TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 21, No. 3
March 2011

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, reports no financial relationships relevant to this field of study. Executive Editor Russ Underwood and Specialty Editor Shelly Morrow Mark report no financial relationships relevant to this field of study.

Should We Adopt a Pre-exposure Prophylaxis Approach for HIV Prevention?

ABSTRACT & COMMENTARY

This article originally appeared in the January 2011 issue of Infectious Disease Alert.

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Chief, Division of AIDS Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine.

Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics. *Infectious Disease Alert*'s Editor, Stan Deresinski, MD, FACP, Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, does research for the National Institutes of Health (NIH), and is an advisory board member and consultant for Merck. Peer reviewer Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado Denver Health Medical Center, reports no financial relationship relevant to this field of study.

Synopsis: *In this study, 2,499 HIV-seronegative men or transgender females who have sex with men were randomized to daily tenofovir/emtricitabine (TDF/FTC) vs. placebo. During a median period of follow-up of 1.2 years, TDF/FTC resulted in a 44% reduction in the incidence of HIV.*

Source: Grant RM, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010 Nov. 23 (epub ahead of print).

In this study, 2,499 HIV-seronegative men or transgender females who have sex with men (MSM) were randomized to daily TDF/FTC vs. placebo in a multicenter, controlled trial with clinical sites in North America, Latin America, Thailand, and Africa. In addition to being provided TDF/FTC (or placebo), all subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections. The study subjects were followed for 3324 person-years (median 1.2 years) and were seen every 4 weeks. One hundred subjects became infected during follow-up (36 in the TDF/FTC group and 64 in the placebo group). A subgroup of patients had serum and PBMC's examined for antiretroviral levels.

Of the 2,499 subjects, 10 were found to be infected at study enrollment, and 100 became infected during follow-up (36 in the TDF/FTC group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV. Study drug was detected in 22/43 seronegative subjects and in 3/34 HIV-infected subjects. Excess nausea was reported in the TDF/FTC-treated subjects. No TDF or FTC

resistance was detected in either the TDF/FTC or placebo groups who became infected with HIV during the trial.

■ **COMMENTARY**

Bob Grant and his team should be congratulated for completing this large international trial and conclusively demonstrating that TDF/FTC prevents many cases of HIV when given as pre-exposure prophylaxis. Several weeks ago when the news of this important study hit the lay press, a lot of enthusiasm was generated, and the press in San Francisco declared this a major breakthrough in HIV prevention. While poor adherence likely contributed to the relatively low efficacy of this intervention (based on non-human primate experiments, I would have predicted > 80% efficacy rather than observed 44% efficacy), the success of this approach will undoubtedly be significantly lower in the real world outside of the context of a clinical trial where the patients received regular monitoring and support.

I have some big issues with adopting this approach more widely for HIV prevention. These include the concern about selecting out NRTI-resistant variants of HIV in the community. While it is gratifying that this was not seen in the short-term (median 1.2 years) duration of this trial, the widespread use of this non-fully suppressive regimen will surely drive resistance when many HIV-infected patients will likely get access to TDF/FTC and use it outside of a controlled clinical environment and in the absence of fully suppressive 3-drug HAART.

While I do not lose sleep over the potential renal and bone toxicity of TDF when treating patients with known HIV, I am concerned about exposing millions of HIV-uninfected people (mainly in the developing world) to ARVs for years.

The last concern is simply cost. TDF/FTC currently sells for approximately $40/tablet. Using some back-of-the-envelope calculations, the cost per patient during the 1.2 years of the study would be $16,800. The total drug supply cost for this 2500-person trial was $42 million. Therefore, the cost of preventing each of the 28 cases of HIV was $1.5 million. Is that really an effective use of limited resources? As someone who served as an Air Force physician on the front lines of many of the humanitarian crises our weary world has endured over the last 20 years, I do not think so. Forty-two million dollars spent digging wells could provide enough safe water to prevent hundreds (if not thousands) of childhood deaths due to diarrheal disease. Forty-two million dollars could buy permethrin-treated bed nets for just about every child in Africa and prevent thousands of deaths due to malaria. We could certainly provide routine childhood immunizations to millions of children (again preventing thousands of deaths) for that amount as well. ■

Alcohol Use in Older Women

ABSTRACT & COMMENTARY

This article originally appeared in the January 29, 2011 issue of Internal Medicine Alert.

By Mary Elina Ferris, MD

Dr. Ferris is Clinical Associate Professor, University of Southern California.

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media, a division of Thompson Publishing Group LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone:
(404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Travel Medicine Advisor,*** PO Box 740059, Atlanta, GA 30374-9815.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice @ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Dr. Ferris reports no financial relationship to this field of study. Editor Stephen A. Brunton, MD, Adjunct Clinical Professor, University of North Carolina, Chapel Hill, is a consultant for Amylin, Novo Nordisk, Shionogi Pharma, Takeda, and Teva; he serves on the speaker's bureau for Boehringer Ingelheim, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY, reports no financial relationships to this field of study.

Synopsis: *Although most older women have stable patterns of alcohol use over time, they still need to be periodically questioned about alcohol use since some will increase their intake substantially after age 50 and may develop new risks for alcohol-related problems.*

Source: Bobo JK, et al. Alcohol use trajectories in two cohorts of U.S. women aged 50 to 65 at baseline. *J Am Geriatr Soc* 2010;58:2375-2380.

To investigate the natural history of alcohol intake in women after age 50, two randomly sampled, nationally representative large cohorts of older women initially between the ages of 50 and 65 were followed with biannual questionnaires for concurrent 8-10 year periods. The alcohol use questions covered the preceding 3 months and collected data on days of use and daily amount. These data were used to create group-based models of four drinking trajectories: infrequent or non-drinkers (62% of the largest cohort of 3233 women), increasing drinkers (5%), consistent drinkers (26%), and decreasing drinkers (7%). The percentages from the second cohort of 1017 women were very similar.

The majority of older women studied maintained a stable drinking pattern as they aged: consistent, infrequent, or non-drinkers were 87.7% of the largest cohort and 82.6% of the other cohort. Within the consistent drinkers, there was a trend over time to slightly decrease the amount of drinks per day, from 1.78 to 1.59 drinks in the first group and from 1.62 to 0.99 drinks per day in the second group.

The surprising finding was that 4.9% of the larger cohort and 8.8% of the smaller cohort reported notable increases in the number of drinks per day over the 8-10 years of the study.

■ COMMENTARY

This report demonstrates that the vast majority of older women have stable alcohol intake as they age, and may even decrease their intake with time. A similar study of women enrolled at ages 45-64 also found that 81% of baseline drinkers and 88% of non-drinkers reported no change in drinking status over 6 years of follow-up.[1]

The American Geriatrics Society actually has posted clinical guidelines for low-risk alcohol use in older adults on their web site, and recommends no more than 7 drinks/week with a maximum of 2 drinks on any one occasion. However, these amounts have been questioned since safety may be specific to what medications or chronic diseases are present, and there is scant research support for older adults having different guidelines from younger ages if health status is equivalent.[2]

The group that merits our attention is the small number who actually may increase their alcohol intake over time and put themselves at risk for alcohol-related complications. The authors promise to publish subsequent reports of which risk factors were associated with increasing and decreasing alcohol use to help us target these groups in the future. ■

References

1. Eigenbrodt ML, et al. Alcohol consumption with age: A cross-sectional and longitudinal study of the Atherosclerosis Risk in Communities (ARIC) study, 1987-1995. *Am J Epidemiol* 2001;153:1102-1111.
2. Lang I, et al. What level of alcohol consumption is hazardous for older people? Functioning and mortality in U.S. and English national cohorts. *J Am Geriatr Soc* 2007;55:49-57.

Novel Deer-associated Parapoxvirus Found in Deer Hunters

ABSTRACT & COMMENTARY

This article originally appeared in the February 2011 issue of Infectious Disease Alert.

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine.

Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics. *Infectious Disease Alert*'s Editor, Stan Deresinski, MD, FACP, Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, does research for the National Institute of Health (NIH), and is an advisory board member and consultant for Merck. Peer reviewer Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado Denver Health Medical Center, reports no financial relationship relevant to this field of study.

Synopsis: *In 2009 parapoxvirus infection was diagnosed in two deer hunters in the eastern U.S. who had field-dressed white-tailed deer. Molecular analysis suggested that these infections represented a unique strain.*

Source: Roess AA, et al. Novel deer-associated parapoxvirus infection in deer hunters. *N Engl J Med.* 2010; 363:2621-2627.

TWO CASES WERE REPORTED IN THIS PAPER. THE FIRST CASE was a 52-year-old wildlife biologist who went deer hunting in Virginia in November 2008. He nicked his right index finger while field-dressing a white-tailed deer. The animal appeared healthy, and the patient noted no external lesions on the deer. The cut did not heal, and about 4 weeks after the injury, the wound site enlarged to form a violaceous nodule. The lesion was excised, and the patient was empirically treated with doxycycline. Pathology revealed a vascular lesion with histopathology consistent with pyogenic granuloma. Cultures for bacterial, mycobacterial, and fungal pathogens were negative. The lesion subsequently recurred at the edge of the excised area and enlarged. The lesion was re-excised and histopathology was suggestive of orf virus. Specimens were sent to the CDC. The second case was a 60-year-old hunter from Connecticut who cut his left index finger while field-dressing a white-tailed deer in November 2008. Seven weeks after the injury, the patient sought care for a non-healing, 1 cm violaceous lesion. Biopsy subsequently revealed intracytoplasmic viral inclusions within keratinocytes, suggestive of a poxvirus infection. Specimens also were sent to the CDC.

Electron microscopy examination of sections of material prepared from both patients revealed ovoid virions 113-130 nm X 250-258 nm in the two patients. Histopathology revealed dilated vascular spaces lined with swollen endothelial cells and scattered lymphohistiocytic inflammatory-cell infiltrates. Immunohistochemical staining revealed intracellular viral antigens. "Panpox" universal PCR and parapoxvirus-specific real-time PCR confirmed the presence of parapoxvirus infection in both patients. Phylogenetic analysis of the amplified sequences from the viruses obtained from the two patients showed that the infectious agents were closely related and cluster with pseudocowpox viruses.

COMMENTARY

These two case reports describe infection due to molecularly confirmed novel parapoxviruses. Parapoxviruses cause infections in ruminants (sheep, goats, and cattle), and are common worldwide. A proliferative dermatitis develops in the mouth, teats, and skin of infected animals, and can cause fatal infection in young animals. Previously recognized zoonotic infections due to parapoxviruses include orf and milker's nodule, and result from close contact with infected animals. These infections are an occupational risk for farmers and animal health care workers. These two cases reported in this paper emphasize the importance of taking a careful exposure history and being persistent in the approach to diagnosis of non-healing cutaneous infections. The identification of this previously unrecognized parapoxvirus is a testament to the power of modern molecular diagnostic methods. Since specific antiviral agents to treat parapoxviruses are not available, surgical debridement probably plays a role in treatment.

Due to reforestation in the East Coast of the United States and loss of natural predators, the population of white-tailed deer has increased dramatically over the past 100 years, and humans are now living in closer proximity to deer than at any time in the past. We are certain to see more of this infection in the years to come. ■

PHARMACOLOGY WATCH

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

Escitalopram for Menopausal Hot Flashes

In this issue: Escitalopram for menopausal hot flashes, rifaximin for IBS without constipation, herpes zoster vaccination, antiepileptics drugs and fracture risk, and FDA Actions.

Escitalopram for hot flashes

Since the Women's Health Initiative was published in 2003, the use of hormone therapy for the treatment of postmenopausal hot flashes has dropped dramatically. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been studied to relieve postmenopausal symptoms, but no agent has been conclusively shown to be effective. A new study suggests that escitalopram (Lexapro™) may offer some relief.

In a study recently published in the *Journal of the American Medical Association*, 205 menopausal women were randomized to 10-20 mg per day of escitalopram or matching placebo for 8 weeks. The primary outcome was the frequency and severity of hot flashes with the average hot flash frequency at nearly 10 per day at baseline. Escitalopram resulted in 1.41 fewer hot flashes per day compared to placebo ($P < 0.001$), although both the active drug group and placebo groups noted reductions. Escitalopram also reduced hot flash severity. There was no difference among women of different races, and the discontinuation rate was small. The authors concluded that escitalopram 10-20 mg per day compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks (*JAMA* 2011;305:267-274). Whether the same effect can be expected with racemic citalopram (Celexa™) is unknown. ■

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Elliott reports no financial relationships to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Rifaximin for IBS without constipation

Rifaximin, an oral, nonsystemic (poorly absorbed) broad-spectrum antibiotic, may help relieve symptoms of irritable bowel syndrome according to two identically designed studies published in the *New England Journal of Medicine*. A total of 1060 patients who had IBS without constipation were randomized to rifaximin 550 mg three times daily for 2 weeks or matching placebo. The primary endpoint was a proportion of patients with adequate relief of global IBS symptoms; the secondary endpoint was relief of bloating. Significantly more patients in the rifaximin group had adequate relief of IBS symptoms during the first 4 weeks of treatment (40.7% vs 31.7%; $P < 0.001$), as well as improvement in bloating (40.2% vs 30.3%; $P < 0.001$). The incidence of adverse events was similar in the two groups. The authors concluded that among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of the IBS symptoms of bloating, abdominal pain, and loose or watery stools (*N Engl J Med* 2011;364:22-32).

An accompanying editorial points out that the benefit from rifaximin was sustained over 10 weeks after a short 2-week treatment course, but also points out that benefit of the drug was a mere 9%-12% improvement over placebo, barely clinically relevant. Still, for patients who have IBS without constipation who have not responded to other therapies, a single treatment

cycle could be tried (*N Engl J Med* 2011;364: 81-82). ■

Herpes zoster vaccination rates and incidence of shingles

The herpes zoster vaccine cuts the rate of shingles by 55% in the elderly population according to a new report in the *Journal of the American Medical Association*. Researchers at Kaiser Permanente in Southern California performed a retrospective cohort study of health plan members, 75,000 of whom were vaccinated against shingles (age 60 and older) and 225,000 age-matched controls who did not receive vaccine. The rate of herpes zoster was 6.4/1000 person-years in the vaccinated group and 13.0/1000 person-years in the unvaccinated group (hazard ratio, 0.45; 95% confidence interval, 0.42-0.48). Reduction in herpes zoster occurred in all age groups and among individuals with chronic disease. The rate of ophthalmic herpes zoster and hospitalizations for herpes zoster were also significantly reduced.

The authors of the study concluded that among immunocompetent community-dwelling adults age 60 and older, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster (*JAMA* 2011;305:160-166). The study is important because only 10% of those aged 60 and older received the shingles vaccine in 2009, whereas nearly one of three people in the United States will develop shingles in their lifetime. ■

Fracture risk with antiepileptic drugs

Most antiepileptic drugs (AEDs) are associated with an increased risk of nontraumatic fracture according to a retrospective match cohort study. Nearly 16,000 patients with a history of prior AED use (carphenazine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, or vigabatrin) were compared to up to three matched controls each. Rates of fractures of the wrist, hip, and vertebrae were measured between 1996 and 2004. A significant increase in fracture risk was found for most AEDs, with an adjusted odds ratio of 1.24 for clonazepam to 1.91 for phenytoin. The only AED not associated with increased fracture risk was valproic acid.

The authors concluded that most AEDs are associated with an increased risk of nontraumatic fractures in individuals age 50 or older. They suggested that the risk of fracture with newer AEDs needs to be determined, as well as the effect of bone protective medications in this population (*Arch Neurol* 2011;68:107-112). The mechanism of increased fracture risk in patients using AEDs is unknown, but may be related to accelerated vitamin D catabolism, calcium absorption, or an effect on osteoblasts. ■

FDA Actions

The FDA has approved vilazodone hydrochloride for the treatment of depression in adults. The drug is a selective serotonin reuptake inhibitor as well as a partial agonist of the 5HT 1a receptor. The drug was approved in dosages of 10 mg, 20 mg, and 40 mg for major depressive disorder or major depression. Vilazodone is touted as having fewer sexual side effects than other antidepressants. It carries the same boxed warning as other antidepressant regarding suicidal thinking and behavior in children, adolescents, and young adults. Vilazodone will be marketed by Clinical Data Inc. as Viibryd™.

The FDA is limiting the amount of acetaminophen in combination prescription pain medications. The new requirement limits the amount of acetaminophen to 325 mg in each tablet or capsule. Common medications that will be affected include codeine (acetaminophen with codeine), oxycodone (Percocet®), and hydrocodone (Vicodin®). Over-the-counter acetaminophen products are not affected. This action is being taken to limit acetaminophen-related liver failure. It is felt that lowering the amount of acetaminophen in these products will have minimal effect on efficacy for treating pain. The change will be phased in over 3 years.

The FDA has approved a new transmucosal form of fentanyl for the treatment of breakthrough pain for adults with cancer. The drug is indicated for the management of breakthrough pain in patients with cancer ages 18 and older, who use opiate pain medication around the clock. Breakthrough pain is defined as pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain management plan. Patients must be opioid-tolerant to qualify for use with transmucosal fentanyl. The drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program, which is intended to minimize risk of misuse, abuse, addiction, and overdose. Fentanyl sublingual tablets are available as 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. Fentanyl sublingual tablets are marketed by ProStrakan Inc. under the trade name Abstral®. ■