

# Smallpox Revaccination Shows Retained Immunity

BY MICHELE G. SULLIVAN  
Mid-Atlantic Bureau

ST. LOUIS — Patients previously vaccinated for smallpox will, with revaccination, experience a smaller erythematous response, a quicker time to pustulation, and a fourfold increase in antibody titers, compared with vaccine-naïve patients.

“This provides important clinical evidence of retained immunity to smallpox, even in individuals vaccinated more than

30 years ago,” Eric Simpson, M.D., said at the annual meeting of the Society of Investigational Dermatology.

Also, said Dr. Simpson of Oregon Health and Science University, Portland, povidone ointment is effective for controlling viral shedding at the vaccination site. Within 2 hours, it decreases shedding to 0, and it has no effect on antibody titers.

Two recent studies have challenged the long-held theory that smallpox immunity lasts less than 10 years after vaccination, he said. A 2002 study showed that previously vaccinated individuals retained humoral immunity up to 75 years after vaccination. A 2003 study showed that previously vaccinated individuals could be successfully revaccinated with diluted vaccine, because of their more robust immune response.

In Dr. Simpson's study, 26 healthy adult volunteers were vaccinated; 17 of them had been vaccinated an average of 33 years earlier (range 2-50 years). The rest were vaccine naïve. He used a standard vaccination protocol, with the previously vaccinated subjects receiving 15 pokes with a bifurcated needle, while the vaccine-naïve group received 3 pokes.

Measurements included maximum erythema at the vaccine site and maximum time to pustulation. Dr. Simpson also studied the effect of povidone ointment on viral shedding, when applied starting day 7.

The previously vaccinated subjects had

a significantly smaller maximum diameter of erythema around the vaccination site, compared with the naïve group (1.9 cm vs. 3.9 cm). The previously vaccinated group developed an erythematous reaction more quickly, beginning at day 3, compared with day 6 for the naïve group. Erythema for both groups peaked around day 10.



Smallpox vaccination site reaction is shown in a previously vaccinated patient.

It's important that physicians be familiar with the differences in vaccination site reactions, he said.

Maximum time to pustulation was significantly shorter in the previously vaccinated group than in the naïve group (about 7 days vs. 9.6 days).

The previously vaccinated group devel-

oped four times the antibody titers of the naïve group, he said. “This explains the earlier finding that you can successfully vaccinate these patients with diluted vaccine.”

To study the effect of povidone ointment on viral shedding, Dr. Simpson applied the ointment to the vaccination site every 2-3 days, beginning at day 7. Viral



Vaccination site reaction is shown in a smallpox vaccine-naïve patient.

shedding was measured 1 hour after the ointment was applied. “The shedding dropped to 0 within 1-2 hours and stayed that way throughout the entire vaccine response,” he said. “In the untreated group, viral shedding continued to occur until approximately day 20, which is around the time the eschar was shed.”

**Ezetimibe:** The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

**Simvastatin:** Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarcheal girls.

**Geriatric Use**  
Of the patients who received VYTORIN™ (ezetimibe/simvastatin) in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

**ADVERSE REACTIONS**  
VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.

Table 1 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials.

**Table 1\***  
Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class	Placebo (%)	Ezetimibe 10 mg (%)	Simvastatin** (%)	VYTORIN** (%)
Body as a whole – general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and connective tissue disorders				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

\* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.

\*\* All doses.

**Ezetimibe:** Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole – general disorders:* fatigue; *Gastrointestinal system disorders:* abdominal pain, diarrhea; *Infection and infestations:* infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders:* arthralgia, back pain; *Respiratory system disorders:* coughing.

**Post-marketing Experience**  
The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

**Hypersensitivity reactions,** including angioedema and rash; increased CPK; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely in patients taking an HMG-CoA reductase inhibitor with ezetimibe, rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

**Simvastatin:** Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole – general disorders:* asthenia; *Eye disorders:* cataract; *Gastrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders:* eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy. *Musculoskeletal system disorders:* muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

*Nervous system disorders:* dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paralysis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances. *Ear and labyrinth disorders:* vertigo.

*Psychiatric disorders:* anxiety, insomnia, depression, loss of libido.

**Hypersensitivity Reactions:** An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

*Gastrointestinal system disorders:* pancreatitis, vomiting.

*Hepatobiliary disorders:* hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

*Metabolism and nutrition disorders:* anorexia.

*Skin and subcutaneous tissue disorders:* alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

*Reproductive system and breast disorders:* gynecostasia, erectile dysfunction.

*Eye disorders:* progression of cataracts (lens opacities), ophthalmoplegia.

*Laboratory Abnormalities:* elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

**Laboratory Tests**

Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

**Concomitant Lipid-Lowering Therapy**

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

**Adolescent Patients (ages 10-17 years)**

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

## CLINICAL CAPSULES

### World Health Regulations

The World Health Organization should be notified about all major health events of international concern, international health officials concluded at the 58th World Health Assembly.

The conclusion was prompted mainly by the SARS and avian influenza outbreaks. Reportable disease outbreaks under the newly adopted international health regulations include those involving flu or suspected bioterrorism. The new regulations, which should become effective in 2007, also require that the WHO assist member nations in responding to disease outbreaks and provide a basis for improved international cooperation in responding to such outbreaks.

The regulations, which were first adopted in 1969 and revised in 1973 and 1981, were renewed again in May by the World Health Assembly, which includes health ministers and senior health officials from 192 countries.

### Long-Term WNIV Outcomes

Initial disability was high in 22 West Nile virus patients who had acute central nervous system infection, and mortality was confined to the most severely affected patients—usually those with respiratory failure—an 18-month follow-up has shown.

Seven patients (32%) died. The mean time to death was 77 days after hospital admission. Respiratory failure was strongly associated with mortality (odds ratio 24.0), reported Lara E. Jeha, M.D., and associates at the Cleveland Clinic Foundation.

All patients were independent in activi-

ties of daily living prior to their illness, as measured by a Barthel index score of 100 on a 0-100 scale. At hospital or rehabilitation discharge, nearly half of the 15 surviving patients had Barthel index scores below 50. The low scores persisted at 18 months in only 13% of the patients (Infect. Dis. Clin. Pract. 2005;13:101-3).

Ongoing neuropsychiatric symptoms were common among the survivors. About 48% reported ongoing fatigue, memory problems, or difficulty concentrating. These complaints were most common in those who had encephalitis. Sensorimotor deficits, also reported by about 48% of patients, were most common in those who had weakness at presentation.

### Asthma and Pneumococcal Disease

Asthma is an independent risk factor for invasive pneumococcal disease, a nested case-control study suggests. Patients with asthma had a 2.4-fold higher risk, compared with controls.

Asthma was present in about 18% of 635 individuals with invasive pneumococcal disease, compared with 8% of 6,350 controls in the study, Thomas R. Talbot, M.D., of Vanderbilt University in Nashville and his colleagues reported.

Risk was greatest for those with high-risk asthma, defined as having had an emergency department visit, hospital admission, use of rescue therapy, use of long-term oral corticosteroids, or receipt of three or more prescriptions for β-agonists in the previous year. They had an annual incidence of 4.2 episodes of invasive pneumococcal disease per 10,000 persons,

compared with 2.3 episodes per 10,000 persons with low-risk asthma (those diagnosed with or treated for asthma, but not qualifying as high risk), and 1.2 episodes per 10,000 controls (N. Engl. J. Med. 2005;352:2082-90).

The findings suggest asthma should be included in the list of conditions that increase risk of invasive pneumococcal disease, and pneumococcal vaccination for asthma patients should be studied.

### Gonorrhea Screening

Clinicians should perform routine screening of all sexually active women at increased risk for gonorrhea, because of the high risk for pelvic inflammatory disease, ectopic pregnancy, and chronic pelvic pain associated with asymptomatic gonorrhea infection, according to the U.S. Preventive Services Task Force.

Those at risk include sexually active women under age 25, those with previous gonorrhea or other sexually transmitted infections, those with new or multiple sex partners, those who don't consistently use condoms, sex workers, and drug users. Pregnant women with these risk factors should be screened at the first prenatal visit, and those with ongoing or new risk factors should also be screened during the third trimester because gonorrhea increases the risk of preterm rupture of membranes, chorioamnionitis, and preterm labor (Ann. Fam. Med. 2005;3:263-7).

The task force recommended against routine screening in women and men at low risk for gonorrhea, and found insufficient evidence for or against routine screening in men at high risk.

—Sharon Worcester

MERCK / Schering-Plough Pharmaceuticals

Manufactured for: MERCK/Schering-Plough Pharmaceuticals

North Wales, PA 19454, USA

©Merck/Schering-Plough Pharmaceuticals, 2005.

All rights reserved.

20502352(1)(602)-VYT