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Modern Clinical Practice: Pros and Cons of Treatment Alfacalcidol for Patients with Osteoporosis

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Relevance. Currently, medications used to treat osteoporosis (OP) have been shown to be effective in reducing the risk of fractures in multicenter placebo-controlled studies. These are primarily bisphosphonates and denosumab (antiresorptive agents), teriparatide (a bone anabolic) and strontium ranelate (a drug with a dual mechanism of action). For primary prevention of the disease and as part of combination therapy for AP, calcium and vitamin D are used. Among vitamin D preparations, its active metabolites occupy a special place, one of which is alfacalcidol - 1α(OH)D3. When ingested, it is hydroxylated in the liver by 25-hydroxylase and converted into D-hormone, or calcitriol (1α,25(OH)2D3). The mechanism of action of the drug is the binding of 1α, 25(OH)2D3 with vitamin D receptors in target organs. In the intestines, this leads to an increase in the absorption of calcium and phosphorus, and in the kidneys, to an increase in the reabsorption of calcium in them. The drug normalizes calcium-phosphorus metabolism: it suppresses bone resorption and stimulates bone formation, which leads to an increase in bone mineral density (BMD) and thereby increases the mechanical strength of bone. The advantage of using alfacalcidol compared to another active metabolite, calcitriol, is that its use poses a lower risk of developing hypercalcemia. This is due to the fact that it is a “prodrug”, which, when it enters the intestines and is absorbed into the blood in an inactive form, does not lead to a sharp increase in the concentration of calcium in the blood, unlike calcitriol [1]. In the intestines, this leads to an increase in the absorption of calcium and phosphorus, and in the kidneys, to an increase in the reabsorption of calcium in them. The drug normalizes calcium-phosphorus metabolism: it suppresses bone resorption and stimulates bone formation, which leads to an increase in bone mineral density (BMD) and thereby increases the mechanical strength of bone. The advantage of using alfacalcidol compared to another active metabolite, calcitriol, is that its use poses a lower risk of developing hypercalcemia. This is due to the fact that it is a “prodrug”, which, when it enters the intestines and is absorbed into the blood in an inactive form, does not lead to a sharp increase in the concentration of calcium in the blood, unlike calcitriol [1]. In the intestines, this leads to an increase in the absorption of calcium and phosphorus, and in the kidneys, to an increase in the reabsorption of calcium in them. The drug normalizes calcium-phosphorus metabolism: it suppresses bone resorption and stimulates bone formation, which leads to an increase in bone mineral density (BMD) and thereby increases the mechanical strength of bone. The advantage of using alfacalcidol compared to another active metabolite, calcitriol, is that its use poses a lower risk of developing hypercalcemia. This is due to the fact

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Alfacalcidol is used in the treatment of bone tissue diseases, in particular primary and secondary AP, as well as in patients with chronic kidney disease in whom 1-alpha-hydroxylation of vitamin D3 is impaired.

Studies conducted using alfacalcidol and calcitriol in primary and glucocorticoid AP showed a reduction in the risk of fractures of any location compared to the control group, regardless of whether patients received additional calcium supplements or not, by almost 2 times; it did not depend on BMD values before treatment [2]. In addition, the advantages of taking active metabolites compared to cholecalciferol, the native vitamin D, were shown in terms of increasing BMD and reducing the risk of vertebral and peripheral bone fractures in primary AP. Thus, in a study by R. Nuti et al. demonstrated that treatment with 1 mcg alfacalcidol in combination with calcium in women with postmenopausal AP and normal vitamin D levels resulted in 12 months. therapy to a greater increase in BMD in the spine compared to the group, who received 880 IU of native vitamin D and calcium (2.33% versus 0.70%, p=0.018), and by the 18th month. the increase in BMD in the alfacalcidol group averaged 2.87%, while in the group using native vitamin D there was no further increase in bone density (p = 0.005). The study also showed a decrease in the risk of new fractures in patients of the main group compared to the control group (7.1% versus 11.9%), and the groups did not differ in side effects [3]. Alfacalcidol has shown its effectiveness as monotherapy for glucocorticoid AP. Thus, in a 3-year randomized clinical trial, taking 1 mcg of alfacalcidol and 500 mg of calcium per day was more effective than taking 1000 IU of vitamin D3 and 500 mg of calcium in patients taking long-term systemic glucocorticoids (SGCs). In the group of patients taking alfacalcidol, there was a significantly greater increase in BMD of the lumbar spine (+2.4%) and femoral neck (+1.2%) compared to the control (-0.8% and +0.8%, respectively) ; a reduction in the risk of vertebral fractures by 39%, peripheral fractures by 59%, and fractures of any location by 48% was revealed; In addition, there was a significant decrease in the intensity of back pain compared to the group receiving native vitamin D. Only 3 patients in the alfacalcidol group and 2 patients in the vitamin D group showed an increase in blood calcium levels [4, 5]. A meta-analysis that included 54 studies assessing the effect of active metabolites of vitamin D in patients receiving

long-term SGC on spinal BMD and the risk of fractures showed their positive effect compared with placebo, native vitamin D and/or calcium: ES 0.35 (95% CI 0.18, 0.52) [2]. Similar data were obtained when studying the effect of active metabolites of vitamin D on the risk of vertebral fractures: a 1.8-fold reduction in their risk was shown when taking alfacalcidol compared with taking placebo, native vitamin D and/or calcium (OR 0.56; 95% CI 0 .34; 0.92) [6]. which included 54 studies assessing the effect of active metabolites of vitamin D in patients receiving long-term SGC on spinal BMD and the risk of fractures, their positive effect was shown compared with placebo, native vitamin D and/or calcium: ES 0.35 (95% CI 0.18, 0.52) [2]. Similar data were obtained when studying the effect of active metabolites of vitamin D on the risk of vertebral fractures: a 1.8-fold reduction in their risk was shown when taking alfacalcidol compared with taking placebo, native vitamin D and/or calcium (OR 0.56; 95% CI 0 .34; 0.92) [6]. which included 54 studies assessing the effect of active metabolites of vitamin D in patients receiving long-term SGC on spinal BMD and the risk of fractures, their positive effect was shown compared with placebo, native vitamin D and/or calcium: ES 0.35 (95% CI 0.18, 0.52) [2]. Similar data were obtained when studying the effect of active metabolites of vitamin D on the risk of vertebral fractures: a 1.8-fold reduction in their risk was shown when taking alfacalcidol compared with taking placebo, native vitamin D and/or calcium (OR 0.56; 95% CI 0 .34; 0.92) [6].

One of the causes of fractures in AP is falls. Currently, there are a number of studies devoted to assessing the effect of vitamin D preparations on reducing their risk, and the advantage of using active metabolites compared to native vitamin D has been shown. Thus, in a meta-analysis by F. Richy et al. demonstrated a 21% (RR 0.79; 95% CI 0.64, 0.96) reduction in the risk of falls versus 6% (RR 0.94; 95% CI 0.87, 1.01) with native vitamin D supplementation [7]. Among elderly patients with age-related decline in renal function (creatinine clearance <65 ml/min), while taking alfacalcidol, the number of patients prone to falls decreased by 74% ($p = 0.019$) [8]. In addition, there is evidence of a greater positive effect of alfacalcidol on increasing muscle mass and muscle strength compared to the native form of vitamin D [9, 10]. Alfacalcidol can be used to treat primary AP not only in women, but also in men, as was demonstrated in a study by JD Ringe et al. [eleven]. Men taking alfacalcidol 1 mcg/day as monotherapy had a greater increase in BMD in the spine and hip, and fewer vertebral and peripheral fractures occurred (with a significant reduction in the risk of peripheral fractures in patients with creatinine clearance <60 ml/min), and also a significantly lower number of falls than in patients taking native vitamin D.

Scientists were also interested in the possibility of using a combination of alfacalcidol with other anti-osteoporotic drugs. For example, the effectiveness of alfacalcidol has been proven in postmenopausal men and women with AP when co-administered with alendronate compared with monotherapy with each drug in combination with calcium, and for alendronate - also in combination with native vitamin D. In all groups there was an increase BMD in the spine and hip, however, in the group taking alendronate and alfacalcidol, the result was significantly better after 12 months. treatment than in the group receiving combined alendronate and native vitamin D. In addition, there was a decrease in the incidence of falls, which was lowest in the group receiving alfacalcidol and alendronate [12].

Another study examining the additive effect of 1 mcg alfacalcidol on BMD and bone strength during treatment with alendronate demonstrated a significantly greater increase in BMD in the spine, as well as an increase in volumetric mineral density in the cortical bone of the forearm over 3 years of treatment, which were detected using peripheral CT, according to compared with individuals receiving only alendronate and calcium [13].

Another aspect of prescribing alfacalcidol is its use after 3-5 years of continuous bisphosphonate therapy during the so-called “drug holidays”, which is possible in patients with femoral neck BMD > -2SD and in the absence of vertebral fractures. A study by JD Ringe and E. Schacht showed that alfacalcidol not only stabilized BMD after discontinuation of bisphosphonates, but

also contributed to its increase, and also led to a decrease in the number of falls compared with these indicators when taking native vitamin D, with the same incidence of side effects [14]. Thus, alfacalcidol can be used in patients suffering from both primary and secondary AP; both monotherapy and in combination with bisphosphonates, as well as the drug of choice after long-term use of bisphosphonates. Alfacalcidol was registered in Uzbekistan in the 1990s. and is included in the list of drugs for the treatment of AP in modern clinical guidelines for AP [15]. **Purpose**Our study was to establish the place of alfacalcidol in the treatment of patients with AP in real clinical practice.

Material and methods. The first part of the work consisted of a survey of doctors using a specially designed questionnaire, which included sections on the frequency and number of patients with AP consulted, registration of the disease in statistical reporting cards, diagnostic methods used and treatment. Completed questionnaires were received from 307 doctors of 6 main specialties dealing with the problem of AP.

The second part of the work included a survey of patients with an established diagnosis of AP and who had received at least 1 year of therapy for this disease. The survey involved 1,799 patients aged from 25 to 92 years (average age – 63.3±8.4 years), living in 5 regions of Uzbekistan. Among the respondents, there were 265 (15%) men (average age – 63.0±8.4 years) and 1534 (85%) women (average age – 63.5±8.4 years). Adherence to anti-osteoporotic therapy was assessed over the past 12 months. before questioning on the following parameters: duration, absence of missed doses, compliance with recommendations for taking the drug. The third part of the work included a prospective 3-year follow-up of 196 postmenopausal women (mean age 65.8 ± 9.1 years) who suffered AP fractures of the proximal femur, distal forearm, humeral neck, spine and ankle. All women completed a unified questionnaire after 4, 12, 24 and 36 months. after a fracture, which included questions about anti-osteoporotic treatment and adherence to it.

Statistical processing was carried out using parametric (Student's test for unrelated samples) and nonparametric (Wilcoxon, Mann–Whitney tests, Fisher's exact test) tests. With a normal distribution, data are presented through the mean (M) and standard deviation (SD). Data that are not normally distributed are expressed in terms of the median (Me), 25th and 75th percentiles. Differences were considered statistically significant at $p < 0.05$.

Results and discussion. A survey of doctors showed that on average they consult 12 per month [1; 40] patients with AP, while therapists treated 6 [3; 20], neurologists – 6 [3; 30], gynecologists – 6 [1; 8], traumatologists – 12 [6; 18], endocrinologists – 16 [8; 20] and rheumatologists – 20 [12; 40] patients monthly. Rheumatologists and endocrinologists observed patients with AP more often than doctors of other specialties ($p<0.001$ and $p<0.05$, respectively). In 24% of cases, doctors recommended calcium and vitamin D preparations as the main treatment for AP, with a third of these prescriptions being active metabolites of vitamin D as monotherapy (Fig. 1). In addition, doctors in 19% of cases prescribed alfacalcidol in combination with both antiresorptive drugs and strontium ranelate.

A survey of patients showed that in 43% of cases the diagnosis of AP was made by a rheumatologist, in 17% by a therapist, in 15% by a traumatologist, in 13% by an endocrinologist, in 9% by a neurologist and in 3% by a gynecologist.

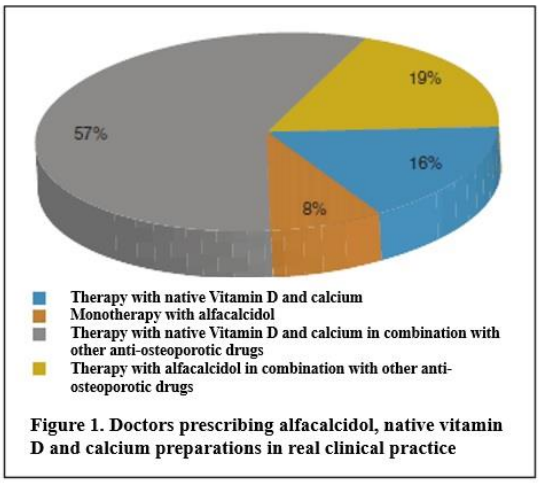

Figure 1. Doctors prescribing alfacalcidol, native vitamin D and calcium preparations in real clinical practice

It was found that 452 (25%) people took alfacalcidol as monotherapy and in combination with other anti-osteoporotic drugs (Fig. 2), men and women with the same frequency (23% and 26%, respectively, p>0.05). Patients received recommendations for taking alfacalcidol in 29% of cases from rheumatologists, less often from traumatologists (24%), neurologists (23%), endocrinologists (21%) and therapists (20%), while rheumatologists prescribed it to patients significantly more often than therapists and endocrinologists ($\chi 2$= 18.02, p=0.006).

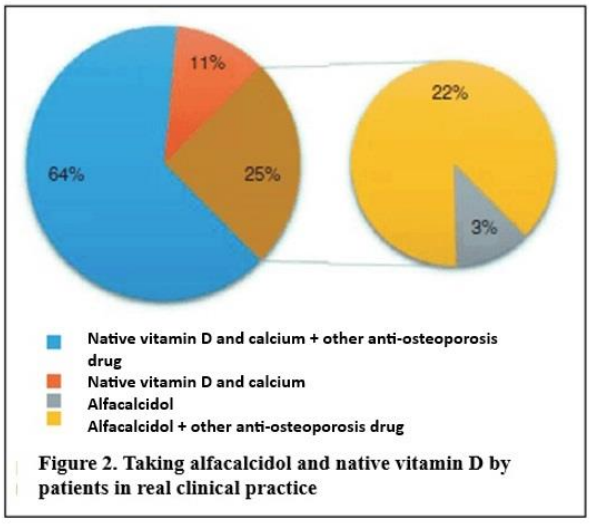

Figure 2. Taking alfacalcidol and native vitamin D by patients in real clinical practice

Patients taking alfacalcidol were older (mean age 64.4±8.6 years) than patients treated with drugs containing calcium and/or native vitamin D (mean age 63.1±8.4 years) (p< 0.01), they were more likely to have previous AP fractures (42% and 35%, respectively, p=0.0083). In addition, those receiving alfacalcidol had a longer duration of illness (p<0.0001), took a higher total number of tablets per day for all other diseases (p=0.007) and were less adherent to treatment for AP (38% compared with 44%, p=0.026). Alfacalcidol was taken as monotherapy for OP by 52 (12%) patients, including 5 (10%) people under the age of 50 years. A survey of patients with AP showed that they received a recommendation for alfacalcidol monotherapy significantly less often from rheumatologists (6% of cases) than from therapists and traumatologists (23% and 21%, respectively, p<0.05). A survey of 196 patients who suffered an AP fracture demonstrated that during the first 4 months. after it, 114 (58%) respondents received some kind of anti-osteoporotic therapy, with women with vertebral fractures receiving significantly more often (p=0.0055). Alfacalcidol was taken by 35 (30.7%) people: 6 (5.3%) as monotherapy, 29 (25.4%) in combination with bisphosphonates. Alfacalcidol was most often prescribed to patients who suffered a fracture of the proximal femur and spine, compared with those who suffered a fracture in the other 4 areas of the skeleton. By 12 months AP treatment was carried out in 106 patients, with 42 (40%) people receiving alfacalcidol, of which 9 women received monotherapy. After 24 and 36 months.

94 and 63 people received anti-osteoporotic treatment, respectively, and alfacalcidol was taken by 22 (23.4%) and 11 (17. 5%) patients, respectively, with monotherapy – 7 and 4 people, respectively (Fig. 3). Alfacalcidol was significantly more often received by persons aged 65 years and older. Overall treatment adherence among patients who started therapy within the first 4 months. after a fracture, was 20% by 36 months, while for alfacalcidol monotherapy this figure was 50%, and for combined therapy – 21%.

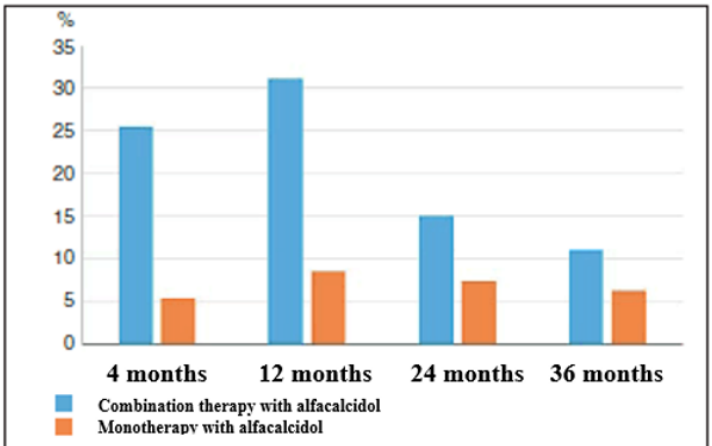

Figure 3. Taking alfacalcidol for 3 years after an osteoporotic fracture occurred in real clinical practice

Thus, our study showed that alfacalcidol has not lost its relevance in the treatment of patients with AP in real clinical practice: it was prescribed in 8% of cases as monotherapy, and in 19% in combination with other anti-osteoporotic drugs. Rheumatologists most often recommended alfacalcidol compared to other doctors, with preference given to combination treatment. An independent survey of patients with AP revealed that 25% of respondents took it as both the main therapy for AP (12%) and in combination with other anti-osteoporotic drugs, while it was used with almost the same frequency in men and women. It should be noted that those taking alfacalcidol were older in age and, as a result, had a longer duration of illness. This is justified, because... in older people, with age, there is a decrease in glomerular filtration rate, which helps reduce the hydroxylation of vitamin D in the kidneys, leads to insufficient formation of D-hormone and is accompanied by the development of tolerance to native vitamin D. Thus, against the background of endocrine-immune dysfunction, a decrease in total muscle mass occurs and muscle weakness syndrome appears, which is accompanied by an increased risk of falls and resulting injuries and fractures. A number of studies have shown a significant reduction in the incidence of falls in elderly patients when using alfacalcidol [8]. leads to insufficient formation of D-hormone and is accompanied by the development of tolerance to native vitamin D. Thus, against the background of endocrine-immune dysfunction, a decrease in total muscle mass occurs and a syndrome of muscle weakness appears, which is accompanied by an increased risk of falls and resulting injuries and fractures. A number of studies have shown a significant reduction in the incidence of falls in elderly patients when using alfacalcidol [8]. leads to insufficient formation of D-hormone and is accompanied by the development of tolerance to native vitamin D. Thus, against the background of endocrine-immune dysfunction, a decrease in total muscle mass occurs and a syndrome of muscle weakness appears, which is accompanied by an increased risk of falls and resulting injuries and fractures. A number of studies have shown a significant reduction in the incidence of falls in elderly patients when using alfacalcidol [8]. Another positive aspect of prescribing alfacalcidol is its sufficient safety during long-term use. Thus, the use of alfacalcidol for ≥6 years at a dose of 0.5–1.0 mcg/day showed that the total incidence of side effects was 1.1%, and hypercalcemia was only 0.22%; no cases of urolithiasis were noted [16]. Another review demonstrated that the relative risk of hypercalcemia in patients taking vitamin D or its analogues (with or without calcium) was only 2.35% [17].

Conclusion. A survey of doctors and patients with AP and AP fractures demonstrated that in real clinical practice, alfacalcidol, having an optimal safety profile, continues to be widely used for both mono- and combination therapy of AP.

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