4.20\%$ (Me 0.43) $p = 0.70$ in zoledronate group, and $4.53 \pm 5.13\%$ (Me 0.64) $p = 0.04$ with denosumab. We conclude that both antiresorptive treatments have a similar effect in biochemical markers after one year of treatment. BMD increase significantly in total hip and changed with a trend toward in lumbar spine with denosumab, but without differences between both groups of treatment.

Key words: post teriparatide treatment, sequential osteoporosis treatment, very high risk of fracture

Resumen ¿Cuál es el mejor tratamiento antirresortivo luego de terminar con teriparatide? Los anabólicos son el tratamiento de elección en la osteoporosis con muy alto riesgo de fracturas. Después del tratamiento anabólico un fármaco antirresortivo mantiene la densidad mineral ósea (DMO) ganada. Las recomendaciones sobre el fármaco antirresortivo ideal no son precisas. El objetivo de este trabajo es comparar la utilidad de zoledronato y denosumab en un grupo de 28 mujeres con muy alto riesgo de fracturas. Todas ellas completaron al menos un año de tratamiento con teriparatide y luego 14 recibieron zoledronato y 14 denosumab durante un año. Revisamos retrospectivamente sus cambios bioquímicos y densitométricos. Ambos grupos de tratamiento experimentaron una reducción de los marcadores de recambio óseo de la misma magnitud al final del segundo año. En columna lumbar la DMO aumentó $3.96 \pm 8.56\%$ Mediana (Me) 2.54, $p = 0.21$ en el grupo zoledronato y $3.55 \pm 5.36\%$ (Me 5.14) $p = 0.07$ en el grupo denosumab. La DMO del cuello femoral cambió $-0.09 \pm 6.50\%$ (Me 0.29) $p = 0.85$ en el grupo zoledronato y $-3.41 \pm 5.08\%$ (Me 5.35) $p = 0.59$ en el grupo de denosumab, sin diferencias entre ambos grupos. En la Cadera Total la DMO aumentó $0.55 \pm 4.20\%$ (Me 0.43) $p = 0.70$ con zoledronato y $4.53 \pm 5.13\%$ (Me 0.64) $p = 0.04$ con denosumab. Concluimos que ambos tratamientos antirresortivos tuvieron un efecto similar en los marcadores bioquímicos después de un año de tratamiento. La DMO aumentó significativamente en la cadera total y mostró una tendencia similar en columna lumbar con denosumab, sin diferencias entre ambos tratamientos.

Palabras clave: tratamiento pos teriparatida, tratamiento secuencial de la osteoporosis, muy alto riesgo de fractura.

KEY POINTS

- Anabolics drugs are the treatment of choice for osteoporotic patients with very high risk of fracture. Post anabolic treatment with an antiresorptive drug maintains bone mineral density gain.
- The recommendations regarding the ideal antiresorptive drug are not precise in the international guidelines
- Both denosumab and zoledronate appeared to be useful alternatives after completing a course of treatment with teriparatide.

The treatment of patients with severe osteoporosis, characterized by very low bone mass, recent fractures or very high risk of fractures represents the most difficult challenge for doctors who treat patients with osteoporosis^{1,2}. These severe forms require long-term treatments, and therefore, the therapeutic approach should be based on a sequential strategy, taking into account the increasing life expectancy of the population^{3,4}. The success of the treatment will depend on the right sequencing of the available drugs in the long term.

International guidelines recommend the use of anabolic drugs as the first option in the treatment of the most severe forms of osteoporosis^{1,2} because they reduce the risk of vertebral and nonvertebral fractures more rapidly and to a greater extent than antiresorptive drugs⁵.

Once the anabolic treatment is finished, the use of an antiresorptive drug has demonstrated to be useful in maintaining the densitometric gain, making it possible to continue the acquisition of bone mass and to lower the risk of fracture^{6,7}. Nevertheless, the recommendations are not precise enough regarding the ideal resorptive drug to be used in this setting^{1,2}. Some publications show that oral bisphosphonates^{8,9}, raloxifen¹⁰ and denosumab maintain the gain obtained with teriparatide¹¹; however, none compares them with each other. The only study that compares two antiresorptives after 24 months on teriparatide shows that with denosumab it is possible to obtain a greater densitometric gain in the lumbar spine, femoral neck and total hip, when compared to alendronate. The difference in the results seems to be due to a greater antiresorptive power, assessed according to the higher degree of inhibition of bone turnover markers⁷.

Our aim was to compare bone mineral density (BMD) changes measured by dual X-ray absorptiometry (DXA) and changes in bone turnover markers, between postmenopausal women with osteoporosis previously treated for at least one year with teriparatide and then for one year with zoledronate or denosumab.

Materials and methods

This is a retrospective study that included osteoporotic postmenopausal women treated in our institution between June 2012 and November 2019. These patients had completed at least twelve months of treatment with teriparatide and had received at least, two doses of denosumab or a single dose of 5mg IV zoledronic acid.

All the electronic health records were reviewed to obtain data about health, antropometric features, calcium intake, previous osteoactive treatments and history of fractures. Baseline biochemical and densitometric data were obtained at the end of treatment with teriparatide (post-teriparatide) and after a year of treatment with denosumab or zoledronate (post-antiresorptive).

BMD was evaluated using DXA (Lunar Prodigy equipment GE Lunar, Madison WL, USA) in lumbar spine, total hip and femoral neck. The equipment was calibrated on a daily basis, following the manufacturer's recommendations. According to precision studies carried out in our institution, the intra assay coefficient of variation of the densitometries were 1.53% for lumbar spine and total femur and 1.68% for femoral neck. BMD is expressed as g/cm² and T score (TS).

Biochemical data obtained at the three time points were the following: 25(OH)D3 (chemiluminescence, sufficiency > 30 ng/ml), osteocalcin (electrochemiluminescence, VN 11-43 ng/ml), β Crosslaps (electrochemiluminescence, VN 556 \pm 226 ug/ml), and PTH (electrochemiluminescence, VN 10-65 pg/ml).

The baseline features of the groups were compared using the unpaired t-test and the proportions test. Responses to treatment in each group were evaluated by the paired samples t-test and between groups by the independent samples t-test. The statistical analyses were performed with the GraphPad Prism 8.4.3 version for Windows (GraphPad Software, San Diego, CA, USA.) and IBM SPSS Statistics 26.0 (64-bit). The results are expressed as media \pm SD and in those cases in which the standard deviation is very large, they are also expressed as median (Me). A P < 0.05 was considered statistically significant.

This work was approved by our ethics committee and the data of the participants remained anonymous.

Results

We identified 28 patients who met the requirements for inclusion in the study, 14 had received zoledronate after completing the treatment with teriparatide and 14 denosumab. The median of teriparatide treatment was 18 months. Both groups were comparable in terms of baseline characteristics, the only difference being that baseline BMD was lower in the zoledronate group (p < 0.01), as shown in Table 1.

Densitometric changes In the lumbar spine: baseline BMD in the zoledronate group was 0.831 \pm 0.07 g/cm² (TS -2.80 \pm 0.77), which 18 months post-teriparatide increased significantly to 0.925 \pm 0.09 g/cm² (TS -1.93 \pm 1.53, + 11.44 \pm 7.85 % (p = 0.0003). After one year of treatment with zoledronate, BMD rose to 0.952 \pm 0.125 g/cm² (TS -1.93 \pm 1.2) p = 0.21, with an increase of 3.96 \pm 8.56% (Me 2.54), without statistical significance.

TABLE 1.— Baseline characteristics of the treatment subgroups

	Zoledronate	Denosumab	p
N	14	14	NS
Age (years)	66.7 ± 13	64.7 ± 8.3	0.64
BMI (kg/m ²)	23 ± 3.1	25 ± 4.3	0.21
Calcium intake (mg/day)	893.5 ± 448	725 ± 419	0.33
Previous biphosphonates	8/14 (57%)	9/14 (64%)	0.64
Months of previous biphosphonates	58.67 ± 70.62	71.77 ± 55	0.66
Teriparatide (months)	20.28 ± 4.76	18 ± 5	0.22
Baseline BMD LS (g/cm ²)	0.831 ± 0.07	0.875 ± 0.08	0.01
Baseline BMD FN (g/cm ²)	0.706 ± 0.04	0.702 ± 0.14	0.94
Baseline BMD TH (g/cm ²)	0.644 ± 0.09	0.637 ± 0.04	0.89
Vertebral fractures	9/14	7/14	0.70
Hip fractures	4/14	1/14	0.32
Other fractures	6/14	4/14	0.69
CTX (ug/ml)	424 ± 234	511 ± 158	0.20
Osteocalcin (ng/ml)	26.42 ± 17	27.26 ± 11	0.60
VIT D (ng/ml)	30.81 ± 9.9	33.51 ± 20	0.70
PTH (pg/ml)	45.02 ± 13.6	47.45 ± 19.8	0.18

BMI: body mass index; BMD LS: bone mineral density lumbar spine; BMD FN: bone mineral density femoral neck; BMD TH: bone mineral density total hip; CTX: β Crosslaps; VIT D: vitamin D; PTH: parathyroid hormone

The results are expressed as media ± SD

Basal BMD in the denosumab group was 0.750 ± 0.08 g/cm² (TS -3.38 ± 0.78), which 18 months post- teriparatide increased significantly to 0.819 ± 0.06 g/cm² (TS -3.03 ± 0.51) ($p = 0.0002$), (+ 9.93 ± 7.29 (Me 10.79)). BMD after one year of treatment with denosumab was 0.838 ± 0.05 g/cm² (TS -2.96 ± 0.43) $p = 0.07$, an increase of $3.55 \pm 5.36\%$ (Me 5.14).

No significant densitometric variations were found between the groups after treatment with teriparatide ($p = 0.60$) or after antiresorptive treatment ($p = 0.88$).

In the femoral neck, the basal BMD in the zoledronate group was 0.706 ± 0.04 g/cm² (TS -2.37 ± 0.45), which after 18 months post- teriparatide increased to 0.727 ± 0.07 g/cm² (TS -2.11 ± 0.63) $p = 0.15$, + $2.71 \pm 7.39\%$ (Me 3). BMD after one year of zoledronate treatment was 0.724 ± 0.06 g/cm² (TS -2.13 ± 0.46) $p = 0.85$, a change of $-0.09 \pm 6.50\%$ (Me 0.29).

Basal BMD in patients treated with denosumab was 0.702 ± 0.14 g/cm² (TS -2.45 ± 0.79), which after 18 months post- teriparatide treatment changed to 0.698 ± 0.10 g/cm² (TS -2.24 ± 0.69) $p = 0.59$, + 1.48 ± 3.67 (Me 1.23). BMD after a year of treatment with denosumab was 0.712 ± 0.11 g/cm² (TS -2.01 ± 1.17) $p = 0.59$, a variation of $-3.41 \pm 5.08\%$ (Me 5.35).

No significant differences were found in densitometric variations between both groups after teriparatide treatment ($p = 0.59$) or after one year post-antiresorptive therapy ($p = 0.37$).

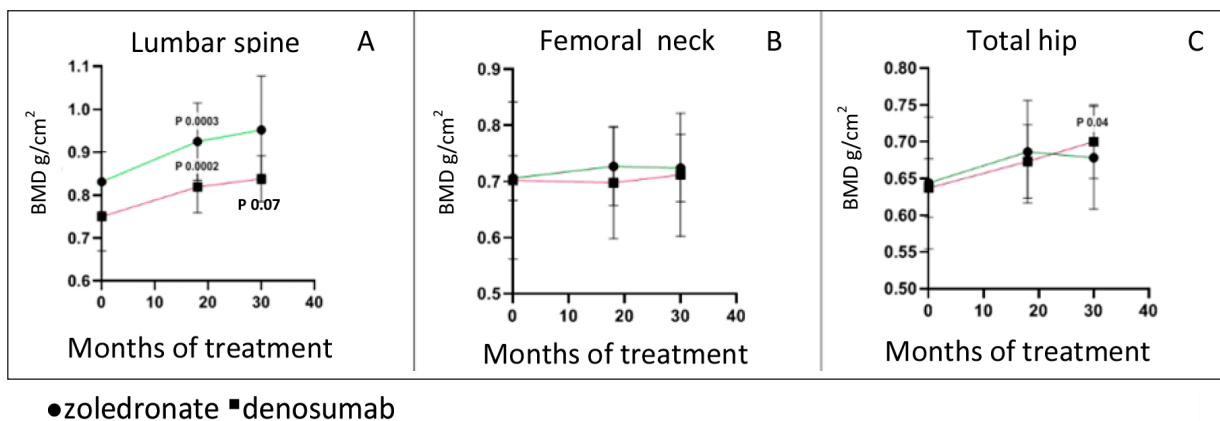
In total hip basal BMD of patients treated with zoledronate was 0.644 ± 0.09 g/cm² (TS -2.80 ± 0.80), which at 18 months post-teriparatide increased to 0.686 ± 0.07 g/cm² (TS -2.30 ± 0.8) $p = 0.48$, + $4.45 \pm 5.78\%$. BMD after a year of zoledronate treatment was 0.678 ± 0.07 g/cm² (TS -1.85 ± 2.0) $p = 0.70$, an increase of $0.55 \pm 4.20\%$ (Me 0.43).

Basal BMD of patients treated with denosumab was 0.637 ± 0.04 g/cm² (TS -2.43 ± 1.30). At 18 months post-teriparatide it increased to 0.673 ± 0.05 g/cm² (TS -2.66 ± 0.45) $p = 0.95$, + 3.13 ± 2.91 (Me 2.15). BMD after a year of treatment with denosumab was 0.700 ± 0.05 g/cm² (TS -2.34 ± 0.48) $p = 0.04$, an increase of $4.53 \pm 5.13\%$ (Me 0.64).

No significant differences were found in the densitometric variations between both groups of treatment at 18 months ($p = 0.64$) or after one year of antiresorptive treatment ($p = 0.11$). Desitometric changes during treatment are shown in Figure 1.

Biochemical changes: considering the patients in both groups of treatment together, CTX at 18 months post-teriparatide was 457.66 ± 209.91 ug/ml, which decreased to 157.96 ± 87.67 ug/ml ($p < 0.0001$). Osteocalcin at the end of the anabolic treatment was 32.4 ± 23.36 ng/ml, decreasing progressively to 14.164 ± 5.07 ng/ml ($p < 0.0001$) after antiresorptive treatment. After a year of treatment, there were no significant differences between both anti resorptives regarding the decrease in bone turnover markers.

Fig. 1.— This graph shows the densitometric gain after 18 months of treatment with teriparatide, only significant in lumbar spine (A), and the changes in the lumbar spine after one year of treatment with zoledronate or post-teriparatide denosumab (A). Femoral neck (B) and total hip (C). After the sequential treatment with teriparatide and denosumab, statistically significant changes were found in total hip and a similar trend in lumbar spine



Discussion

In this short study we intended to answer the question of which is to the best antiresorptive treatment following a cycle of teriparatide. We compared two groups of post-menopausal women with osteoporosis who had received teriparatide but who were treated with two different antiresorptive drugs afterwards: zoledronate or denosumab.

Ebina et al.⁷ showed the superiority of post-teriparatide denosumab compared to oral bisphosphonates, both in the densitometric gain in all the assessed sites and in the capacity to inhibit bone turnover assessed according to the percentage of decline in biochemical markers.

We found no references in the medical literature to compare between the effectiveness of denosumab and zoledronate after anabolic treatment. Both drugs are potent antiresorptives which use different mechanisms; the first inhibiting Rank Ligand, and the second inhibiting the prenylation of mature osteoclasts. When compared in their pivotal studies, both drugs achieved similar increases in bone mineral density and reduction of hip risk fractures, by 40%, after three years of treatment. Apart from their mechanism of action, the big difference between denosumab and zoledronate is in the dynamic of the densitometric gain. With zoledronate, bone mineral density remains steady after the third year of treatment, whereas with denosumab bone mineral density increases up to ten years after starting the treatment¹². Only a large population-based cohort study shows that denosumab and zoledronic acid have comparable clinical safety and effectiveness with regard to the risk of serious infection, cardiovascular side effects and osteoporosis fracture within 365 days after initiation of medications¹³.

We know, due to our daily practice of treating patients with severe forms of osteoporosis, that many of them

require a very long treatment and therefore, rationally administered sequential therapies will allow us to ensure them an adequate treatment for many years.

It is important to point out that teriparatide is part of a sequential treatment which ends with the prescription of an antiresorptive, either zoledronate or denosumab. If the latter is chosen, It is important to keep in mind that discontinuation of denosumab following at least two denosumab injections carries a significant risk of rebound effect, with a considerable augmented risk for multiple vertebral fractures. To limit this risk, it is currently recommended either to continue denosumab therapy or to prescribe a potent bisphosphonate when denosumab is stopped¹⁴.

An important point to take into account when choosing a post-anabolic treatment is the cost of the medication, especially in a developing country such as Argentina. At the time of writing this work, the annual cost of denosumab treatment is twice that of zoledronate.

Leaving aside the economic aspects and taking into account the risk of post-denosumab multiple vertebral fractures, we speculate that the ideal sequential treatment in patients at very high risk of fractures could be teriparatide followed by denosumab and ending with zoledronate.

As a conclusion, despite we did not get a clear answer. The analysis of bone turnover parameters suggests that both drugs have a similar antiresorptive power. As regards densitometric results, both drugs maintained and even increased bone mineral density in the lumbar spine and in the femoral neck in a similar proportion, but denosumab significantly increased BMD in total hip and changed with a trend toward in lumbar spine after one year of treatment.

This research has all the limitations of retrospective studies with a small number of patients, but this is may be the first step towards starting a retrospective or prospec-

tive multicentric study which will finally reveal the best possible sequential treatment after teriparatide.

Conflict of interest: None to declare

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