

Zoster Risk Declined in Young Varicella Vaccinees

BY BRUCE JANCIN

VAIL, COLO. — The risk of herpes zoster in children under age 10 years who've been vaccinated against varicella was 4- to 12-fold less than in those with naturally acquired varicella in a large population-based study.

Moreover, when herpes zoster did occur, the pain was significantly less if the eruption was caused by the vaccine

strain varicella zoster virus (VZV). This has previously been anecdotally reported, but the new study by the Los Angeles County Department of Public Health and the Centers for Disease Control and Prevention provides the first actual proof that herpes zoster in varicella vaccinees is a generally benign disease, Dr. Myron J. Levin said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

The study was conducted during 2000-2006 in Antelope Valley, Calif., a long-time CDC active surveillance site. During the study period, the incidence of herpes zoster among children less than 10 years old declined by 55%, from 74.8 cases per 100,000 in 2000 to 33.3 per 100,000 in 2006.

In contrast, the incidence jumped by 63% among 10- to 19-year-olds, from 59.5 to 96.7 cases per 100,000. The investigators said they couldn't explain this increase and would like to see it confirmed in other data sets in order to be confident the phenomenon is real (Pediatr. Infect. Dis. J. 2009; 28:954-9).

One possible explanation for the increase over time in the older youths is waning VZV immunity, with resultant reactivation of the latent vaccine strain of the virus, according to Dr. Levin, professor of pediatrics and medicine at the University of Colorado at Denver.

Another possibility—and one he favors—is that the varicella vaccine is a suboptimal immunogen. Although the vaccine's primary failure rate is 4%-5%, as with other vaccines, the fact is that the

boost in immunogenicity to varicella antigen following a first dose of the MMR vaccine is markedly less than the resultant immunogenicity boost to

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DR. LEVIN

measles, mumps, and rubella antigens. That's the basis for the two-dose strategy recommended by the CDC Advisory Committee on Immunization Practices in 2007.

The second vaccine dose boosts antibody to levels similar to those seen in adults after varicella. But boosted immunity will wane, and only time will tell how varicella vaccination will affect the incidence of herpes zoster. "We are in the midst of a very large clinical experiment," Dr. Levin said of the two-dose strategy.

It makes sense that herpes zoster in VZV vaccine recipients should be less frequent and less severe than in naturally infected individuals because the vaccine virus is attenuated. Plus, the latent VZV that causes herpes zoster comes from skin lesions—and skin lesions are rare following vaccination of normal individuals. Dr. Levin disclosed that he is a consultant to, is on the speakers bureau for, and receives royalties from Merck & Co. ■



Vigamox®

(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

DESCRIPTION: VIGAMOX® (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

CLINICAL PHARMACOLOGY:

Microbiology:

The following *in vitro* data are also available, but their clinical significance in ophthalmic infections is unknown. The safety and effectiveness of VIGAMOX® solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less (systemic susceptible breakpoint) against most (≥ 90%) strains of the following ocular pathogens.

Aerobic Gram-positive microorganisms:

| | |
|-------------------------------------|---------------------------------------|
| <i>Listeria monocytogenes</i> | <i>Streptococcus mitis</i> |
| <i>Staphylococcus saprophyticus</i> | <i>Streptococcus pyogenes</i> |
| <i>Streptococcus agalactiae</i> | <i>Streptococcus</i> Group C, G and F |

Aerobic Gram-negative microorganisms:

| | |
|------------------------------------|------------------------------|
| <i>Acinetobacter baumannii</i> | <i>Klebsiella pneumoniae</i> |
| <i>Acinetobacter calcoaceticus</i> | <i>Moraxella catarrhalis</i> |
| <i>Citrobacter freundii</i> | <i>Morganella morganii</i> |
| <i>Citrobacter koseri</i> | <i>Neisseria gonorrhoeae</i> |
| <i>Enterobacter aerogenes</i> | <i>Proteus mirabilis</i> |
| <i>Enterobacter cloacae</i> | <i>Proteus vulgaris</i> |
| <i>Escherichia coli</i> | <i>Pseudomonas stutzeri</i> |
| <i>Klebsiella oxytoca</i> | |

Anaerobic microorganisms:

| | |
|--------------------------------|--------------------------------|
| <i>Clostridium perfringens</i> | <i>Prevotella</i> species |
| <i>Fusobacterium</i> species | <i>Propionibacterium acnes</i> |

Other microorganisms:

| | |
|-------------------------------|------------------------------|
| <i>Chlamydia pneumoniae</i> | <i>Mycobacterium marinum</i> |
| <i>Legionella pneumophila</i> | <i>Mycoplasma pneumoniae</i> |
| <i>Mycobacterium avium</i> | |

Clinical Studies:

In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX® solution produced clinical cures on day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 84% to 94%. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

INDICATIONS AND USAGE: VIGAMOX® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-positive microorganisms:

| | |
|------------------------------------|-------------------------------------|
| <i>Corynebacterium</i> species* | <i>Staphylococcus hominis</i> |
| <i>Micrococcus luteus</i> * | <i>Staphylococcus warneri</i> * |
| <i>Staphylococcus aureus</i> | <i>Streptococcus pneumoniae</i> |
| <i>Staphylococcus epidermidis</i> | <i>Streptococcus viridans</i> group |
| <i>Staphylococcus haemolyticus</i> | |

Aerobic Gram-negative microorganisms:

| | |
|--------------------------------|-------------------------------------|
| <i>Acinetobacter lwoffii</i> * | <i>Haemophilus parainfluenzae</i> * |
| <i>Haemophilus influenzae</i> | |

Other microorganisms:

Chlamydia trachomatis

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS: VIGAMOX® solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS:

NOT FOR INJECTION.

VIGAMOX® solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemically administered quinolones, including moxifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS:

General: As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemically administered quinolones including moxifloxacin have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Drug Interactions: Drug-drug interaction studies have not been conducted with VIGAMOX® solution. *In vitro* studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis).

Moxifloxacin was not mutagenic in four bacterial strains used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

Pregnancy: Teratogenic Effects.

Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day.

Since there are no adequate and well-controlled studies in pregnant women, VIGAMOX® solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when VIGAMOX® solution is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of VIGAMOX® solution in infants below 1 year of age have not been established.

There is no evidence that the ophthalmic administration of VIGAMOX® solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS:

The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

Nonocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

Rx Only

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Zoster Vaccine Could Have Off-Label Use, Expert Says

BY BRUCE JANCIN

VAIL, COLO. — Giving herpes zoster vaccine to children who are immunocompromised, or are about to become so, is an off-label use that is nonetheless worthy of strong consideration in selected cases.

That's the view of vaccine expert Dr. Myron J. Levin, who notes that herpes zoster in immunocompromised children tends to be extremely severe. "It makes sense to give the vaccine to children who've had chicken pox and are going to have a transplant. Maybe you can protect them from zoster down the road by giving them the zoster vaccine up front. It's a new thought," he said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

As for children who are already immunocompromised, it is important to look for safe opportunities in which to administer the herpes zoster (HZ) vaccine, which contains 14-fold higher titers of varicella zoster virus than the childhood varicella vaccine.

"It's probably going to be safe wherever it's safe to give the varicella vaccine to immunocompromised kids. That's where I would start. The reason I can say that is because they already have some preexisting immunity. You're not giving this vaccine to a naive person, you're giving

it to someone who has a history of varicella. So it's unlikely they're going to have serious side effects unless they're very, very immunocompromised," explained Dr. Levin, professor of pediatrics and medicine at the University of Colorado at Denver. Thus, HZ vaccination is to be avoided in situations of severe immune compromise because it could result in a fulminant case of zoster.

In contrast, circumstances in which giving varicella vaccine—and, by extension, HZ vaccine—appears to be safe and beneficial include HIV-infected patients with more than 15% CD4 cells, particularly if highly active antiretroviral therapy is on board; recipients of a solid organ transplant 6 months or more before without complications or need for rejection therapy; lymphoma patients who successfully completed treatment at least 3 months earlier; and individuals who are 18-24 months post stem-cell transplant with no rejection episodes or other problems, who have good cell counts, and who are off immunosuppressive therapy, according to Dr. Levin. The HZ vaccine is licensed for immunocompetent individuals aged 60 years and older. It is now in large clinical trials looking at enlarging the recipient pool to include 50- to 59-year-olds.

Dr. Levin disclosed that he is a consultant to, is on the speakers bureau for, and receives royalties from Merck & Co. ■