Impact of a Phone Follow-Up Program on Persistence with Teriparatide or PTH(1-84) Treatment.

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Impact of a phone follow-up program on persistence with teriparatide or PTH 1-84 treatment.

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Abstract

Purpose A follow-up program to help patients suffering from severe osteoporosis during their therapy with teriparatide or PTH 1-84 has been designed and performed. The objective of this study is to evaluate the 18-month persistence on these therapies in patients participating in the program.
Methods We enrolled 383 patients who started teriparatide or PTH 1-84 following this program and compared them with a historical cohort of 398 patients treated with the same therapies, but who did not participate in any follow-up program. At the beginning of the therapy, nurses trained patients on self-injection. Patients received one phone call per week during the first month, then one phone call per month and per three months during the following five and twelve months respectively. In every call, nurses helped patients to resolve any possible issues and collected adverse event information.
Results Persistence rate of the group following the program is 87%, 10% higher than the group not following any program (77%). Log rank-test on persistence rates on therapy in patients enrolled and not enrolled in the program was performed; the difference was statistically significant (p=0.001). Discontinuation in the follow-up program group occurred mainly at early stages of the treatment due to adverse events.
Conclusions Our results show that patients suffering from severe osteoporosis treated with teriparatide or PTH 1-84 and enrolled in a follow-up program have higher persistence rates than patients not following the program.

Keywords osteoporosis, persistence, adherence, teriparatide, PTH 1-84

Introduction

Osteoporosis is a systemic condition characterized by a low bone mineral density (BMD) and deterioration of bone tissue, associated with an increased risk of fracture. Osteoporosis is a clinical and public health important chronic disease, because osteoporotic fractures are one of the most common causes of disability and a major contributor to medical costs worldwide. Osteoporosis affects 50% of women over 65, and 30% of men [1]. In particular, in Italy the prevalence rate of osteoporosis in women 40-79 years old was approximately 18.5%, while the rate of osteopenia was about 44.7%; in men 60-79 years of age the rates were 10% and 36%, respectively [2]. Fracture is proven to be associated to osteoporosis and osteopenia regardless of sex or age [3]. Mortality is also increased; 35% of affected patients die within one year of a hip fracture and 8% die within one year of a spine fracture [4].
Osteoporosis is a chronic, asymptomatic disease before fracture, and poor persistence with anti-resorptive drugs is a relevant problem in preventing its adverse consequences [5-7]. This phenomenon is not unique to osteoporosis: low adherence is a common problem in many asymptomatic conditions and this problem has also been shown for other interventions in other chronic diseases such as hypercholesterolemia, heart disease, hypertension and diabetes [8-10].
The most common pharmacological agents used to treat osteoporosis are proven to be effective when used in the long term. Randomized controlled clinical trials have shown that intervention decreases vertebral fracture risk by about 50% [11]. However, adherence to osteoporosis medications is still suboptimal; many patients discontinued treatment within the first year, persistence rates at 12 months for oral bisphosphonates have been reported to be as low as 18-22% for daily administration and 31-44% for weekly administration [12,13], 7-50% for oestrogen [14,15], 16-39% for raloxifene [16,17] and 36.7% for calcium and vitamin D [18]. Several observational studies have shown that efficacy is lower in patients that are not adherent to prescribed therapy [19].

Low adherence is associated with higher fracture rates [5, 6]: either discontinuation or non-adherence with anti-resorptive therapies have been associated with smaller decreases in bone turnover markers, smaller BMD gains, and an increased risk of fractures [7]. A recent meta-analysis provided a pooled 46% increased fracture risk in non-compliant patients versus compliant patients: the increased fracture risk was lower for non-vertebral (16%) and hip (28%) fractures than for clinical vertebral ones (43%) [20]. Moreover, low compliance and failure to persist with osteoporosis medications results not only in deteriorating health outcomes, but also in a decreased cost-effectiveness of drug therapy [21-23].

Many factors can influence persistence on therapy: administration modalities, number of medications taken, occurrence and severity of side-effects, comorbidities, age, history of fractures, bone mineral density, patient–physician relationships, lack of patient education, absence of symptoms at early stages of the disease, possible educational and regular follow-up program.

Several options to improve adherence are available, e.g., easier formulations and dosages schemes, nurse follow-up, educational and monitoring programs, improved relationship between physician and patient [24-27]. The persistence is higher if patients are included in some educational programs and regular follow-up: for example for oral bisphosphonates increases from 30-40% to 77% for daily alendronate, and 90% for etidronate [28].

Teriparatide (1-34 human parathyroid hormone active fragment, PTH 1-34) or full-length parathyroid hormone (PTH 1-84) are anabolic agents used in the treatment of severe osteoporosis. They stimulate new bone formation on the trabecular and cortical bone surfaces by preferential stimulation of osteoblastic over osteoclastic activity. Teriparatide and PTH 1-84 reduce the risk of vertebral fracture by 65% and 58% respectively and teriparatide the risk of non-vertebral fracture by 53% [29, 30]. In the US only teriparatide is approved for treatment of postmenopausal osteoporosis, instead in Europe both teriparatide and PTH 1-84 are available for this use. Teriparatide has also been licensed for glucocorticoid-induced and male osteoporosis. In Italy, they are licensed for a treatment course of 18 months, with therapeutic plan that has to be renewed every six months, and their method of administration is a daily subcutaneous injection.

In particular, teriparatide and PTH 1-84 in Italy can be reimbursed by National Health Service to patients with severe osteoporosis and the following characteristics:

1. a new femoral fracture or a moderate-severe vertebral fracture in patient already treated, for at least 1 year, with other osteoporosis drugs for previous femoral fracture or moderate-severe vertebral fracture (since November 2004)
2. three severe cumulative vertebral or femoral fractures, even in the absence of previous osteoporosis-treatments (indication added in July 2007)
3. one severe or two moderate vertebral fractures in patient aged 50 or older and in treatment for more than 12 months with doses > 5mg/die of prednisone or equivalent (only for teriparatide, indication added in July 2009)

In the literature little informations is available on adherence and persistence associated with teriparatide or PTH 1-84.

The objective of the present study is to evaluate the 18-month persistence on therapy with daily subcutaneous injections of either teriparatide or PTH 1-84 in patients participating in an education and phone follow-up program, compared with patients who were treated with the same therapies, but who did not participate in any follow-up program.

Materials and Methods

An educational and phone call follow-up program started in April 2008 in the San Giovanni Battista Hospital of Torino and in other Hospitals in the north-west of Italy (Giovanni Bosco of Torino, Maggiore della Carità of Novara, S. Croce e Carle of Cuneo, SS A. Biagio-C. Arrigo of Alessandria, Acqui Terme and S.Corona of

Pietraligure) to help patients during therapy with daily subcutaneous injections of either teriparatide or PTH 1-84.
Women and men, examined in the previously reported Hospitals, that presented the criteria for prescription of teriparatide or PTH 1-84 were eligible for inclusion in the study. All consenting patients who started teriparatide or PTH 1-84 from April 2008 to May 2010 were enrolled in the educational and follow-up program (intervention group). At the beginning of the treatment, nurses explained the injection technique and trained patients on self-injection. Every two months nurses gave new drug-pens to the patients; this guaranteed the surveillance on patients' compliance. Patients received one phone call per week during the first month, then one phone call per month and per three months during the following five and twelve months respectively. During each call, nurses helped patients to resolve any possible issue, scheduled the next visit, and, if applicable, collected adverse events information, dates and reasons for treatment discontinuation. Patients had also the opportunity to call for possible questions or problems between the regular scheduled phone interviews. All data were collected using a standard form.
A physician visit was scheduled by nurses at 6, 12 and 18 months of treatment; in every visit, a physician evaluate results from blood tests, discussed any possible issue with the patient and, where applicable, renewed the therapeutic plan as requested by italian regulation.
We compared the intervention group with a historical cohort of patients, examined in the San Giovanni Battista Hospital of Torino or in the other Hospitals in the north-west of Italy (Giovanni Bosco of Torino, Maggiore della Carità of Novara, S. Croce e Carle of Cuneo, SS A. Biagio-C. Arrigo of Alessandria, Acqui Terme and S.Corona of Pietraligure), who started therapy from November 2004 to March 2008 and who did not participate in any follow-up program (not intervention group).
The choice to prescribe teriparatide or PTH 1-84 was a personal decision of the physician, the study protocol does not include any recommendation. In males and in patients taking steroids, teriparatide was prescribed in accordance with the European Medicines Agency (EMEA) and locale reimbursement criteria. All patients were supplemented with calcium and vitamin D.
Persistence was defined as the number of patients continuing treatment until the end of the 18-month course. A patient was considered as non-persistent if he stopped treatment before the end of the 18-months course. Compliance was measured by the Medication Possession Ratio (MPR). This is usually defined as the number of days of treatment dispensed divided by the number of days between prescription refills. Patients were considered to be compliant if their MPR was ≥ 0.80. This value is commonly used as a cut-off point when evaluating compliance.
Patients who died were excluded from the analysis.
Patient enrolled in this study signed an informed consensus to participate in the educational and follow-up program.
The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Proportions were compared with 95% Confidence Interval (C.I.). Survival analysis with Kaplan-Meier curves and log-rank tests was used to calculate persistence on therapy. Factors associated with persistence were assessed using Cox proportional hazards models. For all statistical analysis SPSS version 17.0 was used.

Results

The cohort analyzed consists of 781 patients; 383 patients have been enrolled in the intervention group: 50 male (13.1%) and 333 female (86.9%), 286 (74.7%) were treated with teriparatide and 97 (25.3%) with PTH 1-84.
The indications to treatment were diagnosis of severe osteoporosis in the presence of fracture despite already being on other osteoporosis therapy (38%), presence of severe cumulative fractures (58%) or presence of fractures occurred during chronic steroidal treatment (4%).
The not intervention group consisted of an historical cohort of 398 patients treated with teriparatide or PTH 1-84: 9 male (2.3%) and 389 female (97.7%); 360 (90.4%) treated with teriparatide and 38 (9.5%) with PTH 1-84.
The mean age of patient enrolled and not enrolled in the program was 72 (±8.1 SD) and 73(±8.4 SD) years respectively and was not significantly different.
The intervention and not intervention groups are different for sex and type of therapy (PTH 1-34 or PTH 1-84). To analyse possible confounding effect we introduced all these variables (sex, type of therapy, monitoring) in a Cox proportional hazards models (table 1) that showed that the persistence was influenced only by the educational and follow-up program and not by sex or type of therapy (p=0.01).
The persistence rate for patients was 87% and 77% in the intervention and non intervention group respectively (p=0.001); the relative risk of treatment discontinuation was 1.476 (95% Confidence Interval: 1.164-1.871) for patients who did not follow the phone call program.
Log rank test-survival curve on persistence rates of PTH 1-34 or PTH 1-84 in patients enrolled in the intervention and not intervention groups was performed (Fig. 1). Also considering only the female subgroup (333 in the intervention group and 389 in the not intervention group) the results were identical: the persistence rate for patients in the intervention group was 87%, whereas in the not intervention group it was 77% (p=0.001). None of the male subjects (50) discontinued therapy in the intervention group, while in the not intervention group (9 subjects) five patients discontinued the treatment.
During the first 6 months of therapy persistence rates were similar in the intervention and in the not intervention group (92% vs 93%, p ns); after 6 months of therapy the difference (91% vs 82%, p=0.001) becomes statistically significant; this difference remains statistically significant at 12 (88% vs 78%, p=0.001) and 18 (87% vs 77% p=0.001) months of treatment.
In the intervention group the majority of patients who discontinued treatments did so in the first months and nobody discontinued therapy after 13 months of therapy. Discontinuation of therapies (teriparatide or PTH 1-84) occurred mainly at early stages: 24 patients (49%) discontinued therapy during the first three months, 9 patients (18%) between three and six months, 14 patients (28%) between six and twelve months, and 2 patients (4%) after twelve months. In the intervention group the most common causes of discontinuation (Table 2) were drug-related adverse events (AEs), the majority of them are known to be side effects. The most common AEs reported were: gastro-intestinal symptoms (16.5%), arthralgie (10.5%) and cutaneous symptom (8%). After 6 months of treatment patients discontinued therapy mainly for comorbidities. None of the patients discontinued therapy for hypercalcemia; in some patients hypercalcemia was resolved by calcium-vitamin D suspension, dosage-reduction or temporary suspension of the drug. Thirteen patients died for reasons that were not drug-related. Table 3 shows the discontinuation causes in the two different groups of therapy (PTH 1-34 or PTH 1-84), in the intervention group.
In the not intervention group discontinuation of therapy occurred mainly at 6 and 12 months of treatment, because the therapy plan was not renewed. In this group six patients died due to unknown causes.
Table 4 shows that the difference in the persistence is not due to the prescribed drug in the intervention group, whereas in the non-intervention group persistence on PTH 1-34 is significantly higher than on PTH 1-84.
In May 2009 a new device for teriparatide has become available: 176 patients used the old device and 110 patients used the new one. The persistence on PTH 1-34 with the new device was higher than with the old device: 93% vs 86% (p=0.039); this could be due to an easier use of the new device.

Regarding compliance, in the intervention group the overall proportion of patients with an 18 months MPR of > 80% was 100%. In the not intervention group we have no data about compliance.

Discussion

In this study persistence on PTH 1-84 has been studied for the first time in a clinical practical setting. The study show that, even without any follow up program, the persistence after 18 months of therapy on teriparatide or PTH 1-84 for severe osteoporosis is high (77%), and comparable to literature data [31-33], this persistence on teriparatide or PTH 1-84 is higher than the one observed on anti-resorptive osteoporosis treatment [12-17]. This finding could be due to different reasons: patient treated with PTH 1-34 or PTH 1-84 are symptomatic, with multiple fractures and therefore more willing to tolerate eventual side-effects; the drug is prescribed by specialists, hence these patients are more likely to receive more information about their disease and about treatment.

A previous study reported a male persistence (74.3%) comparable to that described in the literature for postmenopausal women [34]. Our data show that persistence on therapy in male patients in the intervention group was 100%; whereas in the not intervention group, more than one half of the male patients did not persist on therapy. The number of male subjects enrolled in our study is low, especially in the not intervention group; teriparatide use in men was registered in Italy only since March 2008.

Several studies demonstrated that educational or phone-call follow-up programs could increase persistence with bisphosphonate [28]. There are few studies providing these indication for teriparatide: a French study [35] reports a persistence rate of 81.5% at 15 months in patients included in an educational and follow-up program, in a study design similar to our; a UK study [36] reports a persistence of 79%-87% in patients monitored by a Home Care Service. Our study confirms these results and shows that coupled educational and phone call follow-up programs are effective in providing higher persistence rates over the 18 month course of treatment, than the one observed in patients not following any program (87% vs 77%).

Our results show that discontinuation in the intervention group mainly occur at early stages of therapies due to AEs while in the not intervention group discontinuation occurs between 6 and 12 months. This result could be explained with the non renewal of the therapeutic plan in the non interventional group, instead in the intervention group the nurses periodically booked its renewal. These data could suggest that in the early months of therapy the major causes of discontinuation are related to therapy side effects, whereas later on the phone follow-up has a greater influence.

Moreover, the causes of discontinuation in the interventional group were AEs in the 53% of patients; these data are similar to those reported in the French study (46.7%) [35], but higher than those reported in the UK study [36] where only 3.8% of women stopped teriparatide for AEs. The reason of these differences may be due to a less tight follow-up program in the UK study, probably the exact side-effects and reasons for discontinuation were missed. In our study, in the not intervention group, the discontinuation rate for AEs was 9.8%.

The majority of AEs have been already known as possible side effects and they are similar to those described by other Authors [37]. In our study the more frequent AEs were gastro-intestinal symptoms (8%) and arthralgie (5%).

Our study also demonstrates that persistence was similar in the PTH 1-34 and PTH 1-84 groups participating in the monitoring program, whereas in patients not following any program the persistence was significantly different, and in particular higher in patients in therapy with PTH 1-34. The reasons are not yet clear, but this could be due to the fact that teriparatide-devices (both the old or the new device) are easier to use, even without any nurse assistance, than PTH 1-84 device; a previous study reported that 98% of patients on teriparatide-therapy found that the pen injection procedure is simple [32].

One of the strength of our study is the long-term follow-up and the periodic phone calls coupled to a final assessment performed by the physician, and not only with the number of delivered drug boxes as reported in other studies [36].

Furthermore, the compliance was guaranteed by the regular distribution of the drug by nurses, hence the overall proportion of patients with an MPR of > 80% was 100%. Compliance (MPR of > 80%) with teriparatide has been previously reported by several studies and ranged between only 19.6% to 82% at 18 months of therapy [31-33, 37]. In our study the educational and follow-up program permitted to obtain the excellent compliance.

On the other hand, our study shows some limits: it is not randomized and the intervention and not intervention groups were not parallel. Further investigation might be addressed to collect other data such as fracture incidence, impact of high persistence on fracture risk, correlation between adherence and bone mineral density, as reported in other studies [32, 37].

In conclusion, we found that persistence on anabolic drugs (teriparatide or PTH 1-84) for severe osteoporosis is comparable to that previously described by other authors, and it is higher that persistence on anti-resorbtive osteoporosis treatment. Moreover our study shows that patients with severe osteoporosis treated with PTH 1-34 or PTH 1-84 and enrolled in an education and follow-up program have a high persistence over the 18 month course of treatment.

It is noteworthy that a periodic follow-up interaction between patients and health professionals is beneficial. It is well known that good treatment compliance and persistence with osteoporosis therapies is fundamental to achieve a significant therapeutic benefit and thereby to reduce the burden that osteoporosis and associated fractures place on individuals and healthcare systems.

Table 1 Cox proportional hazards models of confounding factors about persistence

	BETA	SE	RR	p
therapy	0.223	0,234	1.250	NS
sex	-0.014	0.377	0.986	NS
monitoring	**0.621**	**0.188**	**1.860**	**0.001**

Table 2 Discontinuation causes in the intervention group

Comorbidity	22.5%
Gastro-intestinal symptom	16.5%
Arthralgie	10.5%
Cutaneous symptoms	8%
Tachycardia	4%
Dizziness	4%
Headache	4%
Acute renal failure	2%
Guillain-Barré	2%
Allergy	2%
unknown	24.5%

Table 3 Discontinuation causes in the two different groups of therapy (PTH 1-34 or PTH 1-84), in the intervention group

	PTH 1-34	PTH 1-84
Comorbidity	20.5% (C.I. 7.4-33.2)	30% (C.I. 1.6-58.4)
Gastro-intestinal symptom	17.9% (C.I. 5.9-30.0)	10% (C.I. -8.6-28.6)
Arthralgie	10.2% (C.I. 0.7-19.8)	10% (C.I. -8.6-28.6)
Tachycardia	2.6% (C.I. -2.4-7.5)	10% (C.I. -8.6-28.6)
Headache	---	20%
Cutaneous symptoms	10.2%	---
Dizziness	5.1%	---
Acute renal failure	2.5%	---
Guillain-Barré	2.5%	---
Allergy	2.5%	---
unknown	26%	20%

Table 4 Persistence in patients in therapy with PTH 1-34 or with PTH 1-84 as two separate groups

	PTH 1-34	PTH 1-84
Intervention group	86.4% (C.I. 82.4-90.3)	89.3% (CI.82.9-95.5)
NOT intervention group	78.9% (C.I. 74.7-83.1)	63.1% (C.I. 47.8-78.5)

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Conflicts of interest

No disclosures

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Fig.1 Survival functions of PTH 1-34 or PTH 1-84 persistence in relation to phone monitoring