Osteoporos Int (2005) 16: 1141–1149
DOI 10.1007/s00198-005-1927-z

ORIGINAL ARTICLE

Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease

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Received: 22 July 2004 / Accepted: 24 September 2004 / Published online: 1 June 2005

Abstract Patients with inflammatory bowel disease (IBD) have frequently a bone mineral density (BMD) significantly lower than age-matched healthy subjects. The low BMD observed in IBD patients is related also to a higher incidence of bone fractures. In this prospective randomized study we evaluated the effect of 1-year risedronate administration on bone mass and turnover, and on vertebral fractures in osteoporotic postmenopausal women with IBD in remission. Ninety osteoporotic postmenopausal women were randomized to receive oral risedronate 35 mg/week (risedronate group) or placebo tablets (placebo group; one tab/week). The duration of treatment was 12 months. At entry and after treatment, lumbar spine and hip BMD, and serum osteocalcin (OC) and urinary deoxypyridinoline/creatinine ratio (DPD-Cr) levels were evaluated. Vertebral fractures were assessed from thoracic and lumbar lateral and anterior-posterior spinal radiographs taken at baseline, and from lateral spinal radiographs taken at the end of the study. At study entry, no difference between groups was also detected in BMD and in bone turnover markers. At the end of the study, lumbar spine, trochanter and femoral neck BMD was significantly ($p < 0.05$) higher in comparison with baseline in the risedronate group, whereas a significant ($p < 0.05$) decrease was observed in the placebo group. For the same visit, a significant ($p < 0.05$) difference in lumbar spine, trochanter and femoral neck BMD was detected between groups. After 12-month follow-up, serum OC and urinary DPD-Cr levels were significantly ($p < 0.05$) lower and higher in comparison with basal values in risedronate and placebo group, respectively. At the same time, a significant ($p < 0.05$) difference in serum OC and urinary DPD-Cr levels was observed between groups. Throughout the study, the incidence of vertebral fractures was significantly ($p < 0.05$) lower in the risedronate group than in the placebo group (12.5% vs 34.1%). The relative risk (RR) to develop a new vertebral fracture after 1 year of risedronate administration was of 0.36 (95% confidence interval, 0.14–0.85). In conclusion, risedronate administration is an effective anti-osteoporotic treatment in osteoporotic postmenopausal women with IBD in remission.

Keywords Bisphosphonates · Clinical trials · Menopause · Osteoporosis · Risedronate · Treatments

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Introduction

Osteoporosis is a multifactorial disease characterized by a low bone mineral density (BMD). Several hormonal and environmental factors affect the risk of osteoporosis, and many genetic factors may influence the sensitivity of the bone [1].

Crohn's disease (CD) and ulcerative colitis (UC), collectively termed inflammatory bowel disease (IBD], represent chronic relapsing and remitting inflammatory disorders of the gastrointestinal tract, characterized by leukocytic infiltration of the intestinal mucosa and submucosa. Specifically, in CD this inflammation is transmural and frequently associated with granuloma formation. Patients with IBD have frequently a BMD significantly lower than age-matched subjects without IBD [2–4]. The low BMD observed in IBD patients is related also to a higher incidence of bone fractures [5–8].

Although glucocorticoids use induces a well recognized osteoporotic entity [9–11], it is unclear how and in what proportion the steroids administration could play a role in the pathogenesis of osteoporosis in women with IBD. Recent data show that glucocorticoids administration is an important but independent cofactor [3,4]. In fact, other factors are involved in the pathogenesis of IBD-related osteopenia or osteoporosis, such as malabsorption, deficiency of vitamin D, calcium, and phosphate, high inflammatory activity, and malnutrition [3,4].

Also, although the American College of Rheumatology [12] recommends the use of bisphosphonates to prevent bone loss in most patients who use glucocorticoids, fewer than one in four patients receive any treatment to prevent or treat osteoporosis [9,13]. In addition, only a small percentage of postmenopausal women with IBD have previously used anti-osteoporotic drugs to preserve their bone mass, and only 13% of patients with IBD who already sustained a bone fracture receive any form of anti-fracture treatments [5].

There is no doubt regarding the deleterious effect of postmenopausal hypogonadism on bone metabolism [1]. In postmenopausal women, the presence of IBD can be an important additive risk factor that makes these patients a subgroup of subjects at high risk to develop osteoporosis and bone fractures [4]. To date, several therapeutic options are currently available for the prevention and treatment of postmenopausal osteoporosis, such as calcium (Ca), vitamin D, sodium fluoride, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), and bisphosphonates [14–17]. Specifically, risedronate, a third-generation bisphosphonate, is currently employed in the prevention and the treatment not only of postmenopausal but also of glucocorticoid-induced osteoporosis, with high success rates [18–19].

The aim of this prospective, randomized placebo-controlled study was to investigate the effectiveness of the risedronate administration on bone metabolism and vertebral fractures in osteoporotic postmenopausal women affected by IBD.

Materials and methods

The procedures used during the study were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The protocol was approved by the local ethics committee of the University of Catanzaro. Before entering the study, the purpose of the protocol was explained to all women attending the departments of gynecology of the University of Catanzaro and the University of Naples. Written informed consent was obtained by all subjects.

Between December 2001 and March 2003, using the databases of two gastroenterological units (University of Naples and University of Catanzaro), postmenopausal women with IBD were recruited and selected at the unit of gynecological endocrinology (University of Catanzaro). Ninety ambulatory osteoporotic postmenopausal women with IBD in remission [20,21] for at least 6 months were enrolled in the study.

In all women, the IBD was previously diagnosed by endoscopic means and confirmed by histology. The postmenopausal state was defined with assays of follicle-stimulating hormone (FSH) and 17β-estradiol (E_2) (FSH >40 IU/l and E_2 <20 pmol/l). Osteoporosis was defined with a BMD values of at least 2.5 standard deviations (SD) below the mean bone density of the peak value for sex-matched healthy young adults (-2.5 T -score) at posterior-anterior lumbar spine.

Exclusion criteria were: active rheumatoid arthritis; liver disease; metabolic, neoplastic or endocrine diseases; other secondary causes of osteoporosis, such as hyperparathyroidism, osteomalacia, Paget's disease of bone, or renal osteodystrophy; treatment with thiazide diuretics or other drugs interfering with bone metabolism; serum creatinine (Cr) >133 μmol/l, plasma 25-OH-vitamin D (normal values: 20–200 nmol/l) levels below 20 nmol/l or deranged levels of serum Ca (normal values: 2.2–2.6 mmol/l), phosphorus (P; normal values: 1.0–1.4 mmol/l) and parathyroid hormone (PTH; normal values: 10–65 ng/l); body mass index [BMI (kg/m^2)] <18 or >30. Subjects were excluded if they had been treated during the 12 months before the enrolment with glucocorticoids (steroid-dependent women) and/or with anti-osteoporotic drugs (bisphosphonates, sodium fluoride, calcitonin, estroprogestins, and anabolic steroids). Also excluded were women who regularly used any medication that had the potential of causing gastrointestinal irritation, or drugs to inhibit gastric acid secretion, women smoking more than ten cigarettes per day, or who drank more than three alcoholic beverages per day.

At the entry, all subjects were randomized in single blocks into a double-blind placebo-controlled study design using a computer-generated randomization list. The subjects were assigned to one of two treatment groups. Forty-five women received risedronate (risedr-

onate group; Optinate, Aventis, Milan, Italy) at a dose of 35 mg/week, while another 45 women received placebo tablets (placebo group; one tablet/week p.o.). Patients were instructed to take the medication (risedronate or placebo) orally in the morning at least 30 min before breakfast with abundant water and on an empty stomach after an overnight fast, and to remain upright for at least 30 min after dosing. The duration of the treatment was 12 months.

At baseline and after 12 months of treatment, BMD and bone metabolism were measured in two groups as detailed below. Both patients and clinicians were blind in respect to these results throughout the study period.

At baseline and every 3 months of treatment, Ca intake, alcohol consumption, and physical activity were carefully evaluated as previously described [22]. Ca intake, and alcohol consumption were assessed by a dietary history of patients using a semiquantitative diet questionnaire developed by dieticians at the University of Naples. No dietary restrictions or changes were implemented during the study. To ensure adequate Ca intake, all patients with a Ca intake of less than 1,500 mg or with serum Ca levels abnormally low received daily supplements of elemental Ca in the form of an effervescent tablet (500 mg each) composed of Ca carbonate (Cacit, Procter & Gamble, Rome, Italy) to achieve a total daily Ca intake of at least 1,500 mg [14]. This supplement was taken at lunch. All women with serum vitamin D levels ranging between 20 nmol/l and 40 nmol/l received at dinner a 1.25-diydroxi-vitamin D supplementation (Rocaltrol, Roche, Milan, Italy) at a dose of 0.50 μg daily (one tablet/day).

At entry, serum FSH and E_2 levels were assayed in all women to confirm the postmenopausal status. At entry and after treatment, osteocalcin (OC) and urinary Cr and deoxypyridinoline (DPD) levels were determined using commercial kits [22]. In particular, serum OC levels and urinary Cr-corrected free DPD were used as markers of bone formation and of bone resorption, respectively. Serum OC levels (reference range: 0.53–2.34 nmol/l) were determined by an immunoradiometric assay (Diagnostic Products, Los Angeles, CA, USA) with a sensitivity of 0.02 nmol/l, and an intra-assay and inter-assay coefficient of variation (CV) of 3.5% and 4.5%, respectively. Urinary DPD concentrations (reference range normalized for Cr levels: 3.0–7.4 nmol/mmol) were determined by an enzyme immunoassay (Metra Biosystems, Milan, Italy) with a sensitivity of 1.1 nmol/l, and an intra-assay and inter-assay CV of 5.5% and 7.6%, respectively.

Blood and 24-hour urine samples were collected between 8:30 a.m. and 9:30 a.m., after an overnight fast, to avoid the interference of circadian changes. The urine samples were taken using tubes covered with light-resistant paper. Patients were asked to refrain from eating foods containing fat or gelatin within 12 h of their clinic visit. Serum samples were separated within 1 hour from collection and kept frozen at −80°C, and urine was stored at −20°C until biochemical analysis. All samples from the same woman were analyzed in the same assay and were assayed blind by a central laboratory (University of Catanzaro).

Standard clinical evaluations and laboratory analyses, including hematologic, renal function and liver function tests, and microscopic examinations of sediment from midstream urine specimens were performed before treatment and after every 6 months. The subjects were instructed to report the appearance of adverse experiences (AEs) in a personal daily diary.

BMD was determined by dual energy X-ray absorptiometry (DEXA) (Hologic QDR 1000, Waltham, MA, USA) at posterior-anterior lumbar spine (vertebrae L2 to L4) and at hip (trochanter and femoral neck). The precision of the measurements were expressed as coefficient of variation (CV). The CV in vitro for repeated BMD determinations in two standard phantoms in our laboratories was 0.41% and 0.43% for the University of Naples and Catanzaro, respectively. The CV in vivo was evaluated comparing two measurements performed at 7-day intervals in 30 osteoporotic volunteers and was 1.1%, 1.7% and 1.0% for lumbar spine, trochanter and femoral neck, respectively, for the University of Naples, and 1.2%, 1.8% and 1.0% for lumbar spine, trochanter and femoral neck, respectively, for the University of Catanzaro. Individual BMD values were expressed as g/cm^2. The BMD changes after 12 months of treatment were expressed as a percentage of the baseline value. Quality control was maintained by daily scanning of an anthropomorphic spine phantom. The reference population adopted in this study was the international pooled sample provided by the manufacturer. The absorptiometries were examined by the same observer blind in respect to different treatments.

Vertebral fractures were assessed from thoracic and lumbar (T4–L4), lateral and anterior-posterior spinal radiographs taken at baseline, and from lateral spinal radiographs taken at the end of the study. Potential fractures were identified by quantitative morphometry, according to the guidelines of the US National Osteoporotic Foundation Working Group on Vertebral Fractures [23].

The evaluation of all X-ray films was performed by the same experienced skeletal radiologist of the University "Federico II" of Naples, blind to the treatment regimes. The intra-observer CV of our radiologist to identify incident vertebral fractures with the use of quantitative morphometry was previously evaluated in our laboratory, comparing in a double-blind fashion 100-fold the same X-ray film at 14-day intervals in a sequence of at least 30 radiograms of osteoporotic patients. The intra-observer CV was tested using κ statistics. The κ score for intra-observer agreement for quantitative morphometry in our laboratory was 0.89.

The lateral spinal radiographs were also scored for spinal osteophytosis (SPO) and for facet joint osteoarthritis (FOA) [24–26]. Nonvertebral fractures were determined by direct questioning every 3 months.

Our primary end point was lumbar-spine BMD change. Based on previous data [22], the sample size

required was calculated to be 40 subjects/group to detect an effect (2% difference in the mean percentage change from baseline in BMD within and between group) on the size of 2 SD with an α value of 0.05 (two-sided) and a power 1-β of 0.8. Considering a dropout rate of about 10% in 1 year of observation, we enrolled 45 patients per group. A post-study power analysis was performed at the end of the study for the difference in vertebral fracture incidence.

Continuous data normally distributed were analyzed with the paired or the unpaired t -test. The Mann–Whitney U-test and Wilcoxon signed rank-test were used to compare parity, cigarettes smoked, Ca intake, alcohol consumption, physical activity, and SPO and FOA scores. The proportions of patients who underwent surgery, of women receiving Ca and vitamin D supplements, of different smoking habits, and of different IBD diagnosis were compared using the chi-square test. The Fisher exact test was used to compare the incidence of vertebral fractures and of AEs. The data were analyzed using the intention-to-treat method. Specifically, the data were analyzed on the basis of treatment assignment and not on treatment receipt. Only the subjects who missed the first follow-up visit after randomization were excluded from the final analysis. The statistical analysis was performed with the SPSS 11.5.2.1 software package (SPSS, Chicago, IL, USA). The statistical significance was set at $p < 0.05$. Data were expressed as mean ± standard deviation (SD).

Results

Fig. 1 shows the trial profile according to CONSORT guidelines [27]. Eighty-one of 90 enrolled osteoporotic postmenopausal women with IBD were analyzed. Specifically, 57/81 (70.4%), 21/81 (25.9%), and 3/81 (3.7%) women were affected by CD, UC, and indeterminate colitis (IC), respectively.

Five and four women in risedronate and placebo group, respectively, dropped out of the study because they stopped treatment during the first weeks of treatment for personal reasons. These women were excluded from final analysis because of missed first follow-up visits (12th month of treatment). No dropout was due to drug-related AEs.

No difference in incidence of AEs was detected between the two treatment groups. Gastralgia and nausea were the gastrointestinal drug-related AEs reported by two patients alone of risedronate group. Back pain and arthralgia were also reported by two other women receiving risedronate.

After randomization, the two groups were similar for demographic data, proportion of women with CD, UC and IC, and of patients who underwent bowel resection(s), time since IBD diagnosis and remission, previous use of corticosteroids, biochemical assays, alcohol intake and physical activity scores, and in mean lumbar spine T -score (Table 1).

All women with IBD enrolled in the protocol study had previously used oral glucocorticoids and, specifically, prednisone. Throughout the 1-year study, one and two women in risedronate and placebo group, respectively, had a flare of IBD symptomatology, but no patient used corticosteroids.

At study entry, no difference between groups was detected in lumbar spine, trochanter and femoral neck BMD, in serum OC or in urinary DPD-Cr levels (Table 2).

At the end of the study, lumbar spine, trochanter and femoral neck BMD were significantly ($p < 0.05$) higher

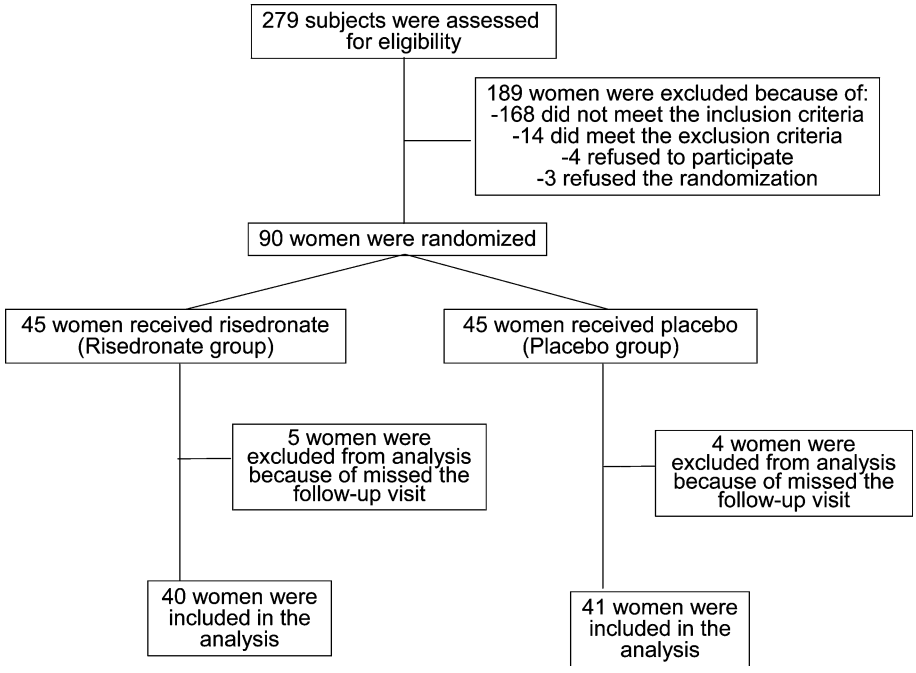

Fig. 1 Trial profile

Table 1 Baseline characteristics of the subjects. Values are expressed as mean ± standard deviation (SD), (*BMI* body mass index, *Ca* calcium, *CD* Crohn's disease, E_2 estradiol, *FOA* facet joint osteoarthritis, *IC* indeterminate colitis, *P* phosphate, *PTH* parathyroid hormone, *SPO* spinal osteophytosis, *UC* ulcerative colitis)

Group No.	Risedronate 40	Placebo 41	*p*
Age (years)	52.3 ± 3.2	51.4 ± 3.0	0.114
BMI (kg/m^2)	24.4 ± 1.9	25.2 ± 2.1	0.076
Time since menopause (months)	16.4 ± 3.3	17.5 ± 3.1	0.126
FSH (IU/l)	66.9 ± 15.6	69.7 ± 17.2	0.445
E_2(pmol/l)	14.7 ± 1.4	15.5 ± 1.6	0.019
Parity (number)	2.0 ± 0.5	2.1 ± 0.6	0.418
Smoking history			
Never smoked (%)	25 (62.5)	27 (65.9)	0.876
Past smoker (%)	12 (30.0)	12 (29.3)	
Current smoker (%)	3 (7.5)	2 (4.9)	
Cigarettes smoked (number/day)	3.1 ± 2.5	3.6 ± 2.8	0.400
Inflammatory bowel disease (IBD) diagnosis			
No. of CD women (%)	28 (70.0)	29 (70.7)	0.824
No. of UC women (%)	11 (27.5)	10 (24.4)	
No. of IC women (%)	1 (2.5)	2 (4.9)	
Time since IBD diagnosis (years)	30.5 ± 6.8	32.5 ± 7.3	0.206
Time since IBD remission (months)	11.2 ± 4.1	12.2 ± 4.5	0.303
Previous bowel resection (%)	11 (27.5)	10 (24.4)	0.750
Previous extensive and/or multiple bowel resections (%)	5 (12.5)	5 (12.2)	0.967
Previous corticosteroid treatment			
Duration (months)	13.3 ± 6.2	12.2 ± 6.8	0.449
Daily dose (mg)	19.5 ± 5.7	18.3 ± 4.8	0.308
25-OH-vitamin D (nmol/l)	64.2 ± 16.2	70.5 ± 17.3	0.095
Ca (mmol/l)	2.4 ± 0.2	2.4 ± 0.1	1.000
P (mmol/l)	1.1 ± 0.1	1.1 ± 0.2	1.000
PTH (ng/l)	41.3 ± 15.2	42.0 ± 13.6	0.828
Ca intake score[a]	1.7 ± 0.6	1.6 ± 0.6	0.456
Women who received Ca supplementation (%)	23 (57.5)	26 (63.4)	0.586
Women who received vitamin D supplementation (%)	17 (42.5)	19 (46.3)	0.728
Alcohol intake score[b]	1.1 ± 0.3	1.2 ± 0.4	0.208
Physical activity score[c]	1.3 ± 0.6	1.3 ± 0.5	1.000
SPO score	0.72 ± 0.10	0.73 ± 0.09	0.755
FOA score	0.71 ± 0.12	0.69 ± 0.11	0.361
Lumbar spine *T* -score	-3.4 ± 0.5	-3.6 ± 0.6	0.158
No. of vertebral fractures	23	26	-
Prevalence of vertebral fractures (%)	18 (45.0)	20 (48.8)	0.733

[a] 1 = < 500 mg/day; 2 = 500–1,500 mg/day; 3 = > 1,500 mg/day
[b] 1 = < 1,000 mg/day; 2 = 1,000–2,000 mg/day; 3 = > 2,000 mg/day
[c] 1 = low; 2 = moderate; 3 = high

after treatment in comparison with baseline in risedronate group, whereas a significant ($p < 0.05$) decrease was observed in the placebo group (Table 2). At the same visit, a significant ($p < 0.05$) difference in lumbar spine, trochanter and femoral neck BMD was detected between groups (Table 2).

After 1-year follow-up, serum OC and urinary DPD-Cr levels were significantly ($p < 0.05$) lower and higher in comparison with basal values in the risedronate and placebo groups, respectively (Table 2). At the same time, a significant ($p < 0.05$) difference in serum OC and urinary DPD-Cr levels was observed between groups (Table 2).

At study entry, no difference between groups was detected in total number of vertebral fractures and in proportion of patients with previous vertebral fractures (prevalence of vertebral fractures) (Table 1). No patient enrolled had previous nonvertebral fractures. At the end of the study, we observed 14 new vertebral fractures in the placebo group, whereas, after risedronate administration only five new vertebral fractures were detected. The incidence of vertebral fractures was significantly ($p < 0.05$) lower in risedronate group than in placebo group (12.5% vs 34.1%). The relative risk (RR) to develop a new vertebral fracture after 1 year of risedronate administration was of 0.36 (95% confidence interval [CI] 0.14–0.85) and the number needed to treat (NNT) was of 5 benefit (range 3–26 benefit).

The distribution of new vertebral fractures according to specific IBD is shown in Table 3.

No woman had nonvertebral fractures in risedronate group, whereas in placebo group four women had

Table 2 Bone mineral density (BMD) and bone turnover markers before and after 1 year of risedronate or placebo administration. Data analyzed with the intention-to-treat method and expressed as mean ± standard deviation (SD). (*BMD* body mass density, *OC* osteocalcin, *DPD/Cr* deoxypyridinoline/creatinine)

Group	Risedronate	Placebo	*p*
Lumbar spine BMD (gr/cm^2)			
Baseline	0.561 ± 0.063	0.540 ± 0.062	0.153
After treatment	0.602 ± 0.053	0.504 ± 0.073	< 0.001
p (baseline vs post-treatment)	< 0.001	0.008	-
Trochanter BMD (gr/cm^2)			
Baseline	0.502 ± 0.060	0.484 ± 0.059	0.164
After treatment	0.525 ± 0.057	0.454 ± 0.059	< 0.001
p (baseline vs post-treatment)	0.023	0.046	-
Femoral neck BMD (gr/cm^2)			
Baseline	0.493 ± 0.059	0.479 ± 0.060	0.299
After treatment	0.513 ± 0.057	0.461 ± 0.060	< 0.001
p (baseline vs post-treatment)	0.036	< 0.001	-
OC (nmol/l)			
Baseline	1.79 ± 0.19	1.78 ± 0.17	0.852
After treatment	1.36 ± 0.19	1.95 ± 0.19	< 0.001
p (baseline vs post-treatment)	< 0.001	< 0.001	-
DPD/Cr (nmol/mmol)			
Baseline	6.02 ± 0.78	5.89 ± 0.77	0.447
After treatment	4.88 ± 0.71	6.41 ± 0.67	< 0.001
p (baseline vs post-treatment)	< 0.001	< 0.001	-

nonvertebral fractures (three women had femoral neck fractures and one had a Colles' fracture).

Discussion

Risedronate is a novel pyridinyl bisphosphonate for oral administration approved for prevention and treatment of osteoporosis [19]. This drug reduces bone turnover and decreases bone resorption through an osteoclast-mediated action, so producing a significant increase of BMD [19]. It has been successfully used in preventing postmenopausal bone loss in women without osteoporosis, but also in women who have already developed osteoporosis [18,19]. The use of risedronate reduces rapidly the incidence of vertebral and nonvertebral fractures in postmenopausal osteoporotic women with or without preexisting fractures [18, 19,28]. Also after a long-term follow-up of 5 years, risedronate administration has been shown to preserve its effectiveness in terms of spine and hip BMD gain, decrease in markers of bone turnover, and reduction in new vertebral fractures [29]. This anti-fracture efficacy of risedronate treatment is explained only partially with an increase in BMD or a decrease in bone metabolism. In fact, risedronate seems to act also on the trabecular architecture, as demonstrated by three-dimensional microcomputed tomography [30]. Prolonged and continuous treatment with risedronate has also been shown to be effective in preventing and treating glucocorticoid-induced bone loss [19,31].

To date, no study has been available in literature regarding the efficacy of risedronate in a subgroup of osteoporotic postmenopausal women with IBD previously treated with glucocorticoids. Patients with IBD, in fact, frequently develop osteopenia or osteoporosis, and several factors are involved in the pathogenesis of IBD-related bone loss [2,4]. At present, high inflammatory activity [32] and glucocorticoids administration are considered, respectively, two pivotal dependent and independent cofactors [3,4].

Table 3 Distribution of new vertebral fractures according to specific inflammatory bowel disease during 1 year of risedronate or placebo administration. Data analyzed with the intention-to-treat method (*CD* Crohn's disease, *IBD* inflammatory bowel disease, *IC* indeterminate colitis, *UC* ulcerative colitis)

Group	Risedronate (*n* = 40)			Placebo (*n* = 41)		
IBD	CD (%)	UC (%)	IC (%)	CD (%)	UC (%)	IC (%)
Vertebral fractures incidence (%)	4/28 (14.3) [a]	1/11 (9.1) [a]	0/1 (0)	11/29 (37.9)	3/10 (30.0)	0/2 (0)

[a] $p < 0.05$ vs group B

Fracture incidence from glucocorticoid-induced bone loss is estimated to be 1.3-fold to 2.6-fold higher in subjects receiving glucocorticoids than in those who are not receiving glucocorticoids [11], and the stronger predictor of vertebral fracture in subjects receiving steroids seems to be daily, but not cumulative, glucocorticoids dose [33]. Although one-quarter to one-half of patients who take long-term glucocorticoids will experience bone fracture, fewer than one in six patients undergoing long-term glucocorticoid treatment receive therapy to prevent bone loss [11].

A wide case-control study [5] has shown that women with IBD have an increased risk of bone fractures. Specifically, the relative risk (RR) of vertebral and hip fracture was 1.72 and 1.86, respectively, in CD patients and 1.59 and 1.40, respectively, in UC patients. The total risk of fractures even after adjusting for corticosteroid use remains significantly higher (RR 1.4), demonstrating that the majority of bone fracture risk in IBD patients can not be attributed to corticosteroid use. Also a more recent population-based cohort study [8] has confirmed that IBD patients have a significant risk of hip fractures (RR 1.62), that CD patients have a risk significantly higher than UC patients (RR 2.08 vs RR 1.49), and that corticosteroid use is only a cofactor to this risk. Notwithstanding this data, Bernstein et al. [6] have defined patients with CD who have used corticosteroids as a high-risk subgroup for bone fracture. In this subgroup of subjects, the prevalence of vertebral fractures reaches 22% [7].

At entry, our study population was characterized by a lower risk profile for bone loss and fractures than those studied in the other papers. In fact, only a percentage of women were affected by CD, whereas the others were affected by UC and IC. In addition, our women were in remission and not corticosteroid users for the past 12 months, all had an adequate Ca and vitamin D intake/supplementation, a BMI >18, a normal physical activity, and, finally, no patients smoked more than ten cigarettes per day or drank more than three alcoholic beverages per day. Based on these considerations, the findings regarding the bone loss and the vertebral fractures obtained in the placebo arm demonstrate that postmenopausal hypogonadism has an highly deleterious effect on already-damaged bone tissue and that all postmenopausal women with IBD should be considered a high-risk subgroup.

The present parallel randomized placebo-controlled study demonstrates that oral administration of risedronate at a dose of 35 mg weekly for 1 year significantly increased BMD in comparison with baseline and placebo in this high-risk subgroup of postmenopausal women. The effectiveness in terms of BMD gain was detected in all bone sites evaluated. A significant suppression of bone turnover markers was also observed after 1 year of risedronate treatment.

At the moment, only one other paper has selectively studied postmenopausal women with IBD [34]. In this last study it is shown that 2-year treatment with HRT is effective in the prevention of bone loss in postmenopausal women with CD and UC, and that its effectiveness is unrelated to basal BMD values.

Our study confirms that bisphosphonates [35–37] induce a significant BMD gain in IBD patients with low BMD. In particular, Haderslev et al. [35] have demonstrated that 10 mg daily alendronate increases lumbar spine and hip BMD 4.6% and 3.3%, respectively, after 1-year treatment. Also Bartram et al. [36] have showed a significant increase of 2.6 and 1.6%, respectively, in lumbar spine and hip BMD after 1-year of pamidronate plus Ca and vitamin D supplementation vs Ca and vitamin D supplementation alone. While the efficacy of HRT [34] and bisphosphonates [35–37] on bone metabolism has been clearly demonstrated in subjects with IBD, there are contrasting data in the literature regarding the effectiveness of Ca and vitamin D supplementation in IBD patients with low BMD [36–39]. Von Tirpitz et al. [38] have shown the efficacy of sodium fluoride in comparison with Ca plus vitamin D administration in patients with CD. Also, more recently it has been confirmed that Ca plus vitamin D supplementation is ineffective in osteoporotic/osteopenic patients with CD, whereas sodium fluoride or ibandronate treatments induce a significant increase in lumbar BMD (5.7% and 5.4%, respectively) [37]. On the contrary, in osteoporotic patients with IBD and with normal serum vitamin D levels, Abitbol et al. [39] have observed no superiority of sodium fluoride treatment compared with calcium plus vitamin D administration.

Furthermore, BMD is only a surrogate marker of fracture risk. In this view, also in IBD patients it has been demonstrated that mean BMD is not different between patients with and without fractures, showing the lack of correlation between BMD and prevalence of fractures [40]. The current main aim of the treatment with anti-osteoporotic drugs is to decrease the fracture rate, the most disabling complication of osteoporosis. In this regard, our study, despite being based on a small study population size and a relatively short follow-up period, shows a significant reduction in developing new vertebral fractures after risedronate administration. In fact, in osteoporotic postmenopausal women with IBD, 1 year of risedronate treatment reduced the risk of new vertebral fracture by about 67% in comparison with those treated with placebo alone.

It is necessary to emphasize that IBD was in remission for at least 6 months and throughout the study-period, and that all women enrolled in our study protocol had previously used glucocorticoids. On the contrary, new therapeutic tools such as infliximab, a chimeric anti-TNF alpha monoclonal antibody, and budesonide, a non-halogenated glucocorticoid with potent anti-inflammatory activity and low bioavailability, are currently available [41]. These treatments seem to be effective on the disease without any significant deleterious effect on bone metabolism [41].

Risedronate was well tolerated in our patients, and no patient dropped out because of AEs possibly related to the drug. These data agree with the results of a previous meta-analysis showing that risedronate

administration was not associated with increased frequency of adverse gastrointestinal tract effects, even among patients at high risk for these events [42]. Back pain and arthralgia, reported also by other authors during the risedronate treatment were mostly light and self-limited.

In conclusion, the results of the present randomized clinical trial show that the risedronate administration is effective to treat established osteoporosis in postmenopausal women with IBD in terms of BMD gain and of reduction of new vertebral fractures. Further studies on wider samples are needed to confirm the efficacy of risedronate treatment on bone fractures in this high-risk subgroup of patients.

Acknowledgements No financial support was provided by any pharmaceutical company to realize the present research

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