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# A NEW TREND IN TREATING OSTEOPOROSIS WITH BISPHOSPHONATES IN DENTAL PATIENTS IS DRUG HOLIDAYS: FOR WHOM, WHEN AND FOR HOW LONG?

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**Abstract**
The article discusses the problems of the treatment of osteoporosis in dental patients and the expediency of long breaks (so-called medicinal vacations in the treatment of bisphosphonates. The mechanism of action and clinical efficacy of bisphosphonates, particularly zoledronic acid, which has the most pronounced antiresorptive effect compared with other bisphosphonates used for the treatment of osteoporosis, are considered. The clinical and pathogenetic rationale for drug holidays is presented, and possible indications and contraindications for drug holidays in bisphosphonate therapy are considered in detail. It is concluded that the question of the possibility of prescribing and duration of medicinal vacations should be decided by a doctor individually for each patient with osteoporosis receiving bisphosphonate therapy.

**Keywords**: osteoporosis, bisphosphonates, zoledronic acid, drug holidays.

## INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone strength and an increased risk of fractures. Osteoporotic fractures lead to huge social and economic losses, which is why this disease is one of the most important health problems worldwide. The number of cases of disability as a result of osteoporosis and its complications is higher than that of cancer and is comparable to that of rheumatoid arthritis, bronchial asthma and arterial hypertension. The average length of hospitalization for women with osteoporotic fractures is significantly higher than for those with diabetes mellitus, myocardial infarction, and breast cancer [3]. To reduce the risk of fractures, and maintain physical, social activity and work capacity, patients with osteoporosis need timely appointment of pathogenetic therapy. Currently, a wide range of drugs is used for the treatment of osteoporosis: bisphosphonates, denosumab, teriparatide and strontium ranelate (second line), which are prescribed against the background of basic therapy with vitamin D, its active metabolites and calcium. Based on the extensive scientific and clinical experience gained over the past decades, clinical guidelines for the treatment of osteoporosis have been developed in most countries of the world, including ours. However, there are still many debated issues in the treatment of this disease: the tolerability and long-term effects of therapy, patient adherence to treatment, duration and tactics of treatment. One of these widely discussed issues is the possibility



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and expediency of prescribing long breaks in treatment, the so-called drug holidays, to patients receiving bisphosphonate therapy.

## MECHANISM OF ACTION AND CLINICAL EFFICACY OF BISPHOSPHONATES

Bisphosphonates are pyrophosphate analogues widely used for the treatment of osteoporosis and other metabolic diseases of the skeleton, They have a unique ability to actively and permanently accumulate in bone tissue, mainly in its resorption zones, and form strong chelate complexes with calcium ions in bone hydroxyapatite crystals [4, 5]. Hydrogen ions and enzymes that osteoclasts secrete into the space between themselves and the bone surface, bone resorption is induced. Bisphosphonates block this secretion, slowing down bone resorption, which, in turn, is reflected in a decrease in the level of markers of bone remodelling [6]. The key point of the molecular mechanism of the antiresorptive action of nitrogen-containing bisphosphonates is the inhibition of the enzyme farnesyl diphosphate synthetase, which inhibits the mevalonate pathway of cholesterol biosynthesis in osteoclasts, stops prenylation of specific low-molecular-weight G proteins of the Rab, Rac, Rap and Rho families, and potentiates osteoclast apoptosis [7].

Bisphosphonates can be recycled, i.e. returned to the systemic bloodstream from the bone surface resorbed by osteoclasts. Such bisphosphonate molecules, released from bone tissue, can attach to another part of the bone. Continuous use of bisphosphonates increases the “bisphosphonate load” on the bone, which determines the unique feature of this class of drugs – the preservation of the clinical effect for a long time after discontinuation of therapy [8].

Most bisphosphonates have a good evidence base of clinical efficacy: reducing the risk of vertebral fractures and non-vertebral fractures in patients with osteoporosis [9, 10]. According to in vivo and in vitro studies, zoledronic acid has the most pronounced antiresorptive effect in comparison with other bisphosphonates used in clinical practice for the treatment of osteoporosis [11]. In a large, double-blind, placebo-controlled HORIZON-PFT study involving 7,765 women with postmenopausal osteoporosis, 3-year treatment with 5 mg intravenous zoledronic acid once a year was associated with a 70% reduction in the relative risk (RR) of vertebral fractures (3.3% in the treatment group and 10.9% in the placebo group; RR 0.30; 95% confidence interval 0.24–0.38) and fractures of the proximal femur – by 41% (1.4% in the treatment group and 2.5% in the placebo group; HR 0.59; 95% confidence interval 0.42–0.83). There was also a proven reduction in the risk of peripheral fractures, all clinical fractures, and clinical vertebral fractures by 25, 33, and 77%, respectively, compared with the placebo group ($p < 0.001$ in all cases) [12].

Zoledronic acid has the highest affinity for bone hydroxyapatite in comparison with other bisphosphonates – alendronate, ibandronate, and risedronate [14]. Due to this, zoledronic acid is prescribed for the treatment of osteoporosis with a frequency of 1 time per year and has a long-term clinical effect that persists for a certain time even after the end of therapy [15].

## CLINICAL AND PATHOGENETIC JUSTIFICATION OF MEDICINAL VACATIONS

Prolonged bisphosphonate therapy is associated with a persistent clinical effect to reduce the risk of new fractures. For example, in the FLEX protocol, women who received alendronate for 10 years had a lower risk of vertebral fractures compared to the group that was switched to placebo after 5 years of taking alendronate. With continuous 10-year therapy with alendronate, there was



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a decrease in the RR of vertebral fractures by an average of 55% [16]. According to the HORIZON-PFT study, patients who received 5 mg of zoledronic acid intravenously once a year for 6 years had a lower risk of morphometric vertebral fractures compared with women who were transferred to placebo after 3 years of therapy [17]. At the same time, when considering the long-term use of bisphosphonates, the long-term safety factor of this therapy should not be ignored. It has been proven that bisphosphonate treatment is generally well tolerated. Possible side effects are damage to the upper gastrointestinal tract when taking bisphosphonate tablets and flu-like syndrome when using intravenous bisphosphonates. In rare cases, severe adverse reactions such as myalgia, bone pain, atrial fibrillation, skin hypersensitivity, and decreased renal filtration function are reported.

Due to the pronounced inhibition of bone remodelling processes (not only resorption but also bone formation) and increased BMD, bisphosphonates increase bone mineralization and make it more rigid, which, with prolonged treatment, may increase the risk of femoral fractures of atypical localization for osteoporosis – subcutaneous or diaphyseal (the so-called atypical femoral fracture (APB)) [10, 18-20]. According to R.M. Dell et al., APB occurs with a frequency of 2 cases per 100,000 patients after 2 years of therapy and 78 cases per 100,000 patients after 8 years of bisphosphonate therapy. [21]. J. Schilcher et al. The number of 50 cases per 100,000 patients per year is given [22].

Osteonecrosis of the jaw is another rare complication of long–term bisphosphonate therapy. The American Society for Bone and Mineral Research estimates the incidence of Osteonecrosis of the jaw the range from 1 case per 10,000 patients to 1 case per 100,000 patients per year [23]. American Association of Oral and Maxillofacial Surgeons (American Association of Oral and Maxillofacial Surgeons) based on data from J.C. Lo et al. He estimates that this number is 210 cases per 100,000 patients per year [24, 25]. The risk of osteonecrosis of the jaw increases with the use of bisphosphonates for more than 4 years, the risk of developing APB increases with their use for more than 5 years [21]. In this regard, there is a hypothesis that a break in taking bisphosphonates may favourably affect their safety profile and reduce the risk of delayed adverse events. The data obtained led to an active discussion of the concept of drug holidays, a temporary pause in the treatment of bisphosphonates.

The clinical possibility of drug holidays in patients with a relatively low risk of new fractures has been substantiated in several large randomized, placebo-controlled trials, which demonstrated that BMD decreases slowly upon discontinuation of bisphosphonate therapy and eventually remains higher than before the start of therapy or when taking placebo [26-28]. Even though discontinuation of therapy in such patients is associated with an increase in the level of biochemical markers of bone remodelling and a slight decrease in BMD, it is not accompanied by an increase in the frequency of fractures [26-28]. Thus, after discontinuation of zoledronic acid after 3 years of treatment, women with a low risk of fractures (with a T-criterion for the femoral neck above -2.5, the absence of new fractures during treatment and with no more than one risk factor for osteoarthritis) had a low probability of any fractures over the next 3 years: 3.2% for vertebral fractures and 5.8% for non-vertebral fractures [28]. At the same time, in women with a T-criterion for the femoral neck below -2.5 or with a history of fractures, 3 more years of treatment with zoledronic acid (6 years in total) were associated with a statistically significant reduction in the



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risk of vertebral fractures compared with patients transferred to placebo after 3 years [28]. Treatment with zoledronic acid for more than 6 years had no advantages over using a placebo. In general, after 6 years of therapy, there was no significant reduction in the risk of non-vertebral fractures during therapy with both oral and intravenous bisphosphonates.

The possibility of prescribing medicinal vacations and their duration depends primarily on the type of bisphosphonates used. In a study by L.H. Xu et al. The course of the medicinal holidays after alendronate and risedronate therapy was compared: the therapy was carried out for 4-5 years, and the duration of the medicinal holidays was approximately 3 years [29]. It was concluded that after discontinuation of risedronate, there is a more pronounced loss of BMD than after discontinuation of alendronate therapy. In the work of N.V. Watts noted a more rapid decrease in BMD after discontinuation of risedronate and ibandronate than after completion of treatment with alendronate and zoledronate [30].

It is also necessary to take into account the peculiarities of BMD dynamics against the background of drug holidays in the trabecular and cortical bone sections. There is evidence that BMD in the total hip index (total hip) begins to decrease after the 1st year of medical holidays, in the femoral neck and vertebrae - after 3 years [31]. In another study, against the background of a 2-year break in treatment after previous long-term therapy with oral bisphosphonates (for 6-7 years) There was a significant decrease in BMD in the femoral neck, but no loss of BMD was detected in the lumbar vertebrae [32].

Differences in BMD reduction in vertebrae and femurs are most likely due to the pharmacodynamic properties of bisphosphonates, depending on the type of bone structure. Bisphosphonates accumulate more actively in the trabecular (spongy) substance, where bone metabolism occurs much faster than in the cortical bone. Therefore, bisphosphonates accumulate better in the vertebrae, which have a predominantly trabecular type of structure, which leads to a more significant increase in BMD during treatment. Having accumulated in large quantities in the spongy substance of the vertebrae, bisphosphonates, respectively, are washed out of them more slowly during the medicinal holidays [27].

The affinity of the drug to bone hydroxyapatite is also important for the long-term maintenance of a good level of BMD. Zoledronic acid binds to it most actively, slightly weaker – alendronate and ibandronate, and to a lesser extent – risedronic acid [33].

## MEDICINAL HOLIDAYS: PROS AND CONS

The advantage of drug holidays is that they can reduce the risk of side effects of bisphosphonates, increase adherence to therapy in individual patients, and reduce the financial costs of treatment. Osteoporosis therapy is a long and expensive process, so taking a break from treatment for several years may be a rational economic decision for the patient. According to M.D. Kostoff et al., patients with a low risk of fractures account for 36.8% of the total population of patients receiving bisphosphonates. It is in such patients that it is advisable to initiate drug vacations under the control of densitometry and the level of biochemical markers of bone resorption. On the contrary, many patients with a high risk of fractures unnecessarily interrupt therapy early on the recommendation of a doctor or their own volition [34].



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However, there are still many questions: to whom, when, for how long to prescribe medical holidays, and most importantly, by what parameters to evaluate their effectiveness. By continuing bisphosphonate therapy, we prevent up to 35 clinically significant vertebral fractures at the cost of one case of severe adverse effects such as VLF and APB. This indicates the expediency of long-term treatment with bisphosphonates in women with a high probability of fractures. Mortality associated with vertebral fractures is extremely high and in the first 3 years after injury is almost comparable to the risk of death after a hip fracture. Thus, in women at high risk of fractures, long-term continuous intake of bisphosphonates to prevent new vertebral fractures certainly justifies the risk of rare side effects.

Finally, many publications are highlighting other advantages and possible positive effects of long-term bisphosphonate therapy, such as reducing the risk of breast cancer, colorectal cancer, stomach cancer, stroke, myocardial infarction, and increased life expectancy in general [35-44].

## CONCLUSIONS AND RECOMMENDATIONS

Summarizing the accumulated clinical experience, leading foreign experts give the following recommendations on the duration of bisphosphonate therapy and the appointment of drug holidays [29, 44, 45].

1. All patients with diagnosed osteoporosis should be prescribed pathogenetic therapy of the disease in order to prevent fractures, while bisphosphonates are considered first-line drugs. Most experts have concluded that the treatment of osteoporosis with bisphosphonates should last at least 5 years in the case of tablet forms and at least 3 years for intravenous forms.
2. 2. Drug holidays can be initiated in patients with a low or medium risk of fractures (the T-criterion for the femur after treatment is higher than -2.5 and the absence of fractures on the background of osteoporosis therapy for 3-5 years). In such patients, drug vacations may continue until a significant loss of BMD begins according to bone densitometry, an increase in the level of markers of bone metabolism occurs, or a low-energy fracture occurs.
3. 3. In patients with a high risk of fractures (T-criterion below -2.5 or -2.0 if there is a history of femoral fracture or multiple vertebral fractures, in case of prolonged use of glucocorticosteroids at a dose of 5 mg or more in prednisolone equivalent or with a high 10-year risk of fractures according to the FRAX algorithm (Fracture Risk Assessment Tool – A fracture risk assessment tool)) pathogenetic treatment should last 6-10 years or more.
4. Monitoring of the clinical well–being of patients on the background of drug holidays should be carried out at least once a year: bone densitometry is performed, if possible, a study of the level of markers of bone resorption (CTx or s-PINP (serum procollagen type I N-terminal propeptide)). It is also useful to determine body mass index, height dynamics, and body weight [31, 44].
5. In any case, the decision to start a drug vacation with bisphosphonate therapy is made by the doctor individually together with the patient after evaluating all clinical, laboratory and instrumental parameters.



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## CONCLUSION

Bisphosphonates are unique antiresorptive therapy drugs that have the property of accumulating in bone tissue for a long time, due to which the risk of fractures in patients with osteoporosis remains low even for several years after completion of treatment. Taking into account these features of the clinical effect of bisphosphonates, the concept of LC is approved worldwide. Other drugs for the treatment of osteoporosis do not have this effect: they are quickly eliminated from the body, and they should not be changed. Taking into account the heterogeneity of information and the lack of a single consensus, the question of the possibility of prescribing and duration of drug holidays should be decided by a doctor individually for each patient with osteoporosis receiving bisphosphonate therapy.

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