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Postmenopausal Osteoporosis: Managing Patients at High Risk for Fracture

Announcer:

Welcome to ReachMD. This medical industry feature, titled “*Postmenopausal Osteoporosis: Managing Patients at High Risk for Fracture*” is sponsored by Radius Health, Incorporated. This program is intended for US physicians.

See the full prescribing information including Boxed Warning for TYMLOS at www.tymlospi.com.

Dr. David Dempster, is a paid consultant for Radius Health, Inc.

Dr. Dempster:

Hello, my name is Dr. David Dempster, and I am a professor of clinical pathology at Columbia University in New York. We will be taking a look at *Postmenopausal Osteoporosis, Past and Present, and Managing Patients at High Risk for Fracture*.

Imagine a postmenopausal woman experiences chest pain with radiation to the jaw and/or arm. Understanding that these are common warning signs of a heart attack, her family instantly calls her doctor, who urges them to go immediately to the hospital. She is promptly attended to, diagnosed with an underlying cardiovascular condition, and counseled to manage risk factors, and before even leaving the hospital, she is put on treatment.

Now, imagine a postmenopausal woman sneezes and then experiences pain in the middle of her back. The patient is sent to the ER and found to have a spinal fracture. While the severity may be less imminent, the subsequent sequence of events is important. She may not realize she is at high risk for more fractures to come. She is unlikely to see a specialist and would probably not be either diagnosed or treated for her underlying postmenopausal osteoporosis, based on currently available data. Just as a heart attack is an urgent indicator of heart disease, and immediate management of the underlying disease is critical, a fragility fracture in the postmenopausal woman signals that she may have underlying postmenopausal osteoporosis, and there should be urgency to treat the disease. We don't ignore the symptoms of a heart attack, so why do we often ignore a sign of postmenopausal osteoporosis, a fragility fracture?

The goal of this presentation is to share some historical perspectives on postmenopausal osteoporosis, and information about a treatment option for those patients with postmenopausal osteoporosis at high risk for fracture.

Before we continue, I wanted to let you know the following: I am a paid speaker for Radius Health, Inc. This is not a CME presentation, and I am presenting information that is consistent with the FDA approved package insert for TYMLOS.

The product that I will be discussing is TYMLOS. TYMLOS is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, TYMLOS reduces the risk of vertebral fractures and nonvertebral fractures. It does have a limitation of use to consider.

Because of the unknown relevance of the rodent osteosarcoma findings to humans, cumulative use of TYMLOS and parathyroid hormone analogs, for example teriparatide, for more than two years during a patient's lifetime is not recommended.

TYMLOS does have a warning for risk of osteosarcoma. Abaloparatide caused a dose-dependent increase in the instance of osteosarcoma, which is a malignant bone tumor, in male and female rats. The effect was observed at systemic exposures to abaloparatide ranging from four to twenty times the exposure in humans receiving the 80-microgram dose. It is unknown if TYMLOS will cause osteosarcoma in humans.

The use of TYMLOS is not recommended in patients at increased risk of osteosarcoma, including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation involving the skeleton.

Now, let's go a little into the past. Although osteoporosis had been identified in 4,000-year-old Egyptian mummies, with the telltale dowager's hump, it took centuries to give the disease a name and discover its postmenopausal origins.

In 1822, Sir Astley Paston Cooper, a British surgeon and anatomist, commented on an observed association between abnormal bones and fractures. The French pathologist, Jean Lobstein, first coined the term osteoporosis, or porous bone, in the 1830's after observing that some patients' bones were riddled with larger-than-normal holes. About a hundred years later, in the 1930's and 1940's, Fuller Albright, an American endocrinologist, discovered the link between estrogen loss after menopause and osteoporosis in women, noting its association with vertebral fractures. With this discovery, Albright renamed what had previously been described as idiopathic osteoporosis, or osteoporosis of unknown origin, to what we currently understand as postmenopausal osteoporosis. These findings were the basis for defining postmenopausal osteoporosis and establishing a link between postmenopausal osteoporosis and fractures.

More recently, the abilities to recognize and characterize postmenopausal osteoporosis has also changed. Throughout the 1960's and 1970's, osteoporosis was characterized as highly viable, and the only time when osteoporosis could be confidently detected was after a fracture, such as fragility fractures in the spine or some other bone, as a result of minor trauma.

The introduction of dual X-ray absorptiometry, or DEXA, in 1987 allowed physicians to readily measure bone mineral density, or BMD, in routine clinical practice. The statistical approach to evaluating risk for osteoporosis based on BMD had been pioneered by Norton in the 1970's and 1980's, intended at the time to evaluate risk for fractures through a practical measure. His concepts took into account that the apparent risk for fracture would increase when bone density fell below a critical fracture threshold, determined from a normal distribution of bone density in a healthy population.

In 1994, the World Health Organization operationally defined osteoporosis as a BMD T-score, measured with DEXA, of less than -2.5, or two and a half standard deviations below the mean for young, healthy women. In 2001, the National Institutes of Health Consensus Development Panel On Osteoporosis issued a consensus definition of osteoporosis.

Osteoporosis is defined as a skeletal disorder, characterized by compromised bone strength, predisposing a person to an increased risk of fracture. Notably, changes in bone strength are only partly accounted for by BMD, and the BMD-based definition of osteoporosis does not account for other factors that contribute to bone quality.

Failing to recognize a fragility fracture in a postmenopausal patient as a sign of postmenopausal osteoporosis is like ignoring the obvious. If you saw smoke coming out from under the hood of your car, you wouldn't ignore the engine just because the check engine light didn't turn on. Just as the check engine light in a vehicle is an easy-to-observe sign for a problem with your engine, raw BMD is an easy-to-measure risk factor for a problem with your patient's bones.

But BMD doesn't tell the whole story. Both fragility fracture and BMD can be utilized to recognize the underlying postmenopausal osteoporosis in a patient. It's important to reiterate this message because fragility fractures can occur in postmenopausal women without BMD T-scores indicative of osteoporosis.

A 2004 study using data from the National Osteoporosis Risk Assessment, or NORA, examined the relationship between different T-scores on fracture instance and the number of white postmenopausal women with fractures, within the year following BMD measurement. Fracture rates, that is the number of women who fractured per thousand person years, were highest among postmenopausal women with the lowest T-scores. Additional studies have reported similar findings. For instance, Wainwright, et al. reported that more than half of women with an instant hip fracture did not have hip osteoporosis defined by a total hip BMD T-score less than -2.5. Nevertheless, among participants with BMD above the criteria used to define osteoporosis, several characteristics increased fracture risk, including advancing age, lack of exercise in the last year, reduced visual contrast sensitivity, falls in the last year, prevalent vertebral fracture and lower total hip BMD. As a reminder, TYMLOS is only indicated for postmenopausal women with osteoporosis at high risk for fracture.

So, what other factors contribute to the bone fragility that results in these fractures, other than low BMD? The quality of the bone structure, though something we cannot measure as readily, also contributes to bone strength. The structure of trabecular bone helps the skeleton stay lightweight, yet strong. When Gustav Eiffel designs the crisscrossing beams that shape the Eiffel Tower, which enable the structure to withstand its weight, yet rise high above the other Parisian landmarks, he was inspired by the microarchitecture of trabecular bone. Like a building without support beams, bone with thin cortices and poor microstructure may easily crack or collapse. Although diminished bone strength, which is only partially accounted for by BMD, predisposes patients to fracture, and fracture itself is a well-recognized risk factor for future fractures to come, many postmenopausal patients with a fragility fracture do not receive an

osteoporosis diagnosis.

In an observational cross-sectional study at one university medical center, in which an automated alert was integrated into the electronic medical record to identify patients with a fragility fracture, the results revealed that many patients with fragility fractures do not receive a diagnosis of osteoporosis. Approximately 67% of 143 patients with a historical fragility fracture had undiagnosed osteoporosis. Approximately 84% of 80 patients with a new, or first, fragility fracture had undiagnosed osteoporosis. The data in this study reflect a single institution, with a small total population of fracture patients. And this is within the year following a fracture – a critical intervention period. A prompt diagnosis of postmenopausal osteoporosis is important to help patients receive appropriate care, because the risk for additional fractures is high, particularly in the first few years post-initial fracture. A study that evaluated the time that elapsed between a first and subsequent clinical vertebral or nonvertebral fracture, in a population of postmenopausal women, found that of the 924 women with an initial fracture, 243 – that's 26.3% – sustained a subsequent fracture. 54.3% of subsequent fractures occurred within five years after the first fracture, and 23% occurred within the first year. 31.3% fractured during years 2-5, 25.9% fractured during years 6-10, 11.5% during years 11-15, and 3.7% during years 16-20.

The high immediate risk for fracture in this underdiagnosed patient population would suggest an urgency to test for and treat postmenopausal osteoporosis after a fracture. Yet, overall rates of testing and treatment after a fracture are low, suggesting that only approximately 30-40% of women with a fracture received either BMD testing or pharmacotherapy. One study evaluated osteoporosis-related health services utilization following first hip fracture among a cohort of privately insured women in the U.S. Just 18% of women underwent bone mass testing within 12 months of first hip fracture, 10% initiated pharmacotherapy for osteoporosis, and 5% did both. Patterns of osteoporosis screening and initiation of pharmacotherapy following hip fracture were assessed based on medical and pharmacy claims in the Optum Labs data warehouse. Data were obtained from a national sample of 8,349 women, 50 years of age or greater, enrolled in private, commercial or Medicare Advantage plans, with no prior history of osteoporosis diagnosis, osteoporosis pharmacotherapy or hip fracture, and who experienced a hip fracture between 2008 and 2013.

The revised 2016 Healthcare Effectiveness Data and Information Set (the HEDIS measures) encouraged providers to be more proactive in identifying and treating osteoporosis patients. The 2016 HEDIS measure osteoporosis management for women who had a fracture, looks at the percentage of women, 65-85 years of age, who suffered a fracture and who had either a bone mineral density test or a prescription for a drug to treat osteoporosis in the six months after fracture. In 2016, within six months of fracture, only slightly over 40% of women had received a DEXA scan or osteoporosis drug treatment.

A study looking at trends in osteoporosis medication used after hip fracture found that treatment rates are declining. This study of patients hospitalized for hip fractures and discharged between January 1, 2002 and December 31, 2011 found that osteoporosis medication use rates decreased from 40.2%, in 2002, to 20.5% in 2011. Therefore, in 2011, only approximately one in five patients were treated with osteoporosis therapy within a year after suffering a hip fracture. In addition to prior fractures, these other factors may contribute to overall bone health and risk for future fracture, including demographics, lifestyle, falls risk, additional medications the patient may be taking, and comorbidities.

Current postmenopausal osteoporosis treatments can be broadly grouped into two classes – anabolic agents and antiresorptive agents. The majority of osteoporosis medications are antiresorptive agents. Both anabolic and antiresorptive agents can help improve BMD, and help reduce risk of fracture, albeit by different effects on bone remodeling. Anabolic agents help to build bone, and antiresorptive agents slow bone resorption, which helps to maintain bone.

TYMLOS is an anabolic agent for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Abaloparatide is an analog of parathyroid hormone related peptide (PTHrP), a well-characterized agonist of the parathyroid hormone-1 (PTH1) receptor, that modulates bone formation and resorption. In preclinical animal studies, abaloparatide had an anabolic effect on bone.

The history of abaloparatide starts with a paper published in 1929. A team of doctors from Massachusetts General Hospital, including Fuller Albright, first reported the potential anabolic effects on bone of daily injections of PTH. It was in 2001, when abaloparatide, a synthetic analog of PTHrP, which is another agonist of the PTH1 receptor, first showed the potential as a treatment for osteoporosis. A few years later, in 2003, Radius Health was founded by a group of renowned scientists and physicians. They later went on to acquire abaloparatide in 2005, leading to the first dose finding clinical trial for abaloparatide in 2007. The first Phase 3 randomized clinical trial was started in 2011, and resulted in approval by the FDA for TYMLOS (abaloparatide) in 2017.

The ACTIVE trial started in 2011, and was the pivotal Phase 3 trial for TYMLOS. The ACTIVE study was a randomized, multi-centered,

double-blind, placebo-controlled clinical trial to study the efficacy of TYMLOS for postmenopausal osteoporosis. Postmenopausal women, aged 49-86 years, were randomized to receive 80 micrograms TYMLOS or a placebo, administered as daily subcutaneous injections for 18 months.

The ACTIVEExtend Study enrolled patients who completed 18 months of TYMLOS or placebo in ACTIVE, to receive open-label alendronate, an antiresorptive, for an additional 24 months. A total of 1,139 patients were enrolled in the study, representing 92% of the 1,243 eligible patients who completed ACTIVE. A preplanned interim analysis was conducted after six months of open-label alendronate. The primary efficacy endpoint for the ACTIVE and ACTIVEExtend trials was the percentage of participants with one or more incidents of new vertebral fracture. Secondary endpoints included the incidence of nonvertebral fractures and changes in BMD from baseline of the lumbar spine, total hip, and femoral neck. The primary and secondary efficacy endpoints were evaluated at 18 months for ACTIVE, and at 25 months for ACTIVEExtend, following six months of open-label alendronate, after the 18-month treatment period with TYMLOS. Evaluations at 43 months, after 18 months' treatment with TYMLOS and an additional 24 months of open-label alendronate, are exploratory endpoints.

Now let's look at important safety information for TYMLOS.

Orthostatic hypotension may occur with TYMLOS, typically within four hours of injection. Associated symptoms may include dizziness, palpitations, tachycardia or nausea, and may resolve by having the patient lie down. For the first several doses, TYMLOS should be administered where the patient can sit or lie down, if necessary.

TYMLOS may cause hypercalcemia. TYMLOS is not recommended in patients with preexisting hypercalcemia, or in patients who have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, because of the possibility of exacerbating hypercalcemia.

First, I'll show you the data for the primary efficacy endpoint of new vertebral fractures in the ACTIVE study. TYMLOS resulted in a significant reduction in the incidence of new vertebral fractures, compared with placebo at 18 months, thus meeting the primary endpoint of the study. The absolute risk reduction in new vertebral fractures were 3.6% at 18 months, for patients treated with TYMLOS, compared with placebo. The relative risk reduction was 86% at 18 months, for patients treated with TYMLOS, compared with placebo. The primary endpoint was the incidence of new vertebral fractures in patients treated with TYMLOS compared with placebo. At 18 months, new vertebral fractures occurred in 0.6% of participants in the TYMLOS group, compared with 4.2% of those in the placebo group.

This illustrates the primary endpoint of ACTIVEExtend, evaluated at 25 months. Eighteen months of TYMLOS, followed by six months of open-label alendronate significantly reduced the incidence of new vertebral fractures, compared with placebo followed by open-label alendronate. The incidence of new vertebral fractures at 25 months was 0.6% in patients treated with TYMLOS followed by open-label alendronate, compared with 4.4% in patients treated with placebo followed by open-label alendronate.

The relative risk reduction was 87% for patients treated with TYMLOS followed by open-label alendronate, compared with patients treated with placebo followed by open-label alendronate, and the absolute risk reduction was 3.9%. Reductions in the incidence of new vertebral fractures with 18 months of TYMLOS were maintained at 43 months, when followed by open-label alendronate for 24 months. The absolute risk reduction for new vertebral fractures was 4.7% for patients treated with TYMLOS followed by open-label alendronate, compared with placebo followed by open-label alendronate. The relative risk reduction for new vertebral fractures was 84% for patients treated with TYMLOS followed by open-label alendronate, compared with placebo followed by open-label alendronate.

The incidence of new vertebral fractures at 43 months was an exploratory endpoint. New vertebral fractures occurred in 0.9% of participants in the TYMLOS followed by open-label alendronate group, compared with 5.6% of those in the placebo followed by open-label alendronate group.

Let's review additional important safety information for TYMLOS.

TYMLOS may cause hypercalciuria. It's unknown whether TYMLOS may exacerbate urolithiasis in patients with active or a history of urolithiasis. If active urolithiasis or preexisting hypercalciuria is suspected, measurement of urinary calcium excretion should be considered.

The most common adverse reactions, with an incidence of 2% or more, are hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.

In addition to reducing the risk of vertebral fractures, TYMLOS also significantly reduced the risk of nonvertebral fractures at 18 months, compared with placebo. Patients receiving TYMLOS showed a significant reduction in the incidence of nonvertebral fractures, compared with placebo, at the end of 18 months of treatment plus one-month follow-up, where no drug was administered. At 18 months, the Kaplan-Meier estimated event rate for nonvertebral fractures was 2.7% in the TYMLOS group, compared with 4.7% in the placebo

group. The relative risk reduction in nonvertebral fractures for TYMLOS compared with placebo was 43%, whereas the absolute risk reduction was 2%.

Eighteen months of TYMLOS followed by six months of open-label alendronate, significantly reduced the incidence of nonvertebral fractures, compared with placebo followed by open-label alendronate. The relative risk reduction in nonvertebral fractures was 52% for patients treated with TYMLOS followed by open-label alendronate, compared with patients treated with placebo followed by open-label alendronate, and the absolute risk reduction was 2.9%.

The cumulative incidence of nonvertebral fractures at 25 months was 2.7% for women treated with TYMLOS followed by open-label alendronate, compared with 5.6% for women treated with placebo followed by open-label alendronate. Reductions in the incidence of nonvertebral fractures with TYMLOS at 18 months were maintained at 43 months, when followed by open-label alendronate for 24 months. The relative risk reduction in nonvertebral fractures for TYMLOS followed by open-label alendronate, compared with placebo followed by open-label alendronate was 39%, whereas the absolute risk reduction was 3%. At 43 months, the Kaplan–Meier estimated event rate for nonvertebral fracture was 5% in the TYMLOS followed by open-label alendronate group, compared with 8% in the placebo followed by open-label alendronate group.

Treatment with TYMLOS for 18 months was also associated with improvements in BMD compared with placebo. Treatment with TYMLOS for 18 months resulted in significant increases in BMD, compared with placebo at the lumbar spine, femoral neck and total hip. Percent change in BMD at the lumbar spine, total hip and femoral neck at 18 months, versus placebo, was a prespecified secondary endpoint. The data in this slide represent an analysis of covariance model, with missing data imputed and based on the last observation carried forward.

Compared with placebo at 18 months, the TYMLOS treated group demonstrated significant changes from baseline BMD. At the lumbar spine, 9.2% versus 0.5% – that's a treatment difference of 8.8%; at the total hip, 3.4% versus -0.1% – a treatment difference of 3.5%; and at the femoral neck, 2.9% versus -0.4% – a treatment difference of 3.3%. Eighteen months of TYMLOS followed by six months of open-label alendronate significantly increased bone mineral density, or BMD, compared with placebo followed by open-label alendronate at 25 months, a secondary endpoint.

Eighteen months of TYMLOS followed by six months of open-label alendronate resulted in significant increases in BMD from baseline at the lumbar spine, total hip and femoral neck, compared with placebo followed by open-label alendronate.

At 25 months, the TYMLOS followed by open-label alendronate group, versus placebo followed by open-label alendronate, demonstrated the following changes in BMD from baseline and corresponding treatment differences: lumbar spine – 12.8% versus 3.5%, for a treatment difference of 9.3%; total hip – 5.5% versus 1.4%, for a treatment difference of 4.1%; and femoral neck – 4.5% versus 0.5%, with a treatment difference of 4.1%.

Increases in BMD at the lumbar spine, total hip and femoral neck, with TYMLOS at 18 months were maintained at 43 months when followed by open-label alendronate for 24 months. Percent change in BMD at the lumbar spine, total hip and femoral neck at 43 months was an exploratory endpoint. Missing BMD data were imputed and based on the last observation carried forward.

Compared with placebo followed by open-label alendronate at 43 months, the TYMLOS followed by open-label alendronate group maintained changes from baseline BMD: at the lumbar spine 14.4% versus 6.5%; at the total hip 6.4% versus 2.8%; and at the femoral neck 5.3% versus 1.6%. The data in this slide represents an analysis of covariance model, with missing data imputed and based on the last observation carried forward. Adverse events were studied across both the ACTIVE and ACTIVEExtend trials.

The safety of TYMLOS was assessed by evaluating adverse events. In the ACTIVE study, the incidence of all caused mortality was 0.4% in the TYMLOS group, and 0.6% in the placebo group. The incidence of serious adverse events was 10% in the TYMLOS group, and 11% in the placebo group. The percentage of patients who discontinued study drug, due to adverse events was 10% in the TYMLOS group and 6% in the placebo group. The most common adverse reactions leading to study drug discontinuation, in the TYMLOS group were nausea 2%, dizziness 1%, headache 1%, and palpitations 1%. In the ACTIVEExtend study, the incidence of adverse events occurring during open-label alendronate treatment were similar in patients with prior placebo or TYMLOS therapy.

An adverse event is any untoward occurrence that may present during treatment with a pharmaceutical product, but that does not necessarily have a causal relation to the treatment. An adverse reaction is a response to a drug that is noxious and unintended, and occurs at doses normally used for the prophylaxis diagnosis or therapy of disease.

This table shows the most common adverse reactions in the ACTIVE trial. These adverse reactions were generally not present at baseline, occurred more commonly with TYMLOS than with placebo, and occurred in at least 2% of the patients treated with TYMLOS.

So, I shared with you an option for postmenopausal women with osteoporosis at high risk for fracture. I recognize that treatment is only one of the factors that contribute to what has been, time and time again, defined as a crisis.

In an international study, more than 80% of postmenopausal women with fragility fractures were not treated with osteoporosis medications. Under diagnosis, poor coordination of care for fracture patients, misunderstanding about fracture risks, concerns about adverse events, and low rates of testing all contribute to this crisis.

While there are many factors that contribute to the crisis, the team caring for postmenopausal women with osteoporosis can be an important component of the solution. Just like you depend on the expertise of a group of professionals, from architects to contractors when building a home, the management of postmenopausal osteoporosis requires of team of experienced professionals caring for the patient.

I hope that with the information you learned in this presentation, you will remember the link between fragility fracture and postmenopausal osteoporosis, and consider TYMLOS as an option for your patients with postmenopausal osteoporosis at high risk for fracture.

Thank you very much.

Announcer:

This program was sponsored by Radius Health, Incorporated. If you missed any part of this discussion, visit www.ReachMD.com/PMO. This is ReachMD. Be part of the knowledge.

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