Original Investigation

High-Dose Isotretinoin Treatment and the Rate of Retrial, Relapse, and Adverse Effects in Patients With Acne Vulgaris

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IMPORTANCE Isotretinoin is the most effective treatment for acne. The ideal dosing regimen is unknown.

OBJECTIVE To determine the rates of relapse of acne vulgaris and retrial of isotretinoin after high cumulative-dose treatment and the changes to the adverse effect profile.

DESIGN, SETTING, AND PARTICIPANTS A prospective, observational, intervention study was conducted from August 1, 2008, to August 31, 2010, in a single academic tertiary care center with multiple providers. A total of 180 patients with acne resistant to other treatments were enrolled. Of these, 116 participated in the 12-month follow-up survey, for a response rate of 64.4%.

EXPOSURE Patients received isotretinoin, with dosing based on the providers' judgment. Patients were divided into 2 groups on the basis of cumulative dosing (<220 mg/kg and ≥220 mg/kg).

MAIN OUTCOMES AND MEASURES Relapse (treatment with a prescription topical or oral acne medication after a course of isotretinoin) or retrial (retreatment with isotretinoin) at 12-month follow-up and adverse effects experienced during and after 12 months of treatment.

RESULTS The mean age of the participants was 19.3 years, 51.9% were female, and 74.1% were white. At 12 months' follow-up, 97.4% of the patients reported that their acne was improved. Overall, acne in 32.7% of patients in the study relapsed at 12 months, and 1.72% of the patients required a retrial. In the lower-dose treatment group (<220 mg/kg), the relapse rate was 47.4% (95% CI, 32.3%-63.0%) compared with 26.9% (95% CI, 18.3%-37.8%) in the high-dose group (P = .03). Almost 100% of the patients in both treatment groups developed cheilitis and xerosis during treatment. Retinoid dermatitis was significantly more common in the high-dose treatment group (53.8% vs 31.6%; P = .02). None of the other adverse effects was significantly different between the 2 groups.

CONCLUSIONS AND RELEVANCE The dosing regimen used in the present study is considerably higher than that used in previous studies of isotretinoin. At 1 year after completion of isotretinoin treatment, we found that patients receiving 220 mg/kg or more had a significantly decreased risk of relapse. Rash was the only adverse effect that was significantly more common in the high-dose group during treatment. This study suggests that significantly higher doses of isotretinoin are effective for treating acne and decreasing relapse rates without increasing adverse effects.

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Isotretinoin is the most effective treatment for severe nodular-cystic acne vulgaris, and it is the only treatment option for acne that offers the potential for remission or permanent cure.[1-3] The current literature is divided on ideal dosing of isotretinoin to optimize treatment response. Most studies[1,4-6] support a cumulative dose of 120 to 150 mg/kg to decrease the risk of relapse and retrial. Some newer studies reported lower rates of relapse and retrial with higher doses,[7] and others found equal response rates with decreasing adverse effects during lower-dose treatment.[4,8-16] In the present study, we defined *relapse* as the need for prescription acne medication after isotretinoin treatment and *retrial* as the need for an additional course of isotretinoin.

Because different combinations of daily dose regimens and treatment durations are used, study results are difficult to compare. Acne "severity" and "relapse" lack standardized definitions.[14,17] In addition, many of the previous studies are limited by small sample size, lack of a comparison group, short duration of follow-up, or retrospective design. To further elucidate the effects of high-dose isotretinoin on retrial rates, we conducted a prospective observational study evaluating a very high cumulative dose of isotretinoin compared with a lower-dose therapy.

Isotretinoin is associated with several potential adverse effects; therefore, using a dose that improves response rates while minimizing adverse effects and retreatment is critical. Common adverse effects associated with isotretinoin include cheilitis, xerosis, and dermatitis.[10,18,19] Some studies[10,19,20] have found that higher doses of isotretinoin are associated with higher rates of mucocutaneous adverse effects but not systemic adverse events. It is unknown whether higher rates of mucocutaneous adverse effects are clinically relevant, given that they are easily treatable, or whether they lead to increased rates of attrition. Systemic adverse events are less common and include elevations in cholesterol, triglycerides, or transaminase levels.[21] The clinical significance of these elevations is unknown.[22] There are also controversial, unproved links between isotretinoin and suicide, depression, or inflammatory bowel disease.[23-27] The relationship between higher isotretinoin dosing and adverse effects was evaluated in our study during treatment and 1 year after treatment.

Methods

In this prospective observational study, patients with severe nodular-cystic acne resistant to other treatments were enrolled from August 1, 2008, through August 31, 2009. The target end point for each patient was treatment with isotretinoin until there were no new acne lesions during 1 month of therapy. All providers agreed to use no topical or prescription medications when isotretinoin therapy was completed. We divided the patients into 2 isotretinoin treatment groups: those who received a cumulative dose of 220 mg/kg or more and those who received less than 220 mg/kg. A cumulative dose of 220 mg/kg was chosen on the basis of a review of medical records performed at our institution,[7] which found that doses less than 220 mg/kg were associated with higher rates of relapse and retrial. Cumulative treatment dose in the present study was used as the measure of dose because it is more reproducible and reliable than daily dose. Patients were asked to use all remaining medication as the treatment period ended to ensure standardized adherence to prescribed cumulative doses. Patients were monitored for 12 months after their last day of isotretinoin. We chose this length of follow-up because previous studies[7,17] have found that 80% to 90% of patients experience relapse within 12 to 24 months. Information was collected on demographics, adverse events, relapse, and retrial by medical record review and patient surveys conducted 12 months after treatment. This study was approved by the University of North Carolina Institutional Review Board, and participants provided written informed consent.

Details of Patient Survey

Patients were contacted by mail and telephone survey 12 months after completing isotretinoin treatment (August 31, 2010). The survey assessed whether patients had used any prescription treatment for acne since their last clinic visit and whether they were currently using any other treatments, including prescription and over-the-counter medications. The survey also included subjective assessments of the presence of acne within the previous month and whether the patients observed that their acne symptoms were better, the same, or worse. Finally, patients were assessed for a variety of symptoms related to isotretinoin therapy.

Definitions of Laboratory Values

Laboratory values, including liver enzymes, cholesterol, and triglycerides, were obtained from the patient's electronic medical record for each visit. We defined elevated liver enzymes as aspartate aminotransferase (AST) level greater than 90 U/L (to convert to microkatals per liter, multiply by 0.0167) and alanine aminotransferase (ALT) level greater than 105 U/L (to convert to microkatals per liter, multiply by 0.0167). Elevated cholesterol and triglyceride levels were defined as greater than 300 mg/dL (to convert to millimoles per liter, multiply by 0.0259). Patients were not required to fast prior to laboratory sampling; those who developed elevated cholesterol or triglycerides were asked to fast before their next appointment. Patients with elevated AST or ALT level were asked to return to the clinic in 2 weeks for a second round of laboratory testing.

Statistical Analysis

We reported patients' demographic characteristics and response to treatment using percentages and means, with SD determined when appropriate. A bivariate analysis was used to compare each adverse effect during and 12 months after treatment between the 2 dosing groups using a Pearson χ^2 test. A bivariate analysis also was used to compare demographic characteristics and response to treatment of patients in the 2 dosing groups using a Pearson χ^2 or 2-tailed, 2-sample t test. Using a logistic regression model, we adjusted for factors that were associated with relapse in previous studies to evaluate the relationship between treatment dose and relapse rate. For final reporting, we used a significance level of $P \leq .05$. All analyses were performed using commercial software (Stata, version 12; StataCorp).

Results

Patient Demographics

We initially received institutional review board approval for a study involving 180 patients. A total of 116 patients returned the 12-month follow-up survey and were included in the study for a response rate of 64%. The mean age of the participants was 19.3 years, and 51.9% were female (**Table 1**); 74.1% of the participants were white and 25.9% were defined as nonwhite. The mean cumulative treatment dose of isotretinoin was 264.3 mg/kg during a mean of 6.3 months. The mean cumulative high dose was 309.8 mg/kg compared with 170.8 mg/kg in the lower dosing group.

The mean age of participants in the lower-dose treatment group, who received less than 220 mg/kg of isotretinoin, was 21.1 years compared with 18.3 years in the high-dose group, who received 220 mg/kg or more (P = .03) (**Table 2**). Of patients receiving the lower dose, 60.5% were female vs 46.1% in the high-dose group (P = .15). In the lower-dose group, 73.7% of patients were white and 26.3% were nonwhite compared with 74.4% white and 25.6% nonwhite in the high-dose group (P = .94). Patients received treatment for a mean of 6.5 months in the high-dose group and 5.8 months in the lower-dose group (P = .03).

Table 1. Characteristics of 116 Patients

Characteristic	%
Age, mean (SD), y	19.3 (6.5)
Female sex	51.9
White	74.1
Relapse	33.6
Retrial	1.72
Acne improved at 12-mo follow-up	97.4
Acne in the past month at 12-mo follow-up	64.7
Cumulative dose, mean (SD), mg/kg	264.3 (85)
Length of treatment, mean (SD), mo	6.3 (1.5)

Relapse, Retrial, and Response to Treatment

At the 12-month follow-up, 32.7% of patients in the study experienced relapse and 1.72% required a retrial of isotretinoin. Both patients who required a retrial were in the high-dose treatment group. In the lower-dose treatment group (<220 mg/kg), the relapse rate was 47.4% (95% CI, 32.3%-63.0%) compared with 26.9% (18.3%-37.8%) in the high-dose group (P = .03). After adjustment for age, sex, race, treating physician, and duration of treatment, the rate of relapse in the lower-dose group was 43.8% (95% CI, 16.3%-40.3%) compared with 26.6% (24.1%-65.7%) in the high-dose group (P = .22).

In all, 97.4% of patients reported that their acne was improved from before treatment at the 12-month follow-up. Of patients in the lower-dose group, 42.3% were given a prescription for another acne medication after completing isotretinoin compared with 28.1% of patients in the high-dose group (P = .12). At the 12-month follow-up, 55.6% of patients in the combined groups were using no acne medications, 0.9% were receiving a second course of isotretinoin, 1.7% were receiving an oral antibiotic, 1.7% were using an oral antibiotic and a topical prescription, 25.2% were receiving a topical prescription, and 14.8% were using an over-the-counter acne treatment. In the lower-dose group, 12.8% of patients reported using over-the-counter acne treatments compared with 16.2% of patients in the high-dose group. This difference was not statistically significant (P = .23).

Adverse Events

Laboratory abnormalities during the treatment were uncommon and not significantly different between the 2 dosing groups (**Table 3**). Laboratory values were more elevated in the high-dose group, but the differences were not statistically significant. Overall, 14.0% of patients in the study had laboratory abnormalities during treatment. No patients in the lower-dose group had elevated AST, ALT, or cholesterol levels. Of patients in the high-dose group, 6.4% had elevated AST, 1.3% had elevated ALT, and 1.3% had elevated cholesterol levels. Triglycerides were elevated in 5.3% of lower-dose group pa-

Table 2. Dosing Group and Baseline Characteristics of 116 Patients

Characteristic	Isotretinoin Dose, mg/kg		P Value[a]
	<220 (n = 38)	≥220 (n = 78)	
Age, mean (SD), y	21.1 (6.7)	18.3 (6.3)	.03
Female sex, %	60.5	46.1	.15
White race, %	73.7	74.4	.94
Duration of treatment, mean (SD), mo	5.8 (2.1)	6.5 (0.9)	.03
Cumulative dose, mean (SD), mg/kg	170.8 (33.6)	309.8 (61.9)	<.001

[a] Means and P values based on 2-sample t test or Pearson χ^2 test.

Table 3. Laboratory Abnormalities During Treatment Based on Dose

Laboratory Test (Abnormal Value)	Abnormal Values, %			P Value[a]
	Total (N = 116)	<220-mg/kg Group (n = 38)	≥220-mg/kg Group (n = 78)	
AST level (>90 U/L)	4.3	0	6.4	.11
ALT level (>105 U/L)	0.9	0	1.3	.48
Cholesterol level (>300 mg/dL)	0.9	0	1.3	.48
Triglycerides level (>300 mg/dL)	9.6	5.3	11.5	.28

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

SI conversion factors: To convert ALT and AST to microkatals per liter, multiply by 0.0167; cholesterol and triglycerides to millimoles per liter, multiply by 0.0259.

[a] P values based on Pearson χ^2 test.

Table 4. Adverse Effects of High-Dose vs Lower-Dose Therapy During Treatment

Adverse Effect	Patients With Adverse Effects, %			P Value[a]
	Total (N = 116)	<220-mg/kg Group (n = 38)	≥220-mg/kgGroup (n = 78)	
Dry lips	97.4	100.0	96.2	.22
Dry skin	98.3	100.0	97.4	.32
Dry eyes	39.7	31.6	43.6	.22
Itching	36.2	31.6	38.5	.47
Retinoid dermatitis	46.5	31.6	53.8	.02
Headaches	16.4	13.2	17.9	.51
Vision changes	6.0	5.3	6.4	.81
Mood changes	7.8	7.9	7.7	.97
Suicidal ideation	0.9	0	1.3	.48
Muscle aches	22.4	26.3	20.5	.48
Joint aches	34.5	28.9	37.2	.38
Nose bleeds	37.9	34.2	39.7	.56
Hair changes	6.9	10.5	5.1	.28
Hearing changes	1.7	0	2.6	.32
Nail changes	13.8 (7.8 with paronychia)	10.5	15.3	.32
Abdominal pain	5.2	0	7.7	.08

[a] *P* values based on Pearson χ^2 test.

tients and 11.5% of high-dose group patients (*P* = .28). One patient in the study had familial hypertriglyceridemia; she received the lower dose of isotretinoin for 7 months and required a 1-month break in treatment because of elevated triglycerides. A second patient developed a triglyceride level greater than 600 mg/dL after fasting and diet modification. He stopped treatment for 1 week and then continued a dose of 40 mg/d for a total of 7 months without further complications.

During treatment, cheilitis and xerosis were very common in both treatment groups, with almost 100% of patients reporting these effects regardless of treatment group (**Table 4**). Retinoid dermatitis was significantly more common in patients receiving higher-dose treatment; 53.8% of patients in the high-dose group developed rash compared with 31.6% of those in the lower-dose group (*P* = .02). The most common systemic effects during treatment were arthralgias (34.5%), myalgias (22.4%), and epistaxis (37.9%). Other than dermatitis, none of the recorded adverse effects was significantly different between the 2 groups during treatment (Table 4).

Twelve months after treatment, the most commonly reported adverse effects continued to be cheilitis (20.7%) and xerosis (17.2%). Headaches were the next most common (12.1%). None of the recorded adverse effects was significantly different between the 2 dosing groups 12 months after treatment (**Table 5**).

Two patients in the high-dose group electively discontinued treatment secondary to adverse effects. The first discontinued treatment at 6 months (total dose, 300 mg/kg) because of worsening xerosis, dry eyes, arthralgias, myalgias, occasional blurry vision, and headaches. At the 12-month follow-up, the patient reported xerosis, cheilitis, arthralgias, and abdominal pain. A second patient discontinued treatment at 8.5 months (total dose, 422 mg/kg) because of worsening mood changes, arthralgias, and sweating. At the 12-month follow-up, the patient reported xerosis, rash, and hair changes.

Discussion

Patient Demographics

The baseline characteristics of patients in our study, including age, sex, and race, were similar to those in previous studies on isotretinoin dosing.[4,7,8] Our response rate of 64.4% likely results from the age group of our study participants. Nonresponding patients probably had moved for college or employment, limiting our ability to contact them at the 12-month follow-up.

Relapse and Retrial

The present study compared a mean cumulative dose of 220 mg/kg or more with less than 220 mg/kg; this is considerably higher than any previous study conducted on isotretinoin treatment for acne vulgaris. A medical record review of high-dose isotretinoin previously conducted at our institution[7] led us to perform the present prospective study to further investigate the effect of high-dose isotretinoin treatment on relapse and retrial rates. Inconsistent definitions of relapse and retrial, combined with varying dosing regimens, study designs, and durations of treatment, make comparisons between studies difficult.

Many studies[4-6,17,28,29] advocate the use of 120 to 150 mg/kg as the total cumulative dose. This dosing regimen results in reported relapse rates of 20% to 60% and retrial rates of 7% to 20%. In a review of the literature during the past 10 years, we found 12 studies[4,5,7-16] investigating the relationship between different dosing regimens and retrial or relapse rate. Only one study evaluated the use of high-dose therapy; a medical record review of 80 patients conducted by Cyrulnik et al[30] found a retrial rate of 12.5% with 3 years of follow-up and an average cumulative dose of 290 mg/kg. Our study found an unadjusted relapse rate of 26.9% for patients who received 220 mg/kg

Table 5. Adverse Effects of High-Dose vs Lower-Dose Therapy at 12-Month Follow-up

Adverse Effect	Patients With Adverse Effects, %			*P* Value[a]
	Total (N = 116)	<220-mg/kg Group (n = 38)	≥220-mg/kg Group (n = 78)	
Dry lips	20.7	13.2	24. 4	.16
Dry skin	17.2	10.5	20.5	.18
Dry eyes	8.6	10.5	7.7	.61
Itching	4.3	2.6	5.1	.53
Rash	2.6	0	3.8	.22
Headaches	12.1	15.8	10.3	.39
Vision changes	3.4	7.9	1.3	.07
Mood changes	2.6	2.6	2.6	.98
Suicidal ideation	0	0	0	
Muscle aches	7.8	5.2	9.0	.48
Joint aches	6.9	5.3	7.7	.63
Nose bleeds	4.3	5.3	3.8	.72
Hair changes	6.9	7.9	6.4	.77
Hearing changes	1.7	2.6	1.3	.60
Abdominal pain	6.3	10.5	3.8	.16

[a] *P* values based on Pearson χ^2 test.

or more of isotretinoin, and we found an overall retrial rate of 1.7%. Although the adjusted relapse rate (43.8% vs 26.6%; *P* = .22) was not statistically significant, likely because of the small sample size, the large difference in relapse rate between the 2 groups is clinically significant. To our knowledge, this is the first study to evaluate the efficacy and safety of very high-dose treatment.

Adverse Effects

In the present study, as in all previous studies[9,30,31] of isotretinoin, the most common adverse effects were xerosis and cheilitis. Although previous studies[16] have shown that groups receiving lower cumulative dosing had lower rates of xerosis and cheilitis, our results showed no statistically significant difference between groups, with nearly all patients reporting these adverse effects. Retinoid dermatitis was the only adverse effect in our study that was significantly increased in the high-dose group during treatment (53.8% vs 31.6%; *P* = .02). These rates are similar to the rates observed in previous studies[8] with lower-dose regimens. At the 12-month follow-up in the present study, the percentage of patients reporting rash decreased to less than 10%, with no statistically significant difference between the dosing groups, suggesting that isotretinoin has a transient, dose-dependent effect.

Controversial associations of isotretinoin with suicidal ideation and depression have been reported in the literature.[32] Consistent with recent studies,[32] no patients in our study without previous psychiatric history reported suicidal ideation, and there was no significant difference between the dosing groups. The mood changes experienced in both groups likely reflect natural characteristics of the adolescent and young adult population that make up most patients in the study.

Arthralgias were present in 28.9% and 37.2% of patients during treatment with lower and higher doses of isotretinoin, respectively. In patients with disorders of keratinization who were receiving long-term regimens of isotretinoin, adverse bone effects, such as osteophyte formation and premature closure of the epiphysis, have been reported.[33,34] During our study, none of these effects was reported in either treatment group. Although there was no statistically significant difference in arthralgias between lower and higher dosing regimens in this study, further evaluation of the source of these symptoms, as well as the long-term effects of isotretinoin dosing, could be warranted.

It has been known for many years that isotretinoin use causes nail changes, which are not limited to paronychia.[35] Very few studies[9,18,28,30,31,35] have reported these events, and those that did have shown very low rates. Our study suggests that the overall rate of paronychia in all patients receiving isotretinoin may be higher than previously reported. However, we detected no statistically significant difference between the 2 treatment groups. Unfortunately, although we were able to obtain the diagnosis through medical records at 12 months' follow-up, assessing for these events through survey methods was difficult.

The overall percentage of patients with elevated levels of total cholesterol or triglycerides was low, which is consistent with previous studies.[8,9,16,31] Kaymak and Ilter[31] found that 16% of patients receiving a low cumulative dose of 100 mg/kg of isotretinoin had triglyceride levels above 210 mg/dL. In our study, a similar, but slightly higher, number of patients had triglyceride elevations. Of 116 patients, 34 individuals (29.3%) had triglyceride levels above 210 mg/dL. Kaymak and Ilter also found that 5% of their patients experienced total cholesterol elevations above 278 mg/dL. In our study, only 5 patients (4.3%) experienced cholesterol elevations of this magnitude. Additionally, in our study, patients were not asked to fast prior to blood samples being obtained for laboratory testing. This suggests that the higher triglyceride levels, as compared with other studies, were a result of nonfasting lipid levels, and total cholesterol levels were similar.

We also observed very low rates of AST and ALT elevations in both treatment groups. Amichai et al[9] found that 4.8% of patients receiving low-dose isotretinoin (66-70 mg/kg cu-

mulative dose) to have transaminitis. In our study, only 6.4% and 1.3% of patients in the high-dose group had AST and ALT transaminitis, respectively. Many of these elevations were limited to a single clinic visit during the entire treatment regimen. In addition, potential confounders, such as viral infections, as well as alcohol and legal or illicit drug use, could have caused isolated elevations in transaminase levels.

Limitations

There was no randomization or blinding in our study, and patients were assessed and treated by different providers. All of the patients in the study had nodulocystic acne; however, we did not stratify patients by acne severity because of the absence of a reliable scoring system among the providers. Although all patients had some degree of facial acne, a limitation would be the lack of grouping based on the predominant distribution of the lesions, such as truncal or facial acne. Although no patients in the study received a diagnosis of or were reported to have adult hormonal acne, it cannot be excluded as an underlying risk factor for relapse, especially in female participants. Patients were not given specific instructions as to when or how to take isotretinoin to control for interindividual differences in the bioavailability of the drug. All of these factors might account for variability in relapse rates between the treatment groups. Also, because we allowed physicians to prescribe therapy until they observed no clinical lesions, the mean cumulative dose was higher than intended in the lower-dose group (170.8 mg/kg) and did not allow an assessment of high-dose isotretinoin compared with more traditional dosing approaches (<150 mg/kg).[4] Differences in the daily dosing regimen by which each attending physician achieved the cumulative dose also may have affected relapse and retrial. In addition, our follow-up period was only 12 months. Although most relapses associated with isotretinoin occur within 1 year,[7,17] whether the low retrial rate observed is associated with higher dosing or limited follow-up is unknown.

Conclusions

This prospective observational study compared less than 220 mg/kg with 220 mg/kg or more of isotretinoin, given during a mean of 6.3 months, with 12 months of follow-up for treatment of acne vulgaris. This dosing regimen is considerably higher than that used in previous studies of isotretinoin. At the 12-month follow-up, 97.4% of patients reported that their acne was improved. At 1 year after completion of isotretinoin therapy, we found that patients in the high-dose group had a significantly decreased risk of relapse, which was defined as the need for prescription acne medication. Our overall rate of retrial or retreatment with a second course of isotretinoin was so low that we are unable to draw conclusions about the effect of dose on retrial rate. Retinoid dermatitis was the only adverse effect that was significantly more common in the high-dose group during treatment. We observed a trend of increased laboratory test values in the high-dose group that was neither statistically nor clinically significant. This study suggests that higher cumulative doses of isotretinoin are effective for treating acne and decreasing relapse rates without increasing adverse effects to a significant level.

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Study concept and design: Morrell.
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Invited Commentary

PRACTICE GAPS

Challenges in Optimizing Isotretinoin Use for Acne Vulgaris

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Acne vulgaris is one of the most common skin disorders affecting adolescents and young adults. Food and Drug Administration approval of isotretinoin in 1982 dramatically changed the management of nodulocystic and severe, recalcitrant acne. Isotretinoin remains the only acne treatment associated with complete remission and "cure" of nodulocystic acne. Yet despite the dramatic effect of the drug, disease relapse can occur after isotretinoin therapy.

Multiple treatment algorithms and dosing regimens have been proposed for isotretinoin, and a cumulative dose of 120 to 150 mg/kg is widely accepted as the standard treatment protocol. Alternative strategies have been designed to optimize drug dosing to achieve acceptable clinical results while minimizing adverse effects. Such regimens range from 0.2 mg/kg/d to greater than 2 mg/kg/d of isotretinoin with variations in treatment duration. These differing opinions on the dosing of isotretinoin expose a gap in our medical knowledge about optimal isotretinoin dosing for acne vulgaris.

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Blasiak et al[1] present their single institution's experience with the use of high-dose isotretinoin for acne. Their prospective observational study compared treatment outcomes and adverse effects in patients receiving cumulative isotretinoin dosages of 220 mg/kg or more with those receiving less than 220 mg/kg. The intervention was not controlled; participating study providers were allowed discretion in selecting isotretinoin dosages. The investigators found a lower rate of acne relapse (defined as use of a prescription acne medication within 12 months after completion of isotretinoin treatment) in patients receiving 220 mg/kg or more vs those who received less than 220 mg/kg (26.6% vs 43.8%). Retreatment with an additional course of isotretinoin occurred in only 2 patients receiving the higher dose. Analysis of isotretinoin adverse effects found the only statistically significant difference to be an increase in retinoid dermatitis in patients receiving 220 mg/kg or more.[1] The rates of mood changes and suicidal ideation were the same in both treatment groups, consistent with recent reports[2] finding a lack of causality with isotretinoin and these psychiatric disorders.

This study suggests that a "high-and-dry" approach to isotretinoin dosing may lead to better long-term outcomes without increased risk for significant adverse effects. Comparison with prior studies is difficult, however, because of wide variation in methods of acne assessment and in the definition of outcomes, such as relapse and retrial. For example, more than 25 acne severity assessment tools have been developed and used in acne studies. In addition, some studies define relapse as an increase in acne lesion scores after treatment, and others define relapse as any use of prescription acne medication after isotretinoin therapy. Standardization of acne severity assessment and therapeutic outcomes is needed to compare studies effectively.