Risk From Topical Tretinoin Use Still Debatable

BY MARY ANN MOON
Contributing Writer

A recently reported association between topical tretinoin and increased mortality is not causal and most likely is due to chance, according to a report.

The interim finding of an unexpected rise in lung cancer incidence and all-cause mortality prompted the premature halt of the Department of Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) trial, a large 6-year study designed to determine whether the treatment could prevent basal and squamous cell skin cancers in patients who already had at least two such keratinocyte carcinomas. Increased lung cancer incidence and mortality had previously been reported with systemically administered compounds closely related to tretinoin.

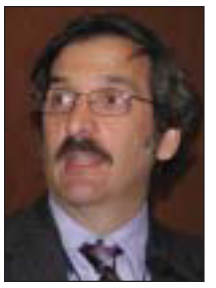
Dr. Martin A. Weinstock of the Providence (R.I.) VA Medical Center, and his associates in the VATTC trial conducted a post hoc analysis of the mortality data and confirmed an association with mortality—but no definitive causal links. "We do not conclude that this trial provides appropriate grounds for hesitating to use topical tretinoin in clinical practice," they wrote in the Archives of Dermatology.

In an editorial comment accompanying the report, Dr. Lisa M. Schilling and Dr. Robert P. Dellavalle said that even though the investigators "chalk their results up as a chance finding," debate about the safety of topical tretinoin will likely continue. Until further evidence emerges to definitively establish the safety or harmfulness of the treatment, physicians should "at a minimum" discuss the VATTC results with their patients who use tretinoin cream—particularly with elderly men, who composed the bulk of the study population.

"This dialogue should include that the results of the VATTC may have been due to chance, but also that the outcome of death was not initially anticipated," Dr. Schilling and Dr. Dellavalle noted. In addition, "owing to the ad hoc analysis, various important risk factors, such as smoking status, might not have been completely ascertained."

In their post hoc study, Dr. Weinstock and his associates at six VA medical centers randomly assigned 566 patients to use tretinoin 0.1% cream on the face and ears once or twice daily, and 565 patients to use only the vehicle cream as a control. The mean patient age was 71 years, and 97% were men.

Six months before the scheduled end of the trial, the intervention was terminated because of a statistically significant excess of deaths at that time (82 deaths) in the treatment group, compared with the control group (53 deaths). More deaths were later identified, for a total of 122 in the intervention group and 90 in the control group.



This trial does not provide appropriate grounds for hesitating to use topical tretinoin in clinical practice.

DR. WEINSTOCK

The VATTC trial data showed no dose-response relationship between exposure to topical tretinoin and death risk, as well as no interaction between the medication and smoking in mediating mortality risk. Moreover, "we found it difficult to construct biologically plausible mechanisms that would explain a direct causal link … and we were unable to conceive of a plausible mechanism by which tretinoin could indirectly lead to a fatal outcome," they wrote (Arch. Dermatol. 2009;145:18-24).

That implausibility, together with "lack of specificity of causes of death, inconsistency with previous experience, weakness of other supportive evidence in our data, and weak statistical signal" led the researchers to their conclusions.

In their editorial comment, Dr. Schilling and Dr. Dellavalle of the VA Medical Center in Denver noted that, unlike other researchers, Dr. Weinstock and the VATTC investigators publicized their unexpected mortality data (Arch. Dermatol. 2009;145:76).

"We highly commend Weinstock et al. for reporting and highlighting these results," they said.

Dr. Weinstock has received support from Galderma Laboratories L.P., Johnson & Johnson, and Ligand Pharmaceuticals Inc. ■

Online Skin Term Dictionary May Facilitate Payment

BY ALICIA AULT
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The American Academy of Dermatology is launching an online dictionary of common terms that it hopes will aid dermatologists, primary care physicians, and other practitioners in communicating, securing reimbursement, and reporting adverse events.

DermLex grew out of a 5-year grant issued by the National Institute of Arthritis and Muscoloskeletal and Skin Diseases in 2001 to Dr. Art Papier and Dr. Lowell Goldsmith at the University of Rochester (N.Y.) dermatology department to develop a universal dermatology lexicon. Five years later, the AAD took over the project, and the initial version 1.0 was expected to be live on its Web site (www.aad.org/research/lexicon) at press time.

Dr. Mark Pittelkow, chairman of the AAD's Medical Informatics Committee, said that the most important goal of DermLex is to create a common language among dermatologists but also between specialties. It should help make coding more accurate, he said in an interview. DermLex will also contribute to better patient care and improve provider education.

"Hopefully, it will be facilitating documentation, as well," he said, noting that the push for electronic health records is likely to accelerate in the Obama administration.

Eventually, DermLex should have online tools so it seamlessly integrates into an electronic medical record, said Dr. Pittelkow.

The compendium is similar to SNOMED-CT (Systematized Nomenclature of Medicine–Clinical Terms), which was developed by the College of American Pathologists and is owned, maintained, and distributed by the International Health Terminology Standards Development Organisation (IHTSDO), a not-for-profit association in Denmark.

Dr. Pittelkow said that hopefully, DermLex will be used as a companion to SNOMED-CT.

DermLex is primarily a compendium of terms organized in a hierarchical fashion, he said. The Medical Informatics Committee still is working on formal definitions.

The database will be open to the public, but AAD members will likely get additional tools that will not be available to nonmembers, Dr. Pittelkow said.

The AAD is providing the technical and financial support for the project, although it has been a largely volunteer effort up until this point. The need for ongoing support will be great, he said.

"Some may view (DermLex) as a sort of stamp collecting, but it's supposed to be very alive and dynamic," said Dr. Pittelkow. He made no disclosures. ■

Jury Out on Screening for Skin Cancer in Primary Care Setting

BY KERRI WACHTER
Senior Writer

The U.S. Preventive Services Task Force still cannot recommend for or against whole-body skin examination by a primary care physician or by patient self-examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer in the adult general population.

The task force concluded that there is not enough evidence to assess the benefits and harms from such examinations in its recommendations published in the Annals of Internal Medicine (2009;150:188-93).

The previous recommendation came in 2001, when the group also concluded that there was insufficient evidence to recommend for or against routine whole-body skin examination for skin cancer screening.

"This is not to say that studies have shown that it's not effective, what they're saying is that there are just no studies out there," commented Dr. Darrell S. Rigel, a clinical professor of dermatology at New York University.

The task force did note two critical gaps in knowledge. First, there is insufficient evidence (a lack of studies) to determine whether early detection of skin cancer reduces morbidity or mortality from skin cancer. Second, there is insufficient evidence to determine the magnitude of harms from screening for skin cancer.

The task force found no randomized studies that examined whether screening by clinicians is associated with improved clinical outcomes. Screening appears to consistently identify thinner melanomas on the average than those found during usual care, the task force noted. However, it's not known whether the detection of the thinner lesions leads to decreased morbidity or mortality.

Based on the current review, the USPSTF noted that there is fair evidence that screening by clinicians is moderately accurate in detecting melanoma. They determined primary care physicians to be moderately accurate in diagnosing melanoma—with sensitivity ranging from 42%-100% and specificity ranging from 70%-98%.

"What I recommend to primary care physicians is to incorporate the screening as part of the full-body exam … the marginal cost is nothing," said Dr. Rigel.

The task force noted that the recommendation applies only to the adult general population without a history of premalignant or malignant lesions. They did not assess the outcomes related to surveillance of patients at extremely high risk.

Primary care clinicians should be aware that fair-skinned men and women older than 65 years, patients with atypical moles, or those with more than 50 moles are groups that are known to be at a substantially increased risk for melanoma.

The task force urged primary care clinicians to remain alert for skin lesions with malignant features that are noted during physical examinations performed for other purposes. The ABCD criteria—asymmetry, border, color, and diameter—or rapidly changing lesions are features associated with an increased risk for cancer, they noted. Biopsy of suspected lesions is warranted. ■