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INSIDE

Insurance Status Predicts Surgical Outcomes for Patients with Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *Patients without insurance have been reported to have less satisfactory health outcomes, and this has been attributed to a number of factors including access to health care and a greater burden of comorbid conditions. In the current retrospective analysis, short-term outcomes including surgical complications and in-hospital mortality were greater for uninsured or Medicaid recipient colorectal cancer patients (aged, 40-64 years) compared with those with private insurance. By multivariate analysis, insurance status was found to be an independent predictor of short-term outcome with regard to perioperative complications and mortality.*

Source: Kelz RR, et al. *Cancer*. 2004:101;2187-2194.

For a number of reasons, uninsured or underinsured patients might be at increased risk for negative health outcomes. These include impaired access to health care, delayed treatment, and the receipt of substandard care. With regard to surgical outcomes, it is also quite possible that poor outcomes may be related to an increased disease burden or a greater likelihood of emergent, rather than elective, operative intervention. In the current study, Kelz and associates at the University of Pennsylvania examined associations between insurance provider and short-term surgical outcomes after surgery for colorectal cancer and evaluated the extent to which two risk factors (comorbid disease and admission type) might explain any observed association.

For this, Kelz and colleagues conducted a nationally representative retrospective cohort study of 13,415 adults ages 40-64 years who were admitted for surgery for colorectal carcinomas throughout the > 1000 hospitals that participated in the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) National Inpatient Study (NIS) releases 6 and 7, from 1997 and 1998.

To arrive at this cohort, data from 169,206 subjects who were admitted for colorectal surgical procedures of which 56,493 had a

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diagnosis of nonmetastatic carcinoma of the colon or rectum were examined. Of these, 15,183 were in the 40-64 year old (non-Medicare) age group. Incomplete or missing data required the exclusion of 1776 patients, thereby resulting in the study population of 13,415. Of these, approximately 85% had private insurance, 6% were uninsured and 9% were recipients of Medicaid. Approximately 14% of the admissions were classified as emergent and a comorbid illness was identified in 57% of patients. As expected, a lack of insurance and Medicaid receipt were associated with increased comorbidity and more emergent admissions compared with patients with private insurance ($P < 0.0001$).

By univariate analysis, it was clear that insurance status was associated with adverse surgical outcomes. It was also clear that there were several risk factors more prevalent among patients without private insurance (emergent admission type, comorbidity, and advanced age) and the presence of any of these was associated with higher rates of both postoperative complications and mortality. Accordingly, multivariate and logistic regression models were developed to describe the correlations between insurance status and the risks of postoperative complications or postoperative death after adjustment for socio-economic factors, comorbid conditions, and admission type. In this analysis, uninsured and Medicaid recipients were found to have more emergent admissions and a greater comorbidity burden compared with those with private health insurance. Patients without private health insurance had higher rates of postoperative complications and in-hospital death compared with those patients with private insurance. Emergent admission type, high comorbid burden (3+) and several specific comorbid conditions were associated with a higher odds ratio of postoperative complications in this analysis for the population as a whole (ie, independent of insurance status). However, after adjusting for these factors, patients with Medicaid were found to be 22% more likely to develop a complication during their hospital admission (odds ratio [OR] of 1.22; 95% confidence interval [CI], 1.06-1.40) and 57% more likely to die postoperatively (OR of 1.57; 95% CI, 1.01-2.42) compared with patients with private insurance.

COMMENT BY WILLIAM B. ERSHLER, MD

In general, it has been widely acknowledged that uninsured and underinsured patients have less satisfactory outcomes when compared to those with private insurance[1-4] and this is frequently attributed to fragmented care, poor access to prevention and screening, delay in diagnosis, more advanced disease at presentation and the presence of a greater burden of comorbid conditions. In the current analysis, however, patients with clinically apparent non-metastatic disease were found to have more adverse short-term outcomes on the basis of insurance status alone (ie, after controlling for these other factors in a multivariate model). Explanations for this may relate to a tendency for uninsured to receive fragmented medical care, often in emergency departments and possibly to be referred to less experience surgeons for treatment. It is also possible that within the current cohort, uninsured patients had more locally-advanced disease, thereby increasing the complication and perioperative mortality rate; a variable for which data was not available in the current analysis. Nonetheless, as we currently address the crisis in health care, and keeping in mind that approximately 25% of the US population is uninsured,[5] the implications are sobering but intuitive. Patients without

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health insurance have a greater risk of receiving substandard care and in a specific disease (colorectal cancer) and procedure (surgical resection) focused retrospective analysis such as this, the difference in outcome is quite apparent. ■

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Risk Factors for Brain Relapse in Patients with Metastatic Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *The presence of lung metastases as the first site of relapse and a negative hormone receptor status are predictive for the occurrence of brain metastases in patients with metastatic breast cancer. A prophylactic treatment should be evaluated in these subsets of patients.*

Source: Slimane K, et al. Ann Oncol. 2004;15: 1640-1644.

There is evidence suggesting that the incidence of brain metastases is rising in patients with breast cancer. One explanation is the selective destruction of non-brain metastases by new chemotherapy regimens, allowing a later development of brain metastases. It has been shown that the occurrence of brain metastases in patients with breast cancer decreases survival and alters the quality of life. The possibility of detecting early or preventing the occurrence of brain metastases could therefore lead to increased survival and better quality of life. Some approaches have been shown antitumor activity in brain metastases and could therefore be evaluated as a preventative treatment for brain metastases. This may include prophylactic cranial irradiation, high-dose methotrexate, and temozolomide. There is a need to identify the patients with metastatic breast cancer who are at risk of developing brain metastases. In the present study, predictive factors of brain metastases in patients with metastatic breast cancer were determined, in order to propose a targeted strategy aimed at screening or preventing brain relapse in these patients.

■ COMMENT BY STUART M. LICHTMAN, MD

This study was conducted in 2 parts. Risk factors for brain metastases were first determined in a series of metastatic breast cancer patients, and then confirmed in a second series.

Patients were included in prospective, randomized trials for the 2 series of patients. Two hundred and fifteen patients were included in the present study. These patients were selected from the database of a randomized trial that compared post-operative castration vs no castration in pre-menopausal patients with breast cancer. It included 557 patients at the Institut Gustave Roussy between 1989 and 1998. The results of this trial have been previously reported.[1] Among the 557 patients, 220 patients developed a metastatic relapse of breast cancer before August 2003. The follow-up of the trial did not include any systematic brain CT scan, nor brain MRI. The clinical files of these 220 metastatic patients were reviewed in August 2003 in order to determine which patients had presented brain metastases. Five patients presenting brain metastases as first relapse were excluded from the analysis. The predictive factors for brain metastasis were therefore analyzed in the remaining 215 patients. A number of variables were evaluated. The age, tumor size, lymph node status, tumor grade, interval between primary and first metastatic relapse, first sites of metastases, loco-regional treatment and adjuvant medical treatment were extracted from the database of the clinical trial. Hormone receptor status was extracted from the clinical charts. These variables were tested for their association with the occurrence of brain metastases.

Two hundred and fifteen metastatic breast cancer patients were included in the present series. The median follow-up between diagnosis of metastatic relapse and last visit or death was 22 months (range, 0-117 months). The median follow-up for living patients was 35 months. Thirty-one patients (14%) presented a brain relapse prior to the diagnosis of the first systemic metastasis. The 2-year incidence of brain metastases was 13%. The median interval

between the first metastatic relapse and the occurrence of brain metastases was 13 months. Lung metastases as the first site of relapse, negative hormone receptor status, absence of bone metastases at first relapse and short disease-free interval (> 24 months) were associated with a higher risk of developing brain metastases in the univariate analysis.

Fifteen out of 50 patients (30%) presenting with lung metastases as the first site of relapse subsequently developed brain metastases during the follow-up. Ten out of 29 patients (34%) with negative hormone receptor status subsequently presented a brain relapse. The 2-year incidence of brain metastases were 24% and 7% in patients with and without lung metastases, respectively (P = 0.0001). The 2-year incidence of brain metastases were 6% and 37% in patients with positive and negative hormone receptor status, respectively (P = 0.0001). In the multivariate analysis, lung metastases (hazard ratio, 4.3; 95% CI, 1.9-9.3; P = 0.0003) and negative hormone receptor status (hazard ratio, 4.2; 95% CI, 1.7-11; P = 0.002) were associated with and increased risk of brain metastases. The confirmatory series included 199 patients with metastatic disease. The median follow-up was 21 months (range, 0-122 months). The median follow-up for living patients was 34 months (range, 0-122 months). Lung metastases and negative hormonal receptor status were confirmed as predictive factors for the occurrence of brain metastases.

In the present study, the presence of lung metastases and negative hormone receptor status are strong predictive factors for the occurrence of a brain relapse in 2 prospective series of patients with metastatic breast cancer. Previous studies in the same population reported that negative hormonal receptor status[2,3] and, more recently, Her2-neu overexpression[4,5] may be associated with a higher risk of developing brain metastases. The present study confirms that negative hormone receptor status is a predictive factor for brain metastases in 2 sets of homogeneously treated, prospectively assessed metastatic breast cancer patients. Her2-neu was not performed in this series since most of the patients relapsed before the introduction of trastuzumab in daily practice. Only a few studies specifically evaluated the correlation between the first sites of metastases and the subsequent development of brain metastases. Crivellari et al reported that 11 out of 28 breast cancer patients presenting a brain relapse had lung metastases as the first site of relapse.[6] The presence of lung metastases was associated with a higher risk of further developing brain metastases in this series. Miller et al[4] reported that the presence of lung metastases was associated with a 2.4-fold increased risk of brain metastases (P = 0.07) in a series of 155 consecutive patients with metastatic breast cancer. In the present series, the presence of lung metastases was strongly associated with the occurrence of brain metastases. Indeed, 30% of the patients presenting lung metastases as the first site of relapse subsequently developed a brain relapse. Slimane et al raise questions regarding the management of breast cancer patients at the time of metastatic relapse: 1) Should a screening of brain metastases be performed in patients with lung metastases and/or negative hormone receptor status? and 2) Should a prophylactic treatment of brain metastases be considered? Randomized trials in these high risk populations should be considered to prevent or delay relapse and hopefully maintain or improve quality of life. ■

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MOHS vs Standard Surgical Excision for Facial Basal Cell Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *In a randomized, clinical trial, patients with primary or recurrent basal-cell carcinoma were treated either by traditional surgical excision or Mohs' micrographic surgery. At 30 months of follow-up, recurrence rates were low in both groups. For those with recurrent disease, there was a suggestion that the Mohs technique might be superior with regard to later recurrence. However, there were no aesthetic differences and overall costs were significantly higher for the Mohs technique. For those with larger lesions or recurrent disease, there was a trend towards more favorable outcome with the Mohs technique.*

Source: Smeets NJ, et al. *Lancet*. 2004;364:1766-1772.

BASAL-CELL CARCINOMA IS THE MOST COMMON skin cancer in Caucasians and its incidence con-

tinues to rise.[1] Although such carcinomas rarely metastasize, some cause substantial morbidity and even mortality,[2] particularly those that are larger or incompletely resected. Complete tumor removal (ie, prevention of recurrence), preservation of healthy skin, aesthetic outcome, and costs are important in the treatment of this predominantly facial skin tumor. Most basal-cell carcinomas are treated by surgical excision (SE) although radiotherapy remains an alternative approach. Mohs' micrographic surgery (MMS) has been shown to improve cure rates over SE, cryosurgery or radiation for these tumors. However, basal-cell cure rates by SE are quite high and the need for MMS has been questioned. Inasmuch as MMS is more time consuming and expensive, Smeets and colleagues from the Netherlands performed a randomized trial comparing SE with MMS in the treatment of primary and recurrent facial basal-cell carcinoma.

Patients with primary and recurrent facial carcinomas were randomized to SE or MMS and tumor recurrence after 30 months was the primary outcome for analysis. Of the patients with primary tumors (n = 397) 198 were randomized to MMS and 197 to SE. For those with recurrent basal-cell carcinomas (n = 201), 99 received MMS and 102 SE. Of the primary carcinomas, 5 (3%) recurred after SE compared with 3 (2%) after MMS during the 30 months of follow-up. Of the recurrent carcinomas, 3 (3%) recurred after SE and none after MMS. Furthermore, although there did not appear to be any differences in post-operative complications (ie, infection, necrosis, bleeding, etc) or aesthetic outcomes for those that received SE or MMS, this was not true for those who were operated upon for recurrent disease. More complications occurred after SE than after MMS (19 [19%] vs 8 [8%]; $P = 0.021$) for recurrent carcinomas. Although the differences in recurrence rates were not statistically significant, the total operative costs were almost twice as high for MMS.

COMMENT BY WILLIAM B. ERSHLER, MD

Physicians commonly encounter patients with basal-cell cancers and a number of options are currently available for treatment. It has been apparent that surgical approaches are most satisfactory but a comparison between the traditional surgical excisions and the more precise, albeit more cumbersome Mohs technique had not, heretofore been examined in a prospective, randomized trial. In this report, it is evident for those receiving primary treatment the recurrence is low by either technique. For those with recurrence there is a trend suggesting the Mohs technique might be more efficacious. Smeets et al suggest that this trend might become more evident upon later analysis, such as at 5 years, or in another trial with a larger sample size.

This was a well conducted clinical trial that, unfortunately, was insufficiently powered to demonstrate either a difference or no difference. The reader gets a sense from Smeets et al, and in the accompanying editorial,[3] that the Mohs technique might be a superior approach, but unnecessary for the management of small and uncomplicated primary basal-cell carcinomas. For larger or recurrent lesions, it is likely that the added time and expense of the Mohs technique will ultimately be shown to be worth the effort. Yet, despite the laudatory efforts put forth in the current trial, the data remains inconclusive. Accordingly, factors other than clearly demonstrated evidence will drive which of these techniques surfaces as the standard approach in any specific community. ■

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Ductal Lavage: Sensitivity and Specificity in Women with Proven Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *The technique of ductal lavage was examined in women who immediately thereafter underwent mastectomy for breast cancer. A physiologic solution was injected into cannulated breast ducts and then aspirated and examined for atypical or frankly malignant cells. Although the presence of such cells had demonstrably high specificity, the sensitivity was disappointing (only 5 of 38 [13%] of cancerous breasts had marked atypia or frankly malignant cells). Thus, ductal lavage remains an interesting research parameter but is likely to not be useful in cancer screening.*

Source: Khan SA, et al. *J Natl Cancer Inst*. 2004;96: 1510-1517.

DUCTAL LAVAGE, A TECHNIQUE WHICH involves the cannulation of breast ducts and the

infusion and subsequent aspiration of a physiological solution for cytological examination has theoretical appeal as a screening tool for women at high risk of breast cancer. Included would be those women with more dense breasts, as these have proven more difficult to examine by routine mammography, magnetic resonance imaging (MRI), and digital mammography.[1,2] To assess the use of ductal lavage as a cancer diagnostic test, Khan and associates at Northwestern University, the University of California at San Francisco and the Fox Chase Cancer Center investigated the association between ductal lavage cytologic findings and histological findings in women with known breast cancer undergoing mastectomy.

They performed ductal lavage in the operating room prior to the removal of 44 breasts from 32 women with known cancer and on eight breasts from seven women undergoing prophylactic mastectomy. When possible, they also injected ducts with dye for analysis on subsequent mastectomy specimens. Associations between cytologic and histologic results were compared.

Although ductal lavage was not always possible, at least one duct was lavaged in 36 breasts (mean of 1.4 ducts per breast). Markedly atypical or malignant cytology was found in five cancer containing breasts. In 39 ducts with complete cytologic and histologic data, ductal fluid cytology was shown to have a sensitivity of 43% (95% confidence interval [CI] = 23%-72%), specificity was 96% (95% CI = 86%-100%) and accuracy was 77% (95% CI = 63%-89%). When including mild atypia as well as marked atypia or the presence of frankly malignant cells, sensitivity was calculated at 79% (95% CI = 57%-96%), specificity was 64% (95% CI = 46%-83%) and accuracy was 69% (95% CI = 55%-83%). When all 31 cytologically evaluable breasts were analyzed, sensitivity was 17% (95% CI = 7%-35%), specificity was 100% (95% CI = 5%-100%) and accuracy was 19% (95% CI = 9%-38%). Khan et al concluded that for breasts with proven cancer, ductal lavage appears to have low sensitivity and high specificity for cancer detection.

COMMENT BY WILLIAM B. ERSHLER, MD

These findings must be considered discouraging for those who had high hopes for ductal lavage as an answer for the screening dilemma observed in high risk patients with more dense breasts for whom mammography and other imaging techniques have proven unsatisfactory. Of the 38 cancerous breasts, only 5 (13%) had marked atypia or malignant cells present in the ductal effluent. And, if including those with mild atypia, the number of positives was 16 (42%). Thus, as pointed out by Fabian, Kimler and Mayo in the accompanying editorial,[3] by either definition, the sensitivity (13% to 42%) is too low for the technique to be considered as a screening procedure for the majority of women at risk of developing breast cancer. In fact, the sensitivity may well be lower than mammography or MRI in the same population. Nevertheless, as an adjunct to these imaging studies there may ultimately be proven value to ductal lavage.

The technique, however, may well have value as a marker of biological importance in some women with high risk for breast cancer. Current cancer prevention trials have incorporated nipple aspiration fluid cytology as an outcome of interest, and ductal lavage may be similarly incorporated in such research schemes. However, for the time being, ductal lavage cytology can not be considered a sensitive screening tool and its use remains to be established in the clinical setting. ■

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Timing Isn't Everything, Right?

ABSTRACT & COMMENTARY

Synopsis: *Nearly 70% of patients achieving a CR after primary therapy eventually recurred. Most recurrences occurred more than 6 months from completion of primary chemotherapy, and the use of second line agents at the time of recurrence was effective. In this study, the median time from CR to start of third-line agent at 43 months compares favorably with the median PFS of 28 months following 12 months of Taxol reported in GOG 178 and challenges the concept of consolidation chemotherapy in ovarian cancer. A randomized trial to evaluate when to institute second line agents should be performed.*

Source: McMeekin DS, et al. *Gynecol Oncol.* 2004; 95(1):157-164.

Results from a recently published randomized clinical trial addressing the use of consolida-

tion chemotherapy strongly suggested that the strategy improved progression-free survival in selected ovarian cancer patients. Early trial termination and recommended cross-over from the control arm limited any conclusion of an overall survival benefit, concerning some clinicians who contend the added toxicity from prolonged therapy must be accompanied with an overall survival advantage to change the standard of care. McMeekin and colleagues attempted to address this latter issue by evaluating the survival outcomes of patients in complete remission and approached by their wait and see clinical standard. In this approach patients completing primary therapy were observed until clinical progression was documented.

At that point treatment was recommended and administered. From 217 reviewed patients, 59 met a strictly defined parallel enrollment criteria—that is, they met eligibility criteria for the published randomized trial. However, all of these patients were given their second chemotherapy at the time of a documented recurrence. Times to second- and third-line chemotherapy as well as overall survival were generated. With a median follow-up of 51 months, nearly two-thirds of the patient cohort recurred. The median time to progression for this group overall was 20 months. All but 2 patients received second-line chemotherapy at that time and from this cohort, all but 7 patients received a third-line treatment. The time from complete remission to the start of this therapy was 43 months. Relative to the randomized consolidation trial, this treatment time point would be similar to the progression-free survival time point a patient given consolidation chemotherapy and followed to recurrence (the start of their third-line treatment). By way of reference, the experimental cohort (12 months of paclitaxel) in that study had a median progression-free survival of 28 months or 40 months from complete remission. McMeekin et al concluded that while it would be improper to compare the outcomes of the two studies directly, observations from their wait and see policy suggest that overall survival may rival that achieved by consolidation.

COMMENT BY ROBERT L. COLEMAN, MD

Additional therapy after successful completion of a planned first-line regimen (consolidation) has become a popular strategy to address the 70%-plus recurrence risk ovarian cancer patients experience after achieving a primary complete remission.[1] Many different modalities have been evaluated including radiation therapy, immunotherapy, high-dose chemotherapy, intraperitoneal therapy and standard chemotherapy. Given the wide variance in patient cohorts and likely benefactors of these modalities, the most proper methodology to evaluate these treatments is a randomized clinical trial. Although many such trials have been conducted, to date, the only published clinical trial demonstrating any survival benefit, albeit progression-free survival, is the GOG/SWOG intergroup trial (GOG-178) comparing 3 cycles of paclitaxel (control) to 12 cycles of the same therapy.[2] The benefit demonstrated by the additional cycles of chemotherapy in this trial was sufficiently large to trip an early stopping rule agreed to and set ahead of the trial's initiation. Adhering to the recommendations outlined by the Data Safety Monitoring Board overseeing the trial, its principal investigators closed the trial to further entry, released interim results, and recommended that patients participating in the trial but randomized to the control group be offered extended therapy. While the recommendations were completely legitimate given the trial's design, some have argued the primary endpoint, progression-free survival, is insufficient to alter standard of care in this setting. Citing incurability and long term toxicity, advocates of this position argue only a trial demonstrating improved longevity warrant adoption of any new such treatment paradigms.

The current trial by McMeekin et al raises another point in that in the long run whether one initiates therapy at recurrence or before recurrence (consolidation) you may end up at the same place—equivalent survival. The trial's results are curious and speculative. If one attributes consolidation treatment as the patient's second-line, a time off therapy until recurrence was 28 months on the median—or 40 months from initiation. Waiting to treat until recurrence, in a similar cohort as presented, left one-third of patients without having to receive any therapy—they hadn't recurred.

Those that did were off treatment for 20 months and by the time they progressed again 43 months had passed; curiously closed to that seen in the randomized trial. But given the retrospective nature of its design, it can only be hypothesis generating. In fact, one could argue that the efficacy of the two trials' third-line therapy might not be equivalent. That is, the likelihood of response and survival in a patient receiving consolidation but remaining off therapy for 28 months might be superior to a patient remaining off therapy for less than 10 months. While difficult to estimate the survival difference, it is clear following the results of ICON-IV many clinicians would opt for combination chemotherapy in the former

cohort, which demonstrated an overall survival benefit over non-taxane, platinum-based therapy. Patients in the McMeekin trial would likely be treated with this combination at second-line and something else, likely single agent at third-line. It is clear that this issue needs to be readdressed. A randomized controlled clinical trial involving two treatment arms vs no treatment is planned by the GOG. ■

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CME Questions

17. In the report from Kelz et al, regarding insurance status and outcomes for colorectal cancer patients, which of the following were shown to be more common in those without private insurance (ie, uninsured or Medicaid recipients)?

a. A greater comorbidity burden
b. A higher incidence of emergent surgery
c. A higher incidence of perioperative complications
d. A higher in-hospital mortality rate
e. All of the above

18. In the report on ductal lavage for the detection of breast cancer, the sensitivity of the technique, defined by the presence of marked atypia or frankly malignant cells in the ductal effluent in patients demonstrated to have cancer in the mastectomy specimen was approximately:

a. 13%.
b. 40%.
c. 80%.
d. 95%.

19. In the report from The Netherlands regarding surgical approaches for facial basal-cell carcinoma, which of the following statements about the Mohs' technique can be concluded:

a. cosmetic results are favorable when compared to standard surgical excision.
b. recurrence rates are less after excision of primary lesions when compared to standard surgical excision.
c. complications, such as bleeding or infection are less after excision of primary lesions when compared to standard surgical excision.
d. All of the above.
e. None of the above.

Answers: 17 (e); 18 (a); 19 (e)

In Future Issues:

Chemotherapy Sensitivity/Resistance Assays in Gyenocolic Cancer

PHARMACOLOGY WATCH

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ACE Inhibitors and Receptor Blockers: Which is Inferior?

The first head-to-head comparison study of an ACE inhibitor and an angiotensin receptor blocker, to assess renoprotective effects in type 2 diabetes, has shown that the drugs are comparable in their benefit. It has been known for more than a decade that ACE inhibitors prevent progression of microalbuminuria in type 2 diabetes, out of proportion to their blood pressure lowering effects. It has also been shown that angiotensin receptor blockers are renoprotective, but it has not been shown that the drug classes are equivalent in their benefit. The Diabetics Exposed to Telmisartan and Enalapril Study Group (DETAIL study) was designed in 1996 to compare the 2 drugs in 250 patients with type 2 diabetes and early nephropathy. Patients were randomized to 80 mg of telmisartan or 20 mg enalapril daily. The primary end point was the change in Glomerular Filtration Rate (GFR) during 5 years of the study. Secondary end points included annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; the rates of end stage renal disease and cardiovascular events; and all-cause mortality. After 5 years, the change in GFR was -17.9 mL/min with telmisartan and -14.9 mL/min with enalapril (the 95% CI, -7.6- 1.6 mL/min). The data suggest that telmisartan is not inferior to enalapril in providing long-term renotection in patients with type 2 diabetes (*N Engl J Med*. 2004;351:1952-1961). In the same issue of the *Journal*, researchers in Italy compared the ACE inhibitor trandolapril plus verapamil, trandolapril alone, verapamil alone, or placebo in patients with hypertension and type 2 diabetes, and normal urinary albumin excretion. The end point was the development of persistent microalbuminuria. Over 3 years of treatment, the percentage of those patients developing microalbuminuria were: trandolapril 6%, trandolapril plus verapamil 5.7%, verapamil alone 11.9%, and placebo 10%. The authors conclude that trandolapril plus verapamil and trandolapril alone decrease the incidence of microalbuminuria to similar extent, whereas the effectiveness of verapamil alone was similar to that of placebo (*N Engl J Med*. 2004; 351:1941-1951).

The Infection Risk of Acid-Suppressing Drugs

Ever since cimetadine was first marketed in 1977, physicians have been concerned about the risk of infection associated with acid-suppressing drugs. Now researchers from the Netherlands have shown that concern is warranted, by demonstrating a link between acid-suppressing drugs and community-acquired pneumonia (CAP). Utilizing the Integrated Primary Care Information database in the Netherlands between 1995 and 2002, incidence rates for pneumonia were calculated for those exposed to acid-suppressive drugs and those who were unexposed. A case control analysis was conducted, nested in a cohort of incident users of acid-suppressive drugs, with up to 10 controls matched to each case for practice, year of birth, sex, and index date.

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The main outcome was CAP. The incidence rates for pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 in 2.45 per hundred person-years, respectively. The adjusted relative risk for pneumonia among persons currently using a proton pump inhibitor (PPI), compared with those who stopped using a PPI, was 1.89 (95% CI, 1.36-2.62). The risk for current users of H2 antagonists was 1.63 (95% CI, 1.07-2.48). The authors conclude that acid-suppressive drugs, especially proton pump inhibitors (PPIs), are associated with an increased risk of pneumonia, and suggest that these drugs should be used with caution, and at the lowest possible doses in patients who are at risk for pneumonia (*JAMA.* 2004;292:1955-1960). An accompanying editorial points out the biological plausibility of the findings and suggest that, while acid-suppressive drugs are indicated for a wide variety GI conditions, long-term, chronic use of these drugs should always be balanced with patient safety (*JAMA.* 2004;292:2012-2013).

Is Rosuvastatin As Safe As Other Statins?

Rosuvastatin (Crestor), AstraZeneca's entry into the high potency statin market, has not achieved marketshare comparable to Pfizer's atorvastatin (Lipitor) or Merck's simvastatin (Zocor). This, despite the facts that the drug is very potent and AstraZeneca has priced the drug 15-20% lower than Lipitor. Some physicians remember the cerivistatin (Baycol) withdrawal from the market, and may be concerned regarding the highest doses of rosuvastatin, especially since European regulators issued a warning earlier this year about the drug. New postmarketing data suggest, however, that rosuvastatin is as safe and well-tolerated as other statins. The records of 12,400 patients who received 5-40 mg/day were reviewed, representing 12,212 continuous patient years. In fixed dose trials with comparator statins, 5-40 mg of rosuvastatin showed an adverse event profile similar to those for 10-80 mg of atorvastatin, 10-80 mg of simvastatin, and 10-40 mg of pravastatin. Clinically significant increases in liver transaminases were uncommon (≤ 0.2%) in all groups. Myopathy with creatine kinase increases > 10 times the upper limit of normal, with muscle symptoms occurring in ≤ 0.03 % of patients who took rosuvastatin at doses of 40 mg or less. Proteinuria, at the same doses, was comparable to the rate seen with other statins as well. There were no deaths and no cases of rhabdomyolysis in patients on 40 mg or less of rosuvastatin. The authors conclude that rosuvastatin was well-tolerated, and out of safety profile similar to other commonly statins (*Am J Cardiol.* 2004;94:882-888).

Which Estrogen Preparation is the Safest?

Is esterified estrogen safer than conjugated equine estrogen? At least with regard to venous thrombosis, the answer may be yes, according to a recent study. Group Health Cooperative in Washington State, a large HMO, switched their patients from conjugated equine estrogen (CEE) to esterified estrogens (EE) in 1999. Records of perimenopausal and postmenopausal women were studied between January 1995 and the end of 2001. The primary outcome was the risk of first venous thrombosis, in relation to current use of either estrogen with or without a progestin. There were 586 cases of venous thrombosis identified. Compared with women not currently using hormones, current users of EE had no increase in venous thrombotic risk (odds ratio, 0.92; 95% CI, 0.69-1.22). Women taking CEE however, had an elevated risk (OR, 1.65; 95% CI, 1.24-2.19). Comparing users of the 2 estrogens, current users of CEE had an odds ratio of 1.78 for venous thrombosis, compared to users of EE (95% CI, 1.11-2.84), and higher doses of CEE were associated with a higher risk. Among all estrogen users, concomitant use of progestin was associated with an increased risk, compared to use with estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). The authors conclude that conjugated equine estrogen, but not esterified estrogen, is associated with an increased risk of venous thrombosis (*JAMA.* 2004; 292:1581-1587). While the authors acknowledge that these data need to be replicated, the study raises the interesting question of the differences between various estrogen preparations and the potential risks associated with them, especially when noting that conjugated equine estrogen was the only estrogen preparation used in the Women's Health Initiative.

FDA Actions

Serono has been given approval to market recombinant human luteinizing hormone (Luveris) for the treatment of infertility in women. The drug, which was granted orphan status, has been available in more than 60 countries for several years.

The FDA and Centocor have issued a warning to health care professionals about the increase risk of lymphoma associated with inflixamab (Remicade) in patients with rheumatoid arthritis and Crohn's disease. The warning applies to all tumor necrosis factor blocking agents. The drugs are associated with a 1 in 1400 risk of lymphoma, according to MedWatch, the FDA's safety information program.