Dermatol Ther (Heidelb) (2021) 11:79–91
https://doi.org/10.1007/s13555-020-00481-w

REVIEW

New Acne Therapies and Updates on Use of Spironolactone and Isotretinoin: A Narrative Review

Jane J. Han · Adam Faletsky · John S. Barbieri · Arash Mostaghimi

Received: October 26, 2020 / Published online: January 6, 2021

ABSTRACT

Acne vulgaris is a chronic inflammatory skin disease with a multifactorial pathogenesis. Although a variety of acne treatments are available, limitations of current therapies include tolerability, antimicrobial resistance, and costs and patient burden associated with monitoring. This narrative review focuses on emerging treatments and updates on the management of acne. Clascoterone, sarecycline, trifarotene, and novel lotion formulations of tretinoin and tazarotene have been evaluated in clinical trials and provide new options for treatment. Emerging data on the safety and efficacy of spironolactone and isotretinoin challenge current conventions and suggest a need to reconsider drug monitoring guidelines and risk prevention systems. Additional head-to-head data are needed to confirm these novel treatments' utility in treating acne.

Keywords: Acne; Clascoterone; Isotretinoin; Retinoids; Sarecycline; Spironolactone

Key Summary Points

Acne vulgaris is a common dermatological condition with evolving treatments and management guidelines.

Clascoterone is the first topical hormonal treatment for acne and has demonstrated efficacy and a tolerable safety profile in clinical trials.

New treatments such as sarecycline, trifarotene, and lotion tretinoin and tazarotene show promise, but data for head-to-head studies comparing these agents with existing options are limited.

Spironolactone is an important alternative to antibiotics, with ongoing trials for head-to-head comparison in progress.

Emerging data on isotretinoin suggest a benefit for reduced laboratory testing and reinforce a need to balance the safety benefits of regulations with their impact on access to care.

Jane J. Han and Adam Faletsky are co-first authors.

J. J. Han · A. Faletsky · A. Mostaghimi (✉)
Department of Dermatology, Brigham and Women's Hospital, Boston, MA, USA
e-mail: amostaghimi@bwh.harvard.edu

J. S. Barbieri
Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA

J. J. Han
Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA

A. Faletsky
Tufts University School of Medicine, Boston, MA, USA

DIGITAL FEATURES

This article is published with digital features, including a summary side, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13387886.

INTRODUCTION

Acne vulgaris is a chronic inflammatory skin disease with a multifactorial pathogenesis involving disordered keratinization, androgens resulting in sebum overproduction, and microbial colonization with *Cutibacterium acnes* [1–4]. Although a number of acne treatments are available, efforts to reduce side effects such as skin irritation, dryness, and photosensitivity and to improve efficacy via improved formulations and drugs with novel mechanisms of action are underway. Emerging treatments with novel mechanisms of action and improved formulations target various points along acne's multifactorial pathogenesis (Fig. 1). In this review, we aim to highlight new therapeutic developments and updates on the use of spironolactone and isotretinoin in acne.

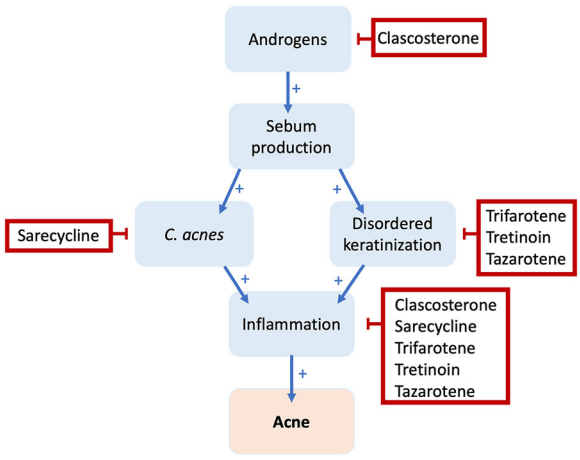

Fig. 1 Pathogenesis of acne (blue) and novel treatments' mechanism of action (red)

METHODS

A literature review was performed for the most recent clinical trials on novel acne treatments and papers with significant implications in the management of spironolactone and isotretinoin. Studies published between 2010 and 2020 were considered for this review. Studies on any severity of acne could be included in the review. The article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

NEW TREATMENTS

Clascoterone

Mechanism of Action

Clascoterone 1% cream is a novel Food and Drug Administration (FDA)-approved topical acne treatment. It is a steroidal antiandrogen and antiinflammatory without the risks of systemic adverse effects seen with systemic hormonal treatments such as oral spironolactone and combined oral contraceptives [5, 6].

Efficacy

Two phase III vehicle-controlled trials of clascoterone 1% cream demonstrated a significant reduction in inflammatory lesion counts at week 12 compared with vehicle (study 1: 44.8% versus 36.5%; study 2: 46.9% versus 29.6%) [7]. Additionally, a phase II randomized trial comparing clascoterone with tretinoin 0.05% cream also found that clascoterone was more efficacious in decreasing inflammatory lesion counts (67.3% versus 50.7%) and had a higher incidence of Investigator's Global Assessment (IGA) success (22.0% versus 12.0%) compared with tretinoin 0.05% cream, although this difference in IGA success was not statistically significant [6].

One benefit of clascoterone may be its quick onset of action, with improvements as early as week 2 and with increased efficacy through week 8 [6].

Safety

Clascoterone was well tolerated with the most common side effects in the two phase III vehicle-controlled trials being nasopharyngitis (study 1: 1.7% versus 3.7%; study 2: 1.1% versus 1.9%), headaches (study 1: 0.6% versus 0.3%; study 2: 1.1% versus 0.8%), oropharyngeal pain (study 1: 0.6% versus 0.3%; study 2: 1.1% versus 1.1%), and vomiting (study 1: 0.6% versus 0.6%; study 2: 0.5% versus 0.3%) compared with vehicle [7]. Clascoterone had a lower incidence of adverse effects compared with tretinoin 0.05% cream (10.7% versus 20.0%) [6]. Since clascoterone is rapidly hydrolyzed to cortexolone, there is a theoretical risk of adrenal suppression, though clinical evidence of symptomatic adrenal suppression was not observed in any of the clinical trials [8].

Clinical Implications

Clascoterone has an exciting new mechanism of action that has shown both efficacy and a tolerable side effect profile in phase III studies. It may be particularly useful due to its rapid efficacy.

Sarecycline

Mechanism of Action

Oral sarecycline is a narrow-spectrum tetracycline-class antibiotic with antiinflammatory properties [9]. Sarecycline displays antibacterial activity against *Cutibacterium acnes* equal to that of other tetracyclines. Its narrow spectrum has less activity against the host microbiome such as *Enterococci*, *Enterobacteriaceae*, and Gram-positive and Gram-negative anaerobes in comparison with other tetracyclines [10]. Another benefit of sarecycline compared with other tetracyclines is its low propensity to cross the blood–brain barrier, reducing the incidence of vestibular side effects [11].

Efficacy

In two identically designed phase III clinical trials, administration of sarecycline resulted in statistically significant reduction in inflammatory lesion counts (study 1: 51.8% versus 35.1%; study 2: 49.9% versus 35.4%) and improvement in IGA scores of both chest (study 1: 29.5% versus 19.6%; study 2: 36.6% versus 21.6%) and back (study 1: 32.9% versus 17.1%; study 2: 33.2% versus 25.7%) compared with placebo, with improvements starting as early as week 3 [11].

Another phase III double-blind, placebo-controlled trial evaluated efficacy in patients who had participated in a prior study for sarecycline: placebo/sarecycline group received placebo in the prior study, sarecycline/sarecycline group received sarecycline in the prior study, and both groups received sarecycline in the current study. Both groups demonstrated improvement in IGA success (placebo/sarecycline: 9.7–29.1%; sarecycline/sarecycline: 18.6–29.9%), defined as a two-point decrease from baseline IGA and an IGA score of clear (zero points) or almost clear (one point) if IGA score was more than three points [12].

Sarecycline has not been compared directly with other tetracyclines, limiting our ability to directly compare efficacy and side effect profile.

Safety

Pooled data from the identical paired phase III placebo-controlled studies found the most common side effects to be nausea (3.2% versus 1.7%), nasopharyngitis (2.8% and 2.3%), headache (2.8% versus 3.8%), and vomiting (1.3% versus 0.9%) compared with placebo [11]. Tetracycline specific adverse effects were also seen with sarecycline use including vulvovaginal candidiasis (study 1: 1.1% versus 0%; study 2: 0.3% versus 0%), vulvovaginal mycotic infections (study 1: 0.7% versus 0%; study 2: 1.0% versus 0%), and sunburn (study 1: 0.6% versus 0.4%; study 2: 0.2% versus 0.2%) compared with placebo [11]. No vestibular side effects were reported with the exception of vomiting [11], and no QT prolongation was identified even at supratherapeutic levels [9]. Similar to other tetracyclines, sarecycline is not recommended for use during pregnancy or breastfeeding [9].

Clinical Implications

Due to sarecycline's narrow spectrum of antibacterial activity, it has potential to be a

tetracycline alternative with less risk of antibiotic resistance. However, sarecycline is significantly more expensive than others in its class and its accessibility to patients should be considered [9]. Direct comparisons with other tetracyclines are needed to establish its efficacy within the tetracycline class.

Trifarotene

Mechanism of Action

Topical retinoids are vitamin A analogs used as first-line treatment options for acne [13]. These medications normalize follicular keratinization and proliferation within the pilosebaceous unit and have antiinflammatory properties [14, 15]. There has been interest in developing novel topical retinoids to reduce the incidence of common retinoid-associated side effects such as burning, erythema, and peeling [16, 17]. Trifarotene, a fourth-generation tretinoin, has selective agonist activity for retinoic acid receptor gamma (RAR-γ), and has increased stability in keratinocytes while being rapidly metabolized in hepatic microsomes, indicating a potentially more favorable safety profile when compared with first- and third-generation tretinoins [18].

Efficacy

In two phase III double-blind, randomized, vehicle-controlled studies assessing trifarotene use over the course of 12 weeks, trifarotene was effective in reducing inflammatory lesion counts (study 1: 54.4% versus 44.8%; study 2: 24.2% versus 18.7%) and had greater IGA treatment success (study 1: 29.4% versus 19.5%; study 2: 42.3% versus 25.7%) compared with vehicle [19]. A separate multicenter, open-label study of trifarotene demonstrated overall success rate (IGA and physician global assessment) to be 57.9% at week 52 [20].

Safety

Adverse events were seen in 48.1% of patients, with most occurring in the first 3 months of the study with decreased local irritation after 4 weeks of use [20]. The most common adverse effects in the double phase III study were erythema [study 1: 23.7% (moderate), 2.5% (severe); study 2: 33.2% (moderate), 10.0% (severe)], scaling [study 1: 21.4% (moderate), 2.9% (severe); study 2: 32.9% (moderate), 6.8% (severe)], dryness [study 1: 23.0% (moderate), 2.5% (severe); study 2: 36.4% (moderate), 7.1% (severe)], and stinging/burning [study 1: 16.3% (moderate), 4.2% (severe); study 2: 24.9% (moderate), 7.6% (severe)] [19]. No data were provided on the incidence of adverse effects in the vehicle group.

To date, there have been no head-to-head investigations comparing trifarotene with existing topical retinoids. Further studies are needed to demonstrate whether trifarotene has improved efficacy or safety compared with these standard-of-care retinoids.

Clinical Implications

Trifarotene holds promise as an acne treatment and has been marketed as being less irritating. However, there are no comparative effectiveness trials of trifarotene with other retinoids. Additional evidence is needed to support these claims.

Lotion Retinoids: Tretinoin and Tazarotene

In an effort to improve tolerability and effectiveness, existing tretinoin and tazarotene have been reformulated into new lotion vehicles.

Mechanism of Action

Polymerized emulsion releases topical retinoids uniformly across the skin, and allows for more efficient antiinflammatory effects. Uniform distribution theoretically decreases risk of adverse effects [21].

Efficacy

Tretinoin A randomized, double-blind, vehicle-controlled phase III study of 0.05% tretinoin lotion found significantly reduced number of inflammatory lesions at week 12 (52.1% versus 41.0%) and higher rates of IGA treatment success (17.7% versus 9.3%) in the tretinoin lotion compared with vehicle group [22].

Tazarotene Tazarotene 0.045% lotion was assessed in two phase III double-blind, randomized, vehicle-controlled studies, which demonstrated significantly greater reduction in inflammatory lesions by week 12 (study 1: 55.5% versus 45.7%; study 2: 59.5% versus 49.0%) compared with vehicle [21]. In a phase II double-blind, vehicle-controlled study comparing tazarotene 0.045% lotion with tazarotene 0.1% cream, tazarotene lotion had statistically significant reduction of inflammatory lesion counts (63.8% versus 51.4%) and had increased IGA treatment success (18.8% versus 10.1%) compared with vehicle [23]. When compared with tazarotene cream, tazarotene lotion was superior in reducing mean percentage of inflammatory lesions at week 12 (72.4% versus. 66.7%) and had superior IGA treatment success (18.8% versus 16.7%), although neither finding was statistically significant [23].

Safety

Tretinoin The overall incidence of adverse effects with tretinoin lotion was similar to vehicle (23.5% versus 19.3%) with most adverse effects being mild in severity [22]. A randomized, double-blind study also demonstrated a similar incidence of adverse effects compared with vehicle (23.5% versus 19.3%) [24]. Most common side effects compared with vehicle were pain (3.1% versus 0.4%), dryness (3.7% versus 0.1%), and erythema (1.4% versus 0.1%), which appeared to be dose dependent [24]. Although no direct comparisons of tretinoin lotion and tretinoin gel are available, separate vehicle-controlled studies of tretinoin gel at concentrations similar to tretinoin lotion demonstrated less reduction of inflammatory lesions by week 12 (36.0%) and higher incidence of adverse effects (52%) [17].

Tazarotene Tazarotene lotion overall had greater incidence of adverse effects compared with vehicle (14.7% versus 13.4%) but less than tazarotene cream (14.7% versus 26.8%) [23]. Most common side effects compared with vehicle were pain (5.3% versus 0.3%), dryness (3.6% versus 0.1%), exfoliation (2.1% versus 0%), and erythema (1.8% versus 0%) [21].

Clinical Implications

Lotion formulations of tretinoin and tazarotene offer acne treatment using the same mechanism of action as their established counterparts, but may be less irritating. Comparative effectiveness trials between both lotion tretinoin and tazarotene with their respective existing formulations are needed to support these claims.

UPDATES ON SPIRONOLACTONE USE

Spironolactone, an antiandrogen which prevents sebum production [25], is commonly used off-label as acne treatment and represents an important opportunity to improve antibiotic stewardship.

An Emerging Alternative to Antibiotics

Given the growing risk of antibiotic resistance, current guidelines recommend limiting oral antibiotic use to a maximum of 3–4 months and avoiding both topical and oral antibiotic monotherapy [26]. Although use of oral antibiotics for acne has declined, they are still the dominant systemic treatment prescribed for acne with many of these courses exceeding 6 months duration [27]. In addition, a survey of acne patients identified that they are aware of antibiotic resistance and are willing to try nonantibiotic treatments, though many were not aware such treatments are available [28].

A retrospective cohort study between 2010 and 2016 evaluated frequency of treatment switching in women started on oral antibiotics or spironolactone. The study found similar rates of treatment switching between oral tetracyclines and spironolactone (13.4% versus 14.4%) within 1 year, potentially indicating similar clinical efficacy in acne [29]. Although spironolactone use appears to be gaining traction as the number of prescriptions between 2004 and 2013 significantly increased, it still remains relatively underutilized, with antibiotics prescribed 3–7 times more often for women with acne [30].

Lab Monitoring

Concerns regarding tumorigenicity and hyperkalemia may contribute to spironolactone underutilization. However, no association between spironolactone use and breast cancer recurrence was found among patients with history of breast cancer [31]. In addition, several large cohort studies have highlighted that spironolactone use in routine clinical practice is not associated with increased risk of cancer [32]. Historical concerns around the potential for hyperkalemia among patients taking spironolactone were questioned in a 2015 study identifying low utility for checking potassium among healthy young women (< 45 years old) taking spironolactone for acne [33]. These findings have been confirmed in other studies [34]. Limited data for older populations suggest that closer monitoring for patients over 45 may be warranted [34].

These findings have led to changes in American Academy of Dermatology (AAD) guidelines to recommend against monitoring potassium levels for spironolactone use, except in certain populations such as older patients and those on other medications that affect potassium levels [26]. For these special populations, the AAD recommends obtaining baseline potassium levels, and rechecking once starting spironolactone or with changes in dose [26].

Although current literature supports the use of spironolactone in the use of acne, there is no high-quality evidence of its efficacy and clinical practice is based mostly on expert opinion [35].

Two separate randomized, double-blind clinical trials comparing spironolactone with other tetracyclines and placebo (FASCE [36] and spironolactone for adult female acne (SAFA) [37] clinical trials, respectively) are currently recruiting patients. The results of these trials may help establish spironolactone use as an alternative to oral antibiotics.

UPDATES ON ISOTRETINOIN USE

As the only acne medication with long-term disease-modifying potential [38], isotretinoin continues to be commonly used despite an exhaustive list of potential adverse effects [39]. Several recent studies have elaborated the utility of laboratory monitoring and the side effect profile of isotretinoin.

Lab Monitoring

Although clinically relevant lab abnormalities for patients taking isotretinoin are rare and monitoring practices vary by dermatologist, one common approach is to order lipid and hepatic panels prior to starting treatment and again 2 months after treatment initiation [40].

In a cohort study evaluating acne patients for laboratory abnormalities during isotretinoin therapy, grade 3 or greater triglyceride and hepatic abnormalities were seen in only 1% and 0.5% of patients, respectively [41]. Lab monitoring did not change the course of isotretinoin treatment even among patients over the age of 35 years and patients with baseline lab abnormalities [42, 43]. Pancreatitis is a potential consequence of hypertriglyceridemia and may contribute to frequent triglyceride monitoring. A systematic review of pancreatitis in the setting of isotretinoin use found pancreatitis to be rare, with only four cases over the past 35 years. Of the few cases, the etiology was most commonly idiopathic [44].

These results contribute to a growing literature suggesting that frequent lab monitoring, including obtaining baseline lab values, does not appear to have a meaningful impact on clinical management. Simplifying the standard of care for lab monitoring may decrease the burden of office visits for patients and decrease associated costs to the healthcare system.

iPLEDGE

Pregnancy

The teratogenic potential of isotretinoin has led to the use of risk evaluation and mitigation strategies, including the iPLEDGE system in the USA. One requirement of the iPLEDGE agreement is to use two forms of birth control, regardless of type and efficacy.

Amendments to iPLEDGE to consider the efficacy of different birth control methods may be helpful to improve patient compliance [45].

A recent modeling study examining the use of highly effective contraception including subdermal implants, hormonal intrauterine devices (IUDs), and non-hormonal IUDs demonstrated greater than 99.5% efficacy in preventing pregnancy within the first 6 months of use, with minimal (< 0.1%) increase in efficacy with the addition of secondary contraceptive methods [46]. Less effective contraceptive methods including depot medroxyprogesterone acetate (DMPA) injection, and combined hormonal contraception had similar rates of efficacy as subdermal implants and IUDs, but only when a secondary form of contraception was used simultaneously (99.5% and 99.2%, respectively) [46]. Presenting patients with the option to simplify iPLEDGE requirements by using a single method of highly effective contraception such as subdermal implants or IUDs may help decrease the burden of using multiple forms of contraception and frequent pregnancy monitoring.

Race and Sex

A retrospective review evaluated differences in treatment course among patients enrolled in iPLEDGE between the years 2008 and 2016 [47]. Non-White patients were found to have statistically significant interruptions in treatment (12% versus 4.8%) and early termination of isotretinoin treatment (43.5% versus 30.1%) compared with White patients. iPLEDGE was the most common reason for delays and interruptions in treatment, disproportionately affecting non-White patients [47]. A separate retrospective study focused on the association between race and sex on acne prescribing patterns confirmed that systemic therapies for the treatment of acne, such as isotretinoin, are underused in non-Hispanic Black patients and women compared with their non-Hispanic White and male counterparts, respectively [48].

Both strict contraceptive guidelines and logistical difficulties of abiding to iPLEDGE requirements are barriers to receiving appropriate acne treatment. Removing unnecessary obstacles may benefit patients by expediting treatment, reducing the psychosocial sequelae of permanent scarring, and mitigating the issue of antibiotic overprescription. Addressing these factors may increase isotretinoin accessibility from both the patient and prescribing physician's perspective [49].

Psychiatric Side Effects

A retrospective study evaluating reports of psychiatric adverse events in patients taking isotretinoin between the years 1997 and 2017 was conducted to characterize the relationship between isotretinoin and psychiatric effects. The study found that suicide rates among patients on isotretinoin were found to be lower than the national average, with most common psychiatric adverse effects being depressive disorders (42.3%), emotional lability (16.3%), and anxiety disorders (13.5%) [50]. Despite suicide being a highly publicized adverse effect, broadening our attention to other potential psychological adverse effects may be a more pragmatic approach given that patients with acne may be more susceptible to increased psychiatric burden [50].

Alopecia

A retrospective review of FDA reports on isotretinoin use from 1997 to 2017 was conducted to assess the incidence of alopecia as a side effect. Alopecia was found to make up a significant portion (9%) of all dermatological side effects [51]. Although not commonly cited or obviously related to isotretinoin, clinicians should remain aware of alopecia as a potential side effect [51].

CONCLUSION

In recent years, significant improvements in acne treatments have been developed with the goals of improving efficacy and tolerability (Table 1). Recent data supported reduced lab monitoring and warrant changes in guidelines for patients taking spironolactone and isotretinoin (Table 2). Future studies should focus

Table 1 Key findings of new treatments

Treatment	Mechanism of action	Efficacy: IGA success	Safety: most common side effects
Topical clascoterone	Steroidal antiandrogen and antiinflammatory effects	Greater compared with tretinoin 0.05% cream (22.0% versus 12.0%) [2]	Nasopharyngitis: 1.1–1.7% [3] Headaches: 0.6–1.1% [3] Oropharyngeal pain: 0.6–1.1% [3]
Oral sarecycline	Tetracycline antibiotic with antiinflammatory effects	Greater compared with placebo on chest (study 1: 29.5% versus 19.6%; study 2: 49.9% versus 35.4%)[a] [7] Greater compared with placebo on back (study 1: 32.9% versus 17.1%; study 2: 33.2% versus 25.7%)[a] [7]	Nausea: 3.2% [7] Nasopharyngitis: 2.8% [7] Headache: 2.8% [7]
Topical trifarotene	Selective vitamin A analog	Greater compared with vehicle (study 1: 29.4% versus 19.5%; study 2: 42.3% versus 25.7%)[a] [15]	Erythema: 23.7–33.2% (moderate), 2.5–10% (severe) [15] Scaling: 21.4–32.9% (moderate), 2.9–6.8% (severe) [15] Dryness: 23.0–36.4% (moderate), 2.5–7.1% (severe)
Lotion tretinoin	Emulsified vitamin A analog with more uniform distribution	Greater compared with vehicle (17.7% versus 9.3%)[a] [15]	Pain: 3.1% [20] Dryness: 3.7% [20] Erythema: 1.4% [20]
Lotion tazarotene		Greater compared with vehicle (18.8% versus 10.1%)[a] [19] Greater compared with tazarotene cream (18.8% versus 16.7%) [19]	Pain: 5.3% [21] Dryness: 3.6% [21] Exfoliation: 2.1% [21]

[a] Statistically significant

Table 2 Updates on management of spironolactone and isotretinoin

Spironolactone	Recent findings	Recommendations
Potential role in reducing antibiotic use	May be similar in efficacy compared with oral antibiotics	Although head-to-head trials are pending, consider spironolactone as an alternative to chronic oral antibiotics in the management of acne in females
Lab monitoring	There is low usefulness of potassium monitoring in young (< 45 years old), healthy women	Potassium monitoring is not required in young, healthy women taking spironolactone

Isotretinoin	Recent findings	Recommendations
Lab monitoring	Lab abnormalities are rare, and monitoring does not appear to influence the course of treatment	Consider reducing laboratory testing, including eliminating baseline laboratory tests for patients without risk factors for abnormalities. There is no value to monitoring complete blood count, and likely minimal value for liver function and triglyceride testing
iPLEDGE: pregnancy	Despite the regulatory burden of iPLEDGE, pregnancies and fetal exposure continue to be a challenge	There is a need for continued efforts to study and improve iPLEDGE to reduce fetal exposure to isotretinoin while minimizing administrative burden and eliminating barriers to care
iPLEDGE: race and sex	Non-White patients may have more delays in isotretinoin initiation and interruptions compared with White patients, potentially due to iPLEDGE requirements	iPLEDGE reforms are needed to improve access to care. Awareness of unconscious biases is important to prevent unintended consequences for patients of lower socioeconomic status

Table 2 continued

Isotretinoin	Recent findings	Recommendations
Psychiatric side effects	Psychiatric comorbidities such as depression, emotional lability, and anxiety are common among patients taking isotretinoin	Physicians should consider screening for psychiatric side effects of isotretinoin at monthly iPLEDGE visits
Alopecia	Alopecia is a reported effect of isotretinoin use	Remain vigilant for more rare adverse effects such as alopecia

on direct comparisons of the efficacy of acne treatments.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Dr. Mostaghimi reports personal fees from Pfizer, hims, and 3Derm and holds equity in hims and Lucid. Dr. Barbieri receives partial salary support through a Pfizer Fellowship grant to the Trustees of the University of Pennsylvania. Jane Han and Adam Faletsky have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

1. Degitz K, Placzek M, Borelli C, Plewig G. Pathophysiology of acne. J Dtsch Dermatol Ges. 2007;5(4):316–23.
2. Webster GF. The pathophysiology of acne. Cutis. 2005;76(2 Suppl):4–7.
3. Platsidaki E, Dessinioti C. Recent advances in understanding *Propionibacterium acnes* (*Cutibacterium acnes*) in acne. F1000Res. 2018;7:F1000 Faculty Rev-1953.
4. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. J Am Acad Dermatol. 1999;39(2 Pt 3):S34–7.
5. Barbieri JS. A new class of topical acne treatment addressing the hormonal pathogenesis of acne. JAMA Dermatol. 2020;156(6):619–20.
6. Trifu V, Tiplica G, Naumescu E, Zalupca L, Moro L, Celasco G. Cortexolone 17α-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study versus. placebo and tretinoin 0. 05% cream. Br J Dermatol. 2011;165(1):177–83.
7. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. JAMA Dermatol. 2020;156(6):621–30.
8. Mazzetti A, Moro L, Gerloni M, Cartwright M. Pharmacokinetic profile, safety, and tolerability of clascoterone (cortexolone 17-alpha propionate, CB-03-01) topical cream, 1% in subjects with acne vulgaris: an open-label phase 2a study. J Drugs Dermatol. 2019;18(6):563.
9. Haidari W, Bruinsma R, Cardenas-de la Garza JA, Feldman SR. Sarecycline review. Ann Pharmacother. 2019;54(2):164–70.
10. Zhanel G, Critchley I, Lin L, Alvandi N. Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris. Antimicrob Agents Chemother. 2019;63(1):e01297.
11. Moore AY, Charles JEM, Moore S. Sarecycline: a narrow spectrum tetracycline for the treatment of moderate-to-severe acne vulgaris. Future Microbiol. 2019;14(14):1235–42.
12. Pariser DM, Green LJ, Lain EL, et al. Safety and tolerability of sarecycline for the treatment of acne vulgaris: results from a phase III, multicenter, open-label study and a phase I phototoxicity study. J Clin Aesthet Dermatol. 2019;12(11):E53.
13. Kolli SS, Pecone D, Pona A, Cline A, Feldman SR. Topical retinoids in acne vulgaris: a systematic review. Am J Clin Dermatol. 2019;20(3):345–65.
14. Gollnick HPM. From new findings in acne pathogenesis to new approaches in treatment. J Eur Acad Dermatol Venereol. 2015;29:1–7.
15. Chien A. Retinoids in acne management: review of current understanding, future considerations, and focus on topical treatments. J Drugs Dermatol. 2018;17(12):s51.
16. Baldwin HE, Nighland M, Kendall C, Mays DA, Grossman R, Newburger J. 40 years of topical tretinoin use in review. J Drugs Dermatol. 2013;12(6): 638.
17. Webster G, Cargill DI, Quiring J, Vogelson CT, Slade HB. A combined analysis of 2 randomized clinical studies of tretinoin gel 0.05% for the treatment of acne. Cutis. 2009;83(3):146.
18. Aubert J, Piwnica D, Bertino B, et al. Nonclinical and human pharmacology of the potent and selective topical retinoic acid receptor-γ agonist trifarotene. Br J Dermatol. 2018;179(2):442–56.
19. Tan J, Thiboutot D, Popp G, et al. Randomized phase 3 evaluation of trifarotene 50 μg/g cream treatment of moderate facial and truncal acne. J Am Acad Dermatol. 2019;80(6):1691–9.
20. Blume-Peytavi U, Fowler J, Kemény L, et al. Long-term safety and efficacy of trifarotene 50 μg/g cream, a first-in-class RAR-γ selective topical retinoid, in patients with moderate facial and truncal acne. J Eur Acad Dermatol Venereol. 2020;34(1): 166–73.
21. Tanghetti EA, Werschler WP, Lain T, Guenin E, Martin G, Pillai R. Tazarotene 0.045% lotion for once-daily treatment of moderate-to-severe acne vulgaris: results from two phase 3 trials. J Drugs Dermatol. 2020;19(1):70–7.
22. Tyring SK, Kircik LH, Pariser DM, Guenin E, Bhatt V, Pillai R. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of efficacy and safety in patients aged 9 years and older. J Drugs Dermatol. 2018;17(10):1084.

23. Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. J Drugs Dermatol. 2019;18(6):542.

24. Harper JC, Roberts WE, Zeichner JA, Guenin E, Bhatt V, Pillai R. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. J Dermatol Treat. 2020;31(2):160–7.

25. Akamatsu H, Zouboulis CC, Orfanos CE. Spironolactone directly inhibits proliferation of cultured human facial sebocytes and acts antagonistically to testosterone and 5α-dihydrotestosterone in vitro. J Investig Dermatol. 1993;100(5):660–2.

26. 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.e33.

27. Barbieri JS, James WD, Margolis DJ. Trends in prescribing behavior of systemic agents used in the treatment of acne among dermatologists and non-dermatologists: a retrospective analysis, 2004–2013. J Am Acad Dermatol. 2017;77(3):456-463.e4.

28. Del Rosso JQ, Rosen T, Palceski D, Rueda MJ. Patient awareness of antimicrobial resistance and antibiotic use in acne vulgaris. J Clin Aesthet Dermatol. 2019;12(6):30–41.

29. Barbieri JS, Choi JK, Mitra N, Margolis DJ. Frequency of treatment switching for spironolactone compared to oral tetracycline-class antibiotics for women with acne: a retrospective cohort study 2010–2016. J Drugs Dermatol. 2018;17(6):632.

30. Guzman AK, Barbieri JS. Comparative analysis of prescribing patterns of tetracycline class antibiotics and spironolactone between advanced practice providers and physicians in the treatment of acne vulgaris. J Am Acad Dermatol. 2020;S0190-9622(20)31141–5.

31. Wei C, Bovonratwet P, Gu A, Moawad G, Silverberg JI, Friedman AJ. Spironolactone use does not increase the risk of female breast cancer recurrence: a retrospective analysis. J Am Acad Dermatol. 2020;83(4):1021–7.

32. Mackenzie IS, MacDonald TM, Thompson A, Morant S, Wei L. Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. BMJ. 2012;345(7868):17.

33. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. JAMA Dermatol. 2015;151(9):941–4.

34. Thiede RM, Rastogi S, Nardone B, et al. Hyperkalemia in women with acne exposed to oral spironolactone: a retrospective study from the RADAR (research on adverse drug events and reports) program. Int J Women's Dermatol. 2019;5(3):155–7.

35. Layton AM, Eady EA, Whitehouse H, Del Rosso JQ, Fedorowicz Z, van Zuuren EJ. Oral spironolactone for acne vulgaris in adult females: a hybrid systematic review. Am J Clin Dermatol. 2017;18(2):169–91.

36. Randomized double-blind study on the benefit of spironolactone for treating acne of adult woman. (FASCE). https://www.clinicaltrials.gov/ct2/show/NCT03334682. Accessed 12 Oct 2020.

37. Spironolactone for adult female acne: a pragmatic multicentre double-blind randomised superiority trial to investigate the clinical and cost-effectiveness of spironolactone for moderate or severe persistent acne in women. https://www.southampton.ac.uk/ctu/trialportfolio/listoftrials/safa.page. Accessed 28 Sept 2020.

38. Barbieri JS, Spaccarelli N, Margolis DJ, James WD. Approaches to limit systemic antibiotic use in acne: systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments. J Am Acad Dermatol. 2019;80(2):538–49.

39. Medication guide: accutane. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018662s061MedGuide.pdf. Accessed 28 Sept 2020.

40. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. JAMA Dermatol. 2015;152(1):1–10.

41. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. J Am Acad Dermatol. 2020;82(1):72–9.

42. Tkachenko E, Sharma P, Mostaghimi A. Abnormal baseline lab results rarely lead to treatment modification for patients on isotretinoin. Dermatology. 2020;236(6):517–20.

43. Sharma P, Tkachenko E, Mostaghimi A. A retrospective evaluation of routine isotretinoin laboratory monitoring in patients above 35 years old. J Am Acad Dermatol. 2020;84(1):201–2.

44. Opel D, Kramer ON, Chevalier M, Bigby M, Albrecht J. Not every patient needs a triglyceride check, but all can get pancreatitis: a systematic review and clinical characterization of isotretinoin-associated pancreatitis. Br J Dermatol. 2017;177(4): 960–6.

45. Tkachenko E, Singer S, Sharma P, Barbieri J, Mostaghimi A. US food and drug administration reports of pregnancy and pregnancy-related adverse events associated with isotretinoin. JAMA Dermatol. 2019;155(10):1175.

46. Barbieri JS, Roe AH, Mostaghimi A. Simplifying contraception requirements for iPLEDGE: a decision analysis. J Am Acad Dermatol. 2020;83(1): 104–8.

47. Charrow A, Xia FD, Lu J, Waul M, Joyce C, Mostaghimi A. Differences in isotretinoin start, interruption, and early termination across race and sex in the iPLEDGE era. PLoS ONE. 2019;14(3):e0210445.

48. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. Association of race/ethnicity and sex with differences in health care use and treatment for acne. JAMA Dermatol. 2020;156(3):312–9.

49. Barbieri JS, Frieden IJ, Nagler AR. Isotretinoin, patient safety, and patient-centered care—time to reform iPLEDGE. JAMA Dermatol. 2019;156(1): 21–2.

50. Singer S, Tkachenko E, Sharma P, Barbieri JS, Mostaghimi A. Psychiatric adverse events in patients taking isotretinoin as reported in a food and drug administration database from 1997 to 2017. JAMA Dermatol. 2019;155(10):1162–6.

51. Tkachenko E, Singer SB, Sharma P, Barbieri J, Mostaghimi A. FDA reports of alopecia as an adverse event to isotretinoin. J Cutan Med Surg. 2019;23(4): 451–2.