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INSIDE

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Diagnostic Open Laparoscopy in the Management of Advanced Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *Diagnostic open laparoscopy (DOL) could be considered a valid diagnostic tool in evaluating the extent of disease in advanced ovarian cancer (AOC). These data suggest that the use of DOL leads to a decrease in the rate of primary cytoreductive surgery for AOC; on the other hand, a higher optimal debulking rate (no residual tumor) at primary surgery is achieved.*

Source: Angioli R, et al. Diagnostic open laparoscopy in the management of advanced ovarian cancer. *Gynecol Oncol.* 2006;100:455-461.

Optimal surgical cytoreduction is a recognized staple of initial advanced ovarian cancer care. However, within the spectrum of patients who undergo this surgery are those in whom complete resection is either impossible or unwarranted in the face of certain unacceptable morbidity. Identifying these patients before laparotomy is generally relegated to preoperative imaging and biomarkers—with limited success. Angioli and colleagues report their experience with laparoscopic evaluation of intraperitoneal disease to make this decision. Over the 50-month accrual period, 87 patients were consecutively evaluated. All were to have suspected metastatic disease (stage IIIC-IV) and were evaluated for the outcome of no post-operative tumor residual.

Those deemed unresectable were treated with neoadjuvant standard combination chemotherapy. Those in this latter group who did not progress during 3 cycles of chemotherapy were taken to cytoreduction. The primary end point of this observational study was to quantify their success in predicting cytoreduction in these patients. Overall, 53 (61%) were deemed appropriate surgical candidates at laparoscopy, in whom 51 (96%) were cytoreduced to no visible residual. Among the 34 in whom surgery was deferred, 25 (74%)

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were ultimately operated upon; 20 (80%) were similarly optimal at interval cytoreduction. Overall survival was best in those in whom surgery could be done initially; those undergoing surgery after chemotherapy had a significantly worse survival but was substantially better than those in whom chemoresistance was documented. Similar survival outcomes were observed for those patients who completed both surgery and chemotherapy, regardless of the sequence. Complication rates were also low in both surgical cohorts. The authors concluded that the open laparoscopy is a valuable tool to evaluate the extent of disease at presentation and may select patients in whom complete cytoreduction can be achieved at initial surgery.

COMMENTARY

The standard clinical approach to newly diagnosed ovarian cancer is primary surgical cytoreduction followed by combination chemotherapy for patients with high-risk or advanced-stage disease. Several studies have suggested that better cytoreduction is important to response to chemotherapy and overall survival.[1] However, approximately 50% of patients who undergo attempt at cytoreduction are left with macroscopic disease—in some cases bulky macroscopic disease, in whom poorer response to treatment (and overall survival) is observed. Since previously unexposed ovarian cancer is largely sensitive to chemotherapy, an alternative treatment approach for patients with bulky intraperitoneal disease is to administer chemotherapy ahead of surgery. This not only identifies patients with chemoresistant disease (by progression on therapy) but also can substantially reduce the volume of tumor to be resected, thereby increasing the rate of optimal cytoreduction and reducing the morbidity of surgery. To date, there have been 3 randomized trials that have been performed to evaluate the benefit of interval cytoreduction in this manner.[2-4] The 3 studies span the decades of platinum and, most recently taxane use in the primary management of ovarian cancer. Each of these trials identified patients largely through a failed (suboptimal) cytoreduction attempt and randomized their care to either standard chemotherapy or interval surgery after an abbreviated treatment course. Two of the trials, including one utilizing a regimen considered a current standard of care combination did not identify a benefit by interval (or in this case, secondary) surgical attempt. One trial, using a non-taxane combination, did suggest improved progression-free and overall survival for those undergoing an interval surgery. However, a significant fraction of women enrolled in this trial did not have an aggressive first attempt and essentially underwent a neoadjuvant program. A randomized trial of each surgical approach (neoadjuvant, interval cytoreduction and standard cytoreduction) is underway.

The current trial is unique in that the bar set for cytoreduction is high (no visible disease). Although various definitions of "optimal" have been used over the years, none have specifically used this degree of resection as a primary goal. As listed in the authors procedures, the extent of radical resection in order to achieve this outcome is greater than that generally reported in studies conducted in the multi-institutional setting. Nonetheless, it is a desired result if one accepts the relationship between tumor volume residual and survival. The current study demonstrates that laparoscopy (better than clinical or radiographic measures) may be helpful in selecting patients in whom a radical approach is warranted. There are several unknowns that still require elucidation: what percent of patients deemed as poor candidates for cytoreduction could indeed by cytoreduced? What are the implications on survival for purposefully waiting to cytoreduce in these patients? What is the impact on survival for port site metastases seen in the delayed surgical cohort? Can a lower cytoreduction bar achieve the same result? Finally, is this strategy reproducible in the multi-institutional setting? These ques-

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tions will need to be formally addressed before such an approach can be globally recommended. However, the bar for complete resection should be embraced as we approach primary surgical management. ■

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EVRA and Venous Thrombosis

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Two case-control studies produce conflicting results regarding the risk of venous thrombosis with the contraceptive patch.*

Source: Jick SS, et al. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. *Contraception*. 2006;73:223-228.

JICK AND COLLEAGUES, EPIDEMIOLOGISTS AT BOSTON University School of Medicine, performed a case-control study of nonfatal venous thrombosis using information derived from a very large database that records prescriptions and diagnoses longitudinally in managed health care plans. The study over a 3-year time period compared new users of the contraceptive patch with new users of an oral contraceptive containing 35 µg ethinyl estradiol and norgestimate. Sixty eight cases of venous thrombosis and 266 controls were identified and matched for year of birth and for the date of the thrombotic episode (thus providing comparable dates for exposure). A comparison of the patch to the oral contraceptive indicated no difference in the risk of venous thrombosis:

Comparison to OCs			
Contraceptive patch	31 cases	127 controls	OR = 0.9 (0.5-1.6)

A strength of the current report is that only new users were studied, eliminating the problem known as attrition of susceptibles (comparing new users to old users would be comparing 2 different groups of subjects). Adjusting for age, duration of exposure, hospitalization or non-hospitalization, and frequency of health care visits did not change the result. The risk for nonfatal venous thrombosis was similar in new users of the contraceptive patch compared with new users of oral contraceptives. An analysis for myocardial infarction and stroke risks in the database will be reported in the future.

■ COMMENTARY

The US Food and Drug Administration issued a press release on November 10, 2005 calling attention to the fact that women using the oral contraceptive patch are exposed over time to a greater amount of estrogen. Subsequently, the patch labeling was updated to include a warning about this higher exposure.

Here are the facts:

1. The contraceptive patch delivers daily 20 µg ethinyl estradiol and 150 mg norelgestromin (the primary active metabolite of orally administered norgestimate).
2. The serum ethinyl estradiol concentration averages 50 pg/mL, with a range of 25 to 75 pg/mL.[1,2]
3. The peak estrogen blood levels with the contraceptive patch are about 25% to 35% lower compared with oral products containing 30 µg or 35 µg ethinyl estradiol.[3,package label]
4. Over time, patch users are exposed to about 60% more estrogen compared with an oral product containing 35 µg ethinyl estradiol.

Which is more important, a higher peak level or greater exposure over time? Or maybe it doesn't make a difference. The first concern that there might be an increased risk of venous thrombosis with the patch was a consequence of reports in the media based on anecdotal reports provided to the FDA (a numerator without a denominator). Johnson & Johnson, the parent company for the EVRA patch, provided research funds for 2 epi-

demiologic studies. One is the case-control study reported above, the other is a case-control study that has not yet been published, but results were publicized by the FDA. The unpublished study using information from a different medical insurance database apparently had a different conclusion compared with the published report, a 2-fold increase in risk for non-fatal venous thrombosis compared with a 35 µg ethinyl estradiol oral contraceptive. The unpublished study is also assessing the risks of myocardial infarction and stroke, and thus far, has found no increase in either.

Comparison to OCs		
Contraceptive patch	22 cases 57 controls	OR = 2.05 (1.02-4.14)

It is difficult to make a valid comparison prior to the publication of the second study; however, the FDA has stated that the confidence intervals overlap and both studies may indicate no increased risk compared to oral contraceptives. (www.medpagetoday.com Neurology/Strokes/tb/2697).

So where does that leave clinicians and patients? These are the first epidemiologic data on this important issue. One study is reassuring, one is disturbing. But note that the confidence interval in the second study is relatively wide, indicating imprecision of the conclusion. Overall, the results do not support a unique, adverse impact of the contraceptive patch on the risk of venous thrombosis.

I believe the strategy of the FDA in issuing press releases and making conclusions public before the publications are available for assessment by clinicians is harmful. Meaningful decision-making by patients and clinicians requires careful appraisal of published reports. Clinical decisions should not be based on FDA sound bites! At this point in time, there is little evidence that the contraceptive patch has a greater risk of venous thrombosis. ■

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Randomized Double-Blind Trial of Estrogen Replacement Therapy vs Placebo in Stage I or II Endometrial Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *Although this incomplete study cannot conclusively refute or support the safety of exogenous estrogen with regard to risk of endometrial recurrence, it is noteworthy that the absolute recurrence rate (2.1%) and the incidence of new malignancy were low.*

Source: Barakat RR, et al. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24:587-592.

THE ASSOCIATION BETWEEN EXOGENOUS ESTROGEN use and endometrial cancer development has been well documented. Nonetheless, the hazard of estrogen replacement therapy in women with a personal history of endometrial cancer has not been well studied and, despite anecdotal evidence of its safety, is largely discouraged among clinicians. In this regard, Barakat and colleagues from the Gynecologic Oncology Group (GOG) set out to quantify the risk/benefit of estrogen replacement in women with early stage endometrial cancer. Women undergoing primary extirpative surgery for stage IA-IIB (occult) endometrial cancer were randomized to either estrogen (premarin 0.625 mg) or to placebo. All women were to have an indication for estrogen therapy including vasomotor symptoms, vaginal atrophy, increased risk for cardiovascular disease or an increased risk for osteoporosis. The intent of therapy was 3 years administration. Strata were considered for stage based on differing survival factors. The primary end point was time to recurrence with all cause survival a secondary objective.

Based on anticipated rates of recurrence and loss to crossover, 2108 women were to be recruited. Over 66

months, 1236 women were randomized to the trial. Effects on accrual following the announcement of data from the Women's Health Initiative (WHI) caused the GOG to terminate the study early. Half of the cohort were randomized to each treatment group. Just 41% of patients on ERT and 50% on placebo remained compliant over the course of 3 years. Recurrence was lower than expected at 2.1%, which was countered by the GOG through closure to Stage IA patients. Nonetheless, just 9 of the 45 deaths observed on the trial were from endometrial cancer (0.7% of total population). There was no observed difference in recurrence or all-cause death between the treatment arms but the trial did not meet its accrual goals in order to infer this result in this population. New malignancy rates were low (1.3% for ERT, 1.6% for placebo) in both cohorts.

COMMENTARY

Endometrial cancer is the most common gynecologic malignancy diagnosed in the United States. Fortunately, most are confined to the uterus at presentation, which generally translates into a favorable survival profile compared to other malignancies of the genital tract. While the median age of diagnosis is older than 60, a sizeable fraction of patients are perimenopausal at diagnosis and suffer from significant estrogen deprivation following primary surgical management. Since estrogen use has been linked with the development of this disease, clinicians have been reticent to use ERT even in symptomatic women with a personal history of endometrial cancer based on the theoretical risk of "activating" dormant cells leading to recurrence. Retrospective studies have failed to confirm this suspicion.[1-3] However, the issue of ERT use is relevant as the likelihood for long-term, cancer-free survival for these women is high and their exposure to other life-threatening factors related to estrogen deprivation is significant.

Data from the WHI caused a dramatic effect in the worldwide use of ERT. While the initial reports detailed outcomes based on the use of combined estrogen and progestin, the reduction in popularity heavily influenced the trial's accrual necessitating early termination. Subsequently, data from WHI with estrogen alone regimens have been published which confirmed increased risks of thromboembolic events but no increase in cardiovascular disease or breast cancer. Protection of osteoporosis was confirmed but no specific evaluation of the influence of this therapy on quality of life was detailed. Arguably, this is of primary importance in the population being studied. While the current trial cannot be used to support or refute the use of ERT in women with endometrial cancer, the data provided do suggest that recurrence in this setting is low; but the compliance with therapy is also low. Short-term use for symptomatic patients does not appear to be associated with a dramatic acceleration of recurrence although safety cannot be definitively inferred. Similar to the discussion of ERT use in women without cancer, it would be prudent for symptomatic women with an endometrial cancer history desiring ERT to carefully counsel them to the known risks/benefits of ERT use and limit usage to the shortest practical period. ■

Suggested Reading

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The WHI Studies on Calcium and Vitamin D

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The Women's Health Initiative finds that calcium/vitamin D supplementation provides protection against hip fractures, and no reduction in colorectal cancer.*

Source: Jackson RD, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006; 354:669-683.

THE WOMEN'S HEALTH INITIATIVE (WHI) CONDUCTED A randomized trial of Calcium and Vitamin D supplementation.[1] The 36,282 postmenopausal women were part of the WHI clinical trials involving postmenopausal hormone therapy or dietary modification. The average follow-up was 7 years; 37% of the women were age 50 to 59, 45.5% were 60 to 59, and 17.5% were 70 to 79. The treated group was supplemented with 1000 mg cal-

cium and 400 IU vitamin D daily. Most of the women were overweight, with 37% having a BMI of 30 or higher. A subset of 1431 women were followed with bone density measurements. There were no bone density differences between treatment and placebo in the spine or whole body measurements, but in the hip, the treated group gained slightly more bone at year 3, and by year 6 the placebo group lost more bone at the hip. Fracture results were as follows:

Intention-to-treat analysis			
	Calcium/Vitamin D	Placebo	Hazard Ratio
Hip fractures	175	199	0.88 (0.72-1.08)
Vertebral fractures	181	197	0.90 (0.74-1.10)
Analysis of adherent participants			
Hip fractures	68	99	0.71 (0.52-0.97)
Vertebral fractures	91	104	0.89 (0.67-1.19)

Thus, the overall analysis indicated no significant reduction in fractures with calcium/vitamin D treatment. The women treated with calcium/vitamin D had a 17% greater risk of kidney stones (HR, 1.17; CI = 1.02-1.34).

This same study also assessed the impact of calcium/vitamin D on the risk of invasive colorectal cancer.[2] No difference was observed between the treated group and the placebo group, even when only women adherent to treatment were analyzed. However, it is recognized that the latency period for colorectal cancer is 10 to 20 years. The length of follow-up in this study may have been insufficient to detect an effect. Furthermore, colorectal cancer was not a primary outcome in the study design, and the study design was very complicated by the fact that the women were simultaneously enrolled in 3 overlapping trials (calcium/vitamin D, low-fat diet, and hormone therapy).

COMMENTARY

Do you remember when you first heard of the calcium/vitamin D study? I was watching NBC news prior to the Olympics telecast. The next day I heard it on NPR radio, and later I read it in *Newsweek*. All presentations said the same thing: New study produces disappointing news, no benefit for calcium/vitamin D supplementation. This was a typical demonstration of the guiding principle for the media: good news is no news. Contrary to the presentation in the media, the news in this WHI report was good. The women who most needed a benefit experienced a reduction in hip fractures with calcium/vitamin D if they continued to supplement their dietary intake. The results further support the conclusion that maximal protection against fractures is gained by combining calcium/vitamin D supplementation with hormone therapy.

Careful reading of the full report provides this good news:

1. Correcting for compliance by analyzing just those women who continued their medication revealed a statistically significant 29% reduction in risk for hip fractures. Only 59% of the treated women at the end of the trial were taking the intended dose.
2. Women who were 60 years and older had a 21% significant reduction in hip fracture (HR, 0.79; CI, 0.64-0.98).
3. The reduction in hip fracture was greater in those women who were not taking calcium supplements other than what the study provided.
4. The reduction in hip fractures was greatest (42%) in those women who combined calcium/vitamin D supplementation with postmenopausal hormone therapy (HR, 0.58; CI, 0.37-0.93).

In my view, the public presentation of these results in the WHI calcium/vitamin D study was not accurate. The population at greatest risk for fractures (the oldest women in the study) actually benefited, and the study confirmed something already known, that hormone therapy combined with calcium/vitamin D supplementation achieves the best results. Keep in mind that the women in this study were not at high risk for fractures. Indeed, whole body and spinal bone density increased in the placebo group. This is hard to explain; the average postmenopausal untreated woman loses spinal bone density. In this study, only hip bone density demonstrated a loss, and thus, it is not surprising that significant benefits were demonstrated only with hip fractures.

The fact that most of these women were overweight probably contributed to the protection against bone loss in the spine. In a population of women losing bone density in both hip and spine, and in women with other risk factors for fractures, I would expect calcium/vitamin D supplementation to yield even better results than those reported by the WHI, including a reduction in spinal and arm fractures.

The impact of calcium/vitamin D supplementation on the risk of colorectal cancer remains unsettled. A possible reduction in colorectal cancer is still possible in those women who have low levels of calcium and vitamin D prior to treatment, as documented in the Nurses Health Study and in the current WHI report (if you examine the report closely).[2,3]

What about the kidney stones? The women in this trial were allowed to continue their own programs of supplementation. Thus many took calcium and multi-

vitamins (which contain 400 IU vitamin D). The average daily calcium intake of the study population was 1100 to 1200 mg, 2-fold higher than the average American woman. The WHI does not provide data to answer this most important question: Was the small increase in kidney stones observed in women who were taking excessive amounts of calcium and vitamin D?

These results support the following clinical recommendations. Because the average woman receives daily only about 500 mg of calcium in her diet, most women not on hormone therapy require a daily supplement of 1000 mg calcium (best as single doses of 500 mg with meals). Most women on hormone therapy require only an additional 500 mg calcium because estrogen improves calcium absorption. Vitamin D is recommended for all women (and men) younger than age 70 in a daily dose of 400 IU, and 800 IU daily in women age 70 and older. To be sure, there are some women who derive sufficient amounts of calcium and vitamin D from their diets, and supplementation would be both unnecessary and perhaps risky for kidney stones. ■

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Assisted Reproductive Technology and Pregnancy Outcome

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

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

In November the authors of the now famous FASTER trial, which was initially focused on the use of nuchal translucency (NT) in the first trimester, published one of many spin-off reports. This one dealt with outcomes of singleton pregnancies conceived through assisted reproductive technology (ART). In this large study 1,222 pregnancies were accomplished through ovulation induction and 554 were conceived by in vitro fertilization (IVF). The remaining 34,286 spontaneously occurring pregnancies were used as controls.

The abstract of the paper says it all. When compared with no ART, ovulation induction carried a significantly greater risk of placental abruption (OR, 2.4), fetal loss after 24 weeks (OR, 2.1), and gestational diabetes (OR, 1.5). IVF was associated with a higher risk of preeclampsia (OR, 2.7), gestational hypertension (OR, 1.6), placenta previa (OR, 6.0), placenta abruption (OR, 2.4), and risk of Cesarean section (OR, 2.3).

COMMENTARY

The above results that were easiest to explain were IVF's predisposition towards placenta previa, preeclampsia, and abruption, which could be secondary to an inability for the placenta to find a receptive decidual bed. This would also explain the rather high rate of vasa previa with IVF as noted in a previous *Clinical Alert*. The higher rate of Cesarean section after IVF is not surprising in IVF patients in whom the reasons for Cesarean sections might be more socially related rather than medically indicated. The higher rate of gestational diabetes in those with ovulation induction (and not with IVF) could well be due to a higher proportion of patients with polycystic ovarian syndrome (PCOS) in the former group.

Although the study did not show a significant relationship between ART and low birth weight (LBW) an analysis by the CDC involving data from 1996-1997 showed almost a doubling of the LBW and a similar review from Sweden showed a 6-fold increase in LBW with IVF pregnancies.

The point is that not all is rosy for the often desperate and vulnerable patients conceiving through ART. It is my impression that these patients often turn a deaf ear (if they are properly informed) to the downside of carrying twins or triplets. In fact, recent data suggest that the perinatal mortality and morbidity is higher in multiple gestations conceived through ART then those occurring spontaneously. Now, the data from the above FASTER trial and from other studies show similar trends with singletons.

One hopes that this information will find its way

into ART consent forms in large print. ■

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3. Bergh T, et al. Deliveries and children born after in-vitro fertilisation in Sweden. 1982-95: a retrospective cohort study. *Lancet*. 1999; 354: 1579-85.
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CME Questions

5. **The following statements are true regarding calcium/vitamin D supplementation *except*:**
   a. The WHI reported that calcium/vitamin D supplementation reduces the risk of hip fractures.
   b. The WHI reported that all women taking calcium/vitamin D are at risk for kidney stones.
   c. Hormone therapy and calcium/vitamin D supplementation have an additive effect on protection against bone loss and fractures.
   d. Short-term studies do not demonstrate calcium/vitamin D protection against colorectal cancer.

6. **The following statements are true regarding laparoscopy in the management of ovarian cancer *except*:**
   a. Laparoscopy can be used to predict which patients would benefit from cytoreduction.
   b. Greater cytoreduction is associated with better survival.
   c. The benefit of chemotherapy prior to cytoreduction is established.
   d. Laparoscopy evaluates which patients would benefit from radical cytoreduction better than radiographic imaging.

Answers: 5 (b); 6 (c)

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Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

Treatment of Benign Prostatic Hyperplasia

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments? Please call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■