THE TERIPARATIDE IN THE TREATMENT OF SEVERE
SENILE OSTEOPOROSIS

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SUMMARY

The osteoporosis is a systemic disease of multicausal etiopathogenesis. A progressive bone loss and qualitative alterations in the macro- and micro-architecture of the remaining bones, resulting in a loss of strength of bones to such an extent that even very modest traumas will cause fractures characterize it. Three forms are defined (i) postmenopausal appearing after the menopause, (ii) senile appearing with advancing age, and (iii) the idiopathic forms. Severe osteoporosis is declared when the patients suffer vertebral or femoral fractures without any trauma during a treatment with anti-reabsorptive medicines of at least 1-year. The treatment of osteoporosis is based on various categories of pharmacas, such as bisphosphonates, selective estrogen receptor modulators (SERMs), dianinobutyric acid (DABA), parathyroid hormone (PTH), estrogens and non-hormonal drugs. The teriparatide, the recombinant human (rh)PTH(1-34), is identical in amino acid sequence until the 34th (N-terminal) amino acid of the endogenous, human PTH. It is produced in E. coli using the recombinant DNA technology. It is a pharmacon having a strong trophic-anabolic action on the bone tissue, assuring both the inhibition of the bone loss, and the formation of new bones of good quality. It acts as a stimulant of the osteoblast functions, and at the same time, increases the absorption of calcium from the intestine, and also the renal reabsorption of calcium, and decreases the excretion of phosphates in the kidney. This study summarizes our own experience with the use of rhPTH(1-34) in the treatment of senile patients with severe osteoporosis. Our sample consisted of 40 elderly women of the mean age of 78 ± 5 years, having severe osteoporosis. They displayed a columnar T-score > -3.5 and femoral T-score > -2.5, had been under antireabsorptive treatment since at least 12 months. In particular, 15 patients were treated with Alendronate (70 mg/week), 10 of them with Risedronate (35 mg/week), and 15 of them with Raloxifene (60 mg/day). These patients in our study were treated for 1 year with 20 µg/day of rhPTH (1-34), injected subcutaneously, and supplemented also with a daily dose of 1 g of calcium and 800 IU of Vitamin D, per os. At start of this treatment (time t0), after 6 months (time t6) and after 12 months (time t12) patients underwent a bone mineral density (BMD) analysis (Dexa-Lunar-DPX-P) on the lumbar vertebral column, (L1-L4 zone), as well as a femoral BMD. We applied also quality of life (QoL) questionnaire of the European Foundation for Osteoporosis (QUALIEFFO), and evaluated also the use of non-steroidal anti-inflammatory drugs (NSAIDs). Our final considerations are that the teriparatide therapy increases significantly the bone mass density, expressed in terms of T-Score, reduces the occurrence of new fractures, improves the QoL, and decreases also the consumption of NSAIDs.

Keywords: senile severe osteoporosis, teriparatide treatment, quality of life (QoL)
INTRODUCTION

Osteoporosis is a disease of social relevance. Its incidence increases with age to such an extent that the great part of the population above 80 years of age becomes interested. It is estimated that today in Italy, there are about 3.5 million women and 1.0 million men with osteoporosis. Because during the next 20 years the Italian population above 65 years will increase by about 25%, one has to expect a proportional increase also of the incidence of osteoporosis. The osteoporotic fractures have important social and economic implications, not to mention the sanitary ones (Cummings and Melton, 2002; Lin and Lane, 2004). Among the elderly, the osteoporotic fractures represent one of the most frequent causes of mortality: their incidence is of equal size with those of stroke and mammary cancer.

The osteoporosis is a systemic disease of multicausal etiopathogenesis. It is characterized by a progressive bone loss and qualitative alterations in the macro- and micro-architecture of the remaining bones, resulting in a loss of strength of bones to such an extent that even very modest traumas will cause fractures (Kulenovic et al., 2006). The bone loss is not equal in all regions of the skeleton, but involves particularly those of trabecular and spongy structure, i.e., the vertebral corps, and the femoral neck. As a matter of fact, the fracture in this last region is the most disabling one, and displays very high risk of mortality: RR = 4.5 in 3 years. With advancing age, one can observe a progressive bone loss in both sexes. This is due to different mechanisms. The post-menopausal osteoporosis starts already around 30-35 years of age at the vertebral level; however; it becomes significant only in the 6th-7th decades of age. This type is called "senile osteoporosis", it occurs in both the cortical and trabecular bones. It is assumed that this process is due to atrophy connected with the lower load during the reduced physical activity, the decreased level of androgen hormones, and to a decreased nutrition. Reduced nutrition is very frequent, because the intestinal absorption of calcium becomes less efficient with advancing age, meanwhile the alimentary intake also decreases in parallel. Thus the diet of the elderly becomes inadequate in double sense (Eriksen and Glerup, 2002). It has been shown just in these elderly subjects that that an adequate intake of calcium is of particular importance in the prevention of fractures. The supplementation of Vitamin D is also of great importance, because both the production and absorption of it is reduced in the elderly, due to a decreased functional value of the kidney, and to a consequent incapacity for transformation the 25-hydroxy-cholecalciferol into its active metabolite through hydroxylation, i.e., to form 1,25-dihydroxy-cholecalciferol (Slovik et al., 1981).
The response of human organism to this insufficient supply with calcium is an increased production of PTH in the parathyroid glands, i.e., a secondary hyperparathyroidism comes into being. The PTH stimulates the remodeling and mainly the osteoclastic reabsorption of the bones, which is an attempt to maintain safely stabilized serum levels of calcium, using the skeleton as a source of this cation.

"Severe osteoporosis" is defined as the condition of the so-called inadequate clinical responders (IACRs), i.e., the disease of the patients who had been treated already at least 1 year with anti-reabsorptive drugs (alendronate, risedronate and raloxifene), who displayed a compliance higher than 50%, and in spite of that, a new vertebral or femoral fracture occurred without effective traumas. The treatment of osteoporosis should aim at reducing the risk of fractures, and this is based, apart from the non-pharmacological interventions (diet, physical activity) and the elimination of risk modifiable factors (smoking, hygienic life), on the application of various categories of pharma (Gass and Dawson-Hughes, 2006) as follows: (i) Bisphosphonates (alendronate, risedronate, ibandronate); (ii) SERMs (raloxifene); (iii) DABA (remlate of strontium, available in Italy since September, 2005); (iv) PTH (registered by the European Agency for the evaluation of medical products for the therapy of severe osteoporosis; (v) hormone-replacement therapy (HRT) (particularly by estradiol). (vi) Non-hormonal pharma, like calcitonin, ipriflavone, fluoruri, tiazidi-diuretics (however, today none of these are registered in Italy for the treatment of osteoporosis).

ON THE TERIPARATIDE

The rhPTH(1-34) is produced in E. coli using the recombinant DNA technology. It is a medicine, which has a strong trophic-anabolic effect on the bone tissue. It stops the bone loss, and stimulates the deposition of new bone mass of good quality (Khan and Khan, 2006). Its action is realized through the stimulation of the osteoblastic activity, and increases the intestinal absorption of calcium, the tubular reabsorption of calcium in the kidney, as well as the renal elimination of phosphorous. The PTH is generally considered as an essentially catabolic hormone for the bones. As a matter of fact, its increase provokes an increased bone reabsorption and loss of bone mass. Nevertheless, the therapeutic rationale of its application is based on its dichotomic effect (Neer et al., 2001): if its level is continuously high in the serum, it stimulates the osteoclastic activity, while a pulse-like application has an opposite action. Small doses of rhPTH(1-34) injected every day stimulate mainly the osteoblastic cell lines, and consequently increase the bone neoformation, i.e., increase the bone mass. The (1-34) N-terminal fragment of PTH seems to act at different
levels compared to the total PTH molecule: it results in a net neoformation of bone tissue, and also acts directly on the "lining cells", stimulating the differentiation of the osteoblasts. It inhibits also their apoptosis, i.e., increases their survival, stimulates the production of osteoprotegrine in the osteoblasts, and inhibits the synthesis of the receptor activator of nuclear factor-kappa ligand (RANKL) which is necessary for the differentiation of the osteoclasts, which means a slowing down of the pro-reabsorptive activity of these cells (Jilka et al., 1999; Ma et al., 2001).

Another characteristics of this compound, the use of which is actually reserved for the patients with very low bone mineral density (BMD) values, with at least 1 osteoporotic fracture, and belonging to the IACRs (Lems et al., 2006), is the length of its action. Namely, the effect remains at least for 50 months from the end of a therapeutic cycle of 18-20 months. The teriparatide is available in Italy in injectable solutions, in a charged pen, containing 3 ml (with a total amount 750 µg of teriparatide, i.e., 250 µg/ml). Each single dose contains 20 µg of teriparatide.

The use of rhPTH(1-34) is contraindicated in cases of (i) hypersensibility to this compound or to any of the components of the solution; (ii) pre-existing hypercalcemia; (iii) severe renal insufficiency; (iv) metabolic diseases of the bones different from the primary osteoporosis (Paget disease, hyperparathyroidism); (v) preceding radiation therapy on the skeleton; (vi) increases of unknown origin of the serum alcaline phosphatase.

The present study was aimed at evaluating the efficacy of rhPTH(1-34) in elderly patients with severe, but stabilized osteoporosis (vertebral and femoral T-Score > -3.5; and > -2.5, respectively, the occurrence of a new vertebral (or other) fracture during the last year of anti-reabsorptive therapy. For this purpose we measured the changes in BMD, expressed in terms of the T-Score, measured at t0, t5 and t12 time points. The consumption of NSAIDs was also monitored during the rhPTH(1-34) treatment. Modifications of QoL during the treatment was also evaluated by using the QUALEFFO-Test. This latter consists of 41 questions divided in 7 groups, in order to obtain information on the QoL of the subjects, created specifically for this purpose by the International Osteoporosis Foundation. All questions may have multiple, standardized answers, and each answer has a value expressed in points. The groups of questions are: (i) Presence of pains; (ii) the ability to perform the everyday activities; (iii) the capacity to perform domestic works; (iv) the walking functions; (v) free time activities; (vi) social activities; (vii) self-perception of the health state and humor.
SUBJECTS AND METHODS

Our study pool consisted of 40 elderly women, patients of our Center with severe osteoporosis. Their age was between 73 and 83 years (mean: 78 ± 5), and had been treated with anti-reabsorptive pharmacca (15 patients with alendronate, 70 mg/week, 10 with risedronate, 35 mg/week, and 15 with raloxifene, 60 mg/day). All these patients received for 1 year 20 µg/day of rhPTH(1-34), injected subcutaneously, together with a supplementation of 1 g/day calcium and 800 IU of vitamin D₃.

The inclusion criteria were: age > 73 years; previous treatment for at least 1 year with oral anti-reabsorptive pharmacca, occurrence of a new fracture after at least 1 year of anti-reabsorptive treatment without effective traumas. All the patients included in this study underwent a BMD analysis (Dexa-Lunar-DPX-P) on their lumbar vertebral column, and on the proximal portion of the femur at start of this treatment (t₀), after 6 and 12 months, respectively (t₆ and t₁₂). In addition, we monitored the changes in use of NSAIDs during treatment and the QoL by using the QUALEFFO-Test.

RESULTS

By the end of the study period, the BMD values expressed in terms of T-scores in our total pool displayed important changes. Namely, the mean value of -3.89 ± 0.28 at t₀, measured in the lumbar L1-L4 vertebrae increased to a value of -3.58 ± 0.34 (-7.88%) by t₆ and it increased further by the t₁₂ to -3.40 ± 0.40 indicating a total of 12.03% increase of the BMD.

The same trend could be observed in the femoral region. The mean value of T-score in the total pool was -2.89 ± 0.29 at start, it increased to -2.78 ± 0.32 (3.55%) after 6 months, and to -2.66 ± 0.43 (7.93%) after 12 months. These average values have also been analyzed in the 3 subgroups of our sample, based on the previous anti-reabsorptive treatments (Table I).

The consumption of NSAIDs also decreased considerably in both the total pool and in the subgroups (Table I). The total reduction of the use of these drugs reached 65% by the end of 12 months, which is quite an important result.

As regards the results with the QUALEFFO-test, the values obtained at the 3 time-points of evaluation (t₀, t₆ and t₁₂) were 144 ± 20, 120 ± 18 and 86 ± 16, respectively. These data indicate a serious reduction of the pain (16.7 and 40.3%) after 6 and 12 months of treatment with rhPTH(1-34).
Table I
EVALUATION OF THE BASIC PARAMETERS OF THE STUDY POOL

<table>
<thead>
<tr>
<th>Groups</th>
<th>T-score at t₀</th>
<th>T-score at t₆</th>
<th>T-score at t₁₂</th>
<th>Consumption of NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously risedronate-treated patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vertebr.</td>
<td>-3.9 ± 0.3</td>
<td>-3.6 ± 0.3</td>
<td>3.4 ± 0.4</td>
<td>-50% (at t₆)</td>
</tr>
<tr>
<td>% changes</td>
<td>-7.7</td>
<td>-12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>femoral</td>
<td>-2.9 ± 0.2</td>
<td>-2.8 ± 0.2</td>
<td>2.7 ± 0.5</td>
<td>-65% (at t₁₂)</td>
</tr>
<tr>
<td>% changes</td>
<td>-3.4</td>
<td>-8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously alendronate-treated patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>vertebr.</td>
<td>-3.9 ± 0.2</td>
<td>-3.7 ± 0.3</td>
<td>-3.5 ± 0.4</td>
<td>-50% (at t₆)</td>
</tr>
<tr>
<td>% changes</td>
<td>-5.2</td>
<td>-9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>femoral</td>
<td>-3.0 ± 0.3</td>
<td>-2.9 ± 0.2</td>
<td>-2.8 ± 0.3</td>
<td>-65% (at t₁₂)</td>
</tr>
<tr>
<td>% changes</td>
<td>-3.0</td>
<td>-5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously raloxifene-treated patients</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(15)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>vertebr.</td>
<td>-3.9 ± 0.3</td>
<td>-3.5 ± 0.4</td>
<td>-3.4 ± 0.3</td>
<td>-50% (at t₆)</td>
</tr>
<tr>
<td>% changes</td>
<td>-10.7</td>
<td>-14.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>femoral</td>
<td>-2.8 ± 0.2</td>
<td>-2.7 ± 0.3</td>
<td>-2.5 ± 0.3</td>
<td>-65% (at t₁₂)</td>
</tr>
<tr>
<td>% changes</td>
<td>-4.3</td>
<td>-9.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As regards the everyday activities, an average of 120 ± 20 was measured at start, which is an indicator of the disabilities occurring in this pool. After 6 month of treatment, this value was 100 ± 18, i.e., the disabilities decreased 16.7%, and after 12 months the mean was 80 ± 20, i.e., further decreased proportionally reaching a total improvement of 33.3%. This proves unanimously that rhPTH(1-34)-treatment is beneficial also for the everyday activities.

The performance of domestic jobs displayed also a significant improvement under the rhPTH(1-34)-treatment. We measured for this parameter mean values of 126 ± 22 at start, 108 ± 20 after 6 months (-14.3% e) and 78 ± 18 after 12 months (-30.1%). These data indicate also considerable improvements.

Also the locomotor functions were improved during the treatment period. The mean was 150 ± 30 at start, 126 ± 28 after 6 months (-16.0%), and after 12 months it was 80 ± 16 (-46.7%).

Application of the QUALEFFO-Test revealed a mean value of 120 ± 24 at start, 98 ± 22 and 68 ± 24 after 6 and 12 months, respectively. These data show that all the patients gained in the quality of free time and in the social activities under this treatment, 18.3% already after 6 months, and 43.3% after 12 months of treatment.
The efficacy of rhPTH(1-34)-treatment seems to be evidenced also in the self-perception of own health state: the sum of measured values were 140 ± 30 at start, decreasing to 128 ± 28 after 6 months (14.3% improvement) and to 90 ± 22 (35.7% improvement) by the end of 12 months..

Identical tendencies were observed in the humor of the patients. The mean sum of the indices was 160 ± 24 at start, it became 110 ± 20 after 6 months, and decreased further to 90 ± 18 after 12 months, i.e., decreased 31.3% and 43.8%, respectively, indicating an improvement of the humor of patients to the same extents.

DISCUSSION AND CONCLUSIONS

The studies of Teriparatide go back to the middle of 20th century, when it had been observed that that injection of PTH extracts in rats increased the mineral content of the bones. It was observed also that daily injections of small doses of a synthetic fragment of human PTH (h-PTH-1-34) in 4 women with osteoporosis resulted in an increased bone formation (Reeve et al., 1976). The bone neoformative action of rhPTH(1-34) is subject of numerous, controlled clinical trials even today. Jiang et al. (2003) have analyzed the changes of cortical and spongy bone tissues before and after a daily subcutaneous injection of 20 μg of Teriparatide for 19 months in osteoporotic women.

Considering the literary data regarding the action of rhPTH(1-34), we intended to test the effects of Teriparatide in the treatment of severe senile osteoporosis. We have been convinced to do so particularly by the fact that this molecule gave positive results also in the non-responder subjects to the commonly used, oral therapy with anti-reabsorptive compounds (Khan and Khan, 2006). Our studies have proven that the application of Teriparatide causes a complex increase of BMD after 12 months of treatment, even if the first data are somewhat contradictory between the vertebral column and the femoral region. In reality, the trabecular bone responds more quickly to the remodeling stimulation, therefore, the vertebral column reacts earlier to this pharmacon, while the compact bone tissue responds more slowly to those stimuli, therefore, gives definitive responses with some delay. The analysis of the cortical bone reveals that Teriparatide induces apposition on the periosteum and favors, at least at the beginning, the endocortical bone reabsorption, i.e., causes a transitory and reversible increase of its porosity. The consequent increase of the periosteal circumference, being responsible for the apparent reduction of the BMD, produces an improvement of several mechanical properties of the cortical bone, such as the "cross sectional moment of inertia". This is an indicator of the resistance of the bone against
bending and torsion forces. The increased porosity at the same time does not have a negative influence on the quality of the bone, because it is transitory and is balanced by the apposition of bone tissue on the endosteal and periosteal surfaces, which improves the bone resistance through a modification of its architecture (Zanchetta et al., 2003).

The following mechanism would explain the increased bone resistance and the consequent reduction of fracture risks. As a matter of fact, during the study period none of the enrolled subjects displayed any new vertebral fracture, as revealed by the morphometric evaluation of the vertebral column, neither they had non-vertebral fractures. The studies of Neer et al. (2001), in which there were 1,637 randomly selected osteoporotic women in menopause, who had previously vertebral fractures, subcutaneous teriparatide treatment of 21 months has shown a reduction of the vertebral and non-vertebral fracture risks. In addition we observed also how the therapy applied before the use of rhPTH(1-34) could influence the response to this new pharmacon. Namely, the patients having been treated with bisphosphonates, the action of which is prevalently the inhibition of bone reabsorption, responded less rapidly to the rhPTH(1-34) treatment. This is more relevant for the alendronate, having a larger inhibitory potential than that of risedronate. This delay of the response is lower in the subjects having been treated previously with raloxifene, due to the lower anti-reabsorptive capacity of raloxifene, compared to the bisphosphonates. In addition, the use of rhPTH(1-34) caused a considerable decrease of pains, accompanied by a consequent reduction of the needs of NSAIDs of the patients. Although the mechanism of action in this sense is not yet known, it is a fact that the treated patients showed a reduction of the back pains caused by the vertebral fractures, in agreement with the findings of other authors (Genant et al., 2005). At last, the most striking aspect of the results is an improvement of the QoL, observed in all patients included in this study. This was the main factor, which assured an absolute compliance of the patients. Actually there are only scarce data regarding the psychological impact of osteoporosis and its consequences, like the fractures. This situation is due, at least in part, to the conviction that only the femoral neck fracture has permanently invalidating consequences, and in other part, to the fact that valid methods of evaluation have been developed only recently. In reality, also other consequences of osteoporosis, like the vertebral fractures may modify radically and permanently the life style and autonomy of the patients. In addition, a sufficiently wide collection of data regarding a consistent evaluation of how the osteoporotic patients live together with their disease is still missing in Italy.
Even if our sample is relatively small, it shows how the consideration of all the aspects of life style in the QUALEFFO-test may be helpful to reveal a significant improvement already after several months of the therapy. In the light of these results, Teriparadate may be considered a pharmacon, which is quite efficient in the treatment of osteoporosis in the non-responders, or all other patients with severe osteoporosis.

After all, we conclude that the therapy with teriparadate increases the BMD considerably, reduces the occurrence of new fractures, improves the QoL, and reduces the consumption of NSAIDs. The results obtained so far indicate that teriparadate represents a new therapeutical option for the patients with severe senile osteoporosis, and also for their doctors. The particularities of the mechanism of action of teriparadate, as well as its optimal tolerability are important factors in the treatment of the metabolic bone diseases.

REFERENCES