

COMMENTS AND OPINIONS

Methodological Limitations of the Study "Isotretinoin Use and Risk of Depression, Psychotic Symptoms, Suicide, and Attempted Suicide"

The studies conducted by Jick et al¹ in the Canadian Saskatchewan Health database and the United Kingdom General Practice Research database did not find an increase in the relative risk of depression, psychotic symptoms, suicide, and attempted suicide in individuals prescribed isotretinoin compared with those prescribed antibiotics for acne. However, aside from noting that their sample size was too small to "generate stable estimates for suicide and attempted suicide," the investigators did not mention several methodological problems that limited their ability to draw the conclusion of no increase in risk. These include underascertainment of psychiatric disorders (apparently only diagnosis codes and not psychoactive drug prescriptions or interviews were used to define cases); underascertainment of suicides (death certificate data were not included as a source of information); and lack of data on acne severity and dose and duration of isotretinoin treatment. Also, because there was no control group without acne, a result of no difference in rates of depression between the groups might be due to an effect of acne.

Additionally, the results may have limited applicability to the United States because the recommended doses in the United States are higher than in England and Canada. The maximum recommended dose in the United States is 2 mg/kg per day compared with 1 mg/kg per day in England and 2 mg/kg per day in exceptional instances in Canada.^{2,3} In England, isotretinoin is restricted to hospitals only and is prescribed by dermatologists or under the supervision of consultant dermatologists.⁴ Consequently, patients prescribed isotretinoin would not be fully represented in the general practice research database.

Although comorbidity of psychiatric disorders is well recognized,⁵ the investigators reported higher frequencies of anxiety disorders than mood disorders in the patients with acne. In Saskatchewan, 61% of patients had diagnoses of anxiety disorders (anxiety and neurosis) compared with 29% with diagnoses of mood disorders (depressive disorders), 6% with diagnoses of affective disorders (bipolar disorder), and 3% with diagnoses of nonaffective disorders (schizophrenia and paranoid states). Nevertheless, the title of the article and the terminology used in the text imply that the major out-

comes were depression, psychotic symptoms, suicide, and attempted suicide rather than anxiety disorders.

The US Food and Drug Administration, Rockville, Md, has received reports of depression, suicidal ideation, suicide attempt, and suicide in patients prescribed isotretinoin for treatment of cystic acne and other skin disorders.⁶ The industry-sponsored study conducted by Jick et al¹ was intended to help resolve the question of etiology of depression in patients treated with isotretinoin. However, because of the limitations of the study, we believe that the findings are inconclusive and that further studies on the association between isotretinoin and depression should be initiated.

One additional point should be mentioned—the text states that there were 37 cases of suicide or attempted suicide, although Table 3 contains data for 38.

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The views expressed herein are those of the authors and do not necessarily represent the official position of the Food and Drug Administration.

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In reply

Wysowski and Beitz point out several limitations of our study on isotretinoin and the risk of depression, psychotic symptoms, and attempted suicide.¹ Indeed, we have addressed some of these in our manuscript. Other concerns are perhaps not of relevance in this instance. Whereas it is likely that we missed some cases of depression, psychotic behaviors, or suicidal behaviors, it is unlikely that there would be any differential underascertainment between the patients treated with isotretinoin and those treated with antibiotic, and thus

it is unlikely to have an effect on our results. Case-control studies often fail to capture all cases.

With regard to information on the severity of acne, if we had found an association between isotretinoin treatment and depression and/or suicide, we would have been concerned about acne severity as a possible explanation for the finding. However, where we have found no association, the severity of acne cannot explain the null finding. Indeed, as suggested by Wysowski and Beitz, it is possible that any association between isotretinoin and psychiatric outcomes could be explained by the presence of the acne itself.

We therefore limited our study population to people with acne to control for presence of acne as a confounder. We agree that additional formal studies evaluating this relation should be conducted, and that this study is not, by itself, conclusive. However, we believe that it provides useful information on the topic under study.

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VIGNETTES

Cutaneous Warts in HIV-Positive Patients Undergoing Highly Active Antiretroviral Therapy

Cutaneous warts in patients with human immunodeficiency virus (HIV) are prevalent and respond poorly to conventional treatment. Recent studies suggest that highly active antiretroviral therapy (HAART) is associated with wart regression (unpublished data, November 2000).¹ The purpose of this study was to determine whether immune reconstitution plays a role in the natural history of cutaneous warts in HIV-positive individuals.

Patients and Methods. This is a prospective cohort study that included 12 HIV-positive patients (primarily homosexual white men) with a clinical diagnosis of cutaneous warts. All patients underwent 3 examinations at the San Francisco General Hospital Dermatology Clinic from 1996 through 1999. This period was selected because it is when the patients began HAART, which is defined as a combination therapy with 2 nucleoside reverse transcriptase inhibitors and either 1 protease inhibitor or 1 nonnucleoside reverse transcriptase inhibitor.

The original diagnosis was based on retrospective review of the charts of patients who had documented evidence of cutaneous warts. Information including the presence of cutaneous warts, absolute CD4 cell counts, CD4

nadir, and viral loads was obtained for each patient for each clinic visit. Statistical analysis was performed using the exact χ^2 test for stratified and nonstratified 2×3 tables (StatX-act, version 3; Cytel Software Corp, Cambridge, Mass).

Results. During the 3-year follow-up period, 7 HIV-positive patients had persistent warts (duration, >2 years) (mean age, 40 years; median age, 35 years), and 5 patients had warts that regressed (mean age, 45 years; median age, 49 years). The mean CD4 nadir was lower in patients with persistent warts ($0.047 \times 10^3/\mu\text{L}$; range, 0.010 - $0.104 \times 10^3/\mu\text{L}$) than in patients whose warts regressed ($0.258 \times 10^3/\mu\text{L}$; range, 0.114 - $0.385 \times 10^3/\mu\text{L}$) ($P=.01$). The median values were 0.044 and $0.229 \times 10^3/\mu\text{L}$, respectively.

The mean absolute CD4 cell count was lower in the HIV-positive patients with persistent warts ($0.141 \times 10^3/\mu\text{L}$) than in those with regressed warts ($0.411 \times 10^3/\mu\text{L}$) ($P=.01$). The mean values were 0.127 and $0.411 \times 10^3/\mu\text{L}$, respectively. Most HIV-positive patients experienced an increase in their CD4 cell counts between the first and third visits. The increase in the number of CD4 cells over time was higher in the regressed wart group. The persistent wart group had an average increase in CD4 cells of $0.037 \times 10^3/\mu\text{L}$ per month vs $0.088 \times 10^3/\mu\text{L}$ per month in the regressed wart group ($P=.45$). More than half of the patients with regressed warts had viral load levels recorded as zero. Therefore, the median and mean viral load values could not be determined.

Comment. Cutaneous warts are one of the most commonly diagnosed skin diseases in HIV-infected patients, accounting for 2.9% to 27% of all skin diseases (unpublished data, November 2000).² In immunocompromised patients, cutaneous warts can be extensive (in both size and area of involvement) and refractory to conventional therapy.

It has been suggested that an intact cell-mediated immune system is an important factor for wart regression, although the mechanism is not completely understood.³ In a cohort of 60 HIV-infected patients examined in the dermatology clinic at San Francisco General Hospital, there was an association between an increasing CD4 cell count and the absence of cutaneous warts (unpublished data, November 2000). In addition, there has been at least 1 case report of an HIV-infected patient with recalcitrant hand warts that resolved only after initiating potent antiretroviral therapy.¹ In non-HIV-infected patients, the role of immune mechanisms is supported by findings that cutaneous warts regress after administration of compounds that stimulate the immune system such as interferons and dinitrochlorobenzene.⁴

In a subset of HIV-positive patients, however, cutaneous warts persist despite an increase in the number of CD4 cells. Results from this study demonstrate that HIV-positive patients with low CD4 nadirs ($<0.120 \times 10^3/\mu\text{L}$) or low mean CD4 cell counts ($<0.135 \times 10^3/\mu\text{L}$) will have persistent warts despite rising CD4 cell counts. This suggests that although CD4 cell counts may increase after HAART, individuals with low CD4 nadirs or low CD4 mean cell counts may not yet have the fully functional CD4 cells necessary for eradication of human papilloma virus and regression of warts. It may also be that pa-