

Review Article

Factors affecting the role of zoledronic acid and alendronic acid on inflammation level and efficacy in elderly patients with osteoporosis

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Abstract: Objective: This study was designed to investigate the effects of tumor necrosis factor- α (TNF- α) and interleukin -6 (IL-6) on zoledronic acid (ZA) and alendronate sodium (ALN) in the treatment of aged osteoporosis (OP) patients, and to analyze the risk factors affecting their efficacy. Methods: A total of 140 aged OP patients admitted to our hospital were selected. Among them, 80 cases treated with ZA were regarded as ZA group and 60 cases treated with ALN were seen as ALN group. Inflammatory factors (TNF- α , IL-6) in patients were detected by enzyme-linked immunosorbent assay (ELISA), and the effects on TNF- α and IL-6 before and after treatment were analyzed. Results: The effective rate of ZA group was significantly higher than that of ALN group, and the incidence rate of adverse reactions was significantly lower than that of ALN group. There was no significant difference in the levels of inflammatory factors between the two groups before treatment. After treatment, the levels of inflammatory factors in both groups decreased significantly, and the levels of inflammatory factors in ZA group were significantly lower than those in ALN group. Before treatment, the AUC of serum TNF- α and IL-6 for predicting the efficacy of aged OP patients were 0.849 and 0.869 respectively. Multivariate Logistic regression analysis showed that serum TNF- α and IL-6 concentrations and treatment methods before treatment were risk factors affecting the treatment effect of aged OP patients. Conclusion: ZA is more effective than ALN in the treatment of aged OP patients and it can inhibit inflammatory reaction effectively.

Keywords: Zoledronic acid, alendronate sodium, senile osteoporosis, inflammation

Introduction

Osteoporosis (OP) is a major global challenge to the physical and skeletal health of the elderly. Aging will increase the risk of bone fragility and fracture [1, 2]. Its main characteristics are low bone density, impaired bone strength and changes in bone tissue microstructure, which lead to an increased risk of vertebral or hip fractures in OP patients, thus increasing their mortality rate [3]. According to statistics, the prevalence rate of female OP is 25.41%, while that of male OP is 15.33%, and it increases with age [4]. The first-line strategies to prevent fractures in aged OP patients are fall prevention, smoking cessation, moderate alcohol consumption and bisphosphonate therapy, of which bisphosphonate is a common drug that can act on osteoblasts and osteocytes actively and is effective in reducing OP fractures [5, 6].

However, treatment for aged OP patients is still inadequate [7]. Therefore, we conducted research on bisphosphonate therapy applied to aged OP patients, which is of great significance for improving their treatment efficiency and quality of life.

Bisphosphonates are widely used in OP therapy due to their advantages of inhibiting osteoclast-mediated bone resorption and increasing bone mineral density [8]. Zoledronic acid (ZA) is a bisphosphonate that inhibits osteoclasts effectively and reduces osteolysis caused by OP [9]. Some studies in OP rat models have shown that ZA has the potential to improve the formation of new bone in OP rats [10]. In addition, OP rabbit experimental models have revealed that single dose ZA has certain positive effect on OP fracture healing after ovariectomy [11]. Alendronate (ALN), as a bisphosphonate against bone catab-

olism, is a first-line drug for OP [12]. Some studies have shown that ALN can inhibit bone resorption by inhibiting phosphatase, and can also promote osteoclast apoptosis at high doses [13]. Concerning ALN treatment of OP patients with the highest age (≥ 80 years old), Axelsson and others [14] reported that ALN was used to treat patients with fracture, and it could reduce the risk of hip fracture sustainably and safely. Based on the above research, we chose ZA and ALN to carry out treatment research on aged OP patients. Besides, since many studies have reported that inflammatory factors participate in the pathological process of OP patients [15, 16], we also studied the effects of ZA and ALN on their inflammatory factors.

ZA and ALN are bisphosphonates that can improve the bone mineral density of aged OP patients [17], but there are few studies on the comparison of efficacy and influence on inflammatory factors between them. This study aimed to supplement this blank by detecting the concentrations of relevant inflammatory factors and recording relevant indicators, hoping to provide reference value for the treatment of aged OP patients.

Materials and methods

General information

A total of 140 aged OP patients were admitted to our hospital from January 2017 to August 2018. Eighty aged OP patients treated with ZA were taken as ZA group, including 35 males and 45 females, aged 55-79 years, with an average age of 66.98 ± 5.35 years; sixty elderly OP patients treated with ALN were taken as ALN group, including 23 males and 37 females, aged 56-77 years, with an average age of 66.54 ± 5.27 years. Inclusion criteria were as follows: patients conformed to OP diagnostic criteria of the World Health Organization (WHO) [18]; their weight loss in the past half year was less than 2 kg; in the past three months, no drugs affecting the indicators of this study had been used. Exclusion criteria were as follows: patients with malignant tumor or severe organ dysfunction; those with mental diseases, immune diseases, or infectious diseases; those who were allergic to this medication. The study was approved by the ethics committee of our hospital. The subjects and their guardians were informed and signed a fully informed consent.

Treatment methods

Treatment plan of ALN group was as below: 70 mg of ALN (Beijing Wansheng Pharmaceutical Co., Ltd., China, batch number: H20059029), once a week for one year. Treatment plan of ZA group was as below: intravenous drip of 5 mg ZA, once a year (Jiangsu Hengrui Pharmaceutical Co., Ltd., China, batch number: H20041953).

Efficacy evaluation

Visual analogue scale (VAS) [19] was applied to evaluate the pain degree of the two groups one year after treatment. A reduction of at least 80% in the VAS score of patients was considered as excellent, 60-79% was considered as good, 40-59% was considered as general, and that of no more than 39% was considered as poor. We defined excellent and good as effective treatment, and general and poor as ineffective treatment. The total effective rate = [excellent (number of cases) + good (number of cases)]/total number of cases $\times 100\%$.

Detection methods

Altogether 3 mL venous blood was taken from patients in both groups before and 3 months after treatment, and it was placed in anticoagulants. Enzyme-linked immunosorbent assay (ELISA) [20] was used to detect the levels of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) (Shanghai Qiaoyu Biotechnology Co., Ltd., China, item numbers: QN-PS0122, QN-PS0049) in serum. The detection was carried out strictly according to the operation instructions of the kit. After adding liquid, sealing plates, incubating at 37°C , washing plates and adding liquid again, the OD value of each well was detected at 450 nm wavelength by Tecan Freedom Evolyzer[®] full-automatic enzyme immunoassay analyzer (Deacon (Shanghai) Trading Co., Ltd., China), and the TNF- α and IL-6 levels were calculated.

Statistical analysis

GraphPad Prism 6 (GraphPad Software, San Diego, USA) was used for statistical analysis and pictures drawing. The measurement data were expressed by mean \pm SD, their comparison between groups was conducted by independent-samples T test, and that before and after treatment was conducted by paired T test,

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Table 1. Baseline data in the two groups [n (%), mean \pm SD]

| Factor | n | ALN group (n=60) | ZA group (n=80) | χ^2/t | P |
|---------------------------------------|-----|--------------------|--------------------|------------|-------|
| Gender | | | | 0.415 | 0.520 |
| Male | 58 | 23 (38.33) | 35 (43.75) | | |
| Female | 82 | 37 (61.67) | 45 (56.25) | | |
| Age (years) | | | | 0.486 | 0.486 |
| <65 | 56 | 22 (36.67) | 34 (42.50) | | |
| \geq 65 | 84 | 38 (63.33) | 46 (57.50) | | |
| Average age (years) | 140 | 66.54 \pm 5.27 | 66.98 \pm 5.35 | 0.485 | 0.629 |
| Average body mass (kg) | 140 | 58.87 \pm 7.53 | 58.39 \pm 7.41 | 0.377 | 0.707 |
| History of drinking | | | | 0.157 | 0.692 |
| No | 58 | 26 (43.33) | 32 (40.00) | | |
| Yes | 82 | 34 (56.67) | 48 (60.00) | | |
| History of smoking | | | | 1.061 | 0.303 |
| No | 63 | 24 (40.00) | 39 (48.75) | | |
| Yes | 77 | 36 (60.00) | 41 (51.25) | | |
| Diet | | | | 1.039 | 0.308 |
| Light | 115 | 47 (78.33) | 68 (85.00) | | |
| Spicy | 25 | 13 (21.67) | 12 (15.00) | | |
| Milk-drinking habits | | | | 0.367 | 0.545 |
| No | 88 | 36 (60.00) | 52 (65.00) | | |
| Yes | 52 | 24 (40.00) | 28 (35.00) | | |
| Diabetes | | | | 0.809 | 0.369 |
| No | 84 | 39 (65.00) | 46 (57.50) | | |
| Yes | 56 | 21 (35.00) | 34 (42.50) | | |
| Comorbid with cerebrovascular disease | | | | 2.150 | 0.143 |
| No | 66 | 24 (40.00) | 42 (52.50) | | |
| Yes | 74 | 36 (60.00) | 38 (47.50) | | |
| SBP (mmHg) | 140 | 143.29 \pm 13.60 | 139.52 \pm 16.42 | 1.445 | 0.151 |
| DBP (mmHg) | 140 | 95.02 \pm 12.47 | 92.46 \pm 13.19 | 1.163 | 0.247 |
| TNF- α (pg/mL) | 140 | 46.14 \pm 7.38 | 46.23 \pm 7.41 | 0.071 | 0.943 |
| IL-6 (pg/mL) | 140 | 55.89 \pm 5.31 | 56.12 \pm 5.44 | 0.250 | 0.803 |

Table 2. Comparison results of clinical efficacy of patients in the two groups before and after treatment [n (%)]

| Group | n | Excellent | Good | General | Poor | Total efficiency |
|----------------|----|------------|------------|-----------|-----------|------------------|
| ALN group | 60 | 25 (41.67) | 21 (35.00) | 8 (13.33) | 6 (10.00) | 76.67 |
| ZA group | 80 | 45 (56.25) | 27 (33.75) | 6 (7.50) | 2 (2.50) | 90.00 |
| χ^2 value | - | - | - | - | - | 4.602 |
| P value | - | - | - | - | - | 0.032 |

for example, the average age and body mass in **Table 1**. The counting data were expressed by the number of cases/percentage [n (%)], their comparison between groups adopted chi-square test, and when the theoretical frequency in chi-square test was less than 5, the continuity correction chi-square test was adopted,

for instance, **Tables 2, 3** and **5**. Receiver operating characteristic curve (ROC) was used to evaluate the diagnostic value of serum TNF- α and IL-6 in aged OP patients, for example, **Figures 1, 2** and **Table 4**. Logistic regression equation in SPSS20.0 (IBM Corp, Armonk, NY, USA) data

statistics software was used to judge the predictive value of TNF- α and IL-6 on the efficacy of aged OP patients. Multivariate logistic regression analysis was used to explore the risk factors affecting their efficacy, for instance, **Tables 6, 7**. A p value lower than 0.05 was considered to be statistically different.

Table 3. Adverse reactions [n (%)]

| Category | ALN group (n=60) | ZA group (n=80) | χ^2 value | P value |
|---------------------------------|---------------------|--------------------|----------------|---------|
| Fever | 0 (0.00) | 1 (1.25) | - | - |
| Myalgia | 0 (0.00) | 0 (0.00) | - | - |
| Gastrointestinal tract reaction | 2 (3.33) | 0 (0.00) | - | - |
| Total | 2 (3.33) | 1 (1.25) | 0.710 | 0.400 |

Table 4. ROC parameters of inflammatory factors in predicting efficacy of aged OP patient

| Indicators | AUC | 95% CI | S.E | Cut-off | Sensitivity (%) | Specificity (%) |
|---------------------|-------|-------------|-------|-------------|-----------------|-----------------|
| TNF- α | 0.849 | 0.751-0.948 | 0.050 | 39.76 pg/mL | 79.66 | 81.82 |
| IL-6 | 0.869 | 0.780-0.957 | 0.045 | 50.41 pg/mL | 94.92 | 68.18 |
| TNF- α +IL-6 | 0.928 | 0.859-0.997 | 0.035 | 0.80 | 93.22 | 86.36 |

Results

Baseline data

There were no significant differences between ALN group and ZA group in gender, age, average age, average body mass, history of drinking, history of smoking, diet, milk-drinking habits, diabetes, cerebrovascular disease, SBP, DBP, TNF- α and IL-6 ($P>0.05$). More details were shown in **Table 1**.

Clinical effect analysis

The total effective rate of ALN group was 76.67%, and that of ZA group was 90.00%; the rate of ZA group was significantly higher than that of ALN group ($P<0.05$). More details were shown in **Table 2**.

Occurrence of adverse reactions

The incidence rate of adverse reactions was 3.33% in ALN group and 1.25% in ZA group. The incidence rate of adverse reactions in ZA group was lower than that in ALN group, but the difference was not statistically significant ($P>0.05$). More details were shown in **Table 3**.

Analysis of inflammatory factors in aged OP patients

Inflammatory factors TNF- α and IL-6 had no significant difference between the two groups before treatment ($P>0.05$). After treatment, the levels of inflammatory factors in the two groups reduced significantly, and those in ZA group

were significantly lower than those in ALN group, with statistical significance ($P<0.05$). More details were shown **Figure 1**.

Value of inflammatory factors in predicting the efficacy of aged OP patients

A total of 118 patients in ALN group and ZA group were treated effectively and taken as the effective group, while 22 patients with ineffective treatment were

treated as the ineffective group. We drew the ROC curve of inflammatory factors TNF- α and IL-6 in predicting the efficacy of aged OP patients. AUC of TNF- α in diagnosing their efficacy was 0.849, the optimal cut-off value was 39.76 pg/mL, and the sensitivity and specificity were 79.66% and 81.82% respectively. AUC of IL-6 in their diagnosis was 0.869, the optimal cut-off value was 50.41 pg/mL, and the sensitivity and specificity were 94.92% and 68.18% respectively. Further binary logistic regression analysis was carried out, with TNF- α and IL-6 as independent variables. Logistic regression model was obtained: $\text{Logit}(P) = 30.555 + 6.379 \text{ TNF-}\alpha + 22.941 \text{ IL-6}$. AUC value of combined diagnostic efficacy of TNF- α and IL-6 was 0.928. More details were shown in **Figure 2** and **Table 4**.

Multivariate logistic regression analysis on efficacy of aged OP patients

The differences of clinical parameters and related indexes between effective and ineffective patients were compared. The optimal critical values of TNF- α and IL-6 for predicting the efficacy of aged OP patients were 39.76 pg/mL and 50.41 pg/mL as split points. There was no significant difference in gender, age, history of drinking, history of smoking, diet, milk-drinking habits, diabetes and cerebrovascular disease between the effective and ineffective patients ($P>0.05$), while there was statistical difference in treatment mode, TNF- α and IL-6 ($P<0.05$). Multivariate logistic regression analysis was carried out on the different factors, and the

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Table 5. Relationship between clinical parameters, indicators and efficacy of aged OP patients [n (%), mean \pm SD]

| Factor | n | Ineffective group (n=22) | Effective group (n=118) | χ^2/t | P |
|---------------------------------------|-----|--------------------------|-------------------------|------------|-------|
| Gender | | | | 0.993 | 0.319 |
| Male | 58 | 7 (31.82) | 51 (43.22) | | |
| Female | 82 | 15 (68.18) | 67 (56.78) | | |
| Age (years) | | | | 0.009 | 0.925 |
| <65 | 56 | 9 (40.91) | 47 (39.83) | | |
| \geq 65 | 84 | 13 (59.09) | 71 (60.17) | | |
| History of drinking | | | | 1.851 | 0.174 |
| No | 58 | 12 (54.55) | 46 (38.98) | | |
| Yes | 82 | 10 (45.45) | 72 (61.02) | | |
| History of smoking | | | | 3.663 | 0.056 |
| No | 63 | 16 (72.73) | 47 (39.83) | | |
| Yes | 77 | 6 (27.27) | 71 (60.17) | | |
| Diet | | | | 0.002 | 0.966 |
| Light | 115 | 18 (81.82) | 97 (82.20) | | |
| Spicy | 25 | 4 (18.18) | 21 (17.80) | | |
| Milk-drinking habits | | | | 3.386 | 0.066 |
| No | 88 | 10 (45.45) | 78 (66.10) | | |
| Yes | 52 | 12 (54.55) | 40 (33.90) | | |
| Diabetes | | | | 3.245 | 0.072 |
| No | 56 | 5 (22.73) | 51 (43.22) | | |
| Yes | 84 | 17 (77.27) | 67 (56.78) | | |
| Comorbid with cerebrovascular disease | | | | 2.460 | 0.117 |
| No | 66 | 7 (31.82) | 59 (50.00) | | |
| Yes | 74 | 15 (68.18) | 59 (50.00) | | |
| Treatment methods | | | | 6.836 | 0.009 |
| ALN therapy | 60 | 15 (68.18) | 45 (38.14) | | |
| ZA therapy | 80 | 7 (31.82) | 73 (61.86) | | |
| TNF- α (pg/mL) | | | | 7.488 | 2.737 |
| <39.76 | 98 | 10 (45.45) | 88 (74.58) | | |
| \geq 39.76 | 42 | 12 (54.55) | 30 (25.42) | | |
| IL-6 (pg/mL) | | | | 5.791 | 0.016 |
| <50.41 | 119 | 13 (59.09) | 106 (89.83) | | |
| \geq 50.41 | 21 | 9 (40.91) | 12 (10.17) | | |

results showed that the treatment methods ($P=0.021$), TNF- α ($P=0.003$), and IL-6 ($P=0.004$) were independent risk factors affecting the efficacy. Aged OP patients treated with ALN, high expression of TNF- α (>39.76 pg/mL) and high IL-6 (>50.41 pg/mL) have an increased risk of ineffective treatment. More details were shown in **Tables 5, 6**.

Discussion

OP is a degenerative disease of bone function, and its main complication fracture has great

influence on the quality of life of the elderly [21]. It is understood that about 33.33% of the elderly women and about 20% of the elderly men will experience brittle fracture after the age of 50, causing huge medical costs to the society [22]. Therefore, studying the drugs to prevent fractures in aged OP patients is of great value to reduce the incidence rate of fractures in the elderly and social medical costs.

There were numerous previous studies on ZA and ALN in OP therapy. For example, as to the effect of ZA on cognitive function of aged OP

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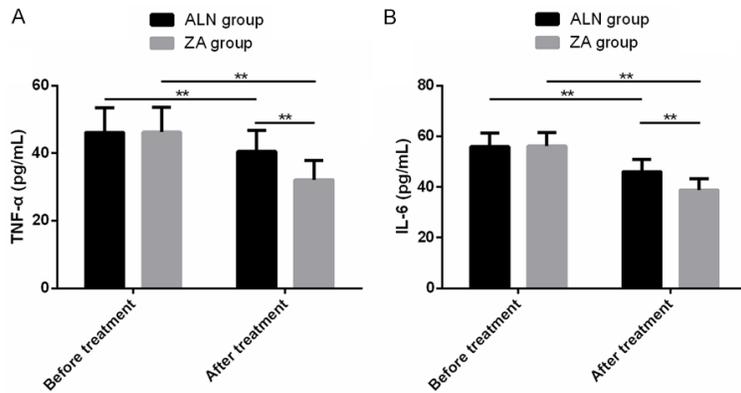


Figure 1. Levels of inflammatory factors in aged OP patients before and after treatment. A. TNF- α in ZA group decreased significantly after treatment and was significantly lower than that in ALN group. B. IL-6 in ZA group decreased significantly after treatment and was significantly lower than that in ALN group. Note: **P<0.01.

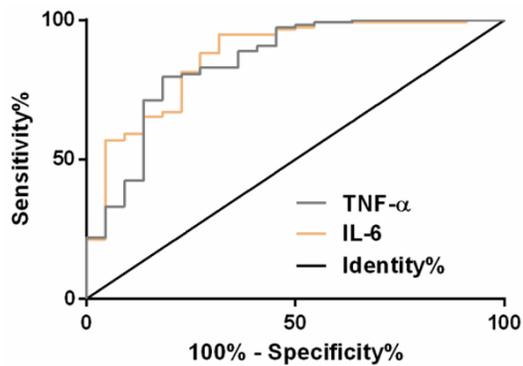


Figure 2. ROC curve of inflammatory factors in predicting the efficacy of aged OP patients.

patients, Tasci and others [23] found that the cognitive function of patients maintained a stable level one year after the first ZA therapy, suggesting that ZA had no risk of cognitive function decline. In the study of ALN on male OP patients, Orwoll and others [24] explained that ALN could significantly increase bone mineral density in spine, buttocks and even whole body, and it can effectively avoid height reduction caused by vertebral fracture. This study showed that the effective rate of ZA group was significantly higher than that of ALN group, and the incidence rate of adverse reactions was lower than that of ALN group, which indicated that ZA was superior to ALN in the treatment of aged OP patients, and its safety was also higher than that of ALN, and it had more clinical promotion value. Although ALN and ZA have many advantages in treating OP patients, they also have certain side effects. For example, as to ALN

side effects, Wang and others [25] discovered that OP patients treated by ALN had gastrointestinal side effects; however, in this study, 2 patients in ALN group had gastrointestinal discomfort. As to ZA side effects, Vandembroucke and others [26] conformed that adverse reactions that might occur within three days after ZA injection to aged OP women included fever, myalgia and flu-like diseases, however, in this study, there was one patient with fever, no myalgia and gastrointestinal reactions in ZA group. At present, we do not know the mechanism of side effects of aged OP patients caused by ALN and ZA.

OP is also a common complication induced by chronic inflammatory diseases. Its pathological mechanism is the increase of body pro-inflammatory factors, which promotes bone absorption and inhibits bone formation, thus causing bone loss [27]. More and more studies showed that inflammatory factors played a certain role in the pathological mechanism of OP patients. In regard to inflammatory factors TNF- α in OP patients, Zha and others [28] verified that postmenopausal OP women had abnormally high levels of TNF- α , and they also confirmed in vitro studies that TNF- α could promote the formation of osteoclasts induced by NF- κ B ligand (RANKL) by activating nuclear factor- κ B (NF- κ B) and phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) pathways. In regard to pro-inflammatory factor IL-6 in OP patients, Wakabayashi and others [29] reported that IL-6 was one of the factors causing pain in postmenopausal OP, and anti-IL-6 receptor antibody was helpful to maintain bone health and relieve OP pain, suggesting that IL-6 might participate in the mechanism of pain in postmenopausal OP patients, and anti-IL-6 preparation might be a potential treatment. In this study, as inflammatory factors, TNF- α and IL-6 levels of patients in the two groups reduced significantly after treatment, and the levels of two inflammatory factors in ZA group were significantly lower than those in ALN group, indicating that ZA treatment could inhibit significantly inflammatory reactions in aged OP patients. We also drew the

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Table 6. Logistic multivariate regression analysis assignment

| Factor | Variable | Assignment |
|-------------------|----------|--|
| Treatment methods | X1 | ALN therapy =0, ZA therapy =1 |
| TNF- α | X2 | The data belong to continuous variables and are analyzed with original data. |
| IL-6 | X3 | The data belong to continuous variables and are analyzed with original data. |

Table 7. Multivariate logistic regression analysis on efficacy of aged OP patients

| Variable | B | S.E | Wals | P | OR | 95% CI |
|-------------------|-------|-------|-------|-------|-------|--------------|
| Treatment methods | 1.020 | 0.452 | 5.113 | 0.021 | 2.697 | 1.132-6.810 |
| TNF- α | 1.892 | 0.597 | 9.958 | 0.003 | 6.703 | 2.048-13.674 |
| IL-6 | 1.350 | 0.474 | 8.616 | 0.004 | 4.021 | 1.596-10.175 |

ROC curves of TNF- α and IL-6 for predicting the efficacy of aged OP patients, and the results showed that the AUC of TNF- α and IL-6 for predicting their efficacy were 0.849 and 0.869 respectively, and the AUC of joint prediction was 0.928, which indicated that TNF- α and IL-6 had high predictive value for their efficacy. Finally, we also carried out a multivariate logistic regression analysis that affected the efficacy of aged OP patients, and found that treatment methods, TNF- α and IL-6 were independent risk factors that affected their efficacy, suggesting that the risk of ineffective treatment for those treated with ALN increased with high levels of TNF- α and IL-6.

Although this study confirmed the better efficacy and safety of ZA and its significant inhibition on inflammatory reaction in aged OP patients, there is still room for improvement. First of all, we can increase their prognosis analysis to understand whether ZA or ALN has long-term potential impact. Then, we can supplement the cell biology research of TNF- α and IL-6 and explore potential therapeutic targets by exploring specific regulatory mechanisms. Finally, we can increase the research on the mechanism of adverse effects of ZA and ALN. We will carry out supplementary research based on the above deficiencies in the future.

In summary, ZA is more effective than ALN in the treatment of aged OP patients and it can inhibit inflammatory response significantly.

Disclosure of conflict of interest

None.

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