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INSIDE

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An Analysis of HPV Vaccine Efficacy in Preventing Cervical Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In an analysis of four clinical trials designed to assess the efficacy of two different human papilloma virus (HPV) vaccines, the appearance of pre-neoplastic lesions and neoplastic cervical adenocarcinoma was dramatically reduced in vaccinated subjects. The three inoculation schedule was most effective, but, even for those who received less than the full number of injections, efficacy was clearly apparent. Duration of protection and overall cost effectiveness remains to be established.*

Source: Ault KA, Future II Study Group. Effect of prophylactic papillomavirus L1-virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomized clinical trials. *Lancet.* 2007;369:1861-1868.

CERVICAL CANCER CONTINUES TO BE THE SECOND LEADING cause of cancer-related death in women under 45 years of age, resulting in more than 200,000 deaths per year worldwide. It has been well established that a significant majority of these cancers (approximately 70%) are caused by Human Papilloma Virus serotypes HPV 16 and HPV 18. Routine Pap testing has reduced the rates of squamous cell cervical cancer, but the rates of adenocarcinoma have actually increased as these lesions are not readily detected by cytology. Two vaccines targeted against these serotypes have been developed, including the monovalent vaccine against HPV 16 and a quadrivalent vaccine which targets HPV 6 and 11 in addition to HPV 16 and 18. The quadrivalent form has been approved by the FDA for prevention of cervical cancer and is produced by Merck marketed under the name GARDASIL®.

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Cervical cancer risk is greatest in the 5-10 years following the first sexual experience (which in most cases worldwide is between the ages of 15 and 17 years). In addition, studies have established that antibody response is most robust in girls 10-15 year old, and significantly exceeds that found in women 16-23 years of age.[1]

This analysis was designed to evaluate vaccine efficacy in an unrestricted susceptible population of young women who were seronegative and PCR-negative to HPV 16 and 18. In addition, an intention to treat analysis was performed that included all women regardless of serostatus. Women between the ages of 16 and 26 years (n = 20,583) were randomized to receive either the monovalent or quadrivalent vaccine or placebo in 4 randomized placebo controlled trials between October 1998 and May 2003 worldwide. Of these, 17,129 met study criteria established for being "susceptible" (ie, seronegative/PCR negative for HPV16/18). Subjects were recruited from university health centers and urban clinics. Three doses of vaccine were administered: at day 1, and at month 2 and month 6. Participants were followed for a mean of 3 years following the first dose. Of a total of 8550 women in the placebo group, 85 developed HPV 16/18 related cervical intraepithelial neoplasia grades 2/3 (CIN2/3) or adenocarcinoma in situ (AIS) vs only 1 (CIN2/3) and no AIS of 8579 in the vaccine group. Based on this analysis, vaccine efficacy was found to be 98%.

In the intention to treat population in which the vaccine was administered to seronegative young women, but including those who did not receive the full course (three injections) or had other major protocol violations, 255 out of 10292 women developed HPV 16/18 related CIN2/3 or AIS in the placebo group, compared to 142 out of 10291 in the vaccine group. In this group, vaccination reduced the incidence of HPV 16/18 related CIN2/3 or AIS by 44%.

COMMENTARY

These findings show that prophylactic administration of a vaccine against HPV 16 or HPV 6/11/16/18 can lead to substantial reductions in cervical cancer worldwide. Although the current analysis is of relatively short term and HPV infection risk remains as long as women remain sexually active, it has been established that the highest risk for acquisition of HPV infection occurs in the first 5-10 years after initial sexual contact.[2] Thus, although the duration of protection is not established, even over the short haul, widespread immunization programs would prevent HPV associated cervical cancer and its associated morbidity/mortality in a large number of women. Furthermore, a health economics analysis developed by the manufacturer predicts that universal administration of vaccine to girls between the ages of 11-12 with a catch-up program in the 12-24 year olds would prove cost effective.[3] This type of analysis needs to be performed independently and on a larger scale. Decisions regarding the implementation of this major advance in preventive medicine should not be political, but based upon established evidence and humane principles.

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Hepatic Intra-Arterial Paclitaxel for Breast Cancer Metastases

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a pilot study, ten women with liver predominant metastatic breast cancer were treated with intra-hepatic arterial infusion of paclitaxel (200 mg/m2 over 24 hours, monthly). The treatment proved well tolerated and somewhat effective. Three patients attained criteria for partial response and four others exhibited stable disease which lasted for several months. Prior systemic taxane therapy did not preclude response when administered by this route.*

Source: Camacho LH, et al. Pilot study of regional, hepatic intra-arterial paclitaxel in patients with breast carcinoma metastatic to the liver. *Cancer.* 2007;109:2190-2196.

The liver as a site of dominant metastatic disease for patients with breast cancer is a well-recognized indicator of poor prognosis. In fact, approximately 25% of women with breast cancer will develop hepatic metastasis during the course of their illness.[1] Camacho and colleagues at the M.D. Andersen Cancer Center in Houston performed a pilot study to test the feasibility and effectiveness of intrahepatic arterial infusion of paclitaxel in this setting. Ten women with chemotherapy-refractory breast carcinoma and predominant liver involvement were enrolled in the study. These patients were of good functional status (ECOG Performance Status 0 or 1) and did not have biochemical evidence of liver failure. Total bilirubin was less than 1 mg/dL and the prothrombin time and activated partial thromboplastin time were within in the normal limits. Furthermore, serum creatinine was less than 1.5 mg/dL. The patients underwent angiographic placement of a hepatic artery infusion catheter. Prior to drug infusion, a nuclear medicine flow study using Technetium-99 macroaggregated albumin particles was performed to demonstrate the flow distribution within the liver and to rule out the possibility of extrahepatic flow that might have resulted in gastrointestinal complications. Upon completion of the flow study, paclitaxel (200 mg/m2) was administered by 24-hour continuous infusion through the catheter. The regimen was repeated every four weeks until tumor progression, toxicity, or withdrawal of consent. All patients had been heavily pretreated and several had previous experience with taxanes.

Three of the 10 patients attained partial response that lasted for 6 months, 7 months, and 48 months; and four other patients had stable disease for five months to nine months. One patient underwent liver resection after receiving the hepatic arterial infusion and remained disease-free at 48 months. Eight of the 10 patients had received prior systemic taxane therapy either alone or with other cytotoxic drugs. However, no association between previous taxane exposure and the efficacy of the current regimen was established. In fact, all three patients who experienced partial response had had prior treatment with a taxane.

The most common treatment related toxicities were leukopenia, fatigue, nausea, and vomiting. With the exception of one patient who experienced grade 4 leukopenia, the remaining courses were well tolerated and not dissimilar from paclitaxel administered intravenously.

COMMENTARY

Thus, it appears that hepatic intra-arterial infusion with paclitaxel for women with liver-dominant metastatic breast cancer is feasible, well tolerated, and somewhat effective. It is encouraging to note that responses were seen in patients considered refractory to taxane administered intravenously. Perhaps the higher tissue level achieved or the prolonged exposure of the drug were factors involved in overcoming resistance.

Previous studies of hepatic arterial infusion using combined drugs (cisplatin and vinblastine) showed significant response rate, but the treatment was compromised by excessive toxicity.[2]

In colon cancer metastatic to the liver, there has been a reemergence of enthusiasm for intrahepatic arterial infusion. For example, Kemeny and colleagues[3] have recently updated an earlier trial demonstrating that many patients had prolonged survival after such an approach was administered in the colon cancer setting. At 10 years, the overall survival was 41% for those that had received intrahepatic arterial infusion compared to 27% that had been given the same medicine intravenously. Whether such will be observed for breast cancer remains to be determined, but this pilot trial would suggest that a larger scale randomized control trial is warranted. ■

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Chronic Illness and the Success of Adjuvant Colon Cancer Chemotherapy: Some Good News

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *The effectiveness of adjuvant chemotherapy for patients with stage III colon cancer is well established but it is less frequently prescribed in older patients. One possible explanation is a concern that existing comorbidities may reduce effectiveness of treatment. In an analysis of SEER-Medicare data on a large sample of elderly (median age, 76 years) stage III colon cancer patients. Gross and colleagues demonstrated reduced use of adjuvant therapy when patients had coexisting congestive heart failure, diabetes or chronic obstructive lung disease. However, for those that were treated, there was a demonstrable survival advantage.*

Source: Gross GP, et al. *Cancer.* 2007;109:2410-2419.

It has long been suspected that the presence of comorbidity influences both the use and effectiveness of chemotherapy. To address this issue, Gross and colleagues at Yale University queried the Surveillance, Epidemiology, End Results-SEER Medicare Claims database to explore whether patients with comorbidity that included stage III colon cancer between the years 1993 and 1999 were treated with adjuvant chemotherapy. Specifically, the correlations between receipt of adjuvant chemotherapy in the presence of heart failure, diabetes, and/or chronic obstructive pulmonary disease were assessed. Multivariable regression analysis was used to assess the risk of death or hospitalization as a function of treatment and comorbidity status.

The sample included 5330 patients from the SEER database. This population-based tumor registry has been linked with Medicare Administrative Claims data and includes in addition to those claims, characteristics such as cancer type, site, histologic grade, and disease staged. For this analysis, patients aged greater than 67 years (median age for the sample studied, 76 years) were diagnosed with primary adenocarcinoma of the colon. Medicare claims data were used to identify those with existing comorbidity.

Of the 5330 patients in this analysis, it was found that the use of adjuvant therapy was related significantly to heart failure (36.2% for those with heart failure and 64.9% for those without). The adjusted odds ratio (OR) was 0.49; a 95% confidence interval (95% CI) was 0.40 to 0.60. Similar but less robust findings were observed for COPD (OR, 0.83; 95% CI, 0.70 to 0.99) and diabetes (OR, 0.81; 95% CI, 0.68 to 0.97). Among patients who had heart failure, the five-year survival was significantly higher among those who received adjuvant chemotherapy (adjusted five-year survival rate, 43%; 95% CI, 40% to 47%) than among those who did not receive adjuvant chemotherapy (30%; 95% CI, 27% to 34%). Among patients without heart failure, the five-year survival estimates among treated and untreated patients were 54% (95% CI, 52% to 56%) and 41% (95% CI, 38% to 44%), respectively. The probability of all cause, condition specific, or toxicity-related hospitalization associated with adjuvant therapy was not altered by the presence of any of the three comorbid conditions.

COMMENTARY

It will probably come as no surprise to practicing oncologists that adjuvant chemotherapy was offered less commonly in this older age group with existing comorbidity. In fact, even in the absence of comorbidity there was a relatively low rate of adjuvant chemotherapy offered (approximately 65% of patients).

This reflects practice patterns of approximately a decade ago, and possibly the numbers would be better today inasmuch as there have been reported trials indicating the effectiveness of adjuvant chemotherapy in this age group.[1,2] Of the three study comorbidities, CHF appeared to have the largest negative impact upon the offering of adjuvant chemotherapy. This may be because physicians are aware that congestive heart failure itself is associated with limited survival and the drugs used for adjuvant chemotherapy might have been considered to negatively influence the effectiveness of congestive heart failure treatment. Nonetheless, it is gratifying that for those patients who had stage III colon cancer and CHF, the benefits of adjuvant chemotherapy were clearly apparent. The five-year survival was significantly higher for those who received adjuvant chemotherapy than for those who did not (43% vs 30%). Furthermore, the hospitalization rate for all treated patients (with or without any of the three comorbidities) was not different. Thus, this report should bolster the moxie of oncologists when approaching the more typical older patients with recently diagnosed

stage III colon cancer. The presence of comorbidity is not an absolute contraindication to therapy as its effectiveness has been clearly demonstrated in the community for those selected patients who were treated. ■

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Racial Impact of Anemia And Mortality in The Elderly

ABSTRACT & COMMENTARY

By Andrew Artz, MD, MS

Division of Hematology/Oncology University of Chicago, Chicago, IL

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

Synopsis: *Anemia is a common problem associated with increased mortality among older adults. The higher prevalence of anemia in black older adults compared to white older adults has raised concern whether different hemoglobin (Hb) thresholds should differ by race. Patel and colleagues evaluated a biracial population of community-dwelling adults 71 to 82 years. They used the standard WHO anemia criteria f of Hb < 13 g/dL (130 g/L) for men and < 12 g/dL (120 g/L) for women. In whites, anemia predicted for increased age adjusted-mortality. However, in blacks, anemia status did not influence mortality. Mobility disability also developed more often in whites having anemia but not in anemic blacks. In this study, anemia by WHO criteria was associated with increased mortality in whites but not blacks. Further study on outcomes and anemia etiologies by race will be needed before developing Hb thresholds that define anemia by race.*

Source: Kushang Patel, et al. *Blood.* 2007;109:4663-4670.

ANEMIA IS A COMMON PROBLEM AMONG OLDER adults occurring in over 10%[1,2] and up to 50% in hospitalized or institutionalized elderly.[3,4] Epidemiologic research has uncovered a striking independent association between anemia in the elderly and adverse outcomes. Anemia prognosticates for functional impairment, increased hospitalization, and increased mortality. The hemoglobin (Hb) threshold below which anemia is defined has generated considerable controversy. The World Health Organization (WHO) standard of Hb < 13 g/dL for men and < 12 g/dL for women remains the most common benchmark. However, epidemiologic studies have shown the lowest mortality occurs when Hb was 14-15 g/dL for women and 15-16 g/dL for men. Hb varies by race, such that blacks have lower median Hb concentrations and higher anemia prevalence. In one population-based study of older adults, anemia prevalence was 28% for blacks and 9% for whites.[1] This has led to proposals for a lower Hb threshold to define anemia in blacks.[5]

The limited data on the adverse effect of anemia by race led Patel and investigators to examine racial variation of anemia on mortality and mobility. The study population comprised community-dwelling adults aged 70-79 years from the Health ABC study. They evaluated 1018 black and 1583 white adults aged 71 to 82 years. Whites were randomly selected but all blacks were recruited. Anemia was defined by the WHO criteria of < 13 g/dL for men and < 12 g/dL for women. Mortality and mobility difficulty were longitudinally assessed.

Among blacks, 26% of men and 21% of women had anemia at baseline compared to 14% of white men and 7% of white women. In whites, anemia increased the chance of developing mobility difficulty although in women, the statistical significance was reduced after multi-variable adjustment. In blacks, anemia did not predict for developing mobility difficulty. For whites, anemia was associated with an increased mortality in men (HR = 1.96, 95% CI: 1.35-2.83) and women (HR = 2.86, 95% CI:1.69-4.82). Anemia had no statistical impact on mortality in black men (HR = 1.15, 95% CI: 0.77 - 1.72) or women (HR = 1.39), 95% CI: 0.91-2.14). The only threshold showing an increase in mortality for blacks was found in black men having Hb value 2 g/dL below the WHO threshold (ie < 11 g/dL).

COMMENTARY

Anemia occurs in over 10% of adults 65 years and older. Further, an emerging body of data has shown that anemia, and even mildly reduced Hb (eg, Hb < 14 g/dL), is associated with worse survival. Anemia prevalence is three-fold higher in older blacks compared to older whites but data on the adverse impact by race has been limited.

In this observational study, Patel and colleagues showed increased mobility difficulty and confirm other reports of worse survival among anemic older whites. However, anemia as defined by the WHO criteria did not increase mobility difficulty or mortality in blacks. The authors suggest considering using Hb lower than the WHO threshold of < 13 g/dL for men and < 12 g/dL in elderly blacks.

Although the analysis was careful, study limitations may preclude generalization. The recruitment strategies

for blacks and whites differed as did number of patients lacking baseline Hb values (56% in blacks compared to 39% in whites). This may have led to bias that abrogated the mortality impact of anemia. Further, the data conflict with another recent study showing increased mortality in older anemic blacks.[6] In addition, we do not know if anemia might lead to other important impairments, such as quality of life.

Oncologists are frequently referred anemic elderly adults without cancer. The main struggle, however, is not the prognostic impact but the necessary evaluation. Should one rest on a focused history, physical and laboratory evaluation? Or, should one complete an exhaustive evaluation, including endoscopy and a bone marrow evaluation to find a cause? Unfortunately, no evidence based guideline exists as to the appropriate evaluation and most studies show no proximate cause in approximately 1/3rd of cases.[1,7] Even should the results of this manuscript be validated that anemia by WHO threshold does not predict mortality in blacks, it will not prove that we should employ a lower Hb threshold in defining anemia in elderly blacks. Some blacks may have a lower Hb due to genetic changes, such as α-thalassemia,[8] which may lower the population based median Hb. However, defining anemia on a population basis using a lower Hb threshold runs a serious risk of missing important causes. Only a rigorous study documenting anemia etiology by race and Hb threshold will clarify the Hb concentration where we can safely defer an etiologic evaluation.

Finally, we must recognize that observational data on Hb and mortality do not necessarily dictate Hb criteria for corrective therapy. The Hb concentration where treatment should be initiated and the target Hb concentration must be guided by prospective interventional trials. This analysis raises the provocative hypothesis that race should be analyzed in these interventional trials.

This manuscript should increase awareness of anemia in older adults and the markedly higher prevalence in blacks. It is likely that genetic differences account, at least in part, to the lower median Hb in blacks and higher anemia prevalence. However, whether a lower Hb threshold should be used for all blacks remains unknown. For now, it seems premature to use a lower Hb value for etiologic evaluation in blacks compared to whites until further data are published. ■

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Hepatitis C Virus And Non-Hodgkins Lymphoma: VA Study Confirms Association

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a retrospective case-control analysis conducted within the U.S. Veterans Affairs hospitals, the incidence of cryoglobulinemia, Waldenstrom's macroglobulinemia, and non-Hodgkin's lymphoma were each found to be significantly increased in patients with hepatitis-C viral infection.*

Source: Giordano TP, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with Hepatitis C Virus. *JAMA.* 2007;297:2010-2017.

An estimated 4.1 million US residents representing 1.6 percent of the total population are infected with the Hepatitis C Virus (HCV). This prevalence is increased over three fold (approximately 5%) in US military veterans. Many previous stud-

ies have suggested an association between the HCV and cancer, particularly hematological malignancies and related lymphoproliferative disorders.[1] Furthermore, it has been shown that effective treatment of HCV, for example, with interferon alfa, occasionally results in lymphoma remission for those with coexisting disease.[2,3]

The current study was designed to test the hypothesis that HCV infection has a role in the pathogenesis of lymphoproliferative malignancies. In a US Veterans Administration-wide study capitalizing on the excellent medical records maintained throughout the 150 hospital system, a retrospective case-control cohort study was conducted. This was a particularly suitable strategy in light of the high prevalence of HCV infection among VA patients.

Data from hospitalization and clinic visits between the years 1997 and 2004 identified 146,394 HCV patients. For comparative purposes, an HCV uninfected control cohort was randomly chosen (4 controls for each HCV patient) who were matched by age, sex, and baseline visit type. There were a total of 572,293 control subjects. Both groups (cases and controls) were predominantly men (97%) and were of the same mean age [52 years; SD, (8 years)]. Individuals infected with HIV were excluded from the analysis. Patients were followed for a mean of 2.3 years.

As expected, the risk for hepatocellular carcinoma was markedly increased, (hazard ratio [HR] 24.15; 95% confidence interval [CI], 20.92-27.88). The risk of NHL was increased by 20-30% (HR 1.21; 95% CI, 1.07-1.37). The risk of Waldenstrom's macroglobulinemia nearly tripled (HR 2.72; 95% CI, 2.00-3.72). In addition, there was an increase in non-malignant plasma cell dyscrasias including MGUS and cyroglobulinemia (HR 3.93; 95% CI 3.32-4.64). The incidence of other hematological malignancies was not increased in HCV patients, nor was the incidence of thyroid cancer, as had been previously reported.[4] Curiously, acute lymphoblastic leukemia (ALL) was significantly less common in HCV patients (HR 0.57; 95% CI 0.38-0.85).

COMMENTARY

This, by far, is the largest study to date assessing the increased risk of hematopoietic malignancies in people with HCV, and the data are quite convincing. HCV confers an increased risk for lymphoproliferative disorders (most notably cryoglobulinemia), Waldenstrom's macroglobulinemia, and non Hodgkin lymphoma (NHL). Now, of course, the issue is what do we do with this information? The findings support a hypothesis that chronic HCV infection serves as an immunological stimulus for progression to hematological malignancy. Whether the virus itself is directly responsible for transforming susceptible lymphoid cells, or the lymphomagenesis is merely the result of a chronic lymphoproliferative response to HCV infection is unclear. However, it seems that HCV patients are particularly susceptible to developing malignancies of B cell lineage. Accordingly, this might be a very suitable population for introducing cancer prevention strategies. At the very least, patients with HCV infection should be scrutinized carefully and regularly for the development of associated lymphoproliferative disorders, and this evaluation might well include serum protein analysis as well as imaging studies to identify autonomous lymphoid tissue proliferation. ■

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CME Questions

27. Administration of HPV vaccine is effective in preventing cervical neoplasia in:

a. HPV naïve young women if administered prior to sexual activity.
b. HPV naïve young women even if administered after first sexual activity.
c. Both of above.
d. Neither of above.

28. Intra-hepatic arterial infusion of paclitaxel for patients with liver predominant breast cancer was recently been demonstrated to be:

a. Somewhat effective but too toxic to warrant further investigation.

b. Ineffective and very toxic.
c. Somewhat effective and well tolerated.
d. Ineffective but well tolerated.

29. For older patients with stage III colon cancer and coexisting congestive heart failure, examination of the SEER-Medicare data indicates that adjuvant chemotherapy, when offered, is:
a. More likely to result in hospitalization for toxicity.
b. Less likely to be associated with efficacy (prolongation of survival).
c. Neither of the above.
d. Both of the above.

30. From this article by Gupta and colleagues, what did the authors show about the impact of anemia and mortality by race?
a. Anemia was associated with increased mortality in whites.
b. Anemia was associated with the development of mobility difficulty in whites.
c. Anemia was not statistically significantly associated with mortality in blacks.
d. Anemia was not statistically significantly associated with mortality in blacks.
e. All of the above.

31. The incidence of which of the following diseases is elevated is NOT increased in patients with hepatitis C viral infection.
a. Non-Hodgkin lymphoma.
b. Cryoglobulinemia
c. Acute Lymphoblastic Leukemia.
d. Waldenstrom's macroglobulinemia.

Answers: 27 (c); 28 (c); 29 (c); 30 (e); 31 (c)

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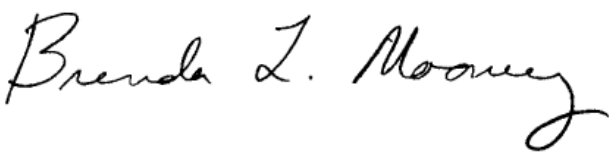

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PHARMACOLOGY WATCH

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.

Avandia, Risk of Congestive Heart Failure Significant Safety Risk

GlaxoSmithKline's rosiglitazone (Avandia) will receive a black box warning by the FDA because of concerns over heart failure associated with use of the drug. Pioglitazone (Actos) will also be subject to a black box warning for the same reason. The drugs, used for treatment of type 2 diabetes, have been scrutinized because of a recent meta-analysis that suggested that rosiglitazone was associated with a significant- increase risk of myocardial infarction and a borderline significant-increase risk of death from cardiovascular causes. (published www.NEJM. org on June 21, 2007 [10.1056/NEJMoa 072761]). Soon on the heels of the publication of this study, Glaxo rushed an interim analysis of its own trial to press. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published online in the *New England Journal of Medicine* on June 5, 2007. In the RECORD study, 4,447 patients with type 2 diabetes who had inadequate control with metformin or a sulfonylurea were randomized to receive add-on rosiglitazone or a combination of metformin and a sulfonylurea. The primary endpoint was hospitalization or death from cardiovascular causes. After mean follow-up of 3.75 years, 217 patients in the rosiglitazone group and 202 patients in the control group had the primary endpoint (hazard ratio 1.08), and after adding in pending primary end points the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There was no statistically significant difference between either group with regard to myocardial infarction or death from cardiovascular causes or any cause. There was a significantly higher rate of heart failure in rosiglitazone group (HR 2.15; 95% CI, 1.30 to 3.57). The authors conclude that the study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes, as there was no evidence of an increased death rate of cardiovascular causes or all causes associated with the drug, but there was a significantly higher rate of heart failure. There was insufficient data to determine if there was an increase risk of myocardial infarction (published at www.NEJM.org June 5, 2007 [10.1056/NEJMoa 073394]). The study was accompanied by 3 editorials that recommended caution in use of rosiglitazone and similar drugs especially in patients at risk for congestive heart failure. And while GlaxoSmithKline sees the study as vindication of the safety the drug, others, including the FDA, see the risk of congestive heart failure as a significant safety risk. Soon after publication of the RECORD study, a congressional hearing was held to discuss the safety of rosiglitazone and within days the FDA issued the black box requirement for rosiglitazone and pioglitazone. During the hearing, it came to

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light that at least one official at the FDA had suggested stronger warnings on rosiglitazone nearly a year ago, but her recommendation was ignored; she was reassigned and subsequently left the agency. Within several days of the rosiglitazone hearing, legislation was introduced to bolster the FDA's ability to monitor prescription drug side effects, a bill which also includes many of the Institute of Medicines recent recommendations on drug safety, and also included limiting direct-to-consumer advertising for newly approved medications.

Aspirin, Higher Doses No More Effective, Risky

What is the best dose of aspirin for prevention of cardiovascular disease? More than 50 million people take aspirin regularly in doses that range from 50 mg to over 1000 mg per day. The most commonly used doses are 81 mg and 325 mg per day. A recent systematic review of the English-language literature revealed that doses as low as 30 mg/day are effective at fully inhibiting platelet thromboxane production and preventing platelet aggregation. Despite this, higher doses are frequently used. The available evidence, primarily from secondary prevention trials, suggest that doses greater than 81 mg do not enhance efficacy, but do increase risk of GI bleeding and other toxicities. The authors conclude that aspirin doses of 75 mg to 81 mg/day are optimal for the indication of cardiovascular disease prevention, and higher doses are no more effective but are associated with higher risk (*JAMA* 2007; 297:2018-2024).

Subclinical Hypothyroidism Treatment Benefits

Subclinical hypothyroidism is defined as raised TSH levels with circulating thyroid hormones within the normal range. A new study suggests that treatment of subclinical hypothyroidism improves cardiovascular risk factors and quality of life. One hundred patients with a mean TSH of 6.6 mIU/l who had never received thyroid treatment and did not have cardiovascular disease were enrolled in a randomized, double-blinded crossover study of 100 µg of l-thyroxine or placebo daily for 12 weeks. Treatment with L-thyroxine reduced total cholesterol from an average of 231.6 to 220 mg/dl (P <0.001), LDL cholesterol from 142.9 to 131.3 mg/dl (P < 0.05), and waist to hip ratio from 0.83 to 0.81 (P < 0.006). Treatment also significantly improved endothelial function based on brachial artery flow mediated dilation, an early marker of atherosclerosis. Patients also reported decreased tiredness in the active treatment group, and there was a trend towards improvement in the perceived negative impact of hypothyroidism on sexual function. The authors conclude that treating subclinical hypothyroidism with l-thyroxine lead to significant improvements of cardiovascular risk factors and symptoms of tiredness (*J Clin Endocrinol Metab* 2007; 92:1715-1723).

FDA approvals

The FDA has approved a new transdermal patch for the treatment of early stage idiopathic Parkinson's disease. Rotigotine transdermal is a once-daily patch that is available in 2, 4 and 6 mg strengths. The drug is a dopamine agonist that affects D3/D2/D1 receptors and is thought to exert its effect via stimulation of dopamine D2 receptors. In clinical trials the patch was shown to improve scores on standardized rating scales for daily living and motor components in Parkinson's disease. The most common side effects are site reactions, dizziness, nausea, vomiting, somnolence and insomnia. Rotigotine transdermal will be available by the end of 2007 and will be marketed by Schwartz Pharma under the trade name Neupro.

The FDA has approved a new continuous contraceptive for women that is designed to eliminate menstruation. Wyeth pharmaceuticals Lybrel is a 28-day pill pack of levonorgestrel and ethinyl estradiol (90 µg/20 µg) that does not contain a placebo or pill-free interval. In clinical trials 59% of women achieved amenorrhea without bleeding or spotting, while 20% experienced spotting but did not require sanitary protection, and 21% required sanitary protection due to breakthrough bleeding. There was also no delay to return of menses after discontinuing the product nor any significant delay in fertility. Lybrel is scheduled to be available by July 2007.

Risedronate (Actonel) has received approval for a new once-a-month dosing schedule for the treatment of osteoporosis. The dose regimen requires patients to take 75 mg tablets on 2 consecutive days each month. The approval was based on a study that compared the monthly regimen with a daily regimen of 5 mg per day and showed no significant difference in efficacy for increasing bone mineral density at the lumbar spine, total hip, and hip trochanter. Risedronate is marketed by Procter & Gamble pharmaceuticals. ■