Individualized treatment of osteoporosis with medication: preventing fractures by increasing bone mineralization and quality

Today, an entire range of highly effective osteoporosis medications is available. While the therapeutic potential of a drug for this indication was traditionally evaluated based on the increase in bone mineral density during treatment, in recent years this criterion has been replaced by the documented reduction in fractures. Current focus is therefore increasingly placed on achieving improvement in bone quality. Several medications, including the selective estrogen receptor modulator raloxifene, appear to be particularly noteworthy in this regard. New diagnostic methods such as high-resolution computed tomography facilitate not only bone density measurement, but also the qualitative and quantitative 3D representation of bone microarchitecture *in vivo* for the first time. Using this more modern technique, improvement in 'bone quality' has been documented in clinical practice in a retrospective as well as prospective analysis of postmenopausal osteoporotic patients receiving treatment with raloxifene.

KEYWORDS: bisphosphonate ■ bone quality ■ high-resolution computed tomography ■ osteoporosis treatment ■ raloxifene

Helmut Radspieler

Osteoporosis Center, Karlsplatz 4, 80335 Munich, Germany
Tel.: +49 89 592 524
Fax: +49 89 550 2513
info@osteoporosezentrum.de

Osteoporosis has long been viewed as a widespread disease and has thus been designated by the WHO as one of the ten most important diseases worldwide. Previously, osteoporosis was defined by insufficient bone density. Since 2001, osteoporosis has been recognized as a systemic skeletal disease that leads to increased susceptibility of fractures due to insufficient bone strength [1]. Bone strength primarily reflects the interaction between bone density and bone quality. The latest version of the Osteoporosis Guidelines (Leitlinie Osteoporose) from the German Umbrella Association for Osteology (Dachverband Osteologie e.V) explicitly highlights the significance of bone microarchitecture destruction in defining the disease [2]. The term 'bone fracture disease' was proposed by Professor Klaushofer of Vienna, Austria, in his presentation entitled 'Pathophysiology of Osteoporosis' at the 2008 Osteology Convention in Hannover, Germany, which describes the pathology of osteoporosis first and foremost as the occurrence of bone fractures without commensurate cause.

The recognition that bone strength is a more relevant criterion than bone density in the current definition of osteoporosis is having a major impact on the manner in which treatment efficacy is viewed. This is further enhanced by the availability of modern sophisticated equipment – specifically, high-resolution peripheral quantitative computed tomography (HRpQCT) – that can quantitatively evaluate changes in bone microarchitecture over time and provide more clinically relevant information than simple bone density measurements. Against this background, this article examines current prescribing practice for osteoporosis (based on German data) and provides a brief comparative analysis relative to the characteristics of the selective estrogen receptor modulator (SERM) raloxifene. The results of a retrospective study and interim findings of a prospective study of raloxifene conducted using HRpQCT in postmenopausal women with osteoporosis at our center in Germany are also presented.

Clinical presentation of osteoporosis

In osteoporosis, loss of bone mass and increasing destruction of the bone microarchitecture generally proceed without initial pain or discomfort (i.e., without clinical symptoms). However, when the loss of bone mass becomes advanced, uncharacteristic skeletal pain can occur. Routine physical activities such as lifting heavy objects, heavy coughing or even an awkward movement can lead to (new) vertebral fractures (bone fracture disease). In addition to vertebral fractures, fractures of the hip and distal radius are especially typical of osteoporosis. Radial fractures, which are among the most common in osteoporotic patients, are the earliest to appear.

The prevalence of osteoporosis increases markedly with age. Osteoporosis affects an estimated 75 million people in Europe, the USA and Japan [3]. Approximately one in three women over the age of 50 years and one in five men will experience osteoporotic fractures [4–6].

future medicine part of fsg

In the year 2000, there were an estimated 9 million new osteoporotic fractures worldwide, of which 1.6 million involved the hip, 1.7 million the forearm and 1.4 million were clinical vertebral fractures. Europe and the Americas accounted for 51% of the total number of new fractures, while most of the remainder occurred in the Western Pacific region and Southeast Asia [7,101]

A previous fracture history is associated with an 86% increase in the risk of further bone fractures [8]. Patients with documented vertebral fractures also have higher mortality rates [9]. As well as reducing life expectancy, vertebral fractures may reduce thoracic volume, resulting in a higher risk of pulmonary diseases which, in turn, require further treatment [9].

Options for treatment

Current goals of drug therapy for osteoporosis are fracture prevention and reduction in the risk of new fractures (bone fracture disease). But this has not always been the case. Until the mid-1990s, fluorides were considered to be the treatment of choice as they were shown to facilitate a significant increase in bone density. However, subsequent studies showed that, despite an increase in bone density during fluoride therapy, susceptibility to fractures actually increased [10]. Since then, use of fluorides has become largely obsolete. The major reason for this is that bone mineral density (BMD) rose significantly, but 'bone quality' decreased, possibly due to fluorosis. These findings also cast doubt on the significance of bone density as the almost exclusive criterion for treatment evaluation.

Approval of the bisphosphonate alendronate (remodeling inhibitor) in the early 1990s revolutionized the treatment of osteoporosis. The randomized, double-blind, placebo-controlled Fracture Intervention Trial (FIT) was the first study to demonstrate that treatment with alendronate significantly reduced vertebral and hip fractures [11]. Since then, other bisphosphonates and a range of medications with different modes of action (antiresorptive and/or osteoanabolic drugs) have been approved for the treatment of osteoporosis. Irrespective of drug class, all approved medications (i.e., bisphosphonates, parathyroid hormone-based preparations, strontium ranelate, hormone replacement therapy and raloxifene [currently the only SERM to be approved for osteoporosis treatment]) have been shown in their relevant approval studies to elicit significant and relatively equivalent reductions in the risk of fractures.

Beyond BMD

Table 1 summarizes data from approval studies with regard to reduction in the risk of vertebral and peripheral fractures for all medications currently approved for the treatment of osteoporosis and classified as 'A' medications in the osteoporosis guidelines of the German Umbrella Association of Osteology [2]. These data derive from several clinical studies with differences in criteria, such as patient groups, age, disease severity, pre-existing fractures, and thus are not directly comparable [11–23]. Notably, the increase in BMD varied greatly in these studies.

As Table 1 indicates, vertebral fracture reduction is relatively similar for all preparations; data for peripheral fractures are available for only some of these medications. Changes in BMD, which ranged from 2.6 to 14.4% in the approval studies, indicate considerably larger differences. This apparent discrepancy may be explained by looking beyond bone density to postulate other factors responsible for the actual reduction in fracture risk. The highest measured increase in BMD was with strontium ranelate treatment; this is at least partially due to the (temporary) deposit of strontium in the bones, also known as the 'strontium effect'. As an alkaline earth metal (like calcium), strontium has a higher atomic number in the periodic table of elements than normal bony substance and thus also absorbs more radiation. This could be responsible for approximately 40–50% of the reported increase in BMD [24].

Quest for optimal individual therapy

With the abundance of medications currently available to treat osteoporosis, the question of optimal therapy arises. There is no simple answer to this question. A patient who does not tolerate oral bisphosphonate because of stomach problems may gain greater benefit from intravenous bisphosphonate or raloxifene. Patients with the most severe osteoporosis and multiple vertebral fractures may be candidates for osteoanabolic treatment [25]. A postmenopausal woman with climacteric difficulties may benefit most from hormone replacement therapy, while very elderly patients may do better with strontium ranelate [26]. An optimal solution must be determined for each individual patient.

Given that all medications listed in Table 1 show broadly similar results with regard to the reduction of, at minimum, vertebral fracture risk, it might be assumed that prescriptions were likewise evenly distributed across all preparations, apart from parathormone-based drugs, which are usually reserved for special (most severe) cases

Table 1. Changes in bone mineral density of the lumbar vertebrae determined by dual x-ray absorptiometry (Δ areal bone mineral density in %) and reductions in vertebral and peripheral fractures (%) following treatment of osteoporosis with approved medications in accordance with their respective approval studies.

Medication	Active substance	Intake (as specified in the literature)	Mechanism of action	Δ aBMD (%; lumbar spine)	Fracture reduction (%; lumbar spine)	Fracture reduction (%; peripheral)	Ref.
Alendronate	Bisphosphonate	Oral	Remodeling inhibitor	+6.8	47	32	[11]
Risedronate	Bisphosphonate	Oral	Remodeling inhibitor	+5.9	49	33	[12]
Ibandronate†,‡	Bisphosphonate	Oral; daily or intermittently	Remodeling inhibitor	+6.5 +5.7	62 50	No data	[13]
Zolendronate	Bisphosphonate	Intravenous	Remodeling inhibitor	+6.7	70	25	[14]
Raloxifene‡	SERM	Oral	Primarily antiresorptive	+2.6	55	47‡	[15–17]
1-34-PTH	Parathormone fragment§	Subcutaneous	Osteoanabolic	+9.7	65	53	[18]
1-84-PTH	Parathormone§	Subcutaneous	Osteoanabolic	+6.9	58	No data	[19]
Strontium ranelate	Strontium	Oral	Dual (osteoanabolic + antiresorptive)	+14.4	41	36	[20,21]
HRT	Estrogens (+ gestagens)	Oral	Primarily antiresorptive	+4.5	34	No data	[22,23]

†Fracture data for ibandronate are from a study with daily oral treatment of 2.5 mg or intermittent oral treatment (20 mg every second day for 12 dosages every 3 months). These data were combined in a comparative study with the approved dosage of ibandronate (2.5 mg per day orally vs 150 mg once a month orally vs 3 mg/ml intravenously every 3 months) with regard to changes in bone mineral density and bone marker as end points.
‡No approval was available for reduction of hip fractures.
§Treatment duration was 18 months.
aBMD: Areal bone mineral density; DXA: Dual x-ray absorptiometry; HRT: Hormone replacement therapy; PTH: Parathormone; SERM: Selective estrogen receptor modulator.

primarily because of their considerably higher costs. In fact, there is a strong imbalance in the number of prescriptions for the various groups of medications. Data from the BoneEVA study conducted in Germany showed that between 2000 and 2003, bisphosphonates accounted for the largest proportion of all specific osteoporosis medications at 10%, followed by hormone replacement therapy at 8%. The virtually obsolete fluorides, and drugs such as calcitonin, each accounted for 2% of all prescriptions. Raloxifene accounted for only 1% of all prescriptions. Analgesics not specifically indicated for osteoporosis treatment inexplicably accounted for 22% of all prescriptions [27].

Why the imbalance in prescription numbers?

Why is there such an imbalance in the number of prescriptions for the various osteoporosis medications? It is probable that pharmaceutical company marketing budgets/strategies and a 'first to market' competitive advantage play an important role in defining clinicians' attitudes towards a certain drug or class of drugs. Clinical experience and behavioral factors such as being an early or late adopter of new technology as well as 'force of habit' may also go some way to explaining the apparent discrepancy between evidence and practice.

More specifically, price alone is clearly not the reason. At the time that data for the BoneEVA study were collected, alendronate generics were not yet available. Moreover, the cost of the original bisphosphonates and raloxifene do not differ much. Thus, the neglect of raloxifene's potential in the treatment of osteoporosis cannot be due to cost considerations. Differences in efficacy also do not provide a plausible explanation. Data with regard to reduction in risk for vertebral and peripheral fractures do not show any truly significant differences between frequently prescribed bisphosphonates and raloxifene (Table 1). The reason for the restraint is sometimes cited as being that, in contrast to most bisphosphonates (with the exception of ibandronate), there are no data for raloxifene with regard to the reduction in risk of hip fractures. This is in fact true of the Multiple Outcomes of Raloxifene Evaluation (MORE) study, which nevertheless, led to the approval of raloxifene [15]. The patient group in the MORE study was significantly younger than those in corresponding bisphosphonate studies. Given that the frequency of osteoporotic hip fractures rises steeply only at the age of 75 years [28], the patient group in the MORE study was possibly too young to document a reduction in the risk of hip fractures. In subgroups of the MORE study that had higher fracture risks, reduction of the extravertebral fracture rate during treatment with raloxifene was

documented [16]. However, these data were not incorporated into the European approval. Similar findings were documented in the Women's Health Initiative (WHI) study for treatment with hormone replacement therapy [23]. It is also interesting to note that ibandronate is prescribed relatively frequently for patients with postmenopausal osteoporosis, despite the absence of data to indicate a reduction in the risk of hip fractures.

Current prescription practice is all the more surprising when other aspects such as the mechanism of action, mode of intake, adverse effects and additional positive effects, are considered. For instance, bisphosphonates are integrated into the bone and remain there for an extended period of time with a half-life of up to 10 years [29]. Raloxifene, on the other hand, acts physiologically on bone cells via estrogen receptors located within the cells [30].

While the risk of jaw necroses associated with bisphosphonate treatment is undoubtedly overestimated (especially during treatment for osteoporosis), cumulative safety data collected over the past 10 years indicate that raloxifene treatment carries no such risk. With regard to methods of intake, raloxifene presents few concerns [31], whereas this is not the case for bisphosphonates taken orally [29]. Overall, the range of adverse side effects associated with raloxifene is comparable to that of bisphosphonates [30].

In view of current recommendations for bisphosphonate therapy that suggest a treatment period of 3 to 5 years, in younger patients a sequential treatment plan starting with raloxifene followed by bisphosphonates should be considered as a possible long-term strategy. The new guidelines of the German Umbrella Association for Osteology state that continuation of specific drug therapy is recommended depending on the level of fracture risk. Currently, there is insufficient evidence for or against interrupting specific therapy after initial completion of the period for which fracture reduction has been documented in randomized studies [2]. However, the EUROFORS study has documented good efficacy with raloxifene as follow-up therapy after initial treatment with teriparatide in maintaining the achieved increase in bone density [32]. Importantly, there were many older female subjects in this study.

A certain degree of pain reduction during treatment was documented for practically all preparations, including raloxifene [33]. Beyond its effect on bones, clinical studies with raloxifene also demonstrated improvement in serum lipids [34] and a significant reduction in the risk of invasive estrogen receptor-positive breast cancer [35,36].

Effect of raloxifene on breast tissue

In addition to demonstrating significantly greater fracture reduction after 4 years' treatment with raloxifene compared with placebo, the MORE study showed a reduction in the risk of invasive breast carcinoma by 72% and of invasive estrogen receptor-positive breast carcinoma by 84% [36]. Analysis of the MORE plus Continuing Outcomes Relevant to Evista® (CORE) studies after a combined total of 8 years showed a 76% reduction in invasive estrogen receptor-positive breast carcinoma [37]. The Study of Tamoxifen and Raloxifene (STAR), a comparative study of raloxifene versus tamoxifen commissioned by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in the USA also documented the noninferiority of raloxifene in the prevention of estrogen receptor-positive breast carcinoma [38]. Inexplicably, the US approval of raloxifene based on relevant data from the MORE study regarding prevention of breast cancer in high-risk postmenopausal patients with osteoporosis does not exist in the EU.

'Bone quality' versus bone density

Until recently, the diagnosis of osteoporosis was largely equivalent to the measurement of bone density. Density is defined as mass per volume and is a physical property. In contrast to this definition, the most frequently used means to measure bone density is by dual x-ray absorptiometry (DXA), which specifies only the measurement of integral mineral content in grams per cm^2 averaged over the surface area (expressed as BMD). A range of factors such as bone geometry ('thin bones') and degenerative changes (spondylosis, scoliosis) can influence the result to produce false negatives or false positives, as the evaluation is carried out on a purely statistical basis via comparison of individual mineral density with the average value for healthy young adults. The deviation, expressed as a T-score, is used for the evaluation. However, only a statistical risk of fracture can be calculated using this method. A new definition of osteoporosis places additional focus on aspects such as trabecular microarchitecture, geometry, corticalis thickness and material properties, summarized under the general term 'bone quality', which refers to architecture, turnover, damage accumulation (e.g., microfractures) and mineralization [1]. The latest version of the osteoporosis guidelines of the German Umbrella Association for Osteology explicitly notes the importance of bone microarchitecture destruction in defining the disease [2]. This cannot be documented with 'bone density' measurement alone.

Although an increase in BMD was previously considered a parameter for evaluating the success of a drug therapy, this has since been revised in nearly all therapeutic studies [1]. A lack of increase in bone density during antiresorptive treatment is not necessarily linked to lesser effectiveness of the medication. This treatment concept should be considered only if BMD values show a clear drop during drug therapy [39]. The German Umbrella Association for Osteology guidelines state the following: "Changes in bone density measurements are only of limited use in clarifying the therapeutic success of drug treatment. Failure to increase bone density during antiresorptive therapy is not an indication of decreased fracture reduction. Conversely, the initial bone density value before commencement of treatment is decisive for the estimate of future risk of fracture even with increases in bone density during antiresorptive therapy" [2]. The relatively small increases in BMD during drug therapy (TABLE 1) can therefore explain the significant reduction in fracture rates to a minor extent only; this also applies to raloxifene. Other factors such as changes in 'bone quality' must be responsible for the improved bone strength and fracture reduction.

With modern methods it is technically possible to evaluate 3D structural parameters of the bone and to document these quantitatively. Analytical parameters such as number of trabeculae, average trabeculae thickness, trabecular spacing, bone volume (trabecular bone volume per total volume [BV/TV]), corticalis thickness and nonhomogeneity of the (trabecular) network can be made visible in high resolution *in vivo*, and can be measured and evaluated over the course of the disease. Indeed, for the first time a method is available that can actually evaluate 'destruction of the bone microarchitecture', which is crucial according to the current definition of osteoporosis [1,2] and provides more clinically relevant information than simple bone density measurements. Since 2005 we have been working with this special, HRpQCT (XtremeCT®, Scanco Medical AG, Zurich, Switzerland) and are currently examining, among other things, changes in bone quality in patients receiving raloxifene treatment in a prospective study at our osteoporosis center.

Quantitative determination of bone quality over disease course

At the European Congress on Calcified Tissue 2009 our group presented a retrospective analysis which showed that raloxifene produced an increase in trabecular and cortical bone densities, and improved microarchitectural parameters [40]. In some patients from this retrospective study, particularly those with advanced osteoporosis, we were also able to observe visible improvement in bone structures, as depicted by the images in FIGURE 1. After 3 years' treatment with raloxifene, the female patient in whom these bone structure changes were documented showed a visible and significant increase in the number of trabeculae by more than 9%. Trabecular bone densities were increased by approximately 6% overall and by as much as 19% in the inner areas typically affected by osteoporosis.

In 2008, we initiated a prospective study to demonstrate the effects of raloxifene treatment on volumetric bone densities and microarchitectural parameters in postmenopausal osteoporotic and osteopenic women. To date, more than 40 women have been included in the study. After baseline measurements with HRpQCT, two further measurements after 1 and 2 years of treatment are either planned or have been completed. Measurements of bone markers, calcium, vitamin D and parathyroid hormone levels in the blood at baseline and after 3–6 months' therapy with raloxifene are also planned, or have already taken place in approximately half the patients. In addition, all patients receive individualized dosages of calcium and vitamin D, depending on their measured vitamin D levels.

High-resolution peripheral quantitative computed tomography measurements and laboratory results are currently available for 15 patients after an average of 15.1 months of raloxifene

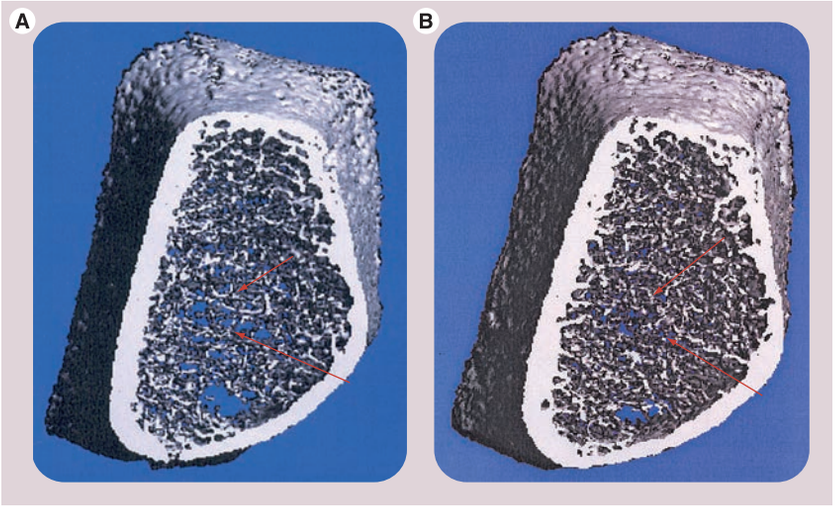

Figure 1. Change in bone structure in a female patient with osteoporosis treated with raloxifene. (A) Before commencement of treatment. **(B)** After 3 years of treatment.

treatment; these first interim results were presented at the Osteologie Kongress in Berlin, Germany, 3–6 March 2010 [41].

Selective measurements were performed of trabecular and cortical volumetric bone densities as well as trabecular bone densities in the inner and outer areas using the aforementioned quantitative structural parameters. Relevant changes in these parameters during raloxifene therapy were documented in the nondominant radius and tibia under body weight load and annualized progression rates were calculated. Up to March 2010, and after the first control measurement, we found a significant increase in volumetric trabecular and cortical bone densities as well as in microarchitectural parameters represented by BV/TV and trabecular number in nearly all 15 postmenopausal women examined. Table 2 provides a summary of the changes.

During treatment with raloxifene, total density increased by 1.3% per year in the radius and by 2.1% per year in the tibia. This corresponds to 3.9% and 6.3% for 3 years, which correlates well with the increase of 2.7% over 3 years in lumbar vertebrae as measured in the MORE study (BMD measured using DXA). The overall increase in trabecular bone density of 2.9% was even greater, with increases in the inner areas of 6.0% per year in the radius and of 6.2% per year in the tibia. Trabecular bone loss in the inner areas is generally most pronounced and is the earliest that can be detected, akin to radius fractures in typical locations representing the earliest osteoporotic fractures. Cortical bone densities also increased by 1.1% in the radius and 0.7% in the tibia per year. With regard to the structural parameters responsible for 'bone quality', increases were noted primarily in the number of trabeculae (0.5% in the radius, 2.4% in the tibia) and BV/TV (3.0% in the radius, 3.7% in the tibia). Owing to the increase in the number of trabeculae, the average trabecular spacing declined by 0.2% (radius) and 2.2% (tibia), while average trabecular thickness increased by 4.2% (radius) and 1.8% (tibia). Cortical thickness also increased by 1.1% in the radius and 2.7% in the tibia.

Table 2. Overview of changes in bone densities/structures after an average of 15.1 months' treatment with raloxifene.

Bone densities/structures	Change per year (%)	
	Radius	*Tibia*
Total density vBMD	+1.3	+2.1
Trabecular density	+2.9	+3.9
Inner trabecular density	+6.0	+6.2
Cortical density	+1.1	+0.7
Trabecular bone volume BV/TV	+3.0	+3.7
Number of trabeculae	+0.5	+2.4
Average trabecular thickness	+4.2	+1.8
Average trabecular spacing	-0.2	-2.2
Cortical thickness	+1.1	+2.7

BV: Bone volume; TV: Total volume; vBMD: Volumetric bone mineral density.

As shown in our retrospective study, raloxifene increases trabecular and cortical bone densities as well as bone quality represented by a number of microarchitectural parameters. The data now emerging from an interim analysis of the ongoing prospective trial of raloxifene in postmenopausal osteoporotic and osteopenic women appear to confirm these retrospective findings. More detailed results of the first 15–20 patients who completed at least 1 year of therapy will be presented at the next European Calcified Tissue Society (ECTS) meeting in Glasgow, Scotland, in June 2010.

It must be noted that the data currently available from our prospective study do not show statistical significance due to the small patient sample. The data show a clear trend, however, and represent 'real-life' data obtained during daily practice. We acknowledge that double-blind, placebo-controlled randomized controlled trials are required to further clarify the effects of raloxifene on bone quality and whether this translates to a reduction in fracture risk.

In contrast to the simple measurement of BMD, HRpQCT provides insight into the structural changes that occur within the bone for the first time. Consequently, a range of sources of error to which conventional bone density measurements are subject is eliminated. HRpQCT also permits visualization of the bone parameters being measured. This makes truly individual diagnosis and follow-up possible, and provides clinical insight that far exceeds that possible with simple bone density measurements. Unfortunately, this highly sophisticated technology is available routinely in only a few places in Europe. In Germany, for example, there is one imaging unit in Munich and one in Hamburg.

Conclusion & future perspective

Despite their relatively similar benefit/risk profiles, the medications available for osteoporosis treatment with the highest level of evidence as per the current guidelines of the German Umbrella Association for Osteology are used very differently in practice. Currently, few patients with postmenopausal osteoporosis are receiving treatment with the SERM raloxifene, such that its

therapeutic potential is not being fully realized, even though its benefits in the prevention of osteoporotic vertebral fractures are well documented [15–17]. Furthermore, clinical studies with raloxifene have shown a significant reduction in the risk of estrogen receptor-positive breast carcinoma in postmenopausal women with osteoporosis [36–38].

The current one-sided focus on BMD measured by the DXA method to diagnose osteoporosis provides an explanation for the discrepancy between evidence and practice. In line with the current guidelines of the German Umbrella Association for Osteology [2], it is suggested that bone quality (in addition to BMD) needs to be

Executive summary

Introduction

- Osteoporosis is designated by the WHO as one of the ten most important diseases worldwide.
- Over the last decade, bone quality has largely superseded bone mineral density as the main criterion for defining the disease.

Clinical presentation of osteoporosis

- Loss of bone mass and increasing destruction of the bone microarchitecture lead to fractures of the vertebrae, hip and radius.
- Prevalence increases markedly with age, with women over 50 years at greatest risk of osteoporotic fractures.
- Vertebral fractures reduce life expectancy.

Options for treatment

- Goals of drug therapy for osteoporosis are fracture prevention and reduction in the risk of fractures.
- Irrespective of drug class, all currently approved medications (remodeling inhibitors, antiresorptives and/or osteoanabolics) elicit significant and relatively equivalent reductions in the risk of fractures.
- Raloxifene is currently the only selective estrogen receptor modulator approved for osteoporosis treatment.

Beyond bone mineral density

- Large differences (2.6–14.4%) in bone mineral density changes reported in approval studies for osteoporosis medications emphasize the need to look beyond bone density when postulating factors responsible for the reduction in fracture risk.

Quest for optimal individual therapy

- There is no simple solution as regards optimal therapy for osteoporosis, and it should be determined based on the needs of the individual patient.
- Current prescribing patterns suggest a large gap between clinical evidence and clinical practice.

Why the imbalance in prescription numbers?

- The imbalance in prescription numbers for the various osteoporosis medications cannot be explained by price or efficacy.
- Specifically, raloxifene is similar in cost and shows similar efficacy and equivalent or better safety to other approved osteoporosis medications, yet is relatively under-prescribed.
- Emerging evidence indicates that raloxifene may be useful as initial or follow-up therapy in a sequential treatment plan, and has positive effects on serum lipids and a reduced risk of breast cancer.

Effect of raloxifene on breast tissue

- The Multiple Outcomes of Raloxifene Evaluation (MORE), Continuing Outcomes Relevant to Evista® (CORE) and Study of Tamoxifen and Raloxifene (STAR) studies have documented significant reductions with raloxifene in the risk of estrogen receptor-positive breast carcinoma in postmenopausal women with osteoporosis.
- Inexplicably, these data have not been incorporated into the European approval of raloxifene.

'Bone quality' versus bone density

- Estimation of 'bone density' via dual x-ray absorptiometry is no longer considered to be an adequate method to diagnose osteoporosis.
- The newer definition of osteoporosis focuses on additional aspects such as trabecular microarchitecture, geometry, corticalis thickness and material properties, which are summarized under the term 'bone quality'.
- High-resolution peripheral quantitative computed tomography (HRpQCT) allows for 3D evaluation of bone microarchitecture destruction over time and represents a major advance in the diagnosis and ongoing treatment of osteoporosis.

Quantitative determination of 'bone quality' over disease course

- A retrospective analysis indicated that raloxifene produces an increase in trabecular and cortical bone densities and improves microarchitectural parameters.
- Interim results of a subsequent prospective study using HRpQCT to evaluate the effects of raloxifene on volumetric bone densities and microarchitectural parameters in postmenopausal osteoporotic and osteopenic women provide initial confirmation of these findings.
- HRqQCT permits actual visualization of the bone parameters being measured and provides genuine insight into the structural changes that occur within the bone for the first time.

Conclusion & future perspective

- Prescribing patterns for medications available to treat osteoporosis are not in line with their benefit/risk profiles.
- Specifically, the therapeutic potential of raloxifene is under-realized in view of its documented efficacy in preventing osteoporotic vertebral fractures and reducing the risk of estrogen receptor-positive breast carcinoma in postmenopausal women with osteoporosis.
- The ability to evaluate 'bone quality' by newer and highly sophisticated means such as HRpQCT may bring about an evidence-based improvement in the diagnosis and treatment of osteoporosis.

10.2217/IJR.10.33

taken into account and used to determine individually optimized and sustainable treatment of osteoporosis. Indications of such improvement in bone quality during treatment with raloxifene are provided by the author's present interim analysis of 15 postmenopausal patients (as of March 2010) who were examined at least twice with HRpQCT in a prospective study with a measurement interval of approximately 20 months [41]. Based on these early results, primarily younger postmenopausal women with osteoporosis would appear to be well-suited to treatment with raloxifene.

As HRpQCT technology continues to become more widespread in clinical practice, the ability to measure bone quality is expected to further advance the successful treatment of osteoporosis by allowing direct comparison of the efficacy of current and future medications in terms of bone fracture prevention and reduced risk of bone fracture disease.

Financial & competing interests disclosure

This article was financed by Daiichi Sankyo Europe GmbH. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. Medical writing assistance by Content Ed Net.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy: Osteoporosis prevention, diagnosis and therapy. *JAMA* 285(6), 785–795 (2001).

▪ **Presents scientific rationale for prevention, diagnosis and treatment of osteoporosis.**

2 DVO-Leitlinie 2009 zur Prophylaxe, Diagnostik und Therapie der Osteoporose bei Erwachsenen. *Osteologie* 18(4), 304–328 (2009).

▪▪ **New guidelines for the prevention, diagnosis and treatment of osteoporosis with medication.**

3 Consensus Development Statement, European Foundation of Osteoporosis and Bone Disease and the National Osteoporosis Foundation of the USA: Who are candidates for prevention and treatment for osteoporosis? *Osteoporos. Int.* 7(1), 1–6 (1997).

4 Melton LJ 3rd, Chrischilles EA, Cooper C, Kane AW, Riggs BL: Perspective. How many women have osteoporosis? *J. Bone Miner. Res.* 7(9), 1005–1010 (1992).

5 Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL: Bone density and fracture risk in men. *J. Bone Miner. Res.* 13(12), 1915–1923 (1998).

6 Kanis JA, Johnell O, Oden A *et al.*: Long-term risk of osteoporotic fracture in Malmö. *Osteoporos. Int.* 11(8), 669–674 (2000).

7 Johnell O, Kanis JA: An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos. Int.* 17(12), 1726–1733 (2006).

8 Kanis JA, Johnell O, De Leet C *et al.*: A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 35(2), 375–382 (2004).

9 Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR: Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch. Int. Med.* 159(11), 1215–1220 (1999).

10 Riggs BL, Hodgson SF, O'Fallon WM *et al.*: Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N. Engl. J. Med.* 322(12), 802–809 (1990).

▪ **Provides evidence that an increase in bone density with fluoride treatment does not correlate with reduced fracture rate.**

11 Black DM, Thompson DE, Bauer DC *et al.*: Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J. Clin. Endocrinol. Metab.* 85(11), 4118–4124 (2000).

12 Reginster JY, Minne HW, Sorensen OH *et al.*: Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos. Int.* 11(1), 83–91 (2000).

13 Chestnut CH III, Skag A, Christiensen C *et al.*: Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J. Bone Miner. Res.* 19(8), 1241–1249 (2004).

14 Black DM, Delmas PD, Eastell R *et al.*: Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* 356(18), 1809–1822 (2007).

15 Ettinger B, Black DM, Mitlak BH *et al.*: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 282(7), 637–645 (1999).

▪▪ **Pivotal clinical trial of raloxifene in the treatment of postmenopausal women with osteoporosis.**

16 Delmas PD, Ensrud KE, Adachi JD *et al.*: Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J. Clin. Endocrinol. Met.* 87(8), 3609–3617 (2002).

17 Delmas PD, Genant HK, Crans GG *et al.*: Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. *Bone* 33(4), 522–532 (2003).

18 Neer RM, Arnaud CD, Zanchetta JR *et al.*: Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N. Engl. J. Med.* 344(19), 1434–1441 (2001).

19 Greenspan SL, Bone HG, Ettinger MP *et al.*: Effect of recombinant human parathyroid hormone (1–84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis. *Ann. Intern. Med.* 146(5), 326–339 (2007).

20 Reginster JY, Seeman E, De Vernejoul MC *et al.*: Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study. *J. Clin. Endocrinol. Met.* 90(5), 2816–2822 (2005).

21 Meunier PJ, Roux C, Seeman E *et al.*: The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N. Engl. J. Med.* 350(5), 459–468 (2004).

22 Rossouw JE, Anderson GL, Prentice RL *et al.*: Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 288(3), 321–333 (2002).

23 Cauley JA, Robbins J, Chen Z *et al.*: Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 290(13), 1729–1738 (2003).

24 Seeman E: Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? *Bone* 41(3), 308–317 (2007).

25 Girotra M, Rubin MR, Bilezikian J: The use of parathyroid hormone in the treatment of osteoporosis. *Rev. Endocr. Metab. Disord.* 7(1–2), 113–121 (2006).

26 Boonen S: Addressing the age-related needs of osteoporotic patients with strontium ranelate. *Osteoporos. Int.* 21(Suppl. 2), S415–S423 (2010).

27 Häussler B, Gothe H, Mangiapane S, Glaeske G, Pientka L, Felenberg D: Outpatient care for osteoporosis patients in Germany. *Dtsch. Ärztebl.* 103(39), A2542–A2548 (2006).

▪▪ **Interesting study showing that prescribing patterns for osteoporosis medications in Germany fail to match clinical evidence of their benefit/risk.**

28 Winner SJ, Morgan CA, Evans JG: Perimenopausal risk of falling and incidence of distal forearm fracture. *BMJ* 298(6686), 1486–1488 (1989).

29 Fachinformation FOSAMAX. Summary of product characteristics. October 2008.

30 Ziller V, Gottschalk M, Hadji P: Möglichkeiten und Grenzen des Einsatzes von Raloxifen in Prävention und Therapie der postmenopausalen Osteoporose. *Journal für Menopause* 11(1), 30–35 (2004).

31 Evista® 60 mg, summary of product characteristics. Daiichi-Sankyo, Tokyo, Japan (2008).

32 Boonen S, Marin F, Obermayer-Pietsch B *et al.*: Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J. Clin. Endocrinol. Metab.* 93(3), 852–858 (2008).

33 Scharla S, Oertel H, Helsberg K, Kessler F, Langer F, Nickelsen T: Skeletal pain in postmenopausal women with osteoporosis: prevalence and course during raloxifene treatment in a prospective observational study of 6 months duration. *Curr. Med. Res. Opin.* 22(12), 2393–2402 (2006).

34 Barrett-Connor E, Grady D, Sashegyi A *et al.*: Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 287(7), 847–857 (2002).

35 Cummings SR, Eckert S, Krueger KA *et al.*: The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 281(23), 2189–2197 (1999).

36 Cauley JA, Norton L, Lippman ME *et al.*: Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res. Treat.* 65(2), 125–134 (2001).

37 Martino S, Cauley JA, Barrett-Connor E *et al.*: Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J. Natl. Cancer Inst.* 96(23), 1751–1761 (2004).

▪ **Presents 8-year results of the decreased risk of estrogen receptor-positive breast cancer with raloxifene in postmenopausal women with osteoporosis.**

38 Vogel VG, Costantino JP, Wickerham DL *et al.*: Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. *JAMA* 295(23), 2727–2741 (2006).

39 Pfeilschifter J: Guidelines for the management of osteoporosis. [Article in German]. *Internist (Berl.)* 49(10), 1178, 1180–1182, 1184–1185 (2008).

40 Radspieler H, Dambacher M, Neff M, Zulliger M: Raloxifene improves bone-densities and micro-architectural parameters (bone quality). *Bone* 44, S432 (2009).

▪▪ **Presents evidence of the beneficial effects of raloxifene on bone quality via a newer technique utilizing high-resolution peripheral quantitative computed tomography.**

41 Radspieler H, Dambacher MA, Neff M: Raloxifen und knochenqualität – eine prospektive anwendungsbeobachtung. Presented at: *Osteologie 2010*. Berlin, Germany, 3–6 March (2010) (Poster 127).

Website

101 International Osteoporosis Foundation: Facts and statistics about osteoporosis and its impact www.iofbonehealth.org/facts-and-statistics/references.html