The Italian Observational Study on Severe Osteoporosis (ISSO): 24-month results on incidence of fractures and adherence to treatment

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Abstract

Objective

To estimate the proportion of patients with very severe osteoporosis (those covered by the reimbursement criteria of the Italian National Health Service) experiencing new vertebral and non-vertebral fragility fractures in the first 24 months of a new anti-osteoporosis treatment.

Methods

Prospective observational study in men and post-menopausal women (aged > 21 years) initiating anti-osteoporosis treatment for very severe osteoporosis. Eligibility was based on teriparatide (TPD) reimbursement criteria in Italy: incident of vertebral or hip fracture during anti-resorptive treatment (minimum 1 year), or at least three prevalent severe vertebral fractures, or two prevalent severe vertebral fractures and a historical proximal hip fracture. Incidence of new clinical vertebral and non-vertebral fractures was documented by original x-rays and/or radiological reports, and a post-hoc analysis compared data from the TPD monotherapy population versus the total treated group.

Results

Overall, 767 patients (mean age 72.8 years, 90.7% women) were enrolled in the study, of whom 628, 538, 419 and 424 attended visits at 6, 12, 18 and 24 months, respectively. The most commonly prescribed therapy was TPD (single-agent; 64.5%), then bisphosphonates and other anti-resorptives (33.3%). A combination of different oral treatments was given to 22.5% of the patients. Overall treatment adherence at 24 months was 65.7%. In a post-hoc analysis, the overall incidence of new clinical vertebral and non-vertebral fractures in the total treated population was, respectively, 4.7% and 2.3% in the first 6 months; 1.8% and 1.6% in the 6–12 month period; 2.9% and 1.4% in the 12–18 month period; and 2.2% and 1.0% in the 18–24 month period.

Conclusion

In patients with very severe osteoporosis, the risk of new vertebral and non-vertebral fractures declined after the first 6 months and remained low throughout the study.

Key words

spine, spinal fractures, observational study, teriparatide, parathyroid hormone, osteoporosis, fractures, osteoporosis therapy

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Introduction

Vertebral and non-vertebral fractures are common clinical consequences of osteoporosis, and it has been widely established that the risk of bone fractures is increased in patients with osteoporosis with a history of previous fractures, particularly of the vertebrae (1-4). The frequency of fractures and mortality during osteoporosis treatment has been widely studied (5). All available treatments for osteoporosis have been registered based on the results of large randomised clinical trials (RCTs) that demonstrated the ability to prevent new vertebral fractures (6-8), and in some cases also non-vertebral (6) or hip fractures (7, 9, 10). Historically, most clinical trials of treatments for osteoporosis were conducted in patients who had been diagnosed with osteoporosis or established osteoporosis as defined by the World Health Organisation (WHO) (at least one prevalent vertebral fracture and T score <-2.5 for bone mineral density [BMD]). However, after placebo-controlled trials demonstrated the efficacy of available treatments, standard guidelines were introduced recommending the administration of pharmacotherapy to patients with established osteoporosis, and the inclusion of such patients in placebo-controlled trials was considered unethical. Thus, the more recent registration trials included mainly patients with moderate osteoporosis or patients already receiving treatment with mild anti-resorptive therapies.

Although some treatments have proven, in RCTs, to have efficacy over a wide range of osteoporosis severity (11, 12), these findings cannot be extrapolated to other treatments and RCTs. For example, for some treatments the relative risk reduction (RRR) of fracture seems to be constant over the examined range of severity within the same RCT (11), although in the case of strontium ranelate, the RRR appears to decline with increasing osteoporosis severity (13).

In many countries, including Italy, osteoporosis treatments are reimbursed exclusively for patients with established osteoporosis. The Italian Study on Severe Osteoporosis (ISSO) is a 24-month, prospective observational study in an outpatient setting designed to evaluate the incidence of new clinical vertebral and non-vertebral fractures in a population affected by very severe osteoporosis. Patients with severe osteoporosis are defined by the WHO as having a T score <-2.5 for BMD with one or more fragility fractures (14). The patients included in ISSO were, in addition, covered by the reimbursement criteria set out in the second part of the restrictive Italian National Health Service Note 79 (patients with incident moderate/severe vertebral or hip fractures occurring during treatment with anti-resorptives prescribed for a prevalent hip or vertebral fracture, or patients with three or more prevalent severe vertebral fractures, or patients with two prevalent severe vertebral fractures and a past proximal hip fracture) (15) and hence are referred to here as having very severe osteoporosis.

The baseline clinical characteristics of the patients participating in the study have been described in detail elsewhere (16), and they highlight the severity of osteoporosis in patients entitled to reimbursement in Italy (average of 3.6 prevalent vertebral fractures, multiple previous non-vertebral fractures and very low BMD values). Patients such as these, with very severe osteoporosis, were not included in the older pivotal RCTs and were excluded from the most recent registration placebo-controlled RCTs for ethical reasons (7, 17).

Materials and methods

The ISSO was a multicentre, prospective observational study carried out in 57 osteoporosis centres in Italy, designed to evaluate over 24 months the clinical evolution of patients with very severe osteoporosis, treated in routine clinical practice according to Italian national recommendations (15).

The baseline characteristics of the patients have been published previously (16) and are also summarised in the Results section of this manuscript; the inclusion/exclusion criteria are summarised in Table I.

All treatments provided to patients for the entire study duration were at the discretion of the participating study physicians, and based on their clinical judgment and the local standard of medical

Table I. Inclusion criteria of the ISSO study based on the reimbursement criteria for teriparatide in Italy (second part of Italian National Health Service Note 79 [15]) and additional exclusion criteria.

Inclusion criteria	Exclusion criteria
Men or postmenopausal women aged >21 years	Any contraindications for the use of any drug for the treatment of osteoporosis; pregnancy and lactation.
Patient presenting with an incident moderate/severe vertebral or hip fractures occurring during treatment with anti-resorptives* prescribed for a prevalent hip or vertebral fracture.	Hypersensitivity to the active substance or to any of the excipients.
Patients with three or more prevalent severe vertebral fractures OR Two prevalent severe vertebral fractures and a past proximal hip fracture.	Pre-existing hypocalcaemia, severe renal iimpairment, metabolic bone diseases (including hyper-parathyroidism and Paget's disease of the bone), unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, skeletal malignancies or bone metastases.

*Bisphosphonates, strontium ranelate, oestrogens, tibolone.

care. According to Note 79 (15), the very high risk patient population participating in ISSO was entitled to full reimbursement (*i.e.* they did not pay anything) for all drugs registered for the treatment of osteoporosis, including oral and intravenous bisphosphonates, teriparatide (TPD), parathyroid hormone, raloxifene and strontium ranelate. When the study started, the period allowed for the reimbursement for TPD in Italy was 18 months. To reflect this, ISSO was planned as an observational study of patients undergoing 18 months of treatment in routine practice followed by a 6-month post-treatment period. In June 2011, during the study, the period allowed for the reimbursement for TPD was extended by the Italian National Health Service to 24 months.

All patients gave written informed consent granting access to their personal health information, and they could withdraw from the study at any time for any reason and without providing any explanation. This study was approved by the local Ethics Committees of each participating site and was conducted in compliance with the Italian Guidelines for Observational trials (issued by the Italian Drug Agency [Agenzia Italiana del Farmaco – AIFA] in 2007) (18).

Although the frequency of clinical evaluation was at the discretion of the study physician, it was suggested that patients who enrolled in the study undergo a medical evaluation after approximately 6, 12, 18 and 24 months. As the primary objective of this study was to evaluate the incidence of new vertebral and non-vertebral fractures based on clinical changes, patients were asked about the occurrence of such new fractures at each visit. Patients reporting signs and symptoms of a new vertebral fracture (such as acute back pain, persisting for more than a week, localised to specific vertebra and relieved by bed rest, or worsened when upright) underwent a vertebral x-ray or a dual-energy x-ray absorptiometry (DXA) scan for vertebral morphometry, according to the study physician's usual clinical practice. Study physicians reviewed original x-rays and/or radiology reports to confirm any new clinical vertebral or non-vertebral fractures, or the worsening of pre-existing fractures. The occurrence of a new vertebral fracture was defined as a reduction in any of the three vertebral heights (anterior, middle, posterior) by ≥20% and ≥4 mm as reported using radiological or DXA imaging (15, 19). Fracture incidence was calculated as the number patients with at least one new fracture.

Adherence to therapy was established at each observation by patients' self-reports, where patients were asked to estimate the number of doses they had missed since their most recent visit. A patient was considered non-adherent to therapy from baseline if she/he was judged non-adherent by the treating physician at least once since baseline; otherwise patients were considered always adherent since baseline. Adherence in patients with missing/unknown data was considered unknown. Non-adherence was not a cause for discontinuation from the trial.

Statistics

The planned sample size of 650 patients was based on the assumption that 10% of patients would experience at least one new clinical fracture in the 24-month observational period, with a 95% confidence interval of 5% width (7.5%–12.5%), and with a 15% drop-out rate (patients dropping out of the study or being lost to follow-up before experiencing a fracture).

The number and percentage of patients with new fractures were summarised for each 6-month interval during follow-up for the different fracture types (vertebral, non-vertebral) in the overall evaluable population. A sub-analysis was pre-planned to assess the incidence of new fractures in groups of patients receiving different types of osteoporotic therapies; a formal comparative analysis was not planned because of the lack of any randomisation procedure. However, the extension, during the study, of the period allowed for the reimbursement for TPD by the Italian National Health Service in 2011 (from 18 to 24 months) resulted in a growing number of patients who would previously have stopped therapy after 18 months but who continued to receive treatment until 24 months. Because of the observational nature of the ISSO study, we were unable to control for these patients. This, together with the large number of patients receiving TPD monotherapy and the low numbers of patients receiving other types of therapy precluded such an analysis. Hence, new fracture data for each 6-month interval during follow-up were pooled for all evaluable patients at each time point (total treated group) and compared with data from patients receiving TPD monotherapy in a post-hoc analysis.

Patients who reported that they had discontinued treatment were considered as having been treated up to and including the time of their last visit,

Table II. Patient population features and risk factors for fractures at baseline.

Risk factor	Patient population (n=760)
Gender, n (%)	
Women	689 (90.7)
Men	71 (9.3)
Age, years	
Mean ± SD	72.8 ± 8.8
Range	45–94
BMI, kg/m²	
Mean ± SD	25.6 ± 4.5
Range	14.5–44.1
Mother with osteoporosis, n (%)	121 (15.9)
Mother with fragility fractures, n (%)	114 (15.0)
Hip	83 (10.9)
Vertebral	29 (3.8)
Other	24 (3.2)
Number of falls in last year	
Mean	0.7 ± 1.5
Range	0–15
Alcohol consumption, n (%)	104 (13.7)
Smoker, n (%)	
Current	92 (12.1)
Former	94 (12.4)
Regular physical activity, n (%)	148 (19.5)
Uses arms to rise from chair, n (%)	484 (63.7)
Immobilised for >3 months in last 5 years, n (%)	110 (14.5)
Previous non-vertebral fracture	
Patients affected, n (%)	293 (38.6)
Number*, mean ± SD	1.4 ± 0.7
Range	1.0–6.0
Previous vertebral fracture	
Patients affected, n (%)	733 (96.4)
Number*, mean ± SD	3.4 ± 1.8
Range	1.0–11.0

BMI: body mass index; SD: standard deviation. *In patients with a previous fracture.

Table III. Anti-osteoporosis therapies taken at the time of recruitment and during the study. The proportion of the patients taking vitamin D supplements either with calcium or alone is also given.

Previous anti-osteoporosis therapies	n (%) (n=*760)*
Bisphosphonates*	507 (66.7%)
Strontium ranelate	85 (11.2%)
Teriparatide	14 (1.8%)
Raloxifene	11 (1.4%)
Others	10 (1.3%)
Prescribed therapies at recruitment	n *(%)*
Number of patient with at least one therapy	759 (99.9%)
Single agent (any therapy)	588 (77.4%)
Teriparatide (single agent)	490 (64.5%)
More than one therapy (concomitant or consecutive)	171 (22.5%)
Only anti-resorptive therapy (bisphosphonates or others**)	79 (10.4%)
Concomitant use of Calcium and Vitamin D	n *(%)*
Calcium	170 (22.4%)
Vitamin D	363 (47.8%)

*Alendronate, risedronate, ibandronate, neridronate, clodronate. **Includes patients on strontium ranelate, tibolone, oestrogen replacement therapy.

and were excluded from analyses from this point onwards.

All statistical tests were conducted using a two-sided significance level of 0.05. Data were analysed using SAS software® v. 9.2.

Results

Patient disposition, demographic and baseline characteristics and types of therapy

Overall, 767 patients from 56 osteoporosis centres were enrolled in the study and 760 provided signed informed consent and attended the baseline visit. A total of 438 patients completed the study. The main reason for discontinuation from the study was loss to follow-up in 178 participants (23.1%). Results were recorded for 628, 538, 419 and 424 patients at 6, 12, 18 and 24 months, respectively. A proportion (213 out of 490, 43.5%) of the patients treated for the duration of the study only with TPD completed the original maximum allowed reimbursement duration of 18 months. For 158 of the 490 TPD patients (32.2%), the 18-month time point fell after the maximum duration of TPD therapy reimbursement had been extended to 24 months and they completed their final visit at 24 months.

Demographic and other baseline characteristics of patients have been previously reported (16) and are summarised in Table II. The study population had a mean age of 72.8 years (standard deviation 8.8; range 45–94) and the majority were women (90.7%). Patients had experienced a minimum of 1 and a maximum of 11 previous fractures (either vertebral or non-vertebral fractures; data not shown). Additional important risk factors (smoking, family history, recurrent falls) were present in 82% of all patients (data not shown).

Table III summarises the anti-osteoporosis therapies taken prior to and prescribed at the time of enrolment. Since the study inclusion criteria included patients with very severe osteoporosis, according to Italian reimbursement criteria, we found it unsurprising that 64.5% of the patients were prescribed TPD alone, while 33.3% were prescribed at least a bisphosphonate (alendronate, risedronate, ibandronate, neridronate,

Table IV. Post-hoc analysis of the incidence of new vertebral and non-vertebral fractures in patients with very severe osteoporosis treated with teriparatide monotherapy compared with data from all evaluable patients at each time point (total treated group) for each 6-month interval during follow-up.

	0–6 months				6–12 months				12–18 months				18–24 months			
		Patients with ≥1				Patients with ≥1				Patients with ≥1				Patients with ≥1		
	n	Vertebral n (%)	Non-vertebral n (%)	Fracture n (%)	n	Vertebral n (%)	Non-vertebral n (%)	Fracture n (%)	n	Vertebral n (%)	Non-vertebral n (%)	Fracture n (%)	n	Vertebral n (%)	Non-vertebral n (%)	Fracture n (%)
Teriparatide	420	19 (4.5)	8 (1.9)	24 (5.7)	394	2 (0.5)	5 (1.3)	7 (1.8)	366	9 (2.5)	2 (0.6)	11 (3.0)	283	4 (1.4)	3 (1.1)	7 (2.5)
Total treated	663	31 (4.7)	15 (2.3)	41 (6.2)	630	11 (1.8)	10 (1.6)	21 (3.3)	591	17 (2.9)	8 (1.4)	25 (4.2)	493	11 (2.2)	5 (1.0)	16 (3.3)

Fracture incidence was calculated as the number of patients with at least one new fracture.

clodronate) or other anti-resorptive (strontium ranelate or raloxifene). In 22.5% of patients the prescribed therapy was a combination of agents given concomitantly or sequentially; none of these patients had been taking both TPD and PTH (1-84) at the same time or in sequence during the evaluation time. The number of patients taking a concomitant therapy with TPD (n=5) was too small to affect the study conclusions. Therapy was switched from prior therapy to a bisphosphonate or to TPD in 14.2% and 0.3% of patients, respectively.

Incidence of new fractures

In the overall evaluable population (n=663), the incidence rate of new fractures during the first 12 months of observation was 8.9%, declining to 6.0% during the second 12 months. Corresponding data for new vertebral fractures were 6.2% and 4.1%. The incidence of new non-vertebral fractures during the first 12 months was 3.5%, but it declined to 2% during a 12- to 24-month period of the study.

In the post-hoc analysis, the incidence of both new vertebral and non-vertebral fractures (based on the numbers of patients available at each time point) was lower in the TPD monotherapy group than in the total treated group during each 6-month period of the study, with the exception of that for non-vertebral fractures at the 18–24-month period (Table IV).

Adherence to treatment

Adherence to treatment was 65.7% considering all the treatments; it was 72.9% for patients receiving TPD at month 18. Of the patients who could continue TPD treatment for an additional 6 months (to 24 months), adherence was 69.3% *versus* baseline and 78.5% *versus* the previous visit.

Discussion

The pivotal phase 3 TPD study (20) was a RCT in patients with severe osteoporosis (the mean number of vertebral fractures at baseline was 2.3–2.4), and the patients' mean age was 69 years. In our observational study cohort the mean patient age was 72.8 years, the mean number of previous vertebral fractures was 3.4 and a relevant proportion of patients (38.6%, Table II) had experienced a non-vertebral fragility fracture, making this population more severely affected by osteoporosis than the one in the pivotal RCT.

Overall, our results show that the incidence of new vertebral and non-vertebral fractures in patients with very severe osteoporosis at high risk of new fractures decreased over the 24-month period of the trial; hence, ongoing treatment for osteoporosis decreased the risk of new fractures as has been reported for other osteoporosis therapies (21). TPD monotherapy was generally found to be associated with lower fracture rates than those seen in the total treated group; however, no statistical analysis was performed as the patients receiving TPD monotherapy formed the majority of the total treated group. Hence, the post-hoc analysis was used to clean the data as much as possible, so as to provide more information on the TPD monotherapy group.

The overall incidence rates for new vertebral and non-vertebral fractures reported here are slightly lower than those reported in the Fracture Prevention Trial (FPT) conducted in post-menopausal women after a median TPD treatment duration of 21 months (20). The reductions in incidence rates of new overall, vertebral and non-vertebral fractures over time are also consistent with those reported in the European Forsteo Observational Study (EFOS), conducted in post-menopausal women after 18 months of TDP therapy (6), and after 18 months of follow up (data reported only for overall fractures) (22), and those in the US Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) observational study conducted in men and women with osteoporosis after 24 months of TDP therapy (data reported only for non-vertebral fractures) (23). Our observations therefore support the efficacy of TPD in the treatment of patients with very severe osteoporosis.

All patients included in this study received a pharmacological treatment. Patients in the anti-resorptives group received one of a variety of agents from this class, preventing any comparisons between this study and RCTs of single anti-resorptive therapies.

Treatment adherence was very good in all patients, and higher than reported in a number of observational studies among patients with osteoporosis (24). However, it should be taken into consideration that the method by which adherence was monitored in this study was self-report. Although this subjective method of assessment is commonly used in studies of osteoporosis management (24, 25), discordance with objective methods of adherence has been re-

ported (26). This and the lack of information on the difference in adherence between patients receiving mono- and polytherapy must be acknowledged as limitations of this study.

Another limitation is that the study may have been underpowered to detect clinically meaningful effects as the 10% fracture rate on which the study sample size was based was not achieved in the study. Nevertheless, the results from this study clearly suggest that the presence of very severe osteoporosis in patients who have experienced more than one new fracture represents a strong motivation to continue treatment with adequate adherence.

In conclusion, this 24-month observational study in patients with very severe osteoporosis reported good rates of osteoporotic treatment adherence that are essential in achieving optimal therapeutic outcomes (27). New vertebral and non-vertebral fracture rates among patients treated with TPD remained low throughout the study, reflecting the reduction in fracture risk reported with TPD (28). This finding, combined with the reduction in direct and indirect healthcare costs expected to result from fewer fractures (29) and the fact that TPD is fully reimbursed in Italy in patients with very severe osteoporosis who are at very high risk of new fractures (15), suggests that TPD is a cost-effective treatment for Italian patients with very severe osteoporosis.

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