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CROSSFIRE®

DEBATES, PEER EXCHANGE, AND INSIGHTS IN MEDICINE®

SPECIAL EDITION

Osteo-Opportunities

Steps Along the Path of Treatment

CME-Certified Activity

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1. c. “Bisphosphonates work by reducing the amount of bone turnover by direct effects on the activity of the osteoclasts, the cells in bone responsible for bone resorption,” explained Dr. Bilezikian. “As a result, with bone formation being allowed to continue, there is a net positive calcium balance in bone.” Parathyroid hormone works by stimulating bone turnover, which is a counterintuitive mechanism of action, he observed. “The beneficial way PTH seems to work is to primarily stimulate the osteoblasts the cells responsible for bone formation—in a way that allows bone formation to be stimulated preferentially over bone resorption.”

Locator: Background on Available Osteoporosis Therapies/Mechanisms of Action

2. d. PTH(1-34), which is the first 34 amino acid sequence of the full-length molecule, is believed to contain all the classical biological actions of parathyroid hormone. There are, however, other activities that have been attributed to the rest of the molecule, that is, the mid-portion and even the c-terminal portion of PTH. According to Dr. Bilezikian, there are theoretical reasons why one might think that there are distinctions between the PTH (1-34) and the full-length molecule human parathyroid hormone (1-84). “PTH(1-84) is likely to contain other actions. We do not know whether these actions are specifically related to the anabolic qualities of PTH, but they may be,” he noted. Although data from placebo-controlled trials of PTH(1-34) and PTH(1-84) indicate that the two agents are similar in efficacy, “no definitive conclusion can be drawn at this time as there are no head-to-head trials with meaningful endpoints—i.e., fracture—with these agents,” noted Dr. Watts.

Locator: Background on Available Osteoporosis Therapies/Mechanisms of Action

3. b. Although all three agents are equally effective in reducing the risk of vertebral fracture, evidence for nonvertebral-fracture risk reduction appears to be weakest for ibandronate. The panelists pointed out, however, that ibandronate appears to confer better nonvertebral-fracture risk reduction in the subgroup of patients with T-scores below -3.

Locator: Differentiating Currently Available Agents/Fracture Efficacy of the Bisphosphonates

4. c. “The data for PTH(1-84) clearly show a reduction in vertebral fractures but no reduction in nonvertebral fractures,” stated Dr. Bilezikian, noting that the study population in this trial was at much lower risk of fracture than the study population in the pivotal trial of PTH(1-34).

Locator: Differentiating Currently Available Agents/Fracture Efficacy of Parathyroid Hormones

5. d. Although PTH and the bisphosphonates achieve similar effects on bone density, PTH achieves better effects on bone microarchitecture and bone geometry, stated Dr. Bilezikian. “For the same bone density, [these two effects], from a biomechanical point of view, will strengthen bone,” he remarked. “It would seem that by virtue of these very important differences in how these drugs work, they cannot be considered to be similar.”

Locator: Differentiating Currently Available Agents/Fracture Efficacy of Parathyroid Hormones

6. a. “The main safety issues with respect to bisphosphonates relate primarily to upper gastrointestinal tolerability,” observed Dr. Black, who noted that this problem is much less common with the weekly and monthly—rather than daily—dosing regimens of bisphosphonates. Oversuppression of bone and osteonecrosis of the jaw may occur with the bisphosphonates but are very uncommon.

Locator: Differentiating Currently Available Agents/Issues of Safety and Tolerability

7. b. Noting that the forthcoming WHO paradigm will place previous fracture paramount to all other considerations, including low bone density by T-score, Dr. Bilezikian predicted, “Previous fracture is going to dominate our thinking. If the patient has had a previous fracture, you are going to treat.”

Locator: Therapeutic Strategies and Considerations/Guidelines in Clinical Practice

8. c. One study of secondary contributors found that 32% of postmenopausal women with osteoporosis had a previously undiagnosed disorder of bone and mineral metabolism, most frequently calcium metabolism disorder and hyperparathyroidism. Therefore, asserted Dr. Bilezikian, “Rather than just pulling a drug off a shelf for the patient with a low T-score, with or without risk factors, we should tailor the evaluation to rule out some of these other more common causes.”

Locator: Therapeutic Strategies and Considerations/Testing Prior to Therapy Initiation

9. d. “When teriparatide became available,” explained Dr. Bilezikian, “one attractive hypothesis was to use teriparatide and a bisphosphonate together, the thinking being that because the mechanisms of these two drugs were different sides of the bone turnover equation, the combination would be better than either one alone.” However, this hypothesis was disproved in the PaTH study, which determined that the concurrent use of a bisphosphonate actually reduced the anabolic effect of PTH. Based on this study, recommended Dr. Bilezikian, “One should choose monotherapy with teriparatide or with bisphosphonate” rather than a combination of the two.

Locator: Therapeutic Strategies and Considerations/Combination and Sequential Therapy/Combination Therapy

10. c. PTH is approved for only 18 to 24 months of use; however, bone density falls fairly dramatically when PTH is discontinued. Because the PaTH study showed that bisphosphonate therapy maintains bone density after PTH is discontinued, Dr. Bilezikian advised, “The standard of care seems to be that after using teriparatide one wants to follow it with bisphosphonate.”

Locator: Therapeutic Strategies and Considerations/Combination and Sequential Therapy/Sequential Therapy

Osteo-Opportunities

Steps Along the Path of Treatment

CME-Certified Activity



Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)–Center for Continuing and Outreach Education and *Medical Crossfire*®/Liberty Communications Network.



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Educational Overview

Antiresorptive and anabolic agents, the two main classes of drugs used by endocrinologists to manage osteoporosis, can be differentiated by their mechanisms of action. Bisphosphonates, the cornerstone of antiresorptive therapy, and the anabolic agents have been shown to be effective as monotherapy in increasing bone mass and reducing the risk of fracture. Emerging clinical data suggest that newer strategies which integrate both classes of agents may offer additional benefits, however how such strategies might be optimized in clinical practice remains to be defined.

Through debate and authoritative peer exchange, this *Medical Crossfire*® activity, conducted in conjunction with UMDNJ, will confront the opportunities and clinical challenges associated with the management of osteoporosis.

Target Audience

This educational activity is designed for endocrinologists and other health care professionals interested in or involved with managing patients with osteoporosis.

Learning Objectives

- Discuss commonly utilized treatment options for osteoporosis, with a focus on mechanism of action and physiologic effects of bisphosphonates and the parathyroid hormones.
- Differentiate these agents according to the benefits and risks associated with each using key clinical trial data.
- Consider potential algorithms that address initiation of therapy in treatment-naïve patients across the spectrum of disease.
- Discuss therapeutic strategies for the long-term management of patients with moderate and moderate-to-severe osteoporosis.

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions. The activity is complemented with references that contain the rationale for the correct answer to each question as well as a description identifying the section in the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding AMA/PRA category 1 credit three to four weeks after receipt of the registration and evaluation materials. Estimated time to complete this activity as designed is one (1) hour.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ–Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network. UMDNJ–Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

UMDNJ–Center for Continuing and Outreach Education designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Sunil Wimalawansa, MD, PhD, FRCP, DSc; Sheri Gillis Funderbark, MD; Syed Hasan, MD; and Gretchen Perilli, MD.

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Disclosure Declarations

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Faculty Disclosure Declarations

Dr. Black has received grant/research support from Novartis Pharmaceuticals Corp.; has been a consultant for NPS Pharma and Roche Laboratories; has served on the speakers' bureau of Merck & Co., Inc.; and has been a member of the scientific advisory boards of Novartis Pharmaceuticals Corp. and Roche Laboratories.

Dr. Bilezikian has received grant/research support from Procter & Gamble Pharmaceuticals and sanofi-aventis; and has been a consultant for Eli Lilly & Co., Merck & Co., Inc., NPS Pharma, Procter & Gamble Pharmaceuticals, sanofi-aventis and Roche Laboratories.

Dr. Salgo has no financial arrangements or affiliations to disclose.

Dr. Watts has received grant/research support through the University of Cincinnati from Amgen, Eli Lilly & Co., Merck & Co., Inc., Novartis Pharmaceuticals Corp., Procter & Gamble Pharmaceuticals, and sanofi-aventis; has been a consultant for Eli Lilly & Co., GlaxoSmithKline Pharmaceuticals, Merck & Co., Inc., Novartis Pharmaceuticals Corp., NPS Pharma, Procter & Gamble Pharmaceuticals, Roche Laboratories, sanofi-aventis, Servier, and Wyeth Pharmaceuticals; and has received honoraria for lectures from Merck & Co., Inc., NPS Pharma, Procter & Gamble Pharmaceuticals, Roche Laboratories, and sanofi-aventis.

Dr. Wimalawansa, Dr. Funderbark, Dr. Hasan, and Dr. Perilli have no financial arrangements or affiliations to disclose.

Off-Label Usage Disclosure

This activity contains discussion of unlabeled use of commercial products or non-FDA approved use of investigational agents. The prescription agent teriparatide is not approved for the prevention of osteoporosis in postmenopausal women. Parathyroid hormone (1-84) is under investigation for the treatment of osteoporosis in postmenopausal women.

Disclaimer

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that they are expressing the views of NPS Pharma, any other manufacturer of pharmaceuticals, UMDNJ, or *Medical Crossfire*/Liberty Communications Network.

It should be noted that the recommendations made herein, with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating panelists. The drug selection and dosage information provided in this activity are believed to be accurate. However, the participants are urged to consult the full prescribing information on any drug mentioned in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently prescribed.

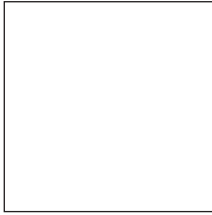
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Osteo-Opportunities

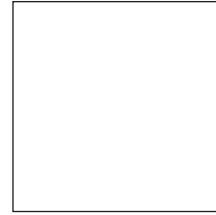
Steps Along the Path of Treatment

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Osteoporosis—once thought to be a natural process of aging—is now known to be largely preventable with the optimization of bone health. Unfortunately, 10 million American men and women already have osteoporosis, and another 18 million Americans have low bone mass that puts them at increased risk of developing this disorder.¹ For these patients, endocrinologists and other interested practitioners have access to two effective drug classes from which to choose: antiresorptive agents and anabolic agents. Both classes increase bone mass and reduce risk of fracture; the challenge for clinicians is choosing the right drug for the right patient while incorporating emerging data on combination and sequential therapy. In order to explore these and other issues associated with the field of bone health and osteoporosis, **Medical Crossfire** has convened a panel of national experts to lend their expertise and offer their insight.

Background on Available Osteoporosis Therapies

Mechanisms of Action

The two major classes of agents that are currently available for the treatment of osteoporosis are the antiresorptive agents, of which bisphosphonates are the most widely used; and the anabolic agents, which includes at this time only one approved agent, teriparatide or PTH(1-34).² “One can distinguish these two classes very clearly in terms of their mechanisms of action,” began John P. Bilezikian, MD. “The bisphosphonates reduce the level of bone turnover, a process by which the skeleton removes old bone and replaces it with new bone in discrete packets of space called bone remodeling units. In the adult, this natural process leads to bone loss over time because there is more bone loss than bone gain in each bone remodeling unit. Bisphosphonates work by reducing the amount of bone turnover by direct effects on the activity of the osteoclasts, the cells in bone responsible for bone resorption. Bone formation continues, albeit at a slower pace. The net effect on bone turnover is positive calcium balance in bone.

“The parathyroid hormone (PTH) class works in a completely different manner,” continued Dr. Bilezikian, “which is, in fact, to stimulate bone turnover. This may seem paradoxical, considering that I just said bone turnover generally leads to bone loss. The beneficial way in which the PTH class seems to work is primarily by stimulating the osteoblasts—the cells in bone responsible for bone formation—in a way that allows bone formation to be stimulated preferentially over bone resorption. Again, as with the bisphosphonates, net calcium balance ensues with the PTH class of moleculars, but their actions are directed at a different cell, by a different mechanism and, ultimately by actually stimulating formation of new bone.”

“So the PTH class seems relatively counterintuitive in its mechanism,” remarked Peter L. Salgo, MD, who served as moderator of this **Medical Crossfire**.

“That is correct,” confirmed Dr. Bilezikian.

Dr. Salgo noted that there are currently two PTH products, one that has been approved and one that is under review. “How can physicians differentiate between these two?” he asked. “How are they different?”

Reviewing the two existing PTH products, Dr. Bilezikian stated, “The agent that is currently available is known generically as teriparatide. This is PTH(1-34), which is the first 34 amino acid sequence of the full-length molecule. It is believed that PTH(1-34) contains all the classical biological actions of parathyroid hormone. I say classical because there are other activities that have been attributed to the rest of the molecule, that is, the mid-portion and even the c-terminal portion of PTH.”

“That brings us to the other PTH product, which is not yet approved but is in review at this time, and that is the full-length molecule human parathyroid hormone (1-84),” continued Dr. Bilezikian. “There are theoretical reasons why one might think that the two molecules can be distinguished from each other. As I said, PTH(1-84) may harbor other actions that are distinct from the activities resident in the teriparatide molecule. We do not know whether these actions, if indeed they exist, are specifically related to the anabolic qualities of PTH, but they may be. So, at the moment, the distinctions between these two agents are theoretical ones. Whether, in fact, they are going to be shown to be different by mechanism and by therapeutic action remains to be seen.”

“I agree with Dr. Bilezikian that the data are not fully in yet,” affirmed Dennis M. Black, PhD. “Studies have been done of each of the PTH agents versus placebo. In those studies, at the doses that were given, the two PTH agents appear relatively equally effective in terms of increasing bone mass, and increasing rates of bone formation and resorption. On a gross level they seem quite similar. In terms of efficacy, there does not seem to be much difference in the magnitude of effect between the two.”

“The problem, clinically, is that there are no head-to-head trials with meaningful endpoints—that is, fracture—with any of these agents,” asserted Nelson B. Watts, MD. “And, in some cases, the differences in char-

acteristics between patients in one trial or another are fairly subtle. In the case of the two PTH products, the characteristics of the study populations are quite different than those in the pivotal trials.^{3,4} That makes it even more difficult to draw judgments about comparability of effect. There is no reason, at this point, to believe that there is a major difference in efficacy between teriparatide and the full parathyroid hormone molecule. But we just do not have enough information to say, definitively, that there is not a difference.”

Effects on Bone Mineral Density

“It would seem to me that a fracture is a very late outcome,” remarked Dr. Salgo. “What effects do the bisphosphonates and the parathyroid hormones have on bone mineral density, Dr. Watts? And, incidentally, is bone mineral density a fair way to judge in the absence of fracture?”

“Let us start with your second question,” suggested Dr. Watts. “Bone mineral density turns out not to be the best way to judge the efficacy of any of these agents. It is quite clear for the antiresorptive drugs that regaining bone density accounts for a small proportion of the fracture risk reduction. In an analysis that I have done with risedronate, risk reduction was less than 20% for vertebral fractures and even smaller for nonvertebral fractures.⁵ The antiresorptive drugs work to reduce fracture risk through improving bone strength, working on properties that are not fully captured by measuring bone density with dual energy X-ray absorptiometry [DXA].

“There are not as much published data for teriparatide, and there are no data that I know of for the full-molecule parathyroid hormone,” continued Dr. Watts. The data that are available come from the pivotal trial of teriparatide in 1,637 postmenopausal women with prior vertebral fracture.⁶ “The researchers used two different doses of teriparatide, the 20-microgram dose that is currently on the market and a 40-microgram dose,” explained Dr. Watts. “And while bone

density went up 40% more on average with the higher dose than it did with the approved dose, reductions in fractures were relatively the same in both treatment groups. Subsequent analyses suggest that with teriparatide, the magnitude of gain in bone mineral density does not correlate with the fracture risk reduction.”

Therefore, cautioned Dr. Watts, although, “theoretically, it may be appealing to say, ‘Teriparatide increases bone density more than the antiresorptive agents,’ or ‘Antiresorptive agent A increases bone density more than antiresorptive agent B,’ we do not have the information to go any further. Bone density does not help in determining whether one agent is more effective than another for fracture reduction.”

Agreeing with Dr. Watts, Dr. Black added, “I would emphasize that there is also a fairly broad literature base within the anti-resorptive drugs showing that changes in bone density do not correlate perfectly with anti-fracture effects. There are a number of studies, for example, of alendronate in which the bone density effects in different populations are similar but the anti-fracture effects are different, particularly for nonvertebral fracture. It is true that bone density might be a rough guide, but it is definitely not very precise in terms of being able to differentiate one agent from another within classes or across classes in terms of bone-fracture efficacy.”

Differentiating Currently Available Agents

Fracture Efficacy of the Bisphosphonates

“There are currently three oral bisphosphonates available: alendronate, risedronate, and ibandronate,” reviewed Dr. Black. All three agents have been tested in placebo-controlled trials that provide data on fracture outcome.⁷⁻¹² “There are good data that all three agents reduce the risk of vertebral fracture,” he noted, “but in terms of nonvertebral

fractures, the story is a little more complex. Clearly, there are good data that among women with osteoporosis, alendronate and risedronate can reduce the risk of nonvertebral fractures as well as hip fractures, but the data for daily ibandronate did not show a reduction in nonvertebral fractures overall in the one published trial that is available, except in a subgroup of women with very low BMD.”

Dr. Black continued, “One of the complicating factors with bisphosphonates—Dr. Watts alluded to this in terms of PTH, but it is also true for bisphosphonates—is that the efficacy in reducing fractures, particularly nonvertebral fractures, seems to be a function of the population studied. In particular, the lower the patients’ bone density, the larger the percentage reduction generally seen for nonvertebral fractures. This has been shown in a number of studies of alendronate and was very evident in the recent ibandronate study.”^{7,10,12} In this study, he explained, there was no reduction in nonvertebral fracture overall; however, there was a reduction in nonvertebral fracture in the subgroup having a bone density T-score below -3. “Therefore, it is difficult to compare agents across the board,” he pointed out.

“I agree with everything that Dr. Black has said as far as the evidence that is available,” seconded Dr. Watts. “Another element that is important is the speed of onset of anti-fracture efficacy, which is difficult to delineate because the existing trials really were not designed to do so. But in post-hoc analyses, risedronate has been shown to reduce clinical vertebral fractures and nonvertebral fractures within twelve months, and alendronate has been shown to have an effect by twelve months. Speed of onset is another factor to consider when looking at the antifracture effect, not only the spectrum of data.” He added that there are also data indicative of hip fracture reduction efficacy for alendronate and risedronate, but not for ibandronate.¹³⁻¹⁶

“The issue of nonvertebral fracture is confounded by the different study popula-

tions,” commented Dr. Bilezikian, seeking to elaborate on a point made earlier by Dr. Black. “In the post-hoc analysis of ibandronate, the group of individuals whose T-scores in the femoral neck were less than -3 achieved an effect on nonvertebral fractures with the daily dose.” Another point that may differentiate among study populations is the baseline rate of fracture in the placebo groups, he observed, returning to the ibandronate study as an example. “The ibandronate study had a relatively low rate of baseline placebo fractures. Some people have argued that, on that basis, it would have been more difficult to show an effect as opposed to a higher rate of placebo fractures. This view is not universally accepted.”

Fracture Efficacy of Parathyroid Hormones

“Let us take a look at parathyroid hormone, both the full molecule, PTH(1-84), and the fragment, PTH(1-34),” suggested Dr. Salgo. “What effect do these hormones have on the risk of vertebral and nonvertebral fractures?”

“I will start with teriparatide, which is the one agent that has been approved and is available,” stated Dr. Bilezikian. Citing the pivotal trial of teriparatide published by Neer and associates,⁶ he noted, “The cohort in this study was a very-high-risk group” of postmenopausal women with prior vertebral fractures. “The average number of fractures per study patient was 2.3, and the T-scores were concomitantly very low,” he stated. New vertebral fractures occurred in 14% of women on placebo and 5% and 4%, respectively, of women on 20 micrograms and 40 micrograms of teriparatide. New nonvertebral fractures occurred in 6% of women on placebo and 3% and 3%, respectively, of women on 20 micrograms and 40 micrograms of teriparatide. In addition, teriparatide increased vertebral, femoral, and total-body bone mineral density as compared with placebo. “In this study, there clearly was an effect of teriparatide to reduce vertebral and

nonvertebral fractures,” commented Dr. Bilezikian. “One could not tease out the nonvertebral fractures in relation to hip and other fractures because of the relatively small numbers of patients, namely 1,637. But there is no doubt, based on these data, that teriparatide reduces both vertebral and nonvertebral fractures.”

Moving on to PTH(1-84), Dr. Bilezikian cited data from the TOP Study.¹⁷ “Again, we must be mindful of the fact that the study cohort in the TOP study of PTH(1-84)¹⁷ was very different than the cohort described in the teriparatide trial,” cautioned Dr. Bilezikian. “For example, the baseline number of fractures in the PTH(1-84) pivotal trial was 0.2, meaning that only about 19% of study patients had even one vertebral fracture. It is true that the T-scores were low, but nevertheless, this is not a group that was at the same high risk for fracture as was the teriparatide group.” Keeping this background in mind, however, “The data for PTH(1-84) clearly show a reduction in vertebral fractures, but in the Intention to Treat analysis there was no reduction in nonvertebral fractures,” he reviewed. “Again, one cannot say whether this means that there is an intrinsic difference between these two PTH products or whether the difference in outcomes in terms of nonvertebral fractures is due to the differences in the study populations.”

“I would like to add one thing,” requested Dr. Black. “It is intriguing to note the parallels between the PTH literature and the bisphosphonate literature in terms of nonvertebral fracture, in that there is a general trend toward the more severe population tending to show larger reductions in nonvertebral fractures. It may be something intrinsic to do with the population study.”

“That is true,” remarked Dr. Watts. “In the patient with more severe osteoporosis, first of all, it is easier to show a statistical significance. And while the absolute reduction is greater, the relative risk reduction with the available agents is often very similar, that is,

even in the lower risk versus higher risk population relative risk reductions are on the order of 30% to 50%.”

Dr. Black offered “a small point of disagreement. There are some data to suggest that the relative risk reduction for nonvertebral fractures tends to be larger in the populations with lower bone density.”

“It is difficult to make general statements about nonvertebral fracture reductions because there are so few studies that show nonvertebral fracture reduction,” commented Dr. Watts, who noted that his previous comments “mainly applied to vertebral fracture.”

“Am I being naïve to think that the full hormone—as secreted in the body—likely has functions we have not yet analyzed, functions that may provide better treatment in the long run?” inquired Dr. Salgo.

“That is very insightful,” complimented Dr. Bilezikian, stating that Dr. Salgo’s observation is something that “we have all wondered about. Why is PTH secreted by the parathyroid glands as an 84 amino acid protein when there is a smaller molecule, one that contains only 34 amino acid residues, that seems to do the trick as well? I come back to the notion that parathyroid hormone is likely to be a polyfunctional molecule. Is it polyfunctional by virtue of the activities contained in the primary sequence, or is it polyfunctional by virtue of the metabolism of the molecule as it is cleaved at various critical points to be released in forms that then have other actions on tissues? This is a very important but open question. You are correct, Dr. Salgo, to wonder whether PTH(1-84) has important functions that cannot be mimicked exclusively by PTH(1-34).”

“Could you compare the parathyroid hormones with the bisphosphonates in terms of their effectiveness?” requested Dr. Salgo.

Dr. Bilezikian first cautioned, “We cannot compare outcomes—not only between classes of these drugs but within classes—because head-to-head studies are not available.” Lacking definitive head-to-head data,

he continued, “It would appear that teriparatide reduces the incidence of vertebral and nonvertebral fractures to about the same degree as does the bisphosphonate class. However, because we do not have head-to-head data, it is treacherous even to reach that conclusion. It is also noteworthy, as a distinguishing point between these two classes of drugs, that anabolic agents are clearly improving bone strength in ways that are not mimicked by the antiresorptives, specifically the bisphosphonates.”

Two points are especially important in understanding the differing actions of the anabolics and the antiresorptives, continued Dr. Bilezikian. “One is the effect of the anabolic agents on microarchitecture. There now are abundant data for both teriparatide and the full molecule showing microarchitectural features of quality—for example, trabecular conductivity—that are improved. That is, the drugs seem to—if I could use the term *reconstruct*—reconstruct the deteriorated microarchitecture of the osteoporotic bone.” The second point that distinguishes the activity of the two classes, he explained, “comprises the effects on bone geometry within the PTH class. Accrual on bone occurs on the periosteal, whereas initially there may be resorption of endosteal bone. These actions of PTH will lead to an increase in cross-sectional diameter. For the same bone density, therefore, from a biomechanical point of view, bone is strengthened. It would seem,” concluded Dr. Bilezikian, “That by virtue of these very important differences in mechanism of action, antiresorptive and anabolic agents cannot be considered to be similar.”

Dr. Black provided an example to emphasize the points made by Dr. Bilezikian. “In the first PaTH study on which Dr. Bilezikian and I collaborated,¹⁸ we compared PTH(1-84) to alendronate over a one-year period. Similar effects were seen in bone density as measured by DXA, but quite different effects were seen when looking more specifically at cortical and trabecular bone. With

trabecular bone, for example, there was approximately a 30% increase with PTH(1-84), but only about a 6% increase with alendronate.^{18,19} So, despite similarities in terms of overall DXA bone mineral density, the effect within the specific compartments of the bone could be quite different.”

Issues of Safety and Tolerability

“Let us talk about safety and tolerability,” suggested Dr. Salgo. “When differentiating the bisphosphonates from each other and from the parathyroid hormones, what are the key issues to note?”

“The main safety issues with respect to bisphosphonates relate primarily to upper gastrointestinal [GI] tolerability,” replied Dr. Black, adding that this problem occurs particularly when bisphosphonates are used daily. “More recently, however, bisphosphonates have been used weekly for alendronate and risedronate and monthly for ibandronate,” he explained, “and in that context, as far as I can see, the safety issues in terms of upper GI effects are much less. In terms of safety, there are data on millions of women using these agents, and no important safety issues have been identified. There are some concerns now coming out in a very small portion of our patients in particular cases of very rare phenomena. But I do not believe any of these have been shown to be clinically important, especially for the oral bisphosphonates.”

“The clinical tolerability of the bisphosphonates is extremely good,” agreed Dr. Watts. “A small number of patients will have outlier problems, and a more substantial number—maybe 5% or so—will have trouble tolerating oral bisphosphonates.” The long-term extension of the Fracture Intervention Trial provides 10-year data with alendronate showing no significant long-term safety problems,²⁰ added Dr. Watts, and seven- to eight-year data with risedronate confirm the long-term safety of that agent.

Despite the positive safety profile of the bisphosphonates, Dr. Watts pointed to two

issues of concern. “One is the possibility of oversuppression of bone, something that has been speculated about for years with little evidence.” But one recently published paper has now reported severely suppressed bone turnover in nine patients who sustained non-spinal fractures while on long-term alendronate therapy.²¹ “These patients were treated for three years or longer, and most were given other agents—such as steroids or estrogen—that might have bone effects,” pointed out Dr. Watts. Six of the nine patients demonstrated delayed or absent fracture healing, and eight of the nine patients showed little or no bone turnover on biopsy. “While all nine patients were given alendronate, that does not mean that this is a problem for alendronate and not the other agents,” he noted.

The second concern, continued Dr. Watts, is osteonecrosis of the jaw, which has been reported in a small number of patients being treated for osteoporosis.²² “But, as Dr. Black has said, we have experience with millions of patients treated with these drugs, and only a handful of problems have been reported,” he emphasized. “The likelihood of a patient being treated for osteoporosis having either of these problems is very small.”

“In regard to osteonecrosis of the jaw, we hold a similar view,” remarked Dr. Black. “The FDA has now added a caution regarding osteonecrosis of the jaw with the bisphosphonates. However, the data are extremely uncertain—if present at all—with regard to their use for osteoporosis. If there is any relationship between osteonecrosis of the jaw and the bisphosphonates, it is derived almost exclusively from patients with metastatic bone disease in whom potent bisphosphonates are used intravenously in very frequent administration.”

Because of the strict usage requirements of bisphosphonates, suggested Dr. Salgo, these agents have acquired a reputation for being difficult. “But from what I hear from the experts on this panel, the bisphospho-

nates are fairly well tolerated. Dr. Bilezikian, is that a fair statement?”

“Yes,” confirmed Dr. Bilezikian, explaining that the strict prescribing approaches “are both to prevent GI effects and to maximize absorbability. The bisphosphonates are very poorly absorbed drugs even under optimal conditions, such as in a fasting state with a glass of plain water. Under these favorable conditions, one is absorbing, at most, 1% of the administered dose. Taken with food, juice, tea, or coffee, that small absorption percentage drops even further. With the weekly use of alendronate and risedronate, upper GI toxicity or irritability is much less commonly seen in comparison to when these two drugs were used in daily regimens.”

Seconding Dr. Bilezikian’s comments, Dr. Black advised, “It is always worth noting that the bisphosphonates, to retain their efficacy, need to be taken in a specific manner, which is on an empty stomach, remaining upright, with a full glass of water, 30 to 60 minutes before eating anything.”

Moving on to the safety of the PTH class, Dr. Bilezikian observed, “The safety issues with these agents are primarily related to a high blood or urine calcium, hypercalcemia or hypercalcuria, respectively. We have fairly good experience now in the real world—not just the clinical trial world—with regard to teriparatide. Hypercalcemia is very uncommon, and hypercalcuria is even more rare. When the clinician sees a small elevation in the serum calcium, typical advice would be to reduce the oral calcium supplement from, for example, 1 g to 500 mg. I tend to keep calcium supplements prescribed in patients on teriparatide to 500 mg. If hypercalcemia does occur, reduction of the supplemental calcium to 500 mg usually corrects the problem.”

Concerns about the development of osteosarcoma in rats treated with high doses of teriparatide for prolonged periods led the FDA to require a black-box warning, noted Dr. Bilezikian. However, no cases of osteosarcoma have been reported in more than 200,000 patients treated with teriparatide.²

In addition, pointed out Dr. Bilezikian, “The prolonged exposure periods in a rat’s life were 18 to 24 months, which would be equivalent to 75 years of exposure in a human. There is great uncertainty as to whether or not that rat toxicity has any relationship to human skeletal physiology, which is very different than that of the rat. My view is that this rat toxicity is not relevant to human subjects.”

Therapeutic Strategies and Considerations

Guidelines in Clinical Practice

“How do the National Osteoporosis Foundation [NOF] guidelines define treatment thresholds?” asked Dr. Salgo, shifting the discussion to focus on therapeutic decision-making. “Are these guidelines relevant to clinical practice, specifically with regard to the treatment of newly-diagnosed patients at various stages of disease?”

“The good news in the osteoporosis field is that we have drugs that reduce fracture risk within six to 12 months of starting therapy, which is an opportunity that is lacking in other ‘silent’ diseases,” began Dr. Watts. “One of the push-backs that I hear from some physicians is that we need to be more aggressive and treat patients in their 40s and 50s. My feeling, however, is that if we can predict a fracture 15 to 20 years in a patient’s future, we do not have to rush ahead with therapy; rather, we can wait until we get closer to the time when fractures are likely.”

Dr. Watts then addressed the NOF recommendations, which are summarized in **Table 1**.²³ “The guidelines recommend institution of pharmacologic therapy for patients with baseline T-scores of -2 or below in the absence of risk factors and -1.5 or below if risk factors are present.” However, he noted, “there is likely to be a paradigm shift in this strategy, as the World Health Organization [WHO] is working on a definition of absolute fracture risk that serves as a clinical

tool, allowing local governments or health authorities to set a threshold for intervention.” Dr. Watts stated his conviction that “the NOF criteria are a little aggressive. The National North American Menopause Society and the American Association of Clinical Endocrinologists have set a T-score threshold of -2.5 or below to treat in the absence of risk factors and higher levels in patients who do have risk factors.

“Certainly, in the -2.5 to -2 or below range of T-score, the risk of fracture is high,” continued Dr. Watts, “but other factors need to be considered.” Among the risk factors that predispose a patient to fracture are low bone mass, advancing age, frailty, low body weight, family history of osteoporosis, direction and type of fall, and, most importantly, presence of a previous fracture.²⁴ “One of the challenges in the field is that about half of the fractures that occur due to osteoporosis occur in patients who are above the -2.5 threshold,” pointed out Dr. Watts. “And we hope the new WHO calculation of absolute fracture risk will give us a way to more formally assess those who are above that threshold but who are at increased risk of fracture and would benefit from pharmacologic therapy.”

“I agree, Dr. Watts, we do have to get smarter with therapeutic decision making and not just treat a T-score,” affirmed Dr. Bilezikian. “As we now know, there are more patients who have osteoporotic fractures but do not have osteoporosis as defined by the T-score than do have osteoporosis as defined by the T-score. Clearly, patients who have a reduced bone density but who fail to meet the T-score definition of osteoporotic still may be at risk,” Dr. Bilezikian went on, offering that, “that ‘may be’ has to do with the other risk factors that Dr. Watts mentioned. The forthcoming WHO paradigm will allow us to define risk in much more specific ways than can be done by looking at the T-score alone. It is going to be a real advance in our decision making in terms of who should be treated.”

In the meantime, continued Dr. Bilezikian, the clinician should assess risk factors such as age and previous history of fracture when making treatment decisions. “For example, a 75-year-old woman whose T-score is -2 is clearly at much greater risk than a 60-year-old woman whose T-score is also -2 . One would be justified in being more proactive in the older woman. Another example would be previous fracture; a patient with a previous fracture and a T-score of -2.5 would be at much greater risk than a patient with the same T-score but no previous fracture.” Noting that the forthcoming WHO paradigm will regard previous fracture as paramount to all other considerations, including T-score, Dr. Bilezikian predicted, “Previous fracture is going to dominate our thinking. If the patient has had a previous fracture, you are going to treat.”

“That seems to be particularly true for previous vertebral fractures,” added Dr. Black. “In fact, there are some treatment guidelines

TABLE 1

National Osteoporosis Foundation’s Guidelines for Prevention and Treatment of Postmenopausal Osteoporosis

Who Should Be Treated?

- T-score below -2.0 with no risk factors
- T-score below -1.5 with 1+ risk factors
- Any spine or hip fracture

What Nonpharmacologic Interventions Should Be Used?

- 1,200 mg calcium daily
- 400–800 IU vitamin D daily
- Regular weight-bearing exercise

What Pharmacologic Interventions Should Be Used?

- Antiresorptive agents or anabolic agents

that suggest that a patient who has had a recent osteoporotic vertebral fracture should be treated regardless of their bone density.”

Testing Prior to Therapy Initiation

“What kind of testing, if any, needs to be done prior to the initiation of therapy?” asked Dr. Salgo.

“There is a differential diagnosis to almost all diseases or symptom complexes, and osteoporosis is no exception,” responded Dr. Bilezikian, who provided a typical clinical presentation. “When a postmenopausal woman who is estrogen deficient presents, we risk being too simplistic in our thinking, by saying, ‘She is postmenopausal, and she is estrogen deficient, what else would we expect?’ We might suspect, for example, other disorders: hyperparathyroidism, vitamin D deficiency, malignancy, hyperthyroidism, gluten enteropathy. There is a reasonable differential diagnosis.” Clarifying his position, Dr. Bilezikian stated, “I am not suggesting that every patient needs a full-blown workup for all the causes of osteoporosis, but a baseline workup is appropriate.”

Expanding on the measures to include in a baseline workup, Dr. Bilezikian offered, “I obtain a chemistry profile, which includes a serum calcium concentration. I also obtain a urinary calcium. Every patient needs a 25-hydroxy vitamin D measurement to ascertain the vitamin D status, because it is so often low in this country. It is debatable whether or not to measure endogenous PTH. This may not be considered within the primary investigation, but it becomes important to know after the initial set of data are available.” In general, he stated, he advises “a prudent workup that is not overly extensive but might identify a cause for the osteoporosis.”

In fact, noted Dr. Bilezikian, one study of secondary contributors found that 32% of postmenopausal women with osteoporosis had a previously undiagnosed disorder of bone and mineral metabolism, most frequently calcium metabolism disorder and

hyperparathyroidism. Furthermore, 85% of these secondary contributors were easily detectable through simple and inexpensive screening tests.²⁵ Therefore, asserted Dr. Bilezikian, “Rather than just pulling a drug off a shelf for the patient with a low T-score, with or without other risk factors, we should tailor the evaluation to rule out some of these other more common causes.”

“Yes, my approach to the differential diagnosis is exactly the same,” seconded Dr. Watts. “I feel very strongly that a minimum number of laboratory tests should be done prior to instituting therapy. Every week I see patients who have been on therapy for a year or two, have a bone density measurement, were being monitored, and had a decrease in bone density. These patients then come to me for evaluation and I find that they are vitamin D deficient or they have a calcium wasting problem, something that is easy to treat for pennies a day.” In scenarios like these, pointed out Dr. Watts, “The patient has spent a great deal of money on two years of therapy that did not do what we wanted it to because of an undiagnosed underlying disease.”

Setting Reasonable Expectations

“Let us say that you have done the correct testing, you have ruled out other diagnoses, and you have decided to treat with osteoporosis agents,” posited Dr. Salgo. “What are reasonable expectations for therapy? And, how is treatment failure defined?”

“This is an extremely difficult question because the obvious answers turn out to be oversimplifications,” asserted Dr. Watts. Offering an example to illustrate his point, he proposed, “Let’s say that a patient on therapy comes in with a new fracture; the obvious conclusion to draw is that the therapy failed. But the studies show 40% to 50% reduction in the risk of vertebral fractures and 80% to 90% reduction in the risk of multiple vertebral fractures. So when a patient who has been on treatment comes in with a new fracture, that is certainly regrettable, but my

response would be, in all likelihood, had that patient not been on treatment, she would have had a fracture sooner or would have had multiple fractures.”

Dr. Watts continued by offering that another example “would be the patient on treatment whose bone density has declined or whose bone turnover markers fail to go down.” But, as discussed previously in this *Medical Crossfire*, he noted, “The decrease in bone density turns out not to be a very good marker. On-treatment patients whose bone density stays the same with bisphosphonate have similar fracture reductions and similar low rates of fracture compared with patients whose bone density increases. A failure to increase bone density does not seem to be a mark of treatment failure.”

On the other hand, explained Dr. Watts, “Fracture risk is higher in patients whose bone density goes down on treatment than it is in patients whose bone density stays the same or goes up. In patients being treated with alendronate whose bone density decreases (at the bottom of the bell-shaped curve of BMD distribution for the treatment group), fracture rates are lower compared with patients in the placebo group whose bone density decreases proportionately (i.e., at the bottom of the bell-shaped curve of BMD distribution for the placebo group).”²⁶⁻²⁸

“It is worth noting, as we pointed out earlier, the deficiencies of the bone density test in the monitoring of patients,” suggested Dr. Bilezikian. “However, we are also aware of the fact that it does have a utility. As Dr. Watts mentioned, we are looking for patients to maintain their bone density; we do not want our patients to lose bone mass. The bone density test is helpful because it may define issues of compliance. The patient may be not taking their therapy, or may not be taking their treatment properly. The patient may have become vitamin D deficient. I do believe that bone density testing does have good utility as a monitoring tool. In my view, we have to educate ourselves and our patients against the notion that if the bone

density does not go up they must not be doing well on treatment. We want patients to maintain bone density; perhaps it will go up, but we certainly do not want it to go down.”

Assuming that all explanations besides treatment failure have been ruled out, proposed Dr. Salgo, “How do you adjust your therapy if you are not getting adequate results?”

Reiterating Dr. Watts’ point that an on-treatment fracture does not necessarily indicate complete treatment failure, Dr. Bilezikian stated, “For the patient, there is a practical bottom line. If the patient has fractured on therapy, it is, in a way, a failure, and we do have to adjust or change our therapy.” In his view, stated Dr. Bilezikian, it “makes almost no sense” to switch a patient who has fractured while on a bisphosphonate to another bisphosphonate. “But would it be reasonable to switch that patient to an anabolic like teriparatide?” he asked rhetorically. “It would depend on the patient, but there are circumstances in which one would consider that to be an appropriate course.”

“I agree with my fellow panelists that it is very hard to define what we mean by ‘treatment failure,’ ” noted Dr. Black. “But clearly, a patient who continues to fracture, has multiple fractures, or is losing a substantial amount of bone density—3%, 4%, or 5% per year—is not doing well on that therapy and would be a candidate for a change of therapy.”

“If the clinician is comfortable in saying, ‘This patient has not responded as well as I would like,’ then it does make sense to change,” agreed Dr. Watts, who suggested, “There may be room for the off-label use of intravenous bisphosphonates in patients who are losing ground with an oral drug because they are not taking it correctly or absorbing it adequately. I do look at bone turnover markers as a way of helping me decide which direction to go.” As for those patients who might benefit from a switch to an anabolic agent, Dr. Watts suggested, “A patient who has been on an antiresorptive agent, a bisphosphonate, who is fracturing, or whose bone density is declining despite bone-

turnover markers suggesting that their bone turnover is being adequately restrained by antiresorptive drug, is a patient whom I would consider to be a candidate for a change to anabolic agents.”

Combination and Sequential Therapy

“Let us take a look at the role of combination therapy and the strategies for sequential therapy in patients with moderate and moderate-to-severe disease,” proposed Dr. Salgo.

Noting the complexity of Dr. Salgo’s question, Dr. Bilezikian suggested dividing the answers into three issues: combination therapy; sequential therapy in the patient started on an anabolic; and sequential therapy in the patient started on bisphosphonate.

Combination Therapy. “Let’s first take the issue of combination therapy,” began Dr. Bilezikian. “When teriparatide became available, one attractive hypothesis was to use teriparatide and a bisphosphonate together, the thinking being that because the mechanisms of these two drugs were different sides of the bone turnover equation, the combination would be better than either one alone.”

This hypothesis was explored in two papers appearing in the same issue of *The New England Journal of Medicine*, noted Dr. Bilezikian. The first, by the PaTH study investigators (including Dr. Bilezikian and Dr. Black), examined the efficacy of PTH(1-84), alendronate, or the combination in women with postmenopausal osteoporosis.¹⁸ The second, by Finkelstein and associates, compared the effects of teriparatide, or PTH(1-34), alendronate, or the combination in men with low bone mineral density.²⁹

The PaTH study was conducted in 238 postmenopausal women who were not using bisphosphonates. The women had low bone mineral density at the hip or spine (a T-score less than -2.5 or a T-score less than -2.0 with an additional risk factor for osteoporosis) and were randomized to receive daily treatment with PTH(1-84), alendronate, or the

combination. After 12 months of follow-up, noted Dr. Bilezikian, “We were able to show—perhaps surprisingly—by the use of parameters of bone turnover and, more importantly, bone density by both DXA and computed tomography that the use of PTH(1-84) alone seemed to confer as good or better effects than in combination with bisphosphonate.”^{19, 20}

There was no evidence of synergy between the two agents; in fact, wrote the investigators, changes in the volumetric density of trabecular bone, the cortical volume at the hip, and levels of markers of bone turnover appeared to suggest that the concurrent use of a bisphosphonate actually reduced the anabolic effect of PTH(1-84). Similar results were seen in the Finkelstein et al study of 83 men with osteoporosis randomized to teriparatide, alendronate, or the combination: the bisphosphonate appeared to impair the ability of teriparatide to increase bone mineral density. “It seems, at this point,” recommended Dr. Bilezikian, “that one should choose monotherapy with teriparatide or with bisphosphonate” rather than a combination of the two.

Sequential Therapy. Dr. Bilezikian then turned his attention to sequential therapy. “Teriparatide is a drug that the FDA has advised to be used for only 18 to 24 months. And so the question becomes, after two years of this therapy what do you do next?” This question is especially critical, he explained, because “several observational studies³⁰⁻³³ have suggested that if PTH(1-84) or teriparatide is followed by no specific pharmacological therapy then bone density falls fairly dramatically.”

Therefore, the PaTH study investigators designed a continuation of the combination-therapy trial¹⁸ to prospectively address this issue in the same study population.¹⁹ Women who had received PTH(1-84) monotherapy in the combination trial were randomized to an additional year of treatment with either placebo (60 women) or alendronate (59

women); women who had received alendronate monotherapy or combination therapy also received alendronate for an additional year. “We showed that if a bisphosphonate is not used after PTH(1-84), bone density does in fact fall dramatically; but when bisphosphonate is used after PTH(1-84), it does not,” explained Dr. Bilezikian. “Therefore, the standard of care seems to be that after using an anabolic one wants to follow it with bisphosphonate.”

The reverse situation entails a patient who has been on a bisphosphonate and is now considered to be a candidate for the PTH class, continued Dr. Bilezikian. “There are now data to suggest that the potent bisphosphonates—mainly those that significantly reduce bone turnover—may be associated with a lag in the ability of the body to respond to the PTH class in terms of changes in bone turnover and bone density. I believe that is a function of the level of bone turnover: the lower the bone turnover at the time the PTH is started, the slower the response will be.” Despite the lag time, pointed out Dr. Bilezikian, “the patient will respond eventually, within six months. So this is not a major issue, and the clinician could choose to start the PTH class immediately after bisphosphonate therapy or to wait six months for bone turnover markers to go up before initiating therapy.” Dr. Bilezikian noted that this problem is more often associated with alendronate, due to its greater suppression of bone turnover, than with risedronate. “I would expect the PTH class to act quickly in those patients who have previously been treated with risedronate,” he posited.

“There is actually an ongoing study about that specific question, comparing previous usage of alendronate versus risedronate and the subsequent response to teriparatide,” remarked Dr. Black. “There are no data at the moment, but I agree with Dr. Bilezikian that the delay is likely to be less with risedronate than with alendronate.”

Designing Therapy for Treatment-Naïve Patients

Dr. Salgo asked the panelists to address strategies for treatment-naïve patients. “The patient has not had a fracture yet, but there are other indications that she has moderate-to-severe disease. Would you use monotherapy? Would you use sequential therapy? How do you go about deciding on a therapeutic approach?”

“As Dr. Bilezikian suggested, based on the PaTH¹⁸ and Finkelstein et al²⁹ studies of combination therapy, if one is going to use the PTH class in a treatment-naïve patient, it is likely better not to do it in combination,” advised Dr. Black. “Therefore, this question really comes down to which patients should receive bisphosphonates and which patients should receive a parathyroid hormone as first-line therapy. As a general rule, you would consider teriparatide as a first-line therapy in a patient who has very severe disease, perhaps multiple vertebral fractures as well as low bone density. The primary reasons for limiting the PTH class to this population are the cost and the need for self-injection.”

“I agree, Dr. Black,” seconded Dr. Bilezikian. “In fact, the FDA has described the indications for teriparatide in these patients with advanced osteoporosis at high risk for fracture. Most of us, as Dr. Black has noted, think of teriparatide in terms of patients who have fairly advanced disease with multiple fractures because it is an injectable daily treatment that is very expensive. Therefore, we have tended to reserve this particular therapy for those very severely evolved patients. For the others, of course, we have bisphosphonates. However, this pattern of usage may begin to change as we continue to study parathyroid hormone in lower risk populations. For example, the recent NPS trial of PTH(1-84) was the first trial of an anabolic agent to include women without existing vertebral fractures and showed that first fractures could be prevented with PTH(1-84).”

Dr. Bilezikian then offered to play devil’s advocate and present a counterargument.

“The classic clinical trials with alendronate and risedronate also involved patients very significantly affected by osteoporosis. The bisphosphonates worked; certainly, alendronate and risedronate proved very efficacious.” Therefore, bisphosphonates may also be appropriate for severely affected patients.

Agreeing with Dr. Bilezikian, Dr. Watts elaborated, “There are no clear guidelines because, as mentioned earlier in this *Medical Crossfire*, we do not have the data from head-to-head trials to tell us which of these agents would be best for an individual patient.” Speculating that these data will be available in the next five to 10 years, Dr. Watts posited that the optimal drug choice for the treatment-naïve patient is currently a matter of individual opinion. “When I am discussing the options with a patient who is on the borderline, I explain it like this: If there were a convention of osteoporosis experts in town and they were presented with your case, the majority would probably be inclined to one treatment or the other, but there would never be unanimity—or even consensus.”

Final Thoughts

“Today, we have agents that are effective in reducing the risk of nonvertebral and vertebral fractures, and this is a considerable change from only 10 years ago, when we had no tools to help our patients with osteoporosis,” observed Dr. Black in formulating the first take-away message from this *Medical Crossfire*. “Now there are a number of agents to choose from, agents that are particularly effective in reducing nonvertebral and hip fractures in patients at high risk of fracture.” Dr. Black concluded with an urgent reminder for his fellow practitioners: “Regardless of whether a patient is older or at higher risk, it is never too late to begin therapy.”

In his concluding message, Dr. Watts first succinctly covered several essential points. “We have drugs that are proven to reduce fracture risk, but we need to draw evidence from clinical trials to get a sense of the spectrum of anti-fracture efficacy and the speed of onset to be able to pick the best drugs. In addition, we really do not have good clinical tools in individual patients or even in clinical trials to substitute for fracture reduction. And while we can use bone density to monitor patients on treatment, we should not over-interpret small changes or lack of change as an indication of treatment failure.”

Dr. Watts focused his final message upon therapeutic options and decision-making. “It is nice to have drugs with different mechanisms of action so that if patients do not seem to be getting an optimal response from one drug we can change to another,” he observed. “We need to emphasize the need for sequential therapy, something following the PTH class. I do have patients who say, ‘If I stay on this drug for one or two years, then I will be fine.’ My answer is, ‘No, you will need to be on some type of medication long term.’ If a patient has two years of teriparatide or parathyroid hormone, she probably will need to be on a bisphosphonate after that.”

To conclude this *Medical Crossfire*, Dr. Bilezikian addressed “a crying need” in the field of osteoporosis: recognition and diagnosis. “We have a big challenge in this country to identify individuals who need to be treated for osteoporosis. We have very effective treatments for osteoporosis, but we first have to find the individuals who will benefit from these treatments. With the increasing number of agents becoming available, I look forward to a time when we will be able to tailor our drug choices to the particular patient, with the endpoint being a clear opportunity to reduce the incidence of vertebral and nonvertebral fractures.” ■

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Osteo-Opportunities

Steps Along the Path of Treatment

CME Test

- Which of the following statements best characterizes the primary mechanisms of action of the bisphosphonates and parathyroid hormone?
 - They both suppress bone turnover.
 - They both stimulate bone turnover.
 - Bisphosphonates suppress bone turnover, whereas parathyroid hormones stimulate bone turnover.
 - Parathyroid hormones suppress bone turnover, whereas bisphosphonates stimulate bone turnover.
- Which of the following statements does not accurately describe PTH (1-34) and/or PTH (1-84)?
 - PTH (1-34) contains all of the classical anabolic action of parathyroid hormone.
 - The full length molecule PTH (1-84) may contain additional anabolic activity not provided by the fragment.
 - Lack of head-to-head clinical trials with fracture reduction as an endpoint makes it difficult to draw definitive conclusions about the comparative clinical efficacy of PTH (1-34) and PTH (1-84).
 - All of the above statements describe these agents.
- Evidence for overall risk reduction in nonvertebral fracture appears to be weakest for which of the available bisphosphonates?
 - alendronate
 - ibandronate
 - risedronate
 - The three agents are equally effective.
- Which of the following statements accurately describes the fracture-outcome results of the pivotal trial of PTH(1-84)?
 - Risk reduction was seen in both vertebral and nonvertebral fractures.
 - Risk reduction was seen in neither vertebral nor nonvertebral fractures.
 - Risk reduction was seen in vertebral but not nonvertebral fractures.
 - Risk reduction was seen in nonvertebral but not vertebral fractures.
- The anabolic agents (e.g., PTH) appear to confer more favorable antiosteoporotic effects than the antiresorptive agents (e.g., bisphosphonates) on
 - bone microarchitecture.
 - bone geometry.
 - bone density.
 - Both a and b.
- What is the most commonly anticipated safety issue with the use of bisphosphonates?
 - upper gastrointestinal tolerability
 - oversuppression of bone
 - osteonecrosis of the jaw
 - hypercalcemia and hypercalcuria
- According to the expert panel, it is predicted that the most important of the risk factors predisposing to fracture will be found to be
 - low bone density.
 - previous fracture.
 - advanced age.
 - frailty.
- What proportion of postmenopausal women with osteoporosis may have an undiagnosed secondary contributing cause?
 - one-fifth
 - one-quarter
 - one-third
 - one-half
- Which of the following statements best describes the results of combination therapy with bisphosphonates and PTH?
 - There is a synergistic effect resulting in significantly improved fracture outcomes.
 - There is a synergistic effect resulting in modestly improved fracture outcomes.
 - The concurrent use of PTH reduces the antiresorptive effect of bisphosphonates.
 - The concurrent use of a bisphosphonate reduces the anabolic effect of PTH.
- According to a recently published study, what is the best course of action for the patient who has completed 18 to 24 months of therapy with PTH?
 - No further therapy is required.
 - Perform a bone density tests to determine if the patient is a candidate for an additional course of PTH.
 - Follow with bisphosphonate therapy.
 - The best course of action has yet to be determined.

University of Medicine & Dentistry of New Jersey
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Osteo-Opportunities

Steps Along the Path of Treatment

Registration Form

In order to obtain AMA/PRA category 1 credit(s), participants are required to:

1. Read the learning objectives, review the activity, and complete the self-assessment test.
2. Complete both the activity registration and evaluation forms, and record your answers in the box below.
3. Send the activity registration and evaluation forms to:

UMDNJ—Center for Continuing and Outreach Education
via mail: PO Box 1709, Newark, NJ 07101-1709 or via fax: (973) 972-7128

Self-Assessment Test

Circle the best answer for each question on the CME test.

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | A | B | C | D | 6. | A | B | C | D |
| 2. | A | B | C | D | 7. | A | B | C | D |
| 3. | A | B | C | D | 8. | A | B | C | D |
| 4. | A | B | C | D | 9. | A | B | C | D |
| 5. | A | B | C | D | 10. | A | B | C | D |

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I certify that I have completed the “Osteo-Opportunities: Steps Along the Path of Treatment” activity as designed and I am claiming [up to one (1) credit] _____ AMA/PRA category 1 credit(s).

Signature _____

Date _____

A continuing education credit letter will be mailed to you within 3 to 4 weeks.

Credit for this activity is available until March 31, 2007.

UMDNJ—Center for Continuing and Outreach Education, PO Box 1709, Newark, NJ 07101-1709
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Steps Along the Path of Treatment

Activity Evaluation Form

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters will be issued only upon receipt of a completed evaluation form. Thank you for your cooperation!

Program Objectives

Having completed this activity, are you better able to:

	Strongly Agree				Strongly Disagree
Discuss commonly utilized treatment options for osteoporosis, with a focus on mechanism of action and physiologic effects of bisphosphonates and the parathyroid hormones.	5	4	3	2	1
Differentiate these agents according to the benefits and risks associated with each using key clinical trial data.	5	4	3	2	1
Consider potential algorithms that address initiation of therapy in treatment-naive patients across the spectrum of disease.	5	4	3	2	1
Discuss therapeutic strategies for the long-term management of patients with moderate and moderate-to-severe osteoporosis.	5	4	3	2	1

Overall Evaluation

	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The activity was educationally sound and scientifically balanced.	5	4	3	2	1
The activity avoided commercial bias or influence.	5	4	3	2	1
Overall, the activity met my expectations.	5	4	3	2	1
I would recommend this activity to my colleagues.	5	4	3	2	1

Based on information presented in the program, I will (check one):

- Do nothing, as the content was not convincing. Change my practice.
- Seek additional information on this topic. Do nothing, as current practice reflects program's recommendations.

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.

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