·临床论著·

Risk Factors for Acute Febrile Reaction after Zoledronic Acid Treatment for Primary Osteoporosis

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ABSTRACT **Objective:** To investigate the characteristics and risk factors of acute febrile reaction after zoledronic acid treatment for primary osteoporosis. **Methods:** A total of 517 patients diagnosed with primary osteoporosis and treated with zoledronic acid from January 2012 to December 2020 were recruited, including 40 males and 477 females, among whom 262 were with type Ⅰ osteoporosis and 255 were with type Ⅱ osteoposis, 245 patients with mild-to-moderate osteoporosis, 272 patients with severe osteoporosis, 230 patients with fresh fracture, and 209 patients with operation. The two groups were compared, and the fever rate and clinical characteristics of fever were summarized and further analyzed in the aspects of gender, age, count of white blood cells, neutrophils, lymphocytes, neutrophil-lymphocyte ratio (NLR), type of osteoporosis, degree of osteoporosis, fracture, surgery intervention, medication history, etc. Multivariate *Logistic* regression analysis was conducted and ROC curve was drawn to explore the main risk factors for acute febrile reaction. **Results:** The 175 cases (33.85%) developed acute febrile reaction, most of which occurred within 36 hours after treatment, mainly low and moderate fever (<39 ℃), and the duration was generally no more than 60 hours. Univariate analysis showed significant differences in NLR, type and degree of osteoporosis, fresh fracture, surgery intervention, and zoledronic acid medication history between the fever and non-fever groups (P<0.05). There was no significant difference in gender, count of white blood cells, neutrophils and lymphocytes between the two groups (P>0.05). *Logistic* regression and ROC curve analysis showed that the surgery group had a higher fever rate (P<0.01, area under ROC curve was 0.65). The fracture group had a higher fever rate (P<0.05, area under ROC curve was 0.60). The group with type Ⅰ osteoporosis had a higher fever rate (P<0.01, area under ROC curve was 0.44). The group with medication history had a lower fever rate (P<0.01, area under ROC curve was 0.34). The fever rate of joint fracture group (56.60%) was significantly higher than spine fracture group (38.54%) (P<0.05). **Conclusion:** Surgery, fracture, type Ⅰ osteoporosis and first zoledronic acid medication might be independent risk factors of acute febrile reaction after medication. Patients who had surgery before medication (especially those with joint fracture surgery), fresh fracture, type Ⅰ osteoporosis and first zoledronic acid medication, had a higher risk of acute febrile reaction.

KEY WORDS primary osteoporosis; zoledronic acid; acute febrile reaction; surgery; fracture; type of osteoporosis

1 Introduction

Osteoporosis (OP) is a systemic bone disease characterized by decreased bone mass, damage of bone microstructure, increased bone fragility, and prone to fracture [1]. Over the past 10 years, the number of osteoporosis patients in China has increased significantly. Osteoporotic fracture seriously endangers the health and quality of life of middle-aged and older people. At the

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present time, surgery combined with anti-osteoporosis treatment has become a recognized new principle of fracture treatment in this field. Moreover, bisphosphonate family is the first-line drug recommended by domestic and foreign guidelines, among which zoledronic acid, as the third generation representative product, can strongly inhibit bone resorption and reduce the incidence of osteoporotic fracture [2]. Clinical observation for many years has confirmed the curative effect. However, acute-phase reaction (APR), especially fever, often occurs after medication. It greatly affects clinical treatment and patient compliance.

We observed in the clinical work that the incidence of acute febrile reaction in the treatment of primary osteoporosis with zoledronic acid is related to the surgery before treatment, fresh fracture and type of osteoporosis, but people pay little attention to these problems. At present, most of the studies on febrile adverse reactions after zoledronic acid treatment in osteoporosis are mainly conducted in the department of endocrinology, little attention has been paid to risk factors of surgery and fracture. In this study, we combined the influencing factors in the department of orthopaedics with those in the field of internal medicine. For OP patients who need surgery, how to choose the right time of administration has been a problem for orthopaedics surgeons. To gain more insight, this study retrospectively analyzed the characteristics and influencing factors of acute febrile reaction after zoledronic acid treatment for primary osteoporosis to provide a reference for clinical practice to help doctors better grasp the medication indications and medication plans.

2 Methods

2.1 Ethics statement

The Medical Ethics Committee of Shengjing Hospital of China Medical University approved this study (ethics application number: 2021PS724K) and waived the need for informed consent in the study. All clinical and laboratory variables included in this analysis were retrospectively collected. All the diagnosis and treatment methods mentioned in this study were all clinical routine methods, and did not change in the study. Patient records/information were anonymized before analysis, and all methods were carried out following relevant guidelines and regulations. Our research was performed under the Declaration of Helsinki.

2.2 Subjects

The clinical data of patients diagnosed with primary osteoporosis were collected (type Ⅰ: postmenopausal osteoporosis; type Ⅱ: senile osteoporosis) in Shengjing Hospital of China Medical University from January 2012 to December 2020. Bone mineral density was measured by dual-energy X-ray absorptionmetry (DXA), and the machine model was discovery.

According to guidelines for diagnosis and treatment of primary osteoporosis (2017) [3], those who meet one of the following three criteria can be diagnosed as primary osteoporosis: 1) Brittle fracture of the hip or vertebral body; 2) *T* value of bone mineral density of axial bone or distal 1/3 of radius bone measured by dual-energy X-ray absorptiometry is less than −2.5; 3) Bone mineral density: −2.5< *t* value< −1.0, accompanied by brittle fractures of the proximal humerus, pelvis or distal forearm.

Diagnostic criteria for severe osteoporosis: 1) *t* value of bone mineral density measured by dual-energy X-ray absorptiometry ≤−3.5. 2) The degree of bone mineral density reduction was following the diagnostic criteria of osteoporosis. At the same time, there were one or more brittle fractures, *i.e., t* value ≤−2.5 + brittle fracture.

Inclusion criteria: 1) Patients with type Ⅰ and type Ⅱ osteoporosis who met the diagnostic criteria of guidelines for diagnosis and treatment of primary osteoporosis in 2017; 2) Intravenous infusion of zoledronic acid.

Exclusion criteria: 1) Secondary osteoporosis, metastatic cancer and other metabolic bone diseases; 2) Not using vitamin D and calcium before zoledronic acid treatment; 3) Insufficient hydration before and after zoledronic acid treatment by intravenous infusion of 0.9% sodium chloride injection; 4) The body temperature did not return to normal before discharge from hospital.

2.3 Treatment methods

All patients were given a 5 mg zoledronic acid injection by intravenous drip. The infusion tube maintained a constant rate of 20-30 drops per minute, and the infusion time was 30-60 min. Before and after administration, 500-1 000 mL normal saline was given by intravenous drip for complete hydration.

2.4 Observation indexes

The included patients underwent blood routine tests, liver and kidney function (and the creatinine clearance rate was calculated), blood phosphorus, blood calcium, electrocardiogram, and other tests, and no apparent abnormalities were found. The number of patients with fever and the exact body temperature during fever, the beginning time and duration of fever were recorded. Body temperature ≥37 ℃ was considered as fever, with 37−38 ℃ as low fever, 38−39 ℃ as moderate fever and ≥39 ℃ as high fever. The correlation between acute febrile reaction and gender, count

of leukocytes, neutrophil, lymphocyte, neutrophil-lymphocyte ratio (NLR), type of osteoporosis, degree of osteoporosis, fresh fracture, and surgery intervention were analyzed.

2.5 Statistical methods

The collected data were input into Excel software. SPSS 25.0 software was used for statistical analysis. The data conforming to the normal distribution were described as means ± standard deviation and compared by independent sample *t*-test. The data that did not conform to the normal distribution were described by the median (interquartile spacing) and compared by nonparametric test (Mann Whitney *U* test). The *chi*-square test was used to determine the association between the categorical variables. Multivariate *Logistic* regression analysis was used for multivariate analysis. Receiver operating cure (ROC) curve was used to analyze the factors with a significant difference. When $P<0.05$, the difference was statistically significant. GraphPad Prism 8.0 drawing software was used to draw the diagrams.

3 Results

3.1 Clinical data of patients

Among the 517 patients who met the inclusion criteria, there were 40 males and 477 females, with an average age of (68.69±9.19) years and an average BMD of (−3.18±0.92). Among female patients, those younger than 70 years old were classified as type Ⅰ osteoporosis, and those older than 70 years old were classified as type Ⅱ osteoporosis. See Table 1 for specific grouping information.

Table 1 Grouping information

Grouping		Number of cases
Gender	Male	40
	Female	477
Type of osteoporosis	Type Ⅰ osteoporosis	262
	Type Ⅱ osteoporosis	255
Fresh fracture	Yes	230
	No	287
Degree of osteoporosis	Mild-to-moderate	245
	Severe	272
Surgery	Yes	209
	No	308
Zoledronic acid	Yes	136
Medication history	No	381

3.2 Characteristics of acute febrile reaction induced by zoledronic acid

In this study, among 517 patients, 175 patients developed acute febrile reaction. The fever rate was 33.85%. The average fever temperature was (38.15±0.74) ℃. There were 59 cases of low fever (37.58%), 73 cases of moderate fever (46.50%) and 25 cases of high fever (15.92%). The average occurrence time of acute febrile reaction was (16.08±15.08) h, and it occurred between 0 and 12 h in 236 cases (45.65%), between 12 and 36 h in 269 cases (52.03%), and over 36 h in 12 cases (2.32%) after administration. The average duration of acute febrile reaction was (29.54±21.65) h. The duration of acute febrile reaction in 133 cases was 0 to 12 hours (25.73%). The duration in 206 cases was 12 to 36 hours (39.85%). The duration in 137 cases was 36 to 60 hours (26.50%). The duration in 41 cases was over 60 hours (7.93%). (Figure 1-2)

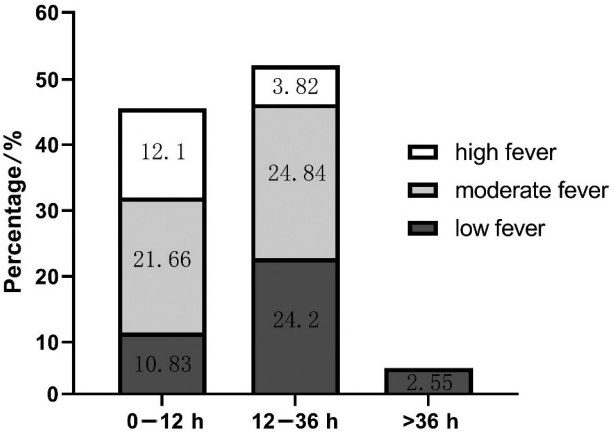

Figure 1 Distribution of fever degree and occurrence time of acute febrile reaction after zoledronic acid treatment for primaty osteoporosis

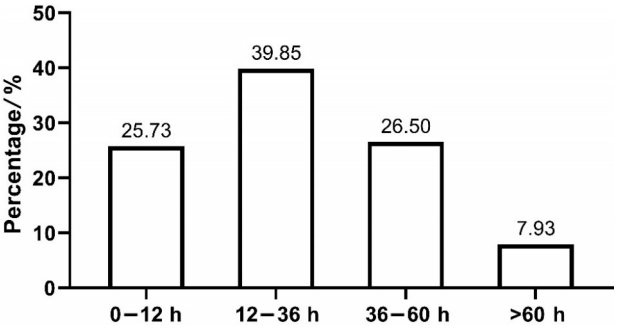

Figure 2 Distribution of duration of acute febrile reaction after zoledronic acid treatment for primaty osteoporosis

3.3 Univariate analysis of various influencing factors on acute febrile reaction induced by zoledronic acid

The results showed that there was significant difference in age between fever group and non-fever group (P<0.05). The average age of fever group was lower than that of non-fever group. The results showed no significant differences in the number of white blood cells, neutrophils, and lymphocytes before zoledronic acid administration between patients in the fever group and non-fever group (P>0.05). However, the mean NLR of patients in the fever group was higher than that in the non-fever group, and the difference between the two groups was statistically significant (P< 0.05). See Table 2.

Table 2 Comparison of age and inflammatory indexes between two groups before medication ($\bar{x}\pm s$)

Factors	Fever group	Non-fever group	t/Z values	P value
Age	67.14±8.73	69.49±9.32	−2.761	0.006
WBC/($\times10^9$/L)	5.82 (2.95)	5.70 (2.78)	−1.522	0.128
Neutrophils/($\times10^9$/L)	3.60 (2.50)	3.50 (2.30)	−1.349	0.177
The lymphocyte/($\times10^9$/L)	1.6±0.59	1.62±0.60	−0.466	0.641
NLR	3.67±4.40	2.94±2.54	−2.025	0.044

Data analysis also showed that the average value of NLR before medication of the surgery group was higher than that of the non-surgery group, and the difference was significant (P<0.001). The average value of NLR of the fracture group before medication was higher than that of the non-fracture group, and the difference was significant (P<0.005). See Table 3. The results suggest that fracture and surgery intervention may promote acute febrile reaction after zoledronic acid administration by enhancing the body's inflammatory response.

Statistical analysis showed that the fever rate of patients with type Ⅰ OP was significantly higher than that of patients with type Ⅱ OP (P=0.008). The fever rate of patients with severe OP was significantly higher than that of patients with mild-to-moderate OP (P=0.005), the fever rates of patients with fresh fracture or surgery were significantly higher than those of patients without them (P=0.000). The fever rate of patients with past zoledronic acid use history was significantly lower than patients without zoledronic acid use history (P=0.000). There was no significant difference in fever rate between male and female patients (P= 0.592). See Table 4.

Table 3 Comparison of NLR values between different groups before medication ($\bar{x}\pm s$)

Factors	NLR	t value	P value
Surgery group	4.08±4.18	6.648	0.000
Non-surgery group	2.25±1.55		
Fracture group	3.72±4.01	3.177	0.002
Non-fracture group	2.76±2.53		

Table 4 Influence of various factors on acute febrile reaction induced by zoledronic acid in treatment of primary osteoporosis

Factors		Fever group	Non-fever group	Fever rate/%	χ^2 value	P value
Gender	male	12	28	30.00	0.287	0.592
	female	163	314	34.17		
Type of osteoporosis	type Ⅰ	103	159	39.31	7.082	0.008
	type Ⅱ	72	183	28.24		
Degree of osteoporosis	mild-to-moderate	98	147	40.00	7.868	0.005
	severe	77	195	28.31		
Fresh fracture	yes	102	128	44.35	20.395	0.000
	No	73	214	25.44		
Surgery	yes	97	112	46.41	24.725	0.000
	No	78	230	25.32		
Zoledronic acid Medication history	yes	9	127	6.62	61.117	0.000
	No	166	215	43.57		

3.4 Multivariate *Logistic* regression analysis of candidate risk factors

Kappa consistency test was performed for the two factors of fracture and surgery, and the *Kappa* value was 0.6, indicating consistency. The two factors should not be included in the multivariate *Logistic* regression analysis at the same time.

3.4.1 Correlation analysis between type of osteoporosis, degree of osteoporosis, fracture, zoledronic acid medication history and acute febrile reaction

Among all factors, acute febrile reaction was taken as the dependent variable, and type of osteoporosis, degree of osteoporosis, fracture, and zoledronic acid medication history were taken as the independent variables. Results in Table 5 showed that fracture, type of osteoporosis, and zoledronic acid medication history were the independent influencing factors of acute febrile reaction.

Table 5 Multivariate *Logistic* regression analysis of the influencing factors of acute febrile reaction after medication 1

Factors		*OR* value	95%*CI*	*P* value
Type of osteoporosis	(type Ⅰ) (50.68%)	2.29	1.51–3.48	0.000
Degree of osteoporosis	(mild-to-moderate) (47.39%)	1.41	0.95–2.11	0.090
Fracture	(yes) (44.49%)	1.62	1.06–2.48	0.027
Zoledronic acid medication history	(No) (73.69%)	9.68	4.65–20.17	0.000

3.4.2 Correlation analysis between type of osteoporosis, degree of osteoporosis, surgical intervention, zoledronic acid medication history and acute febrile reaction

Among all factors, acute febrile reaction was taken as the dependent variable, and type of osteoporosis, degree of osteoporosis, surgical intervention, and zoledronic acid medication history were taken as the independent variables. Results in Table 6 showed that surgical intervention, type of osteoporosis, and zoledronic acid medication history were the independent influencing factors of acute febrile reaction.

Table 6 Multivariate *Logistic* regression analysis of the influencing factors of acute febrile reaction after medication 2

Factors		*OR* value	95%*CI*	*P* value
Type of osteoporosis	(type Ⅰ) (50.68%)	2.16	1.44–3.24	0.000
Degree of osteoporosis	(mild-to-moderate) (47.39%)	1.27	0.84–1.91	0.261
Surgery	(yes)(40.43%)	2.00	1.27–3.15	0.003
Zoledronic acid medication history	(No) (73.69%)	8.05	3.79–17.11	0.000

3.5 ROC curve analysis of independent risk factors of acute febrile reaction

The results in Figure 3 showed that the areas under ROC curve of surgical intervention, fracture, type of osteoporosis, and zoledronic acid medication history were 0.65 (95% *CI*: 0.61–0.70), 0.60 (95% *CI*: 0.55–0.66), 0.44 (95% *CI*: 0.39–0.49) and 0.34 (95% *CI*: 0.29–0.39), respectively.

3.6 Influence of surgical site on the acute febrile reaction of zoledronic acid

The fever rate of patients with joint fracture was significantly higher than those with spinal fracture among surgical patients treated with zoledronic acid (P=0.034). However, in the further comparison of fever rate within the group, there was no significant difference between patients with femoral neck and intertrochanteric fractures or between thoracic and lumbar fractures (P>0.05). See Table 7.

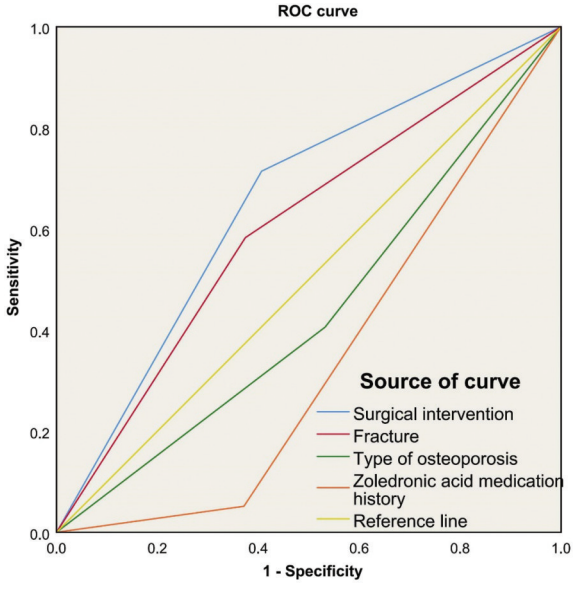

Figure 3 ROC curve analysis of independent risk factors of acute febrile reaction

Table 7 Influence of surgical site on the acute febrile reaction of zoledronic acid

Factors		Fever group	Non-fever group	Fever rate/%	χ^2 value	*P* value
Surgical site of fracture	joint fracture	30	23	56.60	4.5	0.034
	spine fracture	37	59	38.54		
Joint fracture surgery	femoral neck fracture	18	16	52.94	0.008 6	0.93
	intertrochanteric fracture	6	5	54.55		
Spinal fracture surgery	thoracic vertebra fracture	12	28	30.00	2.56	0.11
	lumbar vertebra fracture	22	25	46.81		

4 Discussion

At present, most researchers believe that zoledronic acid, an analog of pyrophosphate, has a strong affinity for bone, especially in the sites where osteoclasts are active and is easy to be absorbed by osteoclasts. Reducing the adherence of osteoclasts on the bone surface, zoledronic acid inhibits activity of osteoclasts, promotes apoptosis, and reduces osteolytic lesions and bone resorption. It has been suggested that zoledronic acid can induce the apoptosis of osteoclasts and their precursors by inhibiting the mevalonate pathway or interfering with the normal cell cycle, thus playing an anti-bone resorption role. Zoledronic acid inhibits the key enzyme of the malyvalic acid pathway in osteoclasts and prevents the isoprene of small G protein, which makes the osteoclasts unable to function normally and promotes their apoptosis. Bisp-hosphonates can bind to hydroxyapatite in bone, specifically to the bone surface where bone transformation is active and inhibit bone resorption by osteoclasts. Zoledronic acid is a representative drug of the third generation of nitrogen-containing bisphosphonates, which has a definite anti-osteoporosis effect and is widely used in clinics. Fever is the most common APR in the treatment of osteoporosis with zoledronic acid by intravenous drip. Zoledronic acid can inhibit farnil pyrophosphate synthetase, thereby preventing the conversion of geranyl pyrophosphate in osteoclasts to farnil pyrophosphate. The increased geranyl pyrophosphate activates γΔT cells in the body, causing them to release many inflammatory mediators, such as IL-6, TNF-a, and IFN- γ, resulting in fever and other symptoms [4-5].

4.1 Characteristics of acute febrile reaction after zoledronic acid treatment

In this study, the incidence of acute febrile reaction in treating primary osteoporosis with zoledronic acid was 33.85%, and the fever degree was mainly low to medium (85.08%). The onset of fever was mainly within 36 h (97.71%), and the duration of acute febrile reaction was mostly within 60 h (92.06%). All patients with febrile reaction were well tolerated.

4.2 Univariate analysis

Univariate analysis of this study showed that NLR, type of osteoporosis, degree of osteoporosis, fresh fracture, surgery intervention, and history of zoledronic acid use were associated with the acute febrile reaction, which was statistically significant. There was no significant difference in the mean value of leukocytes, neutrophils, and lymphocytes between the fever and non-fever groups. There was no significant gender difference between the fever group and the non-fever group. The results showed that the higher the NLR value before zoledronic acid treatment, the more prone to acute febrile reaction. The fever rate of patients with type Ⅰ osteoporosis was higher than that of patients with type Ⅱ osteoporosis. The fever rate of patients with mild-to-moderate osteoporosis was higher than that of patients with severe osteoporosis. Fever rate was also higher in patients with fresh fracture. Patients with surgical intervention had a higher fever rate. Patients with no history of zoledronic acid use had a higher fever rate.

4.3 Multivariate *Logistic* regression analysis

In multivariate *Logistic* regression analysis, the *Kappa* consistency test was performed for the two factors of fracture and surgery, and the *Kappa* value was 0.6 indicating, there was consistency. Therefore the two factors should not be included in multivariate *Logistic* regression analysis simultaneously. The results showed that surgery, fracture, type of osteoporosis, and zoledronic acid medication history were the main influencing factors of acute febrile reaction in treating primary osteoporosis in the department of orthopaedics. Surgery, fresh fracture, type Ⅰ osteoporosis and first use of zoledronic acid were the risk factors of acute febrile reaction. The risk of fever was 1.62

times higher in patients with fracture than patients without fracture. The risk of fever was 2.00 times higher in surgical patients than in non-surgical patients.

4.4 ROC curve analysis

The ROC curve analysis showed that the most important factors affecting the happening of acute febrile reaction were ranked as follows according to the area under ROC curve: surgery, fracture, type of osteoporosis, and zoledronic acid medication history. Therefore, the appropriate medication period can be selected according to the patient's condition to reduce the incidence of acute febrile reaction.

4.5 Summary and analysis of risk factors

4.5.1 NLR

In previous studies, the study of ÖZTÜRK Z A et al.[6] showed that NLR level in patients with osteoporosis was significantly increased, suggesting that inflammation may play an important role in the occurrence and development of osteoporosis. In this study, the higher the NLR value before zoledronic acid treatment, the more likely the patient was to have acute febrile reaction. The higher the level of NLR before treatment, the stronger the chronic inflammatory responses of patients, and the more likely it was to cause APR by cooperating with the release of a large number of inflammatory mediators caused by ZOL intravenous infusion. It can be used as an index to predict APR before medication.

4.5.2 Type Ⅰ osteoporosis

The study of KO Y et al.[7] showed that the secretion of estrogen in postmenopausal women decreased, the RANKL/RANK/OPG signaling pathway was disorderly, and the inflammatory factors such as interleukin (IL) and TNF, which promoted bone resorption, were constantly increased in the body, leading to the increased expression of RNAKL in the microenvironment of bone metabolism, thus accelerating bone loss. Furthermore, studies has shown that [8-9], sex steroid hormones may participate in bone metabolism regulating specific gene expression through negative feedback in the absence of estradiol (E_2), thus accelerating the secretion of pituitary follicle-stimulating hormone (FSH). FSH can promote bone marrow cells, and immune cells secrete tumor necrosis factor α (TNF-α) and interleukin (IL), stimulating bone resorption. Combined with our study, the high fever rate after zoledronic acid treatment in postmenopausal osteoporosis patients may be related to the increase of inflammatory factors after estrogen deficiency in the body.

4.5.3 Zoledronic acid medication history

This study showed that the fever rate of patients with previous zoledronic acid medication was significantly reduced, which was consistent with domestic and foreign studies. ROSSINI M et al.'s [10] study showed that total lymphocytes and their subsets were significantly reduced 2 days after ZOL infusion in patients receiving N-BP for the first time. These changes returned to baseline after 1 year, except for a significant reduction in the proportion and an absolute number of γδT cells, suggesting for the first time that both intravenous and oral N-BP therapy are associated with a long-term reduction in circulating γδT cells, which may explain the lower incidence of APR in patients exposed to N-BP.

4.5.4 Fracture

A growing body of evidence [11-12] has suggested that congenital and adaptive immune responses are required for fracture healing. Immediately after injury, local infiltration of immune cells and immune mediators are required to remove necrotic tissue and initiate angiogenesis. Various cytokines, including interleukin-1β, IL-6, IL-17, IL-23, and TNF-α, are expressed at different stages and play a role in treatment. This initial infiltration of immune cells subsequently suppresses the immune system, leading to enhanced differentiation of osteoblast mesenchymal stem cells and regulatory T (Treg) cells, both of which inhibit the adaptive T cell response and achieve a hypoimmunogenic state at the healing site [13]. In our study, patients with fresh fracture had a higher fever rate after zoledronic acid treatment, which was considered to be related to the early local infiltration of immune cells and immune mediators and the increase of various inflammatory factors after fracture injury. This suggests that, for patients with complicated fractures, it is possible to determine whether new fractures occur, choose the appropriate treatment time, predict the occurrence of APR and do some work of prevention and treatment.

4.5.5 Surgery

Studies have shown that surgical injury can put patients in a state of inflammatory reaction and increase inflammatory factors during the perioperative period. Different types of surgeries have different surgical sites and methods. The greater the injury to patients,

the more the inflammatory factors increased. Compared with open surgery, the increase of inflammatory factors in the patients undergoing minimally invasive surgery is lower. CASSUTO J et al. [14] showed that inflammatory mediators (CRP, IL-6, OPN) in patients undergoing joint replacement increased significantly on the first day after surgery and returned to baseline at 6 W. MARUNA P et al. [15] showed that the common basis of the systemic inflammatory response to surgical trauma is the activation of cytokine cascades accompanied by the release of soluble cytokine receptors. The major cytokine axis stimulates the release of acute-phase protein (APP) from the liver, regulating metabolic pathways and hormonal responses. The study of LI H et al. [16] showed that the rapid rehabilitation surgical nursing program can effectively relieve the negative emotions and pain of patients with hip fractures and reduce inflammation. Our study showed that the higher fever rate of osteoporosis patients in the surgery group after zoledronic acid treatment might be related to the inflammatory state of the body after surgical injury and the increase of inflammatory factors, which were more likely to produce fever reaction occuring together with the APR reaction caused by zoledronic acid. In our study, the fever rate of patients undergoing joint fracture surgery was 56.60%, and that of patients undergoing spinal fracture surgery was 38.54%, $P<0.05$. This may reflect that different surgical sites and methods have different effects of the inflammatory response. Total hip replacement and other joint surgeries are level 4 surgeries with a large degree of openness and greater damage than minimally invasive spinal surgery. In the perioperative period, the body has a higher inflammatory response, more inflammatory mediators are produced, and the synergistic effect with zoledronic acid-induced APR reaction is stronger, which increases the fever rate.

This suggests that we should pay attention to the increasing fever rate after zoledronic acid treatment in perioperative patients with a fracture or surgical intervention in the department of orthopaedics. The timing of zoledronic acid treatment after surgery needs further study, and it can also be combined with rapid rehabilitation surgical nursing program. And for the patients with joint fracture surgery and open surgery, more attention should be paid.

The limitation of this study is that the collection of bone metabolism indicators is not enough, the postoperative medication time is not completely agreed.

5 Conclusion

When zoledronic acid is used to treat patients with primary osteoporosis, acute febrile reaction may occur.

1) The incidence of acute febrile reaction after zoledronic acid treatment was 33.85%. Acute febrile reaction mostly occurs within 36 hours, and the duration of acute febrile reaction is mostly within 60 hours. 2) In the department of orthopaedics, surgical intervention, fresh fracture, type Ⅰ postmenopausal osteoporosis and the first use of zoledronic acid medication are the main independent risk factors of acute febrile response after zoledronic acid treatment for primary osteoporosis. 3) The fever rate of patients with joint fracture was higher than that with spinal fracture; the fever rate of patients with lumbar fracture was higher than that with thoracic fracture.

It needs further studies to update the zoledronic acid treatment plan and considers whether this medication should be administerd before surgery or after a period of time. Close attention should be paid close attention to the patients prone to acute febrile reaction according to the above indicators.

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唑来膦酸治疗原发性骨质疏松症用药后急性期发热反应的相关危险因素分析

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摘要　目的:探讨唑来膦酸治疗原发性骨质疏松症出现急性期发热反应的特点及相关影响因素。**方法:**收集中国医科大学附属盛京医院2012年1月—2020年12月诊断为原发性骨质疏松症并给予唑来膦酸治疗的患者517例,其中男40例,女477例;Ⅰ型患者262例,Ⅱ型患者255例;轻、中度骨质疏松患者245例,重度骨质疏松患者272例;新发骨折患者230例,手术患者209例。对收集的2组资料进行比较,归纳分析发热的临床特点,并分别从性别、年龄、白细胞、中性粒细胞、淋巴细胞、中性粒细胞淋巴细胞比值(NLR)、骨质疏松类型、骨质疏松程度、有无骨折、有无手术、用药史等方面行单因素分析,研究其与发热反应的相关性,进一步行*Logistic*多因素回归分析,绘制ROC曲线,探讨发热不良反应的主要影响因素。**结果:**517例患者中175例(33.85%)出现急性期发热反应,多数发生在用药后36 h以内,以低中热(<39 ℃)为主,持续时间一般不超过60 h。单因素分析显示发热组与不发热组之间NLR、骨质疏松类型、程度、新发骨折、手术及唑来膦酸用药史的差异有统计学意义($P<0.05$)。2组间性别、用药前白细胞、中性粒细胞、淋巴细胞差异无统计学意义($P>0.05$)。*Logistic*多因素回归、ROC曲线分析进一步显示手术组发热率较高($P<0.01$,ROC曲线下面积为0.65),骨折组发热率较高($P<0.05$,ROC曲线下面积为0.60),Ⅰ型骨质疏松组发热率较高($P<0.01$,ROC曲线下面积为0.44),既往有唑来膦酸用药史组发热率较低($P<0.01$,ROC曲线下面积为0.34)。关节骨折手术组发热率(56.60%)明显高于脊柱骨折手术组发热率(38.54%)($P<0.05$)。**结论:**唑来膦酸治疗原发性骨质疏松症时,急性发热反应率为33.85%,手术、骨折、Ⅰ型骨质疏松症和首次唑来膦酸治疗可能是独立的危险因素,手术患者(尤其是关节骨折手术)、新鲜骨折、Ⅰ型骨质疏松及首次唑来膦酸用药的患者急性发热反应风险更高。

关键词　原发性骨质疏松症;唑来膦酸;急性期发热反应;手术;骨折;骨质疏松类型
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