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Are Vaccines Safe after Guillain-Barré and Chronic Inflammatory Demyelinating Neuropathy?

ABSTRACT & COMMENTARY

By Michael Rubin, MD
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Synopsis: *Vaccines appear to be safe for patients who have been previously diagnosed with GBS or CIDP, and are recommended in appropriate individuals.*

Source: Kuitwaard K, et al. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst* 2009;14:310-315.

Is it safe to vaccinate a patient with a prior history of Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP)? What is the likelihood of recurrence of GBS even in the absence of vaccination, and what are the long-term consequences of inflammatory demyelinating polyneuropathy? To address these questions, all members of the Dutch Society of Neuromuscular Disorders were sent a set of questionnaires in June 2008, followed by two reminder letters to improve response rates, asking them to reply if they had a diagnosis of GBS, Miller Fisher syndrome, or CIDP. Issues addressed by the questionnaires encompassed prior vaccinations, family history of GBS or CIDP, presence of other autoimmune diseases, and persistent symptomatology. Also included were the short-form (SF-36) health survey, and standardized sub-questionnaires related to pain, fatigue, anxiety, and depression. Statistical analysis comprised the chi-square test, Fisher exact test, Mann-Whitney U test or t-test, and Spearman's correlation coefficient (rs), with a $p < 0.05$ considered significant.

Of 461 members who received the mailings, 323 responded, two of whom were excluded due to incorrect or lack of diagnosis. Of the remaining 321 patients, 76 had CIDP, and 245 had GBS, four of whom had Miller Fisher syndrome, five had an overlap of Miller Fisher syndrome and GBS, and one had Bickerstaff's encephalitis. Recurrent GBS was reported in 19 patients but could only be confirmed in nine (4%). Immune-mediated polyneuropathy was re-

ported in a family member in eight GBS patients, six of whom had GBS, and one each had CIDP or multifocal motor neuropathy. A single CIDP patient had a grandson with CIDP. Autoimmune disease, usually thyroid, was reported in 23 (9%) and four (5%) patients with GBS and CIDP, respectively. Prior vaccination, usually for the flu, was reported in 23 GBS (9%) and eight (11%) CIDP patients within eight weeks prior to disease onset, but none of 106 GBS patients who were vaccinated (range 1–37 times, total 775 vaccinations) subsequent to their GBS experienced a recurrence. Among 24 CIDP patients who received vaccines (range 1–17 times) following their CIDP, five reported increased symptomatology. Long after diagnosis, pain was reported in 71% and 72% of GBS and CIDP patients, respectively, and it was considered to be severe in 8% and 17%, respectively. Even years following diagnosis, fatigue was reported in 45% and 25% of GBS and CIDP patients, respectively. Although patients with prior GBS or CIDP continue to experience pain and fatigue long after diagnosis, seasonal vaccination of these patients, particularly GBS, appears to carry a low risk of recurrence.

■ COMMENTARY

Review of the peer-reviewed literature between 1950 and 2008 supports the notion that vaccinations are only rarely associated with subsequent development of Guillain-Barré syndrome (Haber P, et al. *Drug Safety* 2009;32;309-323). With the exception of the swine flu vaccine used in 1976–1977, which carries the strongest causal association, such influenza vaccine associations as have been reported appear to be temporal, rather than causal. Current formulations of rabies vaccine, derived from chick embryo cells, are similarly not associated with a greater than expected rate of GBS. No correlation has been confirmed between GBS and oral polio vaccine or tetanus toxoid-containing vaccines, and reported associations of GBS following quadrivalent conjugated meningococcal vaccine (MCV4) lack controlled epidemiological studies and remain inconclusive. From all available data, it appears that the benefits of vaccination outweigh the risks. ■

Update on ACIP Adult Immunization Guidelines

By Carol A. Kemper, MD, FACP

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Sources: ACIP. Recommended Adult Immunization Sched-

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ule: United States, 2010. *Ann Intern Med*. 2010;152:36-39; Hopkins RH, Jr, and Vyas KS. Adult Immunization Guidelines: Challenges and Opportunities. *Ann Intern Med*. 2010;152:59-60.

The revised ACIP adult vaccination schedule, published January 5, 2010, includes the following changes (documented in full at www.cdc.gov/vaccines/recs/ACIP/default.htm):

HPV:

• A second HPV vaccine is now approved for use in young adults within the United States. In contrast to the earlier HPV quadrivalent vaccine, which provided protection against four strains of HPV, including two strains associated with genital warts, the newer bivalent vaccine includes only two HPV strains associated with 70% of cases of genital dysplasia and cervical cancer.

• Vaccination of young men at risk for HPV is now also recommended.

MMR:

• Two doses of MMR vaccine, administered four weeks apart, are now additionally recommended for certain groups, including health care workers, students in post-secondary educational institutions, international travelers, and adults with exposure to measles or mumps.

• All other adults born after 1957 do not require a booster dose of MMR if they have documentation of an initial primary dose.

• Heath care facilities should consider pre-emptively providing MMR for non-immune employees born before 1957.

Hepatitis A Vaccine:

• HAV is now recommended for all parents and caregivers of international adoptees.

Meningococcal Vaccine:

• A one-time booster dose of meningococcal conjugate vaccine is recommended after five years for anyone with ongoing risk factors for meningococcus, except those in campus housing.

***Haemophilus Influenzae* Type B (Hib) Vaccine:**

• A footnote in the guidelines suggests that Hib is not "contraindicated" in adults with leukemia, sickle cell disease, HIV, or splenectomy, for those clinicians wondering what to do for patients at increased risk for encapsulated organisms.

The accompanying editorial discusses the likelihood of an increased focus on adult immunization as a quality measure. Newer electronic medical records will have embedded prompts for routine adult vaccination. Providers should anticipate that audits of electronic medical records may more readily provide feedback to clinicians regarding rates of adult vaccination, and remuneration may eventually be tied to this in some areas. I recommend posting the updated ACIP document (and the ACIP document from 2009) somewhere near your desk for quick reference, as some of the recommendations for adult vaccination are not always as straightforward as the authorities make them out to be, and questions are likely to arise. ■

Schistosomiasis as IRES in HIV

By Carol A. Kemper, MD, FACP

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Source: Psevdos G Jr. *Schistosoma mansoni* colitis in an AIDS patient. *The AIDS Reader*. December 16, 2009.

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An increasing number of HIV-positive immigrants and refugees, many from Africa, are cared for in the United States. The standard battery of HIV-related blood studies does not include screening studies for strongyloides and schistosomiasis. HIV co-infection with these two parasites is common in certain countries. At least 20% of HIV+ patients with bloody diarrhea in Zimbabwe had schistosomiasis. In a 10-year post-mortem survey in Puerto Rico, histologic evidence of *S. mansoni* was found in 10% of AIDS patients who died.

This author describes a patient with newly diagnosed AIDS, who had just started antiretroviral therapy four weeks earlier, who developed non-bloody diarrhea, fever, and peripheral eosinophilia (13%). Stool studies for bacteria, *C. difficile*, and ova and parasites were negative, and he failed to respond to an empiric course of metronidazole. Colonoscopy showed diffuse hyperemia, and biopsy showed an intense granulomatous response to schistosoma ova. Within days of starting praziquantel, his diarrhea resolved. A second, similar case described elsewhere also presented with diarrhea within weeks of initiation of HAART therapy. Colonoscopy revealed patchy colitis with a granulomatous response to schisto-

soma ova.

Schistosoma infection may result in acute symptomatic enteritis in patients with HIV as a manifestation of immune reactivation. ■

Acyclovir for Prevention of HIV Transmission

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

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Synopsis: *In a randomized, placebo-controlled trial of suppressive therapy for HSV-2 (acyclovir 400 mg BID) in HIV-1 serodiscordant couples, acyclovir did not reduce the risk of transmission of HIV-1 despite a reduction in the levels of HIV-1 RNA.*

Source: Celum C, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med.* 2010;362:427-439.

This article originally appeared in the March 2010 issue of Infectious Disease Alert.

In a study of HIV transmission, 3,408 HIV-1 serodiscordant couples were enrolled at 14 sites in Africa. All patients had CD4+ lymphocyte counts ≥ 250/uL, were also infected with HSV-2, and were not receiving antiretroviral therapy (ARVs). Sixty-eight percent of the HIV-1 infected partners were women. There were 132 HIV-1 seroconversions; 84 were linked within couples by sequencing. Of these, 41 occurred in the acyclovir (ACV) group and 43 in the placebo group. ACV treatment reduced the mean plasma concentration of HIV-1 by 0.25 $\log_{10}$ copies/mL and the occurrence of HSV-2 + genital ulcers by 73%. Ninety-two percent of the partners infected with HIV-1, and 84% of the partners not infected with HIV-1, remained in the study for 24 months. ACV adherence was 96%.

COMMENTARY

The correlation between genital ulcer disease and HIV-1 infection, especially in heterosexual couples, has been appreciated since the mid-1980s. The logical postulation is that by disrupting normal cutaneous and mucosal barriers, genital ulcer disease directly facilitates the transmission of HIV-1. In addition, a large body of research over the last 25 years has demonstrated that many HSV-encoded proteins can directly promote the transcription of HIV-1, as well as nonspecifically enhancing host cytokine levels, which generally facilitate NFkB-mediated up-regulation of HIV-1 transcription. In fact, earlier clinical studies have demonstrated that daily therapy with ACV for 8-12 weeks reduced plasma HIV-1 RNA levels by 0.25-0.50 $\log_{10}$ copies/mL.

This large, randomized, placebo-controlled trial represented a logical hypothesis that anti-HSV nucleoside analogs, such as ACV, could reduce the transmission of HIV-1 in serodiscordant couples by both reducing genital ulcer disease and by modestly lowering plasma (and genital fluid) levels of HIV-1. This approach is attractive for a number of reasons, since the majority of HIV-1 transmission in Africa is heterosexual and the prevalence of ulcerative genital disease (mostly due to HSV-2) is high. Additionally, the cost of ACV has come down considerably since it is now available as a generic drug, and is certainly less expensive than antiretroviral therapy.

Unfortunately, despite high levels of adherence to daily ACV therapy (and demonstrated reduction in genital ulcer disease and modest reduction in HIV-1 RNA levels), this intervention is just not good enough to reduce HIV transmission. Interestingly, the authors point out that the rate of HIV transmission in both the ACV and placebo groups were relatively low compared to historical data. The authors attribute this low transmission rate to the effect of intervention on promoting condom use and safer sex practices within the study.

The take-home message, from my perspective, is that the only way we are going to significantly reduce HIV transmission is by making universal antiretroviral therapy available throughout the world. While the cost of nucleoside and nucleotide analogue reverse transcriptase inhibitors and non-nucleoside RT inhibitors has come down, HIV protease inhibitors will likely remain unaffordable in much of the developing world. This is actually not due to greedy pharmaceutical companies, but rather the hard fact that PIs require multiple synthetic steps and use generally costly precursor chemicals in their synthesis. Unfortunately, with the rising prevalence of NRTI and nnRTI resistance in transmitted virus, I remain skeptical about our chances of successfully eradicating HIV infection in the developing world using NRTI/nnRTI combinations alone, even if the goal of universal antiretroviral therapy is achieved. ■

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.*

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.