ACNE & ROSACEA SYMPOSIUM

SBS ~ February 8, 2020 ~ 9:15am

Controversies in Oral Therapy for Acne

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Disclosures

ACLARIS*^#
ALMIRALL*^#
ANAPTYS BIO*
ATHENEX*
BIOFRONTERA^#
BIOPHARMX*^
BOTANIX*
CARA THERAPEUTICS*
CELGENE*^#
DERMIRA*^
ENCORE^#
EPI HEALTH*^#
FERNDALE^#
FOAMIX*^
GALDERMA*^#
GENENTECH*#

INCYTE*
LEO PHARMA*^#
LA ROCHE POSAY^
MC2^
MENLO THERAPEUTICS*^
NOVAN*^
ORTHO DERMATOLOGY*^#
PFIZER^#
RALEXAR*
REGENERON*^#
SANOFI-GENZYME^#
SKINFIX^
SOLGEL*^
SONOMA (INTRADERM)^
SUN PHARMA*^#
VERRICA^

* Research Investigator
^ Consultant/Advisor
# Speaker

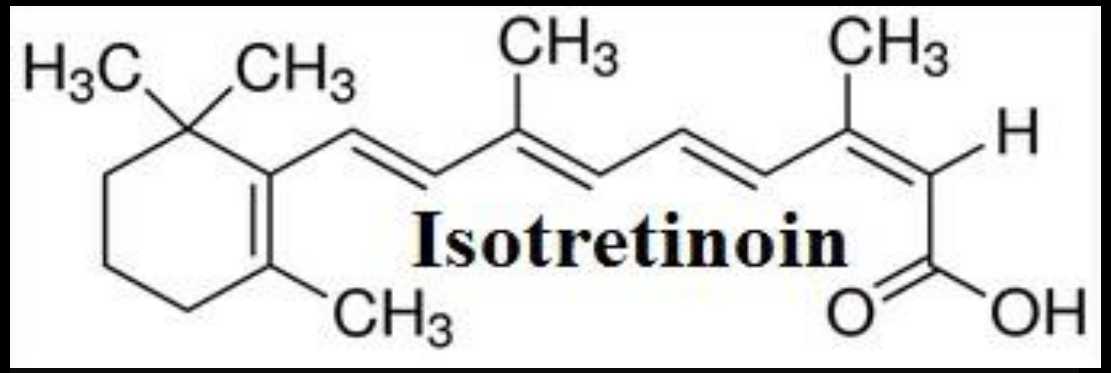
UPDATED 01-23-2020

CONTROVERSY

- **Controversy** is a state of prolonged public dispute or debate, usually concerning a matter of opinion. The word was coined from the Latin *controversia*, as a composite of *controversus* – "turned in an opposite direction," from *contra* – "against" – and *vertere* – to turn, or *versus* (see verse), hence, "to turn against."

Controversies in Oral Therapy for Acne

MAJOR CONTROVERSY RELATES TO
ANTIBIOTIC RESISTANCE CONCERNS
→ MICROBIOME CHANGES



MAJOR CONTROVERSIES
RELATE TO
SAFETY CONSIDERATIONS?
WHO IS A CANDIDATE FOR THERAPY?
DOSING REGIMEN?
POTENTIAL FOR RELAPSE?

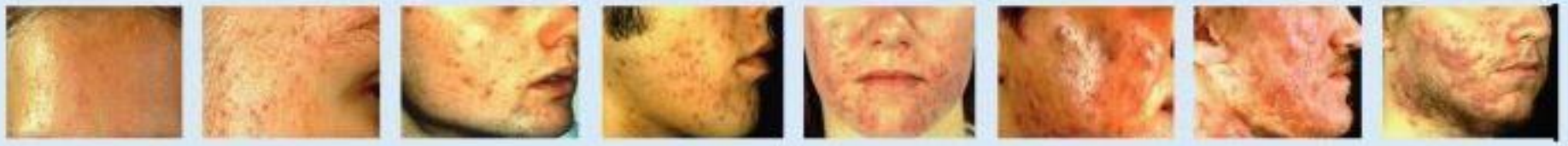
MAJOR CONTROVERSY RELATES TO LABORATORY MONITORING

Therapeutic Options for Moderate to Severe Acne

Therapy	Notes
Combination therapy	Oral antibiotics + topical retinoids ± BPO First line
Hormonal therapy	Women with moderate to severe acne, especially if contraception is desirable Used in combination with other modalities
Isotretinoin	Severe and/or recalcitrant acne Teratogenic; stringently regulated for women with childbearing potential

Gollnick H et al. *J Am Acad Dermatol*. 2003;49(1 suppl):S1-S37.

Acne treatment algorithm



	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular†	Nodular/conglobate
First choice‡	Topical retinoid	Topical retinoid + topical antimicrobial	Oral antibiotic + topical retinoid +/- BPO	Oral antibiotic + topical retinoid +/- BPO	Oral isotretinoin§
Alternatives‡	Azelaic acid or salicylic acid	Alt. topical antimicrobial agent + alt. topical retinoid or azelaic acid¶	Alt. oral antibiotic + alt. topical retinoid +/- BPO	Oral isotretinoin or alt. oral antibiotic + alt. topical retinoid +/- BPA/azelaic acid¶	High-dose oral antibiotic + topical retinoid + BPO
Alternatives for females‡,#	See first choice	See first choice	Oral anti-androgen†† + topical retinoid/ azelaic acid¶ +/- BPO	Oral antiandrogen†† + topical retinoid +/- oral antibiotic +/- alt. antimicrobial	High-dose oral anti-androgen†† + topical retinoid +/- alt. topical antimicrobial
Maintenance therapy	Topical retinoid		Topical retinoid +/- BPO		

Status Report from the Scientific Panel on Antibiotic Use in Dermatology of the American Acne and Rosacea Society

Part 1: Antibiotic Prescribing Patterns, Sources of Antibiotic Exposure, Antibiotic Consumption and Emergence of Antibiotic Resistance, Impact of Alterations in Antibiotic Prescribing, and Clinical Sequelae of Antibiotic Use

[a]JAMES Q. DEL ROSSO, DO; [b]GUY F. WEBSTER, MD; [c]TED ROSEN, MD; [d]DIANE THIBOUTOT, MD; [e]JAMES J. LEYDEN, MD; [f]RICHARD GALLO, MD, PhD; [g]CLAY WALKER, PhD; [h]GEORGE ZHANEL, PhD; [i]LAWRENCE EICHENFIELD, MD

[a]Dermatology Adjunct Faculty, Touro University Nevada, Henderson, Nevada; [b]Department of Dermatology, Jefferson Medical College, Philadelphia, Pennsylvania; [c]Department of Dermatology, Baylor College of Medicine, Houston, Texas; [d]Department of Dermatology, Penn State University, Hershey, Pennsylvania; [e]Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania; [f]Department of Dermatology, University of California San Diego, San Diego, California; [g]University of Florida Dental School, Gainesville, Florida; [h]Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Canada; [i]Department of Dermatology (Pediatrics), University of California San Diego, San Diego, California

ABSTRACT

Oral and topical antibiotics are commonly prescribed in dermatologic practice, often for noninfectious disorders, such as acne vulgaris and rosacea. Concerns related to antibiotic exposure from both medical and nonmedical sources require that clinicians consider in each case why and how antibiotics are being used and to make appropriate adjustments to limit antibiotic exposure whenever possible. This first article of a three-part series discusses prescribing patterns in dermatology, provides an overview of sources of antibiotic exposure, reviews the relative correlations between the magnitude of antibiotic consumption and emergence of antibiotic resistance patterns, evaluates the impact of alterations in antibiotic prescribing, and discusses the potential relevance and clinical sequelae of antibiotic use, with emphasis on how antibiotics are used in dermatology. (*J Clin Aesthet Dermatol.* 2016;9(4):18–24.)

J Am Acad Dermatol. 2014 Jul;71(1):70-6. doi: 10.1016/j.jaad.2014.02.031. Epub 2014 Apr 13.

A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: investigating practice gaps and potential cost-savings.

Lee YH[1], Liu G[2], Thiboutot DM[3], Leslie DL[2], Kirby JS[3].

Author information

1 Department of Dermatology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania. Electronic address: ylee1@hmc.psu.edu.
2 Division of Health Services Research, Department of Public Health Sciences, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania.
3 Department of Dermatology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania.

Abstract

BACKGROUND: Duration of oral antibiotic therapy in acne has not been widely studied. Recent guidelines suggest it should be limited to 3 to 6 months.

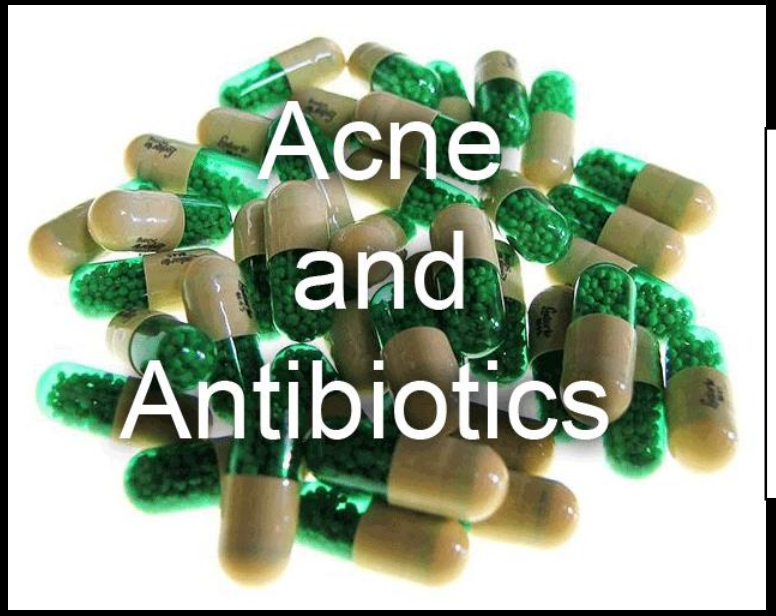
OBJECTIVE: We sought to compare the duration of oral antibiotic use with recent guidelines and determine the potential cost-savings related to shortened durations.

METHODS: This is a retrospective cohort study from the MarketScan Commercial Claims and Encounters database. Claims data were used to determine duration and costs of antibiotic therapy.

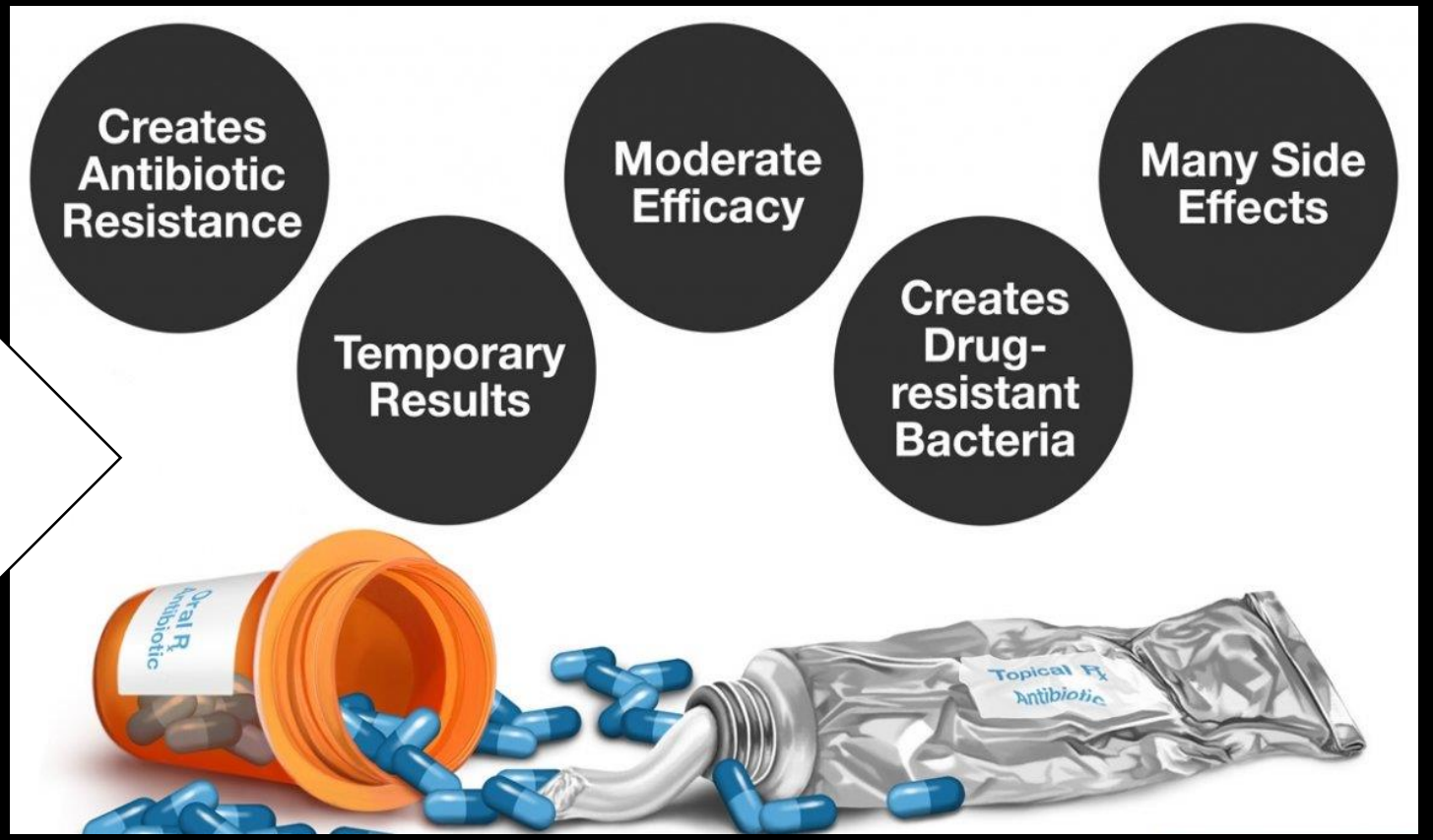
RESULTS: The mean course duration was 129 days. The majority (93%) of courses were less than 9 months. Among the 31,634 courses, 18,280 (57.8%) did not include concomitant topical retinoid therapy. The mean (95% confidence interval) duration with and without topical retinoid use was 133 (131.5-134.7) days and 127 (125.4-127.9) days, respectively. The mean excess direct cost of antibiotic treatment for longer than 6 months was $580.99/person.

LIMITATIONS: Claims cannot be attributed to a specific diagnosis or provider. The database does not provide information on acne severity.

CONCLUSIONS: Duration of antibiotic use is decreasing when compared with previous data. However, 5547 (17.53%) courses exceeded 6 months, highlighting an opportunity for reduced antibiotic use. If courses greater than 6 months were shortened to 6 months, savings would be $580.99/person.



ARGUMENTS AGAINST THEIR USE

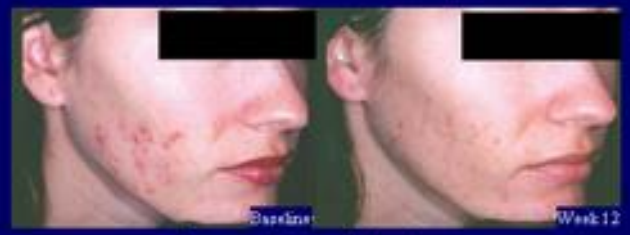


INCREASE IN ANTIBIOTIC-RESISTANT *CORYNEBACTERIUM ACNES* STRAINS

INCREASE IN ANTIBIOTIC-RESISTANT COMMENSAL AND OPPORTUNISTIC BACTERIA

Clinical Expectations: Combination Therapy With an Oral Antibiotic

- Aggressive initial therapy
  - Resolves lesions
  - Prevents scarring
- Inflammatory acne often resolves within 1 to 3 months
- Then move to less aggressive regimen



Doxycycline + Adapalene
Reprinted with permission from
Thiboutot DM et al. *Skinmed.* 2005;4(3):138-146.

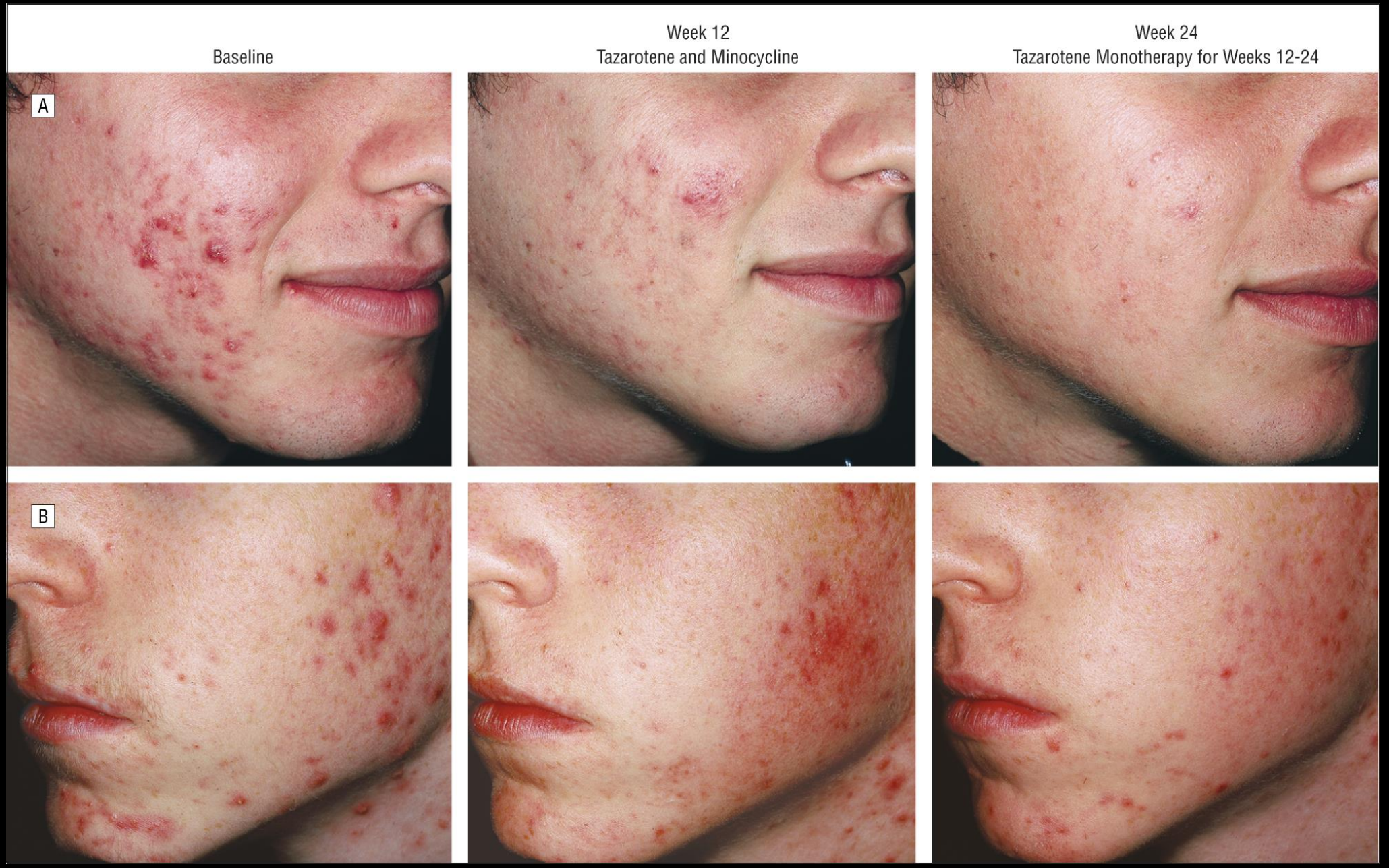
Minocycline + Tazarotene
Reprinted with permission from
Leyden J et al. *Arch Dermatol.* 2006;142(5):605-612.

Gollnick H et al. *J Am Acad Dermatol.* 2003;49(1 suppl):S1-S37.

Oral Antibiotics Used to Treat Moderate to Severe Acne

Antibiotic	Notes	
Doxycycline Minocycline	First-line agents	Antimicrobial and anti-inflammatory effects
Lymecycline	Not approved in the United States	
Tetracycline	Slower response than second-generation tetracyclines	
Erythromycin	Resistance is highly prevalent Used where tetracyclines are contraindicated or not tolerated	
Co-trimoxazole Trimethoprim	Third line; used for acne resistant to tetracyclines and macrolides	

Gollnick H et al. *J Am Acad Dermatol.* 2003;49(1 suppl):S1-S37.



Leyden J, Thiboutot DM, Shalita AR. Arch Dermatol. 2006;142(5):605-612.

What's New!!!

J Drugs Dermatol. 2018 Mar 1;17(3):333-338.

Efficacy and Safety of Sarecycline, a Novel, Once-Daily, Narrow Spectrum Antibiotic for the Treatment of Moderate to Severe Facial Acne Vulgaris: Results of a Phase 2, Dose-Ranging Study.

Leyden JJ, Sniukiene V, Berk DR, Kaoukhov A.

Abstract

BACKGROUND: There is a need for new oral antibiotics for acne with improved safety profiles and targeted antibacterial spectra. Sarecycline is a novel, tetracycline-class antibiotic specifically designed for acne, offering a narrow spectrum of activity compared with currently available tetracyclines, including less activity against enteric Gram-negative bacteria. This phase 2 study evaluated the efficacy and safety of three doses of sarecycline for moderate to severe facial acne vulgaris.

METHODS: In this multicenter, double-blind, placebo-controlled study, patients aged 12 to 45 years were randomized to once-daily sarecycline 0.75 mg/kg, 1.5 mg/kg, 3.0 mg/kg, or placebo. Efficacy analyses included change from baseline in inflammatory and noninflammatory lesion counts at week 12, with between-group comparisons using analysis of covariance. Safety assessments included adverse events (AEs), clinical laboratories, vital signs, electrocardiograms, and physical examinations.

RESULTS: Overall, 285 randomized patients received at least one dose of study drug. At week 12, sarecycline 1.5 mg/kg and 3.0 mg/kg groups demonstrated significantly reduced inflammatory lesions from baseline (52.7% and 51.8%, respectively) versus placebo (38.3%; P=0.02 and P=0.03, respectively). Sarecycline was safe and well tolerated, with similar gastrointestinal AE rates in sarecycline and placebo groups. Vertigo and photosensitivity AEs occurred in less than 1% of patients when pooling sarecycline groups; no vulvovaginal candidiasis AEs occurred. Discontinuation rates due to AEs were low. No serious AEs occurred.

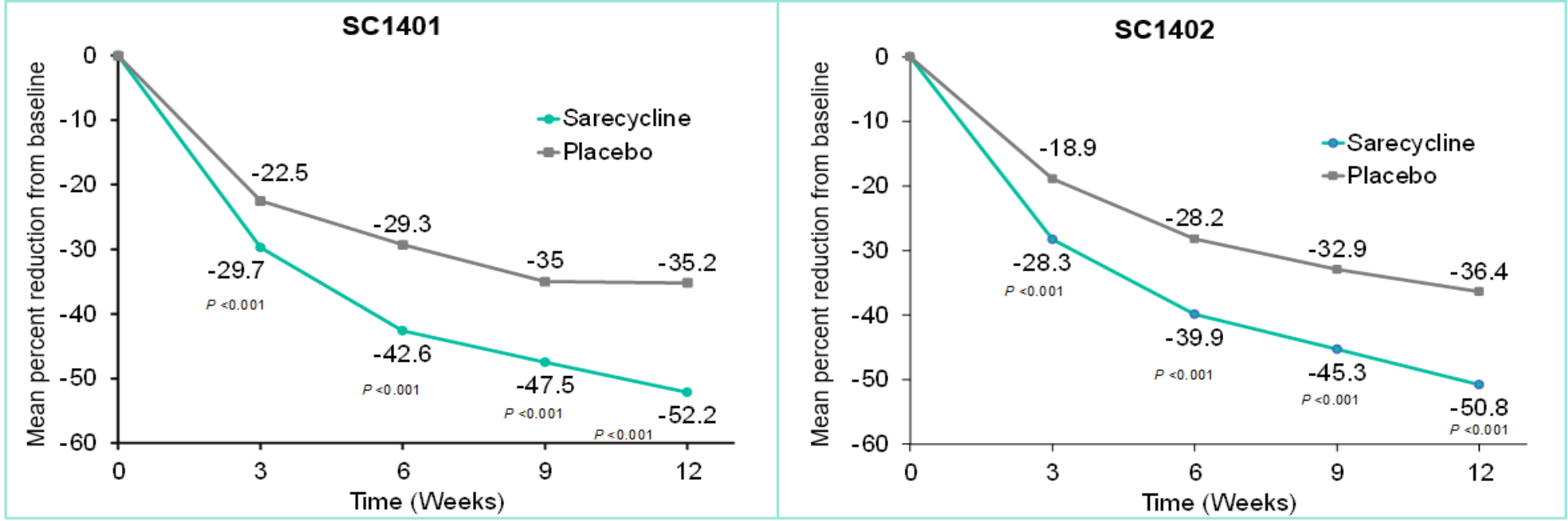
CONCLUSION: Once-daily sarecycline 1.5 mg/kg significantly reduced inflammatory lesions versus placebo and was safe and well tolerated with low rates of AEs, including gastrointestinal AEs. Sarecycline 3.0 mg/kg did not result in additional efficacy versus 1.5 mg/kg. Sarecycline may represent a novel, once-daily treatment for patients with moderate to severe acne. It offers a narrow antibacterial spectrum relative to other tetracycline options, which may lead to less selective pressure on enteric Gram-negative bacteria, resulting in less disruption of commensal organisms and less potential for antibiotic resistance. J Drugs Dermatol. 2018;17(3):333-338. .

Sarecycline vs Placebo in Acne Vulgaris

Inflammatory Lesion Count Reduction (%)

Sarecycline 1.5 mg/kg/day QD (n=1002) vs Placebo – 12-Weeks
Age Range 9-45 Years / ~25% Non-White Skin / 85% Moderate Severity

Mean Percent Change in Inflammatory Lesion Count from Baseline to Week 12



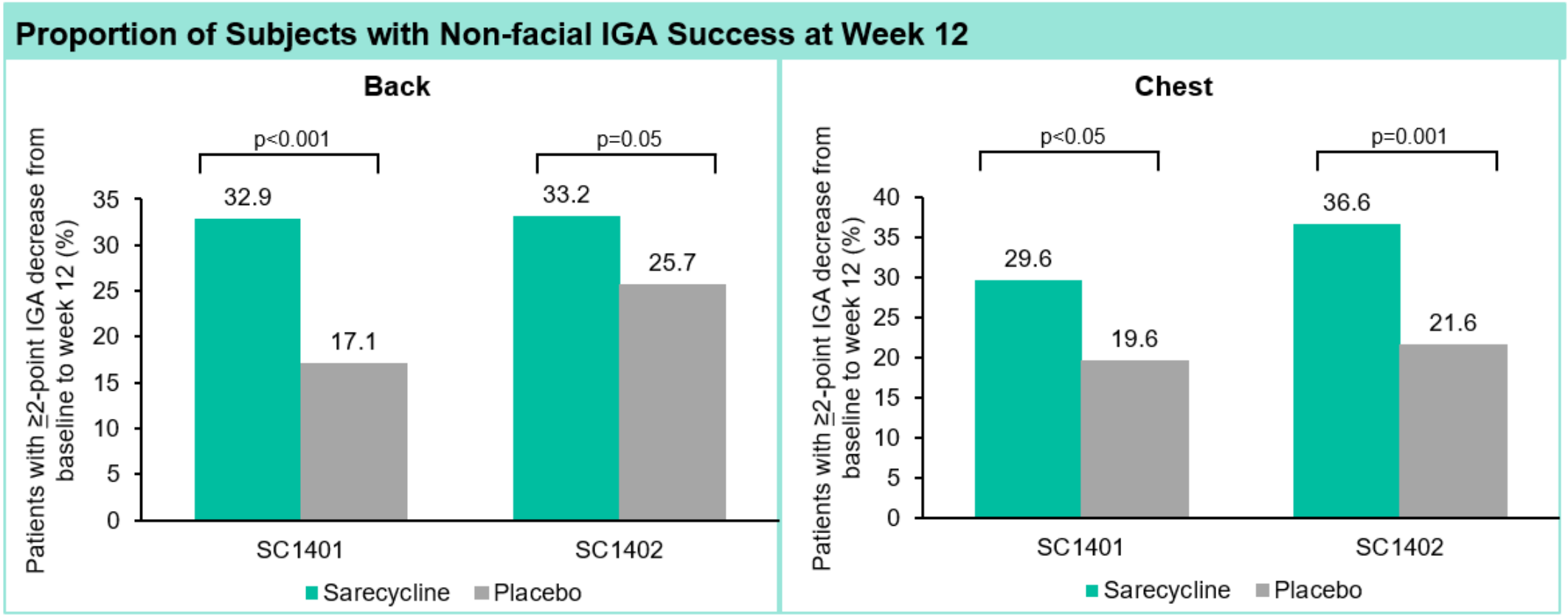
- Mean absolute reduction in lesion count was statistically significant at Week 12 and as early as Week 3

Moore A et al. *J Drugs Dermatol.* 2018;17(9):987-996.

MAY BE TAKEN WITH OR WITHOUT FOOD

Sarecycline vs Placebo in Truncal Acne Vulgaris

Sarecycline 1.5 mg/kg/day Once Daily (n=1002) vs Placebo – 12-Weeks
Age Range 9-45 Years / ~25% Non-White Skin / 85% Moderate Severity

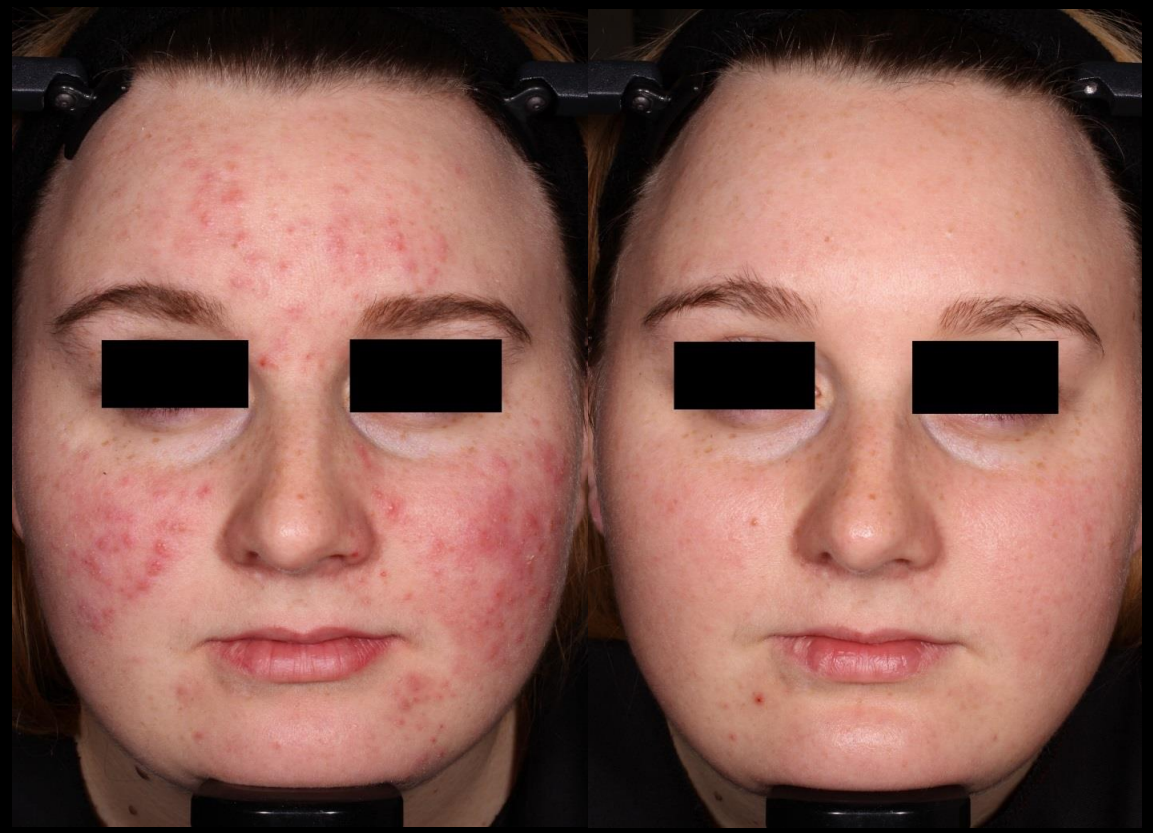


Non-facial IGA success defined as a ≥2-point decrease from baseline and a score of clear/almost clear

Moore A et al. *J Drugs Dermatol.* 2018;17(9):987-996.

Sarecycline Once Daily in Acne Vulgaris

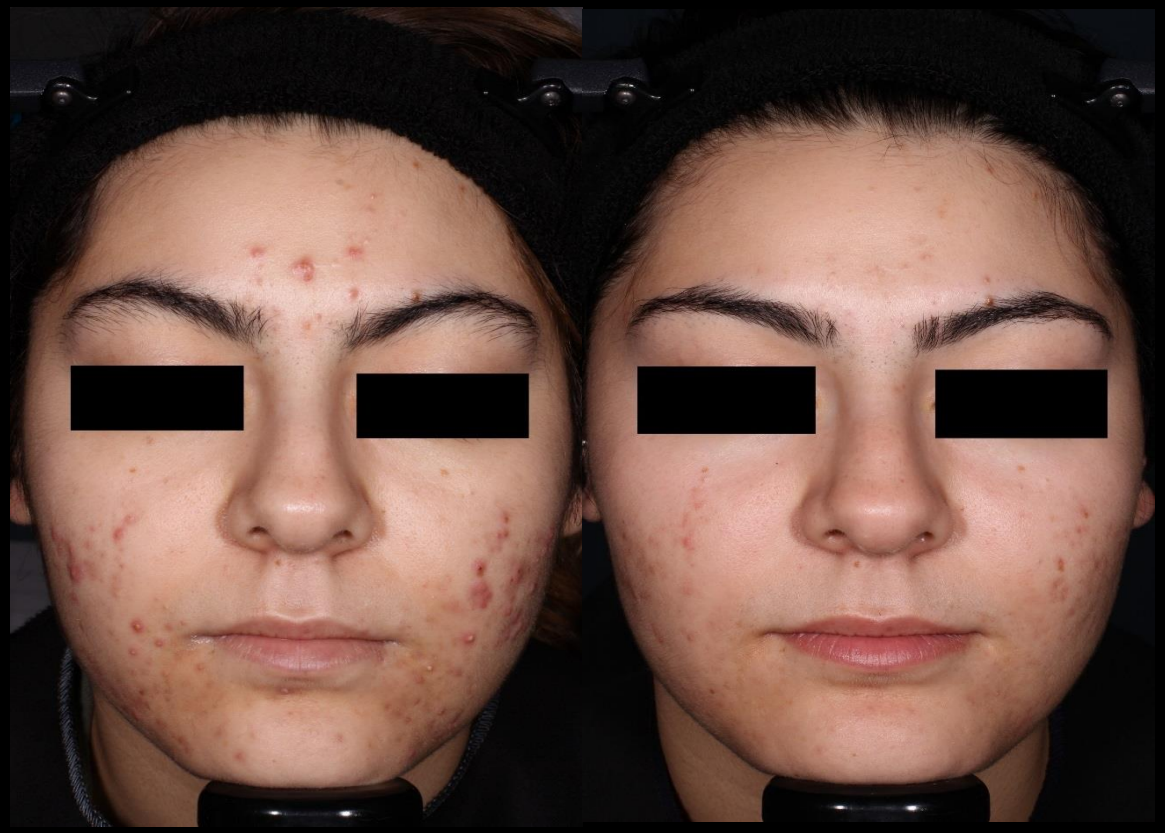
Global Assessment and Inflammatory Lesion Count Improvements



BASELINE
SEVERE

WEEK 12
ALMOST CLEAR

92% LESION REDUCTION FROM BASELINE



BASELINE
SEVERE

WEEK 12
ALMOST CLEAR

76% LESION REDUCTION FROM BASELINE

Practical Considerations with Sarecycline
Concept of Narrow Spectrum Tetracycline

Microbiological Profile of Sarecycline, a Novel Targeted Spectrum Tetracycline for the Treatment of Acne Vulgaris

George Zhanel,[a] Ian Critchley,[b]* Lynn-Yao Lin,[b] Nancy Alvandi[b]

[a]Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada
[b]Allergan plc, Irvine, California, USA

ABSTRACT Sarecycline is the first narrow-spectrum tetracycline-class antibiotic being developed for acne treatment. In addition to exhibiting activity against important skin/soft tissue pathogens, sarecycline exhibits targeted antibacterial activity against clinical isolates of *Cutibacterium acnes*. In the current study, sarecycline was 16- to 32-fold less active than broad-spectrum tetracyclines—such as minocycline and doxycycline—against aerobic Gram-negative bacilli associated with the normal human intestinal microbiome. Also, reduced activity against *Escherichia coli* was observed *in vivo* in a murine septicemia model, with the 50% protective doses, or the doses required to achieve 50% survival, being >40 mg/kg of body weight and 5.72 mg/kg for sarecycline and doxycycline, respectively. Sarecycline was also 4- to 8-fold less active than doxycycline against representative anaerobic bacteria that also comprise the normal human intestinal microbiome. Additionally, *C. acnes* strains displayed a low propensity for the development of resistance to sarecycline, with spontaneous mutation frequencies being 10^{-10} at 4 to 8 times the MIC, similar to those for minocycline and vancomycin. When tested against Gram-positive pathogens with defined tetracycline resistance mechanisms, sarecycline was more active than tetracycline against *tet*(K) and *tet*(M) strains, with MICs ranging from 0.125 to 1.0 μl/ml and 8 μl/ml, respectively, compared with MICs of 16 to 64 μl/ml and 64 μl/ml for tetracycline, respectively. However, sarecycline activity against the *tet*(K) and *tet*(M) strains was decreased compared to that against the wild type, which demonstrated MICs ranging from 0.06 to 0.25 μl/ml, though the decrease in the activity of sarecycline against the *tet*(K) and *tet*(M) strains was not as pronounced as that of tetracycline. These findings support sarecycline as a narrow-spectrum tetracycline-class antibiotic that is effective for the treatment of acne, and further investigation into the potential reduced effects on the gut microbiome compared with those of other agents is warranted.

KEYWORDS *Propionibacterium acnes*, acne vulgaris, antibiotics, doxycycline, microbiological profile, microbiome, minocycline, sarecycline, tetracycline

Tetracyclines have been widely used for the treatment of moderate to severe acne due to their ability to suppress the growth of *Cutibacterium acnes*—an anaerobic organism associated with acne lesions—and their ability to exert anti-inflammatory effects (1, 2). Although tetracycline was frequently used in the 1950s and 1960s, its use has been superseded by that of other tetracyclines, such as doxycycline and minocycline, due to their improved bioavailability, lipophilicity (improved uptake into the pilosebaceous unit), and longer half-lives, allowing less frequent dosing (3, 4). Doxycycline is currently preferred as the first-line oral tetracycline for the treatment of acne (5), as other systemic treatment approaches (with tetracyclines and nontetracyclines, such as minocycline, co-trimoxazole, quinolones, clindamycin, macrolides, and trim-

Citation Zhanel G, Critchley I, Lin L-Y, Alvandi N. 2019. Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris. Antimicrob Agents Chemother 63:e01297-18. https://doi.org/10.1128/AAC.01297-18.

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Received 22 June 2018
Returned for modification 23 July 2018
Accepted 10 October 2018
Accepted manuscript posted online 5 November 2018
Published 21 December 2018

POTENTIAL CONSIDERATIONS RELEVANT TO CLINICAL PRACTICE

EFFICACY FOR ACNE VULGARIS
Inflammatory AND Comedonal Lesions
Face & Trunk

ADVERSE REACTION PROFILE
GI Side Effects / Photosensitivity / Vaginal Candidiasis

ANTIMICROBIAL SPECTRUM
Reduced Risk of Antibiotic Resistance
vs Some Organisms (especially Gram -)

REDUCE SELECTION OF GRAM (-) BACTERIA AND MULTI-DRUG RESISTANCE

Antimicrob Agents Chemother. 2018 Dec 21;63(1). pii: e01297-18. doi: 10.1128/AAC.01297-18. Print 2019 Jan.

Microbiological Profile of Sarecycline, a Novel Targeted Spectrum Tetracycline for the Treatment of Acne Vulgaris.

Zhanel G[1], Critchley I[2], Lin LY[3], Alvandi N[2].

Author information

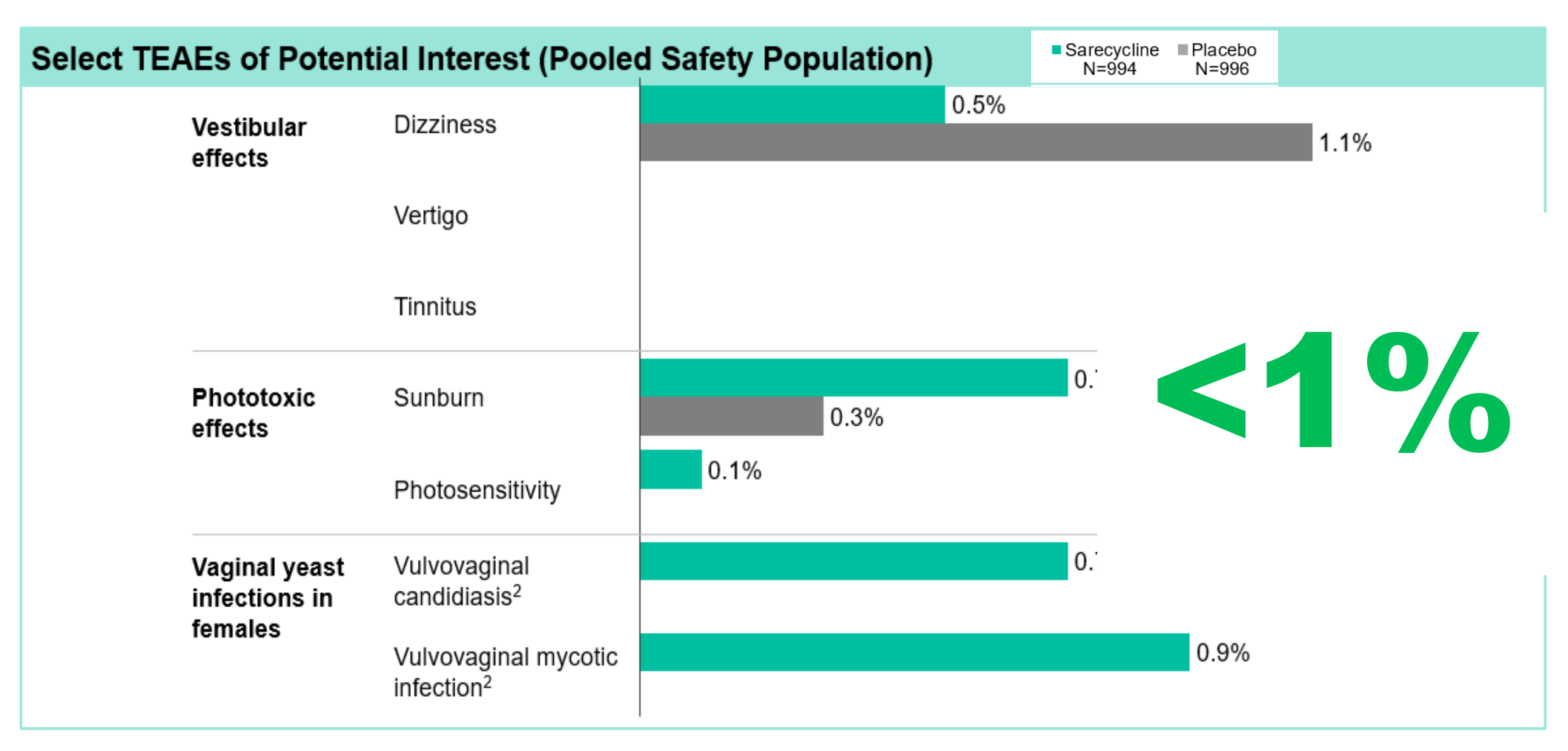
1 Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada.
2 Allergan plc, Irvine, California, USA.
3 Allergan plc, Irvine, California, USA Lin_Lynn-Yao@Allergan.com.

Abstract

Sarecycline is the first narrow-spectrum tetracycline-class antibiotic being developed for acne treatment. In addition to exhibiting activity against important skin/soft tissue pathogens, sarecycline exhibits targeted antibacterial activity against clinical isolates of *Cutibacterium acnes* In the current study, sarecycline was 16- to 32-fold less active than broad-spectrum tetracyclines-such as minocycline and doxycycline-against aerobic Gram-negative bacilli associated with the normal human intestinal microbiome. Also, reduced activity against *Escherichia coli* was observed *in vivo* in a murine septicemia model, with the 50% protective doses, or the doses required to achieve 50% survival, being >40 mg/kg of body weight and 5.72 mg/kg for sarecycline and doxycycline, respectively. Sarecycline was also 4- to 8-fold less active than doxycycline against representative anaerobic bacteria that also comprise the normal human intestinal microbiome. Additionally, *C. acnes* strains displayed a low propensity for the development of resistance to sarecycline, with spontaneous mutation frequencies being 10^{-10} at 4 to 8 times the MIC, similar to those for minocycline and vancomycin. When tested against Gram-positive pathogens with defined tetracycline resistance mechanisms, sarecycline was more active than tetracycline against *tet*(K) and *tet*(M) strains, with MICs ranging from 0.125 to 1.0 µl/ml and 8 µl/ml, respectively, compared with MICs of 16 to 64 µl/ml and 64 µl/ml for tetracycline, respectively. However, sarecycline activity against the *tet*(K) and *tet*(M) strains was decreased compared to that against the wild type, which demonstrated MICs ranging from 0.06 to 0.25 µl/ml, though the decrease in the activity of sarecycline against the *tet*(K) and *tet*(M) strains was not as pronounced as that of tetracycline. These findings support sarecycline as a narrow-spectrum tetracycline-class antibiotic that is effective for the treatment of acne, and further investigation into the potential reduced effects on the gut microbiome compared with those of other agents is warranted.

Sarecycline in Acne Vulgaris: Pooled Safety Data

Sarecycline 1.5 mg/kg/day Once Daily vs Placebo – 12-Weeks
MAJOR ADVERSE REACTIONS OF SPECIAL INTEREST WITH TETRACYCLINES



Multiple Unit Particulate Pellet System (MUPS)

- Multi-particulate solid dosage form
- Compressed mixture of drug-containing pellets and powder excipients
- Can “dial in” delivery characteristics

REPORTED BENEFITS OF MUPS

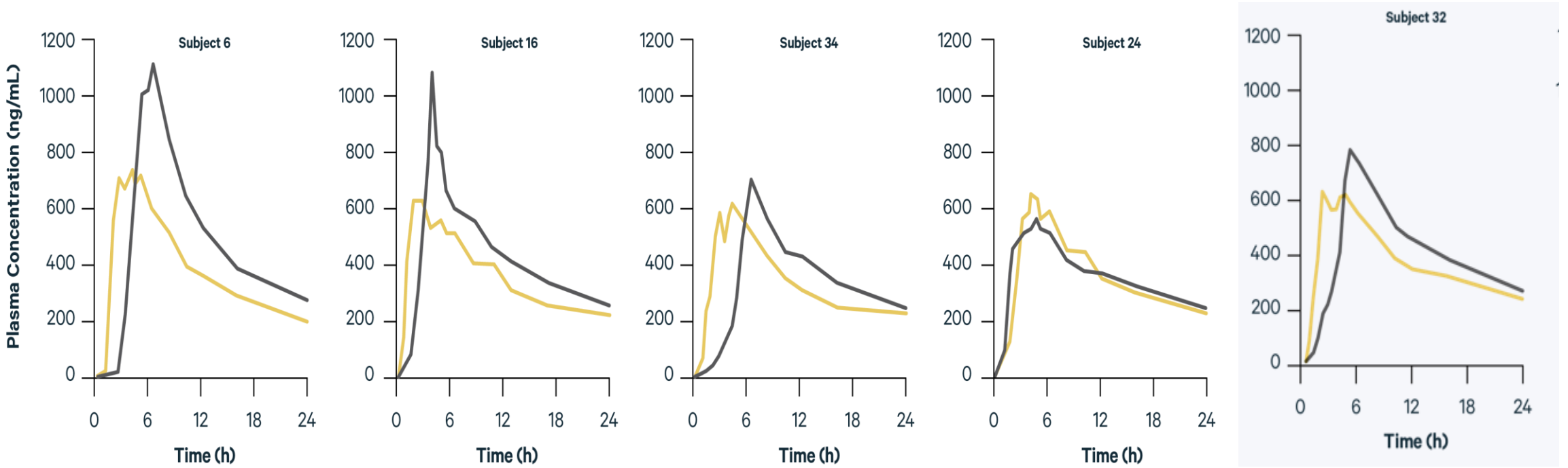
- Minimizes inter/intra subject variability
- Reduces esophageal transit time
- Improves physicochemical stability
- Lowers risk of local irritation and toxicity
- Reduces dose dumping
- Minimizes plasma concentration fluctuations

Solid Dosage – MUPS (Multiple Unit Pellet System) Production. https://www.gea.com/en/applications/pharma/solid-dosage/solid-dosage_mups.jsp.

Minocycline Biphasic Delivery with immediate- and sustained-release pellets.

- 25% immediate and 75% sustained release of minocycline hydrochloride
- **Steady-state plasma concentration**
- **Functionally scored** tablet has an even distribution of drug on each side of the score line
- A spherical core coated with ***micronized minocycline hydrochloride***

Less Variable and More Predictable PK Profile with Minocycline Biphasic Delivery vs Biphasic Minocycline



MINOCYCLINE BIPHASIC DELIVERY

MINOCYCLINE EXTENDED RELEASE

Data on File. EPI Health, Charleston, South Carolina

Optimizing Use of Oral Antibiotic Therapy in Acne

- A continued work in progress
  - Most data available with tetracyclines – "dual mechanisms"
- Use in combination with *maximized topical regimen*
  - Incorporate benzoyl peroxide AND topical retinoid in regimen
- AVOID antibiotic monotherapy or "unopposed" antibiotic use
- Limit duration of oral antibiotic therapy *as best as possible*
  - Assess every 3 months
  - "Maximum" suggested ("hoped for") duration: 3 - 6 months
  - **Consensus agreement: "…a subset of patients for whom alternative therapies are inappropriate and who may require a longer course of antibiotics even while taking topical medications."**

1 Del Rosso JQ, Kim G. Derm Clinics. 2 Zanglein A, et al. J Am Acad Dermatol. 2016;74:945-973. Del Rosso JQ. Sem Cut Med Surg.

What's your tipping point?

The role of isotretinoin in acne therapy: why not as first-line therapy? facts and controversies.

Rigopoulos D, Larios G, Katsambas AD.

Source

Department of Dermatology, University of Athens, Andreas Sygros Hospital, 5 Ionos Dragoumi St, 16121 Athens, Greece. drigop@hol.gr

Abstract

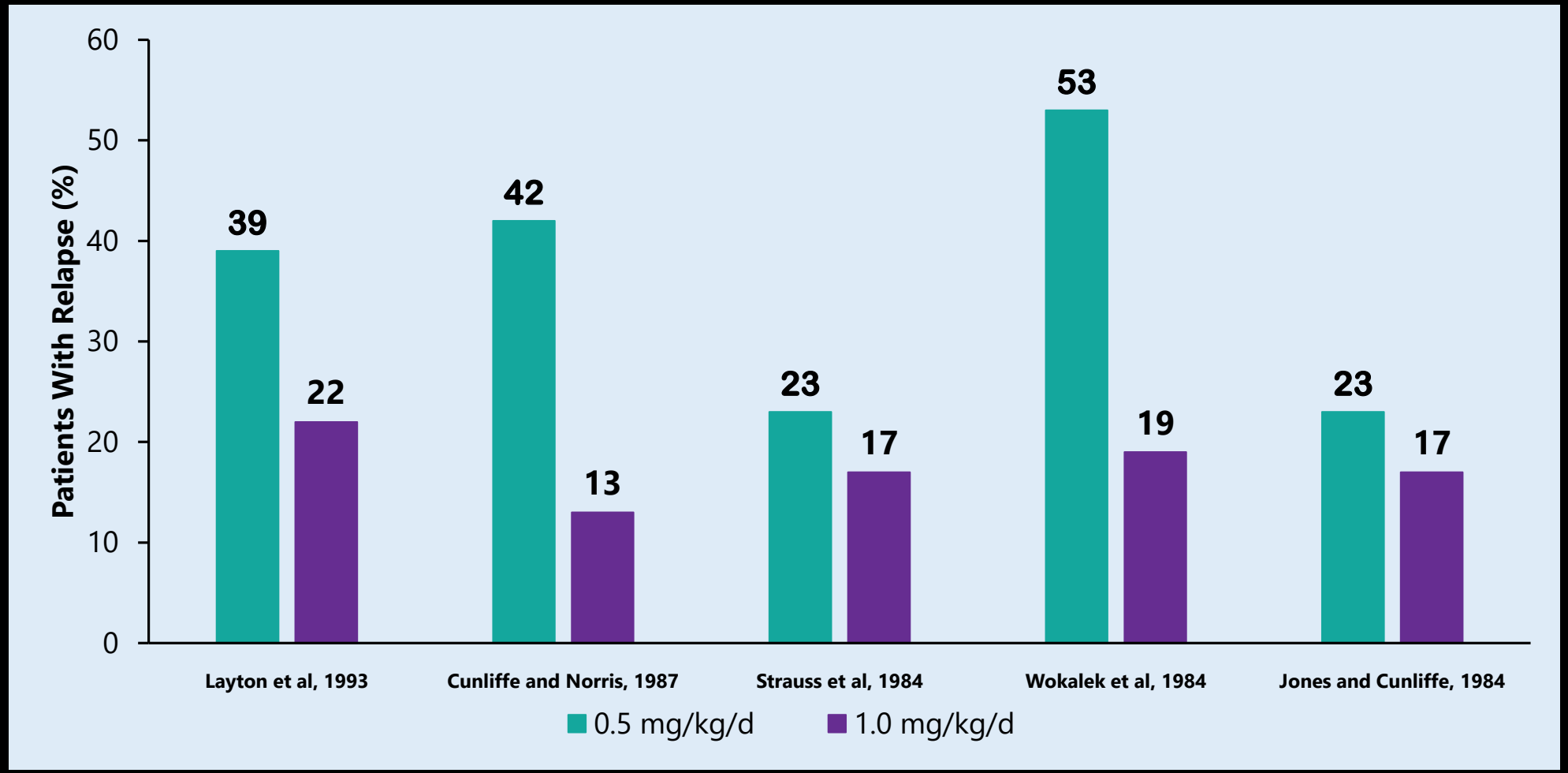
Acne is one of the most prevalent diseases in dermatology: Millions of people worldwide experience this distressing condition. To determine the appropriate therapeutic strategy, there is a strong need for a standardized classification system of acne. The exact molecular mechanism of action of isotretinoin is not completely understood; however, oral isotretinoin targets simultaneously at all major mechanisms of acne pathogenesis. Various mass media reports about the risk of teratogenicity and depression from isotretinoin usage as well as the creation of intense prevention programs have created an obstacle to the use of the most active available drug against acne, presenting isotretinoin as a very dangerous regimen. According to recommendations of several international experts, which we share, oral isotretinoin may be prescribed not only to patients with severe disease but indications should be broadened to also include patients with less severe forms of acne, especially in cases with scarring, significant psychologic stress, or failure to respond to conventional therapy.

Clin Dermatol. 2010 Jan-Feb;28(1):24-30.


RELAPSE

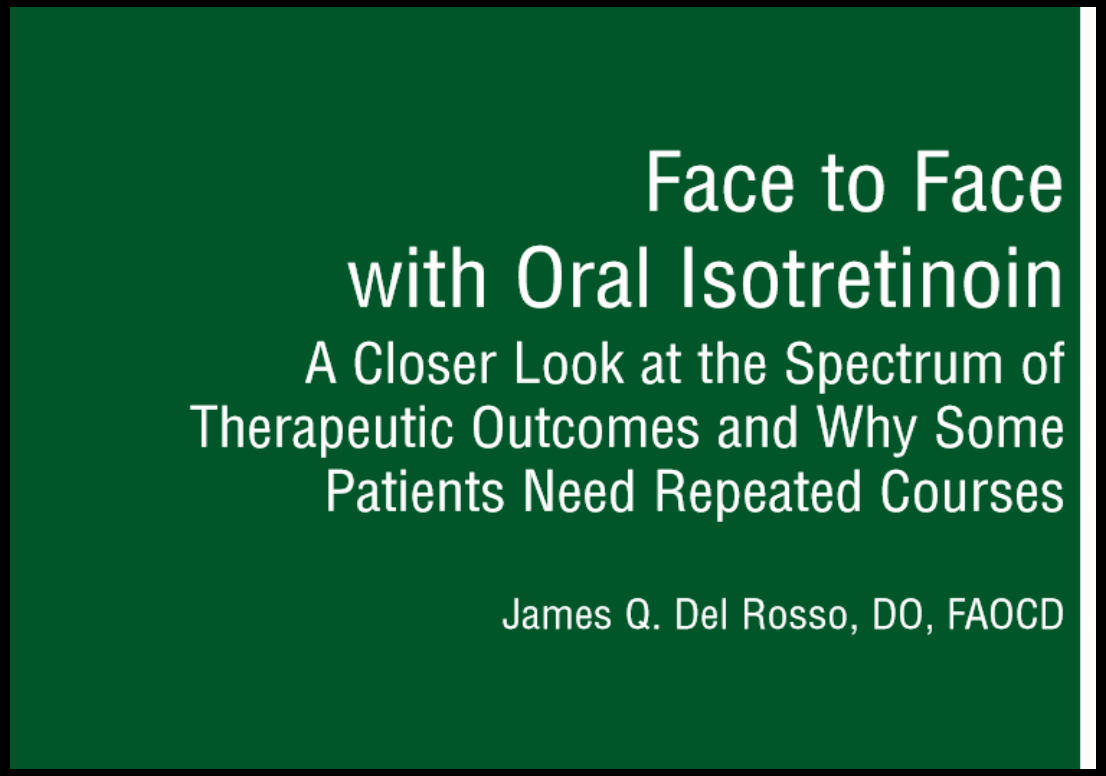
ISOTRETINOIN
ADVANCED FORMULATIONS

Oral Isotretinoin Clinical Studies
Daily Dose and Reported Relapse Rates



1. Layton AM, et al. Br J Dermatol. 1993;129:292–296; 2. Cunliffe WJ, Norris JFB. Dermatologica. 1987;175(Suppl 1):133–137; 3. Strauss JS, et al. J Am Acad Dermatol. 1984;10:490–496; 4. Wokalek H, et al. Retinoid Therapy: A Review of Clinical and Laboratory Research. Lancaster, England: MTP Press Limited; 1984:231–239; 5. Jones DH, Cunliffe WJ. Retinoid Therapy: A Review of Clinical and Laboratory Research. Lancaster, England: MTP Press Limited; 1984:241–251.

Oral Isotretinoin Reported Relapse and Retreatment Rates



REVIEW OF STUDIES EVALUATING ORAL ISOTRETINOIN DOSING REGIMENS, CUMULATIVE DOSING, RELAPSE RATES, RETREATMENT RATES AND ACNE THERAPIES USED

Del Rosso JQ. J Clinic Aesthet Dermatol. 2012;11(5):17-24.

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

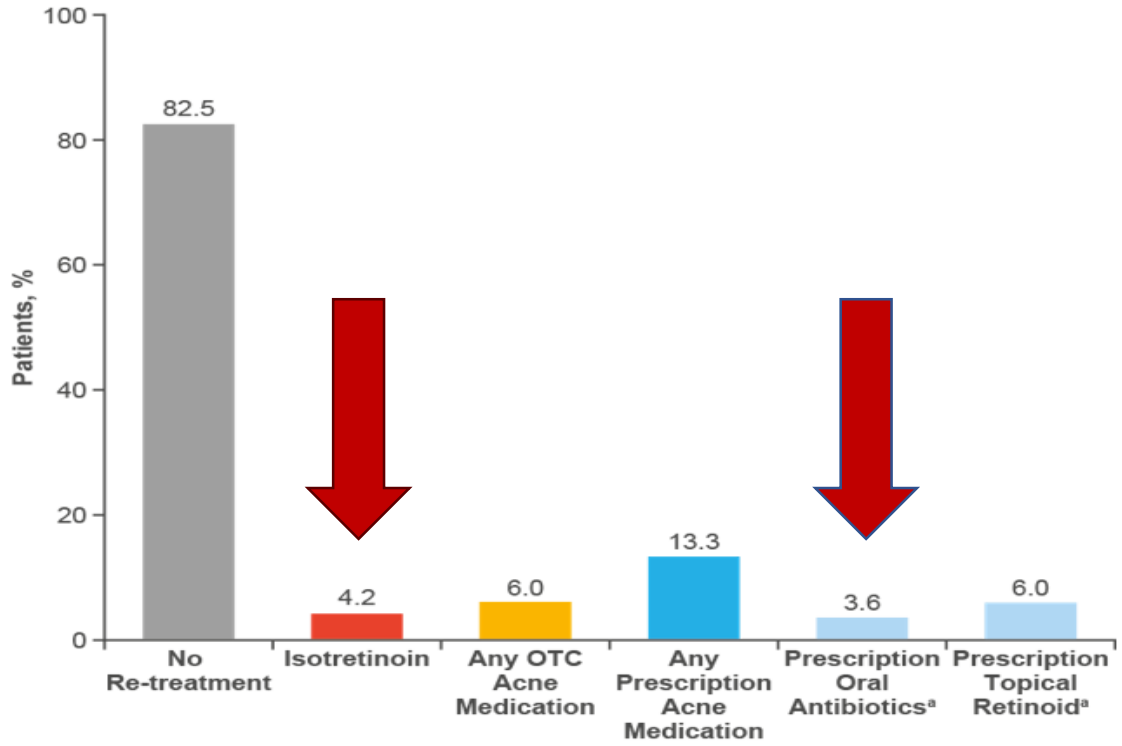
Lidose Oral Isotretinoin (Lidose-ISO) for Severe Recalcitrant Nodular Acne

- Open-label, Single-arm, Phase 4 *Long-Term* Study
- Active Treatment Phase (ATP)
  - Administere d for severe recalcitrant nodular acne
  - Ingested *WITHOUT FOOD*
  - Dosage: 0.5 mg/kg/day x 4 weeks then 1.0 mg/kg/day x 16 weeks
  - Total duration of therapy: 20 weeks
  - Attempted to approximate target cumulative dose of 120-150 mg/kg
- Post-Treatment Phase (PTP)
  - *2-year post-treatment follow-up* (weeks 32, 72, 98, 124)
  - Subjects stratified by Investigator Global Assessment (IGA) ratings
  - **Goal: Assess Relapse Rates with use of LIDOS-ISO**

Del Rosso JQ, Zaenglein A. J Clin Aesthet Dermatol, 2019.

Lidose Oral Isotretinoin (Lidose-ISO)
Severe Nodular Acne (20 Weeks Treatment Without Food)
Types and Rates of Retreatments Used Post-Treatment Period (Week 104)

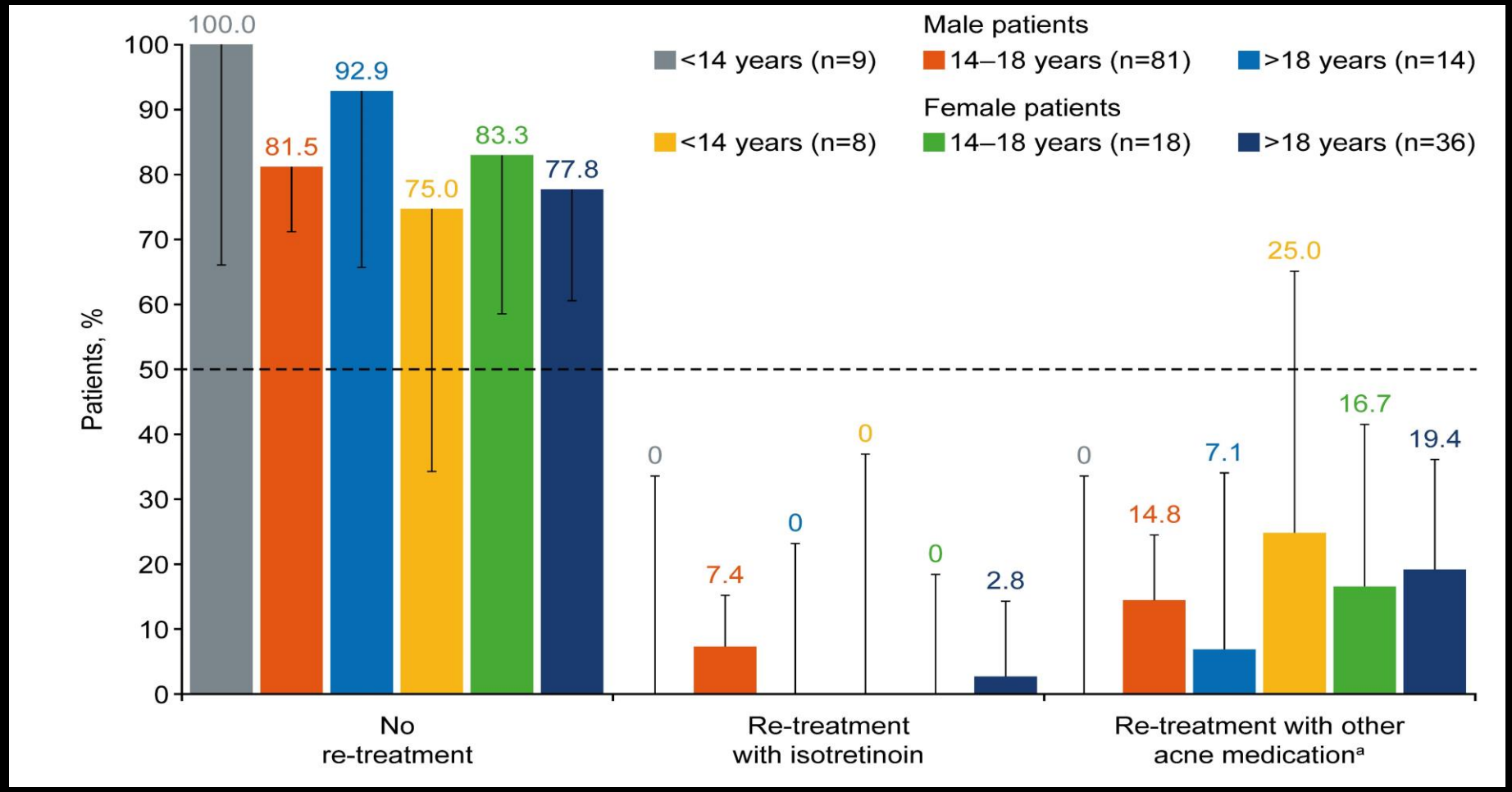
Figure 4. Re-treatments Received in the PTP by Subgroup



Patients could be included in more than 1 re-treatment group if they had received more than 1 treatment type in the PTP. [a]Subgroup of patients receiving prescription acne medication.
OTC, over-the-counter; PTP, post-treatment period.

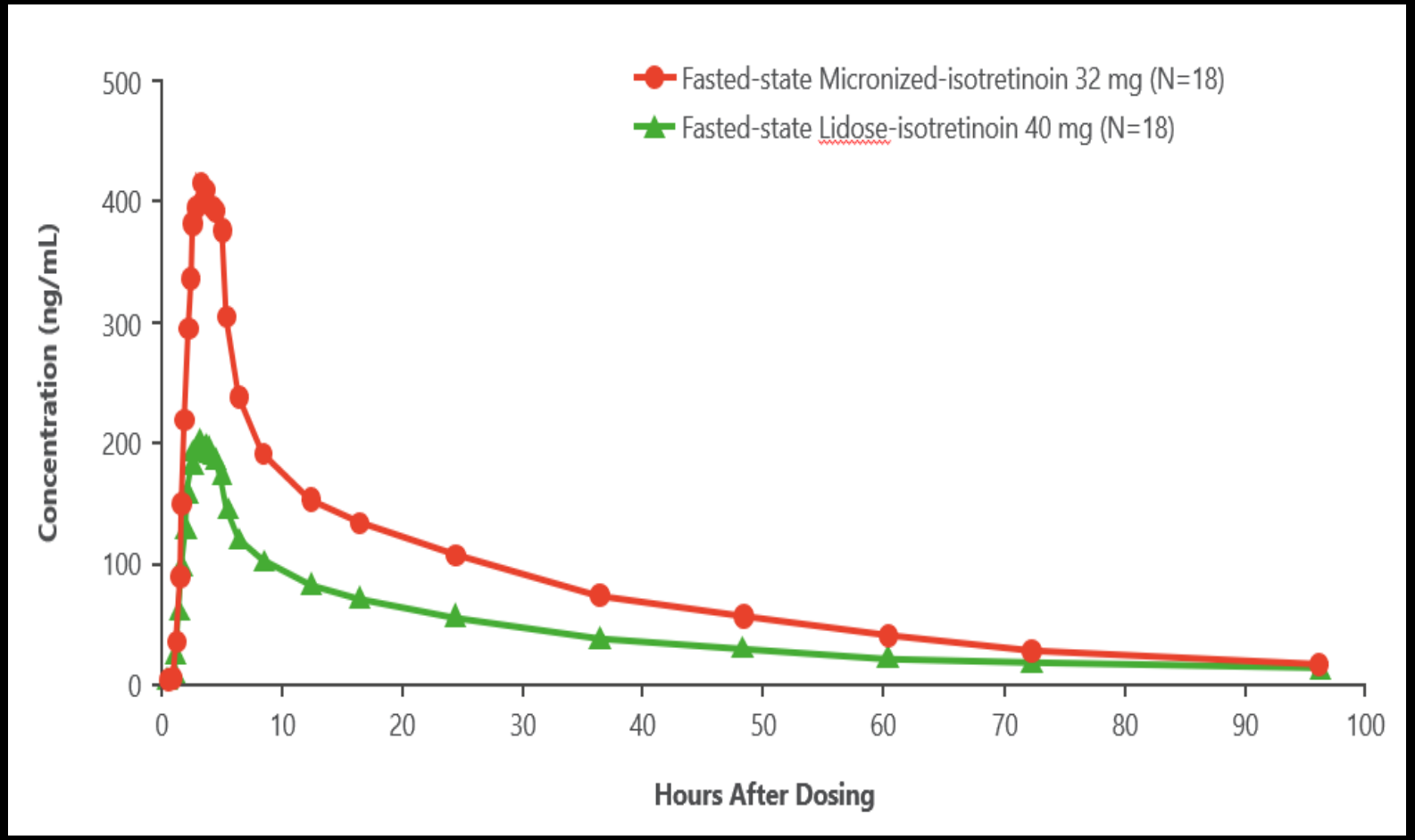
Del Rosso JQ, et al. 2018. Poster presentation. Fall Clinical Dermatology, Las Vegas, NV, October 2018. (submitted for publication)

Lidose Oral Isotretinoin (Lidose-ISO)
Severe Nodular Acne (20 Weeks Treatment Without Food)
Types and Rates of Retreatments Correlated with Age
Post-Treatment Period (Week 104)



Del Rosso JQ, et al. 2018. Poster presentation. Fall Clinical Dermatology, Las Vegas, NV, October 2018. (submitted for publication)

Isotretinoin Mean Plasma Concentration Micronized-Isotretinoin 32 mg vs Lidose-Isotretinoin 40mg Time Curves in FASTED STATE



- Micronized-Isotretinoin **TWICE as bioavailable** as Lidose-Isotretinoin **FASTED**
  - SAME when FED
- Food: No effect on rate and marginal on extent of Micronized-Isotretinoin absorption
  - Less effect than on other marketed isotretinoin products

Madan S, et al. Poster presentation. Fall Clinical Dermatology, Las Vegas, Nevada, October 2019.

J Am Acad Dermatol. 2016 Aug;75(2):323-8. doi: 10.1016/j.jaad.2016.03.019. Epub 2016 May 14.

Standardized laboratory monitoring with use of isotretinoin in acne.

Hansen TJ[1], Lucking S[2], Miller JJ[1], Kirby JS[1], Thiboutot DM[1], Zaenglein AL[3].

Author information

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Abstract

BACKGROUND: Laboratory monitoring for adverse effects to isotretinoin occurs with variability. Standardization of laboratory monitoring practices represents an opportunity to improve quality of care.

OBJECTIVE: We sought to develop an evidence-based approach to laboratory monitoring of patients receiving isotretinoin therapy for acne.

METHODS: We reviewed laboratory data from 515 patients with acne undergoing 574 courses of isotretinoin from March 2003 to July 2011. Frequency, timing, and severity of abnormalities were determined.

RESULTS: Clinically insignificant leukopenia or thrombocytopenia occurred in 1.4% and 0.9% of patients, respectively. Elevated liver transaminases were detected infrequently and not significantly increased compared with baseline detection rates (1.9% vs 1.6% at baseline). Significant elevations occurred with triglyceride (19.3%) and cholesterol (22.8%) levels. The most severe abnormalities were grade 2 (moderate). Mean duration of treatment before abnormalities were detected was 56.3 days for hypertriglyceridemia, 61.9 days for alanine transaminitis, and 50.1 days for hypercholesterolemia.

LIMITATIONS: This was a single-center experience examining variable isotretinoin laboratory monitoring practices.

CONCLUSIONS: In healthy patients with normal baseline lipid panel and liver function test results, repeated studies should be performed after 2 months of isotretinoin therapy. If findings are normal, no further testing may be required. Routine complete blood cell count monitoring is not recommended.

JAMA Dermatol. 2016 Jan;152(1):35-44. doi: 10.1001/jamadermatol.2015.3091.

Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis.

Lee YH[1], Scharnitz TP[2], Muscat J[3], Chen A[3], Gupta-Elera G[2], Kirby JS[4].

Author information

1 Division of Dermatology, Sharp Rees-Stealy Medical Group, San Diego, California.
2 Penn State College of Medicine, Hershey, Pennsylvania.
3 Department of Public Health Sciences, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania.
4 Department of Dermatology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania.

Erratum in
Incorrect Affiliation. [JAMA Dermatol. 2016]

Abstract

IMPORTANCE: Oral isotretinoin has been associated with several adverse effects, but evidence-based estimates of laboratory changes during isotretinoin therapy in large patient samples are limited.

OBJECTIVE: To develop estimates of the laboratory changes that occur during isotretinoin therapy for acne using extant data and meta-analytic methods.

DATA SOURCES: A comprehensive search strategy using Ovid/MEDLINE, EMBASE, and gray literature was conducted (1960-August 1, 2013) to identify all relevant studies of isotretinoin use in acne vulgaris. Terms related to acne treatment, isotretinoin, and diagnostic procedures were searched with all available synonyms.

STUDY SELECTION: Inclusion criteria consisted of clinical trials using oral isotretinoin, doses of 40 mg/d or more, duration of at least 4 weeks, patients aged 9 to 35 years with acne vulgaris, and 10 or more participants. Studies from all countries published in any language were included. Exclusion criteria were use of modified isotretinoin products, isotretinoin therapy for conditions other than acne vulgaris, and concomitant acne therapy. The initial search yielded 342 records; 116 of these were screened for full-text examination.

DATA EXTRACTION AND SYNTHESIS: Two authors independently reviewed the publications to determine eligibility, and disagreements were resolved by a third author. Generated weighted means and 99% CIs were calculated using the reported means (SDs or SEs). A random effects model was created, and statistical heterogeneity was quantified. Data were analyzed from August 25, 2014, to December 4, 2015.

MAIN OUTCOMES AND MEASURES: Laboratory values for lipid levels, hepatic function, and complete blood cell count were evaluated.

RESULTS: Data from 61 of the 116 studies were evaluated; 26 studies (1574 patients) were included in the meta-analysis. The mean (99% CI) values during treatment (nonbaseline) for triglycerides was 119.98 mg/dL (98.58-141.39 mg/dL); for total cholesterol, 184.74 mg/dL (178.17-191.31 mg/dL); for low-density lipoprotein cholesterol, 109.23 mg/dL (103.68-114.79 mg/dL); for high-density lipoprotein cholesterol, 42.80 mg/dL (39.84-45.76 mg/dL); for aspartate aminotransferase, 22.67 U/L (19.94-25.41 U/L); for alanine aminotransferase, 21.77 U/L (18.96-24.59 U/L); for alkaline phosphatase, 88.35 U/L (58.94-117.76 U/L); and for white blood cell count, 6890/μL (5700/μL-8030/μL). This meta-analysis showed that (1) isotretinoin is associated with a statistically significant change in the mean value of several laboratory tests (white blood cell count and hepatic and lipid panels), yet (2) the mean changes across a patient group did not meet a priori criteria for high-risk and (3) the proportion of patients with laboratory abnormalities was low.

CONCLUSIONS AND RELEVANCE: The evidence from this study does not support monthly laboratory testing for use of standard doses of oral isotretinoin for the standard patient with acne.

Serum Potassium Monitoring in Women Taking Oral Spironolactone for Acne

JAMA Dermatol. 2015 Sep;151(9):941-4. doi: 10.1001/jamadermatol.2015.34.

Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne.

Plovanich M[1], Weng QY[1], Mostaghimi A[1].

Author information

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Abstract

IMPORTANCE: Spironolactone has been shown to be an effective treatment option for hormonally mediated acne but can cause hyperkalemia. The prevalence of hyperkalemia among healthy young women taking spironolactone for acne is unclear.

OBJECTIVE: To measure the rate of hyperkalemia in healthy young women taking spironolactone for acne or for an endocrine disorder with associated acne.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective study of healthy young women taking spironolactone for acne. Data from December 1, 2000, through March 31, 2014, were obtained from a clinical data repository. Outpatient data were collected from 2 tertiary care centers in the United States. We analyzed rates of hyperkalemia in 974 healthy young women taking spironolactone for acne. We also analyzed 1165 healthy young women taking and not taking spironolactone to obtain a profile for the baseline rate of hyperkalemia in this population. Exclusion criteria were cardiovascular disease, renal failure, and the use of medications that affect the renin-angiotensin-aldosterone system.

MAIN OUTCOMES AND MEASURES: The rate of hyperkalemia in healthy young women taking spironolactone for acne was calculated. Secondary measures included spironolactone prescriber profiles and potassium monitoring practices.

RESULTS: There were 13 abnormal serum potassium measurements in 1802 measurements obtained among young women receiving spironolactone therapy, yielding a hyperkalemia rate of 0.72%, equivalent to the 0.76% baseline rate of hyperkalemia in this population. Repeat testing in 6 of 13 patients demonstrated normal values, suggesting that these measurements may have been erroneous. In the remaining 7 patients, no action was taken.

CONCLUSIONS AND RELEVANCE: The rate of hyperkalemia in healthy young women taking spironolactone for acne is equivalent to the baseline rate of hyperkalemia in this population. Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.

Int J Womens Dermatol. 2019 Apr 25;5(3):155-157. doi: 10.1016/j.ijwd.2019.04.024. eCollection 2019 Jul.

Hyperkalemia in women with acne exposed to oral spironolactone: A retrospective study from the RADAR (Research on Adverse Drug Events and Reports) program.

Thiede RM[1], Rastogi S[2], Nardone B[2], Sadowsky LM[2], Rangel SM[2], West DP[2], Schlosser BJ[2].

Author information

1 Division of Dermatology, University of Arizona College of Medicine-Tucson, Tucson, Arizona.

2 Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Abstract

PURPOSE: The necessity of serum potassium monitoring for healthy women who are prescribed spironolactone for acne has been debated. The aim of this study was to compare the incidence of hyperkalemia in women 18 to 45 years of age to that in women 46 to 65 years of age, when treated with oral spironolactone for acne.

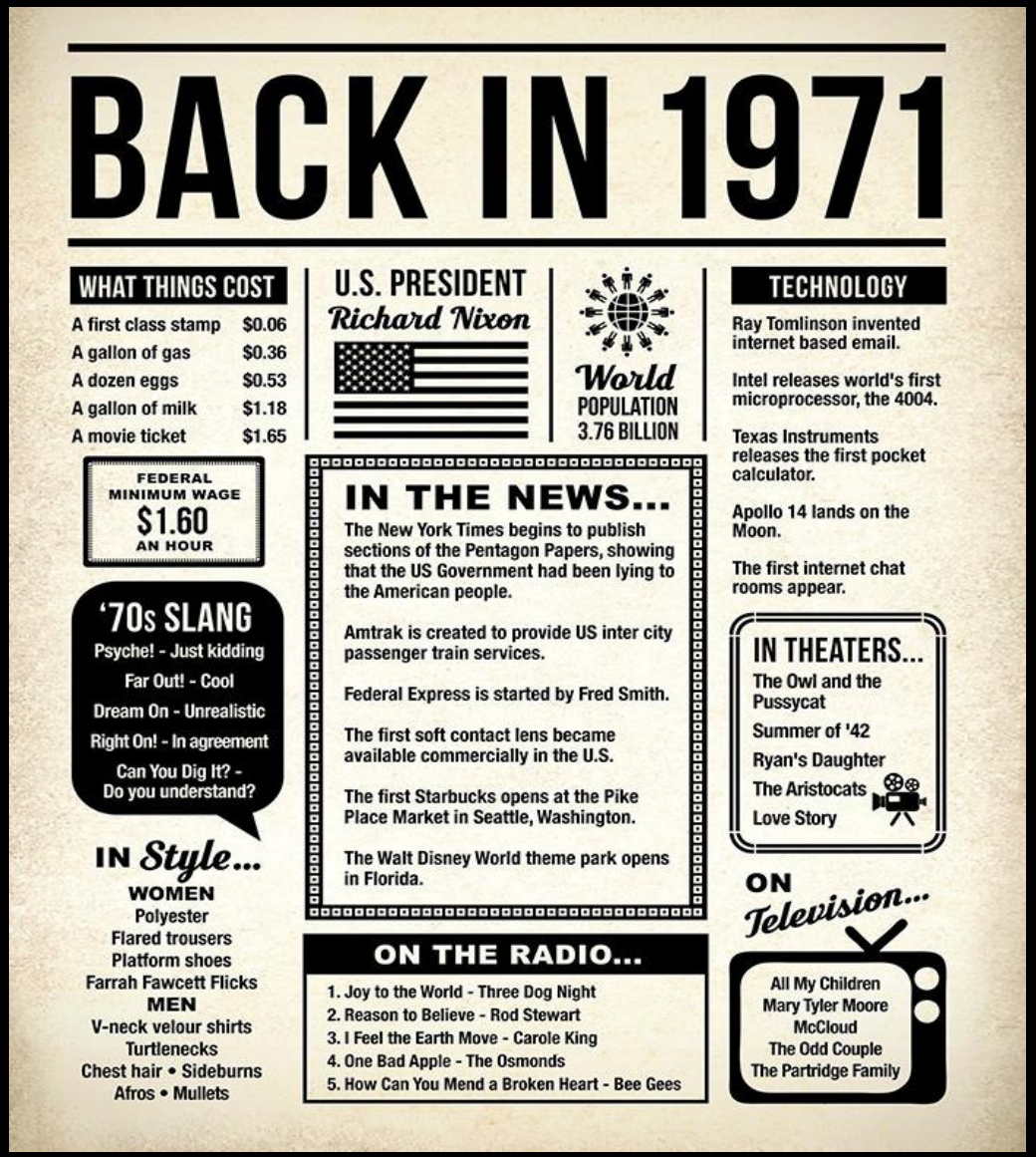
METHODS AND MATERIALS: Data for all women 18 to 65 years of age who were prescribed oral spironolactone by a dermatologist for acne between January 2006 and October 2016 were extracted for analysis. Retrospective data were included for women who exhibited baseline serum potassium within the normal limits and who had repeat serum potassium monitoring within 12 months after initiation of spironolactone. The rate of incident hyperkalemia was determined.

RESULTS: Of 618 women who received spironolactone for acne, 133 had serum potassium monitoring both before and after spironolactone initiation. Nine were excluded due to confounding comorbidities. Of the remaining 124 women, the mean age at initiation of spironolactone was 32 years (range, 18-57 years); 112 women were in the 18 to 45 years age group, and 12 were in the 46 to 65 years age group. All women had serum potassium within normal limits at baseline. Women in the 46 to 65 years age group had a significantly higher rate of incident hyperkalemia after spironolactone initiation compared with women 18 to 45 years of age (2 of 12 women [16.7%] vs. 1 of 112 women [< 1%]; $p = .0245$).

CONCLUSIONS: Although controversy surrounds the clinical utility of serum potassium monitoring in healthy women exposed to spironolactone for acne, based on the findings from this large patient population, monitoring of serum potassium is warranted for women over 45 years of age given an age-related greater risk of hyperkalemia.

AVOID POTASSIUM SPARING AGENTS, POTASSIUM SUPPLEMENTS, SOME ANTI-HYPERTENSIVE AGENTS ("PRILS", "ARTANS")
CAUTION IN PATIENTS WITH RENAL IMPAIRMENT, LITHIUM USE

THANK YOU


BACK IN 1971
WHAT THINGS COST
A first class stamp $0.06
A gallon of gas $0.36
A dozen eggs $0.53
A gallon of milk $1.18
A movie ticket $1.65
U.S. PRESIDENT
Richard Nixon
World POPULATION 3.76 BILLION
TECHNOLOGY
Ray Tomlinson invented internet based email.
Intel releases world's first microprocessor, the 4004.
Texas Instruments releases the first pocket calculator.
Apollo 14 lands on the Moon.
The first internet chat rooms appear.
FEDERAL MINIMUM WAGE $1.60 AN HOUR
IN THE NEWS...
The New York Times begins to publish sections of the Pentagon Papers, showing that the US Government had been lying to the American people.
Amtrak is created to provide US inter city passenger train services.
Federal Express is started by Fred Smith.
The first soft contact lens became available commercially in the U.S.
The first Starbucks opens at the Pike Place Market in Seattle, Washington.
The Walt Disney World theme park opens in Florida.
IN THEATERS...
The Owl and the Pussycat
Summer of '42
Ryan's Daughter
The Aristocats
Love Story
'70s SLANG
Psyche! - Just kidding
Far Out! - Cool
Dream On - Unrealistic
Right On! - In agreement
Can You Dig It? - Do you understand?
IN Style...
WOMEN
Polyester
Flared trousers
Platform shoes
Farrah Fawcett Flicks
MEN
V-neck velour shirts
Turtlenecks
Chest hair • Sideburns
Afros • Mullets
ON THE RADIO...
1. Joy to the World - Three Dog Night
2. Reason to Believe - Rod Stewart
3. I Feel the Earth Move - Carole King
4. One Bad Apple - The Osmonds
5. How Can You Mend a Broken Heart - Bee Gees
ON Television...
All My Children
Mary Tyler Moore
McCloud
The Odd Couple
The Partridge Family