

Baseline characteristics of the population enrolled in the Italian Observational Study on Severe Osteoporosis (ISSO)

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Abstract

Objective

Baseline characteristics of the population enrolled in the ISSO study, designed to evaluate the incidence of vertebral and non-vertebral fractures in Italian patients with severe osteoporosis treated according to clinical practice over 24 months observation.

Methods

Prospective observational study in 783 post-menopausal women and men entering 18-month treatment with teriparatide in a community setting at 57 centres in Italy.

Characterisation included demographics, fracture risk factors, bone mineral density, fracture status, Health-Related Quality of Life (HRQoL) measured by the European Quality of Life Questionnaire, EQ-5D, and back pain assessed by VAS.

Results

Most patients were elderly women (90.5%), mean age \pm SD was 72.9 \pm 8.8 years. Nearly all (91.3%) had experienced ≥ 1 vertebral fracture (mean \pm SD, 3.6 \pm 2.2 per patient), 37.5% had ≥ 1 non-vertebral fracture (mean \pm SD, 1.4 \pm 0.7 per patient). Nearly all patients were suffering from back pain (94.9%), which had significantly restricted their daily activities (51.7%) and had likely or very likely been caused by vertebral fractures (29.2% and 55.8%, respectively). Mean EuroQoL EQ-5D index value was 0.58 \pm 0.25 and VAS score 49.2 \pm 23.6. Non-vertebral fractures, back pain and multiple vertebral fractures were associated with lower HRQoL (EuroQoL-5D Index both $p < 0.001$, EQ-5D VAS score $p = 0.025$ and $p < 0.016$, respectively). Many patients were physically inactive (81.1%). One third (34.7%) of the population had co-morbidities and 60.5% were on chronic concomitant treatments. Few subjects reported a maternal history of osteoporosis (15.5%), regular consumption of alcohol (13.3%) or were current smokers (11.5%).

Nearly two-thirds (71.5%) had already been treated for osteoporosis, mainly with bisphosphonates. Calcium and vitamin D supplements were taken by 13% and 15.5% of the total population, respectively.

Conclusions

At enrolment, the population of ISSO study mostly consisted in aging women, who had osteoporosis with high fracture risk, poor HRQoL and suffered from significant back pain. Most of them had already been treated by bisphosphonates but without calcium and vitamin D supplements. Back pain, as well as non-vertebral and multiple vertebral fractures, were associated with lower HRQoL.

Key words

osteoporosis, observational study, risk factors, fractures, back pain, treatment, quality of life

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Received on May 20, 2010; accepted in
revised form on December 20, 2010.

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EXPERIMENTAL RHEUMATOLOGY 2011.

The data were presented as a poster
at the SIOMMS and AME 2009
congresses.

Competing interests: The study was fully
sponsored by Eli Lilly Italia; S. Silvestri
and D. Valle are employees at Eli Lilly
Italia; L. Tauchmanova, was employed
at Eli Lilly Italy when the paper was first
submitted to the journal and is currently
an employee of Boehringer Ingelheim;
the other co-authors have declared no
competing interests.

Introduction

Osteoporosis has been defined as a skeletal disorder characterised by reduction in bone strength associated with an increase in the risk of fracture. Bone strength mainly reflects the integration of bone density and bone quality (NIH Consensus Development Panel on Osteoporosis 2001) (1). Therefore, low bone mass and microarchitectural deterioration of bone tissue increase bone fragility, with consequent risk of low-energy fractures.

Established osteoporosis has been defined by World Health Organization as a T-score below -2.5 in the presence of one or more fragility fractures. Although many studies have indicated that the risk of fragility fractures progressively increases with bone mineral density (BMD) decline (2-7), prevalent fractures represent the most important risk for further fractures. Therefore, patients who sustained a vertebral fracture are a particularly vulnerable group whose risk of a new incident vertebral fracture within the following year is increased 3- to 5-fold as compared to individuals without a prevalent fracture (8, 9). Furthermore, the risk of developing another clinical fracture within 2 years was estimated to be 10.8% in subjects with a prevalent fracture (10). During the follow-up period of 2.7 years after the STOP-trial, both in the former alendronate and alfacalcidol group (administered for 18 months for glucocorticoid induced osteoporosis), 24% of the patients underwent at least one new vertebral fracture. This finding underlines that prevention of vertebral fractures remains a clinical challenge, even when anti-osteoporosis drugs are prescribed. STOP-trial medication and presence of pre-existing fractures did not predict development of new fractures, whereas age and cumulative glucocorticoid-dose did (11). Moreover, mortality was found to be significantly increased in subjects with clinical vertebral fractures (12, 13). It is uncertain if the link between increased mortality in patients with low BMD or with recent hip and vertebral fractures is casual. Mortality in osteoporotic patients may be related to both co-morbidities and directly or indirectly to fracture it-

self (14). To date, there are few inconclusive data on reduced mortality in patients treated for osteoporosis (14).

The main aim of treatment for established osteoporosis is prevention of the "fracture cascade" triggered by the first fracture, as well as, ultimately, the reduction in morbidity and mortality. On the other hand, several randomised, placebo-controlled clinical trials showed that treatment of post-menopausal osteoporosis with teriparatide decreased the risk of vertebral and non-vertebral fractures and increased vertebral, femoral and total-body BMD (15, 16). Clinical trials documented efficacy of teriparatide also in males with osteoporosis (17, 18). However, the experience within randomised clinical trials, with their tight entry criteria, may differ from that in real-life practice. Patients in common daily practice may have been treated with many different osteoporosis therapies, may have several co-morbidities, may use concomitant medications that is normally excluded in controlled clinical trials and may not appropriately take all vitamin and mineral supplementation. Observational studies provide the opportunity for evaluation of treatment effects in a heterogeneous population in order to complete the information deriving from clinical trials with experience of teriparatide use in patients in routine clinical practice.

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 severe osteoporosis and treated according to the reimbursement criteria set in the restrictive Italian National Health Service Note 79 (19).

Secondary objectives included the assessment of compliance; the identification of reasons for discontinuation of osteoporosis treatment; the assessment of back pain rate and changes in Health-Related Quality of life (HRQoL). In addition, serial measurements of BMD and the bone turnover markers were collected, providing that they were performed as part of routine clinical practice.

This is the report on the baseline demographics and clinical characteristics,

HRQoL and back pain of the total patient cohort recruited in the ISSO study.

Materials and methods

Study design

This prospective observational study was carried out in out-patients that were consecutively enrolled at 57 osteoporosis centres. The aim of this study was to estimate the proportion of patients with severe osteoporosis experiencing vertebral and/or non-vertebral fragility fractures over 24 months, according to the reimbursement criteria of Note 79. Anabolic treatment is being administered for 18 months in routine clinical practice, with a subsequent post-treatment observation period of 6 months. The study was observational, *i.e.* non-interventional. Assessments, frequency of investigations and treatment were at the discretion of the investigators according to their medical judgment and local healthcare standards. All patients gave their written informed consent, granting access to their personal health information and understood that they could withdraw from the study at any time without any consequences. The study was approved by local Ethics Committees and was conducted in compliance with local and European legislation related to clinical trials and with the Italian Guidelines for Observational trials (issued by the Italian Drug Agency – Agenzia Italiana del FARMaco - AIFA – in 2007) (20).

Study population

The target study population consisted of post-menopausal women or males older than 21 years in a community setting, who were starting anabolic treatment for osteoporosis, according to reimbursement criteria for their condition (National Health Service Note 79) (19), presenting with the following: an incident vertebral fracture or hip fracture during treatment; anti-resorptive treatment prescribed for prevalent hip or vertebral fracture assumed for at least 12 previous months according to usual clinical practice and local regulations; 3 or more prevalent severe vertebral fractures; or 2 prevalent severe vertebral fractures and a historical proximal hip fracture. Patients were excluded from the study

if they had any contraindication to the use of drugs for treatment of osteoporosis: hypersensitivity to the active substance or to any of the excipients, pregnancy and lactation, pre-existing hypercalcaemia, severe renal impairment, metabolic bone diseases (including hyperparathyroidism 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.

The target recruitment was set at 650 patients and was reached in 9 months (from June 2008 to February 2009).

The sample size calculation was based on the following assumptions: 10% of patients would experience one or more fractures in the 2-year observation period; 650 patients would yield a 95% confidence interval, 5% wide (*i.e.* 7.5%, 12.5%). If the observed rate was as high as 20%, the width would be 6.7%, assuming that 15% of patients would drop-out or be otherwise lost to follow-up before experiencing a fracture.

Baseline observations

The following demographic variables were collected at the baseline observation: age, race, weight, height, age at menarche, age at menopause, type of menopause and parity.

Details were also obtained regarding risk factors and concomitant chronic diseases: history of fragility fracture after age of 40; history of fragility fracture in mother; falls in the last year; sense organ disorders; smoking status; alcohol use; regular exercise; chair-rising test (21); mobility status; current chronic diseases and/or chronic therapies that could affect bone metabolism/fracture risk. Historical vertebral fractures were confirmed by radiographs, non-vertebral fractures were confirmed by radiographs anytime this was possible and by medical records in all other cases.

Data on any previous anti-osteoporosis treatment were also obtained, and lumbar and femoral BMD measurements by dual x-ray absorptiometry (DXA) were performed.

HRQoL was assessed using the European Quality of Life Questionnaire, EQ-5D (formerly known as EuroQoL

(22)). This is a standardised five-item instrument for use as a measure of health outcome (23). It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. EQ-5D has five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (22). Each dimension comprises three levels (no problems, some problems and extreme problems), generating a total of 243 theoretically possible health states. The health state value (HSV) was calculated using the Italian scoring algorithm to allow for comparisons (24). In addition to the HSV, health status was evaluated by the patient on a visual analogue scale (VAS) ranging from 0 mm (the best) to 100 mm (the worst).

The patients were asked to report any back pain, assessed using a VAS from 0 mm (= no pain) to 100 mm (= worst pain). A back pain questionnaire focusing on pain features during the last month (frequency, severity, impact on daily activities and number of bedridden days) was also used. Patients were also asked if they had no pain, moderate or severe pain during the last month.

Statistical analysis

Data management and analyses were centralised, with analyses conducted by a third party according to a pre-specified statistical analytical plan.

Demographic data, clinical characteristics and risk factors at baseline were analysed. Descriptive summary statistics included mean and standard deviation (SD), median and range for continuous variables, and counts and percentages were provided for categorical variables. Missing values were included in the calculation of percentages for categorical variables.

EuroQol EQ-5D index and VAS score were compared using ANalysis Of VAriance across groups (ANOVA). F-test comparison of groups were based on the following characteristics of past fractures: occurrence of fractures and number of fractures, maximum fracture severity (for vertebral fractures only) and type of fractures. The same

comparisons were performed between groups based on occurrence of back pain during the last month, and on frequency and severity of back pain (assessed using a categorical scale and VAS) during the last month. All statistical tests were exploratory in nature, and were carried out on a 2-sided significance level of 0.05.

Results

Demographics and risk factors for fractures at baseline

A total of 793 patients were recruited within the enrolment timeframe at 57 Italian centres, 787 performed the baseline visit and 783 were eligible in the baseline analysis.

The baseline features are summarised in Table I. Most of the patients were women (90.5%). All patients were Caucasians except for one Hispanic woman. On average the patients were elderly (mean±SD, 72.9±8.8 years); although the age range was broad (45-94 years). Mean BMI±SD was 25.5±4.5 kg/m², and the range varied from severely underweight (14.5 kg/m²) to severely obese (44.1 kg/m²) subjects. Thirty patients had a BMI<19 kg/m², 22 of them took a previous therapy with bisphosphonates and/or vitamin D; only 6 (out of 30) reported intestinal malabsorption as co-morbidity. Most women reported at least one pregnancy (84.9%) and had a natural menopause (81.9%). Mean±SD age at menarche and at menopause were 12.9±1.6 and 48.0±5.9 years, respectively. Mean±SD time elapsed from menopause (calculated as age at baseline visit/age at menopause) was 25.0±9.6 years.

The analysis of lifestyle showed that most of the patients (81.1%) reported no physical activity. A total of 147 (18.8%) patients reported physical activity and mean (SD) number of hours per week was 4.0 (3.1) in 125. Relatively few patients had other known risk factors including regular alcohol consumption (13.3%) and current or former smoking (both 11.5%). Moreover, 111 out of 783 (14.2%) had been bedridden for at least 3 months during the last 5 years (Table I). A minority of patients (15.5%) reported a maternal history positive for osteoporosis.

During the chair rising test, 488/783 (62.3%) used arms to stand up.

Concerning densitometric measurements, mean±SD BMD values in females and in males were 0.77±0.15 g/cm² and 0.83±0.16 g/cm² at the Lumbar Spine (LS) 0.61±0.12 g/cm² and 0.65±0.15 g/cm² at femoral neck and 0.68±0.13 g/cm² and 0.73±0.15 g/cm² at the total hip, respectively.

Co-morbidities and concomitant medications

More than one third of patients (34.7%) had one or more concomitant chronic diseases; chronic pulmonary obstructive disease (7.5%), cerebrovascular disorders (7.2%) and diabetes mellitus (6.8%) were the most frequent.

Most of the patients (60.5%) were taking one or more concomitant medications. The most common treatments consisted in anti-hypertensives (35.9%), followed by glucocorticoids (13.4%) and thyroid hormones (12.0%).

Fracture history

A total of 715 patients (91.3%) had at least one prevalent vertebral fracture; their mean number per patient was 3.6±2.2 (range 1-23). Most of patients (64.5% of all 783 patients) had at least one severe fracture, while moderate and mild fractures occurred in 24.1% and 2.7% of patients, respectively. Fractures occurred throughout the entire spinal column (T4-L4); the most common location was T12-L1 (Fig. 1).

A total of 294 patients (37.5%) had experienced at least one non-vertebral fracture; the mean number being 1.4±0.7 per patient (range 1-6). The most common location was the wrist (Colles' fracture) (n=73/783, 9.3%), followed by the femur (n=66/783, 8.4%) (Fig. 2). Part of the patients (n=263; 33.5%) with a non-vertebral fracture had also one or more vertebral fractures.

Back pain and health-related quality of life

Nearly all the patients (94.9%) had suffered from back pain in the last 12 months; this was mainly located in the lower back (56.4%). More than half of the cohort (53.3%) had experienced moderate pain in the last month. The

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

Risk factor	Population included in the baseline analysis (n=783)
<i>General features</i>	
Gender, n (%)	
Women,	709 (90.5)
Men	74 (9.5)
Age (years)	
Mean ± SD	72.9±8.8
Range	45-94
BMI	
Mean ± SD	25.5±4.5
Range	14.5-44.1
<i>Family history, n (%)</i>	
Mother with osteoporosis	121 (15.5)
Mother with fragility fractures	115 (14.7)
Hip	83 (10.6)*
Vertebral	30 (3.8)*
Other	24 (3.1)*
<i>Falls (n=778)</i>	
Mean number in last year	0.7±1.5
Range	0-15
Sense organ disorders, n (%)	113 (14.4)
<i>Lifestyle, n (%)</i>	
Alcohol consumption	104 (13.3)
Smoker	
Current	90 (12.5)
Former	90 (11.5)
Regular physical activity	147 (18.8)
Uses arms to rise from chair	488 (62.3)
Bedridden for >3 months in last 5 years	111 (14.2)
<i>Number of previous fractures per patients</i>	
Non-vertebral (n=294)	
Mean ± SD	1.4±0.7
Range	1.0-6.0
Vertebral (n=715)	
Mean ± SD	3.6±2.2
Range	1.0-23.0

*Mother were diagnosed with more than one type of fractures. This is why the sum of patients with hip, vertebral or other diagnosed fractures did not correspond to the total number of mothers with fragility fractures.

BMI: body mass index; SD: standard deviation.

frequency of back pain during the last month was reported as once or twice, a few times, quite often or even every day by 9.3%, 27.2%, 29.8% and 28.6%, respectively. Patients had spent on average (SD) 9.3 (8.5) days in bed in the last month due to back pain. For the patients who spent at least 1 day in bed, the mean number of days in which patients were bedridden in the last month was 9.3. Back pain caused moderate or even severe extent of limitations in

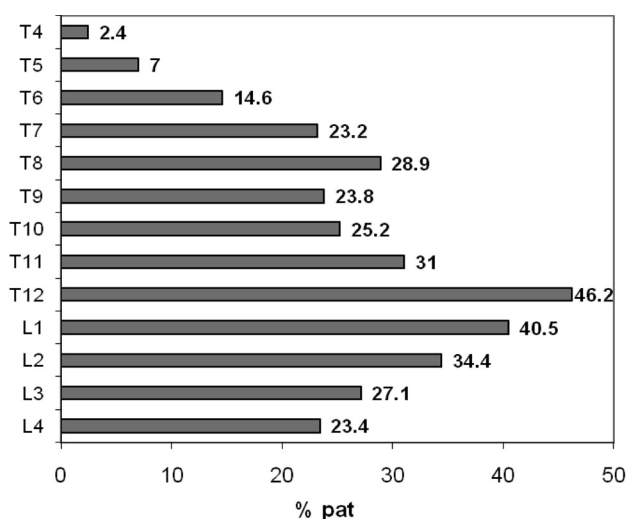


Fig. 1. Site of vertebral fractures expressed as percentage (%) of total population (n=783; patients could have fractures in more than one location).

pat: patients

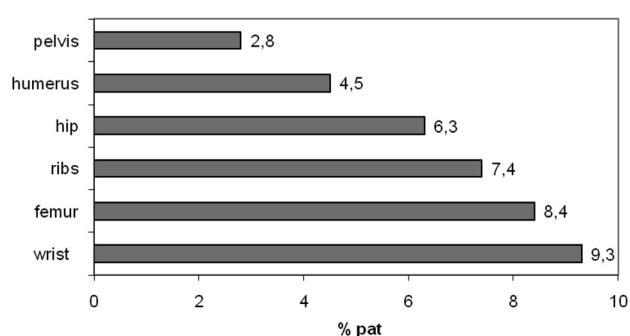


Fig. 2. Site of non-vertebral fractures ($\geq 2\%$ patients) expressed as percentage (%) of total population (n=783; patients could have fractures in more than one location).

pat: patients

daily activities in 35.5% and 16.2% of patients, respectively.

The mean EQ-5D HSV at baseline in patients with back pain in the last 12 months was 0.58 ± 0.25 and VAS score 48.7 ± 23.3 .

There were statistically significant differences between patients with and without back pain during the last 12 months with regards to the EuroQoL EQ-5D index value ($p < 0.001$) and VAS score ($p = 0.016$). Frequency and severity of back pain during the last month significantly contributed to the reduction in quality of life, both in terms of the EuroQoL EQ-5D index and VAS score ($p < 0.001$) (Table III).

No statistically significant differences were observed in the mean EuroQoL EQ-5D index ($p = 0.542$) and VAS score ($p = 0.163$) between patients who experienced fractures in the past and those who did not. When exploring the possible impact of the number of fractures for those patients with fractures in the past, statistically significant differences were observed only in the EQ-5D index ($p = 0.016$) (Table III). When

vertebral and non-vertebral fractures were considered separately, a history of non-vertebral fractures was significantly associated with poorer quality of life (EuroQoL EQ-5D Index and EQ-5D VAS score $p < 0.001$ and $p = 0.025$, respectively), whereas multiple vertebral fractures, (> 5) were associated with a reduction in EQ-5D VAS score ($p = 0.031$).

Previous treatment for osteoporosis

Nearly two thirds (71.5%) of the cohort had been treated with one or more agents for osteoporosis in the past. The most common agents were bisphosphonates (Table IV). The supplement with calcium and vitamin D was taken only by 13.0% and 15.5% of patients, respectively.

Discussion

The population recruited in the multicentre, observational ISSO study was characterised by severe osteoporosis with high fracture risk. The cohort mainly consisted of elderly females with multiple prevalent fractures (av-

Table II. Back pain.

Back pain	Population included in the baseline analysis (n=783) n (%)
Occurrence in last 12 months	743 (94.9)
No back pain	22 (2.8)
Missing information	18 (2.3)
<i>Location</i>	
Upper back	115 (14.7)
Lower back	442 (56.4)
Both	148 (18.9)
Not specified	78 (10.0)
<i>Frequency in last month</i>	
Every day /almost every day	224 (28.6)
Fairly often	233 (29.9)
A few times	213 (27.2)
Once or twice	73 (9.3)
<i>Severity during last month</i>	
Severe	201 (25.7)
Moderate	417 (53.3)
Mild	124 (15.8)
Missing	1 (0.1)
VAS (mean \pm SD)	6.1 \pm 2.4 (n=743)
<i>Extent of limitations of patient's activities during last month</i>	
Severe	127 (16.2)
Moderate	278 (35.5)
Minor	235 (30.0)
None	102 (13.0)
Not specified	41 (5.3)
<i>Days bedridden during last month</i>	
Mean \pm SD	9.3 \pm 8.5 (n=350)

VAS: visual analogue scale; SD: standard deviation.

erage 3.6 vertebral fractures and 1.4 non-vertebral fractures per person) and was characterised by physical inactivity, frequent concomitant diseases and chronic treatments that are known to affect BMD (25). Most women had had at least one pregnancy (84.9%) and a natural menopause (81.9%). The mean age at menopause was 48.0 years and time elapsed since menopause 25.0 years. Other risk factors such as positive family history of osteoporosis, smoking or alcohol use were revealed in a small proportion of patients.

Baseline characteristics of the ISSO population were consistent with those of EFOS, a recent observational study carried out in 1645 post-menopausal female patients treated with teriparatide in an outpatient setting in 8 European countries (not including Italy): in that study mean age was 71.5 ± 8.4 years,

Table III. Impact of fractures and back pain on EuroQol EQ-5D Index and VAS score.

Parameter	Euroqol EQ-5D index mean±SD (n)	p-value	EuroQol EQ-5D VAS score mean±SD (n)	p-value
<i>Past fractures</i>				
Yes	0.58 ± 0.25 (720)	0.542	49.0 ± 23.6 (736)	0.163
No	0.61 ± 0.29 (34)		54.5 ± 23.0 (37)	
Number of fractures		0.016		0.064
0	0.61 ± 0.29 (34)		54.5 ± 23.0 (37)	
1	0.65 ± 0.22 (70)		52.9 ± 21.1 (74)	
2	0.58 ± 0.25 (111)		47.4 ± 22.1 (114)	
3	0.57 ± 0.26 (169)		52.1 ± 22.8 (172)	
4	0.63 ± 0.22 (127)		49.6 ± 23.3 (129)	
5	0.54 ± 0.26 (94)		46.4 ± 25.7 (95)	
>5	0.55 ± 0.26 (149)		45.6 ± 25.0 (152)	
<i>Past non-vertebral fractures</i>				
Yes	0.54 ± 0.25 (282)	<0.001	46.8 ± 22.2 (293)	0.025
No	0.61 ± 0.25 (472)		50.7 ± 24.2 (480)	
<i>Past vertebral fractures</i>				
Yes	0.58 ± 0.25 (690)	0.712	48.9 ± 23.7 (705)	0.224
No	0.60 ± 0.27 (64)		52.5 ± 21.3 (68)	
Number of fractures		0.225		0.031
0	0.60 ± 0.27 (64)		52.5 ± 21.3 (68)	
>5	0.54 ± 0.27 (110)		44.5 ± 25.3 (111)	
<i>Back pain</i>				
Yes	0.58 ± 0.25 (717)	<0.001	48.7 ± 23.3 (737)	0.016
No	0.79 ± 0.20 (22)		61.0 ± 31.5 (22)	
<i>Severity of back pain during the last month</i>				
No back pain	0.79 ± 0.20 (22)	<0.001	61.0 ± 31.5 (22)	<0.001
Minor	0.75 ± 0.17 (119)		62.4 ± 20.1 (122)	
Moderate	0.62 ± 0.21 (405)		50.6 ± 20.5 (415)	
Severe	0.38 ± 0.26 (192)		36.0 ± 24.5 (199)	
<i>Frequency of back pain during the last month</i>				
No back pain	0.79 ± 0.20 (22)	<0.001	61.0 ± 31.5 (22)	<0.001
Once or twice	0.75 ± 0.20 (71)		61.4 ± 19.8 (73)	
A few times	0.65 ± 0.20 (202)		52.1 ± 21.0 (210)	
Fairly often	0.56 ± 0.25 (229)		48.5 ± 23.7 (231)	
Every day or almost every day	0.46 ± 0.26 (215)		41.4 ± 23.6 (223)	

EQ-5D: European Quality of Life Questionnaire-5 dimensions; VAS: visual analogue scale; SD: standard deviation.

EuroQol EQ-5D index and VAS score were compared using ANOVA F-test across the groups.

the proportion of patients with a positive maternal history was 17.3% and of current smokers was 12.8% (26). The proportions of EFOS patients with co-morbidities and on concomitant chronic treatments were similar (33% and 64%, respectively), as well as time since menopause (24.4±9.1 years). The low percentage of patients reporting positive maternal history across Europe (including Italy) may reflect a still poor awareness about osteoporosis as a chronic disorder with clustering within families (26). Compared to the population included in the registration trial (15), the ISSO patients were on aver-

age about two years older, had been post-menopausal for a longer time and had more fractures. Indeed, the patients included in the Fracture Prevention Trial (FPT) were post-menopausal women aged 69±7 years both in the placebo and in TPTD 20 mcg groups, and their mean number of vertebral fractures was 2.3±1.8. The proportion of patients previously treated for osteoporosis was lower (15% in the placebo group and 16% in the TPTD 20 mcg group). Data on prevalent non-vertebral fractures at baseline and presence of risk factors are not specified in the publication of the FPT.

Table IV. Previous treatment related to osteoporosis.

Drug	Patients, n=783 n (%)
Patients with at least one past therapy	560 (71.5)
Alendronate	288 (36.8)
Risedronate	141 (18.0)
Vitamin D	121 (15.5)
Calcium	102 (13.0)
Clodronate	90 (11.4)
Strontium ranelate	80 (10.2)
Ibandronate	32 (4.0)
Neridronic acid	17 (2.2)
Raloxifene	11 (1.4)
Other [#]	6 (0.7)

[#]includes estradiol, pamidronate, calcitonin and zoledronic acid.

Some patients had taken more than one treatment. For compounds with more than one active molecule (e.g. alendronate+vitamin D or calcium+vitamin D), the molecules were considered separately.

On average, quality of life was poor in ISSO patients, the mean EQ-5D index score being 0.58 and VAS, 49.21 mm. This may be related to the severity of osteoporosis, concomitant pain and frequent co-morbidities. In the ISSO study, a history of non-vertebral fractures was statistically significantly associated with poorer quality of life and so was back pain. The adverse impact of vertebral fractures on HRQoL, determined using questionnaires such as SF36, EQ-5D and QUALEFFO, has been well-documented in clinical trials (27-29). In the ISSO study, multiple (>5) vertebral fractures only were associated with reduced lower mean EQ-5D VAS score but not with mean EQ-5D index score. Despite this finding, since the presence of vertebral fractures was an inclusion criterion of the study and back pain was present in 85% of patients with vertebral fractures at the same spine level, vertebral fractures may be indirectly associated with a reduction of quality of life. This is in line with previous findings indicating that there is an association among back pain, poor HRQoL and vertebral fractures (30).

No significant differences were observed in the quality of life between patients who experienced fractures in the past and those who did not. When comparing groups according to the number of fractures, significant dif-

ferences were observed but only in the EQ-5D index. However, this result should be interpreted with caution, since the reduction of the index with increasing number of fractures was not monotonic.

Back pain was moderate or severe in most of the patients (79.0%) and occurred very frequently or even every day in 59% of the ISSO cohort.

The association between back pain and decreased HRQoL in post-menopausal women has been reported from clinical trials and in the general population (29, 30). Pharmacological treatment for osteoporosis, such as bisphosphonates, estrogen and raloxifene has resulted in improved HRQoL (29). In the ISSO study, frequency and severity of back pain during the last month both significantly contributed to the reduction in quality of life, determined by either the EuroQoL EQ-5D index or VAS score. Back pain was also reported as causing moderate to severe disability in more than half of the patients (51.7%). Considering pain results in the EFOS population, 65.8% patients reported back pain every day-almost every day, 44.7% had severe pain and 36.9% severe restriction in daily activities (26). Fractures, back pain and disability were frequent in the EFOS study and HRQoL was poor (26).

The mean EQ-5D index and VAS score in the EFOS population were also similar to our finding (EQ-5D index: 0.41; VAS: 51.9 mm) (24).

For the patients who spent at least one day in bed, the mean number of days in which patients were bedridden in the last month was 9.3 in ISSO and 7 in EFOS study.

Most of ISSO patients (71.5%) received previous anti-osteoporosis treatment that mainly consisted of bisphosphonates. Surprisingly, calcium and vitamin D supplements were given to 13.0% and 15.5% of patients only, respectively. This observation differed considerably from the clinical experience reported in the EFOS study across Europe, in which only 7.7% of patients had not been treated for osteoporosis previously, calcium supplements were given to 73.2% of patients and vitamin D supplements to 68.9%. The small

proportion of patients that received calcium and vitamin D supplements can be explained by an underestimation of the importance of these supplements by Italian physicians; this can mirror either the habits not to prescribe them together with anti-resorptive treatments or the lack of inclusion of this information into the database by study investigators. The extent of the reduction in efficacy of previous anti-resorptive treatment due to this infrequent use of supplements in the Italian population is unclear. Furthermore, 30 patients had a BMI<19. Although 6 of them only reported intestinal malabsorption, this cannot be excluded in others.

In conclusion, our study confirms and extends the recent observation in the European population with severe osteoporosis. The baseline characteristics of the ISSO study show that Italian patients with severe osteoporosis were mostly aging women with high fracture risk, concomitant diseases and medications. Compared to other European countries, fewer Italian patients with severe osteoporosis had received previous anti-resorptive treatments and supplements of calcium and vitamin D. The ISSO patients had poor HRQoL and suffered from significant back pain. Previous fractures and back pain seemed to be major factors associated with lower HRQoL.

Acknowledgments

The authors thank CROS NT s.r.l. for the support in the statistical analysis, Dr J. Hartwig for her support in drafting this manuscript, and Dr. G. Calamai and Dr. Andrea Rossi for their support in the revision of the paper.

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