Isotretinoin Therapy and Mood Changes in Adolescents With Moderate to Severe Acne

A Cohort Study

Christina Y. Chia, MD; Whitney Lane, MD; John Chibnall, PhD; Angel Allen, MD; Elaine Siegfried, MD

Objective: To determine whether patients with moderate to severe acne who were treated with isotretinoin experienced significant increases in depressive symptoms over a 3- to 4-month period compared with patients who received conservative acne therapy.

Design: Cohort study.

Setting: Hospital-affiliated and community-based clinics in St Louis, Mo.

Participants: One hundred thirty-two subjects aged 12 to 19 years with moderate to severe acne.

Main Outcome Measures: Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D), a standardized self-reported instrument. Mean CES-D scores were compared between treatment groups, as were the prevalence and incidence of scores suggestive of clinically significant depression (CES-D score ≥ 16).

Results: A total of 101 subjects completed the study. At follow-up, CES-D scores (adjusted for baseline CES-D score and sex of patient) suggestive of clinically significant depression were no more prevalent in the isotretinoin group than in the conservative therapy group. Similarly, the incidence (new onset) of depressive symptoms suggestive of clinical significance also was not significantly different between the treatment groups.

Conclusions: The use of isotretinoin in the treatment of moderate-severe acne in adolescents did not increase symptoms of depression. On the contrary, treatment of acne either with conservative therapy or with isotretinoin was associated with a decrease in depressive symptoms.

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A CNE CAN BE A PAINFUL AND disfiguring disease that leaves some individuals with permanent physical and psychological scars. Isotretinoin (13-cis-retinoic acid, first marketed as Accutane; Hoffmann-LaRoche Inc, Nutley, NJ), a synthetic vitamin A analogue approved by the Food and Drug Administration in 1982 for the treatment of severe cystic acne, is the most effective treatment available for acne that is unresponsive to other therapies. An increasing number of cases of depression and suicide in patients using isotretinoin reported to the Food and Drug Administration has prompted much concern and yielded new labeling and patient-informed consent regarding possible psychiatric side effects.

Despite the lack of epidemiological evidence for the association of depression in patients treated with isotretinoin, widely publicized anecdotal reports have driven a strong public perception about psychiatric side effects of the drug. These reports may simply reflect the serious problem of new-onset depression and suicide among adolescents. The prevalence of major depressive disorder in adolescents is estimated to be between 0.4% and 8.3%. Suicide is the second leading cause of death in the 15- to 19-year-old population and the fourth leading cause of death in 10- to 14-year-old adolescents.

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Recent reviews of the medical literature and MedWatch have not found enough evidence to establish a causal link between isotretinoin use and suicide or major depression. On the contrary, isotretinoin therapy has been shown to significantly improve anxiety and depressive symptoms in patients with acne. To further investigate this issue, we conducted a cohort study comparing depressive symptoms in adolescents with moderate to severe acne receiving isotretinoin therapy and those receiving conservative therapy.
PARTICIPANTS

This study protocol was approved by the institutional review board of Saint Louis University, St Louis, Mo. All participants and parents or guardians provided written informed consent. Participants were recruited between October 1998 and December 2001 from 2 outpatient clinics: one urban and hospital affiliated and the other suburban and community affiliated. Male and female patients between the ages of 12 and 19 who presented for treatment of moderate to severe inflammatory and cystic acne were eligible. Acne severity was determined by physician clinical assessment. Exclusion criteria included history of or current DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I diagnosis, prior use of or allergy to isotretinoin, and pregnancy. A psychiatric history, including psychiatric diagnoses and treatment by a psychiatrist or psychologist, was obtained from both parent/guardian and patient. Since depression may be undiagnosed, it was not possible to definitively exclude all subjects with a history of major depression.

STUDY DESIGN AND GROUP ASSIGNMENT

This prospective, controlled study used a pretest and a posttest with an alternative treatment control group. Depressive symptoms were assessed at baseline and then again 3 to 4 months after the initiation of isotretinoin therapy or maximal conservative therapy for patients with moderate-severe acne. Maximal conservative therapy was defined as a topical antibiotic, topical retinoid, and twice-daily administration of an oral antibiotic. Isotretinoin was prescribed at approximately 1 mg/kg per day rounded to the nearest 20 mg. In the isotretinoin group, all female subjects of childbearing potential used 2 forms of birth control.

Patients were not randomized to treatment conditions. Factors that influenced the choice of treatment included history of previous treatment failure, patient/parent preference, out-of-pocket medical cost, ability/willingness to comply with treatment requirements for frequent visits and phlebotomy, patient/parental concerns about adverse drug effects, and objections to oral contraceptive therapy. Patients were given the option to participate in the study only after a therapeutic decision had been made about their acne treatment.

OUTCOME MEASURES

The Center for Epidemiologic Studies Depression Scale (CES-D) is a standardized, 20-item self-report questionnaire developed by the National Institutes of Mental Health, Bethesda, Md, to assess symptoms of depression. The CES-D is an effective screening tool for the presence of depressive symptoms and has been validated in adolescents; eg, it was used in a recent study that detected major depression in 8.3% of adolescents tested. It is not a diagnostic clinical instrument; therefore, the results do not need to be interpreted by a psychiatrist or psychologist. It is considered more sensitive and less specific than other depression instruments. The 20 items address depressive symptoms across 4 dimensions: depressed affect, positive affect, somatic symptoms, and interpersonal affect. Subjects indicate how often they experienced each of the symptoms over the previous week. Each response is scored on a 4-point scale: 0, rarely or none of the time (<1 day a week); 1, some or a little of the time (1-2 days a week); 2, occasionally or a moderate amount of time (3-4 days a week); and 3, most or all of the time (5-7 days a week). Symptoms 4, 8, 12, and 16 are worded negatively. A score of 17 or more was considered suggestive of clinically significant depression. The CES-D was administered at baseline and 3 to 4 months after the initiation of acne treatment.

All subjects who scored 17 or higher were further evaluated for suicidal ideation and interviewed using the mood disorder portion of the Structured Clinical Interview for DSM-IV Axis I Disorders. We also screened for other causes of depression, such as medication, substance abuse, general medical condition, or bereavement. All subjects with responses to the interview that were indicative of a major depressive episode or disorder were referred for outpatient psychiatric evaluation and treatment. Any subject with suicidal ideation would have been referred for emergent psychiatric evaluation through the emergency department at Saint Louis University Hospital. Any clinical diagnosis of major depressive episode or disorder was an exclusion criterion.

STATISTICAL ANALYSIS

The study was designed to enroll approximately 50 participants in each of the 2 treatment groups for sufficient power (0.80) to detect effect sizes of approximately 0.60 for differences in means (Cohen d coefficient: ratio of mean difference to pooled SD) and 0.20 for differences in proportions (Cramer φ coefficient: 4-fold point correlation coefficient). By convention, effect sizes of this magnitude are in the small to moderate range.

Comparisons between the isotretinoin and conservative therapy groups regarding the percentage of patients with CES-D scores suggestive of clinically significant depression (>16) were evaluated at follow-up using multiple logistic regression, with baseline CES-D score and patient sex as covariates in the analysis. Mean CES-D comparisons at follow-up between the isotretinoin and conservative therapy groups were evaluated using analysis of covariance, with baseline CES-D score and patient sex as covariates in the analysis. All analyses were conducted using SPSS version 9.0 (SPSS Inc, Chicago, Ill) on an intent-to-treat basis (last observation carried forward), excluding cases that were unavailable for follow-up.

PATIENT CHARACTERISTICS

A total of 132 patients were enrolled in the study (Figure 1). Overall, 55.3% (n=73) were male and 44.7% were female (n=59). The isotretinoin group had a significantly higher percentage of males (n=44 [74.6%]) than the conservative therapy group (n=29 [39.7%]) (difference in proportions, 34.9; 95% confidence interval [CI], 19.1-50.7).

A total of 101 patients completed the study (76.5% of those enrolled), and 31 were unavailable for follow-up. Comparisons of those who were unavailable for follow-up and those who completed the study revealed no statistically significant difference of baseline CES-D scores for the isotretinoin group (difference in means, 3.0; 95% CI, −1.5 to 7.5) or in the conservative therapy group (difference in means, 1.1; 95% CI, −3.7 to 5.9). There also was no statistically significant differential attrition as a function of group assignment (difference in proportions, 11.9; 95% CI, −2.2 to 26.0). Outcome analyses were adjusted for the sex difference in both the intent-to-treat analysis and the analysis that excluded those unavailable for follow-up.
Subjects Analyzed

- 59 Patients (44.7%)
  - Received Isotretinoin Therapy
    - 15 Females (25.4%)
    - 44 Males (74.6%)
- 73 Patients (55.3%)
  - Received Conservative Therapy
    - 44 Females (60.3%)
    - 29 Males (39.7%)

10 Patients (16.9%)
  - Were Unavailable for 3-4 mo of Follow-up
    - 2 Females (20%)
    - 8 Males (80%)

21 Patients (28.8%)
  - Were Unavailable for 3-4 mo of Follow-up
    - 11 Females (52.4%)
    - 10 Males (47.6%)

49 Patients (48.5%)
  - Completed 3 to 4 mo of Follow-up
    - 13 Females (25.4%)
    - 36 Males (74.6%)

52 Patients (51.5%)
  - Completed 3 to 4 mo of Follow-up
    - 30 Females (63.5%)
    - 19 Males (36.5%)

Figure 1. Flow of patients through the study period and analysis.

SCORE DISTRIBUTIONS

The distributions of scores in the isotretinoin and conservative therapy groups were adequate for statistical analysis and comparable between groups.

PRIMARY OUTCOME

At baseline, 14.3% of the isotretinoin group and 19.2% of the conservative therapy group had CES-D scores of 17 or higher, a statistically nonsignificant difference (4.9 percentage points; 95% CI, −0.4 to 19.4 percentage points). At follow-up, the prevalence of CES-D scores suggestive of clinically significant depression were 8.2% in the isotretinoin group and 15.4% in the conservative therapy group, also a nonsignificant difference (7.2 percentage points; 95% CI, 5.3-19.7 percentage points). Of the participants with CES-D scores of 17 or higher in the isotretinoin group, none had suicidal ideation and none was referred for psychiatric evaluation after Structured Clinical Interview for DSM-IV Axis I Disorders assessment. One patient in the conservative therapy group had an episode of suicidal ideation 2 weeks before study entry that resolved; psychiatric referral was declined. Another patient in the conservative therapy group had a baseline CES-D score higher than 16 that persisted at follow-up and accepted referral for psychiatric evaluation at that time.

A multiple logistic regression was used to compare the follow-up prevalence of CES-D scores that were suggestive of clinically significant depression. After adjustment for baseline CES-D and patient sex, the association between treatment status (isotretinoin therapy vs conservative therapy) and follow-up CES-D score suggestive of clinically significant depression was nonsignificant (odds ratio [OR], 1.1; 95% CI, 0.23-5.6). An intent-to-treat analysis did not alter this result (OR, 1.3; 95% CI, 0.31-5.7).

MEAN CES-D CHANGES

At baseline, the mean (SD) CES-D scores in the isotretinoin group (8.1 [6.8]) and conservative therapy group (9.3 [8.7]) were not statistically different (1.2; 95% CI, −1.9 to 4.3). The CES-D scores were also not statistically different at follow-up between the isotretinoin (6.6 [6.1]) and conservative (8.4 [8.1]) therapy groups (95% CI, 1.8; −1.1 to 4.7) (Figure 2). Analysis of covariance, with baseline CES-D score and patient sex as covariates, was used to compare the mean CES-D scores at follow-up between the 2 groups. The score on the Levene test for equality of variance was not significant (P>.26). The covariate-adjusted follow-up means were 7.2 in the isotretinoin group and 7.9 in the conservative therapy group, a nonsignificant difference (0.7; 95% CI, 1.3-2.7). An intent-to-treat analysis did not change this result (0.7; 95% CI, 0.9-2.3).

COMMENT

In this prospective study, the 3-month incidence of CES-D scores suggestive of clinically significant depression (ie, suggestive of new-onset depression) from baseline to follow-up was 4.1% in the isotretinoin group and 3.8% in the conservative therapy group, a difference that was not statistically significant (0.3 percentage point; 95% CI, −7.7 to 8.3 percentage points). Results of an intent-to-treat analysis were also nonsignificant (difference of 0.7 percentage point; 95% CI, −5.4 to 6.8 percentage points). Because of the small number of cases that were suggestive of new-onset depression (n = 4, 2 cases in each group), it was not possible to perform a multivariate analysis of incidence.

Our cohort study indicates that there is no increase in the prevalence of depressive symptoms in the isotretinoin treatment group compared with the group treated with maximal conservative therapy. The incidence of suicidal ideation in the isotretinoin group was 0. The incidence of suicidal ideation in the control group was 1.4% (1 subject at baseline). The use of isotretinoin in the treatment of moderate-severe acne in adolescents did not increase...
depressive symptoms. On the contrary, our study shows that treatment of acne improves depressive symptoms.

One limitation of this study was the small sample size. Convincing reports of positive dechallenge and rechallenge suggest an association between depression and isotretinoin use that this study cannot exclude. Perhaps there is a genetic component. Further studies of patients who experience depression induced by isotretinoin therapy are warranted.

Another limitation of this study was the nonrandomized subject selection. Also, there are potential confounding variables that were not specifically addressed, including age, family history of depression, suicide, suicide attempt, alcoholism, illegal drug use, concomitant illness, and socioeconomic status. Participants were recruited from a population of private practice and university clinic patients seeking medical treatment for their moderate-to-severe acne. The subjects in both treatment groups did, however, have acne of a similar degree of severity at baseline and comparable depressive symptoms at baseline and follow-up. There was an unanticipated sex bias between groups that may be reflected in the general population. Many clinicians are hesitant to prescribe isotretinoin to female patients of childbearing age, because of the risk of teratogenicity, while some female patients are hesitant to use hormonal birth control. Separate sex-adjusted statistical analysis did not reveal any differences. We also explored whether there was any relationship between the type of acne therapy and a participant’s depressive symptoms, and the results indicated that there was no statistical difference between the 2 treatment groups. Another issue was an inherent bias of the CES-D. This highly sensitive screening tool would overestimate rather than underestimate the degree of mood disorder compared with other psychiatric instruments and exaggerate the incidence and any associations between depressive mood changes and treatment in our study.

Most subjects with a CES-D score indicative of depressive symptoms and their legal guardians refused the recommended psychiatric evaluation. This avoidance of psychiatric evaluation and care for a potentially life-threatening and treatable disease, such as depression, is likely attributable to the social stigma of a psychiatric diagnosis.

Significant psychological stress has been documented among patients with even mild or moderate acne. This observation emphasizes that dermatologists must be cognizant of the relationship between skin disease and depression and be able to recognize depressive symptoms in their patients with acne, particularly adolescents. The American Academy of Dermatology Consensus Conference of the Safe and Optimal Use of Isotretinoin supported additional education for dermatologists regarding the evaluation of risk factors of depression and suicide in patients who are using isotretinoin and the development or validation of treatment-specific tools that would be suitable for use in dermatology practice settings to monitor these patients. The CES-D is a screening tool that cannot diagnose major depressive disorders, but it is a highly sensitive and simple tool that can facilitate detection of patients at risk.

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Correspondence: Elaine Siegfried, MD, Kids Dermatology, 621 S New Ballas Rd, Suite 622A, St Louis, MO 63141 (siegfried@kidsderm.com).

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REFERENCES