

OSTEOPOROSIS: UPS AND DOWNS IN TREATMENT UNTIL 2004

Reinhard Ziegler

REZUMAT

Medicamentele utilizate în tratamentul osteoporozei găsesc țesutul osos în diferite faze de turnover. În primii 6-8 ani (până la 10 ani) după menopauză, metabolismul osos este accelerat (turnover crescut) datorită absenței estrogenilor (osteoporoză tip I precoce cu fracturi vertebrale). La vârste cuprinse între 60 și 75 de ani, multe femei prezintă un turnover osos normal sau scăzut (osteoporoză tip I tardivă). După vârsta de 75 de ani, din ce în ce mai mulți subiecți, de data asta de ambele sexe, dezvoltă un turnover crescut prin hiperparatiroidism secundar, produs de obicei prin subnutriție (deficit de aport de calciu și vitamina D) (osteoporoză de tip II cu fracturi de șold). S-a dovedit că dintre medicamentele antiosteoporotice, așa-zisele medicamente anti-resorbitive sunt cele mai potente în osteoporoză cu turnover înalt, față de cea cu turnover scăzut. În ultima situație sunt necesari care stimulează sinteza osoasă. Terapia de substituție hormonală (HTR) (estrogeni) reprezintă cel mai vechi și mai fiziologic tratament anti-resorbtiv. Totuși, recomandarea sa, înainte foarte liberă, este limitată în prezent de creșterea documentată a riscului de cancer de sân.

HRT este indicată numai la femeile cu suferință climacterică importantă. SERMs intră în discuție ca alternativă, deoarece protejează împotriva cancerului de sân, dar ei păstrează riscul tromboembolic al estrogenilor. Tratamentul anti-resorbtiv cu calcitonină pune probleme de doză și de consistență a eficacității. El a fost înlocuit cu bifosonații, care s-au dovedit cele mai eficiente medicamente anti-resorbitive, practic lipsiți de efecte adverse serioase. Cu toate acestea, eficiența lor reală în osteoporoză cu turnover redus rămâne să fie demonstrată. De aproximativ 40 de ani fluorurile au fost singurele medicamente utilizate pentru stimularea directă a sintezei osoase, în cazurile cu turnover redus. Dar studiile limitate și adaptarea inadecvată a dozelor a împiedicat obținerea de date consistente privind eficacitatea preparatelor fluorurate. Există în prezent un medicament nou dar scump, cu efect osteoanabolic, PTH 1-34. Utilizarea sa este limitată la 18 luni, din motive de siguranță, iar dependența eficacității sale de statusul PTH endogen necesită clarificare. Pe viitor, apariția preparatului strontium ranelat, o substanță ce inhibă resorbția osoasă și în același timp stimulează sinteza de os poate duce la schimbarea algoritmului terapeutic actual.

Cuvinte cheie: osteoporoză cu turnover crescut, osteoporoză cu turnover scăzut, anti-resorbitive, HRT, SERM, calcitonină, bifosonați, fluoride, PTH 1-34, strontium ranelat.

ABSTRACT

Drugs for the treatment of osteoporosis meet the bone tissue at different turnover conditions: During 6 to 8 (to 10) years after the menopause, bone metabolism is accelerated to high turnover due to the lack of estrogens (early type I osteoporosis with vertebral fractures). Between 60 and 75 years of age, many women present with normal or low turnover (late type I osteoporosis). After 75, more and more individuals (now from both sexes) develop high turnover due to secondary hyperparathyroidism, caused by the typical undernutrition with calcium and vitamin D at this age (osteoporosis type II with hip fractures). It has been shown that the so-called antiresorptives among the antiosteoporotic drugs are more potent in high turnover osteoporosis compared with the low turnover condition. The latter situation requires bone formation stimulating agents.

HRT (estrogens) is the oldest and most physiological antiresorptive treatment. However, the former most liberal prescriptions are now limited by the now documented increased breast cancer risk: HRT is only recommended in women also suffering from relevant climacteric complaints. SERMs are discussed as an alternative, protecting against the breast cancer risk, but they keep the estrogenic thromboembolic risk. Antiresorptive treatment with calcitonin infers problems with dosing and the consistency of its efficacy. Instead, bisphosphonates proved to be the most potent antiresorptives having almost no serious side effects. However, their true efficiency in low turnover osteoporosis remains to be presented.

For almost 40 years, fluorides were the only drugs for the direct stimulation of bone formation in the low turnover situation. But limited support for studies and inadequate adaptation of dosing prevented the generation of consistent data for fluoride efficiency. A new (but also expensive) osteoanabolic drug is now PTH 1-34. The use is limited to 18 months due to safety concerns, and the dependency of its effectiveness on the endogenous PTH status needs to be clarified. Looking forward, strontium ranelate as a substance inhibiting bone resorption and stimulating bone formation at the same time might revise the actual differential therapeutic scenario.

Key Words: osteoporosis with high turnover, osteoporosis with low turnover, antiresorptives, osteoanabolics, HRT, SERM, calcitonin, bisphosphonates, fluorides, PTH 1-34, strontium ranelate

INTRODUCTION

Since around 20 years, drugs for the treatment of osteoporosis are characterized as antiresorptives or formation stimulating agents. Several times it was stressed that the efficacy of such drugs depends on the bone turnover situation of the skeleton. E.g., antiresorptives exert a better efficiency in high turnover

Department of Internal Medicine I (Endocrinology and Metabolism),
University of Heidelberg, Germany

Correspondence to:
Reinhard Ziegler, Prof. Dr. med. Dr. h. c., Mozartstr. 20, D-69121
Heidelberg, Tel. +49-6221-470618, Fax +49-6221-502618
E-mail: ruz.hd@t-online.de

osteoporosis than in low turnover.^{1,2} The present review deals with our actual knowledge: which medicamental principle is best for which type of osteoporosis? Early postmenopausal osteoporosis (type I) during 6 to 8, sometimes up to 10 years after the menopause presents with high turnover due to the fall in estrogens in the circulation, whereas PTH is not elevated. The following period of 10 to 15 years (late type I osteoporosis) shows normal or low turnover. For osteoporosis type I the typical fracture happens at the spine level. After 70 to 75 years of age more and more patients (and now of both sexes) show high turnover due to secondary hyperparathyroidism as a consequence of the typical deficiency in calcium and vitamin D in this population (osteoporosis type II with hip fracture). How do the published study data respect these dynamics?

ESTROGENS

Based on retrospective studies, HRT was regarded up to the end of the last century as a panacea to maintain women's health after the menopause by preventing climacteric complaints, urogenital discomfort, osteoporosis, cardiovascular disease, Alzheimer's disease and more. However, the more prospective studies were performed, the less global was the documented gain in health in the substituted women. The risk-benefit ratio as a whole was much more differentiated than what had been hoped, and a now individual view of the personal risk factor situation of a woman replaced the former automatism to declare the time after menopause to be an endocrine deficiency disease requiring estrogen replacement therapy, and this possibly lifelong.

Neither HERS^{3,4} nor WHI^{5,6} confirmed the postulated cardiovascular protection by HRT – on the contrary, an increase in coronary heart disease, strokes, thromboembolism was observed. In addition, the formerly denied breast cancer risk showed a clear dose- and time-dependent increase. These relevant health hazards for treated women outweighed the benefits for the bones and the gut: in fact a protection against osteoporotic fractures was confirmed (and there was a certain reduction in colorectal cancers).

Thus, for the prescription of HRT against osteoporosis today a complex view is mandatory: does the patient need estrogens because she also suffers from relevant climacteric complaints which only can be relieved by hormones? Is there a familiar risk for breast cancer? Does she suffer from coronary heart disease? How is her compliance with respect to the necessary gynecological controls (breast examination)? All "pros" and "contras" should be balanced as well as

the patient's opinion after her careful instruction for the final decision to prescribe HRT or alternatives.

Recommendations of HRT for osteoporosis (type I):

- *The patient also should need estrogens because of climacteric complaints.*
- *Familiar breast cancer should have been excluded.*
- *The patient should attend her gynecological controls (breasts) regularly.*
- *The duration of HRT should be limited to the time the climacteric complaints requiring treatment persist. Then alternative antiosteoporotic drugs should be considered.*

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

It was a certain happy surprise that the antiestrogen tamoxifen did not exert the expected osteoporogenic side effect, but on the contrary even showed a certain osteoprotection like estrogen itself.⁷ The further pharmaceutical development led to the SERM raloxifene which is not only estrogen-antagonistic at the breast but also at the uterus (where tamoxifen is still somehow active). Studies in osteoporosis showed that raloxifene increased spinal BMD and significantly reduced vertebral fractures. For hip fractures, no risk reduction was shown. Antifracture efficacy was only shown if bone turnover could be reduced by the treatment (i. e., in the high turnover situation).⁸ In the collective of treated women raloxifene diminished the risk of estrogen receptor-positive breast cancer (not for estrogen receptor-negative invasive breast cancer).⁹ The risk of venous thromboembolic disease was increased, comparable to the situation in women receiving HRT.

When considering a SERM for the treatment of osteoporosis, the prescribing physician is confronted with the following questions: Is the case vertebral (and not femoral) osteoporosis and is she best treated with an antiresorptive drug? Could breast cancer protection be an additional goal for the use of a SERM? Is there no thromboembolic diathesis?

Recommendations of SERM treatment (raloxifene) for osteoporosis:

- *The case should be vertebral osteoporosis (type I) with high turnover (decade after menopause).*
- *Breast cancer predisposition would favour SERM treatment.*
- *Thromboembolic diathesis (procoagulatory status) should be excluded.*

CALCITONIN

Although therapeutic efforts to use calcitonin against osteoporosis started shortly after its discovery, in almost 40 years no convincing data for a stable and calculable efficiency could be worked out. Several reasons are evident: Many studies did not observe that calcitonin may be impotent in low bone turnover osteoporosis.¹⁰ Calcitonin is more an acute hormone being subjected to the escape phenomenon when administered chronically.¹¹ A part of the patients treated with salmon calcitonin develop neutralizing antibodies which are often neglected and not diagnosed. The largest study using nasal calcitonin (PROOF) did not show the mandatory dose-dependency of the calcitonin effect to decrease fractures.¹² With the background of a rather high price (compared with other agents), calcitonin does not play a role as a first line drug against osteoporosis.

Recommendation of calcitonin treatment for osteoporosis:

- *The case should be vertebral osteoporosis (type I) with high turnover (decade after menopause).*
- *There should be an intolerance of or a contraindication against more potent and more consistently active antiresorptives like the bisphosphonates, HRT, or SERMs.*
- *The escape phenomenon and neutralising antibody formation should be monitored.*

BISPHOSPHONATES

Bisphosphonates are established antiresorptives for osteoporosis. The large studies that are the basis for the approval of etidronate, alendronate, and risedronate in many countries did not answer the question whether bisphosphonates are of equal potency in low turnover like in high turnover osteoporosis. However, additional publications revealed that there is a difference: as expected, alendronate had a smaller effect on BMD in low turnover osteoporosis¹³, and fractures were more diminished if bone gain was larger.¹⁴ In a subset of patients from three larger studies on risedronate there was no difference in the relative risk for further vertebral fractures when comparing the half above with the half below the normative median of turnover markers.¹⁵ However, the lacking differentiation of the three studies and the global calculations (e.g., no quartiles or similar) as well as fracture frequency differences in the starting groups cast some doubts on the conclusion that bone turnover does not play a role.

There are no main differences in bisphosphonate effects on BMD whether they are administered daily, weekly, monthly, or every 3 months (then mostly intravenously). For higher potency bisphosphonates even longer intervals are studied, and the results look promising. The intravenous route is of special interest if the patient's gastrointestinal tolerance for oral drugs is poor. In general, undesired side effects due to bisphosphonates are rare. Ten years data on continuous alendronate administration did not reveal unknown health risks (like the theoretically considered "frozen bone")¹⁶ (confirming clinical experiences using longterm treatment with bisphosphonates in other osteopathies (e. g., Paget's disease of the bone).

Thus, bisphosphonates are a first line tool for the treatment of high turnover osteoporosis of type I. Intake rules (fasting with some water, staying upright ½ hour afterwards) should be strictly followed. Patients suffering from gastric ulcer disease or similar could get their bisphosphonate intravenously every three months. Whether treatment longer than 3 – 4 years yields additional benefits, is unclear.¹⁶ For osteoporosis type II we first suggest the substitution with sufficient calcium and vitamin D in order to "heal" the underlying secondary hyperparathyroidism. If afterwards high turnover persists, bisphosphonates are to be considered as second line.

Recommendations of bisphosphonates for osteoporosis:

- *The patient should suffer from high turnover osteoporosis (type I).*
- *Intake rules should be observed.*
- *Intravenous preparations (every 3 months) are useful in GI risk patients.*

FLUORIDES

Whereas several types of antiresorptives were studied and used after approval during the past decades, fluorides were the only bone formation stimulating drugs until the last millennium. Nevertheless, data of high EBM ranking are rare for fluorides. Several reasons shine up: fluorides are cheap and without patents protecting their use. Therefore, there is no economic interest to run expensive studies of today's standards. Study protocols should pay attention to the turnover status of the treated patients and to the individual dosage: if fluorides are overdosed they produce still more bone but without an improved fracture stability.¹⁷ Fluorides decrease the number of vertebral fractures¹⁸ but not of hip fractures. There is no important difference between sodium fluoride (NaF) and monofluorophosphate (MFP) as long as

the different pharmacology is respected.

Thus, the fluoride prescribing physician should have personal experiences with this kind of treatment in order to diagnose the fitting metabolic turnover situation which is low turnover osteoporosis. He should be aware of the narrow therapeutic window for fluorides: 20 mg of bioavailable fluoride ions per day. If side effects like the lower limb pain syndrome (as a signal for exuberant new bone formation in connection with microfractures) show up or increases in BMD after one year of more than 5 to 6 % signalize a "too" good response, fluoride dosis should be halved in such a case.¹⁹

Recommendations of fluoride treatment for osteoporosis:

- The patient should suffer from low turnover osteoporosis of the spine.
- The daily starting dose should be 20 mg bioavailable fluoride ions.
- The dose should be halved in case of the lower limb pain syndrome.
- The dose should be halved, if BMD increases more than 5 – 6 % per year.

PTH 1-34 (TERIPARATID)

Whereas states of chronic elevations of PTH in blood like in primary and secondary hyperparathyroidism or due to continuous infusion in the animal experiment lead to bone loss and "osteoporosis", cyclic PTH peaks are a stimulus for new bone formation. Daily subcutaneous injections with the bioactive PTH fragment 1-34 (without depot effect) produced in patients with osteoporosis distinct increases in bone mass and reduced vertebral fractures.²⁰ PTH 1-34 is now approved for the treatment of osteoporosis, but treatment time is limited to 18 months. This is a safety measure because longlasting PTH 1-34 administration in rats had initiated osteosarcomas in these animals.

There are some open questions: Is PTH treatment of equal potency in early osteoporosis type I presenting with high turnover but low PTH, or in late osteoporosis type I when the low turnover seems to be an open window for the PTH stimulus, or in osteoporosis type II when endogenous PTH is even elevated? The idea to combine an antiresorptive like alendronate with a formation stimulator like PTH was challenging, but a respective study brought forward a disappointing result: The combination was less effective than PTH alone and barely better than alendronate alone.²¹ This illustrates that much more work has to be done, taking into account the

underlying turnover situation as well as its changes through the drugs.

As long as the treatment with PTH 1-34 is rather expensive (e.g., in Germany more than 20 Euro per day), the drug has to be reserved for restricted cases. Examples are: low turnover osteoporosis without sufficient response to fluorides or intolerance of fluorides; bisphosphonate treated osteoporosis without sufficient response; insufficient response of osteoporosis type II to correct treatment with Vitamin D and calcium.

Recommendations of PTH 1-34 treatment for osteoporosis:

- Preferably low turnover osteoporosis with no alternative choice of other drugs: no response to fluorides or intolerance of fluorides.
- Bisphosphonate treated patients without sufficient response.
- Calcium- and vitamin D treated osteoporosis type II without sufficient response.

OUTLOOK

For a still more differentiated treatment of the individual osteoporotic patient between 50 and 80 years of age presenting with the described different states of bone turnover, varying endogenous PTH concentrations, and changing cellular reactivity in his or her skeleton, we hopefully wait for further analyses of existing study data as well as for additional, especially comparative studies with the known agents. Another hope is the generation of still better drugs, perhaps being more universally applicable than the actual drugs. One fascinating drug is arising at the moment: strontium ranelate. This substance on one side inhibits bone resorption, on the other side stimulates bone formation, obviously without conflicts between the involved cell populations. The reported increases in BMD have to be read with caution as strontium deposition in the bone could influence the values of densitometry without improving fracture stability. However, the reduction in the vertebral fracture risk to 0.59 of the placebo arm during 36 months in the treated women looks promising.²¹ Perhaps strontium ranelate turns out to become a kind of a panacea for osteoporosis, solving some of our ongoing therapeutic problems.

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