

# Synthetic HPV Vaccine May Prevent Neoplasia

BY MARY ANN MOON

A vaccine that contained peptides targeting the human papillomavirus-16 oncoproteins E6 and E7 was effective against high-grade, HPV-16-positive vulvar intraepithelial neoplasia, according to the results of a small phase II study.

"This clinical efficacy is probably related to a vaccine-induced HPV-16 T-cell

response," said Dr. Gemma G. Kenter and her associates at Leiden (the Netherlands) University Medical Center (N. Engl. J. Med. 2009;361:1838-47).

In the blood of patients with high-grade vulvar intraepithelial neoplasia, researchers have noted that there are low or undetectable numbers of T cells directed against the HPV-16 oncoproteins E6 and E7.

Reasoning that "vaccination might

overcome this inertia of the immune system," Dr. Kenter and her colleagues proceeded to develop a vaccine containing synthetic long peptides "that represent the entire length" of these two oncoproteins.

They tested the vaccine in 20 women in a single-center observational study conducted in 2004-2007. The study was sponsored by the Dutch Cancer Society, the European Union, and ISA Pharma-

ceuticals B.V. These subjects were slated to receive three or four vaccinations at 3-week intervals and they were followed for 24 months.

At the 3-month follow-up, blood samples showed that 17 of the subjects had an HPV-16-specific immunologic response and enhanced production of interferon. Eleven of the patients reported symptom relief. Five patients showed a complete histologic and clinical response, and seven showed partial responses, Dr. Kenter and her associates reported.

After 1 year, the number of women showing a complete response increased to nine, and six continued to show a par-



## BRIEF SUMMARY

**For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravaginal Use**  
Rx only

## CONTRAINDICATIONS

FINACEA® Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

## WARNINGS

FINACEA® Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

## PRECAUTIONS

**General:** Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA® Gel, 15%, treatment should be discontinued and appropriate therapy instituted. The safety and efficacy of FINACEA® Gel, 15%, has not been studied beyond 12 weeks.

**Information for Patients:** Patients using FINACEA® Gel, 15%, should receive the following information and instructions:

- FINACEA® Gel, 15%, is to be used only as directed by the physician.
- FINACEA® Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA® Gel, 15%. Avoid alcoholic cleansers, tinctures, and astringents, abrasives, and peeling agents.
- Avoid contact of FINACEA® Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA® Gel, 15%.
- Cosmetics may be applied after FINACEA® Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA® Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA® Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occlusive dressings or wrappings.

**Drug Interactions:** There have been no formal studies of the interaction of FINACEA® Gel, 15%, with other drugs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic potential of FINACEA® Gel, 15%. Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* (Ames assay, HGPRT in V79 cells [Chinese hamster lung cells], and chromosomal aberration assay in human lymphocytes) and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

## Pregnancy: Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA® Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits, and cynomolgus monkeys.

An oral peri- and postnatal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the postnatal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

## Nursing Mothers:

Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA® Gel, 15%, is administered to a nursing mother.

**Pediatric Use:** Safety and effectiveness of FINACEA® Gel, 15%, in pediatric patients have not been established.

**Geriatric:** Clinical studies of FINACEA® Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

## ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness, were 19.4% (24/124) for FINACEA® Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA® Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

**Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity\***

	FINACEA® Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild n=99 (22%)	Moderate n=61 (13%)	Severe n=27 (6%)	Mild n=46 (14%)	Moderate n=30 (9%)	Severe n=5 (2%)
Burning/ stinging/ tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/ irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

\*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

FINACEA® Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA® Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA® Gel, 15%, to the eye (see PRECAUTIONS).

## OVERDOSAGE

FINACEA® Gel, 15%, is intended for cutaneous use only. If pronounced local irritation occurs, patients should be directed to discontinue use and appropriate therapy should be instituted (See PRECAUTIONS).

December 2007

Distributed under license; U.S. Patent No 4,713,394

Manufactured by Intendis Manufacturing S.p.A., Segrate, Milan, Italy

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tial response. Twelve women reported symptom relief.

All nine women who showed a complete response were still free of disease at 2-year follow-up. Tumor microinvasion was found in one woman who had shown a partial response, and carcinoma developed in two other patients 2.5 and 3.5 years after vaccination, the investigators said.

In an editorial comment that accompanied this report, Olivera J. Finn, Ph.D., and Dr. Robert P. Edwards, who are both with the University of Pittsburgh, noted that this study was the latest in a series conducted by the same group of investigators "who over the past several years have tested this vaccine in preclinical settings for its tumor-rejection potential and for its safety and immunogenicity in end-stage cervical cancer."

The findings from this small study suggest that "more effective immune responses can be generated against precursor lesions than against late-stage disease. Many cancer vaccines based on nonviral tumor-associated antigens have been judged to be suboptimal because of their lack of efficacy in advanced disease, yet they might perform very differently if used in patients with premalignant disease," Dr. Finn and Dr. Edwards said.

If the vaccine approach is developed further, it may offer a less invasive and more durable treatment than is currently available for vulvar intraepithelial neoplasia, they said.

The Leiden University Medical Center holds a patent on the use of synthetic long peptides as vaccine. Dr. Kenter reported serving as an unpaid member of the strategy team of ISA Pharmaceuticals. Dr. Edwards reported that he received consulting fees from Fresenius SE and grant support from Sanofi-Aventis.