

Making the Case: HPV Vaccine for Young Males

BY DEBRA L. BECK

TORONTO — Genital warts and human papillomavirus-related cancers in men are costly and emotionally burdensome conditions that should be prevented with HPV vaccination, according to Susan Rosenthal, Ph.D.

“Vaccinating males also represents a more equitable public health policy in that it recognizes that both genders

contribute to the transmission of HPV,” Dr. Rosenthal said at the annual meeting of the Society for Adolescent Health and Medicine (SAHM).

The Food and Drug Administration approved the quadrivalent HPV vaccine (Gardasil) for boys aged 9-26 years in October 2009. Since then, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices has given a permissive recom-

mendation for vaccination for boys at the discretion of the physician, a recommendation that is supported by a SAHM position paper, said Dr. Rosenthal, whose research has focused on adolescent sexual health and vaccine acceptability.

Although 13 HPV types cause cervical cancer—a well-known bit of information—Dr. Rosenthal pointed out that in a 2006 study, HPV-16 was determined to cause several other cancers, including

vulvar, vaginal, anal, penile, and oropharyngeal cancers. There is some evidence also linking HPV-16 to laryngeal and nonmelanoma skin cancer, said Dr. Rosenthal, a pediatric psychologist at Columbia University Medical Center and Morgan Stanley Children’s Hospital of New York-Presbyterian.

“So we know that HPV causes cancer in men,” said Dr. Rosenthal. Indeed, based on 2008 estimates of the annual number of new cases of HPV-related cancers in U.S. men, of the 38,260 cases involving the oral cavity and oropharynx, larynx, anus, and penis, 10,969 (28.6%) were attributed to HPV infection, according to data from the American Cancer Society and other sources.

In a recent study (New England Journal of Medicine, in press, 2010), the HPV vaccine was found to be 90% effective in preventing external genital lesions, a category that included external genital warts, penile/perianal/perineal intraep-

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ithelial neoplasia, and penile/perianal/perineal cancers. Of the 1,397 men and women who received the vaccine, there were only three cases of external genital lesions, all three of which were condyloma.

“It’s not fun to have these diseases or the work-up for these diseases. If we use a female-only strategy, we will not protect men who have sex with men, and we don’t know at [age] 11 who are the men who have sex with men. And this is a prophylactic vaccine,” said Dr. Rosenthal.

In the discussion following Dr. Rosenthal’s presentation, some controversy erupted over whether all boys should receive the HPV vaccine or only boys who are likely to have sex with other males should be vaccinated.

“Historically, at least in this country, we’re terrible at gender-based vaccination, we don’t have high uptake when we try to do risk-based strategies. Vaccinating men will also be the fastest way to achieve protection for women, and vaccinating males is an arguably more equitable public health policy because it recognizes that both genders contribute to the transmission of HPV,” argued Dr. Rosenthal.

Audience member Dr. Gary Remafedi of the University of Minnesota Amplatz Children’s Hospital, Minneapolis, countered: “There is observational data indicating the benefits of immunizing young men who have sex with men, but we’re still awaiting comparable data for the general male population. As we await that data, I believe it would be a disservice not to immunize young men who

Continued on following page

DESONATE® (desonide) Gel for topical use only

Initial U.S. Approval: 1972

BRIEF SUMMARY

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1 INDICATIONS AND USAGE

Desonate is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Patients should be instructed to use Desonate for the minimum amount of time as necessary to achieve the desired results because of the potential for Desonate to suppress the hypothalamic-pituitary-adrenal (HPA) axis [see *Warnings and Precautions* (5.1)]. Treatment should not exceed 4 consecutive weeks [see *Dosage and Administration* (2)].

4 CONTRAINDICATIONS

Desonate is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Endocrine System

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, 6 months to 6 years old, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test. As follow-up evaluation of the subject’s adrenal axis was not performed, it is unknown whether the suppression was reversible [see *Use in Specific Populations* (8.4) and *Clinical Pharmacology* (12.2)].

Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of Desonate due to their larger skin surface-to-body mass ratios [see *Use in Specific Populations* (8.4)].

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Cushing’s syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

5.2 Local Adverse Reactions with Topical Corticosteroids

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include skin atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

5.3 Concomitant Skin Infections

If concomitant skin infections are present or develop during treatment, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Desonate should be discontinued until the infection is adequately controlled.

5.4 Skin Irritation

If irritation develops, Desonate should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies of 425 Desonate-treated subjects and 157 Vehicle-treated subjects, adverse events occurred at the application site in 3% of subjects treated with Desonate and the incidence rate was not higher compared with vehicle-treated subjects. The most common local adverse events in Desonate treated subjects were application site burning in 1% (4/425) and rash in 1% (3/425) followed by application site pruritus in <1% (2/425).

Adverse events that resulted in premature discontinuation of study drug in Desonate treated subjects were telangiectasia and worsening of atopic dermatitis in one subject each. Additional adverse events observed during clinical trials for patients treated with Desonate included headache in 2% (8/425) compared with 1% (2/157) in those treated with vehicle.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, skin atrophy, striae, and miliaria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. Therefore, Desonate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. No reproductive studies in animals have been performed with Desonate. Dermal embryofetal development studies were conducted in rats and rabbits with a desonide cream, 0.05% formulation. Topical doses of 0.2, 0.6, and 2.0 g cream/kg/day of a desonide cream, 0.05% formulation or 2.0 g/kg of the cream base were administered topically to pregnant rats (gestational days 6-15) and pregnant rabbits (gestational days 6-18). Maternal body weight loss was noted at all dose levels of the desonide cream, 0.05% formulation in rats and rabbits. Teratogenic effects characteristic of corticosteroids were noted in both species. The desonide cream, 0.05% formulation was teratogenic in rats at topical doses of 0.6 and 2.0 g cream/kg/day and in rabbits at a topical dose of 2.0 g cream/kg/day. No teratogenic effects were noted for the desonide cream, 0.05% formulation at a topical dose of 0.2 g cream/kg/day in rats and 0.6 g cream/kg/day in rabbits. These doses (0.2 g cream/kg/day and 0.6 g cream/kg/day) are similar to the maximum recommended human dose based on body surface area comparisons.

8.3 Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Desonate is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Desonate in pediatric patients less than 3 months of age have not been evaluated, and therefore its use in this age group is not recommended.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test [see *Warnings and Precautions* (5.1)].

In controlled clinical studies in subjects 3 months to 18 years of age, 425 subjects were treated with Desonate and 157 subjects were treated with vehicle [see *Adverse Reactions* (6) and *Clinical Studies* (14)].

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

Adverse effects, including striae, have been reported with inappropriate use of topical corticosteroids in infants and children. HPA axis suppression, Cushing’s syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

8.5 Geriatric Use

Clinical studies of Desonate did not include patients aged 65 and older to determine if they respond differently than younger patients. Treatment of this patient population should reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic or photoco-carcinogenic potential of Desonate or the effect of desonide on fertility. Desonide revealed no evidence of mutagenic potential based on the results of an *in vitro* genotoxicity test (Ames assay) and an *in vivo* genotoxicity test (mouse micronucleus assay). Desonide was positive without S9 activation and was equivocal with S9 activation in an *in vitro* mammalian cell mutagenesis assay (L5178YITK+ mouse lymphoma assay). A dose response trend was not noted in this assay.

17 PATIENT COUNSELING INFORMATION

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- Unless directed by the physician, the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.
- Unless directed by a physician, this medication should not be used on the underarm or groin areas of pediatric patients.
- Parents of pediatric patients should be advised not to use Desonate in the treatment of diaper dermatitis. Desonate should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressing [see *Dosage and Administration* (2)].
- Patients should report to their physician any signs of local adverse reactions.
- Other corticosteroid-containing products should not be used with Desonate without first consulting with the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, contact the physician.

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Pandemic Flu Didn't Faze One Pediatric ED

BY MICHELE G. SULLIVAN

PHILADELPHIA — After presenting to a busy pediatric emergency department, only 3% of children admitted had suspected pandemic influenza during the peak of the outbreak last year.

“Our cases of influenzalike illness were relatively mild and associated with a much lower hospital admission rate than cases we saw for other reasons,” Dr.

Jeffrey Chen said at the annual meeting of the Eastern Society for Pediatric Research. “Most of the admissions [for suspected pandemic flu] were younger children and were associated with pulmonary disease.”

Dr. Chen and his associates at St. Barnabas Hospital in New York assessed the 2009 pandemic flu season by reviewing the charts of patients admitted from April 29 to June 15—the peak of the out-

break in New York City. During the study period, 4,921 patients were seen in the facility—an increase of 77% from the same period in 2008. Of those, 52% (2,543) fulfilled the criteria for flulike illness set forth by the Centers for Disease Control and Prevention: fever, cough, sore throat, myalgia, vomiting, or diarrhea.

Most of the patients with flulike illness (2,472) were discharged; 71 patients (3%) were admitted to the hospital.

Pulmonary symptoms were significantly more common among those admitted with suspected flu than among those discharged (27% vs. 5%).

Despite the finding of probable flu, most patients had no confirmatory testing: 58% of admitted patients were not tested, and 70% of those discharged were not tested. ■

Disclosures: None was reported.

Continued from previous page

have sex with men as soon as they are identified as at least being likely to have sex with men. It is absolutely the job of the physician to identify these people.”

“I can't predict sexual behavior in the young male. ... I think a lot of 11-, and 12-, and 13-year-olds, which is the age at which I think we should immunize, are not clear in their own minds whether they want to have sex with other men,” responded Dr. Rosenthal.

Some of the reasons for not vaccinating males, she said, include the questionable cost effectiveness, particularly if high rates of female vaccinations are achieved, and the issues of overall costs.

In separate interviews, Dr. Carol A. Ford and Dr. Marianne E. Felice both felt comfortable with the recommendation to vaccinate both boys and girls against HPV.

“When you look at cost-effectiveness analyses, it is important to figure out whether you are including negative outcomes for men and women, or just for men. STDs affect both partners, so it's an interesting discussion whether you look at the burden of the sexually transmitted disease for both men and women or if you try to isolate it to one partner or the other,” said Dr. Ford, director of the adolescent medicine program at the University of North Carolina at Chapel Hill and director of the N.C. Multisite Adolescent Research Consortium for Health.

“There are men that we are vaccinating at our clinics in North Carolina so we are taking seriously the recommendation that this is a vaccination that is appropriate for both men and women. My sense is that we're protecting both men and women in doing this,” she said.

Dr. Marianne E. Felice, professor and chair of the department of pediatrics at the University of Massachusetts, Worcester, said in an interview, “Frankly, I think we should just vaccinate all boys. At the division of adolescent medicine at UMass, we are giving the vaccine to boys and most of the parents want their kids to have it. I think if you vaccinate the boys along with the girls, even if they aren't having sex with other boys, this is a way to protect them as well as the girls. They're not going to get warts from someone and then give it to a girl. It's herd immunity.” ■

Disclosures: Dr. Rosenthal disclosed grants from Merck & Co. Dr. Ford, Dr. Felice, and Dr. Remafedi reported no disclosures.

When RSV* activity erupts...

More children may be visiting the hospital or your office for help^{1,2}

RSV is the leading cause of bronchiolitis and pneumonia in pediatric patients^{1,3}

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- From 1997 to 2000, RSV bronchiolitis was the leading cause of hospitalizations for infants <12 months of age¹

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- 22% of infants <1 year of age infected with RSV will develop bronchiolitis⁴
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Estimated RSV-related visits (2000) in US children <5 years of age in several outpatient settings

236,000	402,000	1.7 million
Hospital outpatient department visits	Emergency room visits	Office visits

Adapted from Paramore LC et al. *Pharmacoeconomics*. 2004;22:275-284.²

Potentially serious long-term consequences

- RSV-related lower respiratory tract illnesses (LRTIs) in infancy may be associated with an increased risk of asthma in the first decade of life⁵⁻⁷

Age	Asthma RR† (95% CI‡)
3 years	21.8 (2.90-163.57) ⁵
7 years	9.23 (2.79-30.55) ⁶
13 years	6.8 (2.7-17.3) ⁷

Based on a prospective cohort of 47 (93 control) Scandinavian children <1 year of age in 1989 hospitalized with RSV and followed for 13 years.

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*RSV = respiratory syncytial virus.
†RR = relative risk.
‡CI = confidence interval.

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