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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Absent Influenza Vaccine Response in Rituximab-treated Lymphoma Patients

By William B. Ershler, MD, Editor

SYNOPSIS: Influenza remains a major source of morbidity and increased mortality among patients with cancer, and prior studies had indicated impaired response to vaccination. In the current report, lymphoma patients treated with rituximab, either in combination with chemotherapy or as a single agent, were found to have markedly deficient influenza vaccine response, with not 1 of 67 achieving a protective titer, compared with 42 of 51 controls. Thus, rituximab-treated lymphoma patients are particularly susceptible to vaccine failure and influenza infection should be highly considered in symptomatic patients, even in those who had been appropriately vaccinated.

SOURCE: Yri OE, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. *Blood* 2011;118:6769-6771.

The concern regarding influenza is high among cancer patients as the rate of infection is considerably higher and mortality is four times greater than in the general population.[1] Cancer itself is immunosuppressive, but additional impairment from therapy is also of importance. Patients with lymphoma receiving rituximab may be particularly susceptible as this agent produces a prolonged depletion of B cells and impaired humoral responses.[2] It is known that in patients with rheumatoid arthritis receiving rituximab, antibody responses to both carbohydrate and protein vaccines are impaired.[2,3] Similarly, it is likely that rituximab-treated lymphoma patients also are likely to have diminished vaccine response, although this has not been definitively established.

Yri and colleagues throughout Norway have addressed this in the current report. Their aim was to investigate whether lymphoma patients undergoing rituximab-containing treatment regimens or having received such regimens within the past 6 months were able to mount protective antibody responses to the influenza A (H1N1) 2009 virus vaccine during the 2009 "swine flu" pandemic. A total of 67 lymphoma patients and 51 controls, all of whom had low prevaccination titers, received the monovalent influenza A (H1N1)

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Clinical Oncology [ALERT]

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vaccine (Pandemrix; Glaxo SmithKline) and antibody levels were determined before and 3 weeks or more after vaccination by standard hemagglutination-inhibition assay. An antibody titer of ≥ 40 was considered protective. The patients were somewhat older than controls (mean age 63 years vs 47 years, respectively) and most patients had received combined chemotherapy plus rituximab, although seven had received rituximab alone.

Among the vaccinated lymphoma patients, five persons had a post-vaccine titer of 20 and the remaining 62 patients had no detectable titers at all. In contrast, 42 of the 51 controls (82.4%) had a post-vaccination titer ≥ 40, eight had a titer of 20, and only one showed no response. Thus, the sero-protection rate for this vaccine was 0% in treated lymphoma patients and 82% in controls.

COMMENTARY

These are striking findings with serious clinical implications. Of course, patients on chemotherapy would be expected to have a reduced response to vaccine, especially to one that is only moderately immunogenic, such as influenza vaccine. However, the use of rituximab might be of critical importance in explaining the nearly absent response. In a prior study of vaccination from the same group of investigators, 72% of non-rituximab treated cancer patients, including those with both solid tumor and lymphoma, achieved protective antibody levels after receiving the trivalent influenza vaccine. However, the lymphoma subgroup fared less well than those with solid tumor, only 38% responding, compared to 82% of those with solid tumor.[4] Thus, vaccine response is less among lymphoma patients, but the current data would suggest that the inclusion of rituximab is of incremental importance in this regard. Physicians should be aware that such patients are particularly susceptible to influenza, despite having received vaccine, and if infection is suspected, the threshold for starting antiviral treatment should be lowered.

Under optimal circumstances, response to the commercially available influenza vaccines is far from ideal, and those with compromised immunity remain susceptible to infection despite infection. Improved vaccines are needed, including those that employ various adjuvants or that target influenza antigens other than hemagglutin, yet much research needs to be completed before these become available. In the meantime, other strategies, including vaccines with larger doses of antigen, or double administration (e.g., vaccination twice during influenza season) remain viable options worthy of clinical investigation. ■

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ABSTRACT & COMMENTARY

Prognostic Importance of Serum Light Chains in Patients with CLL

By William B. Ershler, MD

SYNOPSIS: A full panel of prognostic indicators was examined in 449 treatment-naïve CLL patients and it was found that serum light chain ratio was useful in confirming clonality. However, the sum of both κ and λ serum light chains proved of greater prognositc value in determining an early need to offer CLL treatment. A total (κ + λ) level of > 60.6 mg/mL was an independent predictor of limited treatment-free survival.

SOURCE: Morabito F, et al. The cumulative amount of serum-free light chain is a strong prognosticator in chronic lymphocytic leukemia. ***Blood*** 2011;118:6353-6361.

Clinicians are well aware that chronic lymphocytic leukemia (CLL) is a heterogeneous disorder, with some patients experiencing rapid progression and others surviving for years or even decades without ever requiring therapy. Clinical staging, such as by the Rai or Binet classification systems, are useful, as are the incorporation of various biomarkers including ZAP-70, CD38, immunoglobulin heavy chain variable gene (IGHV) mutation status, and cytogenetic abnormalities, which have proven useful in predicting progressive disease and survival.[1] However, these assays are cumbersome, expensive, and not always reproducible or even available outside of the clinical research environment.

In contrast, the measurement of serum free light chain (sFLC) can be reproducibly and inexpensively assayed by straightforward nephelometry.[2] Antibody production by B lymphocytes involves the assembly of an immunoglobulin molecule combining heavy and light chains. Under physiological conditions, light chains, either κ or λ, are produced in excess, pass through the serum transiently, and are excreted renally. In clonal B cell malignancies (such as CLL), certain lymphomas, and most notably multiple myeloma, clonality can be demonstrable by the appearance of an abnormal κ/λ ratio in the serum. In addition to confirming clonality, there has been recent interest in examining the utility of the serum free light chain ratio (sFLC κ/λ) as a prognostic marker for CLL.[3,4]

Identification of patients at risk for early disease progression facilitates the likelihood of tailored management in CLL. Abnormality of κ and λ serum-free light chain ratio [sFLC (κ/λ)] has been proposed as a straightforward prognostic factor in CLL. To determine if assessment of this ratio [sFLC (κ/λ)] is of added value to our existing prognositic factors, Morabito and colleagues analyzed clinical data and blood samples from 449 therapy-naïve patients evaluated throughout Italy. They found that an abnormal sFLC (κ/λ), along with CD38, ZAP-70, IGHV mutations, cytogenetics, and clinical stage, independently predict treatment-free survival (TFS). The investigators also introduced a new measure, the cumulative amount of clonal and nonclonal FLCs [sFLC (κ+λ)], and found that when in excess of 60.6 mg/mL, this measure is associated with cytogenetic risk and significantly predicts short TFS.

COMMENTARY

Approximately 50% of CLL patients display an abnormal sFLC (κ/λ) and/or elevated levels of clonally unrestricted κ or λ sFLC. In their analysis of a large cohort (n = 449) of untreated CLL patients for the panel of established CLL biomarkers, the investigators document that sFLC(κ/λ) and sFLC absolute (summed κ+λ) levels are distinct prognostic variables in CLL. Although abnormal sFLC(κ/λ) was associated with parameters reflecting disease aggressiveness (i.e., stage, CD38/ZAP-70, IGHV mutations) and independently predicted TFS, it did not correlate with cytogenetic risk. In contrast, unfavorable cytogenetics were associated with the quantitative sum of κ and λ serum levels. Accordingly, they demonstrate the prognostic value of an abnormal sFLC(κ/λ) becomes irrelevant if the sFLC(κ+λ) value is above the threshold value of (60.6 mg/mL). In contrast, by multivariate analysis, sFLC(κ+λ) more than 60.6 mg/mL was demonstrated as a strong predictor of TFS together with ZAP-70, staging, and cytogenetics, whereas CD38, IGHV mutations, and sFLC(κ/λ) abnormalities lost their prognostic power. A straightforward model, including sFLC(κ+λ) more than 60.6 mg/mL, Binet staging, ZAP-70, and cytogenetics, was validated to accurately predict time to treatment requirement in untreated CLL patients.

Thus, determination of serum light chains is a useful and inexpensive adjunct to the initial evaluation of CLL patients. An abnormal κ/λ ratio indicates clonality and offers prognostic information. Of note, if the total quantitative serum light chain (κ+λ) exceeds the 60.6 mg/mL threshold, there is likely to be a threshold that is highly predictive of a short interval before treatment will be required. ■

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ABSTRACT & COMMENTARY

Promising Results with Dasatinib Added to Docetaxel for Treating Castration-resistant Prostate Cancer

By William B. Ershler, MD

SYNOPSIS: The tyrosine kinase inhibitor dasatinib was added to docetaxel in the treatment of advanced castration-resistant prostate cancer in a Phase 1-2 trial. The combination was shown to be generally well-tolerated and to result in markers of reduced bone turnover in the great majority of patients and in durable PSA responses in approximately 50%. The findings justify proceeding to Phase 3 clinical trial.

SOURCE: Araujo JC, et al. Dasatinib combied with docetaxel for castration-resistant prostate cancer. Results from a Phase 1-2 study. *Cancer* 2012;118:63-71.

Treatment of castration-resistant prostate cancer remains challenging primarily because of the relentless progression of metastatic disease within bone and visceral tissue. Chemotherapy, such as with docetaxel, has provided limited benefit, and current research has focused on targets that are involved in disease progression. In vitro and animal model research has indicated certain tyrosine kinases are important in the generation of mediators that influence prostate cancer growth, invasion, and metastases.[1,2] Furthermore, tyrosine kinase inhibitors have been shown to modulate the production of these mediators and restrain tumor growth in these models.[3-6] Thus, a rationale for the study of tyrosine kinase inhibitors in the setting of progressive prostate cancer has been established.

In the current report, Araujo and colleagues conducted a Phase 1-2 trial combining docetaxel with dasatinib, an oral SRC inhibitor to determine the potential efficacy of targeting both the tumor and bone microenvironment in patients with castration-resistant prostate cancer. The Phase 1 part of the trial involved escalating doses of dasatinib (from 50 mg once daily to 120 mg once daily) and docetaxel (60 to 75 mg/m^2) every 21 days in to a total of 15 patients. In Phase 2, 30 additional patients received dasatinib 100 mg once daily/docetaxel 75 mg/m^2 every 21 days. Efficacy endpoints included changes in prostate-specific antigen (PSA), measurable disease, bone scans, and markers of bone metabolism. Safety and pharmacokinetics were also studied.

Combination dasatinib and docetaxel therapy was generally well tolerated. Thirteen of 46 patients (28%) had a grade 3-4 toxicity. Pharmacokinetic analysis indicated no drug-drug interactions, and in the Phase 1 study, a maximum tolerated dose was not identified. Durable 50% PSA declines occurred in 26 of 46 patients (57%). Of 30 patients with measurable disease, 18 (60%) had a partial response. Fourteen patients (30%) had disappearance of a lesion on bone scan. In bone marker assessments, 33 of 38 (87%) and 26 of 34 (76%) had decreases in urinary N-telopeptide or bone-specific alkaline phosphatase levels, respectively. Twenty-eight patients (61%) received single-agent dasatinib after docetaxel discontinuation and had stabilization of disease for an additional 1 to 12 months.

COMMENTARY

Chemotherapy for castrate-resistant prostate cancer provides some, but limited, improvement in overall survival and is associated with toxicity.[7-9] However, therapy targeted at mediators of disease progression, particularly in bone, hold some promise. Dasatinib is a potent inhibitor of SRC-family kinases and is one such targeted therapy that is being explored in this regard, either as a single agent,[10,11] or in combination with docetaxel, as in the current report.

In this study dasatinib and docetaxel combination therapy was shown to be well-tolerated and to have encouraging efficacy.

The relatively high objective response rate and favorable toxicity profile are sufficient justification to proceed to randomized studies of docetaxel and dasatinib in castration-resistant prostate cancer. Based on this study, it is quite likely that the combination will prove superior to docetaxel alone, but a number of questions related to the comparative tolerability and safety, the appropriate time to start, and how long the combined or dasatinib treatment alone should continue will need to be addressed. ■

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ILLUSTRATIVE CASE SERIES

Care Options for Breast Cancer Survivors

By Jerome W. Yates, MD

Professor of Medicine, SUNY at Buffalo; Professor of Oncology, Roswell Park Cancer Institute, Buffalo, NY; Senior Clinical Research Scientist, Clinical Research Branch, NIA, NIH

Dr. Yates reports no financial relationships relevant to this field of study.

A 57-year-old postmenopausal librarian, who is 1-year post diagnosis of a stage II invasive cancer of the right breast, is found to be estrogen- and progesterone-receptor positive, and Her2neu negative with one positive axillary node. Following the completion of breast conserving tumor resection, adjuvant chemotherapy, and radiation treatment, she was given the option of being followed by her surgeon, medical oncologist, radiation therapist, primary care physician, or a nurse practitioner in the multidisciplinary clinic. She was not comfortable with the consultant medical oncologist and was favorably inclined toward the nurse practitioner, having been assured that she would see her at each follow-up visit. Her previous primary care physician retired during the course of her adjuvant chemotherapy. She elected to be followed by telephone conversations with a nurse practitioner and customary repeated mammograms.

CASE DISCUSSION

A recent paper using a survey methodology to explore various follow-up options for breast cancer survivors examined patient comfort with providers "most likely to decrease worry and increase survival."[1] Included options were being seen by a medical oncologist, surgeon, radiation oncologist, nurse practitioner, primary care physician, or a virtual visit using either a telephone or internet interaction. This study included 218 breast cancer survivors and reaffirmed some of our knowledge about provider-patient relationships. Those surveyed favored follow-up visits from medical oncologists over the other options. They also favored being followed by their primary care physicians over nurse practitioners and were least interested in virtual visits. The authors note that other investigators found that psychosocial support for patients with cancer had been effectively provided through periodic telephone-based follow-up.[2] Another study demonstrated that telephone conversations with trained nurses as opposed to appointments with specialists failed to demonstrate differences in patient satisfaction, anxiety, or the detection of recurrences.[3]

Although the results of this study appear consistent with most expectations, it has serious limitations. The survey inclusion rate was only 40% in what would normally be a highly motivated cancer population. The respondents were significantly younger than the overall population, were highly educated with 71% having completed college, and 51% had an annual household income of greater than $80,000. It could be expected that in the future, highly educated patients might be more receptive to virtual visits as was the case for the librarian mentioned above. However, in this study, technological expertise did not overcome survivor interest in direct interactions with their providers.

Was the librarian's selection of telephonic follow-up rational or merely based on her discomfort with the medical oncologist responsible for her adjuvant care and the loss of her primary care physician to retirement? As a trained librarian she was comfortable with electronic support services and perhaps more knowledgeable than others confronted with the selection of their survival management. In an effort to better understand why she would select the least personal interaction for her follow-up, some understanding of patient comfort and trust in caregivers deserves exploration.

Multiple factors contribute to patient confidence in their providers, and these include the following: trust in their provider to act in their best interests, their perception of the education and knowledge of the provider, the respect they derive from a patient-focused interaction, and their comfort with the personality and level of interest from the provider.[4] Trust is generally more likely the result of interactions with individual providers, while distrust is often associated with impersonal institutional providers.[5] This is true because the behavior of an individual is easier to predict then the less personal associations with an impersonal institution. The high-risk probability of a recurrence of disease puts the survivors in a vulnerable situation because of their inability to exercise medical control without their dependence on their knowledgeable health care provider. Patient satisfaction is based on past experiences, while confidence in providers is based on future expectations. This librarian had her confidence in the medical oncologist eroded because of past interactions. Lack of confidence translates into a lack of trust.

Provider characteristics that are important to patients include familiarity with their medical and social situation, the amount of time they spend with the patients, the information they provide, and their level of empathy in difficult situations. Patient characteristics that help providers relate favorably include loyalty, ethnicity, satisfaction, adherence to medical recommendations, and a willingness to participate in clinical trials.[4] When patients with cancer entrust their future survival to providers, it is easy to understand why they expect positive interactions with trusted providers. It is also predictable that the results of the survey would reflect the importance of personal interactions with knowledgeable, compassionate, and trusted providers. The impersonal imposition of institutional solutions (clinics, telephone, or Internet support) to solve the shortages of oncologists, primary care physicians, and nurse specialists likely will result in less patient and provider satisfaction in the future. The availability of telephonic follow-up and web-based survivorship planning and general responses to questions may benefit some patients and their families, but it also may introduce confusion and misinterpretation for the most vulnerable patients. There also will be an increase in legal liability for the provider institution. The librarian elected to take control of the situation herself because of her comfort with technological answers and her mistrust or lack of empathy from her medical oncologist. ■

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ABSTRACT & COMMENTARY

Synchronous Breast Cancer

By William B. Ershler, MD

SYNOPSIS: For patients who have synchronous bilateral breast cancer, overall survival has been shown to be less favorable than for patients presenting with unilateral disease. In the current matched case-control series, overall survival was comparable. Clinicians are advised to prescribe systemic therapy based upon the more aggressive of the two lesions.

SOURCE: Nichol AM, et al. A case-match study comparing unilateral with synchronous bilateral breast cancer outcomes. *J Clin Oncol* 2011;29:4763-4768.

When two primary cancers are discovered during the evaluation of a patient with possible breast disease, a number of management issues arise for which there is little but clinical judgment on which to rely. Synchronously discovered breast cancers represent about 2% of all newly diagnosed breast cancers, depending on the definition of the term "synchronous" used, and whether invasive metastatic or noninvasive ductal and lobular carcinoma are included.[1] In fact, there remains uncertainty whether patients with synchronous bilateral breast cancer (SBBC) have similar or worse outcomes compared with patients with unilateral breast cancer.

Nichol and colleagues examined their large database of breast cancer patients in British Columbia to determine whether survival outcomes for patients with SBBC can be estimated from the characteristics of their individual cancers. Patients had invasive breast cancer, without metastases or inflammatory disease, and were diagnosed in British Columbia between 1989 and 2000. SBBC patients were those who had bilateral breast cancers diagnosed within 60 days, with clinical or pathologic stage (T1-T4c, N0-3). Excluded were in situ, inflammatory, and metastatic presentations. In total, 207 SBBC cases met the study entry criteria. Using the same exclusion criteria, a contemporaneous cohort of 15,497 potential matches with unilateral breast cancers (T1-T4c, N0-3) also was identified.

By using 10-year breast cancer-specific survival (BCSS) estimates, the higher-risk cancer of each SBBC case was determined and matched with three patients from the unilateral cohort to select 621 high-risk matches. The priority sequence of matching the prognostic and predictive variables was positive lymph node number, primary tumor size, age, grade, lymphovascular invasion, estrogen receptor status, local therapy used, margin status, treating clinic, diagnosis year, and type of systemic therapy used.

With a median follow-up of 10.2 years, the overall 10-year BCSS was significantly higher for the entire unilateral cohort (81%; 95% confidence interval [CI], 81%-82%) than for the SBBC cases (71%; 95% CI, 63%-77%). However, the SBBC cases had significantly higher mean age and stage at presentation. Accordingly, the 10-year BCSS for those 621 patients matched for the prognostic variables (including age and stage) present in the SBBC group was 74% (95% CI, 69%-77%) for the high-risk matches. Thus, BCSS was not significantly different between the SBBC cases and their high-risk matches.

COMMENTARY

Patients who present with synchronous breast cancer as a group have less favorable 10-year survival than those presenting with a single cancer. However, when matched for prognostic variables, there is no significant difference. This finding is different from others in which survival was demonstrably worse for those with SBBC. For example, Verkooijen reported that BCSS was significantly worse for 155 SBBC cases compared with unilateral cancers.[2] However, after adjustment for age, social class, and public sector medical care, they concluded that the difference in outcome between their cohorts was due to persistent significant differences between the baseline variables. Hartman determined that BCSS was also significantly worse for 355 SBBC cases compared with unilateral cancers.[3] In contrast to Verkooijen's findings, in Hartman's subset of 46 cases with complete treatment information, the 5-year adverse BCSS difference persisted after adjustment for age, year of diagnosis, TNM stage, adjuvant treatment, and estrogen receptor status (hazard ratio, 1.7; 95% CI, 1.2-2.2). In the current study, significant differences in baseline variables between the SBBC cases and the unilateral cohort were demonstrated. The SBBC cases were 9 years older, on average, and had more advanced stage, and these factors contributed to the initial observation that patients with SBBC had worse outcomes compared with patients with unilateral breast cancer. In this case-match study, high-quality matching was made possible by a large registry of breast cancer patients, including 15,497 with unilateral disease.

Synchronous breast cancer is uncommon, but with increased screening compliance and improved imaging techniques, it might be expected to increase. For example in one clinical trial, MRI found additional (i.e., mammographically occult) lesions in 3.1% of contralateral breasts.[4] Thus, as enhanced imaging is becoming more commonly employed in the presurgical staging of breast cancer, it is likely we will be encountering the question of optimal management strategies for those with bilateral disease. The current matched-case control study found that SBBC patients had similar outcomes as those with unilateral disease with comparable risk factors. Thus, for patients with SBBC, appropriate systemic therapy should be prescribed according to those histopathological features of the more aggressive of the two malignancies. ■

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CME Questions

1. Among lymphoma patients receiving influenza vaccine during the 2009 H1N1 epidemic, what percentage achieved a protective antibody titer as determined in the Norwegian study?
a. 0%
b. 20%
c. 50%
d. 82%

2. For CLL patients who have yet to receive treatment, which of the following factors independently (by multivariate analysis) predict a short interval before treatment will be required?
a. CD38
b. IGHV mutations
c. sFLC(κ/λ)
d. sFLC(κ+λ)
e. All of the above

3. Dasatinib, when used with docetaxel in the treatment of castration-resistant prostate cancer was shown to result in all of the following *EXCEPT*:
a. be generally well-tolerated.
b. improve biochemical markers of bone turnover in the majority of patients.
c. result in durable PSA declines in approximately 50% of patients.
d. prolong overall survival.

4. Which of the following possible providers for breast cancer patients once they have completed adjuvant chemotherapy was favored by the majority of patients surveyed?
a. Surgeon
b. Medical oncologist
c. Primary care physician
d. Nurse practitioner

5. Synchronous bilateral breast cancer, when compared to unilateral breast cancer, is associated with:
a. less favorable overall survival by unmatched analysis.
b. comparable overall survival, when appropriately matched.
c. Both of the above
d. None of the above

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

[IN FUTURE ISSUES]

Aspirin Reduces Colorectal Cancer Occurrence in Patients with Lynch Syndrome: Implications for Cancer Prevention

PHARMACOLOGY WATCH

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In this issue: New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group, $P < 0.001$). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

Bleeding concerns with dabigatran

Dabigatran (Pradaxa), Boehringer Ingelheim's blockbuster anticoagulant, is the subject of a December 7, 2011, Drug Safety Communication by the FDA regarding serious bleeding events. The FDA is evaluating postmarketing reports of serious bleeding events that may lead to serious or even fatal outcomes. Experts are working to determine whether the reports of bleeding associated with the drug are occurring more commonly than would be expected based on observations from large clinical trials. The drug was approved in October 2010 to reduce the risk of stroke in patients with non-valvular atrial fibrillation. More than a million prescriptions have been filled by nearly 400,000 patients since approval. ■

All antidepressants are created equal

When it comes to choosing an antidepressant, all modern drugs are roughly equivalent, according to a new study in the *Annals of Internal Medicine*. Researchers performed a large meta-analysis of 234 studies that looked at the treatment of major depressive disorder (MDD) with second-generation anti-

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depressants. There were no differences among the drugs with regard to efficacy or effectiveness for the treatment of acute, continuation, and maintenance phases of MDD. There were also no significant differences when accompanying symptoms were taken into account or other factors such as age, sex, ethnicity, or comorbid conditions. There were differences among the drugs with regard to onset of action, adverse effects, and some quality-of-life issues. There was also a significant difference in cost and dosing convenience. Drugs considered in the study were bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. The authors suggest that familiarity with the broad spectrum of antidepressants is prudent given the difficulty of predicting which medication will be effective and tolerated by any given patient (*Ann Intern Med* 2011;155:772-785). ■

Benefits of treating systolic hypertension

Older adults with isolated systolic hypertension gained about 5 months of life when treated with chlorthalidone-based stepped care 2 decades after completion of the Systolic Hypertension in the Elderly Program (SHEP) trial. SHEP, conducted between 1985 and 1990, was a clinical trial of patients aged 60 years or older (mean age 72) with isolated systolic hypertension who were randomized to chlorthalidone-based antihypertensive therapy or placebo. Over a mean follow-up of 4.5 years, chlorthalidone-based therapy resulted in prevention of approximately 1 of 2 admissions for heart failure, 1 out of 3 fatal or nonfatal strokes, and 1 of 4 coronary heart disease events, but there was no effect on all-cause mortality or cardiovascular death. At the end of the trial, all participants were advised to receive active therapy. The new study reviewed cardiovascular death and all-cause mortality in SHEP trial participants 22 years after the study ended. Life expectancy gain between the active treatment group and placebo group was 105 days (95% confidence interval [CI], -39 to 242; $P = 0.07$) for all-cause mortality and 158 days (95% CI, 36-287; $P = 0.009$) for cardiovascular death. Each month of active treatment was associated with approximately 1 day extension in life expectancy. The authors conclude that treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up (*JAMA* 2011;306:2588-2593). This study may help convince older patients with systolic hypertension that compliance with diuretic-based hypertensive therapy is worth the effort as it will prolong their lives. ■

Aliskiren and ACEIs/ARBs don't mix

Aliskiren (Tekturna), Novartis' direct renin inhibitor, should not be combined with an ACE inhibitor or angiotensin receptor blocker (ARB) to treat hypertension, according to the manufacturer. Novartis recently terminated the ALTITUDE trial when it was found that patients with type 2 diabetes or impaired renal function who were given the combination of aliskiren with an ACEI or ARB had a higher incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension. More information can be found at www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml. ■

FDA actions

The FDA approved generic atorvastatin (Lipitor) on November 30, 2011. Ranbaxy Laboratories will make the first generic in 10, 20, 40, and 80 mg strengths. Atorvastatin as Lipitor was first marketed in 1997 and became the best-selling prescription medication in history with sales of more than $125 billion. It has dominated the statin market in recent years, representing nearly a quarter of Pfizer's annual revenue, and the giant pharmaceutical company aggressively defended their patent against multiple challenges. Ranbaxy has 180 days of exclusivity on generic atorvastatin after which time multiple manufacturers are expected to seek approval for their generic version of the drug.

The FDA has approved Prevnar 13 for adults age 50 and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*. The vaccine was previously approved for children up to 5 years of age. The approval was based on head-to-head studies with Pneumovax 23 which is already approved for use in adults. According to the FDA, "for the 12 common serotypes, Prevnar 13-induced antibody levels were either comparable to or higher than the levels induced by Pneumovax 23." Prevnar 13 is manufactured by Wyeth Pharmaceuticals.

Dronedarone (Multaq) should not be prescribed to patients with permanent atrial fibrillation (AF), based on results from the PALLAS trial which showed that the drug doubles the risk for cardiovascular death, stroke, and heart failure in such patients. The FDA is requiring revised labeling for the antiarrhythmic drug and has issued a Drug Safety Communication after a safety review was completed. If dronedarone is to be prescribed, the FDA recommends ECGs every 3 months and immediately stopping the drug if the patient is found to be in AF. The drug is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). Dronedarone is manufactured by Sanofi-Aventis. ■

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Establishing the CV Safety Profile of ADHD Meds in Children and Young Adults

Source: Cooper WO, et al. *N Engl J Med* 2011;365:1896-1904.

CASE REPORTS OF ADVERSE CARDIOVASCULAR (CV) events in children and young adults taking attention deficit-hyperactivity disorder (ADHD) medications have included myocardial infarction (MI), stroke, and sudden death. These individual cases, however, neither prove causation nor provide insight into event frequency, since the denominator is unknown. Because of the seriousness of these events, a clearer understanding of their epidemiology is important.

Cooper et al performed a retrospective cohort study based on data from four large health plans, which included data from more than 1 million persons 2-24 years of age. Among this population, there were data on 373,667 person-years of ADHD drug treatment in these children and young adults.

In this entire population, there were 81 serious CV events (rate = 3.1/100,000 person-years). However, persons currently using ADHD drugs did *not* demonstrate an increased risk for CV events compared to non-users; in fact, the hazard ratio (HR) demonstrated a trend (not statistically significant) toward *fewer* serious CV events in persons taking ADHD medications (HR = 0.75). Whether CV events were looked at in composite (MI + stroke + sudden death) or individually, the same generally favorable trend was seen (HR = 0.70, *P* = NS). Similarly, former users of ADHD medications were at no greater risk for CV events than never-users. This study was not funded by industry, but by the federal agencies AHRQ and FDA. ■

If You're Already on a Statin, Does Adding Niacin Help?

Source: AIM-HIGH Investigators. *N Engl J Med* 2011;365:2255-2267.

RESULTS FROM INTERVENTION TRIALS WITH statins for secondary prevention of cardiovascular (CV) events are consistently impressive. Nonetheless, significant residual risk remains; that is, even though statin treatment reduces risk of events by as much as 20-30% over 5 years, persons with existing CV disease are still at substantially greater risk of having another CV event than age-matched controls without CV disease. Observational studies suggest that increasing high-density lipoprotein (HDL) might provide an even greater incremental CV risk reduction than LDL modulation, although evidence from interventional trials is conflicting.

The AIM-HIGH trial enrolled patients with existing CV disease (n = 3414) who were already receiving simvastatin (plus ezetimibe if LDL goals were not attained with simvastatin alone). Study subjects were randomized to extended-release niacin or placebo.

Although intended to conclude after 4.6 years, the study was stopped early (at 3 years) subsequent to the recommendation by the data and safety monitoring board that the trial be discontinued due to both a lack of positive efficacy as well as an unanticipated elevation of ischemic stroke in niacin recipients. Adding niacin to statins in persons with stable atherosclerotic vascular disease does not reduce CV events. ■

Adverse Effects on Semen from SSRI Treatment of Premature Ejaculation

Source: Koyuncu H, et al. *Int J Impot Res* 2011;23:257-261.

SEVERAL TREATMENTS HAVE BEEN SHOWN to be highly effective in management of premature ejaculation (pEJ), including behavioral therapy, systemic modulation of serotonin, and topical agents. The most popular current treatment is sustained use of selective serotonin reuptake inhibitors (SSRIs), which typically increase intravaginal latency (the time from intromission to ejaculation) from pretreatment times of < 1 minute to over 5 minutes. There has been little study of the impact of SSRI treatment on parameters such as semen, perhaps because most of the pEJ trials have been short-term. Studies in which SSRIs are added to semen preparations in vitro have shown adverse changes in sperm motility and viability, prompting consideration of potential adverse effects from systemically administered SSRIs.

Escitalopram is an SSRI sometimes used to treat pEJ. To elucidate the effects of escitalopram on semen, subjects with lifelong pEJ (n = 25) and normal baseline semen analysis were enrolled. Additionally, at baseline all subjects had normal scrotal ultrasound, CBC, glucose, hormone levels, lipid levels, and genito-rectal examinations.

At 1 month, no alterations in semen were detected. However, at 3 months there were multiple statistically significant changes: sperm count decreased (68 million/mL to 26 million/mL), number of motile spermatozoa decreased by more than 50%, and the number of morphologically normal sperm decreased by over 50%. In the absence of a control group, these findings cannot be considered definitive. Additionally, it is possible that sperm function might return to pretreatment levels upon drug discontinuation. However, the prominent effects on semen within a short interval merit our awareness. ■

Comparing Two High-Intensity Statin Regimens: Atorvastatin and Rosuvastatin

Source: Nicholls SJ, et al. *N Engl J Med* 2011;365:2078-2087.

Between statin head-to-head trials are uncommon. The PROVE-IT trial convincingly demonstrated that intensive LDL reduction with atorvastatin (achieved LDL = 62 mg/dL) vs pravastatin (achieved LDL = 95 mg/dL) improved outcomes in persons with acute coronary syndromes. In persons with stable atherosclerotic disease, however, it remains controversial whether high-dose statin treatment reduces mortality when compared with "standard" dosages, even though it has been shown to reduce CV events.

Results from clinical trials are sometimes hampered by the limitations of time: In a 5-year window of opportunity, are the long-term effects of intervention adequately represented? Such time limitations have prompted consideration of surrogate markers, which might more promptly reflect the anticipated long-term effects of intervention. Accordingly, Nicholls et al performed a controlled trial (n = 1039) to compare, by means of intravascular ultrasound, the effects of high-dose atorvastatin (80 mg/d) vs rosuvastatin (40 mg/d) on coronary atherosclerosis.

At 2 years, atheroma regression was similar between the two agents, despite the superior performance of rosuvastatin for attained LDL (62.6 mg/dL vs 70.2 mg/dL) and HDL (50.4 mg/dL vs 48.6 mg/dL). Maximal doses of these statins appear to perform similarly for the endpoint of regression of atherosclerosis. ■

The Effect of Adiposity on Insulin Pharmacodynamics

Source: Porcellati F, et al. *Diabetes Care* 2011;34:2521-2523.

It is probably not a surprise to clinicians that adiposity and efficacy of therapeutic insulins are related. We are accustomed to seeing type 2 diabetes (DM2) associated with being overweight and obesity, and watching control of diabetes become more difficult if obesity worsens. The question addressed by Porcellati et al is not whether insulin requirements are affected by obesity, but rather are various insulins differently affected by obesity.

To that end, DM2 subjects (n = 18) were studied using infusions of glucose to maintain constant plasma levels. Three different insulins — NPH, insulin glargine, and detemir — were compared. The threshold at which glucose infusion rates were meaningfully different was a body mass index (BMI) > 29 kg/m^2, at which point all three insulins demonstrated less efficacy to control glucose. That is, as BMI goes up, insulin sensitivity goes down.

Within this study group, however, there was a statistically significantly greater reduction in insulin sensitivity with detemir than with either NPH or insulin glargine. Ultimately, this means that in patients with progressively greater BMI, a higher dose of detemir may be required to achieve glucose control than the other two forms of basal insulin. Some clinical trials have also reflected this requirement for greater doses of detemir than comparators in patients with obesity. Nonetheless, because the amount of data addressing this issue remains small, whether there are meaningful differences that need to be considered when addressing insulin needs of obese DM2 patients in reference to choice of basal insulin is still considered a matter of controversy. ■

Psoriasis Predisposes to Serious Infections

Source: Wakkee M, et al. *J Am Acad Dermatol* 2011;65:1135-1144.

As the use of systemic immune-modulating treatments for rheumatoid arthritis (RA) has evolved, the risk for serious infectious disease complications related to their use has become more evident. Since many of the drugs used to treat RA are now used for patients with psoriasis (PSR), it is logical to evaluate PSR patients for risk of serious infectious diseases.

Wakkee et al looked at a database comprised of PSR patients (n = 25,742) and controls (n = 128,710) from a Dutch registry compiled from 1997-2008. They examined the incidence of infectious disease events resulting in hospitalization during this interval.

Overall, persons with PSR were more than twice as likely to be hospitalized for a serious infectious disease than controls; multivariate analysis (adjustment for confounding issues like age, diabetes, COPD) modified this hazard ratio slightly (down from 2.08 to 1.54).

Perhaps the greatest surprise from this trial was that the use of systemic antipsoriatic medications was *not* associated with risk for infectious disease. Apparently then, it is PSR itself which imposes an increased risk of infectious diseases, not the immunosuppressive agents increasingly used to treat it. ■

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