Effective monitoring of isotretinoin safety in a pediatric dermatology population: A novel "patient symptom survey" approach

Chelsea J. Hodgkiss-Harlow, BS,[a] Lawrence F. Eichenfield, MD,[a,b] and Magdalene A. Dohil, MD[a,b]
San Diego, California

Background: Assessment of adverse effects in pediatric patients on oral isotretinoin has not been standardized and the exact incidence is unknown.

Objective: Our goal was to determine the usefulness of an isotretinoin symptom survey as a screening tool for assessment and quantification of adverse effects, including psychiatric symptoms, during isotretinoin treatment in a pediatric population of different age groups.

Methods: We performed a retrospective chart review on a random sample of patients treated with isotretinoin at a tertiary pediatric dermatology clinic where patients completed an isotretinoin symptom survey at each visit. Responses were stratified by age group and psychiatric history.

Results: The charts of 102 patients, representing 123 courses of isotretinoin and 760 treatment-months, were reviewed. A total of 722 (95.0%) symptom surveys were complete and 38 (5.0%) were incomplete/missing. Recorded side effects were similar to published adult data; dry lips/dry skin were reported in 94.25% and 72.13% of treatment-months of isotretinoin, respectively. Psychiatric symptoms were reported in 1.65%, with no statistical difference between patients with or without a mental health history. Patients aged 11 to 15 years had similar side-effect profiles to those aged 16 to 21 years. Impaired night vision, nosebleeds, and dry/bloodshot eyes were more common in the older age group.

Limitations: This was a retrospective chart review, with known limitations. The study was performed at a tertiary referral center for pediatric dermatology, possibly allowing patient selection bias.

Conclusions: The isotretinoin symptom survey appears to be an effective screening tool to standardize monitoring of isotretinoin side effects in the pediatric population. (J Am Acad Dermatol 2011;65:517-24.)

Key words: acne; adolescent; depression; isotretinoin; pediatrics; symptom survey.

From the University of California, San Diego School of Medicine[a] and Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego.[b]

Supported in part by a grant from the National Institutes of Health.
Conflicts of interest: None declared.
Accepted for publication June 22, 2010.

Reprint requests: Magdalene A. Dohil, MD, Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, and University of California, San Diego School of Medicine, 8010 Frost St, Suite 602, San Diego, CA 92123. E-mail: mdohil@rchsd.org.

Published online June 1, 2011.
0190-9622/$36.00

doi:10.1016/j.jaad.2010.06.040

The efficacy of oral isotretinoin as a treatment for severe acne is well documented.[1-4] Adverse effects, particularly teratogenicity, and concerns regarding depression limit the degree of comfort with which it is used in the pediatric population.[5-8] The high risk for teratogenicity has led to implementation of strict pregnancy prevention policies and programs.[5,9] Frequent side effects include cheilitis and xerosis, which usually respond well to liberal use of emollients.[10] The psychological effects of isotretinoin are less well understood.[11,12] In 1998, the US Food and Drug Administration issued a warning of a possible association with depression, psychosis, suicidal ideation, and suicide, and

recommended the use of signed informed consent forms and printed patient medication guides. It is uncertain if isotretinoin is directly responsible for causing depression, as conflicting reports in the medical literature are based on studies using differing research methodologies.[13-21] One cohort study found that treatment of acne with isotretinoin was associated with a *decrease* in depressive symptoms.[22] Confounding factors such as mood changes associated with adolescence and puberty complicate the interpretation of data.[23,24]

This study examined data from a representative sample of patients attending a pediatric dermatology clinic to assess the incidence and severity of adverse effects and to test the usefulness of a self-reported isotretinoin symptom survey (ISS) as a standardized screening tool.

CAPSULE SUMMARY

- The isotretinoin symptom survey is a useful tool for monitoring, assessing, and documenting side effects of isotretinoin.
- It can be easily implemented in a clinic setting and is simple for pediatric patients to use.
- The incidence of psychologic symptoms identified by the isotretinoin symptom survey was low, symptoms were generally transient, and cessation of isotretinoin was not required.
- The incidence of side effects recorded by the isotretinoin symptom survey showed that younger pediatric patients tolerate isotretinoin similarly to older adolescents.

METHODS

A retrospective chart review was conducted on a random sample of patients, who were prescribed isotretinoin at the pediatric dermatology clinic between February 2003 and August 2007. The study was approved by the institutional review board of Rady Children's Hospital/University of California, San Diego (protocol #070858).

The ISS (Fig 1) was designed to assess the presence or absence of 13 possible adverse effects: dry lips, dry/bloodshot eyes, dry skin, muscle aches/pains, nosebleeds, frequent headaches, mood swings, depression, suicidal thoughts, paronychia, rash, trouble with night vision, and severe sun sensitivity/sunburn. In addition, it assessed the severity on a mild/moderate/severe scale of symptoms predicted to be the most common: dry lips, dry/bloodshot eyes, dry skin, and muscle aches/pains. The clinic staff instructed patients to complete an ISS at each monthly follow-up visit, with or without the assistance of a family member. The treating physician reviewed the survey with the patient, and verified the clinical relevance of reported symptoms. The surveys were retained with the patient's chart.

The data were tabulated using a worksheet that included epidemiologic information, symptom onset and duration, medical history, and age at the beginning of treatment. The patient-completed survey was assessed for its use in identifying and monitoring adverse effects of isotretinoin as they occurred. The overall incidence and statistical significance of each adverse effect was evaluated. The number of patients who experienced psychological symptoms was determined, as was the average number of months they experienced such symptoms, and we assessed whether a history of a psychiatric condition was of significance. Data from all monthly appointments were aggregated to determine the incidence of each symptom. Confidence intervals for each symptom were calculated.

The data were stratified into two age groups, representing the pediatric and young adult patient populations: age 11 to 15 years and age 16 to 21 years. The incidence of symptoms for the two age groups was compared using a two-proportion z test with unequal variances. The calculations assumed an approximately normal distribution, because each individual sample included at least 350 months of data.

RESULTS

The sample size was 102 individual patients, with 123 courses of isotretinoin. There were 760 patient-months of collected data. Of the 123 documented courses of isotretinoin, 73 (59.3%) patients were male and 50 (40.7%) were female. The age range was 11 to 21 years, with an average age of 15.26 years and SD of 1.62. There were 722 (95.0%) complete symptom surveys, 30 (3.95%) with incomplete data entry, and only 8 (1.05%) unsubmitted surveys (Table I).

The incidence of symptoms is demonstrated in Table II and in Fig 2. The 95% confidence intervals for the incidence of each symptom are demonstrated in Table III.

Psychological symptoms

Of 729 survey responses, representing 102 individuals with surveys filled out monthly for the course of treatment, only 12 (1.65%) reported depression, 57 (7.82%) reported mood swings, and 0 (0.0%) reported suicidal thoughts. The 12 surveys with self-reported depression represented 11 (10.78%) of 102 patients. The average onset for symptoms of depression was month 3.27 (SD 1.62), with an average duration of 1.09 months (SD 0.30). Mood swings were reported in 26 (25.49%) of 102 patients. The