A need for predictive and personalized approach in osteoporosis treatment: individual treatment plan

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Abstract
Osteoporosis is a frequent, multifactorial disease and represents a significant and increasing healthcare burden in Europe. For osteoporosis treatment several drugs groups (SERM: bisphosphonates, denosumab, teriparatide) have been approved with different biological effects and further are expected. The question if every medication is suitable for all patients, is opened. We may stratify patients by individual fracture risk assessment but often there many others individual factors affecting medication choice. Age, life expectancy, falls, kidney function are very important. Preparing individual treatment plans for each patient is the way how to handle with it. In younger osteoporotic women we have to expect 20-25 years of care and sequential therapy, long term therapy with "drug holiday" is to be considered. This new strategy should be accompanied by more flexible reimbursement rules.

Key words: bisphosphonates – denosumab – fracture prediction – fracture prevention – preventive, predictive and personalized medicine – fracture risk – individual treatment plan – osteoporosis – personalized therapy – vitamin D

Introduction

Osteoporosis is a frequent, multifactorial disease that represents a significant and increasing healthcare burden in Europe. More than 20 million women and 5 million men are estimated to have an osteoporosis. The most common (major) fractures are hip, forearm and vertebral and proximal humerus fractures. Women have a nearly 50 % (46 %) life time risk of sustaining a major osteoporotic fracture while men have half that risk (22 %). [1] It has been estimated there are more than 400 000 women and 100 000 men with osteoporosis in the Czech Republic. The treatment gap is assumed to be nearly 80 % in women and 90 % in men; similar to other European countries. [2] Therefore the International Osteoporosis Foundation set up a global campaign called "Capture the Fracture" to support secondary fracture prevention. This global project helps implement coordinator-based fracture liaison services worldwide. The main goal is to actively seek out patients with a recent osteoporotic fracture and organize an immediate bone health assessment for them. [3] Fracture incidence and risk increase with age, low bone mineral density, number of falls, parenteral history of fracture, presence of secondary cause of osteoporosis and bone turnover. It differs by sex and ethnicity.

The above-mentioned epidemiological findings cannot, however, contribute directly to an individual patient's evaluation. It is therefore paramount to apply a predictive, personalized approach to osteoporosis, as is the case with many other diseases. [4]

Individual patient risk assessment

Fracture risk calculator development is on its way. The fracture risk assessment tools FRAX [5], Garvan [6] and QFrac-

ture [7] are now used for individual 5 to 10 year fracture risk prediction. None of these three risk calculators however includes all major known risk factors. Garvan does not take into account secondary osteoporosis and glucocorticoids, while FRAX does not include falls. Therefore there is still room for improvement. [8] Falls are one of the most important non-osseous risk factor and fractures can be predicted based on them alone ,independently of FRAX.[9] Once a patient is identified as having osteoporosis, risk factors and co-morbidities are evaluated. Only then is an appropriate treatment suggested. Reparation of vitamin D deficiency and adequate calcium intake is essential. Vitamin D supplementation especially is strictly individual and must reflect the patient´s compliance, sun exposure, baseline 25-hydroxy vitamin D levels and BMI. [10–12]

Osteoporosis treatment choice

Several drugs have been approved for osteoporosis treatment and they can be divided into four groups according to their biological effects. The first group comprises estrogen and selective estrogen receptor modulators (SERMs). The second group is comprised of four bisphosphonates (aledronate, risedronate, ibandronate and zolendronic acid). The third group includes denosumab and the fourth group teriparatide. Drugs with estrogen activity have a moderate impact on bone mineral density and bone turnover, but restore premenopausal bone microenvironment. Bisphosphonates and denosumab are strongly antiresorptive, which leads to an increase in bone mineral content and high antifracture efficiency. Antifracture activity differs among bisphosphonates; the most potent ones being denosumab and zolendronic acid. Zolendronate a single baseline 5 mg dose or 5-yearly doses of 1 and 2.5 mg zoledronate prevented bone loss at hip and spine for 8 to 10 years in older postmenopausal women [13], while alendronate may have a more rapid offset of drug effect than zoledronic acid. [14] None of these drugs can be used lifelong. The main concerns limiting their usage are a higher risk of thromboembolism resulting from long-term SERM usage and the higher cardiovascular and breast cancer risk linked to the use of estrogens. Bisphosphonate usage is limited by its unproven efficiency once 5 years of treatment have been exceeded, rare osteonecrosis of jaw and atypical femoral fractures, as well as gastrointestinal irritation resulting from oral application. [15]Denosumab is a long acting bone agent the discontinuation of which leads to rebound phenomenon that affects bone turnover after therapy. This leads to rapid decrease in bone mineral density and the presence of multiple vertebral fractures in some patients. [16,17] Teriparatide, an effective anabolic drug, should only be taken for a total of 24 months max. [18] Hopefully new therapies will arrive on the market within few years. An anabolic effect similar or better to that of teriparatide is that of abaloparatide (PTH related protein, PTHrP). Romosozumab, a new monoclonal antibody against sclerostin, has a dual effect: it increases bone formation and decreases bone resorption. [19,20]

Individual Treatment Plan

Patients, much like treatment modalities themselves, vary. They may have severe osteoporosis which entails osteoporotic bone mineral density and the presence of at least one osteoporotic fracture. Or they may have an osteoporotic fracture but only low bone density, or osteoporotic density without fractures. Thera are many other fracture contributors in which patients may vary too. Falls frequency is one of most important contributors to an osteoporotic fracture. Some comorbidities may limit usage of some antiporotic drugs (chronic kidney failure, cancer). A very important difference is the patient's age at the time of the osteoporosis diagnosis. A postmenopausal osteoporotic woman in her sixties has a much longer life expectancy than a woman in her eighties. Therefore, in younger postmenopausal women we have to plan a long-term treatment of about 20 to 25 years, with a high probability of therapy discontinuation at some point. Conversely, elderly women will be at high risk of falls and their therapy might include intervention against falls without a planned therapy discontinuation.

I propose that the future of osteoporosis therapy requires a more individual, personalized approach to each patient. This is in strong agreement with the aims of medicine in the early twenty-first century. [21] This individual-focused approach requires precise patient assessments (individual fracture risk, falls risk assessment, bone turnover markers and a comorbidities evaluation, as well as exclusion of secondary causes of osteoporosis). A complex approach in osteoporosis care is in agreement with the new global vision of a consolidated promotion of an integrative medical approach to advanced health care. [22] I call it "An individual treatment plan" for each osteoporotic patient.

The individualization of osteoporosis therapy will not only enable the identification of the right treatment for each patient, it will optimize treatment to the point where the correct dose is prescribed at the right time. [21] An individual plan for elderly women with severe osteoporosis may optimally starts with anabolic therapy and falls prevention, followed by permanent antiresorptive therapy (bisphosphonates or denosumab). This might be more efficient than starting with antiresorptive drugs followed by anabolic therapy.

On the other hand, early postmenopausal osteoporotic women do not necessarily need to focus on falls

prevention, but they should be motived to exercise and use antiresorptive drugs. Being as therapy discontinuation is assumed to take place during the course of treatment, bisphosphonates would be preferred over denosumab due to the rebound phenomenon risk in treatment naive patients. Nevertheless, we may plan to start with denosumab followed by bisphosphonates in order to reach a low bone mineral density range and then interrupt therapy. In a long-term treatment plan we can start with bisphosphonates, then continue with denosumab and after reaching a BMD T-score of around -2.0 we may finish treatment with bisphosphonates again.

Conclusions

- Osteoporosis is a world-wide, highly prevalent disease and patients may profit from a personalized approach, much as they do in cancer. [23]a radical shift in cancer treatment is occurring in terms of predictive, preventive, and personalized medicine (PPPM
- We should evaluate and assess the individual patient´s fracture risk alongside health factors influencing treatment decision precisely.
- A long-term individual treatment plan for any particular patient might be the best approach in terms of achieving better patient compliance and higher treatment efficacy.
- The implementation of predictive and personalized medicine strategies in patients with osteoporosis needs to be evaluated by multicenter, multinational trials.
- It will be very important to implement biobanking as a cornerstone of personalized medicine. Biobank samples with the appropriate clinical data will ensure the identification and validation of genetic risk factors in osteoporosis.

Compliance with the ethical standards

Conflict of Interest *Richard Pikner is a member of advisory board for Amgen and has received a speaker honorarium from Amgen, Takeda, Roche, DiaSorin, Abbott and Beckmann-Coulter. Other authors declare that they have no competing interests.*

Ethical approval *Not applicable.*

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