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ORIGINAL ARTICLE

Zoledronic acid combined with percutaneous kyphoplasty in the treatment of osteoporotic compression fracture in a single T12 or L1 vertebral body in postmenopausal women

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Abstract

Summary We performed a 1-year prospective study to see whether zoledronic acid infusion combined with percutaneous kyphoplasty could provide more benefits in the treatment of T12 or L1 osteoporotic vertebral compression fracture (OVCF).

Introduction To investigate and analyze the clinical effects of zoledronic acid (ZOL) in combination with percutaneous kyphoplasty (PKP) in the treatment of OVCF in postmenopausal women.

Methods Included in this study were 101 postmenopausal women patients with T12 or L1 OVCF who received PKP in our hospital between August 2015 and July 2017. They were randomly assigned to a zoledronic acid (ZOL) group ($n = 50$) or a control group ($n = 51$). Patients in ZOL group were treated preoperatively with IV infusion of 5 mg ZOL in combination with 0.25μg/d calcitriol and D3 600 mg/d calcium carbonate for a year. Patients in the control group were treated with the same dose of calcitriol and calcium carbonate D3 without ZOL.

Results There was no statistically significant difference in age, height, weight, body mass index (BMI), menopause age, and the fractured vertebral body between the two groups. At 6 and 12 months after treatment, bone mineral density (BMD) in ZOL group was higher than that in the control group ($p < 0.01$); bone markers (NMID, P1NP, and β-CTX) and the VAS score in ZOL group were significantly lower than those in the control group. No new fracture occurred in ZOL group. The incidence of recompression vertebral fracture (RVF) in the control group was 11.7%, while no RVF was detected in any patient in ZOL group. Mild adverse reactions in ZOL group were significantly higher than those in the control group, but all of them were relieved after symptomatic treatment.

Conclusions ZOL IV infusion in combination with PKP is beneficial for the treatment of T12 or L1 OVCF.

Keywords Osteoporosis · Osteoporotic vertebral compression fracture · Percutaneous kyphoplasty · Zoledronic acid

Introduction

With the increase in the aged population in communities, the incidence of fragility fracture has been increasing remarkably. Osteoporosis vertebral compressive fracture (OVCF), especially at T12 or L1, is a type of clinical fragility fracture, affecting approximately 1.4 million people worldwide [1, 2]. OVCF is more commonly seen in the elderly with decreased spine bone mineral density (BMD), which is typically associated with severe spinal pain, deformity, and decreased mobility, and may even cause mortality in severe cases [3–5].

Since Garfin et al. [6] reported the use of percutaneous kyphoplasty (PKP) to correct the spinal deformity, relieve pain, and maintain spinal stabilization in addition to supportive care in 1998, PKP has gradually become the most popular treatment for OVCF. Additionally, standard anti-osteoporosis treatment is strongly recommended to improve the therapeutic efficacy of PKP and reduce long-term complications. Zoledronic acid (ZOL) is a kind of nitrogen-containing bisphosphonate which is known to increase bone mineral density (BMD) and decrease the risk of osteoporotic fracture by

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inhibiting the osteoclastic function and inducing osteoclast apoptosis, finally extending overall survival of osteoporosis patients [7, 8]. Yearly administration of ZOL was approved for anti-osteoporosis treatment in reducing the risk of fracture in patients with postmenopausal osteoporosis effectively.

At present, few studies have reported the combined use of ZOL infusion with PKP for osteoporotic compression fracture of the spine, and the therapeutic effect remains uncertain. The aim of the present prospective study was to explore the clinical outcome of ZOL combined with PKP in the treatment of T12 or L1 OVCF in 101 patients who were admitted in our hospital between August 2015 and July 2018.

Materials and methods

Selection criteria

The inclusion criteria were as follows: (1) postmenopausal women with BMD T-score of − 2.5 or less at the lumbar spine measured by dual-energy X-ray absorptiometry (DXA) (the T-score was derived from the Chinese Bone Mineral Density Database (CMDD)); (2) isolated compression fracture of single vertebral body of T12 or L1 within 2 weeks; (3) MRI showing a hypointense signal on T1-weighted images and hyperintense signal on T2-weighted images; (4) relatively severe back pain exacerbated after activities; (5) spinal tenderness and tapping pain on T12 or L1; and (6) pain that did not improve with control management including bed rest, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and bracing. Exclusion criteria included metastasis, multiple myeloma, spinal infection, nerve compression, severe renal insufficiency with a creatinine clearance rate (CCR) ≥ 35 mL/min, and hypocalcemia.

Surgical procedures

Before surgery, all patients were confined to strict bed rest. Patients were positioned prone on the operating table, and anesthesia was performed by two senior orthopedists. A small incision was made under X-ray guidance, and a probe was subsequently placed into the vertebral space at the fracture site. The bone was drilled, and a balloon (Kinetic Inc., Shanghai, China) was inserted on each side and then inflated with the contrast medium in order to obtain the desired height recovery. The spaces created by the balloon were then filled with bone cement carefully under fluoroscopic monitoring. All surgical procedures of PKP were performed by the same group of spinal surgeons in our department. The patients were monitored for 6 h postoperatively.

Research subjects

Altogether, 101 patients with T12 or L1 OVCF who received PKP in the Department of Orthopedics of Changhai Hospital (Shanghai, China) between August 2015 and July 2017 were randomly assigned to a ZOL group and a control group, using a central randomization schedule of randomly permuted blocks, with the use of an interactive online system. The patients and attending clinicians were not blinded to the study protocol because both ZOL and control groups received different methods of drug administration (intravenous vs. oral) and laboratory monitoring and had different drug-related adverse effects.

ZOL group comprised 50 patients who ranged in age from 56 to 84 years with a mean of 64.60 ± 6.70 years, and the control group comprised 51 patients who ranged in age from 56 to 91 years with a mean of 63.98 ± 7.51 years. Among these patients, one patient was also diagnosed with chronic gastritis, four patients with hypertension, two patients with coronary heart disease, one patient with chronic obstructive pulmonary disease, one patient with ulcerative colitis, and one patient with cerebral infarction.

Informed consent about reviewing the medical records was obtained from each included patient. This prospective single-center study was performed based on a protocol approved by the institutional review board of Changhai Hospital and in accordance with the principles of the Declaration of Helsinki.

Treatments

All patients in both groups were treated with PKP. Patients in ZOL group also received once-yearly intravenous (IV) ZOL infusion (Aclasta) for 1 year at a dose of 5 mg in 100 mL solution infused over at least 15 min on the basis of daily 1000 mg calcium and 800 IU vitamin D supplements. Zol was administered 2 days before PKP. Before administration of ZOL, 500 mL saline was given intravenously, and 2.5 mg dexamethasone (Dex) was given to prevent allergy. After administration, 100 mL saline was given intravenously, and 60 mg loxoprofen was given orally three times per day. In the control group, only the same dose of calcitriol and calcium carbonate D3 was administered for 1 year. All patients were advised to drink more water before and after medication to facilitate drug excretion and reduce renal toxicity.

Evaluation indicators

The BMD value, serum bone metabolic indices, VAS score, and adverse reactions were evaluated. All BMD values of the left femoral neck were measured using the dual-energy X-ray with a GE Lunar bone densitometer (Madison, WI, USA) at admission and 6 and 12 months after treatment. The RMS-% CV of the femoral neck was 1.765%; LSC (least significant

change) of the femoral neck was 0.0364 g/cm^2. The analysis of each scan was performed by the same experienced densitometrist and validated by the authors. Quality assurance/quality control observations were recorded according to manufacturer's guidelines throughout the duration of the study. Before and 6 and 12 months after treatment, the serum bone metabolic indices of osteocalcin in the N-terminal molecular fragment (NMID), the total extension of the peptide type I collagen amino end (P1NP), and beta collagen degradation product (β-CTX) levels were determined by providing manufacturing bone metabolism detected by electrochemical luminescence immunity analysis technology. VAS scores before surgery and 1 week, 6 months, and 1 year after surgery were observed in the two groups. In addition, adverse reactions mainly include fever, joint pain, muscle and soft tissue pain, and other flu-like symptoms, such as nausea, vomiting, fatigue, and arrhythmia, and the new fracture situation of the patients conducted by image review were observed.

Statistical methods

Statistical software SPSS 19.0 was used for analysis. The results are presented as means ± SD; Student's *t* test and one-way analysis of variance were applied for continuous data, and chi-square test for categorical data. A *p* value of < 0.05 was considered to indicate statistical significance.

Results

Demographic characteristics

The mean age, height, weight, BMI, and menopausal age of the 50 patients in ZOL group and 51 patients in the control group were 64.60 ± 6.70 vs. 63.98 ± 7.51 years, 156.95 ± 4.93 vs. 158.01 ± 4.37 cm, 64.46 ± 6.22 vs. 65.35 ± 6.89 kg, 26.13 ± 1.81 vs. 26.15 ± 2.23 Kg/m^2, and 49.74 ± 2.41 vs. 50.24 ± 2.45 years respectively. In addition, there were 28 cases of T12 fracture and 22 cases of L1 fracture in ZOL group vs. 24 and 27 cases in the control group. There was no statistically significant difference in age, height, weight, BMI, menopause age, and fracture vertebral body between the two groups ($p > 0.05$) (Table 1).

Clinical outcomes

The baseline of BMD of the left femoral neck was 0.670 ± 0.066 in ZOL group and 0.665 ± 0.047 in the control group, showing no significant difference between the two groups ($p > 0.05$). In ZOL group, BMD of the left femoral neck at 6 and 12 months after treatment was 0.714 ± 0.067 and 0.744 ± 0.069 respectively, indicating that BMD was significantly higher than the baseline ($p < 0.05$). And the significant difference was still found between 6 and 12 months ($p < 0.05$). In the control group, BMD at 6 and 12 months after treatment was 0.676 ± 0.051 and 0.703 ± 0.063 respectively. However, the difference in BMD was found only 12 months after treatment as compared with the baseline and that after 6 months ($p < 0.05$), while no difference was detected between 6 months and before treatment ($p < 0.05$). Similarly, comparison of BMD between the two groups showed that the BMD of ZOL group was significantly higher than that in the control group, either 6 months or 12 months after treatment (Fig. 1).

Table 1 Demographic characteristics of ZOL group, conservative group

Variable	ZOL	Conservative	*p* Value
Number	50	51	
Age (years)	64.60 ± 6.70	63.98 ± 7.51	0.663
Height (cm)	156.95 ± 4.93	158.01 ± 4.37	0.258
Weight (Kg)	64.46 ± 6.22	65.35 ± 6.89	0.496
BMI (Kg/m2)	26.13 ± 1.81	26.15 ± 2.23	0.964
Menopause age	49.74 ± 2.41	50.24 ± 2.45	0.308
Fracture vertebral body			
T12	28	24	0.808
L1	22	27	

T12, the 12th thoracic vertebra; *Ll*, the 1st lumbar vertebra; *ZOL*, zoledronic acid

Bone markers NMID, P1NP, and β-CTX were used to evaluate bone absorption [9]. The baseline of NMID, P1NP, and β-CTX was 20.76 ± 6.88 μg/L, 39.98 ± 1.79 μg/L, and 0.55 ± 0.14 μg/L in ZOL group vs. 22.43 ± 5.58 μg/L, 39.96 ± 1.90 μg/L, and 0.56 ± 0.14 μg/L in the control group respectively, showing no significant difference between the two groups ($p > 0.05$). In ZOL group, NMID, P1NP, and β-CTX were decreased to 15.08 ± 5.56 μg/L, 15.37 ± 1.61 μg/L, and

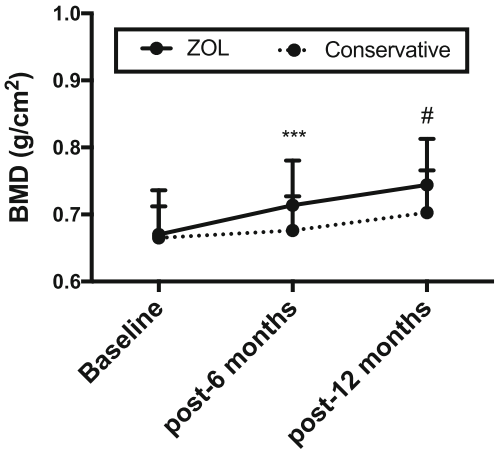

Fig. 1 BMD at the left femoral neck after PKP and/or ZOL infusion. Data are presented as mean ± SD. $^{***}p < 0.01$ ZOL group vs. control group 6 months after treatment, $^{\#}p < 0.001$ ZOL group vs. control group 12 months after treatment

0.35 ± 0.04 μg/L 6 months after treatment, and 13.94 ± 2.79 μg/L, 15.40 ± 1.40 μg/L, and 0.34 ± 0.05 μg/L 12 months after treatment. Similarly, NMID, P1NP, and β-CTX in the control group decreased to 18.81 ± 5.05, 33.13 ± 1.30, and 0.42 ± 0.18 6 months after treatment, and 17.88 ± 4.25 μg/L, 33.23 ± 1.94 μg/L, and 0.40 ± 0.06 μg/L 12 months after treatment. Both in ZOL group and control group, the three bone markers were significantly lower than the baseline values ($p < 0.001$), and there was no significant difference in the bone markers between 6 and 12 months ($p > 0.05$). Intra-group comparison showed that the above bone markers in ZOL group were significantly lower than those in the control group (Fig. 2).

The VAS score was applied in pain assessment. At 1 week, 6 months, and 12 months after treatment, the VAS score in ZOL group was significantly reduced from 8.54 ± 0.50 of the baseline value to 2.62 ± 0.49 in a week, 1.52 ± 0.50 in 6 months, and 1.46 ± 0.50 in 12 months, and the VAS score in the control group reduced from 8.45 ± 0.50 of the baseline value to 2.96 ± 0.66 in a week, 2.22 ± 0.42 in 6 months, and 2.33 ± 0.48 in 12 months respectively ($p < 0.001$). Compared with 1 week after treatment, the VAS score was significantly lower at 6 and 12 months after treatment ($p < 0.001$). Intra-group comparison showed that the VAS score in ZOL group was significantly lower than that in the control group 1 week, 6 months, and 12 months after treatment. However, there was no significant difference in the VAS score between 6 months and 12 months after treatment ($p > 0.05$) (Fig. 3).

Adverse events

In ZOL group, adverse events (AE) occurred after IV infusion of ZOL in 18 (36%) cases, including fever in 10 (55.6%), flu-like symptoms in 3 (16.7%), arthralgia in 3 (16.7%), and myalgia in 2 (11.1%). No AE were observed in the control group. All AE in ZOL group were mild and cured after symptomatic treatment, although the incidence of AE in ZOL group was significantly higher than that in the control group ($p < 0.001$). In terms of the RVF, no new fracture occurred in ZOL group, while 6 (11.7%) new adjacent vertebral fractures occurred in the control group during the treatment, showing a significant difference between the two groups ($p < 0.05$) (Table 2).

Discussion

PKP is one of the main surgical treatments for OVCF at present [10]. However, osteoporosis is a systemic disease, and no sufficient attention has been paid to the prevention and treatment of osteoporosis on the part of orthopedists. Our data showed that ZOL in combination with percutaneous kyphoplasty could improve BMD of the left femoral neck,

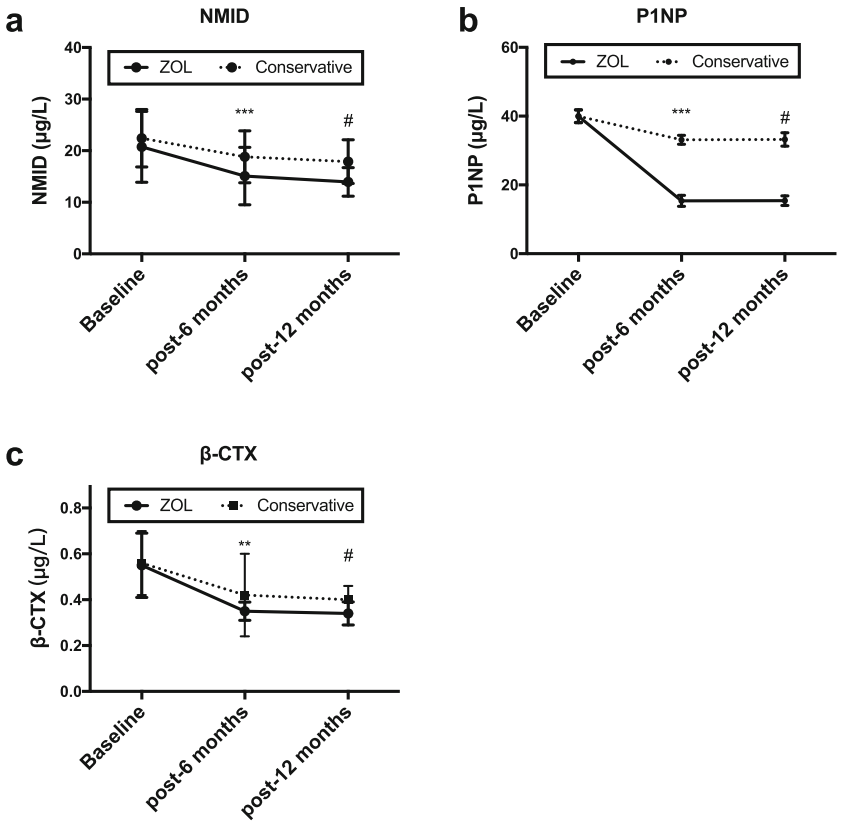

Fig. 2 Bone markers NMID, P1NP, and β-CTX after PKP and/or ZOL infusion. Data are presented as mean ± SD. **a** $^{***}p < 0.001$ NMID levels of ZOL group vs. control group 6 months after treatment, $^{\#}p < 0.001$ ZOL group vs. control group 12 months after treatment. **b** $^{***}p < 0.001$ PINP levels of ZOL group vs. control group 6 months after treatment, $^{\#}p < 0.001$ ZOL group vs. control group 12 months after treatment. **c** $^{**}p < 0.01$ β-CTX levels of ZOL group vs. control group 6 months after treatment, $^{\#}p < 0.001$ ZOL group vs. control group 12 months after treatment

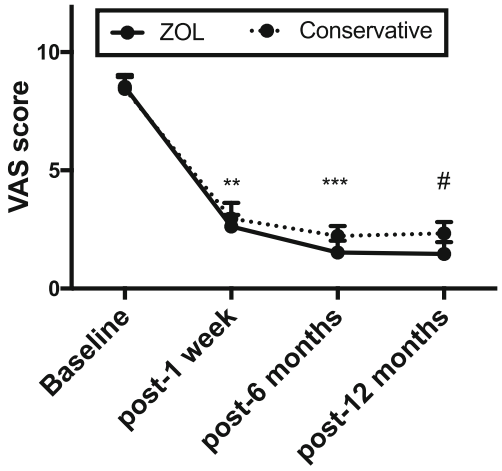

Fig. 3 VAS before and after PKP and/or ZOL infusion. Data are presented as mean ± SD. $^{**}p < 0.01$ ZOL group vs. control group at post 1 week, $^{***}p < 0.01$ ZOL group vs. control group 6 months after treatment, $^{\#}p < 0.001$ ZOL group vs. control group 12 months after treatment

increase the level of bone markers, and reduce the incidence of new fractures.

Safer et al. [11, 12] reported that T value of bone density improved significantly in patients with osteoporosis after 12-month administration of bisphosphonate, calcium, and vitamin D. In addition, ZOL also enhanced bone density of the lumbar vertebra, total hip joint, and the femoral neck, and reduced the risk of vertebral and non-vertebral body fractures. A randomized double-blind study in 285 patients with osteoporosis in East China [13] showed that IV injection of ZOL (5 mg/year) significantly increased bone density of the lumbar vertebra and hip during the 24-month treatment. The anti-osteoporosis effect could be explained by the enhancement of the microstructure parameters and bone strength of bone trabeculae in mouse models [14–16]. Indeed, our data suggest that ZOL was more helpful in improving the femoral neck BMD compared with the control group, and the duration of ZOL treatment could be up to 1 year.

Hip bone density and PINP are considered to be highly sensitive in the prediction of clinical fracture, and PINP and β-CTX also show a good response in the assessment of the therapeutic outcome [9]. Hagino et al. [17] believed that after 5-year administration of bisphosphonates, the level of bone markers remained in the premenopausal range for a long time after the initial level of the bone markers was reduced. It was found in our study that the level of the bone markers remained stable during the observation period in both groups. Definitely, more advantages in reducing bone absorption were seen in the patients receiving ZOL treatment.

Shi et al. [18] performed a two-year retrospective study in 95 patients with osteoporotic compressive fracture and found that the secondary fracture rate of the PKP group was 14.7%, and no fracture occurred in the group of PKP combined with zoledronic acid. Even in high-risk patients, the low fracture rate and high compliance elucidated the benefits of ZOL infusion in the treatment of osteoporosis. Thus, ZOL is strongly recommended by the American College of Physicians for reducing the risk of hip and spinal fractures in women with known osteoporosis [19]. In this study, the rate of new fractures in the control group was 11.7%, while no new fracture occurred in ZOL group, which further confirms the efficacy of ZOL in increasing bone density and reducing the incidence of brittle fractures.

Low-back pain is very common in patients with osteoporosis, especially in women, affecting their quality of life. A systematic review showed that PVP/PKP was more effective than the control treatment in relieving pain in acute/subacute and chronic osteoporotic compression fractures [20]. In this study, the pain symptom was significantly relieved in both groups as compared with that before treatment, and the VAS score in ZOL group was lower than that in the control group at 1 week, 6 months, and 12 months after treatment. Considering that ZOL can promote osteogenesis and bone healing, it should be more favorable for relieving the pain symptom of the patients [21].

Oral azolate phosphoric acid often has an acute phase response, similar to influenza, with fever and pain symptoms, which are usually relieved effectively by oral NSAIDS [22–24]. However, the fever rate was significantly reduced after the first IV injection of ZOL in patients who had been previously treated with alendronate, indicating that the oral history of alendronate containing azodiphosphate is a protective factor for fever [25]. Certainly, there are some other incidental adverse reactions, such as uveal inflammatory macular edema, thrombocytopenia, and hypocalcemia [26–29], which were not found in our patients.

In summary, ZOL as the first-line drug in the treatment of postmenopausal women osteoporosis was applied to patients with osteoporotic compression fracture of a single vertebral body who received PKP treatment. ZOL could effectively improve the patients' BMD, improve bone marker levels, and reduce the VAS score and RVF with a low rate of acceptable adverse reactions and relatively low economic pressure. The long-term clinical effect of ZOL in patients with osteoporotic fractures needs further research.

Table 2 Complications of ZOL infusion with PKP

	ZOL	Conservative	*p* value
RVF, *n* (%)	0 (0)	5 (11.7)	0.02*
AE, *n* (%)	18 (36)	0 (0)	
Fever	10		
Flu-like symptoms	3		
Arthralgia	3		
Myalgia	2		

*$p < 0.05$ was considered statistically significant. AE adverse events

Compliance with ethical standards

Conflicts of interest None.

References

1. Cauley JA, Chalhoub D, Kassem AM, Fuleihan Gel H (2014) Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol 10(6):338–351
2. Kanis JA, Adachi JD, Cooper C, Clark P, Cummings SR, Diaz-Curiel M, Harvey N, Hiligsmann M, Papaioannou A, Pierroz DD et al (2013) Standardising the descriptive epidemiology of osteoporosis: recommendations from the Epidemiology and Quality of Life Working Group of IOF. Osteoporos Int 24(11):2763–2764
3. Ballane G, Cauley JA, Luckey MM, El-Hajj Fuleihan G (2017) Worldwide prevalence and incidence of osteoporotic vertebral fractures. Osteoporos Int 28(5):1531–1542
4. Belhassen M, Confavreux CB, Cortet B, Lamezec L, Ginoux M, Van Ganse E (2017) Anti-osteoporotic treatments in France: initiation, persistence and switches over 6 years of follow-up. Osteoporos Int 28(3):853–862
5. Viswanathan M, Reddy S, Berkman N, Cullen K, Middleton JC, Nicholson WK, Kahwati LC (2018) Screening to prevent osteoporotic fractures: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 319(24):2532–2551
6. Garfin SR, Yuan HA, Reiley MA, Kaur U, Chakrabarti SS, Gambhir IS (2001) New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. Spine 26(14):1511–1515
7. Dhillon S (2016) Zoledronic acid (Reclast((R)), Aclasta((R))): a review in osteoporosis. Drugs 76(17):1683–1697
8. Maricic M (2010) The role of zoledronic acid in the management of osteoporosis. Clin Rheumatol 29(10):1079–1084
9. Looker AC, Bauer DC, Chesnut CH 3rd, Gundberg CM, Hochberg MC, Klee G, Kleerekoper M, Watts NB, Bell NH (2000) Clinical use of biochemical markers of bone remodeling: current status and future directions. Osteoporos Int 11(6):467–480
10. Lange A, Kasperk C, Alvares L, Sauermann S, Braun S (2014) Survival and cost comparison of kyphoplasty and percutaneous vertebroplasty using German claims data. Spine 39(4):318–326
11. Safer U, Safer VB, Demir SO, Yanikoglu I (2016) Effects of bisphosphonates and calcium plus vitamin-D supplements on cognitive function in postmenopausal osteoporosis section sign. Endocr Metab Immune Disord Drug Targets 16(1):56–60
12. Hsieh PC (2016) Effectiveness and safety of zoledronic acid in the treatment of osteoporosis. Orthopedics 39(2):e263–e270
13. Liang BC, Shi ZY, Wang B, Wu P, Kong LC, Yao JL, Li CW, Shi XL (2017) Intravenous zoledronic acid 5 mg on bone turnover markers and bone mineral density in East China subjects with newly diagnosed osteoporosis: a 24-month clinical study. Orthop Surg 9(1):103–109
14. Jeon OC, Seo DH, Kim HS, Byun Y, Park JW (2016) Oral delivery of zoledronic acid by non-covalent conjugation with lysine-deoxycholic acid: in vitro characterization and in vivo anti-osteoporotic efficacy in ovariectomized rats. Eur J Pharm Sci 82:1–10
15. Bell KJ, Hayen A, Glasziou P, Irwig L, Eastell R, Harrison SL, Black DM, Bauer DC (2016) Potential usefulness of BMD and bone turnover monitoring of zoledronic acid therapy among women with osteoporosis: secondary analysis of randomized controlled trial data. J Bone Miner Res 31(9):1767–1773
16. Kim BS, Yang SS, Kim CS, Lee J (2018) Zoledronate suppresses VEGFinduced capillary tube formation and inhibits expression of interferoninduced transmembrane protein1 in human umbilical vein endothelial cells. Int J Mol Med 41(5):2879–2884
17. Hagino H: [Evidence for positive effects of long-term bisphosphonate administration.]. Clin Calcium 2017, 27(2):203–211
18. Shi C, Zhang M, Cheng AY, Huang ZF: Percutaneous kyphoplasty combined with zoledronic acid infusion in the treatment of osteoporotic thoracolumbar fractures in the elderly. Clin Interv Aging 2018, 13:853–861
19. Lewiecki EM (2017) Treatment of low bone density or osteoporosis to prevent fractures in men and women. Ann Intern Med 167(12):902
20. Zuo XH, Zhu XP, Bao HG, Xu CJ, Chen H, Gao XZ, Zhang QX (2018) Network meta-analysis of percutaneous vertebroplasty, percutaneous kyphoplasty, nerve block, and control treatment for nonsurgery options of acute subacute and chronic osteoporotic vertebral compression fractures (OVCFs) in short-term and long-term effects. Medicine 97(29):e11544
21. Dempster DW, Roschger P, Misof BM, Zhou H, Paschalis EP, Alam J, Ruff VA, Klaushofer K, Taylor KA (2016) Differential effects of teriparatide and zoledronic acid on bone mineralization density distribution at 6 and 24 months in the SHOTZ study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 31(8):1527–1535
22. Ding Y, Zeng JC, Yin F, Zhang CL, Zhang Y, Li SX, Liu X, Zhang C, Xue QY, Lin H et al (2017) Multicenter study on observation of acute-phase responses after infusion of zoledronic acid 5 mg in Chinese women with postmenopausal osteoporosis. Orthop Surg 9(3):284–289
23. Popp AW, Senn R, Curkovic I, Senn C, Buffat H, Popp PF, Lippuner K (2017) Factors associated with acute-phase response of bisphosphonate-naive or pretreated women with osteoporosis receiving an intravenous first dose of zoledronate or ibandronate. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis\ Foundation of the USA 28(6):1995–2002
24. Crotti C, Watts NB, De Santis M, Ceribelli A, Fabbriciani G, Cavaciocchi F, Marasini B, Selmi C, Massarotti M (2018) Acute phase reactions after zoledronic acid infusion: protective role of 25-hydroxyvitamin D and previous oral bisphosphonate therapy. Endocr Pract 24(5):405–410
25. Wang H, Hu ZH, Chen L, Pan Y (2016) Influence of history of oral bisphosphonates on the incidence rate of fever after intravenous injection of zoledronic acid in patients with osteoporosis. Beijing Da Xue Xue Bao Yi Xue Ban 48(4):680–682
26. Tian Y, Wang R, Liu L, Ma C, Lu Q, Yin F (2016) Acute bilateral uveitis and right macular edema induced by a single infusion of zoledronic acid for the treatment of postmenopausal osteoporosis as a substitution for oral alendronate: a case report. BMC Musculoskelet Disord 17:72
27. Kulkarni P, Cushman T, Donthireddy V, Rao S (2016) Spontaneously recovered severe thrombocytopaenia following zoledronic acid infusion for osteoporosis. BMJ Case Rep 2016
28. Kaur U, Chakrabarti SS, Gambhir IS: Zoledronate induced hypocalcemia and hypophosphatemia in osteoporosis: a cause of concern. Curr Drug Saf 2016, 11(3):267–269
29. Aktas I, Nazikoglu C, Kepez A, Ozkan FU, Kaysin MY, Akpinar P, Dogan Z, Ileri C, Saymaz S, Erdogan O (2016) Effect of intravenous zoledronic acid infusion on electrocardiographic parameters in patients with osteoporosis. Osteoporos Int 27(12):3543–3547