

COMMENTS AND OPINIONS

Relationship Between Headache and Depression in Users of Isotretinoin

Reports of depression and serious depression in patients treated with isotretinoin (eg, Accutane [Hoffmann-La Roche Inc, Nutley, NJ], Amnesteem [Mylan Bertek Pharmaceuticals Inc, Morgantown, WV]; Sotret [Ranbaxy Pharmaceuticals Inc, Princeton, NJ]; and Claravis [Barr Laboratories Inc, Pomona, NY]) have been submitted to the Food and Drug Administration (FDA)¹ and entered into the Adverse Event Reporting System (AERS; the FDA's database of voluntarily submitted suspected adverse drug reaction reports). In reviewing these reports, we noticed that patients with depression frequently reported accompanying physical symptoms, particularly headache. As a result, we tested the hypothesis that a relationship between headache and depression exists for isotretinoin and for all drugs in AERS.

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We obtained the number of case counts of adverse event reports for all suspect drugs (vs concomitant drugs) entered in AERS with and without headache and with and

Table 1. Distribution of Counts of Depression and Headache in Adverse Event Reports for All Drugs Entered in AERS, 1969 to Mid-August 2004*

	With Headache	Without Headache	Total
With Depression	3601	32 166	35 767
Without Depression	86 800	2 456 010	2 542 810
Total	90 401	2 488 176	2 578 577

Abbreviation: AERS, Adverse Event Reporting System.

* $\chi^2 = 4616.78$; $P < .001$. Estimated relative risk, 3.17 (95% confidence interval, 3.06-3.28).

Table 2. Distribution of Counts of Depression and Headache in Adverse Event Reports for Isotretinoin Entered in AERS, 1982 to Late July 2004*

	With Headache	Without Headache	Total
With Depression	193	1903	2096
Without Depression	1315	21 974	23 289
Total	1508	23 877	25 385

Abbreviation: AERS, Adverse Event Reporting System.

* $\chi^2 = 43.65$; $P < .001$. Estimated relative risk, 1.69 (95% confidence interval, 1.45-1.99).

without depression, constructed a 2×2 table, and performed statistical tests of a relationship between headache and depression. We obtained similar data for isotretinoin and compiled a list of the most frequently reported adverse events for all drugs and for isotretinoin.

Of the approximately 2.6 million reports for all drugs entered in AERS from 1969 to mid-August 2004, about 90.4 thousand (3.5%) reported headache and 35.8 thousand (1.4%) reported depression (**Table 1**). Headache (ranking number 8) and depression (ranking number 39) were among the most frequently reported adverse events for all drugs. The relative risk of depression with headache was 3.17 (95% confidence interval, 3.06-3.28). The relationship between headache and depression for all drugs was highly statistically significant ($P < .001$).

Of the approximately 25.4 thousand reports for isotretinoin entered in AERS from 1982, when marketing of isotretinoin began, to late July 2004, 1.5 thousand (5.9%) included headache and 2.1 thousand (8.3%) included depression among listed adverse events (**Table 2**). Depression (ranking number 1) and headache (ranking number 4) were among the most frequently reported adverse events for the suspect drug isotretinoin. The relative risk of depression with headache for isotretinoin users was 1.69 (95% confidence interval, 1.45-1.99). The relationship between headache and depression for isotretinoin was highly statistically significant ($P < .001$).

The results of this study indicate a positive relationship between headache and depression for all drugs and for isotretinoin in reports of suspected adverse reactions. This study is limited by the inability to determine chronology of headache and depression and by incomplete reporting of adverse events. For isotretinoin (and other drugs), completeness of reporting is affected by the FDA's waiver for submission of reports with adverse events that are already mentioned in the product labeling and that have nonserious outcomes. (Nonserious outcomes are those that do not involve death, hospitalization, disability, or a congenital malformation and are not considered life-threatening and do not they require intervention to prevent permanent impairment/damage.) This deficit in reports might explain the decreased strength of the association for isotretinoin compared with that for all drugs in AERS. Despite these limitations, our results are similar to those of several published studies that found statistically significant associations between headache, particularly frequent and severe headache and depression.²⁻⁵

Many drugs, including isotretinoin, appear to be associated with an increased frequency of headache. We suggest that physicians consider a possible relationship between headache and depression when evaluating patients prescribed isotretinoin (and other drugs) who complain of headache.

Diane K. Wysowski, PhD
Lynette Swartz, MEd, MBA

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Correspondence: Dr Wysowski, Division of Drug Risk Evaluation, HFD-430, Food and Drug Administration, 5600 Fishers Ln, Parklawn Bldg, Room 15B-08, Rockville, MD 20857 (wysowski@cder.fda.gov).

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Do Neoplastic Stem Cells Underlie the Pathogenesis of Cutaneous Lymphomas?

We would like to comment on the hypothesis proposed by Dr Gniadecki¹ in which the cancer stem cell concept was applied to cutaneous T-cell lymphoma (CTCL). Normal hematopoietic stem cells initially give rise to common myeloid or lymphoid progenitors that are committed to differentiation along the myeloid or lymphoid lineages, respectively. The latter line further differentiates into B and T cells, natural killer cells, and a subset of (lymphoid) dendritic cells. Like their normal counterparts, “cancer stem cells” are postulated to have the capacity for self-renewal by giving rise to other stem cells and to progenitor cells that can undergo differentiation to phenotypically mature, nontumorigenic cancer cells.² This capacity for self-renewal implies that cancer stem cells are responsible for the initiation, maintenance, and progression of clinical disease.

To account for the association of mycosis fungoides (MF) and lymphomatoid papulosis (LyP) with B-cell lymphoproliferative disorders, Dr Gniadecki suggests that neoplastic transformation takes place at the level of the common lymphoid progenitor cell before the commitment to the T- and B-cell lineages. Although this theory potentially explains the development of a composite T- and B-cell lymphoma, an alternative explanation is that these lymphomas are separate disease processes that in some patients occur concurrently because of a common risk factor (genetic predisposition or exposure to 1 or more oncogenic stimuli that are capable of causing neoplastic conversion in multiple stem cells of distinct lineages). For example, Hodgkin disease, also a B-cell disorder that is associated with MF (and LyP), appears to be an unrelated disease at the genetic level and, in some cases, may arise as a consequence of concurrent Epstein-Barr virus infection. Similar arguments could be made for any other cancer that occurs at increased frequency in patients with MF.

Nevertheless, Dr Gniadecki presents a persuasive case for a common CTCL stem cell being involved in the patho-

genesis of concurrent MF and primary CD30⁺ lymphoproliferative disorders (LyP and primary cutaneous anaplastic large cell lymphomas) in the same patient with identical clonal T-cell receptor γ gene rearrangements in both types of lesions. However, an alternative interpretation is that MF and associated CD30⁺ lesions are clinical variants of the same disease process, involving the same neoplastic T-cell clone. In this regard, Gellrich et al³ used microdissection and single-cell polymerase chain reaction (PCR) analysis to isolate and study CD30⁺ and CD30⁻ T cells in lesions of type A LyP. Of note, the monoclonal population was restricted to the small CD30⁻ T-cell population, whereas the large CD30⁺ cells were polyclonal and therefore likely to be reactive. Also, identical clones of T cells, as identified for the small CD3⁺ cells in LyP lesions, were found in the blood. Therefore, one might speculate that the lesions in patients with coexisting MF and CD30⁺ lymphoproliferative disease could be derived from the same underlying fully differentiated neoplastic T-cell clone and that CD30⁺ cells in coexisting cases are derived from the clone owing to the effect of local growth factors within the microenvironment of the skin. This hypothesis could be addressed with microdissection and the single-cell PCR technique. Parenthetically, this model also explains the type B variant of LyP that might be regarded as papulosquamous expression of MF without in situ neoplastic T-cell activation and CD30 expression.

Assuming that CTCL stem cells exist, are they present in the bone marrow? Dr Gniadecki¹ acknowledges that neoplastic T cells cannot be identified in bone marrow samples obtained from patients with early CTCL, even with sensitive PCR-based techniques. He addresses this concern by arguing that the failure to detect cells could be attributable to a low density of neoplastic cells (about 0.1% for multiple myeloma) or to a lack of differentiation to the stage of T-cell receptor gene rearrangement. On the other hand, he comments that monoclonal T cells were detectable in bone marrow samples from patients with B-cell lymphoproliferative diseases several years before they developed LyP. Is it therefore likely that PCR-based methods would not detect T-cell clones in bone marrow samples in early MF if it can detect clones in LyP? Indeed, contamination of bone marrow samples by clonal T cells in the peripheral blood might make interpretation of bone marrow samples problematic.

Dr Gniadecki also uses clinical observations to support the hypothesis that CTCL stem cells reside in the bone marrow. Specifically, he points out that MF is often a multicentric disorder, which favors the concept that CTCL stem cells located in the bone marrow might differentiate into cells that express skin-homing receptors (eg, cutaneous lymphocyte antigen), with subsequent colonization of the skin. Related conditions that rarely evolve into frank lymphoma, such as the small-lesion variants of parapsoriasis en plaques, might conceivably represent the accumulation T-cell clones that have also differentiated from CTCL stem cells but that lack the additional genetic alterations that are necessary for progression into bona fide lymphoma, a concept proposed by Burg and Dummer⁴ as “abortive CTCL.” Alternatively, the T cells of clinically benign conditions, such