HPV May Play Role in Skin Carcinogenesis

VIENNA — Cutaneous human papillomavirus infection may play a role in the development of skin cancer, Ingo Nindl, Ph.D., reported at the annual meeting of the European Society for Dermatological Research.

Infection by the same HPV variants was consistently detected in two of four patients with primary, recurrent, and metastatic nonmelanoma skin cancer, whose tumor biopsies were analyzed by polymerase chain reaction (PCR) for the presence of 24 cutaneous HPV types and their variants, according to Dr. Nindl of Charité Hospital in Berlin.

In one immunosuppressed patient, the primary squamous cell carcinoma and 8 of 10 recurrences that developed at sun-exposed sites after 4, 8, 9, 11, 37, 53, and 54 months of follow-up were consistently infected by the –E6 variants of HPV 21 and HPV 36.

In an immunocompetent patient, both the primary squamous cell carcinoma and a metastasis that developed after 8 months of follow-up were infected by HPV 14. Two others showed no consistent pattern of HPV infection in their primary and recurrent squamous cell carcinomas.

HPV's role in the development of genital cancers is well recognized. The first evidence that HPV might also be involved in nonmelanoma skin cancer came from studies of epidermodysplasia verruciformis, a rare disease in which patients present with extensive polymorphic warts that convert to squamous cell carcinoma in roughly 30% of cases, mostly involving sun-exposed sites.

The key carcinogenetic mechanism of HPV in epidermodysplasia verruciformis involves interference with the epidermal repair process by the HPV E6 protein, which inactivates UV induction of the proapoptotic protein BAK, resulting in a survival mechanism for HPV-infected keratinocytes. Whether the same mechanism figures in the development of nonmelanoma skin cancers in patients without epidermodysplasia verruciformis remains to be seen.

—Bruce Jancin

Registry Mandated for Isotretinoin Use

BY TIMOTHY F. KIRN
Sacramento Bureau

The Food and Drug Administration will scrap isotretinoin's handful of voluntary risk management programs in favor of one mandatory, more restrictive system like that used for thalidomide.

Although many physicians are relieved that isotretinoin won't be removed from the market, some expressed concern that the FDA's decision may prompt more doctors to stop prescribing the teratogenic acne drug—and could push patients to seek the drug from sources on the Internet.

Under the new program, physicians will no longer have to adhere to the requirements of four similar programs, each run by different manufacturers.

"In the long run, this [policy] is short sighted," said Hilary Baldwin, M.D., vice chair of dermatology at the State University of New York, Brooklyn. "I'm just very sad."

The new program is expected to go into effect this year. Prescribing physicians, dispensing pharmacies, and patients will be required to register in a program known as RiskMAP (risk minimization action plan). This program will be run by the drug-development services company Convance Inc., which has contracted with Roche, the manufacturer of Accutane, as well as with the manufacturers of generic isotretinoin.

The new program was announced shortly after a senior FDA official testified to the Senate that in his opinion isotretinoin was one of five drugs that ought to be either withdrawn from the market or more severely restricted.

The close timing of the two events may have been coincidence, however. In a statement, the FDA said it was able to make the announcement now because an agreement was reached with Celgene Corp., which owns a patent on the STEPS (System for Thalidomide Education and Prescribing Safety) program, on which the isotretinoin program will be based.

A more restrictive risk management program had been expected since March 2004, when two FDA advisory committees concluded that Roche's System to Manage Accutane Related Teratogenicity (SMART) and similar programs for generic isotretinoin had failed to prevent pregnancy exposures (FAMILY PRACTICE NEWS, April 2004, p.95).

At the meeting of those committees, data were presented that showed 127 pregnancy exposures occurred in the year before SMART was implemented, compared with 120 pregnancy exposures the year after, despite the fact that isotretinoin prescriptions declined by 23%.

Moreover, when SMART and the other programs were approved by FDA, the agency had threatened that further restrictions would be imposed unless 60% of women who were written a prescription enrolled in a voluntary, ongoing survey run by the manufacturers. That goal was not met.

The Shape of Restrictions to Come

Under RiskMAP, the following conditions must be met before isotretinoin can be dispensed:

- documentation of patient education by the provider;
- a signed informed-consent form; and
- a negative pregnancy test, which will have to be repeated in order for the patient to obtain refills.

More specific details of the program have yet to be determined.

A major advantage of the new program is that physicians will no longer have to adhere to the requirements of four similar but distinct programs, each run by different manufacturers. Some physicians found that confusing, the FDA said. Instead, there will be a single, unified program covering all brands of isotretinoin.

In contrast to what has occurred under the isotretinoin risk management programs, pregnancy exposures to thalidomide have been well controlled under the STEPS program. About 4,000 women of childbearing age have taken thalidomide since it was reintroduced into the market for the treatment of cancer and leprosy. Only one pregnancy exposure has occurred, which resulted in a spontaneous abortion.

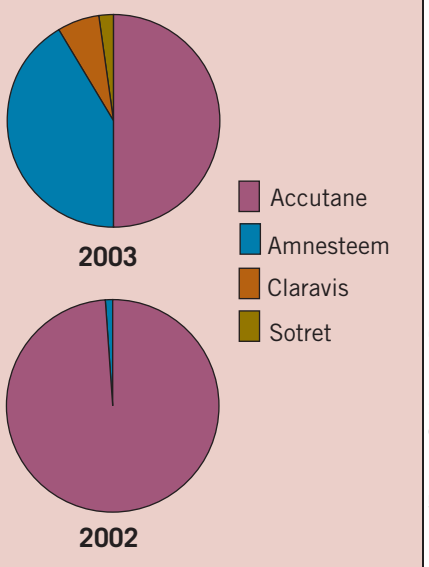
Most patients treated with thalidomide are older, and they are being treated for multiple myeloma. Therefore, they are very sick and probably not inclined to have sexual intercourse.

The FDA's action prompted a statement from Rep. Bart Stupak (D-Mich.), a well-known critic of isotretinoin, whose son committed suicide while taking the drug.

Rep. Stupak's statement suggested that the wrangling over isotretinoin may continue. The congressman vowed to respond if the FDA's final risk management program was not strict enough, and he called for hearings specifically on isotretinoin.

"This latest scheme is a great marketing tool by the manufacturers, but it does not go far enough to ensure the safety of the American people or reduce the number of birth defects caused by Accutane," Stupak said in the statement. ■

Competition Cuts Into Accutane Market



Note: Based on more than 2 billion pharmacy, hospital, and medical transactions per year in the United States.
Source: Verispan

KEVIN FOLEY, RESEARCH/FORHAD S. HOSSAIN, DESIGN