

New Smallpox Vaccine Found Immunogenic

BY MARY ANN MOON

The third-generation smallpox vaccine LC16m8 was found to be as immunogenic as existing smallpox vaccines but appeared to be safer, according to a study of over 3,000 Japanese adults.

The live, attenuated, tissue-cultured LC16m8 vaccine proved to be immunogenic in adults who had never received any smallpox vaccination, and it also produced an adequate booster response in those who had been vaccinated previously.

As important, the LC16m8 vaccine produced minimal local reactions and no severe adverse events, said Dr. Tomoya Saito of the department of tropical medicine and parasitology, Keio University, Tokyo, and associates.

"Developing a vaccine that is safer than first-generation vaccines yet highly immunogenic is crucial to constructing a prevention plan in the event of a bioterrorist attack," the investigators noted.

They assessed the LC16m8 vaccine in healthy personnel in the Japan Self-Defense Forces inoculated in 2002-2005. Nearly 99% were men, and all were Asian. A total of 1,529 had never been vaccinated, and 1,692 had previously been vaccinated against smallpox (JAMA 2009;301:1025-33).

The proportion of "takes"—the visible skin reactions to a single intraepidermal scarification—was comparable to that seen with other vaccines, as were serum levels of neutralizing antibodies. The seroconversion rate was over 90% in those who were never vaccinated and 60% in those who were previously vaccinated.

There were none of the severe adverse events that had been "a major concern" in the U.S. smallpox vaccination program.

The researchers noted that while the total sample size in the study limited their ability to "conclusively confirm that absence of severe adverse events," their results support the conclusion that LC16m8 "causes minimal local manifestations and systemic adverse effects."

The study findings suggest that LC16m8 is "a viable alternative to first-, second-, and other third-generation vaccines in a smallpox preparedness program," they added. ■



Maculopapular lesions on this patient's arm were caused by variola major.

Pertussis Vaccine Not Tied to Wheezing

BY MICHELE G. SULLIVAN

Pertussis vaccination in infancy doesn't appear to increase the risk of wheezing or asthma during childhood and, in fact, may be slightly protective against the disorders, a large population-based study concluded.

The analysis by Ben D. Spycher, a researcher at the University of Bern (Switzerland) and his colleagues, was based on data from Britain's National

Health Service and from a large respiratory cohort study. It compared rates of new-onset wheeze and asthma occurring after 4 months of age with pertussis vaccinations in 6,048 children who were followed for up to 10 years (Pediatrics 2009;123:944-50).

There were 2,426 cases of new-onset wheeze in the group. In both time frames, the univariate analysis showed that children who were fully vaccinated were slightly, but not significantly,

less likely to develop wheezing. The slight, nonsignificant, protective factor remained for both time frames in the multivariate analysis.

The outcomes were similar for diagnosed asthma, the authors noted. A sensitivity analysis suggested that exposure to other vaccines administered concurrently yielded similar results. The work was supported by national grants from Switzerland and the United Kingdom. The authors declared no conflicts. ■

IMPORTANT CORRECTION OF DRUG INFORMATION ABOUT BYSTOLIC® (NEBIVOLOL) TABLETS

An advertisement in professional journal publications for Bystolic® (nebivolol) tablets for the treatment of hypertension was the subject of a Warning Letter issued by the U.S. Food and Drug Administration (FDA) in August 2008.

Forest would like to take this opportunity to clarify the content of this advertisement.

Indications and Usage

Bystolic is indicated for the treatment of hypertension. Bystolic may be used alone or in combination with other antihypertensive agents.

Unsubstantiated Superiority and Mechanism of Action Claims

The FDA objected to claims that Bystolic was a novel and next generation beta blocker with a unique mechanism of action including cardioselective beta blockade and vasodilation. The FDA stated that these claims were misleading because they suggested that Bystolic is different from and superior to other β -adrenergic receptor blocking agents in the treatment of hypertension, when these implications have not been demonstrated by substantial evidence or substantial clinical experience. In extensive metabolizers (most of the population) and at doses ≤ 10 mg, Bystolic is preferentially β_1 selective. The FDA also stated that the presentation of the mechanism of action implied that it had been established, when the package insert states that the mechanism of action of the antihypertensive response of Bystolic has not been definitively established.

Omission and Minimization of Risk Information

The FDA stated that the advertisement did not disclose the following important safety information, which is contained in Bystolic's full Prescribing Information:

Warning: In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation of Bystolic should be considered.

Precautions: CYP2D6 Inhibitors: Use caution when Bystolic is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc).

Drug interactions: Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When Bystolic is co-administered with an inhibitor or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C_{max} for d-nebivolol.

The FDA objected to the claim, "Favorable tolerability profile with a low incidence of beta blocker-related side effects." The FDA determined that this claim implied that the tolerability profile of Bystolic is better than the tolerability profile of other β -adrenergic receptor blocking agents, when this has not been demonstrated by substantial evidence or substantial clinical experience. The FDA also objected to the claim, "Favorable tolerability profile," stating that it minimized the risks associated with Bystolic.

Unsubstantiated Efficacy Claims

The FDA objected to the claim, "Efficacy demonstrated across a broad range of patients." The FDA stated that the cited claim implied that efficacy was demonstrated within each subgroup (obese, poor metabolizers, and diabetic) presented in conjunction with this claim, when this has not been supported by substantial evidence or substantial clinical experience. None of the efficacy trials for Bystolic were specifically designed to evaluate effectiveness in patients who were obese, poor metabolizers, or diabetic. The FDA is not aware of any studies with Bystolic demonstrating efficacy in the above referenced subgroups. Effectiveness was established in black hypertensive patients and was similar in subgroups analyzed by age and sex.

Important Safety Information

Patients being treated with Bystolic should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported following the abrupt cessation of therapy with beta blockers. When discontinuation is planned, the dosage should be reduced gradually over a 1- to 2-week period and the patient carefully monitored.

Bystolic is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh $>B$), and in patients who are hypersensitive to any component of this product.

Bystolic should be used with caution in patients with peripheral vascular disease, thyrotoxicosis, in patients treated concomitantly with beta blockers and calcium channel blockers of the verapamil and diltiazem type (ECG and blood pressure should be monitored), severe renal impairment, and any degree of hepatic impairment or in patients undergoing major surgery. In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation of Bystolic should be considered. Caution should also be used in diabetic patients as beta blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.

When Bystolic is administered with CYP2D6 inhibitors such as fluoxetine, significant increases in d-nebivolol may be observed (ie, an 8-fold increase in AUC).

In general, patients with bronchospastic disease should not receive beta blockers.

Bystolic should not be combined with other beta blockers.

The most common adverse events with Bystolic versus placebo (approximately $\geq 1\%$ and greater than placebo) were headache, fatigue, dizziness, diarrhea, nausea, insomnia, chest pain, bradycardia, dyspnea, rash, and peripheral edema.

Please see the accompanying brief summary of Prescribing Information for full risk information.



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