doi:10.36849/JDD.7863

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy and Safety of Micronized Isotretinoin Administered Once Daily Without Food in Patients With Recalcitrant Nodular Acne

James Q. Del Rosso DO,[a] Leon Kircik MD[b]

[a]Touro University Nevada, Henderson, NV; JDR Dermatology Research, Las Vegas, NV; Advanced Dermatology and Cosmetic Surgery, Maitland, FL

[b]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY

ABSTRACT

Introduction: Micronized isotretinoin 0.4 to 0.8 mg/kg/day administered in 2 divided doses with or without meals is approved for the treatment of severe nodular acne in patients aged ≥12 years. Although practitioners may suggest once-daily dosing to increase patient compliance, supporting data are limited.

Methods: In this pilot study, patients aged ≥12 years with severe nodular acne (Investigator's Global Assessment [IGA] ≥4 and >5 facial nodules) received once-daily micronized isotretinoin 0.4 to 0.8 mg/kg/day without food for 20 weeks. The coprimary efficacy endpoints were changes from baseline in nodular lesion count (NLC) and percentage of patients with a ≥90% reduction in NLC at week 24. Secondary endpoints included percentage of patients achieving IGA 0/1; reductions in inflammatory lesion count (ILC) and noninflammatory lesion count (NILC); adverse events (AEs); and severity of erythema, dryness, peeling, oiliness, burning, and pruritus. Analyses included all enrolled patients with the last observation carried forward.

Results: Twenty-two of 24 patients completed the study. From baseline to week 24, NLC decreased by a median (quartile [Q]1, Q3) of 6 (5, 7), all patients experienced complete clearance of nodules, 23/24 (96%) patients achieved IGA 0/1, and ILC and NILC decreased by a mean ± standard deviation of 97.8% ± 5.7% and 98.4% ± 6.2%, respectively (all $P<0.0001$). There were small, significant, early increases in the severity of erythema, dryness, and peeling; 2 patients experienced 3 AEs considered unrelated to treatment.

Conclusions: Once-daily micronized isotretinoin administered without food was efficacious and well tolerated in patients with severe nodular acne.

J Drugs Dermatol. 2024;23(6):423-428. doi:10.36849/JDD.7863

INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory skin condition that affects a majority of adolescents and young adults[1,2] and is associated with many adverse physical and psychological effects on quality of life.[1,3] Oral isotretinoin (13-cis-retinoic acid) can induce complete or near-complete resolution of AV in most patients, with prolonged clearance after completion of therapy; it is considered to be the most effective treatment for severe nodular AV and is the only therapy shown to consistently provide long-term AV clearance after completion of a recommended course of therapy.[1,4] Due to its poor aqueous solubility, isotretinoin has historically required ingestion with food—specifically a high-fat meal with each dose—to ensure optimal absorption and consistent plasma concentrations of isotretinoin.[5,6] This makes patient adherence a concern, particularly in adolescents and young adults, who often exhibit inconsistent eating patterns such as skipping breakfast,[7-9] and who are most often the recipients of treatment for AV. Failure to adhere to recommendations to ingest each dose of isotretinoin with an adequate high-fat meal to promote drug absorption may result in lower cumulative exposure to isotretinoin over a course of therapy, which may adversely impact the likelihood of long-term remission.[1,10]

A formulation containing micronized isotretinoin diffused in a lipid carrier system is approved for the treatment of severe recalcitrant nodular AV in nonpregnant patients 12 years of age and older with multiple inflammatory nodules.[11,12] Micronization, together with solubilization of isotretinoin in a lipid matrix, significantly improves the bioavailability and absorption of oral isotretinoin, thereby eliminating the dependence on high-fat, high-calorie food intake and allowing for administration without regard to meals with a lower administered dose compared with conventional isotretinoin formulations.[11,12] The dosage of micronized isotretinoin as stated in the approved product labeling is 0.4 to 0.8 mg/kg/day

given in 2 divided doses with or without meals.[11] Although practitioners may suggest once-daily dosing of oral isotretinoin in the hope of increasing patient compliance, only limited data support the efficacy and safety of once-daily treatment with isotretinoin.[13-15] However, the improved bioavailability and lower required weight-based daily dose of micronized isotretinoin, including when administered without food, may make it amenable to once-daily dosing. The purpose of this study was to evaluate the efficacy and safety of once-daily micronized isotretinoin administered without food for the treatment of severe recalcitrant nodular AV.

MATERIALS AND METHODS

Study Design, Patients, and Treatments

This open-label pilot study conducted at 2 centers evaluated the efficacy and safety of once-daily administration of micronized isotretinoin in patients 12 years of age and older with recalcitrant nodular AV. The study was conducted between July 29, 2021, and October 17, 2022. To be eligible, patients had to have an Investigator's Global Assessment (IGA) score ≥4 and more than 5 facial nodules with a diameter ≥5 mm. Patients with uncontrolled psychiatric disorders, current or previous pancreatitis, uncontrolled lipid abnormalities, hearing abnormalities, hepatotoxicity, uncontrolled inflammatory bowel disease, musculoskeletal abnormalities, or ocular abnormalities were excluded from the study, as were those taking high doses of vitamin A or tetracycline class antibiotics. All patients had to follow iPLEDGE® requirements and provide written informed consent to participate in the study. The study was conducted in accordance with the principles described in the Declaration of Helsinki, the current Good Clinical Practice guidelines, and all local legal and regulatory requirements. Institutional Review Board approval was obtained for the study protocol and the informed consent form. All enrolled patients received 0.4 to 0.8 mg/kg/day of micronized isotretinoin according to the recommended daily dosage in the Prescribing Information, to be taken once daily without food for 20 weeks. Patients were instructed to take the medication with a full glass of water or other simple liquid (eg, juice) to facilitate easy passage into the stomach and reduce the risk of physical esophageal irritation.

Assessments

All coprimary and secondary efficacy assessments were performed at baseline, week 4, week 8, and every 4 weeks thereafter through week 24. Efficacy was evaluated by assessing lesion counts (nodules, inflammatory lesions, and noninflammatory lesions) and IGA score graded on a scale from 0 (clear) to 5 (very severe). All efficacy evaluations were performed by the investigator at each study visit; only lesions on the face were included in the assessments.

Safety endpoints included monitoring of adverse events (AEs), tolerability assessments, vital signs, and laboratory abnormalities, which were recorded at each study visit through week 24 except for laboratory assessments performed at screening, which were not repeated at baseline. An AE was defined as any pathological change in body structure, function, or chemistry occurring or worsening during the study. The severities of erythema, dryness, peeling, and oiliness were graded by the investigator on a 5-point scale from 0 (absent) to 4 (severe) at each study visit. The investigator interviewed the patient to determine the severity of pruritus and burning compared with the previous study visit, which was graded on a 6-point scale from 0 (absent) to 5 (severe).

Efficacy and Safety Endpoints

The coprimary efficacy endpoints were changes from baseline in total facial nodular lesion count (NLC) and the percentage of patients with a ≥90% reduction in NLC at the end of the study (week 24). Secondary efficacy endpoints included the percentage of patients achieving an IGA score of clear or almost clear (IGA 0/1) and mean percentage reductions in inflammatory lesion count (ILC; papules and pustules) and noninflammatory lesion count (NILC; open and closed comedones) at week 24. Safety and tolerability were assessed from frequencies of AEs and serious AEs and severity of erythema, dryness, peeling, oiliness, burning, and pruritus.

Statistical Analyses

No formal sample size calculations were performed due to the exploratory nature of this pilot study. Changes in lesion counts, IGA, and tolerability assessments from baseline were analyzed with Wilcoxon rank sum tests performed using R v.4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-sided, and $P<0.05$ was accepted as significant with no adjustment for multiple comparisons. Statistical analyses included all enrolled patients. Missing data were imputed by the last observation carried forward.

RESULTS

Patient Demographics and Baseline Characteristics

This study enrolled a total of 24 patients, 2 of whom were lost to follow-up; all 22 patients remaining completed the study. The majority of patients (14/24 [58%]) were male, the mean ± standard deviation (SD) age was 20 ± 6 years, and 20/24 (83%) patients were White (Table 1). At the baseline assessment, the median (quartile [Q]1, Q3) NLC was 6 (5, 7), and 20/24 (83%) patients had an IGA score of very severe (Table 1).

Efficacy of Once-Daily Micronized Isotretinoin

All coprimary and secondary efficacy endpoints were met. From baseline to week 24, the median (Q1, Q3) NLC decreased from 6 (5, 7) to 0, and the median (%) decrease from baseline was 6 (100%; $P<0.0001$; Figure 1). Therefore, all 24 (100%) patients experienced complete clearance of nodules ($P<0.0001$). Almost all (23/24 [96%]) patients achieved IGA 0/1 at week 24 ($P<0.0001$),

TABLE 1.

Baseline Demographics and Clinical Characteristics	
Characteristics	**Micronized Isotretinoin (N = 24)**
Age, years	
Mean ± SD	20 ± 6
Range, min–max	14–36
Sex, n (%)	
Male	14 (58)
Female	10 (42)
Race and ethnicity, n (%)	
White	20 (83)
Hispanic/Latino	2 (8)
Asian	2 (8)
Baseline values	
ILC, mean ± SD	31.8 ± 15.9
NILC, mean ± SD	29.2 ± 13.8
NLC, median (Q1, Q3)	6 (5, 7)
IGA score, n (%)	--
Clear	0
Almost clear	0
Mild	0
Moderate	0
Severe	4 (17)
Very severe	20 (83)

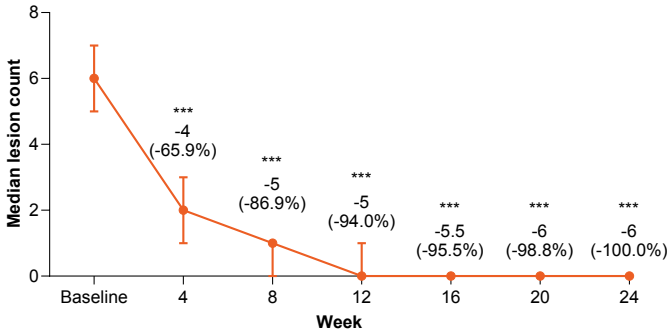
IGA, Investigator's Global Assessment; ILC, inflammatory lesion count; max, maximum; min, minimum; NILC, noninflammatory lesion count; NLC, nodular lesion count; Q, quartile; SD, standard deviation.

with significant improvements from baseline observed at each study visit (Figure 2A). There were also significant reductions from baseline in both ILC and NILC at each visit (Figure 2B). The mean ± SD percentage reductions in lesion counts at week 24 were 97.8% ± 5.7% for ILC and 98.4% ± 6.2% for NILC (both $P<0.0001$).

Tolerability and Safety

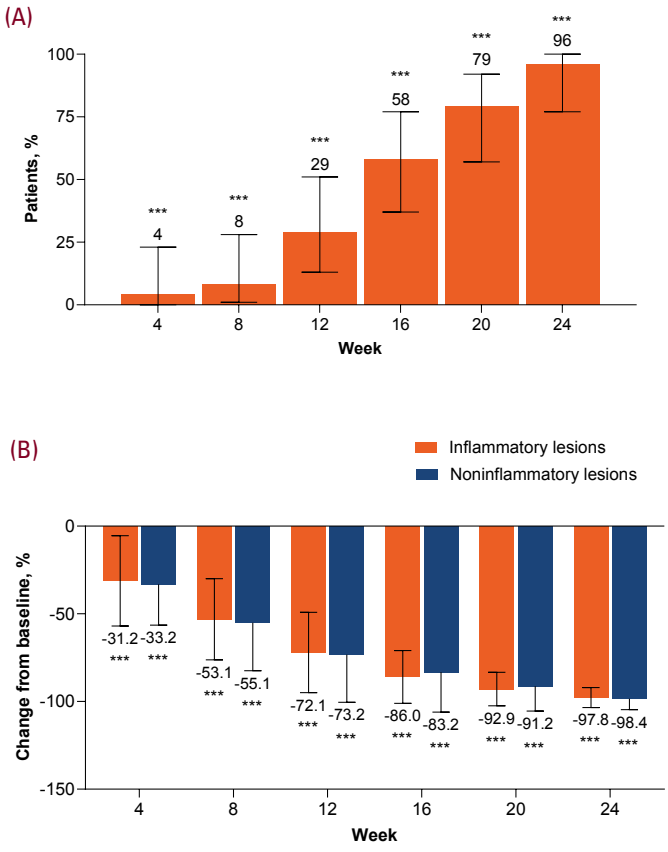
There were small but statistically significant increases from baseline in the severity of erythema, dryness, and peeling at early time points; these were largest at weeks 4 and 8 and generally decreased thereafter (Table 2). Small but statistically significant decreases from baseline in oiliness were noted at weeks 4 and 20 ($P<0.05$; Table 2). There were no significant changes from baseline at any time point in burning or pruritus, both of which were absent or minimal in most patients. A total of 3 AEs were reported in 2 patients during the study, including COVID-19 in 2 patients and pneumonia in 1 patient, none of which was serious or considered related to treatment.

FIGURE 1. Median nodular lesion count through week 24.



Error bars represent the IQR (Q1, Q3). Data labels show the median (%) change from baseline. ***$P<0.001$.
IQR, interquartile range; Q, quartile.

FIGURE 2. (A) Percentage of patients achieving IGA 0/1 and (B) percentage reductions from baseline in inflammatory lesion count and noninflammatory lesion count through week 24.



Error bars in (A) represent the 95% CI; error bars in (B) represent the SD. ***$P<0.001$.
CI, confidence interval; IGA, Investigator's Global Assessment; SD, standard deviation.

TABLE 2.

Summary of Tolerability Assessments Through Week 24							
Measure	**Baseline**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Erythema							
Absent or trace	21 (88)	15 (63)	12 (50)	17 (71)	15 (63)	20 (83)	22 (92)
Mild	2 (8)	7 (29)	9 (38)	4 (17)	9 (38)	3 (13)	2 (8)
Moderate	1 (4)	2 (8)	3 (13)	3 (13)	0	1 (4)	0
P-value	--	**0.0330**	**0.0071**	**0.0330**	0.0593	0.6745	0.1439
Dryness[a]							
Absent or trace	24 (100)	19 (79)	14 (58)	20 (83)	18 (75)	22 (92)	23 (96)
Mild	0	3 (13)	10 (42)	3 (13)	6 (25)	2 (8)	1 (4)
Moderate	0	1 (4)	0	1 (4)	0	0	0
P-value	--	**0.0003**	**0.0001**	**0.0197**	**0.0197**	0.3075	0.5877
Peeling							
Absent or trace	24 (100)	20 (83)	21 (88)	22 (92)	24 (100)	24 (100)	24 (100)
Mild	0	3 (13)	3 (13)	1 (4)	0	0	0
Moderate	0	1 (4)	0	1 (4)	0	0	0
P-value	--	**0.0021**	**0.0232**	0.1236	0.0915	0.7656	0.7656
Oiliness							
Absent or trace	22 (92)	24 (100)	24 (100)	23 (96)	24 (100)	24 (100)	23 (96)
Mild	2 (8)	0	0	1 (4)	0	0	1 (4)
Moderate	0	0	0	0	0	0	0
P-value	--	**0.0083**	0.0658	0.1790	0.0777	**0.0248**	0.0646

Data are presented as n (%). Bold text indicates $P<0.05$.
[a]Data for dryness were incomplete for 1 patient at week 4.

TABLE 3.

Food and Drug Administration–Approved Formulations of Oral Isotretinoin		
Formulation	**Original Approval Date**	**Clinical Relevance**
Conventional (original) isotretinoin[a]	1982	Optimal absorption requires ingestion with a high-fat, high-calorie meal[6,20]
Lidose-isotretinoin[b]	2012	Gastrointestinal absorption of isotretinoin is twice as high vs conventional isotretinoin when taken without food[6]
Micronized isotretinoin[c]	2019	Approximately 2-fold increase in bioavailability with a 20% lower dose compared with lidose-isotretinoin when taken without food[12]

[a]Refers to Accutane™ (Roche Pharmaceuticals) and its branded generic formulations, Myorisan® (Akorn Operating Company, LLC), Zenatane™ (Dr. Reddy's Laboratories, Ltd.), Claravis™ (Teva Pharmaceuticals USA, Inc.), and Amnesteem® (Mylan Pharmaceuticals, Inc.).
[b]Refers to ABSORICA® (Sun Pharmaceutical Industries, Inc.); generic formulation available.
[c]Refers to ABSORICA LD™ (Sun Pharmaceutical Industries, Inc.).

DISCUSSION

The results of this pilot study support the efficacy and safety of once-daily micronized isotretinoin administered for 20 weeks without food for the treatment of patients with recalcitrant nodular AV. The coprimary and secondary efficacy endpoints were all met; and there were significant improvements at each study visit in both IGA score and lesion counts (nodule, inflammatory, and noninflammatory). By the end of the study, all patients exhibited complete clearance of nodules, and nearly all patients had clear or almost-clear skin, with substantial decreases from baseline in ILC and NILC. AEs were reported in only 2/24 (8%) patients, and none was considered related to treatment. Once-daily micronized isotretinoin was well tolerated, with only small increases in the severity of erythema, dryness, and peeling at early time points and no changes in burning or pruritus. Thus, once-daily micronized isotretinoin warrants further consideration as an efficacious and practical approach to the treatment of severe recalcitrant nodular AV.

Only a handful of prior studies have evaluated the efficacy and safety of once-daily oral isotretinoin in patients with AV, especially without concomitant ingestion of food. In a study of

58 patients, conventional isotretinoin was similarly efficacious when given either once daily or twice daily, with no significant differences between the 2 regimens.[13] However, side effects were more commonly observed in patients receiving once-daily vs twice-daily dosing.[13] In a randomized study of 600 patients with severe recalcitrant nodular AV, the efficacy of a once-daily micronized formulation of isotretinoin 0.4 mg/kg/day was comparable with that of conventional isotretinoin 1.0 mg/kg/day given twice daily.[14] In a follow-up safety study that included 600 patients, the once-daily micronized formulation was associated with fewer mucocutaneous AEs vs conventional isotretinoin.[15]

There are 3 distinct formulations of isotretinoin currently approved by the US Food and Drug Administration (FDA) that exhibit unique pharmacokinetic profiles and are therefore not directly substitutable for one another (Table 3).[5,11] Micronized isotretinoin received US FDA approval based on a comparative pharmacokinetic study that demonstrated that micronized isotretinoin 32 mg is bioequivalent under fed conditions and has approximately 2-fold higher bioavailability under fasted conditions relative to lidose-isotretinoin 40 mg (the approved non-micronized lipid matrix formulation).[12,16] Importantly, the non-micronized lidose formulation of isotretinoin exhibited 2 times greater gastrointestinal absorption compared with conventional isotretinoin (ie, original brand and branded generics) when both were administered without food,[6] further highlighting the optimization of bioavailability provided by micronized isotretinoin when given without food.

Higher dosing frequency and/or treatment regimen complexity are associated with lower adherence to treatment[17,18]; for example, treatment compliance was substantially higher in patients receiving antihypertensive medication who were on a once-daily regimen vs those on a thrice-daily regimen.[17] In a systematic review that included 54 studies, patients with more complex regimens—most often evaluated using a complexity index or based on the number of medications, self-perceived complexity, or dose frequency—were less likely to adhere to pharmacotherapy in a majority of studies.[18] The improved bioavailability, lower required daily dose, and lack of dietary requirements with micronized isotretinoin provide more dosing flexibility, and this formulation therefore exhibits greater potential to improve treatment adherence.[19] The findings of this pilot study support future investigation of the efficacy and safety of once-daily micronized isotretinoin as an effective and practical treatment regimen in patients with severe recalcitrant nodular AV. In addition, the lack of dependence on the administration of each dose with a high-fat meal removes the need for the clinician and their staff to educate the patient on specific dietary requirements when taking isotretinoin, which saves time during office visits.

CONCLUSION

Once-daily micronized isotretinoin administered without food for 20 weeks is highly efficacious and well tolerated in patients with severe recalcitrant nodular AV, with no serious AEs reported. Once-daily micronized isotretinoin administered without food provides a more convenient dosing regimen and is thereby likely to increase patient adherence to AV treatment and ultimately improve therapeutic outcomes.

DISCLOSURES

LK has served as an investigator, speaker, advisory board member, or consultant for 3M, Abbott, Aclaris Therapeutics, Allergan, Amgen, Anacor Pharmaceuticals, Assos Pharmaceuticals, Astellas Pharma US, Asubio Pharma, Bayer Healthcare Pharmaceuticals, Berlex Laboratories (Bayer Healthcare Pharmaceuticals), Biogen, BioLife, Biopelle, Blue Willow Biologics, Boehringer Ingelheim, Breckenridge Pharmaceutical, Celgene Corporation, Centocor, ColBar LifeScience, CollaGenex Pharmaceuticals, Combimatrix Molecular Diagnostics, Connetics Corporation, Coria Laboratories, Dermik Laboratories, Dermira, Dow Pharmaceutical Sciences, DUSA Pharmaceuticals, Eli Lilly, Embil Pharmaceutical, EOS Pharmaceutical, Ferndale Pharma Group, Galderma Laboratories, Genentech, GlaxoSmithKline, Healthpoint, Idera Pharmaceuticals, Innocutis Medical, Innovail, Johnson & Johnson, Laboratory Skin Care, LEO Pharma, L'Oréal, Maruho, Medical International Technologies, Medicis Pharmaceutical, Merck, Merz Pharma, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals, Obagi Medical Products, Ortho Neutrogena, Pediapharma, Pfizer, PharmaDerm, Promius Pharma, PuraCap Pharmaceutical, QLT, Quatrix, Quinnova Pharmaceuticals, Serono (Merck-Serono International), SkinMedica, Stiefel Laboratories, Sun Pharma, Taro Pharmaceutical Industries, TolerRx, Triax Pharmaceuticals, UCB, Valeant Pharmaceuticals North America, Warner Chilcott, XenoPort, and ZAGE. JDR has served as a research investigator, consultant, and/or speaker for Allergan, Almirall, Amgen (Celgene), Arcutis, Bayer Pharmaceuticals, Bausch Health (Ortho Dermatologics), Beiersdorf, Biorasi, Bristol-Myers Squibb, Cassiopea, Cutera, Dermavant Sciences, Dr Reddy, Eli Lilly, EPI Health, Evommune, Ferndale, Galderma, JEM Health, Johnson & Johnson, Journey, LEO Pharma, L'Oréal, Mayne Pharma, Novan, Sebacia, Sol-Gel, Sun Pharma, Strata, and Vyne.

ACKNOWLEDGMENT

Research funding for the investigator-initiated study was provided by Sun Pharma. Manuscript development and editorial support were provided by Dana Lengel PhD, of AlphaBioCom, a Red Nucleus company, and funded by Sun Pharma.

REFERENCES

1. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945-973.e933.
2. Heng AHS, Chew FT. Systematic review of the epidemiology of acne vulgaris. *Sci Rep*. 2020;10(1):5754.
3. Almutawa YM, Bhattarai E, AlGhareeb M, et al. Evaluation of psychiatric comorbidities and quality of life as well as brain-derived neurotrophic factor (BDNF) concentrations among patients suffering from acne vulgaris: a systematic review and meta-analysis. *Cureus*. 2023;15(1):e33357.
4. Leyden JJ, Del Rosso JQ, Baum EW. The use of isotretinoin in the treatment of acne vulgaris: clinical considerations and future directions. *J Clin Aesthet Dermatol*. 2014;7(suppl 2):S3-S21.
5. Accutane™ (isotretinoin capsules). Prescribing Information. Nutley, NJ: Roche Laboratories Inc.; 2008.
6. Webster GF, Leyden JJ, Gross JA. Comparative pharmacokinetic profiles of a novel isotretinoin formulation (isotretinoin-lidose) and the innovator isotretinoin formulation: a randomized, 4-treatment, crossover study. *J Am Acad Dermatol*. 2013;69(5):762-767.
7. Deshmukh-Taskar PR, Radcliffe JD, Liu Y, et al. Do breakfast skipping and breakfast type affect energy intake, nutrient intake, nutrient adequacy, and diet quality in young adults? NHANES 1999-2002. *J Am Coll Nutr*. 2010;29(4):407-418.
8. Deshmukh-Taskar PR, Nicklas TA, O'Neil CE, et al. The relationship of breakfast skipping and type of breakfast consumption with nutrient intake and weight status in children and adolescents: the National Health and Nutrition Examination Survey 1999-2006. *J Am Diet Assoc*. 2010;110(6):869-878.
9. Sincovich A, Moller H, Smithers L, et al. Prevalence of breakfast skipping among children and adolescents: a cross-sectional population level study. *BMC Pediatr*. 2022;22(1):220.
10. Del Rosso JQ, Stein Gold L, Segal J, et al. An open-label, phase IV study evaluating lidose-isotretinoin administered without food in patients with severe recalcitrant nodular acne: low relapse rates observed over the 104-week post-treatment period. *J Clin Aesthet Dermatol*. 2019;12(11):13-18.
11. ABSORICA® (isotretinoin) capsules/ABSORICA LD™ (isotretinoin) capsules. Prescribing Information. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2020.
12. Madan S, Kumar S, Segal J. Comparative pharmacokinetic profiles of a novel low-dose micronized-isotretinoin 32 mg formulation and lidose-isotretinoin 40 mg in fed and fasted conditions: two open-label, randomized, crossover studies in healthy adult participants. *Acta Derm Venereol*. 2020;100(4):adv00049.
13. Ahmad HM. Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. *Dermatol Ther*. 2015;28(3):151-157.
14. Strauss JS, Leyden JJ, Lucky AW, et al. A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. *J Am Acad Dermatol*. 2001;45(2):187-195.
15. Strauss JS, Leyden JJ, Lucky AW, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: a randomized trial comparing micronized isotretinoin with standard isotretinoin. *J Am Acad Dermatol*. 2001;45(2):196-207.
16. US Food and Drug Administration, Center for Drug Evaluation and Research. New drug application multi-disciplinary review and evaluation for Absorica LD (isotretinoin capsules) for treatment of recalcitrant nodular acne. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211913Orig1s000MultidisciplineR.pdf. Accessed April 11, 2023.
17. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med*. 1990;150(9):1881-1884.
18. Pantuzza LL, Ceccato M, Silveira MR, et al. Association between medication regimen complexity and pharmacotherapy adherence: a systematic review. *Eur J Clin Pharmacol*. 2017;73(11):1475-1489.
19. Marson JW, Baldwin HE. Isotretinoin update. *Dermatol Rev*. 2021;2:331-342.
20. Del Rosso JQ. Face to face with oral isotretinoin: a closer look at the spectrum of therapeutic outcomes and why some patients need repeated courses. *J Clin Aesthet Dermatol*. 2012;5(11):17-24.

AUTHOR CORRESPONDENCE

James Q. Del Rosso
E-mail:..... jqdelrosso@yahoo.com