Retinoid cream associated with death in clinical trial, but relationship does not appear causal

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Patients using a cream containing tretinoin, a retinoid commonly used to treat acne and other conditions, appeared more likely to die than those using a placebo in a clinical trial that was halted early as a result, according to a report in the January issue of *Archives of Dermatology*, one of the JAMA/Archives journals. However, evidence does not suggest these excess deaths were caused by the therapy.

"The potential of retinoid compounds to prevent cutaneous malignant lesions [skin cancers] has been of considerable interest, and some are effective for this purpose," the authors write as background information in the article. In 1998, the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial was launched to assess whether high-dose therapy with a cream containing one such retinoid, tretinoin, could prevent cancer. A total of 1,131 veterans (97 percent men, average age 71) were randomly assigned to apply either a cream containing 0.1 percent tretinoin or an unmedicated cream daily to their face and ears. They were then examined by a dermatologist every six months, with a planned study end date of Nov. 15, 2004.

A report prepared for one of the study's several oversight committees in 2004 identified a statistically significant increase in the number of deaths among study participants in the group using tretinoin. The trial was therefore halted six months early, in May 2004. Martin A. Weinstock, M.D., Ph.D., of the VA Medical Center and Brown

University, Providence, R.I., and colleagues assessed the data collected during the study to assess the relation of the medication to death risk.

Because death was not an end point in the original study, additional efforts were made to identify study participants who had died and gather more information about cause of death, including accessing the VA master death file. Through these records and original study data, researchers identified 108 patients in the tretinoin group and 76 in the control group who died before the end of the intervention period and an additional 14 in each group who died before the end of the study period (November 2004). After considering other factors that might increase the risk of death—including smoking, age and co-occurring illnesses—there was still a significantly higher risk of death in the treatment group.

However, additional analyses did not support tretinoin as a cause of death. For example, there was no clear association between the number of tubes of cream used and death. There was no consistency in the causes of death among participants. However, in the treatment group, 15 patients died of non-small cell lung cancer, 12 of vascular disorders and 15 of respiratory and other chest disorders—causes associated with smoking, which some previous studies have suggested interacts with compounds in some ways similar to tretinoin, but administered systemically, to produce additional health risks. Participants were asked whether they smoked, but their smoking status was not verified, potentially affecting the detected associations.

"The biological implausibility, lack of specificity of causes of death, inconsistency with previous experience, weakness of other supportive evidence in our data and weak statistical signal cast doubt on a potential causal association of topical tretinoin with death in the VATTC Trial," the authors write. "We do not conclude that this trial provides appropriate grounds for hesitating to use topical tretinoin in clinical

practice in the absence of additional evidence."

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