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INSIDE

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Nicotine Replacement During Pregnancy: Does It Increase Stillbirth Rates?

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Nicotine replacement therapy does not increase the risk of stillbirth in smokers.*

Source: Strandberg-Larsen K, et al. Use of nicotine replacement therapy during pregnancy and stillbirth: A cohort study. *BJOG* 2008 Aug 20; Epub ahead of print.

CIGARETTES AND PREGNANCY ARE A RISKY COMBINATION, AND there is an abundance of data to indicate that perinatal outcome is improved if patients can abstain from smoking. However, cigarettes represent a powerful addiction, and many patients cannot quit completely without help, some of whom will choose a form of nicotine replacement therapy (NRT). Nevertheless, one must be sure that the cure is not worse than the problem.

In an attempt to answer this question, a group of investigators interviewed 87,032 patients between 12 and 16 weeks of gestation as part of a data collection program, the Danish National Birth Cohort. They were questioned regarding their smoking habits and whether they used NRT (nicotine gum, nicotine patches, or inhaled products). All pregnancies were tracked through birth.

The investigators were primarily interested in stillbirth (SB) occurring after 20 weeks of gestation. In the overall population of smokers and non-smokers, the SB rate was 5.7 per 1000 (similar to that in the United States). When comparing the SB rate in smokers vs non-smokers, the former had a hazard risk (HR), which, in essence, is a likelihood ratio, of 1.45 (confidence interval = 1.1-1.8). The users of NRT who did not smoke during pregnancy had a HR

of 0.67 and, if they did smoke during pregnancy, the HR was 0.83, neither of which was statistically significant.

■ COMMENTARY

One study has suggested a higher rate of fetal anomalies in NRT users, causing many to wonder if this type of therapy might be worse than the alternative — smoking. The Danish investigators chose to evaluate only the incidence of SB and found that NRT diminished the rate of SB compared with smokers, in general, and had essentially the same rate of SB as non-smokers. This study had indigenous importance since (and this was a surprise to me) 1 of 5 pregnant Danish women smoke, and 2% of the overall pregnant population is on some form of NRT.

It certainly makes public health sense to find ways to discourage smoking since this habit is associated with virtually every adverse pregnancy outcome except, for some reason, preeclampsia. It is also clear that nicotine is not the only noxious component of cigarette smoke. Animal studies and a randomized trial pitting nicotine patches against placebo patches in smoking women suggested larger offspring with nicotine exposure alone, presumably because the nicotine patch worked to diminish the amount of cigarettes smoked.[1,2] The study from England following children who were significantly growth restricted in utero showed that those children whose mothers were smokers performed more poorly on developmental function evaluations (Griffith DQ tests) than the other children whose mothers were non-smokers.[3]

Numerous other studies have shown that smoking mothers have a higher risk of low birthweight and fetal growth restriction, and higher rates of neonatal morbidity. It is granted that there were confounding variables affecting all of these studies, but it would be silly to suggest that cigarette smoking is innocuous to the developing fetus — and anything to cut down the amount of cigarettes smoked could have a beneficial effect.

This study indicates that NRT may cut down the rate of intrauterine demise in smokers. Putting this type of therapy into play after 11 weeks circumvents the possibility of teratogenic effect, and in this study seems not to increase the rate of SB above non-smokers. ■

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Adding Metformin to Clomiphene

By Leon Speroff, MD, Editor

Synopsis: *Metformin improves pregnancy rates in women with insulin resistance.*

Source: Moll E, et al. Does adding metformin to clomifene citrate lead to higher pregnancy rates in a subset of women with polycystic ovary syndrome? *Hum Reprod* 2008;23: 1830-1834.

MOLL AND COLLEAGUES FROM AMSTERDAM PERformed a subgroup analysis within their randomized clinical trial of women with polycystic ovary syndrome comparing metformin plus clomiphene treatment with clomiphene alone.[1] The overall results of their trial detected no differences in ovulation rates, pregnancy rates, or spontaneous abortion rates achieved by adding metformin to clomiphene treatment.[2] This reanalysis of

the data, derived from a total of 225 patients, indicated no differences based on BMI, testosterone levels, or glucose levels. However, there was a significant increase in pregnancy rates when metformin was combined with clomiphene in women older than age 28 who were centrally obese as measured by a waist:hip ratio of 0.85 or greater.

■ COMMENTARY

The trend to use metformin either alone or with clomiphene began around the year 2000, based on a few small studies.[3,4] Since then, randomized trials in the United States and Canada, plus the above trial in the Netherlands, concluded that metformin did not improve the infertility treatment of women with polycystic ovary syndrome.[2,5,6] In other words, pregnancy rates were similar comparing metformin alone, clomiphene alone, or both drugs in combination. Thus, we returned to the decades-old position that first-line treatment should be clomiphene.

One other study has performed a subgroup analysis, a randomized trial comparing metformin to placebo in only 23 women.[7] Nevertheless the Italian authors concluded that metformin improved ovulation rates in patients with hyperinsulinemia. Unfortunately, the Amsterdam trial did not measure insulin levels. However, the fact that the Dutch subgroup analysis found higher pregnancy rates associated with metformin in older, obese women (who are more likely to be hyperinsulinemic) argues that adding metformin to women with insulin resistance does make sense. This is reinforced by the Dutch finding of a benefit in women with an increased waist:hip ratio, the surrogate marker recognized to be most strongly associated with insulin resistance. Even though this was a relatively large clinical trial, the number of women in the subgroups was relatively small (10-30) making it difficult to achieve statistical power and produce strong conclusions regarding associations with testosterone levels and BMI.

Only a randomized trial comparing different treatment protocols among adequately powered subgroups can provide us with better data. Until then, it seems reasonable to add metformin when women with insulin resistance are unable to achieve pregnancy with multiple cycles of clomiphene treatment. It is also reasonable to assume that older women with central obesity are very, very likely to be hyperinsulinemic, and sometimes it is more cost effective to use metformin empirically.

The clinical trials comparing clomiphene and metformin have documented an increase in gestational diabetes and preeclampsia in the clomiphene-treated groups. It is worth considering metformin treatment of patients throughout pregnancy in overweight women with insulin resistance. Studies have indicated a reduction in pregnancy complications, including the incidence and treatment of gestational diabetes, with metformin administration and no adverse fetal affects with exposure in the first trimester of pregnancy.[8-11]

In addition, we should not forget that metformin treatment improves insulin sensitivity and lowers androgen levels in women with polycystic ovaries and anovulation. These are important and beneficial results in terms of reducing the risks of the long-term consequences of diabetes mellitus and cardiovascular disease. ■

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A Possible New Treatment for Ectopic Pregnancy

By Leon Speroff, MD, Editor

Synopsis: *Photoablation has potential to treat ectopic pregnancies.*

Source: Glinert LS, e al. Photodynamic ablation of a selected rat embryo: A model for the treatment of extrauterine pregnancy. *Hum Reprod* 2008;23:1491-1498.

GLINERT AND COLLEAGUES FROM ISRAEL REPORT THE use of photodynamic therapy to successfully ablate single feto-placental implantations in rats. A photosensitizer drug was injected directly into the placenta, followed 2 minutes later by delivery of a specific wavelength of light to the site. More than three-fourths (78.6%) of the selected embryos were photo-ablated leaving the remaining litter unharmed. Subsequently, the treated animals were able to achieve pregnancy and have normal parturition. Histopathologic examinations of the uteri detected no lesions.

■ COMMENTARY

There seldom is a rat study reviewed in these pages, and that is good. But the potential of this new treatment is so tantalizing, I thought it was worthwhile to tuck it into the backs of our minds.

Photodynamic treatment uses a non-toxic photosensitizer drug that combines at the treatment site with focused light that has a wavelength known to induce cellular damage. There are several drugs already approved by the FDA for this purpose. The light can be delivered via optic fibers to a specific location, where it elicits the generation of cytotoxic oxygen molecules. These molecules have such a short half-life, that the damaging effect is limited to the illuminated area. The method has been developed to treat tumors and macular degeneration of the retina. The new generation of photosensitizer drugs acts immediately after injection and allows deep light penetration. The vasculature of tumors is most affected, leading to hypoxia and necrosis within days.

It is not hard to imagine delivering a photosensitizer drug transvaginally under visualization via an endoscope directly into an ectopic pregnancy. The endoscope would also contain an optic fiber system for delivery of light from a laser source. If the photosensitizer drug is inadvertently delivered into the maternal bloodstream, according to the rat study, the dose is about 50 times less than that used for tumor destruction. The method could also be used to treat endometriosis and uterine fibroids. Forgive me for the rat study, but the potential intrigued me. If you are interested, check out the review by Allison et al.[1] ■

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Special Feature

Maintenance Therapy for Ovarian Cancer: Are We There Yet?

By Robert L. Coleman, MD

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

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

JULY OF THIS YEAR REPRESENTED THE 5-YEAR ANNIVERsary of the publication of Gynecologic Oncology Group (GOG) protocol 178, a pivotal trial demonstrating the significant impact of 9 additional months of paclitaxel chemotherapy to women who had achieved a complete clinical response to primary therapy.[1] The trial was so remarkably positive for women randomized to receive one additional year of monthly paclitaxel therapy that it was closed prematurely for ethical concerns — meeting a predefined early closure benchmark based on progression-free survival (median PFS: 28 months vs 21 months, $P = 0.0023$).

Those unfamiliar with this stream of clinical research may be surprised to know that the results have largely been disregarded. The primary impact has been inconsistent or incomplete use of the strategy as studied, or use of other approaches lacking in evidence base. I draw emphasis to evidence-based treatment, as completion

therapy or "consolidation" is frequently recommended or prescribed; what's missing is the evidence base.

This Special Feature will explain the impetus to develop effective maintenance treatment, present what has been explored in phase III prospective trials, and discuss why, despite the positive results of the pivotal trial, patients and physicians shun routine use of the "winning arm" of this trial. Ongoing and planned confirmatory concepts will also be introduced.

The Problem

Women with advanced stage ovarian cancer have effective chemotherapeutic options for care administered after surgical cytoreduction (debulking). Response rates vary from 50% to 80% with about half of these being complete; that is, no evidence of disease following exam and imaging and resolution of their elevated biomarker (usually CA125).[2,3]

In the office, the discussion with this fortunate patient is positive and upbeat and frequently overshadows attendant cumulative toxicities related to primary therapy, such as neuropathy, fatigue, myalgias, and alopecia. Despite the enthusiastic interaction, probability of recurrence within 2 years is substantive (about 50%-60%) and its occurrence is usually fatal.[3] Even in the setting of a negative reassessment surgical procedure, the risk is only marginally reduced.

Given these statistics, it is logical to hypothesize the clinical observations might be the result of incomplete response to an abbreviated front-line chemotherapy program (6 cycles of therapy). Indeed, part of the historical rationale to perform a second-look surgery in these patients was to provide some guidance as to when therapy could be safely discontinued. Over time, convention settled with 6-8 cycles as adequate. Maintenance therapy is that treatment administered in the specific setting of complete clinical or pathological remission of disease following primary therapy *(see Figure, right)*.

The Strategy

Given the contention that recurrence may have resulted from incomplete primary therapy, several studies were conducted under the premise that additional treatment could favorably impact these women. A simple strategy involved doubling the exposure to primary chemotherapy.

For example, Hakes et al reported a randomized phase III study comparing survival outcomes in women administered 5 cycles of chemotherapy followed by observation compared to those women given 5 additional cycles of the same therapy.[4] Patients having residual disease at second-look surgery were crossed over to the 10-cycle arm. Complete response rate was similar, as was survival; additional chemotherapy only added toxicity.

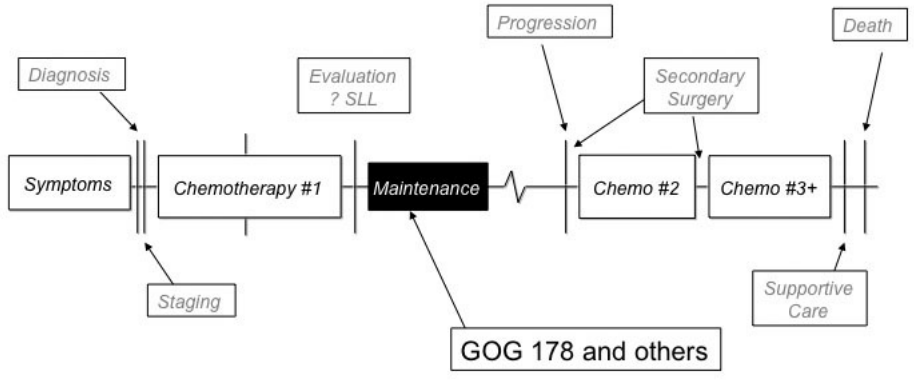
Another strategy, in this same theme, involves the administration of a chemotherapeutic, which has non-cross-resistant cytotoxicity characteristics. Two large randomized clinical trials investigated the topoisomerase I inhibitor, topotecan, which has documented clinical efficacy in women with recurrent ovarian cancer.[5,6] The two trials were slightly different in design, but each prescribed the novel agent for 4 additional cycles following best response to primary therapy. Despite the appeal, no difference in the primary endpoint (PFS) was observed.

To round out the "more is better" theme comes a provocative phase III study, which enrolled 110 women with stage III/IV ovarian cancer who, at second-look, were identified with either no visible disease or small-volume persistent disease, to either standard-dose cyclophosphamide and carboplatin or high-dose cyclophosphamide and carboplatin with stem cell support.[7] As expected, a low, but measurable, treatment-related mortality rate (3%) and lower completed therapy rate was observed in the high-dose arm, but no effect on PFS or overall survival (OS) was recorded. It appears this avenue is unfruitful.

Another strategy, based on our observations of successful treatment of women with early stage disease, is

Figure

Natural history of ovarian cancer



Note: Maintenance therapy is highlighted by the black filled box.

radiation. Since the at-risk target tissue in these patients involves the peritoneal cavity, two strategies were investigated for maintenance: whole abdominal radiation therapy (WART) and intraperitoneal radio-phosphorus (^{32}P).

Sorbe and colleagues conducted a three-arm randomized trial of WART, chemotherapy, or observation following second-look surgery.[8] In the cohort of women identified as being in pathological complete remission (negative second-look surgery), no difference was observed between either therapy arm and observation. A similar experience was observed in GOG protocol 93, in which women with pathological complete response were randomized to either ^{32}P or observation; PFS and OS were similar.[9]

The ability for ovarian cancer cells to grow in the host suggests faulty, escaped, or bypassed immunoregulatory processing. There is intense interest in leveraging the potential immune host response for prevention and therapy in this disease.[9]

Relative to maintenance therapy, several attempts have been unsuccessfully made. In one, interferon-α was administered (up to 2 years) subcutaneously to 149 women in complete clinical remission following primary therapy.[10] Compared to 151 women observed without therapy, no difference in median survival was observed (27 months vs 33 months).

In another, antibody to CA125 (oregovomab) was administered to 145 women with normal CA125 levels and no tumor following primary therapy.[11] Progression-free survival, the primary endpoint, was no different between the arms. Post-hoc analysis suggested a benefit may exist in those women with highly expressing CA125 tumors that demonstrated early response to initial chemotherapy. However, in a follow-up randomized study, even in this enriched population, no benefit was observed for the experimental agent.

A new anti-idiotypic CA-125 antibody (abagovomab) is currently under investigation in this setting.[12]

Since early events in carcinogenesis involve specific interactions of the tumor cell and its microenvironment, several investigators have opined that targeted therapy could be beneficial in the prevention of disease progression or relapse.[13] One randomized clinical trial of a unique biological agent has been reported. In this study, 243 women completing primary chemotherapy were randomized to tanomastat, a matrix metalloproteinase inhibitor, or placebo.[14] Therapy was to continue until progression or 5 years. Despite its novelty, no difference was observed between the cohorts. While disappointing, the premise in this strategy is extremely relevant and likely to serve as an avenue to future investigation, as the menu of interesting compounds expands.

The Kicker

The investigational environment, vis-à-vis this clinical experience, is an important context upon which to consider the results of GOG 178 *(see Table, below)*. There has been much criticism of the study and scrutiny of its results, particularly in light of a similar trial, reported in abstract form, which was closed prematurely due to an unplanned futility analysis demonstrating no impact of 6 cycles of paclitaxel vs no further therapy.[15] The contribution of this latter study to our knowledge base, unfortunately, is suspect, at best, due to this unplanned issuance.

Nevertheless, there are several valid shortcomings to GOG 178, including an incomplete evaluation of the impact of toxicity resulting from the additional therapy, and the lack of overall survival information. Further, it has been intimated that no statistical difference in overall survival is expected between the treatment cohorts.[16] No doubt, these factors, aligned with patient trepidation, have influenced clinicians' practice patterns. In the absence of a confirmatory trial, it is clear that expansion of maintenance therapy will be justifiably muted.

Fortunately, the GOG and other cooperative groups have embraced this challenge (e.g., novel chemotherapeutics, vaccine, and biologicals), and ongoing are trials to address each of these deficiencies, not the least of which is the consideration that not every patient is destined to recur. Our current inability to a priori identify these individuals requires that the study eligibility be broadly defined and intensifies the discrimination of treatment-induced and treatment-enhanced toxicity relative to any attained efficacy endpoints. Future work in patient genomic profiling may avail this requirement.

The Wrap-up

The clinical concern of patients with advanced ovarian cancer and their health care providers is simply —

Table

Maintenance strategies and results in phase III clinical trials

	Maintenance Benefit?	
Strategy	Yes	No
Prolonged initial therapy	X	
Short-duration of non-cross-resistant chemotherapy	X	
High-dose chemotherapy	X	
Whole abdominal radiation therapy	X	
Intraperitoneal ^{32}P	X	
Interferon-α subcutaneously	X	
Anti CA125 antibody	X	
Biological agent (tanomastat)	X	
Paclitaxel: 6 cycles	X	
Paclitaxel: 12 cycles (GOG 178)		?

cure. Statistically, only marginal gains on this endpoint have been observed over the last 3 decades despite the array of therapies available. However, median survival has nearly doubled and continues to improve, largely the result of this therapeutic environment. Strategies to push the envelope, such as maintenance therapy, are worthy ventures, as one just might be identified which could provide the direct inhibition of disease re-growth and provide an avenue for sustained disease-free survival. ■

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CME Questions

29. Maternal smoking is *not* associated with a higher rate of:

a. preeclampsia.
b. preterm birth.
c. smaller babies.
d. adverse developmental effects.

30. The overall rate of SB in patients on nicotine replacement therapy (NRT) is higher than nonsmokers.

a. True
b. False

31. The following statements are true regarding metformin and clomiphene treatment *except*:

a. The evidence is strong that infertile women with PCO should be treated first with clomiphene.
b. It is likely, but not definitive, that metformin treatment increased pregnancy rates in women with insulin resistance.
c. Metformin is not as effective as insulin in treating gestational diabetes.
d. Metformin treatment reduces the risk of preeclampsia in pregnant women with PCO and hyperinsulinemia.

32. Several strategic principles addressing tumor biology have been tested in the phase III setting for maintenance therapy. Which of the following is a noted confounder mentioned in several of these studies which handicaps our interpretation of the trial's contribution to clarify whether maintenance therapy is of value?

a. Insufficient numbers of patients were included to address the primary endpoint.
b. Patients with both complete and partial clinical response to primary therapy were included in the randomization.
c. Use of surgical evaluation prior to randomization was unbalanced.
d. Unplanned futility analyses lead to premature study closure.

Answers: 29. (a), 30. (b), 31. (c), 32. (d).

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The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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PS Form **3526**, September 1999 *(Reverse)*

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Safety of Inhaled Anticholinergics for COPD Scrutinized

In the Issue: Ongoing safety review of tiotropium; raloxifene reduces the risk of endometrial cancer; one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir; new Clinical Practice Guideline from the American College of Physicians regarding pharmacologic treatment for low bone density and osteoporosis; FDA Actions.

THE SAFETY OF INHALED ANTICHOLINERGICS FOR the treatment of chronic obstructive pulmonary disease (COPD) has come under scrutiny in recent months. In July, the FDA issued an "Early Communication" about an ongoing safety review of tiotropium (Spiriva®) the most widely used agent for the treatment of COPD. The review is focused on a possible increased risk of stroke and is based on a pooled analysis of 29 trials which showed the risk of stroke at 8 patients per 1000 treated with tiotropium versus 6 patients per 1000 treated with placebo.

Now two new studies suggest that inhaled anticholinergics (ipratropium [Atrovent®] and tiotropium) increase the risk for all-cause mortality and cardiovascular disease in patients with COPD. In a large meta-analysis (*JAMA* 2008;300: 1439-1450), researchers reviewed 17 trials involving nearly 15,000 patients with COPD who were randomized to an inhaled anticholinergic or control. The primary outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. The primary outcome occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR 1.58, 95% CI, 1.21-2.06; $P < 0.001$). Inhaled anticholinergics significantly increased risk of MI, cardiovascular death, and all-cause mortality (RR 1.26). When the analysis was restricted to long-term trials, the risk was even greater for cardiovascular death, MI, or stroke (RR 1.73). The number needed to harm for MI was 174 per year, while the number needed to harm for cardiovascular death was 40 per year. The authors concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

In a second nested, case-control study (*Ann Intern Med* 2008;149:380-390), the National Veterans Affairs databases were used to review all-cause mortality, respiratory and cardiovascular deaths, and exposure to COPD medications including inhaled corticosteroids, ipratropium, long-acting beta agonists, and theophylline in the 6 months preceding death. The adjusted odds ratios for all-cause mortality were 0.80 for inhaled chronic steroids, 1.11 for ipratropium, 0.92 for long-acting beta agonists, and 1.05 for theophylline. Ipratropium was associated with increased cardiovascular deaths (OR 1.34), whereas inhaled corticosteroids were associated

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with reduced risk for cardiovascular death (OR 0.80). The authors conclude that there is a possible association between ipratropium and elevated risk for all-cause and cardiovascular death and that further studies are needed. They also suggest that the risk of ipratropium may be somewhat mitigated by concomitant use of inhaled corticosteroids, but caution should be exercised if ipratropium is used alone in patients with recently diagnosed COPD.

Raloxifene reduces endometrial cancer risk

It is well known that raloxifene reduces the risk of breast cancer; now there is evidence that the drug reduces the risk of endometrial cancer as well. Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM) that is indicated for treatment and prevention of osteoporosis and for breast cancer prevention. Researchers from the University of Pennsylvania compared endometrial cancer rates in women on raloxifene, tamoxifen, and non-users of SERMs in a case-control study of 547 women with endometrial cancer and 1410 controls. After adjustment for other risk factors the odds of endometrial cancer among raloxifene users was 50% that of non-users (OR = 0.50; 95% CI, 0.29-0.85), whereas tamoxifen users had 3 times the odds of developing endometrial cancer compared to raloxifene users (OR = 3.0; 95% CI, 1.3-6.9). Among raloxifene users who developed endometrial cancer, the tumors had a more favorable histologic profile and were predominantly stage I and low grade. The authors conclude that raloxifene users have significantly lower risk of developing endometrial cancer compared with tamoxifen users and SERM non-users, perhaps even suggesting a role for raloxifene and prevention of endometrial cancer (*J Clin Oncol* 2008; 26:4151-4159).

One-day famciclovir = three-day valacyclovir

For patients with recurrent genital herpes outbreaks, one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir, according to a new study. In a double-blind parallel group study, 1179 adults with a history of recurrent genital herpes were randomized to receive either famciclovir 1000 mg twice daily for one day vs valacyclovir 500 mg twice daily for 3 days. Patients initiated treatment within 6 hours after a recurrence. Approximately one-third of patients in each group aborted genital herpes outbreaks altogether, but for those who went on to develop lesions, median time to healing was 4.25 days for famciclovir vs 4.08 days for valacyclovir. Time to healing was the same in both groups and the incidence of adverse affects was 23.2% for famciclovir vs 22.3% for valacyclovir. The study demonstrates that a single day of famciclovir (1000 mg twice daily) is equivalent to 3 days of valacyclovir (*Clin Infect Dis* 2008;47:651-658). Other regimens for treatment of recurrent HSV episodes include acyclovir 800 mg 3 times daily for two days or 400 mg three times daily for 3-5 days, famciclovir 125 mg twice a day for 3-5 days, or valacyclovir 500 mg twice daily for 3 days. Both acyclovir and famciclovir are available generically, but acyclovir is considerably less expensive; however, the convenience of a one-day treatment with famciclovir may be worth the extra cost for many patients.

New practice guideline for osteoporosis

The American College of Physicians has issued a Clinical Practice Guideline regarding the pharmacologic treatment of patients with low bone density or osteoporosis (*Ann Intern Med* 2008; 149:404-415). The expert committee recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures. They also recommend that pharmacologic treatment should be considered for men and women who are at risk of developing osteoporosis and that the choice of pharmacologic treatment should be based on assessment of risk and benefits in individual patients. The guideline reviews different treatment modalities including bisphosphonates, calcitonin, estrogen, teriparatide, SERMs, testosterone, and calcium plus vitamin D. Left unanswered are the questions of duration of treatment with bisphosphonates and the optimal dose of calcium and vitamin D.

FDA actions

The FDA has issued warning letters to Ranbaxy Laboratories Ltd. of India in an Import Alert for the company's generic drugs produced in two Indian plants. The warning letters identify concerns about deviations from U.S. current Good Manufacturing Practice requirements at Ranbaxy's manufacturing facilities and the Import Alert allows officials to detain at the rest border any active pharmaceutical ingredients manufactured at Ranbaxy facilities. Ranbaxy manufacturers more than 30 generic drugs including commonly used antibiotics, antihypertensives, and antivirals. ■