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Targeted Antibiotic for Acne: A Path for Antimicrobial Stewardship

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A Novel Antibiotic Just for Acne

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Dermatologists consistently rank as the most frequent prescribers of systemic antibiotics, and one of the most common diagnoses for which we recommend these agents is acne vulgaris. Up to three quarters of the antibiotics that dermatologists prescribe are in the tetracycline class.[1] Even though dermatology as a specialty is well-known for off-label prescribing, it may be surprising to note that no systemic antibiotic had been FDA approved solely for treatment of acne—until recently.

The approval last year of sarecycline (Seysara) marked the first time the FDA approved a systemic antibiotic specifically for use in the management of moderate to severe acne and no other conditions. Sarecycline is part of the tetracycline class of antibiotics. However, this novel drug can be differentiated from predecessors in the class. In fact, modification of the chemical structure of sarecycline is thought to account for the drug's targeted activity against *Cutibacterium acnes (C. acnes)*.[2] Additionally, data suggest that sarecycline has a substantially decreased activity against Gram-negative bacteria and hence less effect on the normal human intestinal microbiome.[3] Reduced impact on the normal intestinal flora encourages overall patient health by supporting healthy metabolism, nutrient absorption, and possibly prevention of inflammation in specific cells. Decreased incidence of gut dysbiosis associated with sarecycline may lead to increased tolerability of the drug, relative to older tetracyclines. Doxycycline, for example, has been associated with high rates of new-onset inflammatory bowel disease.[4]

It is exciting to consider the potential long-term clinical benefits we may see by using a systemic tetracycline drug that has targeted activity against *C. acnes* and reduced risk for developing bacterial resistance.[5] As the specialists who prescribe the most antibiotics, dermatologists have been challenged to confront the problem of antibiotic resistance by modifying their approach to acne management over the past two decades. We understand the need to reduce reliance on systemic antibiotics and recognize that adding to the regimen topical antimicrobials, such as benzoyl peroxide and retinoids, can further reduce the risk for developing resistance. While we must continue to adhere to guidelines of care for acne management, and exercise caution by demonstrating good antibiotic stewardship, dermatology providers will be heartened by the knowledge detailed by Dr. Armstrong and Mr. Hekmatjah that sarecycline is less likely to contribute to antibiotic resistance and less likely to impact the gut microbiome.

It should be noted that, despite the potential adverse events and off-target side effects associated with the broad-spectrum activity of tetracycline, doxycycline, and minocycline, they have been used to treat acne in a substantial number of patients over several decades. This history of use is well described in the pages ahead.

Imagine, then, the benefit of having a next-generation drug of the same therapeutic class but with a narrow spectrum of coverage and direct targeting of acne vulgaris.

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Oral Tetracyclines and Acne: A Systematic Review for Dermatologists

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ABSTRACT

Oral tetracyclines are the most widely prescribed systemic antibiotic for acne. Synthesis of efficacy and safety of traditional and novel oral tetracyclines is highly informative to clinical practice. We conducted a systematic search of PubMed to identify large interventional and observational studies utilizing oral tetracyclines as an acne treatment. We identified 13 articles meeting inclusion for this review, which represented 226,019 pediatric and adult acne patients. Oral tetracyclines that were included in this systematic review were sarecycline (a novel narrow-spectrum tetracycline), doxycycline, minocycline, and tetracycline. Based on shared and divergent outcome measures, different oral tetracyclines were variably effective against facial acne. Sarecycline also demonstrated efficacy in truncal acne. Members of the oral tetracycline class also differed in their ability to minimize antibiotic resistance and gut dysbiosis.

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INTRODUCTION

Acne vulgaris is a common skin disease affecting up to 70% of the population during their lifetime.[1] *Cutibacterium acnes* is the primary target of acne pathogenesis, and oral antibiotics, namely oral tetracyclines, have been the mainstay of systemic acne treatment for decades. In addition, oral tetracyclines possess an indirect anti-inflammatory effect against acne.[2,3] Oral tetracyclines are an important part of the acne treatment regimen, and substantial evidence exists for their efficacy and safety for use in inflammatory acne.[4]

Oral tetracyclines demonstrate bacteriostatic (inhibiting bacterial growth) effects against *C. acnes*; however, some tetracyclines also exhibit bacteriostatic effects on beneficial commensal organisms of the gut. This broad-spectrum effect can lead to a less diverse gut microbiome. Disruptions in the symbiotic relationship between the gut microbiome and the host have been associated with chronic diseases, such as obesity and inflammatory bowel disease (IBD).[5,6] Although a compositional definition of an ideal gut microbiome does not exist, greater microbial diversity is important for protection from pathogens, nutrient supply, and vitamin production.[7]

While oral tetracyclines are widely prescribed for acne, a gap exists in synthesizing the most recent data on the efficacy and safety of these agents. We conducted a systematic review of the efficacy and safety of common oral tetracyclines (sarecycline, doxycycline, minocycline, and tetracycline) used for acne.

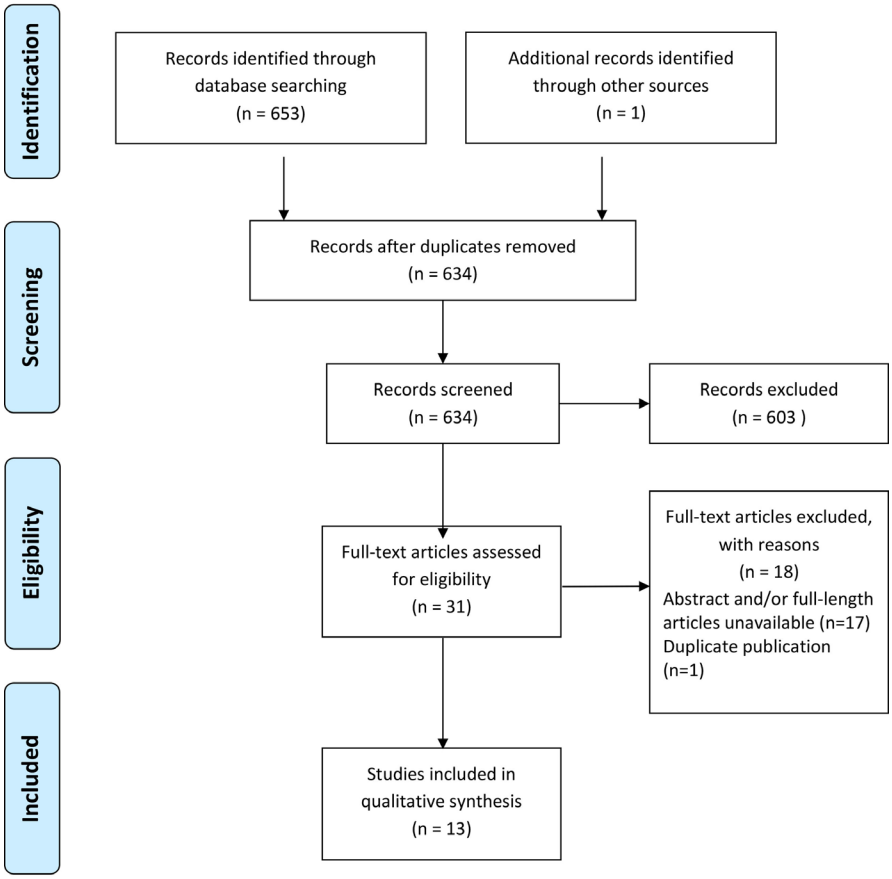
METHODS

To determine the efficacy and safety of oral tetracyclines for acne, we followed the Preferred Reporting Items for Systematic Reviews guidelines and performed a systematic review using PubMed and Embase. Our search included published articles from January 1960 to April 2020, and our search criteria included the following: ("Acne"[MeSH] OR "Acne Vulgaris"[MeSH]) OR "acne vulgaris/drug therapy"[MeSH Major Topic]) AND tetracyclines [MeSH Terms]. This initial search identified 653 articles (Figure 1).

To include adequately powered studies for efficacy and safety assessments, we then applied the following inclusion criteria: large interventional (controlled and uncontrolled) and observational studies utilizing tetracycline antibiotics ($N \geq 200$); acne indication; outcomes included acne severity assessments and/or rates of adverse events (AE). We excluded non-English articles and combination treatments. Lymecycline and oxytetracycline were not included due to their limited use in the U.S.

Two authors (JH and AWA) evaluated titles and abstracts of identified articles to determine eligibility based on inclusion and exclusion criteria. Selected articles underwent full-text review, and subsequently, two authors (JH and AWA) independently extracted the data. We performed quality assessment using the Cochrane Risk of Bias Tool for randomized interventional studies and the Newcastle-Ottawa scale for observational studies. The review protocol was registered with PROSPERO.

FIGURE 1. Selection process for study inclusion in the systematic review.



RESULTS

A total of 13 articles met the inclusion criteria for this review (Figure 1). These studies represented 226,019 acne patients, and study outcomes are summarized in Table 1. Qualitative assessment for randomized interventional and observational studies is reported in Supplemental Tables 1 and 2, respectively.

Common Primary Endpoint Measures

From the examined studies, the most common primary endpoint was the change in inflammatory lesions from baseline. This was measured by the absolute change or percent change of inflammatory lesions from baseline. Some studies also included the change in total lesion count from baseline as additional co-primary endpoints.

Another commonly used outcome measure was the Investigator's Global Assessment (IGA), a 5-point scale where 0 equals clear and 4 equals severe. For example, a study defined IGA treatment success as a score of 0 (clear) or 1 (mostly clear) plus a two-grade improvement from baseline at 12 weeks.[8] Other assessment tools included the Evaluator's Global Severity Assessment (EGSA), a 6-point scale where 0 equals clear and 5 equals very severe, where a study defined treatment success as a score of 0 (clear) or 1 (almost clear) at 12 weeks.[9]

Oral Tetracyclines

Sarecycline

Sarecycline is a novel, narrow-spectrum, oral tetracycline that inhibits bacterial protein synthesis by impeding the 30S ribosomal subunit; it also exhibits anti-inflammatory properties by inhibiting neutrophil chemotaxis and matrix metalloproteinases.[2,3] Sarecycline was developed to specifically treat acne. Similar to other tetracyclines, sarecycline is composed of four six-carbon rings; however, sarecycline is unique because it has been modified at the C-7 position with a distinctive aminomethyl functional group.[10]

TABLE 1.

Treatment, Efficacy, and AE/Other Considerations of Reviewed Oral Tetracyclines

Treatment	Efficacy	Adverse Events (AE)/Other Considerations
Oral Sarecycline, Daily Dosing: 60mg (33–54 kg or 73–120 lb), 100 mg (55–84 kg or 121–185 lb), and 150mg (85–136 kg or 186–300 lb)	At week 12, 1.5 mg/kg daily as compared to placebo[8]: *Facial Acne* • 21.9% and 22.6% vs 10.5% and 15.3% achieved IGA 0 or 1 (P<0.0001, P=0.0038).[8] • -51.8% and -49.9% vs -35.1% and -45.4% mean reduction from baseline in inflammatory lesions (P<0.0001 for both studies).[8] *Truncal Acne* *Back Acne* • 32.9% and 33.2% vs 17.1% and 25.7% achieved IGA 0 or 1 (P<0.0001, P<0.05).[8] *Chest Acne* • 29.6% and 36.6% vs 19.6% and 21.6% achieved IGA 0 or 1 (P<0.05, P<0.0001).[8]	Nausea (1.9–4.6%),[8] vomiting (0.6–2.1%),[8] diarrhea (1.0–1.2%) [8] Headache (2.7–2.9%),[8] dizziness (0.4–0.6%)[8] Sunburn (0.6–0.8%),[8] photosensitivity (0.2%)[8] Vulvovaginal mycotic infection (0.7–1.0%),[16] vulvovaginal candidiasis (0.3–1.1%)[8]
Oral Doxycycline, Daily or Twice Daily Dosing: 50–100mg	At week 16, 40mg daily as compared to placebo[16]: • 16.1 vs 12.6 in the mean reduction in inflammatory lesions (P=0.006).[16] At week 16, 40mg daily as compared to 100mg daily[16]: • 16.1 vs 12.9 in the mean reduction in inflammatory lesions (P=0.024).[16] At week 16, 100mg daily as compared to placebo[16]: • 12.9 vs 12.6 in the mean reduction in inflammatory lesions (P=0.595).[16]	Photosensitivity (15–30.5%)[45] Gastrointestinal (NOS) (10–25%),[46] nausea (3.2–6.3%),[18] vomiting (6.7%)[18] Headache (6.5–6.7%)[18] Vulvovaginal fungal infections with higher doses (2.0–2.8%).[45] Doxycycline treated patients were over 60% more likely to develop new-onset IBD.[18]
Oral Minocycline, Daily Dosing: 50–135mg	At week 12, 1mg/kg daily as compared to placebo[21]: • 45.5% vs 32.4% reduction in inflammatory lesion counts (P<0.001).[21] • 16.6% vs 8.7% achieved EGSA 0 or 1 (P<0.001).[21] At week 12, 100mg daily as compared to zinc 30mg daily[22]: • -66.55% vs -49.84% reduction in superficial inflammatory lesions (P<0.01).[22] At week 12, 50mg daily[24]: • Severity improvement from 62.6 to 22.6 (P<0.0001).[24] At week 18, 100mg daily[25]: • Mean decrease in inflammatory lesions from baseline was 22.3.[25]	General AE rates 6-21%[22, 24, 26] Gastrointestinal (NOS) (1.5–25%),[25,26,45] diarrhea (2%),[25] nausea (~1%)[19] Central Nervous System (NOS) (17%),[45] Acute vestibular events (~10%)[9] Cutaneous (NOS) (1.5%),[25] pruritus (4.5%),[21] rash (~1%),[24] urticaria, photosensitive rash, and pruritus (0.6%)[26] Vulvovaginal fungal infections. Pigmentation was reported significantly more in patients treated with 200mg/daily as compared to 100mg/daily or 100mg/200mg alternately.[26] Minocycline treated patients were approximately two-to-eight times more likely to develop SLE and 20% more likely to develop new-onset IBD.[19,27,28]
Oral Tetracycline, Daily or Twice Daily Dosing; 250–500mg	At week 8, 250mg twice daily as compared to placebo[30]: • 8.3 vs 11.7 mean reduction in papule counts (P<0.05).[30] At week 12, 1000mg/500mg as compared to 1000mg/333mg erythromycin[31]: • Both groups saw significant reductions in mean lesion counts (P<0.0001).[32]	General AE rates 10.3%-22%[31,46] Gastrointestinal (NOS) (3.4%),[46] diarrhea (2.5%),[30] elevated total bilirubin (2.5%),[32] epigastric pain (1.1%)[30] Vaginal candidiasis (1.2%)[31] Pseudotumor cerebri (1.2%)[31] Tetracycline treated patients were approximately 40% more likely to develop new-onset IBD.[18]

NOS: not otherwise specified

This stable modification at C-7 is thought to contribute to sarecycline's targeted activity against *C. acnes* and the 16- to 32-fold decreased activity against the normal human intestinal microflora.[10,11] It has shown little or no antimicrobial activity against Gram-negative bacteria commonly found in the human gut, such as *Enterobacteriaceae*.[10] Due to these unique properties of sarecycline, the potential for antibacterial resistance is low.[10,12] *C. acnes* strains displayed a very low propensity for the development of resistance to sarecycline, with spontaneous mutation frequencies being 10^{-10} at 4–8 × MIC.[10,12] Sarecycline also showed low spontaneous mutation frequencies ranging from 10^{-9} for *S. aureus* and 10^{-8} for *S. epidermidis* at 4- and 8-fold the MIC.[10] Sarecycline was approved by the Federal Drug Administration (FDA) in 2018 for the treatment of moderate-to-severe acne in patients 9 years and older.[12] It is also the only oral tetracycline-class drug with reported truncal efficacy data.[12] Sarecycline is a once daily treatment that can be taken with or without food, and its weight-based dosing is as follows: 60mg (33–54 kg or 73–120 lb), 100mg (55–84 kg or 121–185 lb), and 150mg (85–136 kg or 186–300 lb).[12]

Among 2,002 moderate-to-severe acne patients who are 9–45 years old in two phase III trials, researchers found that at the week 12 assessment of facial acne, 21.9% and 22.6% of those who received sarecycline 1.5mg/kg daily achieved the outcome of IGA 0 or 1 versus 10.5% and 15.3% of the placebo group (P<0.0001and P=0.0038) for trials SC1401 and SC1402, respectively (Table 1).[11] Both trials also demonstrated significant reductions in the mean percentage change in facial inflammatory lesion counts in the sarecycline-group (-51.8% and -49.9%) as compared to placebo (-35.1% and -35.4%) at week 12 (P<0.0001 for trials SC1401and SC1402, respectively) (Table 1).[8] Significant reductions in the mean percentage change in inflammatory lesions in sarecycline-treated patients started as early as week 3.[8]

Sarecycline also had significantly greater mean percentage reductions in non-inflammatory lesions (open and closed comedones) by week 6 in patients with ≥ 10 baseline non-inflammatory lesions (post-hoc pooled analysis).[13]

Based on the truncal data unique to sarecycline, in patients with moderate-to-severe back acne, 32.9% and 33.2% of the sarecycline group achieved IGA 0 or 1 versus 17.1% and 25.7% in the placebo group (P<0.0001 and P<0.05) at week 12, in the two trials, SC1401 and SC1402, respectively (Table 1).[8] In patients with moderate-to-severe chest acne, 29.6% and 36.6% of the sarecycline-group achieved IGA 0 or 1 versus 19.6% and 21.6% of the placebo group (P<0.05 and P<0.0001) at week 12, in the two trials SC1401 and SC1402, respectively (Table 1).[8]

Sarecycline was overall well tolerated. The most common AE was headache (2.7–2.9%).[8] Gastrointestinal AE included nausea (1.9–4.6%), vomiting (0.6–2.1%), and diarrhea (1.0–1.2%).[8] There were low rates of sunburn (0.6–0.8%), photosensitivity (0.2%), dizziness (0.4–0.6%), vulvovaginal mycotic infection (0.7–1.0%), and vulvovaginal candidiasis (0.3–1.1%) (Table 1).[8] A 40-week open-label safety extension study showed similar results, and thus a safety profile was established for up to 12 months.[12,14]

Doxycycline

Doxycycline is an oral tetracycline composed of four six-carbon rings, with a hydroxyl-group at C-5 and a methyl-group at C-6.[15] Similar to other tetracyclines, doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline also inhibits neutrophil chemotaxis and matrix metalloproteinases.[2,3] It is FDA-approved in the adjunctive treatment of severe acne, and dosing ranges between 50–100mg daily or twice daily.[16]

In a Phase 2 study of 662 moderate-to-severe acne patients, ages 12 years and older, researchers found that at week 16, the mean decrease in inflammatory lesions was 16.1 in those prescribed 40mg [modified-release (MR)] daily versus 12.6 in the placebo group (P=0.006).[17] Both the 40mg (MR) group and 100mg group (16.1 and 12.9, respectively) saw comparable decreases in inflammatory lesions at week 12 (P=0.024).[17] The 100mg-group and placebo group (12.9 and 12.6, respectively) saw similar decreases in inflammatory lesions at week 12 with no statically significant difference (P=0.595) (Table 1).[15] In this trial, the severity of AE were mild or moderate and included headache (6.5%–6.7%), nausea (3.2%–6.4%), and vomiting (6.7%) (Table 1).[17]

In one study that assessed doxycycline calcium vs placebo for moderate-to-severe acne, gastrointestinal adverse events ranged from 9.4% to 22.9% in the treatment groups and was 9.0% in the placebo group.[9]

In a retrospective study of 94,487 acne patients, ages 15–35 years old, researchers found that those who received doxycycline (N=15,032) were over 60% more likely to develop new-onset inflammatory bowel disease (IBD) [hazard ratio (HR) 1.63; 95% CI 1.05–2.52] (Table 1).[18]

Minocycline

Minocycline is an oral tetracycline composed of four six-carbon rings with a dimethylamine group attached at C-7, making minocycline one of the most lipophilic tetracycline agents.[15] Similar to other tetracyclines, minocycline inhibits bacterial protein synthesis by impeding the 30S ribosomal subunit and exerts anti-inflammatory properties by inhibiting neutrophil chemotaxis and matrix metalloproteinases.[2,3] Minocycline is FDA-approved in the adjunctive treatment of severe acne,

and dosing ranges between 50–135mg daily.[19] Due to its high lipophilicity, minocycline crosses the blood-brain barrier and achieves high concentrations in the CNS, and this may explain the higher rates of vestibular side effects (such as nausea, vomiting, dizziness, and vertigo), when compared to other tetracycline-class drugs.[20]

In two similarly designed clinical trials involving 1,038 moderate-to-severe acne patients, ages 12 years old, researchers found that, at 12 weeks, those prescribed extended-release minocycline 1 mg/kg daily experienced a 45.5% reduction in inflammatory lesions versus 32.4% in the placebo group (P<0.001).[21] Additionally, 16.6% of the minocycline-group achieved EGSA 0 or 1 versus 8.7% of the placebo group (P<0.001) (Table 1).[21] In these pivotal trials, the severity of AE were mild or moderate and included acute vestibular events (~10%) and pruritus (4.5%) (Table 1).[21]

In another trial of 332 inflammatory acne patients, ages 12 years and older, researchers found that, at 3 months, those prescribed minocycline 100mg daily experienced a 66.55% reduction in inflammatory lesions as compared to a 49.84% reduction in those treated with zinc 30mg daily (P<0.01) (Table 1).[22] Of those treated with minocycline, 21.3% of patients reported AE, which were predominantly gastrointestinal disorders and allergic skin reactions (Table 1).[22]

In one trial, Stewart (2006) reported various measures at 12 weeks, including ear and labyrinth disorders, vertigo, dizziness, and patients with ≥ one acute vestibular adverse event. Incidence of dizziness ranged from 13.6% to 22.0% in the treatment groups and was 5.5% in the placebo group.[23]

In an open-label study of 338 acne patients, ages 13–30 years old, 12 weeks of minocycline 50mg twice-daily resulted in a significant improvement in the mean acne severity score [62.6 to 22.6, (P<0.0001)] (Table 1).[24] Six percent of patients reported AE, which included diarrhea (2%), rash (~1%), and nausea (~1%) (Table 1).[24] In another trial of 649 mild-to-moderate acne patients, ages 11–42 years old, researchers found that at week 18 the mean decrease in inflammatory lesions from baseline was 22.3 for those treated with minocycline 100mg (N=130) daily (Table 1).[25] At week 18, the rates of gastrointestinal and cutaneous AE were <2% for the minocycline-treated patients.[25]

In an open-label safety study of three different minocycline dosing regimens (100mg daily, 100mg/200mg on alternate days, and 200mg daily) involving 700 acne patients, ages 13–48 years old, 13.6% of patients reported AE.[26] Minocycline-induced pigmentation was significantly higher in those treated with 200mg daily as compared to those treated with 100mg daily or 100mg/200mg on alternate days (P<0.01) (Table 1).[26] Rates of gastrointestinal symptoms were similar in all groups (1.1%–2.4%), and cutaneous AE, such as urticaria, photosensitive rash, and pruritus occurred in <1% of all groups (Table 1).[26]

Three large retrospective studies demonstrated associations between minocycline and lupus-like syndrome, systemic lupus erythematosus (SLE), and IBD.[18, 27,28] In a retrospective case-control study of 27,688 acne patients, ages 15–29 years old, researchers found that those who were currently prescribed any dose of minocycline were over eight times more likely to develop a lupus-like syndrome as compared with nonuse or past use of all combined oral tetracyclines [OR 8.5; 95% CI 2.1–35.0] (Table 1).[2] Similarly, a retrospective cohort study of 97,694 acne patients, ages 15–35 years old, found that SLE was over twice as likely to occur in those taking minocycline, but not other oral tetracyclines [HR 2.64; 95% CI 1.51–4.66] (Table 1).[28] Additionally, a retrospective study 94,487 acne patients, ages 15–35 years old, found that those who received minocycline (N=24,085) were approximately 20% more likely to develop new-onset IBD [HR 1.19; 95% CI 0.79–1.79] (Table 1).[18]

Tetracycline

Tetracycline was the first member of the tetracycline class. It is composed of four six-carbon rings with a hydroxyl-group and a methyl-group attached at C-6.[3] Similar to other agents, tetracycline inhibits bacterial protein synthesis by impeding the 30S ribosomal subunit. Tetracycline also displays anti-inflammatory properties by inhibiting neutrophil chemotaxis and matrix metalloproteinases.[2,3] It is FDA-approved in the adjunctive treatment of severe acne, and dosages range from 250–500mg daily or twice-daily.[29]

In a trial of 305 moderate-to-severe acne patients, ages 18–35 years old, the mean papule count was significantly lower in those treated with tetracycline 250mg twice-daily (8.3) versus placebo (11.7) at week 8 (P<0.05) (Table 1).[30] AE in those treated with tetracycline were diarrhea (2.5%) and epigastric pain (1.1%) (Table 1).[30] In another trial of 200 moderate-to-severe acne patients, ages 14–30 years old, those treated with tetracycline (1000mg for 4 weeks followed by 500mg for 8 weeks) and erythromycin (1000mg for 4 weeks followed by 333mg for 8 weeks) saw significant reductions in mean lesion counts from baseline (P<0.0001) at week 12 (Table 1).[31] Approximately ten percent of those treated with tetracycline reported AE, the majority of which included nausea and vomiting; vaginal candidiasis (1.2%), and pseudotumor cerebri (1.2%) were also reported (Table 1).[31]

Two retrospective studies assessed the safety of tetracycline use. In a retrospective hematology and chemistry safety study of 312 acne patients, researchers found that long term (≥3 years) tetracycline (250mg twice daily) use was generally

safe; however, 2.5% of patients were found to have persistent elevations in total bilirubin (Table 1).[32] In another retrospective study 94,487 acne patients, ages 15–35 years old, researchers found that those who received tetracycline (N=38,603) were approximately 40% more likely to develop new-onset IBD [HR 1.43; 95% CI 1.92–2.02] (Table 1).[18]

DISCUSSION

Dermatologists play an important role in antibiotic stewardship because dermatologists write the highest number of antibiotic prescriptions per clinician, and oral tetracyclines account for approximately 75% of these antibiotic prescriptions.[33] In this review, we summarized the efficacy and safety of oral tetracyclines indicated for acne from large clinical trials and observational studies.

Maintaining diversity of the gut microbiome is important. For example, one benefit of a diverse gut microbiome is the production of short-chain fatty acids (SCFA). SCFA have been found beneficial in metabolism, nutrient absorption, and prevention of carcinogenesis and inflammation in specific cells.[33-36] However, the broad-spectrum antimicrobial actions of some oral tetracyclines may be associated with gut dysbiosis.[7] Multiple factors can contribute to the adverse effect of gut dysbiosis, which includes mechanism of action, dose, and duration.[37] For example, 10µg/ml (~10mg/kg) of doxycycline resulted in major reductions in the concentrations of common gut anaerobic bacteria such as *Enterobacteriacea* and *Bacteroides*.[38] In comparison, a minimum inhibitory concentration (MIC) of ~32µg/ml (~32mg/kg) of sarecycline was equivalent to a MIC of ~8µg/ml (~8mg/kg) of doxycycline on reducing *Enterobacteriacea* species by 50%.[11] This demonstrates sarecycline's 16-fold decrease in activity against *Enterobacteriacea*, a common gut anaerobic bacteria, when compared to doxycycline.[11]

Prolonged, non-selective antibiotic use can be associated with the development of antibiotic-resistant organisms. Specifically, regarding *C. acnes*, rates of resistance to antibiotic monotherapy have been increasing from ~20% in the 1960s to ~60% in 2003.[39,40] Furthermore, patients found to have *C. acnes* resistance were less likely to demonstrate clinical improvement.[40] Of note, countries that utilize fewer antibiotics typically have lower resistance rates.[41] Selective therapies, such as sarecycline, have a low propensity for resistance and can be utilized to help reduce the development of antibiotic resistance.[10,11]

Unfortunately, the use of broad-spectrum antibiotics to treat acne vulgaris contributes to the erosion of their activity against Gram-negative bacterial infections, for which few effective antibiotics are available. Oral doxycycline, for example, is FDA-approved for several indications, including rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, and acne, among others. This raises the question whether its long-term repeated use in acne will compromise its efficacy in treating infectious diseases.

In conclusion, oral tetracyclines remain the mainstay of oral treatment for acne. To minimize adverse effects, recommendations for the use of oral antibiotics in acne include combining oral antibiotic therapies with topical treatments, limiting treatment duration to three to four months at a time, and re-evaluation every six to eight weeks.[42] The use of narrow-spectrum antibiotics is one of the main elements of the antibiotic stewardship program.[43,44] The primary goal of antibiotic stewardship is to improve patient outcomes while minimizing side effects and preventing drug-resistant bacterial infections. Future drug developments in oral antibiotics should continue to focus on selecting highly efficacious agents while minimizing antibiotic resistance and gut dysbiosis.

DISCLOSURES

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SUPPLEMENTAL TABLE 1.

Cochrane Risk of Bias Tool for Randomized Interventional Studies

Source	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data Addressed (Attrition Bias)	Selective Reporting (Reporting Bias)
Moore et al,[8] 2018	+	+	+	+	+	+
Moore et al,[17] 2015	+	+	+	+	+	+
Fleischer et al,[21] 2006	+	+	+	+	+	+
Dreno et al,[22] 2001	+	+	+	+	+	+
Ozolins et al,[25] 2004	+	+	?	+	+	+
Gratton et al,[30] 1982	+	+	+	+	+	+
Gammon et al,[31] 1986	+	+	+	+	+	+

+ : Low risk of bias; - : High risk of bias; ? : Unclear risk of bias

SUPPLEMENTAL TABLE 2.

Newcastle-Ottawa Scale for Assessment of Observational Studies

Source	Selection	Comparability	Outcome	Score (Max 9)
Margolis et al,[18] 2010	4	2	3	9
Cohen,[24] 1985	3	0	3	6
Goulden et al,[26] 1996	3	0	3	6
Sturkenboom et al,[27] 1999	4	2	3	9
Margolis et al,[28] 2007	4	2	3	9
Sauer,[32] 1976	3	0	3	6

Quality assessed using the Newcastle-Ottawa Scale (maximum score of 9).

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