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Original Article

Coadministration of zoledronic acid and teriparatide in postmenopausal osteoporosis

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Abstract

Objectives: The purpose of this study is to evaluate the effects of combination therapy with an intravenous infusion of zoledronic acid 5 mg and daily subcutaneous teriparatide 20 μg versus either agent alone on bone mineral density (BMD) and bone turnover markers. **Methods**: From January 2015 to December 2018, 206 postmenopausal women with osteoporosis (aged 55-89 years) were randomized to receive a single infusion of zoledronic acid 5 mg plus daily subcutaneous teriparatide 20 μg (n = 68), zoledronic acid alone (n=69), or teriparatide alone (n=69). The primary endpoint was percentage increase in lumbar spine and total hip BMD (assessed by DXA) at 52 weeks versus baseline. **Results**: At week 52, lumbar spine BMD had increased 7.5%, 7.0%, and 4.4% in the combination, teriparatide, and zoledronic acid groups, respectively while total hip -BMD increments were 2,3%, 1,1% and 2,2% in respective subgroups. Levels for bone turnover markers (PINP and b-CTX) were significantly lower with combination therapy versus teriparatide alone **Conclusions**: The authors concluded that while teriparatide increases spine BMD more than zoledronic acid and zoledronic acid increases hip BMD more than teriparatide, combination therapy provides the largest, most rapid increments when both spine and hip sites are considered.

Keywords: Bisphosphonates, Bone mineral density, Osteoporosis, Teriparatide, Zoledronic acid

Introduction

In women with postmenopausal osteoporosis, the antifracture efficacy of bisphosphonates is well documented[1-4]. Unlike the bisphosphonates which reduce bone remodeling, teriparatide is an anabolic agent which stimulates bone formation and simultaneously increases bone remodeling[4]. While both classes of pharmaceutical agents improve bone mineral density (BMD) and concurrently reduces fracture risk, teriparatide additionally improves microarchitecture of cortical and cancellous bone in the iliac crest[5-7], giving greater improvements in bone strength compared to antiresorptive pharmaceutical agents alone[4,8,9]. In a comparative study between alendronate and teriparatide in patients with glucocorticoid-induced osteoporosis, the incidence of vertebral fractures was lower in patients treated with teriparatide compared to those treated with alendronate[10]. Conversely, the antifracture efficacy of once-yearly zoledronic acid at the hip over three years is well documented (it was observed 41% reduction in hip fracture risk in postmenopausal women with osteoporosis)[10]. In the absence of comparative data regarding the incidence of hip fractures, it is unclear which pharmaceutical agent is preferable for patients at high risk for hip fracture or the combined administration of the anabolic and the antiresorptive agent produce additional effect.

Previous studies which appreciated combined administration of PTH or teriparatide with antiresorptive agents have yielded inconclusive results with differences related to which antiresorptive agent was used[11-17], whether patients are treatment-naive or had received antiresorptive treatment when combined treatment was started[18-19] and for patients who had previously received antiresorptive treatment, whether the antiresorptive agent was continued or stopped when teriparatide was added[20]. In one study[18],

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treatment-naive patients were randomized to receive alendronate or intact PTH (1-84) as monotherapy compared with the combination therapy. The results of DXA indicated no additional improvement of the combination therapy on spine BMD, while the hip BMD results showed a greater increase with the combination therapy than with PTH alone. However, changes in volumetric BMD of trabecular bone identified by QCT and bone turnover levels argued that the simultaneous use of alendronate may reduce the anabolic effect of PTH[18].

In rodents, chronic exposure to bisphosphonates reduces the anabolic activity of PTH[21-23]. The inhibitory effect appears to differ virtually, when bisphosphonates are administered less frequently, perhaps because only small quantities are recruited in each administartion[22]. For this reason, a single intravenous administration of zoledronic acid in humans would have as a consequence a different reaction to coadministration with PTH, compared with bisphosphonates which are more frequently administered.

The aim of our study was to determine whether a single intravenous administration of zoledronic acid with teriparatide would provide an additive or at least no lower effect on BMD of spine or hip compared to administration of zoledronic acid or teriparatide as monotherapy in postmenopausal women with osteoporosis. Bone turn over markers were additionally assessed.

Methods

Study design

Our study was conducted from January 2015 to December 2018 and involved postmenopausal women with osteoporosis. At randomization, all participants who had not previously received treatment received either a single intravenous infusion of zoledronic acid 5 mg plus a daily subcutaneous administration of 20 μg teriparatide, zoledronic acid alone or daily teriparatide 20μg. All participants received daily 1000-1200mg Ca and 400-800 IU of vitamin D.

All participants signed a consent form. The first postmenopausal woman with osteoporosis who participated in the study was screened in February 2016 and the latter completed the trial in June 2019.

Inclusion and exclusion criteria

Women participating in the study were postmenopausal women aged 55-89 years with a BMD T-scores≤-2,5SD at the femoral neck, total hip or at the lumbar spine or BMD T-scores≤-2SD at any site plus one more documented vertebral or non-vertebral fractures (but not because of violent injury). From the study were excluded women who reported prior use of parathyroid hormone or bisphosphonates for more than 3 consecutive months; shorter-term use was acceptable if followed 1-year without taking antiosteoporotic treatment. Other exclusion criteria from the study were chronic systematic corticosteroid use during the past year; raloxifene or hormone therapy the previous three months; creatinine clearance <30 mL/min; serum calcium ≥2,75 mmol/L ή <20 mmol/L; or 25-hydroxyvitamin D levels<15 ng/ml.

Study assessments

Measurements of bone mineral density (BMD) in the lumbar spine (L1-L4) and total hip by DXA were performed in all postmenopausal women who participated in the study at screening and at weeks 13, 26 and 52. Fracture assessment was not an efficacy endpoint of the study but was used in the patient inclusion process and to determine the vertebrae which are excluded from the evaluations of DXA in the lumbar spine.

Measurements of serum markers of bone resorption (b-C-telopeptide of type I collagen [b-CTX]) and bone formation (N-terminal propeptide of type I collagen [PINP]) were performed at baseline and at weeks 4, 8, 26, 39 and 52. Serum samples were taken after fasting throughout the night and study medication, calcium and vitamin D were not administered on the morning prior to sample collection. Lateral radiographs of the lumbar and thoracic spine were performed at baseline to assess pre-existing vertebral fractures. Lateral radiographs of the lumbar (and not the thoracic) were repeated after 1-year antiosteoporotic treatment to identify the incidence of vertebral fractures or degenerative disease that may artifactually affect the BMD analyses.

Safety assessments included recording and monitoring of all adverse events; monitoring of serum chemistry and urine, vital signs body weight and physical examination.

Endpoints

The primary objective of the study was to demonstrate the non-inferiority of the combination therapy with zoledronic acid and teriparatide compared with teriparatide alone regarding the percentage increase in lumbar spine BMD at 52 weeks of study entry. Secondary efficacy endpoints were percentage change in BMD in the lumbar spine in earlier periods; the percentage change in BMD at the total hip, trochanter and femoral neck in all periods; changes in serum b-terminal telopeptide of type I collagen (b-CTX) and serum amino propeptide of type I collagen (PINP) in each time period. Clinical fractures were recorded as adverse events (AEs).

Results

206 women with postmenopausal osteoporosis were randomized into three subgroups of which the first subgroup (n=69) received a single intravenous infusion of zoledronic acid alone, the second subgroup (n=68) zoledronic acid plus daily subcutaneous administration of teriparatide 20 μg and the third subgroup (n=69) daily subcutaneous administration of teriparatide 20 μg. The three subgroups had similar characteristics regarding the BMD values at lumbar spine and hip and serum b-CTX and PINP levels. There

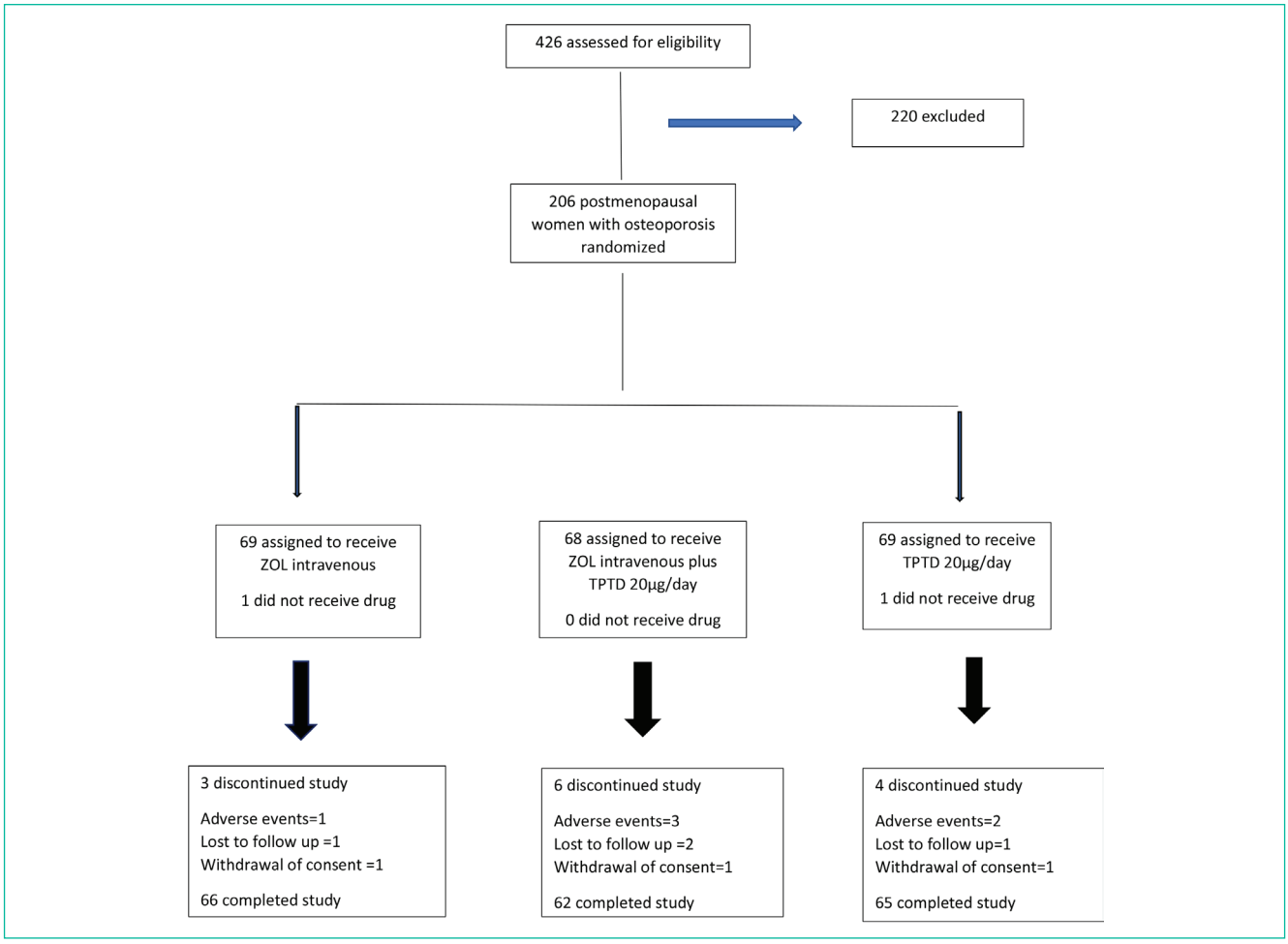

Figure 1. Participants disposition.

Variable	ZOL 5 mg IV n=69	ZOL 5 mg IV+TPTD 20 μg/day n=68	TPTD 20 μg/day n=69
Average age (in years)	66,1	65	63,8
BMI (Kg/m^2)	25,2	25,2	25,2
Prevalent vertebral fractures, n (%)	15(21,9)	10 (15,3)	11 (15,9)
History of clinical fracture n (%)	46 (66,1)	42 (62,0)	38 (55,1)
Lumbar Spine BMD	0,72	0,74	0,73
Lumbar Spine T-score(SD)	-2,88 SD	-2,79 SD	-2,86 SD
Total hip BMD	0,68	0,71	0,71
Total Hip T-score (SD)	-2,04	-1,79	-1,79
Serum b-CTX (ng/mL)	0,44	0,45	0,46
Serum PINP (ng/mL)	53,6	55,72	55,6

Table 1. Baseline characteristics of postmenopausal women with osteoporosis who participated at the start of the study.

Clinical fracture Type	ZOL 5 mg IV n=69	ZOL 5mg IV+TPTD 20 μg/day n=68	TPTD 20 μg/day n=69
Total	**7**	**2**	**4**
Thoracic vertebral	2	0	1
Lumbar vertebral	2	0	0
Ribs	1	0	1
Wrist	1	0	1
Humerus	1	0	0
Pelvis	0	0	0
Upper Limb	0	0	0
Ankle	0	1	0
Fibula	0	0	0
Foot	0	1	1

Table 2. Clinical fractures by fracture type and treatment.

were numerical but not statistically significant differences between subgroups regarding the history of clinical fracture and prevalent vertebral fractures (Table 1). 93,6% of the participants completed the study with adverse events being the most common cause of failure. The disposition of participants is summarized in Figure 1. Compliance was defined as the administration of 80% or more of the amount of teriparatide which much be administered over a period of 52 weeks. Ten participants from the second subgroup (combined administration) and the third subgroup (teriparatide alone) [14,6% and 14,5% respectively] showed compliance less than 80% mainly due to early discontinuation (16 of 20).

BMD - Bone Mineral Density

At 52 weeks increases in BMD of lumbar spine was 7,5% with combined therapy, 7% with teriparatide and 4,4% by intravenous infusion of zoledronic acid. There was no significant difference between the subgroups with combination therapy and teriparatide at week 52; However the increases in BMD of the lumbar spine were higher in the combination subgroup compared with the subgroup of teriparatide the 13th and the 26th week, in the subgroup of the combination therapy compared with the subgroup of zoledronic acid in all time periods and in the subgroup of teriparatide compared with the subgroup of zoledronic acid at week 52.

The increases in BMD of total hip at 52 weeks were 2,3% in subgroup of combination treatment, 1,1% in teriparatide subgroup and 2,2% in the zoledronic acid subgroup. The increases in BMD were higher in the subgroup of combination therapy compared with teriparatide subgroup in all time periods, in the subgroup of combination treatment compared with the subgroup of zoledronic acid at week 13 and in the subgroup of zoledronic acid compared with teriparatide subgroup in all time periods. Increases in BMD of femoral neck and trochanter in the subgroup of the combination therapy compared with the teriparatide subgroup excelled throughout the study (at 52 weeks for femoral neck 2,2% versus 1,1%; for trochanter 4,4% versus 2,4%). Furthermore, the combination therapy induced numerically but not significantly larger increases comparatively with the subgroup of zoledronic acid in all time periods.

Fractures

Clinical fractures (reported as adverse events) were recorded in 7, 2 and 4 participants in the subgroups of zoledronic acid, combined treatment and teriparatide respectively (Table 2). The incidence of clinical fractures was significantly lower in the subgroup of combination treatment compared with the subgroup of zoledronic acid, but it was not significantly different in the subgroup of combination treatment compared with the subgroup of teriparatide alone.

Biochemical markers of bone turnover

Serum b-CTX was reduced to the lowest value by week 4 in the subgroup of zoledronic acid and then increased slightly. In the subgroup of teriparatide, the mean values of b-CTX remained unchanged until the 4th week, then increased to a peak at week 26th and decreased slightly thereafter. In the subgroup of the combined treatment, an initial marked reduction was observed, similar size to the reduction seen in the subgroup of zoledronic acid, then followed by a gradual increase after the 8th week, with levels of b-CTX remaining above the reference value in the second half of the year. Differences were significant between the subgroup of the combination treatment compared with the subgroup of the teriparatide and the subgroup pf zoledronic acid in all time periods and for the subgroup of teriparatide compared with the subgroup of zoledronic acid at all time points.

In the subgroup of zoledronic acid, PINP decreased until the 8th week with small subsequent changes. In the subgroup of teriparatide in contrast to what was observed with b-CTX, PINP increased until the 4th week. In the subgroup of the combined treatment, PINP also increased until 4th week, then decreased slightly between weeks 4 and 8 and then showed a gradual increase over the reference value from 6 to 12 months. However, the decline of PINP in the subgroup of the combined treatment was less pronounced compared with the decline observed in the subgroup of zoledronic acid.

Adverse events

The rates of adverse events were 90,8% in the subgroups of the combined treatment and zoledronic acid and 86,1% in the subgroup of teriparatide. Adverse events occurring with greater frequency in the subgroup of the combined treatment compared with the subgroup of teriparatide alone were short-term post-infusion symptoms (e.g. nausea, flu-like symptoms, chills, fever, fatigue, arthralgia, myalgia and headache) similar to those observed after zoledronic acid infusion. The rates of adverse events within the first 3 days after infusion were 67,9% in the subgroup of the combined treatment, 57,9% in the subgroup of zoledronic acid and 26,8% in the subgroup of teriparatide. On the other hand, the rates of adverse reactions after the first three days were comparable in all three subgroups (84,7%,87,4% and 84,7% respectively). There were no significant differences in serious adverse events between subgroups. Side effects causing study discontinuation were reported in 6 patients (8,8%) in the subgroup of the combination treatment, in 4 patients (5,7%) in the subgroup of teriparatide alone and in 3 patients (4,34%) in the subgroup of zoledronic acid alone.

No incidents of hypocalcemia were reported in any subgroup. Marked hypercalcemia (serum Ca>2,89 mmol/L) occurred in one participant (1,4%) in the subgroup of the combined treatment and two participants in the subgroup of teriparatide. The percentages of participants with normal calcium values at baseline but above the normal range during the study was 13,2% for the subgroup of the combination treatment, 14,9% for the subgroup of teriparatide and 4,3% for the subgroup of zoledronic acid alone. There were no reported long-term effects on renal function (comparing creatinine clearance values at baseline and at 12 months) for each subgroup.

Discussion

The data of our study suggest that coadministration of zoledronic acid and teriparatide increased BMD in the lumbar spine more than teriparatide alone during the first 13 weeks. At 52 weeks, increases of bone mass at the spine in the subgroup of the combined treatment were similar to those observed in the subgroup of teriparatide alone but greater than those seen in the subgroup of zoledronic acid. Moreover, the combined treatment led to rapid increases in BMD at the total hip, trochanter and femoral neck compared with the subgroup of teriparatide and caused a greater increase in total-hip BMD compared with the subgroup of zoledronic acid at 13 weeks. Treatment with all three pharmaceutical agents was safe and well-tolerated; the overall rate of adverse events was comparable in the three subgroups. The study of Cosman et al concluded to similar results with our study[24].

Combined treatment resulted in an immediate decline in bone resorption which was maintained for the first 2 months, with gradual stability of the reduction and increased bone resorption the latter 6 months of treatment. Consequently, the duration of the reduction of bone resorption is less in the presence of teriparatide than when the zoledronic acid is administered alone[10], probably due to the faster removal of the zoledronic acid from the bone surface in the presence of teriparatide. Additionally, BMD increases were greater at both spine and hip during the first 3 to 6 months in the subgroup of combination treatment, probably due to the extension of the anabolic window (the magnitude of stimulation of bone formation versus bone resorption). There was a rapid decrease of bone resorption during this period, compared with a minimal but very brief decline in bone formation. The results support that the zoledronic acid is not involved in the osteoblastic response of teriparatide and that the early anabolic effect of teriparatide in combination with zoledronic acid is independent of the new bone remodeling[25,26]. During the second half of the study, the anabolic effect of the combined treatment occurred by increase of bone remodeling, with the levels of bone formation and bone resorption markers above baseline[6]. One of the potential limitations of treatment with parathyroid hormone (PTH) is that its stimulatory effect in intracortical bone remodeling can increase cortical porosity. This does not translate into reduced mechanical strength, but because the porosity focuses on the endocortical surface (near the neutral axis of bone), it may be offset by increased periosteal deposition and increased cortical thickness[27-29]. Nevertheless, coadministration with zoledronic acid may prevent the increase in cortical porosity which is induced by teriparatide, therefore can potentially strengthen the cortex, as observed in this study, increasing hip BMD beyond values obtained by teriparatide alone[30]. The lack of continuous increase in hip BMD during the latter six months of our study in the subgroup of combined treatment may be due to increased cortical bone remodeling and results in increases in cortical porosity as a consequence of the decreases brought about by zoledronic acid.

We conducted a search in PubMed in English concerning the last decade to identify relevant studies of combination therapy with bisphosphonates and PTH/teriparatide. Another clinical study evaluated combination therapy with PTH and a bisphosphonate in patients with osteoporosis who had not previously received medication[18]. In this study PTH alone and a combination of PTH with 10 mg of alendronate daily increased spine BMD (as calculated by DXA) equally, but there were no periods assessing the effect before 1 year, so that the rapidity of BMD effect could not

be ascertained. In this study combined treatment increased hip BMD significantly more than PTH alone, but the interpretation of DXA results overshadowed by the results of quantitative computed tomography (QCT), indicating that the levels of trabecular bone mass in the spine and hip increased more by PTH alone than by combination therapy. The significance of differences in the findings of QCT and DXA in this study is unclear. It is likely that PTH may affect fat content of bone marrow[31] and technically inflate BMD increases which are calculated by QCT[32,33]. In our study QCT results were not investigated.

Other differences between the current study and the study of Black and colleagues[18] may be due to several factors. First of all, our study involved N-terminal PTH peptide (teriparatide) and not the entire molecule with possible pharmacokinetic and pharmacodynamic differences[34]. Alendronate was given daily in the study of Black and colleagues and the frequent administration of the bisphosphonate, may affect the osteoblastic reaction in PTH, an effect avoided by the annual single administration of the intravenus bisphosphonate. Furthermore, there may be additional factors which involve in the mechanism of action and clinical efficacy of the specific bisphosphonates[35].

Other studies in an attempt to assess the combined treatment with teriparatide and bisphosphonates had registered patients in whom bisphosphonates were given before the onset of teriparatide treatment. In one study[19], alendronate was given only six months before the introduction of teriparatide. In this study after one year of teriparatide treatment the results from the subgroup of the combined treatment and the subgroup of teriparatide were similar. In other studies, the duration of the previous administration of the bisphosphonates before the introduction of teriparatide was longer. Differences in the dynamics of the parathyroid and the amount of active bone surface which may be substantial in the bisphosphonates users compared with those who didn't receive treatment may account for variable results in studies involving long-term users of bisphosphonates compared with those who are treatment-naïve.

Limitations of our study include its short-term duration which may lead to different conclusions after two years of treatment, especially in BMD of femoral neck which increased more during the 2nd year of treatment in several clinical studies[3,19,36]. Additionally our study did not include other endpoints beyond DXA (e.g. QCT for evaluation of bone strength or assessments of bone structure as bone biopsy or high resolution computed tomography). However, those who evaluated as endpoints of the study were blindly randomized to administered medication and these were objective parameters. As a consequence, there was no bias with respect to reporting of efficacy data. Finally, the study was not enhanced for fractures outcomes and didn't identify in detail morphometric vertebral fractures. Further studies are imposed to determine the consequences of the BMD findings in this study to reduce the fracture risk and to define the underlying mechanisms for the observed differences in BMD increases between combination treatment and monotherapy.

Therefore, with respects to the endpoints of BMD in the spine and hip, the concomitant intravenous administration of zoledronic acid (5 mg) with daily subcutaneous administration of teriparatide (20 μg) resulted in larger, more rapid increases than each therapy alone. At one year compared with the combination treatment, teriparatide alone caused similar effects on BMD in the spine and zoledronic acid caused similar effects on BMD at the hip; however, combination treatment caused the greatest increases on BMD in the spine and hip as study endpoints. These observations in the subgroup of combination treatment probably resulting from increases in the osteoblastic activity caused by teriparatide together with decreases in bone remodeling and porosity of the cortex caused by zoledronic acid. Therefore, the combination therapy can be a suitable treatment for patients at high risk for hip and other fractures.

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