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INSIDE

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When in Doubt, Pressurize the Snout!

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips reports no financial relationship to this field of study.

Synopsis: *Patients with mild-to-moderate obstructive sleep apnea (OSA) who were treated with Continuous Positive Airway Pressure (CPAP) experienced an absolute risk reduction in cardiovascular risk compared with those who were not treated.*

Source: Buchner NJ, et al. Continuous Positive Airway Pressure Treatment of Mild to Moderate Obstructive Sleep Apnea Reduces Cardiovascular Risk. *Am J Respir Crit Care Med.* 2007;176:1274-1280.

This report results from a 6 year follow-up of an unselected cohort of patients who were referred to a sleep laboratory with suspected obstructive sleep apnea (OSA). Severity of sleep-disordered breathing was based on the Apnea plus Hypopnea Index (AHI) as follows: mild OSA was defined as AHI 5 to < 15/h, moderate OSA was defined as AHI 15 to < 30/h, and severe OSA was defined as AHI > 30/h. (For well-informed readers, apneas required only 10 seconds of cessation of airflow (not defined further in this paper), and hypopneas required at least a 50% reduction in airflow with an arousal or 4% oxygen desaturation. These definitions are a mishmash of old and new scoring criteria, with a little research criteria thrown in. (It is unlikely that interscorer reliability of these events would be very high, but never mind.) All patients with an AHI of at least 5 and sleepiness (not defined in this paper) were offered CPAP; those with mild OSA who were not sleepy or who refused CPAP were offered an oral appliance. The authors controlled for current smoking, arterial hypertension, diabetes, hypercholesterolemia, cardiovascular disease history or documentation (including coronary artery disease, myocardial infarction, and stroke), and body mass index [BMI].

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Once enrolled, patients were followed yearly, and underwent cardiovascular workups as indicated. Compliance was defined as CPAP use for at least 4 hours a night; this was not objectively confirmed in all cases. Primary outcomes were nonfatal and fatal (death from myocardial infarction or stroke) cardiovascular events. Nonfatal events included myocardial infarction, stroke, and acute coronary syndrome requiring revascularization procedures.

Of 449 patients recruited, 364 accepted positive airway pressure (mostly CPAP, but some bilevel pressure; 20 chose an oral appliance). Their mean age was about 56 years and about 15% were women. Those who were treated were statistically significantly heavier than those who were not (BMI 31.2 vs 29.3 kg/m2, $P = 0.003$), and had higher AHI's and lower oxygen desaturation. Of those who accepted CPAP initially, 21.5% were "noncompliant." Although the mean duration of follow-up was 72 months, the untreated patients were followed for shorter periods (mean 50 months vs 70 months for treated patients).

During follow-up, 76 events occurred in the treated patients, including nine myocardial infarctions (2.4%), 25 revascularization procedures (6.8%), 10 strokes (2.7%), eight cardiovascular deaths (2.2%), and 24 deaths of all cause (6.6%). Among the untreated patients, there were five myocardial infarctions (5.8%), 11 revascularization procedures (12.9%), five strokes (5.8%), and three deaths due to cardiovascular causes (3.5%). Of the treated patients, 14.2% had an event vs 28.3% for the untreated ones, with an absolute risk reduction of 27.9%.

In evaluating only those patients with mild-to-moderate sleep apnea, the reduction in event risk for treatment was similar: more events occurred in untreated (25.3% [n = 20]) than in treated patients (14.4% [n = 30]; $P = 0.024$). After controlling for confounding variables such as BMI, age, smoking, etc, the risk reduction associated with treatment of OSA was 64%, both for the entire group and for those with mild-to-moderate OSA.

COMMENTARY

There is no doubt that obstructive sleep apnea is associated with cardiovascular morbidity and mortality.[1-4] The association with hypertension is particularly strong.[4] While there have been previous observational studies demonstrating a reduction in cardiovascular mortality with CPAP treatment,[5-8] little is known about the benefits of treatment of older patients and of patients with milder disease. By stratifying their patients by disease severity and by including an older cohort (mean age 56 years), these authors have expanded the group of sleep apnea patients who are likely to benefit from treatment.

There are a couple of important caveats here. This study is not a randomized, placebo-controlled trial (and it becomes increasingly unlikely that such a trial will ever happen). Those patients who choose to use CPAP are likely to be different from those who do not. As Gary Taubes put it in a recent *New York Times* article, "the problem is that people who faithfully engage in activities that are good for them—taking a drug as prescribed, for instance, or eating what they believe is a healthy diet—are fundamentally different from those who don't."[8] Further, people who do what their doctors ask are healthier than those who don't. And there are other, difficult to quantify factors between those who follow medical advice and those who don't. I recently had a patient who told me where to stick a CPAP machine in no uncertain terms, then stormed out of the clinic. My guess is that his prognosis is poor for a lot of reasons.

It is notable, however, that the untreated patients in this study had worse outcomes, even though they had fewer risk factors, since they were less likely to be obese and had milder sleep apnea.

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There are a lot of "muddy" issues in this paper, including no discussion of how sleepy and non-sleepy patients were distinguished, lack of objective measurement of adherence, and shorter follow-up for untreated than for untreated patient. These problems would tend to bias the results toward reduced differences in outcomes for the treated patients, however, and tend to strengthen the authors' conclusions.

On the basis of this and other studies, recommendation of CPAP treatment for those patients with even mild sleep apnea is the most prudent course at present. ■

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Relationship Between Testosterone and Mortality in Men

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Absent or low testosterone levels in men appear to have a pathogenic role in the development of cardiovascular disease resulting in increased cardiovascular and all-cause mortality and are not simply "markers" for illness or wellness.*

Source: Khaw K, et al. *Circulation.* 2007;116:2694-2701.

The relationship between endogenous testosterone concentrations and overall health in men is still not well established and, in fact, it is quite controversial in many respects. A recent trial in 87 elderly men confirmed the results of many previous trials[15-18] that revealed no significant benefit from exogenous testosterone replacement on body composition, physical performance or quality-of-life.[3,4] Despite the fact that, in some of these studies, testosterone administration was associated with extremely severe adverse health effects such as sudden cardiac death and liver disease,[15-18] exogenous testosterone is still being widely used because of the growing belief among patients and even among many physicians that hypogonadism is frequently associated with poor health and that the use of relatively low doses of exogenous testosterone has benefits for health and well-being[1,2] whether or not low endogenous testosterone levels are present.[1,2]

The prospective relationship between endogenous testosterone concentrations and mortality due to all causes, cardiovascular disease and cancer occurring in a nested case-control study of 11,606 men was examined and reported by Khaw and his colleagues from Cambridge School of Clinical Medicine and the Royal Marsden Hospital in London.[5] The relationship between a single baseline endogenous testosterone concentration and death in 825 men who did not have cancer or cardiovascular disease was studied and compared to the control group of 1489 men who were still alive and who were matched for age and the date of the baseline visit. Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes (825 deaths), cardiovascular

disease (369 deaths), and cancer (304 deaths). After excluding deaths which occurred in the first two years after the beginning of the study (and adjusting for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, diabetes mellitus, alcohol intake, physical activity, social class, blood levels of dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin), increasing testosterone concentrations appeared to be inversely related to mortality due to all causes, cardiovascular causes and cancer with an approximately 25 to 30% lower risk of total mortality in the highest compared with the lowest quartile of testosterone level.

COMMENTARY

Patients who exhibit reductions in serum testosterone levels resulting from aging or chronic disease have signs and symptoms similar to those seen in classical male hypogonadism and are associated with increased fat mass, decreased lean body mass, decreased muscle strength, and a diminished quality of life.[6] Numerous studies have reported findings similar to Khaw's results.[5] For example, it has been reported that men whose total testosterone levels were in the lowest quartile were 40% more likely to die than were men with higher androgen levels independent of age, adiposity, lipid levels, adipokines and lifestyle.[7] Low testosterone levels have been predictive of increased risk of death due to cardiovascular and respiratory disease which is not surprising because these levels have been found to be independently associated with many of the individual risk factors of heart disease; for example, low testosterone levels are inversely related to fat mass in men which is an independent predictor of cardiovascular death.[8] Also, systolic and diastolic blood pressure levels,[9] arterial calcification,[10] intima-media thickness,[11] type 2 diabetes mellitus,[12] abnormal lipid profiles,[13] inflammatory cytokines,[14] and the metabolic syndrome are all important cardiac risk factors and are inversely related to the endogenous testosterone level. Despite the fact that the Khaw study[5] was extremely well conducted, it should be noted that the testosterone values were based on only a single measurement of total testosterone and that measurements were not made of the free or bioavailable testosterone levels which are said to be more accurate than total testosterone levels especially in obese and diabetic subjects.

Multiple studies have demonstrated that absent or low testosterone levels are not simply "markers" for illness or wellness since they appear to play a pathogenic role in the development of cardiovascular disease and are are associated with increased all-cause and especially cardiovascular mortality. But what should clinicians do at this time—administer androgen therapy to elderly patients? There is no credible evidence suggesting that androgen should be administered to men with normal endogenous androgen levels and the final answer as to whether or not androgen therapy should be administered to men with low testosterone levels is not available at this time. One cannot assume that testosterone replacement will reduce or eliminate the increased risks apparently present in the patient with low endogenous testosterone levels and therefore, long-term, double-blind, randomized, placebo-controlled trials of androgen replacement in men of all ages with low testosterone levels and in elderly men with low and with normal testosterone levels are needed to accurately evaluate the effects of such therapy on cardiovascular disease, cardiovascular death and all-cause mortality. Hopefully, these trials will answer numerous questions such as the critical blood level below which treatment should be started, the optimal dose, what is the target testosterone level to be reached and, most important, the long-term safety of such therapy. The need for these large outcome studies has now been recognized and therefore it is expected that the Institute of Medicine which in the past has not recommended funding of an adequate study in this important area will soon alter its previous stance and recommend funding of these studies.

For the time being, since endogenous testosterone concentrations in men appeared to be universally related to mortality due to cardiovascular disease and all causes, clinicians will have to decide without the benefit of adequate outcome studies or approved guidelines as to whether or not androgen therapy is appropriate or still too risky to give to men with low androgen levels in the absence of pituitary or testicular disease and whether the apparent benefits of such therapy are worth the recognized risks. ■

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When Diabetes Takes a Back Seat

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *The number, type, and severity of comorbidities are important determinants of diabetes self-care.*

Source: Kerr EA, et al. *J Gen Intern Med.* 2007;22:1635-1640.

As physicians, we expect our patients to take an active role in the management of their chronic illnesses. In particular, we expect patients with diabetes to watch what they eat, poke themselves in their fingers several times daily, and take their medications. As daunting as this task may be, it's not difficult to imagine how much worse it would be with a second or third chronic illness to manage. In this study, Kerr and colleagues at the University of Michigan hypothesized that the number of comorbidities is insufficient to fully explain the effect of comorbidities on diabetes. They looked at the type and severity of comorbidities and their effect on how patients prioritize and self-manage their diabetes, using the Health and Retirement Study, sponsored by the National Institute on Aging, as their database. This database has information on more than 30,000 subjects. Of them, 2350 reported having diabetes, and 1900 completed a survey that provided more in-depth information about the disease. The respondents were 53% female and 76% white. Seventy percent (70%) were at least 65 years old, and 65% had at least a high school education. They were relatively well-off financially. The mean duration of diabetes was about 12 years.

The investigators looked at the comorbid chronic conditions the subjects reported, and classified them as "concordant" or "discordant" with diabetes. Concordant conditions included illnesses such as hypertension, retinopathy, and heart disease. They reasoned that these conditions shared the same pathophysiology as diabetes. These conditions were further subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (cardiovascular disease, cerebrovascular disease, hypertension, and heart failure). Discordant diseases (pulmonary disease, cancer, and arthritis) were those that do not share diabetic pathophysiology. The importance that diabetic patients place on their illness, diabetes prioritization (DP), was scored with three questions: "Taking care of my diabetes is a top priority right now," "I have other health problems that are more important than diabetes," "I have many more important things in my life than diabetes to take care of right now." The second variable was diabetes self-management ability (SMA). The subjects were asked to rate their ability to attend to 5 areas: taking medication, exercising, meal planning, monitoring blood glucose, and foot examination with another scale that ranged from "so difficult I couldn't do it at all" to "not difficult, I got it exactly right." Finally, they focused on heart failure, a common comorbidity, and classified it as mild-to-moderate or severe.

Ninety-two percent (92%) of subjects had at least one comorbid condition; 25% had four or more. As the number of all comorbid conditions increased, the subjects' DP and SMA declined. However, when the investigators looked at DP by comorbidity subtype, microvascular conditions had no effect. Macrovascular conditions and discordant conditions were both associated with lower DP. Comorbidity subtype did not affect SMA; greater numbers of any subtype were associated with lower SMA. Looking specifically at heart failure, mild heart failure did not affect DP or SMA, but severe heart failure did.

COMMENTARY

Recently I participated in a seminar for family medicine chief residents. The topic was diabetes mellitus. I began my presentation by asking rhetorically for a show of hands of those residents who had a patient

with diabetes and nothing else. No hands went up.

One thing I like about this study is its attempt to quantify the biopsychosocial model of medicine, so beloved by primary care physicians. Intuitively, I know that when I have two patients with a chronic illness, and one is mastering self-management and the other is not, I need to explore the context of the illness. What else is going on in his life? Does she have other illnesses? As our population ages, more and more of our patients will have not just one chronic illness. A few years ago, I was a co-author of a study that looked at several issues of self-management of diabetes from the patient's point of view. We conducted focus groups, and one of the participants said, "Well, I have so many things wrong that diabetes is not usually my primary concern…They got me a glucometer…but I had so much trouble… ya gotta get the blood right down on one particular spot. And I couldn't see it good enough, and I'd always get blood all over everything. And I'd get four or five of those strips in there and still wouldn't get an answer." Is it any wonder that self-management is so difficult!

What is the lesson here? It is to avoid "oculostenosis" when dealing with patients with diabetes. Osler said it best: "It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has." Specifically for diabetes, it means asking your patient whether his heart failure makes it difficult for him to exercise daily. Does her retinopathy prevent her from accurately drawing up her insulin? Who is the primary cook in the household? Does that person know the patient's dietary requirements? Is his arthritis so bad, he can't bend over to examine his feet or have the dexterity to use his glucometer? Of course, it's so much simpler to order a hemoglobin A_{1C}, but with third-party payers scrutinizing our practices and pay-or-performance becoming a reality, simple is simply not good enough. ■

Pharmacology Update

Sapropterin Dihydrochloride Tablets (Kuvan™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

THE FDA HAS APPROVED, BY PRIORITY REVIEW, THE first drug to help manage patients with phenylketonuria (PKU). PKU is an inherited disorder in the activity of phenylalanine hydroxylase (PAH). Sapropterin is a synthetic version of the naturally occurring tetrahydrobiopterin (BH4), which is the catalytic cofactor for PAH. Sapropterin will be marketed by BioMarin Pharmaceuticals Inc. as Kuvan.

Indications

Sapropterin is indicated to reduce blood levels of phenylalanine in patients with hyperphenylalaninemia due to tetrahydrobiopterin responsive phenyketonuria in conjunction with a phenylalanine-restricted diet.[1]

Dosage

The recommended starting dose is 10 mg/kg/day taken once daily. Phenylalanine levels should be

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

checked after 1 week of treatment and periodically up to one month. If the levels do not decrease from baseline the dose may be increased to 20 mg/kg/day. If no change occurs the patient should be considered to be non-responsive and treatment should be discontinued. For responders, the dose may be titrated between 5 and 20 mg/kg/day.[1]

Sapropterin is available as 100 mg tablets each containing 76.8 mg of sapropterin base.

Potential Advantages

Sapropterin is the first drug approved to lower phenylalanine levels in some patients with PKU. In those who respond, easing or possible elimination of dietary restrictions may be possible.[2]

Potential Disadvantages

Sapropterin is only effective in patients with residual PAH activity (ie, mild to moderate disease). This is estimated to represent 20 to 56% of PKU patients.[1-3] Common adverse events (>10%) include headache, upper respiratory tract infections, pharyngolaryngeal pain, and rhinorrhea.[1]

Comments

PKU is an autosomal recessive disorder caused by mutation in both alleles of the gene for phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine. Deficiency of this enzyme results in a spectrum of the disorder from classic PKU to hyperphenylalaninemia. Accumulation of phenylalanine leads to mental retardation, smaller brain size, behavioral abnormalities, seizures, and neurological complications.

Sapropterin is believed to stimulate PAH activity in those with residual activity. The efficacy and safety of sapropterin was evaluated in four clinical studies.1,4 Study 1 was an open label study in patients not on a phenylalanine diet who had phenylalanine levels ³450 mmols/L and treated at 10 mg/kg/day (n = 489). Study 2 was a randomized placebo-controlled study involving patients who responded in the first study (n = 88). Study 3 was a forced dose titration study involving those who completed study 2 (n = 80). Study 4 was an open label study in children (ages 4-12) with phenylalanine-restricted diets and phenylalanine levels £480 mmole/l and treated at 20 mg/kg/day (n = 50). Response was defined as a 30% or greater decrease in phenylalanine blood levels. In study 1, 20% of patients were responders at Day 8. In study 2, patients randomized to sapropterin 10 mg/kg/day had a mean reduction of 29% compared to an increase of 3% for placebo at week 6. Forty-four percent of patients had at least a 30% reduction compared to 9% for placebo. Forced titration of 5 mg to 20 mg/kg every 2 weeks, in study 3, showed a dose response effect. In study 4, 56% of patients responded at Day 8. Sapropterin is expected to cost about $57,000 per year for children and up to $200,000 per year for adults.

Clinical Implications

PKU occurs in one out of 12,000 to 15,000 live births.[5] Current treatment is limited to eating a special diet low in phenylalanine. Sapropterin is the first drug to be approved and may be beneficial to 20-56% of PKU patients. However, responders cannot be determined *a priori* by laboratory or PAH genotyping but only by a therapeutic trial. The least costly way consists of two doses of sapropterin at 20 mg/kg/day given over 24 hours and blood levels of phenylalanine followed over 48 hours.[6] Responsiveness is defined as a 30% or greater reduction in phenylalanine blood levels. Some have suggested that younger patients on diets but not optimally controlled, and those with mild disease be tested first for responsiveness.[7] It is unknown if sapropterin will improve long-term outcome of PKU or whether any potential improvement in quality of life or easing dietary restriction or elimination in a few patients justifies the high cost of the drug. ■

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CME Questions

4. CPAP treatment for sleep apnea has been demonstrated to reduce cardiovascular risk:

a. in randomized, placebo-controlled trials
b. only for patients with severe disease
c. only for patients whose use of CPAP is measured and documented to be at least 4 hours a night
d. in prospective, observational studies

5. Absent or low testosterone levels in men:

a. appear to have a pathogenic role in the development of cardiovascular disease
b. are simply a "marker" for illness or wellness
c. are not associated with increased all-cause and cardiovascular mortality
d. bear no relationship to fat mass in men

Answers: 4 (d); 5 (a)

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

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Fenofibrate for Diabetic Retinopathy

CLINICIANS MAY RECALL THAT THE FIELD trial (Fenofibrate Intervention and Event Lowering in Diabetes) failed to achieve its primary endpoint: reduction of fatal + nonfatal MI. A substudy of the FIELD trial was comprised of subjects (n=1,012) who underwent standardized retinal photography at baseline and during followup to determine the incidence of new diabetic retinopathy. Subjects were treated with micronized fenofibrate 200 mg QD (or placebo) for 5 years. This substudy trial endpoint was needed for laser treatment of diabetic retinopathy.

A statistically significant relative risk reduction of 31% in the need for first laser retina treatment was seen in the treatment group vs placebo (3.4% vs 4.9%, absolute risk reduction=1.5%). In the group of patients with pre-existing retinopathy at baseline, there was a marked reduction in need for second laser treatment (3.1% vs 14.6%).

The retinal benefits seen in FIELD were in patients who were mostly already receiving standard-of-care interventions such as statins, glucose control, and blood pressure control. The mechanisms by which fibrates provide reductions in progression of diabetic retinopathy are uncertain, although potential effects on apoptosis, inflammation, and oxidation are postulated. The authors suggest that fenofibrate should be considered in the treatment regimen of diabetic eye disease. ■

Keech AC, et al. Lancet. 2007;370:1687-1697.

Does Obesity Cause A Delay in Diagnosis of Prostate Cancer?

IT HAS BEEN DEMONSTRATED IN MORE than one population that obese men have a lower PSA than nonobese men. One explanation of this was that obese men have lower androgens, resulting in lower PSA. However, it has been recently hypothesized that the larger plasma volume seen in obese men might artifactually lower PSA levels by simple hemodilution.

To examine the relationship between obesity and PSA, as well as PSA corrected for plasma volume, three different populations of men (total n= 13,534) who were post-prostatectomy for prostate CA were studied.

There was an inverse association between BMI and PSA level. For instance, men with a BMI over 35 had a PSA that was 11-21% lower than normal weight men; in the Duke population, as an example, the mean PSA at a BMI < 25 was 6.64, vs a PSA of 5.27 for men with BMI > 35. These effects are felt to be due to hemodilution.

Even though the relationship between BMI and PSA has been clarified, these data are retrospective, and represent information from men proven to have prostate cancer. Whether the hemodilution effects on PSA screening are meaningful remains to be prospectively studied. ■

Banez LL, et al. JAMA. 2007;298(19):2275-2280.

Protecting Bone During Glucocorticoid Treatment

CURRENT GUIDELINES SUGGEST that if patients are receiving long term Glucocorticoid treatment (ie, 5 mg/d of prednisone for 90 days or longer), they should be considered for preventive interventions to forestall the anticipated bone loss, and reduce fracture risk.

Teriperatide (TPT) is a parenteral recombinant parathyroid hormone that has been shown to stimulate osteoblasts, increase bone mass, and reduce fracture risk. The relative efficacy of TPT vs bisphosphonate for prevention of glucocorticoid-induced bone mineral density (BMD) loss has not been previously studied.

Adults with osteoporosis who were receiving glucocorticoid therapy for at least 3 months (n=428) were randomized to TPT or the oral bisphosphonate alendronate (ALN), 10 mg qd orally. The study is intended to extend for 36 months, but this initial report provides interim outcome data at 18 months.

BMD at the lumbar spine increased in both groups, but TPT surpassed ALN (7.2% vs 3.4%). Similarly, fewer new vertebral fractures were seen in the TPT group (0.6% vs 6.1%). There were no serious drug-attributable adverse events in either group, however hypercalcemia was seen substantially more commonly in TPT recipients. Based upon this data, TPT emerges as an equally, if not more effective intervention for prevention of glucocorticoid-induced osteoporosis and fracture compared with ALN. ■

Saag KG, et al. N Engl J Med. 2007;357:2028-2039.

In Future Issues:

Diagnosing UTI Is As Simple As 1, 2, 3