Effect of a single course of isotretinoin therapy on bone mineral density in adolescent patients with severe, recalcitrant, nodular acne

John J. DiGiovanna, MD,a Craig B. Langman, MD,b Eduardo H. Tschen, MD,c Terry Jones, MD,d Alan Menter, MD,e Nicholas J. Lowe, MD,f Lawrence Eichenfield, MD,g Adelaide A. Hebert, MD,h David Pariser, MD,i Ronald P. Savin, MD,j Stacy R. Smith, MD,k Michael Jarrett, MD,l David Rodriguez, MD,m Dan K. Chalker, MD,n Steven Kempers, MD,o Mark Ling, MD,p Elyse S. Rafal, MD,q Sabra Sullivan, MD, PhD,r David Pariser, MD,i Ronald P. Savin, MD,j Stacy R. Smith, MD,k Michael Jarrett, MD,l David Rodriguez, MD,m Dan K. Chalker, MD,n Steven Kempers, MD,o Mark Ling, MD,p Elyse S. Rafal, MD,q Sabra Sullivan, MD, PhD,r David Pariser, MD,i Ronald P. Savin, MD,j Stacy R. Smith, MD,k Michael Jarrett, MD,l David Rodriguez, MD,m Dan K. Chalker, MD,n Steven Kempers, MD,o Mark Ling, MD,p Elyse S. Rafal, MD,q Sabra Sullivan, MD, PhD,r

From the Division of Dermatopharmacology, Department of Dermatology, Brown Medical School/Rhode Island Hospital; Department of Dermatology, University of New Mexico; JBS Studies Inc, Bryan; Division of Dermatology, Baylor University Medical Center, Dallas; Department of Dermatology, University of California—Los Angeles School of Medicine; Children’s Hospital and Health Center, University of California, San Diego; Department of Dermatology and Pediatrics, University of Texas Medical School, Houston; Department of Dermatology, Eastern Virginia Medical School and Virginia Clinical Research Inc; Department of Dermatology, Yale University Medical School, New Haven; Dermatology Division, University of California, San Diego School of Medicine, La Jolla; DermResearch Inc, Austin; Department of Dermatology and Cutaneous Surgery, University of Miami; private practice, Augusta; Minnesota Clinical Study Center; MedaPhase Inc, Newman; DermResearchCenter of New York Inc; Division of Dermatology, University of Mississippi; Department of Dermatology, University of Michigan; Hoffman-La Roche, Nutley; and Oregon Health Sciences University.

Disclosures: All coauthors were supported by Roche for this study. Dr DiGiovanna has received honoraria and travel support from Hoffmann-La Roche, and grant support from Hoffmann-La Roche and Allergan, companies with an interest in systemic retinoids for acne. Dr DiGiovanna has served as a consultant to Hoffmann-La Roche. In addition, Dr DiGiovanna has received honoraria, travel, and grant support from companies with an interest in other, general acne medications. Dr Langman has served as a consultant to Roche. Drs Tschen and Jones have received grant support from Allergan. Dr Menter has received grant support and been a consultant to Allergan. Dr Lowe has received research grants from Roche. Dr Eichenfield has received grant support from Roche. Drs Hebert and Pariser have no additional disclosures. Dr Savin has received grant support from Roche and Allergan. Dr Smith has received grant support from Hoffmann-La Roche and Allergan, companies with an interest in systemic retinoids for acne. In addition, Dr Smith has received honoraria, travel, and grant support from companies with an interest in other, general acne medications. Dr Jarrett has received research grants from Hoffmann-La Roche and honoraria, travel, and grant support from Allergan, companies with an interest in systemic retinoids for acne. In addition, Dr Rodriguez has received honoraria, travel, and grant support from companies with an interest in other, general acne medications. Dr Chalker has been a consultant for Roche and Arriva Pharmaceuticals, and owns stock in Genzyme and Wyeth. Dr Kempers has no additional disclosures. Dr Ling has received research grant support from Roche and Allergan; Roche speakers’ bureau. Dr Rafal has received grant support from Roche and Allergan. Dr Rafal has received honoraria, travel, and grant support from companies with an interest in other, general acne medications. Dr Sullivan has received honoraria and travel support from Roche. Dr Kang has no additional disclosures. Drs Shah, Wu, Pak, Eberhardt, Bryce, McLane, Ondovik, Chin, and Khoo were employees of Roche. Dr Newhouse was a Roche postdoctoral fellow. Dr Rich has no additional disclosures.


Accepted for publication April 2, 2004.

Reprint requests: John J. DiGiovanna, MD, Division of Dermatopharmacology, Department of Dermatology, Brown Medical School/Rhode Island Hospital, JBS-1, 593 Eddy St, Providence, RI 02903. E-mail: John.DiGiovanna_MD@Brown.edu.

J Am Acad Dermatol 2004;51:709-17
0190-9622/$30.00
© 2004 by the American Academy of Dermatology, Inc.

709
Objective: The purpose of the study was to evaluate the effect of a standard, single course of isotretinoin (Accutane) therapy on bone mineral density (BMD) of the lumbar spine and hip in adolescents ages 12 to 17 years with severe, recalcitrant, nodular acne.

Methods: In this open-label, multicenter study, 217 adolescents (81 girls) with severe, recalcitrant, nodular acne were enrolled and treated with isotretinoin twice daily with food at the recommended total dose of approximately 1 mg/kg for 16 to 20 weeks. BMD in the lumbar spine and hip was measured at baseline and at the end of therapy by dual energy radiograph absorptiometry.

Results: There was no clinically significant mean change in BMD measured at the lumbar spine (+1.4%, range: −4.9% to +12.3%) or total hip (−0.26%, range: −11.3% to +15.0%). Hyperostosis was not observed in any patient. Typical efficacy expected in the treatment of acne was observed.

Conclusions: A 16- to 20-week course of isotretinoin treatment at the recommended dose for severe acne has no clinically significant effect on lumbar spine and total hip BMD in the adolescent (12-17 years) population. (J Am Acad Dermatol 2004;51:709-17.)

METHODS
This was an open-label, multicenter study without a separate control group. The study design included a screening baseline evaluation. The study protocol was approved by the institutional review boards of either the participating centers or by a central institutional review board (Schulman Associates, Cincinnati, Ohio). Before enrollment, written informed consent was obtained from each patient and his or her parent or guardian.

Study population
A total of 217 patients, recruited from hospital clinics and private practices, were enrolled at 19 centers. Each center enrolled from 2 to 33 patients. In all, 193 patients (88.9%) completed 16 weeks of treatment; 184 (84.8%) continued on to complete 20 weeks of treatment. A total of 36 patients were excluded from the per-protocol analysis because of: (1) protocol violations such as not having both a baseline and a final visit BMD measurement; (2) noncompliance, defined as returning greater than 20% of assigned medication; or (3) completing fewer than 16 weeks of isotretinoin therapy. Thus, the per-protocol analysis was performed on 181 patients. However, 217 patients received at least one dose of study medication and results for BMD data are presented for a subset of the intent-to-treat population who provided baseline and final visit dual energy radiograph absorptiometry (DXA) scans (N = 204 for lumbar spine, N = 201 for total hip). Final visit data contain the sum of the data from patients who had completed either 16 or 20 weeks of treatment.

Patients were treated with isotretinoin twice daily with food for a mean of 133 ± 26 days. Total cumulative dose was 8821 ± 2328 mg, which amounts to a mean daily dose of 66 mg (1 mg/kg/d).
Inclusion criteria
Eligible patients included boys or nonpregnant, nonlactating girls between the ages of 12 and 17 years, who required isotretinoin for the treatment of severe, recalcitrant, nodular acne. Girls of childbearing potential were required to use two separate and effective methods of birth control, unless abstinence was the chosen method, and to have had a negative serum pregnancy test 1 week before the start of isotretinoin therapy, which was begun on the second or third day of the menstrual cycle.

Exclusion criteria
Exclusion criteria included: use of vitamin A supplements in excess of the US recommended daily allowance; sensitivity or allergy to parabens; use of tetracyclines 14 days before, during, or 1 month after drug administration; current use of oral glucocorticoids or receipt of more than 12 cumulative weeks of inhalation glucocorticoid therapy within the previous year; use of thyroid hormone treatment; current use of anticonvulsant medication; recent history of drug or alcohol abuse; recent history of psychiatric disorders, mood or depressive disorders, significant depression, or a history of persistent symptoms of depression; previous therapy with oral retinoids, any metal implants, or bone disease that precluded successful DXA scans; weight less than 30 kg or more than 110 kg; uncontrolled type 1 diabetes mellitus; osteogenesis imperfecta (or other known disorders of collagen); HLA B27-related disease (ie, ankylosing spondylitis); juvenile rheumatoid arthritis; clinical rickets; any degree of vitamin D depletion as evidenced by a serum 25-hydroxyvitamin D level <10 ng/mL or any other type of metabolic bone disease; severe scoliosis (Cobb angle >15 degrees); a history of back operation, or current or history of severe lower back injuries; or presence of cervical hyperostosis at baseline.

Bone density measurements
BMD measurements of the posterior-anterior (PA) lumbar spine (L1-L4) and hip were obtained using DXA instruments (Lunar Corporation, Madison, Wis).

BMD of the lumbar spine (BMD\textsubscript{S}) was calculated as follows using bone mineral content (BMC) and surface area (SA):

\[
BMD_S = \frac{(BMC_{L1} + BMC_{L2} + BMC_{L3} + BMC_{L4})}{(SA_{L1} + SA_{L2} + SA_{L3} + SA_{L4})}
\]

Similarly, the mean of total hip BMD (BMD\textsubscript{H}) was calculated as follows:

\[
BMD_H = \frac{(BMC_{\text{shaft}} + BMC_{\text{neck}} + BMC_{\text{trochanter}})}{(SA_{\text{shaft}} + SA_{\text{neck}} + SA_{\text{trochanter}})}
\]

All DXA instruments (ie, each site) were cross-calibrated (Bio-imaging Technologies Inc, Newtown, Pa) using an appropriate calcium hydroxyapatite-based calibration phantom. All DXA scans were sent for analysis (Bio-imaging Technologies Inc). Triplicate DXA measurements of the PA lumbar spine and hip were taken at both baseline and final visit for each study participant. All BMD data are expressed in g/cm\textsuperscript{2}.

Lumbar z score
The BMD\textsubscript{S} z score is the measurement of BMD\textsubscript{S} relative to a normal, healthy, age-matched, sex-specific population. Explicitly, the difference is expressed as the number of SDs from the population normal, ie:

\[
z \text{ score} = \frac{BMD - BMD_{\text{normal}}}{SD_{\text{normal}}}
\]

Data for calculation of BMD\textsubscript{S} z score were provided by the manufacturer of the DXA instrument (GE-Lunar, Madison, Wis). The z score for BMD\textsubscript{H} was not calculated because a pediatric reference database was not available.

Radiographic assessment of the cervical spine
A single lateral radiograph of the cervical spine was also taken at these visits as a screen for the development of hyperostoses. Although it is not known which body location is the first to develop hyperostosis, the cervical spine may show some of the most clinically important hyperostosis. The radiograph taken at a patient’s final visit was compared with that obtained at the baseline visit during centralized, blinded, independent assessments of films by the same pediatric bone radiologist. Reading of the radiographs was controlled as follows. The session consisted of the randomized display of the baseline and final visit images for each individual patient. The order in which patient images were displayed was determined by the sequential ordering of the randomization numbers. The reader was blinded to the time point of each radiograph represented.

Other study assessments
Acne severity was assessed according to the grading scale of Allen and Smith. A complete safety profile was recorded which consisted of adverse events (AEs) and standardized laboratory tests including: complete blood cell count; serum chemistry; total calcium and phosphate; 25-hydroxyvitamin D; fasting serum lipids and liver function profile; creatine kinase; and urinalysis. At each visit patients completed a musculoskeletal events questionnaire that collected information on prior and current
injuries and musculoskeletal pain events. AEs were defined as any adverse change from the patient’s baseline condition, including intercurrent illness, that occurred during the course of the study after treatment was started, whether considered related to treatment or not. All adverse event terminologies were classified according to MedDRA (Medical Dictionary for Regulatory Activities) version 1.5. The investigator evaluated the intensity of each adverse event on a 3-point scale (mild, moderate, and severe). The number and percentage of patients reporting AEs was summarized by body system, intensity, and relationship to the study drug.

Statistical analysis

The differences between baseline and end of treatment were tested for significance by a paired t test. A 1-sample t test was used to test for significant differences from zero in the percent change from baseline in BMD$_S$ and BMD$_H$.

RESULTS

A total of 217 patients were enrolled at 19 centers. Results for BMD data are presented for the intent-to-treat population. A total of 204 patients provided baseline and final visit DXA scans for lumbar spine, and 201 patients for total hip.

Table I summarizes the demographic characteristics of the study population. Approximately 80% of patients were Caucasian with the remainder distributed among black (3%), Asian (2%), and other (15%) ethnic groups. The distribution of patients according to age and sex in the total population (N = 217) was similar to that in the intent-to-treat population.

The clinical efficacy observed as resolution of acne was consistent with the excellent response typical of isotretinoin (unpublished data, available from Roche).

Changes in BMD from baseline to final visit

Values of BMD$_S$ and BMD$_H$ (the combined average of femoral neck, femoral shaft, and greater trochanter) at baseline and end of treatment are presented in Fig 1.

BMD$_S$ increased from a baseline value of 1.108 ± 0.132 (range: 0.803-1.502) to 1.125 ± 0.127 (range: 0.843-1.502) at the end of treatment (Fig 1, A) (P < .00001). For BMD$_H$ measurements, there was a slight decrease from baseline value of 1.088 ± 0.136 (range: 0.711-1.473) compared with end of treatment value of 1.086 ± 0.136 (range: 0.685-1.522) (Fig 1, B) that was not statistically significant (P = .19). Statistical analyses of data from all individual sites are shown in Table II.

Fig 2 depicts the data as percent change from baseline to end of treatment. Changes from baseline to end of treatment were statistically significantly different from zero for BMD$_S$ (1.403 ± 2.5% [range: -4.9% to +12.3%], P < .00001), but not for BMD$_H$ (-0.258 ± 3.0% [range: -11.3% to +15.0%], P = .226).

Change in z score

In the lumbar spine, the change from baseline at the final visit in z score was 0.090 ± 0.192 (range: -0.539 to 0.707) with a confidence interval of 0.064 to 0.117. The changes from baseline in z score parallel those percent change values for BMD$_S$ previously discussed and presented in Fig 2.

Individual patient changes in BMD

There was considerable variation in BMD values at both baseline and the end of treatment, as would be expected in growing children of diverse ethnicity and size. More boys and girls gained than lost BMD$_S$; approximately equal numbers of both sexes gained or lost BMD$_H$.

Radiograph assessment of the cervical spine

Posttreatment hyperostosis was assessed by comparing the cervical spine radiograph at the baseline and final visit viewed in a randomized sequence, and blinded for time taken. At baseline, 216 patients provided images that were technically adequate; at the final visit, 205 images were of sufficient quality for an assessment to be made.
Hyperostosis and other sclerotic change in the cervical spine were uniformly absent at both baseline and at the final visit. However, other pathologic changes were observed in 8 of 216 patients (3.7%) at baseline and in 9 of 203 patients (4.4%) at the final visit. In 7 patients the condition was present at both baseline and at final visit and, therefore, unrelated to the study. In one patient the condition observed at baseline was not observed at the final visit; and in two patients the condition was observed at the final visit but was not present at baseline. In the latter two patients changes observed were straightening or reversal of the cervical lordotic curve. One patient showed a decrease in disk height between C6 and C7 at both baseline and final visit, which was presumed to be a congenital defect. Other abnormalities were found in 19 patients both at baseline and at the final visit. These mainly took the form of minor anomalies in the spinous process of C2, or the presence of large adenoids.

**Other study assessments**

Mucocutaneous side effects were the most common AEs with 48% of patients reporting cheilitis. Mucocutaneous side effects were the most common AEs with 48% of patients reporting cheilitis. Next most common were back pain (41%), dry skin (32%), and arthralgia (31%). Laboratory test results were typical of other patients receiving isotretinoin for the treatment of severe, recalcitrant, nodular acne, including elevations over baseline in triglycerides (66.7%) and cholesterol (10.2%). No single value for cholesterol exceeded the reference range for abnormal whereas 25% of patients had transient elevations in triglycerides that reached 100% increase over baseline. Six patients had elevated serum phosphate (mean value: 1.74 mmol/L or >20% of upper limit of the normal range), but all had normal alkaline phosphatase.

Elevations in creatine kinase were observed, sometimes in association with reported musculoskeletal AEs, such as back pain, arthralgia, limb injury, and muscle sprain. In these patients, elevations quickly returned to normal. Two patients of 217 (0.92%) had creatine kinase levels of more than 10,000 U/L. In one case the value of 16,040 U/L decreased to 111 U/L 13 days after drug was discontinued; in the other case the value decreased from 12,630 U/L to 239 U/L after 9 days. No cases of rhabdomyolysis were reported.
DISCUSSION

One of the most important determinants of the bone mass lifeline is the magnitude of the gain in bone mass achieved during late adolescence. Accrual of bone mass throughout growth (birth through 18-20 years) determines a plateau from which a decline may start around the time of the menopause, or in older age.\textsuperscript{15} It is believed that the higher the plateau achieved (peak bone mass), the longer the skeleton can delay potential decline to a fracture-susceptible level. Although genetic factors account for 30% to 70% of peak bone mass, environmental factors such as the use of nutrients required for bone building are also important. Environmental factors are potent during periods of active growth, and include general nutrition, threshold effects of mineral and vitamin D intakes, the positive effects of weight-bearing exercise, and the effects of chronic severe diseases and certain medications. However, standardized instruments to quantitate diet and exercise effects on bone mass are lacking, and there is disagreement on the optimal technique to measure bone mass in growing children. Thus, the exact timing of peak bone mass, and relationships between genetic influences and environmental factors, remain to be finalized.\textsuperscript{16}

Although adolescence is the opportunity for accumulation of peak bone mass, it is also a time of vulnerability, because interruption of these normal processes can result in suboptimal peak bone mass, which may have subsequent lifelong effects by lowering the plateau. Examples of interruptions include periods of extended bed rest, inadequate dietary intake of mineral, or therapy with a drug that may affect bone modeling or remodeling.

Our study found no clinically significant effects on BMD levels in adolescents treated with isotretinoin for severe, recalcitrant, nodular acne. The data included a small difference observed at Ward’s triangle, a problematic area of measurement that is considered to be unreliable for evaluation of BMD. The International Society for Clinical Densitometry is a nonprofit multidisciplinary society for which the mission is to promote quality in the performance and interpretation of bone density examination. They conducted a position development conference (July 20-21, 2001) addressing controversies that included: (1) which skeletal sites and regions of interest should be used for the diagnosis of osteoporosis; and (2) the role of serial BMD measurements.\textsuperscript{17} The position statement recommends that the PA spine (first 4 lumbar vertebrae) should be measured as the preferred site, with the total hip used when the PA spine is technically invalid; furthermore, “Ward’s region and lateral spine should not be used.”\textsuperscript{17} Measurement at Ward’s area is imprecise and “would result in overdiagnosis of osteoporosis.”\textsuperscript{18} In addition, “the panel suggested that the manufacturers remove Ward’s area from the default settings of their printouts.”\textsuperscript{18}

In addition to diagnosing osteoporosis, the panel addressed the capability of BMD to measure change over time (monitoring). Once again, they concluded that the PA spine is the preferred site for monitoring patients using DXA because it has the best precision. When PA spine is not measurable, the total hip region should be used for monitoring. “Ward’s area should not be used for monitoring because of poorer precision.”\textsuperscript{19}
The effects on skeletal integrity of long-term, high-dose therapy with isotretinoin for diseases other than acne have been described. Radiographic hyperostosis is the most common observation in children treated for disorders of cornification.\textsuperscript{5,7,20} Another study in patients undergoing long-term therapy for various dermatoses identified osteoporosis in patients treated with etretinate but not with isotretinoin.\textsuperscript{13} Less clear are the effects on bone when the standard doses of isotretinoin are used in acne therapy. The limited data available demonstrate that minor changes in bone structure have been observed, but that they lacked clinical significance.\textsuperscript{9,21,22} Taken together, the reports suggest that, for some skeletal toxicities, there may be a threshold exposure to isotretinoin required to produce a clinically significant effect on bone.

Three recent studies have focused on possible bone effects during an acne therapy regimen. Kocijancic\textsuperscript{10} examined the effect of short-term isotretinoin on lumbar spine bone density in 15 patients undergoing a 6-month course (mean isotretinoin dose 0.4 mg/kg, range: 0.29-0.5 mg/kg). The mean increase in bone density observed was 3.0\% in the adolescents and adults (mean age 19.8 years, range 13.7-30.1 years), comparable with normal bone gain. This study concluded that isotretinoin had no clinically important influence on lumbar bone density in boys with severe acne.

Margolis et al\textsuperscript{11} studied 20 adult patients undergoing treatment for severe acne vulgaris. Patients, age 19 to 35 years, were treated for 20 weeks with a total dose of 122 mg/kg of isotretinoin (range: 108-137 mg/kg; mean daily dose 0.89 mg/kg). These patients had stopped growing an average of 10 years before the beginning of the study. DXA measurements of the lumbar spine and hip were used to assess bone mineralization before and after treatment. No significant changes in mineral density were noted in lumbar spine BMD or at the femoral neck, Ward’s triangle, or the proximal femur.

Leachman et al\textsuperscript{12} studied the effect of a 6-month course of isotretinoin (1 mg/kg) in 18 patients with cystic acne (range: 17-25 years) compared with healthy, age-matched untreated control subjects (N = 14, 19-26 years). These investigators found no significant change in lumbar spine BMD (+1.2\%) or femoral neck BMD (+0.2\%) when patients exposed to isotretinoin were compared with the control subjects. However, at Ward’s triangle, in the isotretinoin group a 4.42\% decrease was found (P = .04). In that study, no other concomitant changes occurred in biochemical markers of bone homeostasis. A subsequent letter reporting only results at Ward’s triangle taken 5 to 9 years later showed a return to baseline in 3 of the 4 men who previously had the greatest percentage loss of density at that area.\textsuperscript{23} Measurements of bone density at Ward’s triangle, an area of trabecular bone with high turnover, are subject to great variability related to differences in positioning, and which are instrument-specific. Precision at this site is decreased because the standard error of measurement is around 2.5\%.\textsuperscript{24} Because of the unreliability of measurements at Ward’s area, we would interpret the lack of change in the lumbar spine and femoral neck to indicate that isotretinoin had no effect on BMD.

A total of 1 SD is usually reserved for the minimum change in an age- and sex-matched normative population to denote adverse change (the World Health Organization definition of osteopenia is a T-score of greater than −1). The data in Fig 1 demonstrate that for both lumbar spine and total hip, the SD at both baseline and end of treatment is of the order of 12\% of the mean value. This is similar to the normative data of the SDs supplied by the manufacturer of the DXA instrument (GE-Lunar, Madison, Wis) (lumbar spine values of approximately 13\% and 16\% for girls and boys, respectively, aged 13-17 years) and other published values (approximately 12%-14\% for girls and 16\% for boys age 13-17 years\textsuperscript{16}). In the current study, the first powered to examine the effects of isotretinoin on bone in adolescents treated for acne, approximately half of the patients of both sexes gained bone mass. Of those who lost, no patient manifested a loss in BMD\textsubscript{5} or BMD\textsubscript{H} of even 1 SD and the vast majority of patients (>95\%) had decreases of less than 30\% to 40\% of 1 SD. There is a well-known temporal delay between height acquisition and bone mineral accretion in rapidly growing children that leads, in some cases, to a transient state of lower bone mass.\textsuperscript{15,25} This most likely explains the occurrence in two patients of decreases in BMD\textsubscript{H} that exceeded 10\% (Fig 2, B).

The wide range in BMD\textsubscript{H} values in the study population as a whole is, at least in part, the result of an areal, as opposed to a volumetric, measurement being performed at an anatomic site where the geometry is changing during the course of the treatment because of normal growth of the study patients,\textsuperscript{26} particularly at Ward’s triangle.\textsuperscript{24} Our observed values for BMD\textsubscript{H} change are within the ranges observed for a population of growing, healthy adolescents.\textsuperscript{27,28}

Our study showed that no hyperostosis occurred after 16 to 20 weeks of isotretinoin treatment, and only two adolescents had any pathologic changes noted at baseline and the end of the study, limited to straightening or reversal of the cervical lordotic curve. Such radiographic features are not clinically

\textsuperscript{5} Organization definition of osteopenia is a T-score of greater than −1.
significant, and the incidence reported here is not unusual in a population of growing adolescents. Effects on laboratory parameters in the adolescent population were minimal and as expected from the known effects of isotretinoin. In this study, patients reported a high frequency of back pain (41%), which we attribute to a data collection phenomenon. At each visit patients completed a musculoskeletal events questionnaire and patients in this study were more likely to report AEs of a musculoskeletal nature. In this athletically active pediatric population, the self-reports were consistent with activity levels or injury reports. Back pain was usually mild or moderate and returned to baseline incidence by week 8.

Could this study have missed an isotretinoin-associated decrease in BMD? It is possible that longer exposures or higher doses might be associated with decreased BMD. One might speculate as to whether the development of calcification in ligaments around measurement areas could confound bone density measurements, and mask the measurement of early osteopenia. However, we did not observe hyperostosis in this study. In addition, some effects of isotretinoin persist after discontinuation of the drug, for example, acne continues to improve after therapy is discontinued; it is possible that effects on bone could continue as well.

The current report demonstrates that BMD_{\text{S}} and BMD_{\text{L}} accrual in a large, adolescent-age population was unaffected by a 16- to 20-week course of isotretinoin. We conclude that a short-term course of therapy for acne has no detrimental effects on adolescent bone mass. Perhaps longer-term therapy and lifelong dietary exposure to vitamin A may influence bone mass in other ways.

We thank Sol Epstein, MD, and Colin Miller, PhD, for their help in the preparation of this article.

REFERENCES


**CORRECTIONS**


Two factual errors in this article were recently brought to our attention. On page 87, A. Benson Cannon’s tenure as Chairman of Dermatology at Columbia University (1947-1950) was not mentioned. He held the position after J. Gardner Hopkins and before Carl Truman Nelson.

On page 88, Urs W. Schnyder is identified as a trainee of Heinrich A. Gottron. Schnyder trained with Guido Miescher and Hans Storck in Zürich and was a colleague of Gottron’s when they invited Helen Ollendorff Curth to write a chapter for the supplementary volumes to Jadassohn’s Handbuch. We apologize to Professor Schnyder for the error.


In the section of the Self-Assessment examination titled Dermoscopy challenges, which begins on page 162, the answer to question 42 was given as “a. True.” The answer should be “b. False.”


Several typographical errors appeared in Dr Weary’s reply to the comments of Dr Robert A. Swerlick. In the first paragraph, second sentence, Dr Swerlick’s name is misspelled. In the final paragraph, the sentence beginning “And finally…” should read as follows: “And finally, by clean I urge them [dermatologists] to remain professional and ethical and put the interests of their patients, both fiduciary and medical, above their own self interests as befit the role of the compassionate physician.”