Face to Face with Oral Isotretinoin

A Closer Look at the Spectrum of Therapeutic Outcomes and Why Some Patients Need Repeated Courses

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Abstract

Oral isotretinoin, available in the United States for four decades, has been used for the treatment of recalcitrant nodular and deep inflammatory acne vulgaris. This drug revolutionized the management of patients affected by severe inflammatory disease due to its ability to markedly induce acne clearance coupled with prolonged durations of remission after completion of a course of therapy, usually over approximately five months. Over time, it has become recognized that prolonged remission correlates with achieving a threshold cumulative exposure range of approximately 120 to 150 mg/kg of oral isotretinoin. Lesser exposures have demonstrated a higher risk of earlier recurrence of acne vulgaris and a greater likelihood that the patient will require retreatment. As the oral bioavailability of oral isotretinoin is variable, and highly dependent on administration with food, it is very conceivable that earlier relapse may occur if patients have often ingested oral isotretinoin on an empty stomach, thus leading to lesser actual cumulative drug exposure despite the daily dose administered. This article provides an overview on the dosing of oral isotretinoin, reported data on factors that influence relapse after oral isotretinoin therapy, and the potential impact of coadministration with food.

Introduction

Since the approval of oral isotretinoin capsules by the United States (US) Food and Drug Administration (FDA) in 1982 and its release into the marketplace, this agent has revolutionized the management of severe and refractory acne vulgaris (AV).[1–8] No other therapy has exhibited the ability to both induce complete or near-complete remission of acne vulgaris and sustain its therapeutic benefit after completion of a course of therapy.[1–4] Subsequent to the availability of oral isotretinoin, the oral aromatic retinoids (etretrinate followed by acitretin) came to the US market with approval for treatment of psoriasis. Interestingly, oral isotretinoin proved to be markedly superior to etretrinate in both reducing acne lesions and suppressing sebum production, suggesting that oral isotretinoin exhibits unique properties that interfere with pathogenic mechanisms of AV.[8,9] Oral isotretinoin remains the only systemic retinoid approved by the FDA for treatment of AV, with an estimated 13 million people treated with this agent over the past four decades. The FDA-approved indication for oral isotretinoin is, "treatment of severe recalcitrant nodular acne." As stated in the approved package insert, "severe by definition means 'many' as opposed to 'few or several' nodules."[2,3] In fact, several studies support the efficacy of oral isotretinoin in patients with severe refractory nodular AV, with many experiencing complete or near-complete clearance of lesions by the end of a course of therapy and prolonged periods of remission after completion of therapy.[5–11]

Multiple clinical trials, retrospective database analyses, extensive global experience, and the consensus opinion of multiple consultants who have participated in the development of acne treatment guidelines strongly support that oral isotretinoin is highly effective in AV.[1–19] Nevertheless, continued clinical research and observations

based on clinical experience and retrospective analyses have helped to better define ways to optimize therapeutic outcomes.[1–19] Over time, refinements in the utilization of oral isotretinoin have included adjustments in starting dose, determination of the targeted total dosage range needed to obtain a successful therapeutic endpoint, a broader understanding of both well-defined and alleged potential risks, patient education and monitoring recommendations, and factors that may predispose to relapse.[1,4,11–24] Unfortunately, the importance of ingesting oral isotretinoin with food in order to maximize bioavailability has not received adequate emphasis, likely due to the justified emphasis on avoidance of pregnancy exposure, proper patient monitoring, potential adverse reactions, and most recently the implementation of the iPledge program, with information on this mandated program available at www.ipledgeprogram.com.

How has oral isotretinoin been a major advance for management of refractory and recurrent acne vulgaris?

Prior to the availability of oral isotretinoin, clinicians had very few options available for the treatment of severe AV characterized by many inflammatory nodules. Prior to oral isotretinoin, effective options for refractory, non-nodular, inflammatory AV were limited, especially in those cases associated with scarring and/or marked psychological distress due to persistent AV. The FDA-approved indication for oral isotretinoin is, "treatment of severe recalcitrant nodular acne," and as specified in the package insert, "severe" by definition means "many" as opposed to "few or several" nodules.[2,3] As noted above, clinical and research experience with oral isotretinoin for the treatment of severe nodular and recalcitrant AV demonstrates that the majority of patients experience complete or near-complete clearance of acne lesions during or shortly after the course of therapy.[1,4–11] Although oral isotretinoin exhibits a marked capacity to clear most, if not all, of the superficial and deep inflammatory lesions that are present at baseline or that occur during treatment, comedonal lesions also decrease in number or clear, but more slowly than inflammatory lesions in many cases.[9–15]

After completion of a course of oral isotretinoin for AV, there is continued improvement (especially with use of an optimal dose) followed by sustained periods of remission lasting over several months to at least 2 to 3 years and often longer in many patients.[5–7,10,11,16–24] This response pattern was noted with patients treated with both lower to intermediate daily doses (0.1mg/kg/day–0.5mg/kg/day) and higher daily doses (≥1mg/kg/day) of oral isotretinoin completed as initial treatment over a designated time period (usually 16–20 weeks).[9–24] However, relapse has been shown to be more common with the lower daily doses due to less cumulative drug exposure over time. Nevertheless, some patients receiving higher daily doses also relapsed usually within the first few years after completing therapy.[10,11,13–22] As the bioavailability of oral isotretinoin is highly variable and markedly increased by the presence of concomitant food ingestion, cumulative drug exposure over time, a factor correlated with prolonged duration of efficacy, may be significantly affected by the daily dose, duration of therapy, and co-ingestion with food, the latter being a factor that has received little attention to date.[9–25]

How does dose-response and duration of oral isotretinoin treatment correlate with optimal therapeutic outcomes in acne vulgaris?

It is interesting to note that the therapeutic response of nodular and recalcitrant AV to the initial course of oral isotretinoin by the end of a usual duration of 16 to 20 weeks is similar with a low daily dose (0.1mg/kg/day), an intermediate daily dose (0.5mg/kg/day), and a higher daily dose (≥1mg/kg/day).[5–7,9–11,13–23] However, it became readily apparent within a few years that if the designated duration of a course of therapy was 20 weeks, the rate of relapse requiring retreatment with oral isotretinoin was highest in those patients treated with 0.1mg/kg/day (42%), which was twofold higher than with 0.5mg/kg/day (20%) and fourfold higher than with 1mg/kg/day (10%).[11] Over the ensuing years, a large body of data has shown that prolonged substantivity of response to a course of oral isotretinoin, and importantly with the initial course, is dependent on achieving a cumulative dose of 120 to 150mg/kg, with >150mg/kg not shown to provide a better therapeutic response for AV.[12–24]

In the earlier days of isotretinoin use based on parameters noted by some dermatologists in the United States, a high daily dose of oral isotretinoin therapy (>1–2 mg/kg/day) was suggested for AV.[14–22] However, as some patients develop severe early flaring of AV with multiple deep inflammatory papules and nodules, and others experience a greater intolerability of dose-related side effects, such as xerophthalmia, xerosis, cheilitis, and myalgia, there is good consensus overall that the optimal initial daily dose of oral isotretinoin is 0.5mg/kg/day; the daily dose can be increased to 1mg/kg/day

in 4 to 8 weeks if no relevant adverse events emerge clinically or by laboratory monitoring.[12–24]

What does this cumulative total dose target for a course of oral isotretinoin translate to in the clinical setting? If a patient weighs 70kg, the cumulative total dose target of 120mg/kg for his or her course of therapy would be 8400mg (70kg x 120mg). Considering convenience and the practical consideration of capsule strengths, if the patient was started on 40mg daily (slightly more than 0.5mg/kg/day) for the first month, then increased to 60mg daily (slightly less than 1mg/kg/day) thereafter, it would take five months for the patient to reach the cumulative total dose of 8400mg based on the 120mg/kg target (1200mg [40mg x 30 days/month x 1 month] + 7200mg [60mg x 30 days/month x 4 months]). If the daily dose needs to be lowered due to side effects, the cumulative total dose target can be reached by lengthening the duration of therapy to what is needed to reach 120 to 150mg/kg.[12,16,18,21,22] These calculated durations of therapy based on the daily dose assume that the patient is fully adherent with medication use.

How does oral isotretinoin modify the course of acne vulgaris?

In order to identify reasons why some patients experience relapse of AV after use of oral isotretinoin and others do not, it would be helpful to know which modes of action of the drug are responsible for inducing sustained remission. Several potential mechanisms may be operative and possibly additive. The following may relate to the prolonged therapeutic benefit of oral isotretinoin in AV based on the various biological effects reported to be associated with isotretinoin.

Sebosuppression. Isotretinoin induces a dose-dependent decrease in the size and cross-sectional area of sebaceous glands; dose-dependent reduction in sebum production; sebocyte apoptosis; and histological changes, such as lobular collapse, follicular atrophy, and greater preponderance of undifferentiated acinar cells.[6,9,13] Augmented production of neutrophil gelatinase-associated lipocalin (NGAL) in the skin by isotretinoin has been correlated with human sebocyte apoptosis within sebaceous glands, which leads to decreased production of sebum.[26]

The clinical relevance of these effects on sebaceous glands are not fully understood; however, suppression of sebum is believed to be an important mode of action of oral isotretinoin in the treatment of AV. Oral isotretinoin is sebosuppressive with a marked dose-dependent reduction in sebum production and secretion during administration. After discontinuation of oral isotretinoin, a slowly progressive and sometimes variable time course of return of sebum production occurs, usually approaching 60 to 95 percent of pretreatment levels over approximately four months, depending on the dose.[9–13,15,16] When compared to three of its metabolites, isotretinoin exhibits the greatest sebosuppressive effect.[13]

In one trial evaluating oral isotretinoin administered for 16 weeks for AV at a low daily dose (0.1mg/kg/day), intermediate daily dose (0.5mg/kg/day), or high daily dose (1mg/kg/day), all doses produced a marked reduction of sebum excretion rate (SER), with the majority of the effect developing within the first four weeks.[10] At 16 weeks, the SER was reduced by 75, 89, and 91 percent with 0.1mg/kg/day, 0.5mg/kg/day, and 1mg/kg/day, respectively. Statistically significant differences in SER as compared to baseline values was noted in all three daily dosage groups ($P<0.0005$) and between the low and the higher daily dosage groups.[10] At 32 weeks, which was 16 weeks after completion of the designated course of oral isotretinoin, the SER returned to 95 percent of the pretreatment (baseline) level in the low dose group, while in the intermediate and high dose groups, the SER returned to 60 to 66 percent of the pretreatment level.[10] The sebosuppressive effects do not appear to fully explain the long-term remission of AV associated with oral isotretinoin use as sebum production returns to 60 to 95 percent of pretreatment levels within four months of completion of oral isotretinoin.[9,10,15]

Effects on inflammatory and immunological cells. Isotretinoin has been shown to reduce chemotaxis of polymorphonuclear leukocytes and monocytes.[13] It has also been shown to increase the levels of immunoglobulins M, G, and A and the number of helper T lymphocytes and B lymphocytes with positivity for surface immunoglobulins.[9] Whether or not these changes relate to prolonged remission after oral isotretinoin use is unknown.

More recently, isotretinoin has been shown to exert a durable effect on monocyte expression of Toll-like receptor-2 (TLR-2).[27] Monocytes from patients with AV expressed high levels of TLR-2, with markedly increased expression following stimulation by *Propionibacterium acnes*. Within one week, oral isotretinoin significantly decreased monocyte TLR-2 expression and subsequent pro-inflammatory cytokine response to *P. acnes* with

these inhibitory effects lasting over a period of six months after stopping oral isotretinoin. Isotretinoin appears to induce "immunologic memory" by potentially normalizing the innate immune response to *P. acnes*.[27] The modulation of TLR-2 expression may correlate with prolonged remission after discontinuation of therapy.

Microcomedo formation. Isotretinoin has also been shown to inhibit comedogenesis, likely by decreasing follicular hyperkeratinization. After six weeks of oral isotretinoin use, comedonal lipid composition changed from pretreatment with a 36-percent decrease, 34-percent increase, and 19-percent increase in glyceride fraction, free sterols, and total ceramides, respectively.[28] An 86-percent elevation of the free sterol/cholesterol ratio was observed. These isotretinoin-induced changes reflect a lipid ratio consistent with normal skin desquamation and appear to correlate with the reduction in comedogenesis and comedo reduction that occurs with isotretinoin therapy. However, it is hard to relate these changes that occur during administration of oral isotretinoin with prolonged remission after the drug is stopped.

What has been reported regarding relapse of acne vulgaris after completion of a course of oral isotretinoin?

Since its inception, some patients with facial and/or truncal AV treated with oral isotretinoin have experienced relapse, with multiple trials and data analyses evaluating the potential for relapse and associated risk factors (Table 1).[9–24] Importantly, relapse of AV at some time point after an initial course of oral isotretinoin may refer to a re-emergence of AV that ranges in severity, varies with regard to the predominant types of acne lesions present (i.e., comedonal vs. superficial inflammatory vs. nodular), and differs in the type of retreatment that is used (topicals only, topicals + oral antibiotic, second course of oral isotretinoin). Studies have reported a broad range of relapse rates of AV, with affected patients retreated with topical therapy alone (16–21%), topical therapy and oral antibiotics (3.3–27%), or at least one repeat course of oral isotretinoin (16–23%).[15–17,21]

In one report of patients followed over five years post-treatment after their initial course of isotretinoin, 22.7 percent required a repeated course of oral isotretinoin, with 17 percent treated with two courses, and five percent treated with three courses.[20] A database review from a large managed care practice demonstrated that 61 percent of patients with AV treated with oral isotretinoin needed retreatment for acne, with 22.9 percent requiring at least a second course of oral isotretinoin.[21] A nested case-control analysis evaluating a population-based cohort of first-time users of oral isotretinoin for AV (N=17,351) and age-matched controls (N=35,500) from 1984 to 2003 reported that 41 percent of subjects (n=7,100) experienced a relapse of AV, with 26 percent (n=4,443) requiring treatment with a second course of oral isotretinoin.[29]

Most of the published study analyses that address relapse after use of oral isotretinoin are based on controlled clinical trials and data captured directly from clinical researchers at academic dermatology centers, including treatment with 0.5 and 1.0mg/kg/day, with some studies evaluating lower (0.1–0.2mg/kg) or higher (>1–2mg/kg) daily doses.[5–11,16–24] In addition, durations of therapy and time course of clinical progress in individual patients have been assessed in many reports.[5,11,16–25] Extensive reviews of the data culminated from these multiple publications indicate that the daily dose (mg/kg/day), duration of the course of therapy, and total drug exposure expressed as cumulative dose (total mg/kg) all directly influence the risk of relapse of AV after an initial course of oral isotretinoin.[9–25]

In most cases of relapse of facial and/or truncal AV, a subset needed at least one additional course of oral isotretinoin, usually within 6 months to 2 to 3 years, but sometimes longer.[1,4,12–24] Given the same duration of a course of oral isotretinoin therapy, usually 16 to 20 weeks, a consistent relapse trend was noted across several studies, with a lower daily dose (0.1–0.2mg/kg/day) associated with a higher relapse rate as compared to higher daily doses (0.5mg/kg/day; 1mg/kg/day).[13,14,16,17,19–21,24] Although the relapse rate has been shown to be higher in patients treated with a lower daily dose, cases of relapse have also been reported in some patients treated with a higher daily dose over the same duration of therapy.[9–11–13–22]

How might concomitant ingestion of oral isotretinoin with food influence therapeutic outcomes, and is co-ingestion with food a clinically relevant concern?

Early studies with oral isotretinoin found that it was 1.5 to 2 times more bioavailable with food ingested one hour before, concomitantly with, or one hour after dosing than when given during a complete fast.[25]

To ensure more consistent gastrointestinal (GI) absorption and maintenance of therapeutic blood

TABLE 1. Studies evaluating relapse of acne vulgaris after an initial course of oral isotretinoin

Publication	N	Comparison (mg/kg/day)	Treatment length and follow up	Study results
Jones DH, King K, Miller AJ, Cunliffe WJ. *Br J Dermatol.* 1983;108(3):333–343	76	0.1mg/kg 0.5mg/kg 1.0mg/kg	16 weeks treatment 16-week follow up	1mg/kg dose had more treatment failures and relapses—45% vs. 27–33%
Strauss JS, Rapini RP, Shalita AR, et al. *J Am Acad Dermatol.* 1984;10(3):490–496	150	0.1mg/kg 0.5mg/kg 1.0mg/kg	20 weeks treatment 8- to 12-week follow up Patient questionnaire at 12–18 months	42% patients who received 0.1mg/kg/d required retreatment 20% patients who received 0.5mg/kg/d required retreatment 10% patients who received 1mg/kg/d required retreatment
Wokalek H, Hennes R, Schell, Vogt HJ. *Retinoid Therapy: A Review of Clinical and Laboratory Research.* Lancaster, England: MTP Press Limited; 1984:231–239	176	0.1mg/kg 0.5mg/kg 1.0mg/kg	12 weeks treatment 17-month follow up	First relapse in 1mg/kg/d group occurred 6 months after end of therapy All patients were in remission at 5 months 6 out of 26 patients had to restart acne treatment First relapse in 0.5mg/kg/d group occurred after 5 months First relapse in 0.1mg/kg/d group occurred after 2 months
Cunliffe WJ, Norris JFB. *Dermatologica.* 1987;175 (Suppl 1):133–137	250	0.5mg/kg 1.0mg/kg	4 months treatment 12- to 50-month follow up	Relapse rates: • 42% with 0.5mg/kg/d • 13% with 1mg/kg/d • $P<0.01$
Layton AM, Knaggs H, Taylor J, Cunliffe WJ. *Br J Dermatol.* 1993;129(3):292–296	88	0.5mg/kg 1.0mg/kg	16 weeks treatment 10-year follow up	39% relapsed and required oral antibiotics or further isotretinoin 82% patients who received <120mg/kg cumulative dose relapsed vs. 30% who were given a larger dose ($P<0.01$) Majority of patients relapsed within 3 years of isotretinoin therapy 78% patients relapsed within 18 months
Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. *Br J Dermatol.* 1993;129:297–301	299	0.1mg/kg 0.5mg/kg 1.0mg/kg	16 weeks treatment 5-year follow up	69% patients taking 0.1mg/kg/d isotretinoin who were followed relapsed 88% patients requiring more than 2 courses of isotretinoin were treated with 0.1mg/kg/d or 0.5mg/kg/d isotretinoin Only 9.5% patients needing >2 courses of isotretinoin were treated with 1mg/kg/d
White GM, Chen W, Yao J, Wolde-Tasadik G. *Arch Dermatol.* 1998;134:376–378	179	Examined total cumulative dose	20 weeks treatment 3-year follow up	34.6% patients had no recurrence 8% patients receiving <90mg/kg isotretinoin had no recurrence 40–50% patients receiving ≥110mg/kg isotretinoin had no recurrence Chance of recurrence is 8.2 times for patients taking a total dose of <100mg/kg vs. patients taking a total dose of ≥100mg/kg
Haryati I, Jacinto SS. *Int J Dermatol.* 2005;44(12):999–1001	193	Examined total cumulative dose	10-year follow up	17.5% patients relapsed and were treated with topical therapy 3.3% patients relapsed and were treated with oral antibiotic plus topical therapy 19.6% patients relapsed and were treated with a second course of isotretinoin Total dose taken by patients who required further therapy was 103.5mg/kg for 6.7 months and 118.55mg/kg for 7.41 months for patients who were cured after one course

concentrations, all conventional formulations of oral isotretinoin should be taken with food, preferably with a high-fat meal.[2,3,25] When taken without food, fasted isotretinoin plasma levels obtained from standard oral formulations can be nearly 60 percent lower than levels in the fed state.[25] Alarmingly, peak plasma concentrations between fed and fasted conditions can vary by a factor of nearly threefold, which may potentially affect both efficacy and safety.[25]

It is important to consider that many people, especially adolescents and young adults, exhibit inconsistent eating patterns, a factor that can introduce variability with GI absorption of oral isotretinoin after ingestion. According to the American Dietetic Association, the meal that young people skip most frequently is breakfast.[30,31] Among adolescents aged 14 to 18 years, 31.5 percent skipped breakfast.[32] Meal consumption does not seem to improve with age, as 25 percent of young adults aged 20 to 39 years continued to skip breakfast.[33] Skipping this meal is highly prevalent in both the United States and Europe, ranging from 10 to 30 percent, depending on definition, population, and age.[31–33] Nearly 1 in 3 girls aged 14 to 15 years in the United Kingdom reported having nothing to eat for breakfast.[34] A poll conducted by the Schools Health Education Unit in England found that 2 in 5 girls from this age group who went without breakfast also went without lunch.[35] In addition, many teenage girls perceive that they need to lose weight, regardless of whether they really need to lose weight or not and decide that skipping meals is the best approach to achieve their goals. Of the girls who did skip breakfast, 18 percent did so in an attempt to lose weight.[35]

Based on the pharmacokinetic profile of oral isotretinoin, it is a realistic clinical concern that the likelihood of prolonged remission after use of oral isotretinoin is compromised if optimal GI absorption is not achieved because the drug was not co-ingested with food. The Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies document published by the FDA and Center for Drug Evaluation and Research (CDER) suggests that meal studies to evaluate bioavailability and bioequivalence utilize a high-fat (50% of total caloric intake) and high-calorie (800–1000 calories) meal, with 150, 250, and 500 to 600 calories derived from protein, carbohydrate, and fat, respectively.[36] As such, it is recommended that oral isotretinoin be ingested with food, especially a meal high in fat content.[2,3] However, consistent daily ingestion of oral isotretinoin with a high-fat, high-calorie meal by all patients treated with this drug is not realistic. To add, as oral isotretinoin may be associated with elevated serum triglycerides in some patients, a reduction in dietary fat intake is often recommended.

As studies evaluating the correlation between cumulative drug exposure and duration of remission did not evaluate adherence, did not include measurements of plasma isotretinoin levels, and did not emphasize the importance of ingestion of oral isotretinoin with food, it is not possible to evaluate the influence of food ingestion on the outcomes from these studies. Therefore, even if a patient takes the proper daily dosage and duration of oral isotretinoin, the lack of co-ingestion with food, especially with high-fat food intake, will lower GI absorption and could adversely affect both efficacy and relapse.

Being able to take isotretinoin in the absence of a high-fat meal without an adverse effect on GI absorption of the drug could be beneficial to adolescents and young adults. Most patients who take isotretinoin for AV are over 14 years of age, with an average age of 22 years. Breakfast consumption during the teenage years is alarmingly inconsistent. In a survey of 1,001 high school students with a mean age of 16.1 years, 59 percent indicated that they skipped breakfast more than three times the previous week.[31] Based on a nationally representative sample from 1991, 30 percent of students aged 15 to 18 years skipped breakfast on any given day. Common reasons cited for skipping breakfast included lack of time, lack of hunger, or dieting to lose weight. Skipping breakfast was more prevalent in girls and in older children and adolescents.[31] Since isotretinoin requires consumption with food due to its pharmacokinetic properties, adolescent patients taking it without food would be receiving less than the optimal dose even if their prescription calls for a daily dose of 1mg/kg/day. In fact, it has been estimated that if all doses of isotretinoin were given during a complete fast, the dose would be effectively reduced by one-third to one-half compared with dosing in the presence of a meal.[25]

As many clinicians are aware, medications are often not taken as directed, with chronic disease conditions often associated with greater medication adherence problems. The Global Alliance to Improve Outcomes in Acne used a validated questionnaire to assess the risk of poor adherence in patients receiving treatment for AV from the Americas, Europe, and Asia and reported an overall adherence rate of

only 50 percent.[13] Of 707 patients using oral isotretinoin, 46 percent exhibited poor adherence. Although reasons for poor adherence were examined, they were not stratified according to the type of treatment for AV. Therefore, it is unknown if and to what extent food intake contributed to poor adherence. Patients may not be aware of the need to take oral isotretinoin with food, as many physicians tend to prescribe isotretinoin without specific instructions to take with food, and others may assume that administration instructions will come from the pharmacy. Unfortunately, pharmacists may not regularly apply "take with food" stickers to the medication bottle, compounding the problem. Physicians who do instruct patients to take isotretinoin with food may not communicate the importance of this requirement well, and others who do stress the importance may not follow up on this instruction in subsequent visits. Inevitably, there are patients who do know to take oral isotretinoin with food, but may forget the instruction over time, especially if it is not written on the bottle or they are not reminded at each prescription refill.

Conclusion

Given the various scenarios in oral isotretinoin prescribing patterns, medication dispensing and administration, and variable eating habits, especially in adolescents, it is easy to recognize that oral isotretinoin is likely to be taken without food on many occasions. If this is the case, then the cumulative dose that dermatologists strive to achieve to increase the long-term success of treatment may fall short and could explain relapses in patients thought to be receiving >120mg/kg of oral isotretinoin.

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QUESTIONS • CHALLENGES • CONTROVERSIES