ВОЗМОЖНОСТИ ДЛИТЕЛЬНОЙ ТЕРАПИИ ПОСТМЕНОПАУЗАЛЬНОГО ОСТЕОПОРОЗА: ОБЗОР РЕЗУЛЬТАТОВ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ ДЕНОСУМАБА И РЕЗОЛЮЦИЯ СОВЕТА ЭКСПЕРТОВ РОССИЙСКОЙ АССОЦИАЦИИ ПО ОСТЕОПОРОЗУ (РАОП)

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Современные препараты для лечения остеопороза (бисфосфонаты, деносумаб, терипаратид) значительно снижают риск развития переломов тел позвонков, переломов бедра и внепозвоночных переломов и отличаются хорошей переносимостью в проспективных и наблюдательных исследованиях длительностью от 1,5 до 10 лет. Некоторые препараты (деносумаб, терипаратид) действуют только в период лечения и не предохраняют в дальнейшем от костных потерь и переломов, в то время как БФ обладают определенным последействием. Несмотря на впечатляющие успехи непрерывного 10-летнего применения деносумаба при тяжелом остеопорозе, недавно появились единичные работы о более высокой частоте переломов тел позвонков, в том числе и множественных после отмены лечения, особенно у пациентов с предшествовавшими терапии переломами. В настоящее время сроки непрерывной терапии остеопороза, вопросы последовательного применения антиостеопоротических препаратов и суррогатных критериев их отмены остаются предметом активных исследований. Эти вопросы в 2017 г. были рассмотрены Европейским медицинским агентством (EMA) и Европейское общество кальцифицированных тканей (European Calcifies Tissue Society, ECTS). EMA расценило развитие переломов после отмены деносумаба как естественное течение остеопороза и не рекомендовало вносить какие-либо изменения в инструкцию к препарату. Основной вывод анализа ECTS оставляет возможность развития множественных переломов тел позвонков после отмены деносумаба, хотя доказательств этого нежелательного явления и мер борьбы с этим эффектом остается недостаточно. Клиницисты и пациенты должны знать о существовании такого потенциального риска. И EMA, и ECTS предлагают пересмотр решения о продолжении лечения деносумабом или его отмены через 5 лет с возможной последующей терапией БФ после окончания лечения деносумабом. Недавно появились сведения о возможности длительного антиостеопоротического лечения в соответствии с концепцией лечение до достижения таргетной цели (например, достижение МПК в бедренной кости до -2,0 SD по Т-критерию). Все эти данные послужили поводом для написания настоящего обзора и обсуждения указанных позиций на Экспертном совете РАОП в Санкт-Петербурге 24 мая 2018 г. под председательством президента РАОП профессора О.М. Лесняк и профессора-эндокринолога Колумбийского университета (Нью-Йорк, США) J.P. Bilezikian. В результате обсуждения согласована резолюция Экспертного совета, которая также приводится в публикуемой статье.

КЛЮЧЕВЫЕ СЛОВА: Остеопороз; переломы; длительность терапии; деносумаб; бисфосфонаты

LONG-TERM TREATMENT OPTIONS FOR POSTMENOPAUSAL OSTEOPOROSIS: RESULTS OF RECENT CLINICAL STUDIES OF DENOSUMAB

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Modern medications for osteoporosis (bisphosphonates, denosumab, teriparatide) are well-tolerated drugs, which can significantly lower vertebral and non-vertebral fracture risk according to prospective and observational studies in up to 10-year period. Certain drugs (denosumab, teriparatide) are active only during the treatment period and do not prevent bone loss and fracture risk after discontinuation, while such protective effect is observed in bisphosphonates. Despite impressive success of continuous 10-year denosumab treatament of severe osteoporosis, some of the recently published data suggest that vertebral fracture incidence is increased after treatment discontinuation, along with multiple vertebral fracture incidence, especially in patients with previous fractures. Issues of osteoporosis treatment duration, sequential use of osteoporosis drugs and criteria for treatment discontinuation are now in focus of attention. European Medicines Agency (EMA) and European Calcified Tissue Society (ECTS) considered these issues in 2017. EMA considered fractures after denosumab discontinuation as a natural disease course and did not recommend any changes in product instruction. The main conclusion of ECTS is that the possibility of multiple fractures development after denosumab discontinuation exists, however, there is still not enough firm evidence, as well as effective countermeasures. Clinicians and patients should be aware of potential risk. Both EMA and ECTS suggest considering denosumab treatment or discontinuation after 5-year treatment period or possibly replacing with bisphosphonates. Recent data suggest that prolonged osteoporosis treatment can be done in accordance with the concept of treatment until target goal (for example, achievement of femoral T-score -2.0SD and higher). In our review, we focus on recent data concerning the issues stated above. This topic was also discussed on Russian Osteoporosis Association (ROA) expert meeting in Saint Petersburg on 24 may 2018, chaired by ROA president, professor Olga Lesnyak and Columbia University professor, J.P. Bilezikian. As a result, an Expert Council resolution was written and introduced in the article.

KEYWORDS: Osteoporosis; bone fracture; denosumab; bisphosphonates; expert opinion

INTRODUCTION

The world's aging population has led to greater emphasis on diseases associated with longevity such as osteoporosis, cardiovascular diseases, cancer, and dementia. Currently available treatment options for osteoporosis (e.g. bisphosphonates, denosumab, teriparatide) significantly reduce the risk of vertebral, hip, and non-vertebral fractures, and demonstrate good tolerability and safety for the duration of recommended therapy [1]. However, most chronic diseases of life, such as diabetes mellitus, hypertension, and hypercholesterolemia, require continuous uninterrupted therapy, while for osteoporosis the discussion has focused recently on limiting duration of therapy. We have more clarify on the decision to begin therapy for osteopprosis because we have a number of surrogate markers, such as high 10-year probability of fracture (FRAX) and bone mineral density (BMD) T-score decreased to –2.5 and worse, that are helpful. In addtion, the presence of a fragility fracture of the vertebral body or hip, or multiple fractures, facilitate the decision to start therapy for osteoporosis [1]. Determination of bone remodeling markers, which reflect bone turnover, and monitoring of BMD are used to assess efficacy of the therapy. While these factors that help to determine the decision to begin therapy, questions related to length of therapy are more pressing due to lack of clinical experience, reliable safety data, and more reliable surrogate markers that could help with regard to targeted end points. Another important point is that the effect of therapies for osteoporosis (e.g, hormone therapy, selective estrogen receptor modulators, denosumab, teriparatide), with the exception of the bisphosphonates are reversible, similar to antihypertensive, , hypolipidemic or antiglycemic medications.. For this reason, questions related to length of therapy for osteoporosis and appropriate targeted endpoints are areas of active investigation.

REVIEW OF THE RESULTS OF DENOSUMAB CLINICAL STUDIES

Denosumab is a monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL). It was developed as a target therapy for osteoporosis to block the main signaling pathway of osteoclast activation — the RANKL/RANK/osteoprotegerin pathway [2]. Denosumab is found in circulation and extravasal space. It does not cumulate in bone tissue. To assess the efficacy of denosumab for the treatment of osteoporosis, 7868 women aged 60–90 years (mean age 72 years) with postmenopausal osteoporosis (lumbar vertebral or hip T-score between –2.5 and –4.0) were enrolled in a multicenter, placebo-controlled study (FREEDOM). Given subcutaneously at a dose of 60 mg every 6 months for 3 years, denosumab reduced the risk of fragility vertebral fractures by 68%, hip fractures by 40%, and non-vertebral fractures by 20%. These significant reductions in fracture risk were associated with a significant increases in BMD and a decrease in markers of bone turnover markers [3]. All patients who completed the 3-year FREEDOM study were eligible to enroll in the 7-year extension in whom 4550 women (2343 received denosumab continuously and 2207 crossed over to denosumab from placebo) were enrolled. Of the 2626 patients who completed the ten-year trial, 1343 received denosumab continuously for 10 years and 1283 received placebo for 3 years and denosumab for 7 years. . Over thise period of time on denosumab, BMD increased continously without any change in slope of the increase.

This is a very unusual pattern, different from all other drugs for osteoporosis in which BMD eventually reaches a plateau without any further increases of time. The cumulative gain in BMD after 10 years for patients on denosumab for that period of time was 21.7% at vertebrae, 9.2% at total hip, 9.0% at femoral neck, and 2.7% at the distal 1/3 radius sites. Patients who crossed over to denosumab from placebo, i.e. received the therapy continuously for 7 years, showed cumulative gains in BMD of 16.5% at lumbar spine, 7.4% at total hip, 7.1% at femoral neck, and 2.3% at radius. The incidence of fractures remained low throughout therapy, the yearly incidence of new vertebral fractures ranging from 1.16% to 1.47%, hip fractures from 0% to 0.42%, and non-vertebral fractures from 0.84% to 1.91%. These incident rates from the 10-year continuous therapy group are lower than the rates observed during the FREEDOM study. The incidence of adverse events fell over the course of 10 years; serious adverse event rates were stable over time. One atypical femoral fracture occurred in each group within 10 years. Seven cases of osteonecrosis of the jaw were reported in both groups (one case in the 10-year use group and six cases in the 7-year use group).

In addition to long-term studies, comparative studies of denosumab were conducted. Denosumab increased BMD more effectively than bisphosphonates. In patients previously treated with bisphosphonates, denosumab was associated with greater increase in BMD compared to continued bisphosphonates including zoledronic acid [5–7].

In view of the observations that denosumab's skeletal actions are reversible, rebound effect when the drug is discontinued is of concern. The first follow-up study of patients after denosumab was discontinued [8] revealed no difference in fracture incidence between placebo and denosumab upon cessation of investigational product. The observational study included 797 patients (470 receiving placebo and 327 receiving denosumab for 2–5 years). It started 7 months after the last injection and lasted for 0.8 years on average (median period 6 months) up to 2 years. During the period of observation, 9% of placebo patients and 7% of denosumab patients sustained a new facture (vertebral or non-vertebral), resulting in a fracture rate per 100 subject-years of 13.5 for placebo and 9.7 for denosumab (OR 0.82; 95% CI, 0.49–1.38) [8].

Cummings et al. extensively analyzed the risk of vertebral or hip fractures in patients who discontinued denosumab or placebo [9]. Denosumab discontinuation is associated with a rapid increase in bone turnover markers 3 months after a scheduled dose is omitted, overshooting baseline levels by 6 months. Concomitantly, BMD falls rapidly by 12 months of follow-up. Of 1001 participants who received and discontinued denosumab, the incidence of vertebral fracture increased from 1.2 to 7.1 per 100 patient-years, similar to placebo group (n=470; 8.5 per 100 patient-years). Patients who received and discontinued denosumab, showed an even greater incidence of multiple compression vertebral fractures (60.9% vs 38.7%; p=0.049 among all fractures). Overall, the risk of new multiple compression vertebral fractures after discontinuation of denosumab was determined to be 3.4%; the risk of multiple fractures after discontinuation of placebo was determined to be 2.2%. The risk of multiple fractures was higher in those with prior fragility vertebral fractures (as on the date of enrollment in the study) and with each additional year of follow-up. The rates of non-vertebral fractures were similar [9]. This analysis has several limitations: the median follow-up period was only 6 months; the study of treatment withdrawals was not designed initially so the findings are incomplete and a number of patients were not monitored by X-rays; correlation between BMD loss and increased risk of fractures could not be estimated; percentage of placebo patients who discontinued the study due to disease progression or requirement for alternative therapy was demonstrably higher. With these reservations, it is nevertheless evident that the salutory effects of denosumab on bone markers, bone density, and fracture incidence are all reversed rapidly upon discontinuation of the drug.

In an official resolution of European Medicines Agency a total of 114 patients who had had fragility fractures after discontinuation of denosumab in the clinical study, were recorded throughout the follow-up period of up to 10 months. In study 20030216, the rates of new vertebral fractures after discontinuation of investigational products were 12.7 (denosumab) and 12.4 (placebo) per 100 patient-years. The groups had comparable baseline risk. In study 20060289, new fracture rate was slightly higher in patients who discontinued denosumab (21.9 per 100 patient-years) compared to those who discontinued crossover denosumab (17.1 per 100 patient-years). The participants of this study were older and had more fractures already while on treatment. Populations at higher risk of fragility fractures have more fractures during treatment and after discontinuation of treatment. The total number of patients who had fragility fractures after discontinuation of denosumab was even slightly lower than among those who discontinued placebo. Having reviewed the information provided, including clinical cases of multiple compression vertebral fractures after discontinuation of denosumab, the European Medicines Agency found no biologically plausible mechanism of increased risk of multiple compression vertebral fractures. The European Medicines Agency came to the conclusion that fractures after discontinuation of denosumab are part of the natural progression of osteoporosis, and recommended no changes to the Product Information. The European Medicines Agency also recognized that the optimal duration of denosumab treatment has not been established. The need for different treatment regimens should be re-evaluated after 5 years of continuous therapy, and the therapy should be continued in populations at high risk of fractures. A randomized withdrawal study was recommended to evaluate the possibility of permanent discontinuation of denosumab [10].

The European Calcified Tissue Society (ECTS) published a systematic review offered its insight on the matter of discontinuing denosumab. The ECTS concluded that that there appears to be a risk of multiple vertebral fractures after discontinuation of denosumab although strong evidence for this serious adverse event and for management recommendations are lacking. It is important for clinicians and patients to be aware of this potential risk. The need for continued denosumab treatment should be re-evaluated after 5 years of the therapy. Patients at high fracture risk are advised to continue denosumab therapy for up to 10 years, since it appears to be effective and safe over this period of time. In patients for whom, discontination is considered, bisphosphonate therapy should be considered to prevent the consequences of stopping as described above. The ECTS concludes that denosumab should not be stopped without

considering alternative treatment [11]. Patients with prior vertebral fractures and/or BMD T-score at femoral neck lower than –2.0 are considered as at high risk population and should continue therapy, unless otherwise contraindicated.

There is an other concept, so cald a treat-to-target, which is not limited by the duration of treatment. Achieveing BMD T-score -2.0 at the Total Hip prevent futher fractures in patients without previos vertebral fractures [12]. To prove this statement Ferrari, et.al. evaluated women received DMAb for 3 years during the FREEDOM trial (N=3902). A large subset of these women enrolled in theExtension and received DMAb for up to an additional 5 years, for a total of up to 8 years of continued treatment (N=2343). A repeated-measures model was first used to estimate each subject's BMD T-scores during the entire follow-up, specifically at each unique nonvertebral fracture time among all subjects at risk at the time of each fracture. Cox's proportional-hazards model was then fitted with time to nonvertebral fracture as the response and total hip BMD T-score time course as a time-dependent covariate. As a result, the incidence of nonvertebral fracture was lower with higher total hip BMD T-score. The relationship flattened at a T-score somewhere between –2.0 and –1.0, similar to what is known to occur in untreated subjects. This inverse relationship between total hip BMD T-score and nonvertebral fracture incidence was maintained regardless of age or prior fracture [12].

While the recommendation that patients who are going to stop denosumab should be switched to another antiresorptive, However, little is known about how this switch should be made. The DAPS study was initially designed to assess patient compliance but showed that alendronate treatment within a year after denosumab preserves BMD [13]. An observational study by McClung et al. showed that BMD loss was less significant in patients who received further therapy for osteoporosis (alendronate — 7 patients, denosumab — 5 patients, risedronate — 4 patients, ibandronate — 2 patients, teriparatide — 2 patients) after discontinuation of denosumab, compared to those who refused further therapy [14].

The logic of followoing denosumab with intravenous zoledronic acid is particularly attractive. In a preliminary report that is limited by small numbers of subjects, the use of zoledronic acid 6 months after the last denosumab injection did not prevent BMD loss among 6 patients who had received denosumab for 7 years [15]. A similar result was reached in 22 women who received an infusion of zoledronic acid after 5 injections of denosumab. These studies are obviously much too small to make any comment about fracture incidence. . Of some interest is the additional observation that thirteen patients who had received bisphosphonates earlier [16] did not show the increase in bone resorption markers after discontinuation of denosumab[17].

The follow-up findings in a group of FRAME study participants who received romosozumab or placebo for 1 year and then switch in each case to denosumab for 2 years are noteworthy [18]. Subjects were treated with zoledronic acid (n=11) 65 days after denosumab was due, or risedronate (n=5) or not treated (n=3). The zoledronic acid group was able to maintain BMD better than the risedronate group. In the small number of subjects were were not followed with any therapy, to 90% of BMD gains were lost within a year [19].

While switching from denosumab to another antiresorptive seems to give salutory results, in general, the transition to teriparatide could be problematical. In the DATA study, there were signficant losses in BMD at the femoral neck and distal 1/3 radius when teriparatide followed denosumab. A option could be to add teriparatide to denosumab, at least initially, before discontinuing denosumab [20].

RESOLUTION OF THE EXPERT COUNCIL OF RUSSIAN OSTEOPOROSIS ASSOCIATION

Denosumab is effective for the prevention of fragility vertebral fractures, hip fractures, and non-vertebral fractures. The therapeutic effect of denosumab with regard to continued increases in bone mineral density and persistent reduction in fragility fractures is maintained for 10 years. . Denosumab increases BMD more effectively than bisphosphonates. In patients previously treated with bisphosphonates, denosumab is associated with greater increase in BMD compared to continued bisphosphonate treatment including zoledronic acid. However, once discontinued, the therapeutic effects of denosumab on bone turnover markers, bone mineral density, and fractures are rapidly reversed. . The risk of multiple vertebral fractures may even rise to even higher levels in patients at high fracture risk. The changes observed after discontinuation of denosumab, are due to the reversible therapeutic effects of the drug and, perhaps also, to the natural progression of osteoporosis. The reversibility of the denosumab effects leads to certain general recommendations while admitting that each patient has to be considered with regard to her own situation. Patients at high risk of fractures, especially those with a history of fragility vertebral fractures, should continue denosumab for 10 years, since this duration of denosumab therapy is effective and safe. In patients at moderate risk of fractures (without previous fragility fractures) who have done well by achieving a target densitometric T-score of (> - 2 at the Total Hip, Neck and Lumbar Spine), it is reasonable to consider stopping therapy. But in these situations, bisphophonates are strongly recommended as follow on therapy. Oral bisphosphonate can be started at the time the next injection of denosumab is due. Zoledronic acid, however, should be started 65 days after denosumab injection was due.

CONCLUSION

It should be emphasized that the above conclusions and recommendations are based on the findings of observational studies. Further investigation of withdrawal effects and defining which populations are best advised when to stop or continue therapy with denosumab are are priority areas of future studies.

ADDITIONAL INFORMATION

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Authors' contribution. All the authors took part in the Expert council of the Russian association of osteoporosis and resolution preparation, manuscript drafting and proofreading. All the authors approved the final version of the article before publication.

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