MODERN TREATMENT WITH TERIPARATIDE IN PATIENTS WITH SEVERE OSTEOPOROSIS

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Abstract: *Teriparatide is the first anabolic agent to stimulate osteoblastic bone formation and improve bone mass and quality. A total of 26 patients with severe osteoporosis were studied, in whom treatment with Teriparatide was initiated, with re-evaluation in the first and second year of therapy. Patients in our study have various levels of 25-hydroxy-vitamin D. In the selected subgroup, an increase in bone mineral density was observed in the first year of therapy. Regarding T-score and Z-score, there was an increase in the first year. An increase of Beta-CrossLaps levels in the first year and then a decrease at the end of therapy in the second year was observed. An increase of osteocalcin levels was observed in the first year, diminished later. Treatment with Teriparatide is generally well tolerated and patients claim significant improvement in the quality of life.*

INTRODUCTION

Osteoporosis is the most common bone metabolic disorder with increased risk of morbidity and mortality, especially because of the presence of osteoporotic fractures, which forces patients to long-term bed rest. Due to the high cost of treating complications, it is more effective to prevent and treat osteoporosis before serious manifestations occur. Treatment includes moderate physical activity, exposure to adequate solar radiation and a balanced diet that provides sufficient calcium intake. Bone antiresorptive medication is the pharmacological therapy of first choice, which inhibits disease progression.(1,2,3) An anabolic drug on bone tissue, Teriparatide, the first agent to stimulate osteoblastic bone formation and improve bone mass and quality, was put on the United States' market in 2002. It has the same mechanism of action as the parathyroid hormone (PTH). Anabolic action is based on two mechanisms: stimulation of bone formation at active remodelling sites and bone growth in previously inactive territories. There are international studies that examine the improvement of bone density and T-score by dual-energy x-ray absorptiometry (DXA) and the evolution of other parameters related to bone metabolism during treatment with Teriparatide.(1,2,3,4)

PURPOSE

The purpose of this study is to evaluate the treatment with Teriparatide administered to patients from the Endocrinology Department of the Clinical County Emergency Hospital of Sibiu.

MATERIALS AND METHODS

A total of 26 patients with severe osteoporosis from the Endocrinology Department of Clinical County Emergency Hospital of Sibiu were studied, in whom treatment with Teriparatide was initiated, with re-evaluation in the first and second year of treatment. Initiation of treatment was done between year 2013 and year 2017.

The diagnosis of severe osteoporosis was based on the criteria established by the World Health Organization and the Ministry of Health, taking into consideration the T-score and the Z-score in the DXA method, assessing the risk of fragility fractures with the Fracture Risk Assessment Tool (FRAX) protocol and taking into account the presence of vertebral and/or peripheral fractures: decrease in bone mineral density (BMD) by more than 2.5 standard deviations from the mean of young persons of same gender, measured by DXA, and the presence of fragility fractures.(3,4,5,6) The criteria for inclusion in treatment with Teriparatide was according to the National Program of Osteoporosis.

The study included patients with severe osteoporosis, with PTH levels within normal reference range or lower. Patients with increased PTH levels, over 65 pg/ml, with bone metastases and/or malignancies were excluded from the study. Monitoring of Teriparatide therapy was according to the National Program of Osteoporosis. In the study group, the following parameters were analysed at the initiation of therapy: the rural or urban area as place of living, gender, age groups (50-70 years and over 70 years), DXA parameters in the lumbar spine scans: T-score, Z-score, BMD (g/cm^2), associated diseases, previous antiosteoporotic medication and Teriparatide-associated medication, number of vertebral and peripheral fractures, PTH, 25-hydroxy-vitamin D and bone markers (osteocalcin and Beta-CrossLaps). At the assessment of a subgroup of 5 patients evolutionary markers were analysed: T-score, Z-score, BMD, PTH, 25-hydroxy-vitamin D, total serum calcium, Beta-CrossLaps and osteocalcin.

Laboratory investigations were performed with chemiluminescent immunoassay (CLIA) or electrochemiluminescent immunoassay (ECLIA) from serum for PTH (normal levels between 15 and 65 pg/ml), osteocalcin (normal levels between 0 and 22 ng/ml), Beta-CrossLaps (normal levels in menopause between 0.104 and 1.008 ng/ml and in men between 0.040 and 0.840 ng/ml). 25-hydroxy-vitamin D was dosed from serum by Enzyme Linked Fluorescent Assay (ELFA) or Enzyme-linked Immunosorbent Assay (ELISA/B Alegria) (deficiency: below 12 ng/ml;

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insufficiency: from 12 to 20 ng/ml; sufficient level: from 20 to 30 ng/ml; optimal level: from 30 to 100 ng/ml). Concentrations of total serum calcium (normal levels between 8.8 and 10.2 mg/dl) were determined by spectrophotometry.

The treatment was given subcutaneously in a daily dose of 20 µg/day, over a 24 month-period. Patients were questioned about possible local side effects at the site of administration and related to changes in intensity of bone pain during Teriparatide therapy.(7,8,9)

RESULTS

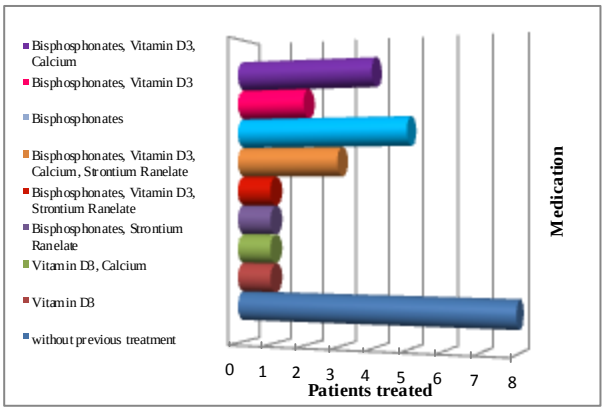
Of all the patients included in the study, a much higher prevalence was observed in urban areas (96%). There is a higher prevalence of severe osteoporosis in the age group of 50-70 years (69%). Taking into account the gender distribution of patients treated with Teriparatide, the vast majority are women (96%).

At baseline, BMD values were between 0.55 g/cm^2 and 1.102 g cm^2 (with a mean of 0.803 g /cm^2). The T-score values in patients treated with Teriparatide at the initiation of therapy was between -1 and -5.4, with a mean of -3.4, and the Z-score was between + 0.2 and - 4.8, with a mean of - 2.0.

The patients in the studied group have various disorders associated to osteoporosis as cardiovascular disease (21%), diabetes and endocrine diseases (21%), osteoarticular disorders (38%) and other diseases (20%).

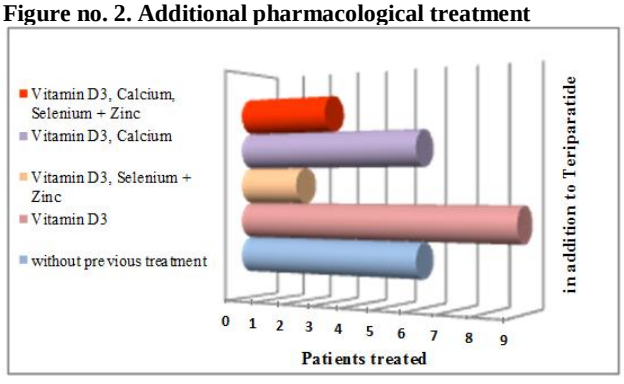
Most patients followed a pharmacological antiosteoporotic treatment before the initiation of Teriparatide (figure no. 1.)

Figure no. 1. Pharmacological antiosteoporotic treatment



Most patients received additional pharmacological treatment with vitamins and minerals in variable combinations, concomitant with Teriparatide (figure no. 2.)

Figure no. 2. Additional pharmacological treatment



From all patients included in the study, 26% have no vertebral or peripheral fractures and 74% have had one or more vertebral fractures and/or peripheral fractures before treatment initiation. 77% of patients from the study group had normal PTH levels and 8% had a serum concentration <15 pg/ml (hypoparathyroidism). Determination of PTH was not performed in 4 patients (15%). Patients in the study were divided according to serum 25-hydroxy-vitamin D concentration. 23% of patients have the optimal level of serum 25-hydroxy-vitamin D and the same percentage have the sufficient level. 12% of patients have an insufficient level and 19% have a deficiency of 25-hydroxy-vitamin D. In 6 patients (23%) 25-hydroxy-vitamin D could not be determined.

Reference values of serum Beta-CrossLaps differ according to gender and age of the patients: for men aged 30 to 51 years ≤ 0.584 ng/ml, 51 to 70 years ≤ 0.704 ng/ml and >70 years ≤ 0.854 ng/ml; for premenopausal women ≤ 0.573ng/ml and postmenopausal women ≤ 1.008 ng/ml. The male in the study group belongs to the 51-70 age group and has a high level of serum Beta-CrossLaps of 0.732ng/ml. Women (in a number of 21 from the total patients included) are in postmenopause and have normal levels of Beta-Crosslaps, of ≤ 1,008 ng/ml. In 4 patients this investigation was not performed. Osteocalcin reference ranges are different depending on gender and age group: in men aged 18 to 30 years are between 24.0 and 70.0 ng/ml, 30 to 50 years are between 14.0 and 42.0 ng/ml, >50 years are between 14.0 and 46.0 ng/ml; in premenopausal women are between 11.0 and 43.0 ng/ml and in postmenopausal women (without hormone replacement therapy) are between 15 and 46.0 ng/ml. The man in the study group belongs to the age group > 50 years and has a normal level of osteocalcin, of 32.67 ng/ml. Women are in postmenopause, 7 of them having normal levels of osteocalcin, of 15.38 to 33.6 ng/ml and 11 of them showing low levels, of 2 to 14.5 ng/ml. In 7 patients osteocalcin was not determined.

A subgroup of 5 patients was selected and, in the first and second year of therapy, PTH, 25-hydroxy-vitamin D, osteocalcin, Beta-CrossLaps, total serum calcium, BMD, T-score and Z-score in spine were followed.

Regarding the evolution of serum PTH levels in the subgroup studied during therapy with Teriparatide, the following were observed: in 1 patient PTH levels increased; in 4 patients the PTH levels decreased; all patients have PTH levels in the normal reference range from the beginning to the end of treatment; in the entire subgroup PTH levels decreased in the first year by 27.73% and in the second year by 48.94% compared to the mean value from the beginning of Teriparatide therapy (figure no. 3.)

Figure no. 3. PTH levels (pg/ml) of patients in the subgroup

Patient	no.1	no.2	no.3	no.4	no.5	Mean level
at baseline	446,14	39,58	48,99	63,13	64,9	52,55
in the 1st year of therapy	37,2	47,63	22,57	37,59	44,9	37,98
in the 2nd year of therapy	26,71	57,85	16,47	16,7	16,4	26,83

In terms of the evolution of serum 25-hydroxy-vitamin D concentration in the subgroup studied during treatment with Teriparatide, the following were observed: in 2 patients the 25-hydroxy-vitamin D levels increased (from deficiency and insufficiency to the optimal level); in 3 patients 25-hydroxy-vitamin D levels decreased from the optimal and the sufficient level to the sufficient, respectively, the insufficient level); the

mean serum 25-hydroxy-vitamin D level in the entire subgroup decreased by 14.94% in the first year and increased by 8.74% in the second year compared to the mean levels at initiation of treatment.

As for the evolution of serum osteocalcin concentration in the subgroup studied during treatment with Teriparatide, the following were observed: in 2 patients the serum osteocalcin decreased (from 67.3 ng/ml to 50.3 ng/ml and from 12.17 ng/ml to 5.31 ng/ml); in 2 patients the osteocalcin concentration increased (from 33.6 ng/ml to 47 ng/ml and from 15.38 ng/ml to 29.6 ng/ml); in 1 patient the osteocalcin level was not modified; serum osteocalcin in the entire subgroup increased by 47.83% in the first year and by 2.69% in the second year compared to the mean value from the beginning of therapy with Teriparatide. Regarding the evolution of serum Beta-CrossLaps concentration in the subgroup studied the following were observed: in 2 patients the Beta-CrossLaps levels increased (from 0.286 ng/ml to 0.52 ng/ml and from 0.209 ng/ml to 0.85 ng/ml); in 2 patients the Beta-CrossLaps levels decreased (from 0.456 ng/ml to 0.31 ng/ml and from 0.64 ng/ml to 0.54 ng/ml); in 1 patient the Beta-CrossLaps level was not modified; in the entire subgroup the Beta-CrossLaps levels increased in the first year by 57.14% and in the second year by 36% compared to the mean value from the beginning of therapy; all patients in the subgroup have Beta-CrossLaps levels in the normal reference range from the beginning to the end of therapy with Teriparatide.

As for the total serum calcium: in 4 patients, total serum calcium increased in the first year of treatment (maintained within the normal reference range); in 1 patient, the total serum calcium concentration decreased (from 10 mg / dl to 9.88 mg/dl); in the entire subgroup, total serum calcium increased by 4.9% in the first year. In terms of BMD: in 4 patients, BMD increased in the first year of treatment; in one patient, the BMD decreased; BMD in the entire subgroup increased by 4% in the first year compared to the mean on initiation of treatment. As monitoring of the entire subgroup from the initial treatment period and up to 24 months was not performed, we cannot have conclusive data on the evolution of total serum calcium and BMD in the subgroup studied in the second year of treatment with Teriparatide.

In terms of the T-score and Z-score in the lumbar spine in the subgroup studied during the treatment with Teriparatide, the following are observed: in 4 patients the T-score increased and in 1 patient the T-score was not modified in the first year; in the entire subgroup the T-score increased by 6.15% in the first year of treatment; in 3 patients the Z-score increased and in 1 patient the T-score was not modified in the first year of treatment; on average, the Z-score increased in the 4 patients monitored in the first year by 8.47%; because the whole subgroup was not monitored from the initial treatment period and up to 24 months, we cannot have conclusive data on the T-score and Z-score on the subgroup studied in the second year of treatment with Teriparatide.

DISCUSSIONS

Antiresorptive therapy is of first choice in osteoporosis, according to the National Guidelines for the Diagnosis and Treatment of Osteoporosis, but there are cases where antiresorptive therapy is contraindicated and cannot be administered to patients.(7) According to the National Program, initiation of Teriparatide therapy require mandatory investigations. Most patients have normal PTH levels and only 8% have low serum levels, below 15 pg/ml. Hyperparathyroidism is an exclusion criterion for treatment with Teriparatide. Patients have various 25-hydroxy-vitamin D levels, from deficiency to optimal. Women in the study group have normal Beta-Crosslaps values and the man in the study group has high Beta-CrossLaps levels. Serum concentrations of osteocalcin are within the reference range or lower in the patients from the study group.

Several international studies have published data on the evaluation of the effects of Teriparatide treatment on BMD, T-score, vitamin D and serum calcium levels, PTH, Beta-CrossLaps and osteocalcin. In this paper a subgroup of 5 patients was selected to observe the evolution of these parameters during Teriparatide therapy.

Mean BMD values of patients included in the study at initiation of therapy with Teriparatide were 0.803 g/cm^2.

The results of the study conducted by Stroup et al. in 2007, regarding the changes in BMD and T-score during Teriparatide therapy, show a significant increase in BMD in the spine of 7.2% after one year of treatment and an increase of 10.9% after two years. An increase in BMD is reported in 93% of patients after two years of treatment. There is also a significant increase in T-score after one year and two years on therapy.(10) In our study, in the selected subgroup, an increase in BMD was observed in the first year on therapy compared to the value from the initiation of treatment. One patient in the total subgroup of 5 patients has a decreased BMD by 1.43%. In the other 4 patients the values increased by 5.1% in the first year of therapy. One patient, followed in the first and second year, reported a total increase of 13.02%. Referring to the evolution of T-score in the studied subgroup, there is an increase of 6.15% in the first year of treatment. In one patient, the T-score was not modified. In one patient it was possible to evaluate the T score at two years of treatment and an increase of 12% compared to the one from baseline was observed. On the Z-score there was an average increase of 8.47% in the first year of treatment. In one patient, the Z-score was not modified and in one patient there was an increase of 26.3% after two years of therapy.

The results obtained in the studied subgroup largely correspond to the results of the study by Stroup et al.(10)

The results of the study conducted by Lindsay et al. in 2016, that evaluates the importance of the duration of anabolic treatment with Teriparatide show increasing levels of Beta-CrossLaps in the first year of treatment (with a maximum titre between 6 and 12 months) followed by a gradual decrease in the second year.(2) In our research a similar evolution is observed: an increase in the entire subgroup by 57.14% in the first year and then a decrease (to a serum level by 36% higher compared to the baseline level) at the end of therapy in the second year. In 4 patients Beta-CrossLaps increased the first year and 3 of them have decreased serum concentration in the second year. In one patient they continued to increase and in one patient they decreased from the beginning of therapy.

The same study by Lindsay et al. mentions hypercalcemia as the adverse reaction present in 5% of patients treated with Teriparatide.(2) In our research, calcium levels are maintained within the normal reference range during therapy.

In the study conducted by Bodenner et al. in 2007, mention is made of the importance of adequate intake of vitamin D and maintenance of an adequate serum level of 25-hydroxy-vitamin D in order to obtain an optimal effect of treatment with Teriparatide.(1) A total of 8.74% increase of 25-hydroxy-vitamin D in the second year of treatment was observed in the subgroup selected in our study. It should be noted that in a patient with 25-hydroxy-vitamin D deficiency at baseline, serum levels increased to the optimal level and in two patients the values decreased from optimal level to insufficient level. It should be noted that not all patients have used additional treatment with vitamins and minerals.

Determination of PTH levels was performed to exclude parathyroid disorders and it is monitored in patients with Teriparatide therapy.(9) In the study conducted by Anastasilakis et al. in 2008, which analyses the effect of treatment with Teriparatide on endogenous intact PTH in menopausal women, serum PTH values are reported to decrease from baseline values and remain low during therapy.(11) In 4 patients in our study the PTH levels decreased during treatment. In one patient the evolution is reverse. There was an average decrease of 27.73% in the first year and of 48.94% in the second year. All patients have PTH in the normal reference range from the beginning to the end of therapy.

The results in the subgroup largely correspond to the results of the study conducted by Anastasilakis et al., except for a patient as mentioned.(11)

Osteocalcin is a marker of the bone formation process, used to monitor antiresorptive therapy and estimate the risk of fractures. In the study of Sarli et al. in 2013, a retrospective study of Teriparatide treatment in 46 patients, comparing the results with those published in the literature, it is noted that serum osteocalcin concentration increases significantly from the initiation of treatment and returns to normal levels during the second year of therapy with Teriparatide.(9,12,13,14) In the studied subgroup of our research an increase of 47.83% was observed in the first year of treatment with Teriparatide, diminished later, resulting in a slight increase of 2.69% in the second year compared to the baseline osteocalcin level.

The results in the studied subgroup correspond to the results of the study by Sarli et al.(12)

In the study by Bodenner et al. in 2007, it is stated that treatment with Teriparatide is generally well tolerated and severe adverse reactions occur only at a small percentage of cases, predominantly on early onset of treatment. The most commonly reported undesirable effects are dizziness, headache, fatigue and local reactions at the injection site in the form of erythema, pain and edema.(1) Patients included in our research did not experience significant side effects. Patients treated with Teriparatide from the study group were questioned about bone pain present prior to the therapy; its intensity diminished significantly over the course of treatment and patients assume an improvement in quality of life

CONCLUSIONS

Treatment with Teriparatide is a new therapy indicated in adults with severe osteoporosis, in postmenopausal women and in men with high risk of fracture, in cases of osteoporosis associated with long-term systemic glucocorticoid therapy in men and women with high risk of fracture. Treatment with Teriparatide is expensive, indications and criteria for inclusion are restricted and the number of patients treated in Sibiu County is small.

In the study conducted by Bodenner et al. (1) and in the National Guidelines for the Diagnosis and Treatment of Osteoporosis (3), the importance of a sufficient daily intake of vitamin D and calcium is mentioned. Patients in our study have various 25-hydroxy-vitamin D levels, from deficiency to optimal level, and values have increased in some and decreased in others during therapy. In the selected subgroup an increase in BMD was observed in the first year of treatment. Regarding the evolution of T-score and Z-score in the subgroup, an increase in the first year of treatment with Teriparatide was observed. The results of this paper correspond to the findings of international studies.

Treatment with Teriparatide is generally well tolerated by patients with severe osteoporosis. In terms of the intensity of bone pain present prior to treatment, patients claim significant improvement in the quality of life.

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