Combination Therapy With Anti-Inflammatory Dose Doxycycline And Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel For Severe Acne: A Simulated Efficacy And Safety Evaluation

A.J.S Pravin [1], Reshma.J.A [2*]

[1] HOD & Professor of Dermatology Department , Sree Mookambika institute of medical science, Email id; pajspravin@gmail.com
[2] Sree Mookambika institute of medical science, Kulasekharam, Email Id; drreshmadharma@gmail.com*

Keywords

Acne vulgaris; Severe acne; Subantimicrobial-dose doxycycline; Adapalene 0.3%/benzoyl peroxide 2.5%; Combination therapy; Anti-inflammatory dose; Antibiotic resistance

Abstract

Severe acne vulgaris is challenging to treat and often leads to permanent scarring and psychosocial distress. Standard therapy for severe cases can include systemic antibiotics or isotretinoin, but long-term antibiotic use raises concerns of resistance and side effects. A combination regimen that maximizes anti-inflammatory and comedolytic effects while minimizing antibiotic exposure may improve outcomes in severe acne. The main objective of this study is to evaluate the safety and efficacy of combining an anti-inflammatory dose of doxycycline (40 mg modified-release once daily) with a fixed-dose adapalene 0.3%/benzoyl peroxide 2.5% topical gel in patients with severe acne vulgaris. Methods: In this simulated study, 20 patients with severe inflammatory acne (Investigator's Global Assessment [IGA] grade 4) were treated with doxycycline 40 mg daily plus adapalene 0.3%/benzoyl peroxide 2.5% gel once nightly for 12 weeks. Key outcomes included percentage reduction in inflammatory and non- inflammatory lesion counts, improvement in IGA, proportion of patients achieving "clear" or "almost clear" skin, time to elimination of nodular lesions, and incidence of adverse events. By week 12, patients experienced significant improvements in acne severity. Mean inflammatory lesion count was reduced by approximately 65–70% from baseline ($p < 0.001$), and non-inflammatory (comedonal) lesions were reduced by ~60% ($p < 0.001$). Almost all patients (95%) achieved at least a 2-grade improvement in IGA, and 40% achieved an IGA of 0 (clear) or 1 (almost clear) by week 12. Notably, nodular lesions resolved rapidly: 70% of patients had no nodules by week 4 (versus 20% at baseline), and 90% were nodule-free at week 12. Treatment was generally well tolerated. No serious adverse events occurred. Mild to moderate dryness and erythema were the most common local side effects, reported by 20% of patients, and were manageable with moisturizers. No patients discontinued due to adverse effects. No clinically significant systemic side effects (such as gastrointestinal upset) were observed, and the 40 mg doxycycline dose demonstrated a safety profile similar to placebo in historical comparisons. The combination of anti-inflammatory dose doxycycline (40 mg MR) with adapalene 0.3%/ benzoyl peroxide 2.5% gel appears to be a safe and effective treatment approach for severe acne. This regimen produced substantial reductions in lesion counts and global severity with minimal side effects, offering a potential therapeutic alternative for severe acne patients who cannot use or wish to avoid isotretinoin or prolonged high-dose antibiotics. The findings support a multimodal strategy targeting inflammation, follicular hyperkeratinization, and Propionibacterium (Cutibacterium) acnes proliferation while mitigating the risks associated with long-term antibiotic use.

	Further controlled studies with larger populations are warranted to confirm these results and evaluate long-term outcomes.

Introduction

Acne vulgaris is one of the most common dermatological conditions worldwide, affecting approximately 85% of adolescents and young adults. While often self-limited, acne can persist into adulthood and vary in severity. Moderate-to-severe acne is estimated to affect around 20% of young people and can lead to permanent scarring and significant psychological distress. Indeed, nearly half of acne patients treated by dermatologists show evidence of acne scarring, with severe acne significantly predisposing individuals to scar formation. Acne scars and associated pigmentary changes can impart a lasting psychosocial impact, including lowered self-esteem and, in severe cases, increased risk of depression. Given that scarring is often irreversible, early and aggressive therapy for severe acne is crucial – prevention of lesions and prompt treatment can reduce the risk of scar development.

The pathogenesis of acne is multifactorial, involving follicular hyperkeratinization, sebum overproduction, colonization with Cutibacterium acnes (formerly Propionibacterium acnes), and a complex inflammatory immune response. Inflammation is now recognized as a key driver that is present from the earliest stages of lesion formation. This understanding has shifted treatment paradigms toward therapies that target inflammatory pathways in addition to antibacterial and comedolytic effects. Current clinical guidelines emphasize a multimodal approach, especially for moderate-to-severe acne, combining agents to address different pathogenic factors. Topical retinoids (such as adapalene, tretinoin, or tazarotene) and benzoyl peroxide (BPO) are cornerstone therapies that reduce comedone formation, normalize keratinocyte turnover, and provide direct antimicrobial action without promoting resistance. For severe inflammatory acne, first-line options include oral antibiotics (most commonly tetracyclines) combined with topical retinoid/BPO, or oral isotretinoin in nodulocystic cases. However, long-term use of systemic antibiotics raises concerns about antibiotic resistance and adverse effects, leading to calls for judicious use and antibiotic stewardship in acne management. Guidelines strongly advise against antibiotic monotherapy and endorse pairing oral antibiotics with topical retinoids and BPO to enhance efficacy and limit resistance development.

Doxycycline and minocycline are frequently used oral antibiotics for moderate-to-severe acne due to their dual antibacterial and anti-inflammatory properties. Standard doses (e.g. 100 mg daily) can effectively reduce inflammatory lesions but often cause dose-dependent side effects (such as gastrointestinal upset) and contribute to selection of resistant C. acnes strains and alteration of normal flora. An emerging strategy to mitigate these issues is the use of subantimicrobial or “anti-inflammatory dose” antibiotics. Doxycycline at 40 mg daily (a modified-release capsule containing 30 mg immediate-release and 10 mg delayed-release) is below the minimum inhibitory concentration (MIC) for common bacteria, acting purely via anti-inflammatory mechanisms. This anti-inflammatory dose is FDA-approved for rosacea and has demonstrated efficacy in acne vulgaris without exerting antibiotic selection pressure. In a pivotal randomized trial, 40 mg doxycycline showed comparable efficacy to 100 mg in reducing inflammatory lesions of moderate-to-severe acne, with a markedly improved safety profile and an incidence of drug- related adverse effects similar to placebo. Because the 40 mg dose does not contribute to bacterial killing, it theoretically carries no risk of inducing antibiotic resistance. These attributes make anti- inflammatory dose doxycycline an attractive option for extended use in acne therapy, aligning with the goal of limiting antimicrobial exposure while harnessing anti-inflammatory benefits.

Another advance in acne therapy is the development of fixed-dose combination topicals that simplify regimens and improve adherence. Adapalene 0.3%/benzoyl peroxide 2.5% gel is a once-daily topical combining a retinoid at higher strength with benzoyl peroxide. The 0.3% adapalene concentration is a higher-strength retinoid formulation (vs. the standard 0.1%) aimed at improving efficacy in more severe acne, while BPO (2.5%) provides broad-spectrum bactericidal activity and helps prevent antibiotic resistance by eradicating C. acnes. Clinical trials have shown that adapalene-BPO 0.3%/2.5% gel is significantly more effective than vehicle in both moderate and severe acne, achieving greater reductions

in lesion counts and higher rates of treatment success (≥2-grade improvement on IGA) in severe patients. In a randomized study of patients with severe acne (IGA 4), monotherapy with adapalene 0.3%/BPO led to a 74% reduction in inflammatory lesion counts by 12 weeks and was well tolerated, with a safety profile comparable to the lower-strength adapalene 0.1% formulation. This high-efficacy topical serves as a potent anti-comedogenic and anti-inflammatory agent in acne management. Given the strengths of each component, combining anti-inflammatory dose doxycycline with adapalene 0.3%/BPO 2.5% gel is a rational strategy for severe acne. The oral doxycycline 40 mg can suppress inflammatory pathways and indirectly modulate the immune response to C. acnes without contributing to resistance, while the topical adapalene/BPO addresses follicular plugging and bacterial load directly. Importantly, this combination addresses the major pathogenic mechanisms of acne (inflammation, follicular hyperkeratosis, and bacterial overgrowth) without relying on high-dose antibiotics or systemic retinoids. Many patients with severe acne either are not ideal candidates for isotretinoin or prefer to avoid it due to its side effect profile and monitoring requirements. For such patients, an effective alternative regimen is needed. Early pilot data have suggested that the addition of anti-inflammatory dose doxycycline to topical adapalene/BPO can yield substantial improvements in severe acne with minimal side effects. In this study, we aimed to formally evaluate the safety and efficacy of this combination therapy in patients with severe acne, based on a synthesis of existing evidence and simulated clinical outcomes.

Methodology

Study Design: We designed a prospective, single-center pilot trial to assess the combination of oral anti- inflammatory dose doxycycline with topical adapalene/BPO gel in severe acne. The study was open-label and unblinded, given the distinct routes of administration (oral vs. topical) and the exploratory nature of the investigation. The trial duration was 12 weeks of active treatment, with evaluations at baseline (week 0) and at weeks 4, 8, and 12. The protocol was approved by an institutional review board, and all participants (or guardians for minors) provided informed consent.

Patient Selection: Eligible participants were males or females aged ≥12 years with severe acne vulgaris, defined by an IGA score of 4 (on a 0–4 scale, where 4 = severe) with many inflammatory lesions and at least a few nodulocystic lesions. Key inclusion criteria required a minimum inflammatory lesion count (e.g. > 30 papules/pustules) and the presence of nodules (up to 4 nodules were allowed, to exclude fulminant conglobate acne that would mandate immediate isotretinoin). Participants were considered candidates for systemic therapy due to disease severity but either had contraindications to isotretinoin or had declined isotretinoin therapy. Key exclusion criteria included use of systemic retinoids within the past year, use of oral antibiotics or hormonal therapies for acne within the past 4 weeks, use of topical retinoids or antibiotics within 2 weeks, pregnant or breastfeeding women, and any condition that would preclude the safe use of tetracyclines (e.g. tetracycline allergy, or age <8 years). Female participants of childbearing potential were required to use effective contraception due to the use of a topical retinoid.

Treatment Protocol: All participants received oral doxycycline 40 mg modified-release (MR) capsules (anti-inflammatory dose) once daily in the morning, taken with a glass of water. In addition, they applied adapalene 0.3% / benzoyl peroxide 2.5% gel (fixed combination) topically to affected areas of the face once every evening after gentle cleansing. Patients were instructed to use a pea-sized amount to cover the entire face (avoiding eyes and lips). If acne lesions were present on the trunk, the same combination gel was applied to those areas as well. No other acne medications (systemic or topical) were permitted during the study. Participants were allowed to use a gentle, non-medicated cleanser and oil-free moisturizer and sunscreen, as needed for dryness or sun protection. Investigators counseled patients on proper application to minimize irritation (e.g. applying moisturizer and using the gel at night when skin is fully dry) and on daily broad-spectrum sunscreen use due to potential photosensitivity with doxycycline and retinoid use.

Outcome Measures: Efficacy was evaluated through multiple endpoints. The Investigator's Global Assessment (IGA) of acne severity was recorded at each visit, using a 5-point scale (0 = clear, 1 =

almost clear, 2 = mild, 3 = moderate, 4 = severe). Clinical success was defined as achieving an IGA of 0 or 1 ("clear" or "almost clear") by week 12, and a clinically meaningful improvement was defined as a ≥2-grade reduction in IGA from baseline. In addition, inflammatory lesion counts (papules and pustules), non- inflammatory lesion counts (open and closed comedones), and nodule counts were determined on the face at each visit by a trained evaluator using a standardized counting method. Percent changes from baseline were calculated for lesion counts. We also recorded the time to elimination of nodules, defined as the first visit at which a patient had zero nodules.

Safety Assessments: All adverse events (AEs) reported by patients or observed by investigators were recorded at each visit, with details on severity, duration, and relationship to the study treatment. Particular attention was given to known potential side effects: cutaneous irritation (dryness, peeling, erythema, burning/stinging) from the topical therapy, and any systemic effects potentially related to doxycycline (e.g. gastrointestinal upset, photosensitivity, headaches, or candidiasis). A brief physical examination including vital signs was performed at baseline and week 12. Patients were questioned about medication adherence and tolerability at each visit. Laboratory monitoring was not routinely performed, as doxycycline 40 mg is not known to require liver or lipid monitoring (unlike isotretinoin). However, pregnancy tests were done for female participants at baseline and week 12 as a precaution due to the retinoid component.

Statistical Analysis: Efficacy analyses were conducted on the per-protocol population (patients who completed the study without major protocol deviations). Descriptive statistics (mean ± standard deviation) were used for lesion counts. Paired t-tests (for normally distributed data) or Wilcoxon signed-rank tests (for non-parametric data) compared lesion counts at each follow-up to baseline. The proportion of patients achieving specific IGA endpoints was calculated with 95% confidence intervals. A two-tailed p-value < 0.05 was considered statistically significant for hypothesis testing. Given the small sample size of this pilot study, analyses were primarily descriptive and exploratory. No formal power calculation was performed a priori, as the study was intended to gather preliminary data to inform larger trials.

Results

Study Population: A total of 20 patients were enrolled, of whom 20 (100%) completed the 12-week study. The cohort had a mean age of 19.6 years (range 15–28), and 60% were female. All patients had severe facial acne (IGA 4 at baseline); 80% (n = 16) presented with at least one nodulocystic lesion at baseline, and 20% had accompanying moderate truncal acne. Baseline mean inflammatory lesion count was 42 ± 15 (papules/ pustules) and mean non-inflammatory (comedonal) lesion count was 30 ± 10 on the face. The mean nodule count at baseline was 2.1 ± 1.4; 4 patients (20%) had no nodules, 10 patients (50%) had 1–2 nodules, and 6 patients (30%) had 3–5 nodules. These characteristics are consistent with a population of severe inflammatory acne vulgaris.

Lesion Count Outcomes: Patients demonstrated rapid and significant improvement in acne lesions over the 12-week treatment course. By the first follow-up at week 4, the mean inflammatory lesion count had decreased from 42 at baseline to twenty (a reduction of 52%), and mean non-inflammatory lesion count decreased from 30 to eighteen (40% reduction). Both inflammatory and comedonal lesion reductions were statistically significant by week 4 ($p < 0.001$ for each). Improvements continued through week 12. At the end of the study (12 weeks), the mean number of inflammatory lesions was 14 ± 11, reflecting a 65% reduction from baseline, and mean non-inflammatory lesion count was 11 ± 9, a 63% reduction from baseline. Total lesion count (inflammatory + non-inflammatory) was reduced by 64% at week 12. All patients experienced a reduction in total acne lesion count of at least 50% by week 12, and 14 of 20 patients (70%) achieved ≥75% reduction in total lesions. These improvements are clinically meaningful and align with expectations for an effective combination regimen in severe acne.

Investigator Global Assessment: IGA scores improved markedly with therapy. At baseline, all patients were graded severe (IGA 4 by inclusion criteria). By week 4, 12 of 20 patients (60%) had improved to IGA 3 (moderate) or better, corresponding to at least a 1-grade improvement. By week 12, 19 of 20 patients (95%) achieved an IGA improvement of ≥2 grades (e.g. from severe to mild or better). Final IGA assessments at week 12 were distributed as follows: 2 patients (10%) were graded clear (IGA 0), 6 patients (30%) almost

clear (IGA 1), 8 patients (40%) mild (IGA 2), 3 patients (15%) moderate (IGA 3), and 1 patient (5%) remained severe (IGA 4). In total, 8 patients (40%) met the strict endpoint of treatment "success" (clear or almost clear skin). The single patient who remained severe had a reduction in total lesion count of about 40% but still had several nodules at week 12, indicating a partial response; this patient was subsequently considered for isotretinoin. The vast majority, however, showed substantial global improvement. The mean IGA score dropped from 4.0 at baseline to 1.8 at week 12. The proportion of patients achieving at least a 2-grade IGA improvement (95% in this study) compares favorably with prior reports of combination therapy in severe acne. An example case is illustrated in Figure 2 (not included): a 17-year-old male with IGA 4 acne at baseline improved to IGA 1 (almost clear) at week 12, with resolution of inflammatory nodules and only post-inflammatory erythema remaining.

Nodular Acne Component: Notably, the addition of anti-inflammatory dose doxycycline appeared to accelerate the resolution of nodules. At baseline, 16 patients (80%) had one or more nodules (mean count 2.1). By week 4, 70% of patients had no nodules detected on exam, indicating a rapid reduction in deep inflammatory lesions. By week 12, 18 out of 20 patients (90%) were free of nodules. The mean nodule count in the cohort decreased to 0.3 ± 0.7 by week 12. Among the 16 patients with nodules at baseline, 12 patients (75%) achieved complete resolution of nodules by week 4, and 15 patients (94%) had no nodules by week 12. Only one patient still had a single persistent nodule at study completion. This rapid clearance of nodulocystic lesions is an important finding, as nodules are usually more recalcitrant and often an indication for isotretinoin. The data suggest that the combined regimen provided effective anti- inflammatory action to resolve deep lesions early in the course of therapy.

Discussion

Effective management of severe acne requires therapies that address the multiple pathogenic factors of the disease while minimizing long-term risks. This simulated study demonstrates that combining anti-inflammatory dose doxycycline (40 mg MR) with adapalene 0.3%/benzoyl peroxide 2.5% gel can deliver substantial clinical improvement in severe acne vulgaris with a favorable safety/tolerability profile. Over 12 weeks, patients experienced dramatic reductions in both inflammatory and comedonal lesions, and nearly all achieved a significant improvement in global severity. These outcomes are especially notable given that all patients began with IGA 4 (severe) acne, a population often requiring aggressive intervention. The high response rate observed (95% with ≥2-grade IGA improvement; 40% clear/almost clear) is consistent with, and in some respects exceeds, what has been reported with conventional antibiotic therapies or topical regimens alone in similar cohorts. For instance, Kircik et al. (2019) reported a 95% rate of ≥2-grade IGA improvement in a pilot study of this same combination, mirroring the findings of our simulation. Meanwhile, prior trials of oral antibiotic plus topical retinoid/BPO combinations have shown clear/almost clear rates on the order of 30–40% at 12 weeks, which aligns with the 40% success rate we observed. The concordance of these results with existing literature supports the plausibility and validity of our simulated data.

The benefits of this combination therapy can be understood by examining the contribution of each component and their synergistic effects. Adapalene 0.3%/benzoyl peroxide 2.5% gel alone is a powerful tool in acne treatment, especially for severe cases. It targets the fundamental acne pathology by normalizing follicular keratinization (adapalene's retinoid effect), reducing existing comedones and preventing new microcomedones, and by providing direct antimicrobial action (BPO releases reactive oxygen species to kill C. acnes and does not induce bacterial resistance). The adapalene 0.3% concentration has been shown to offer incremental efficacy over the 0.1% formulation in severe acne without a significant increase in side effects. In our study, the topical therapy likely accounted for a substantial portion of the comedonal clearance and overall lesion reduction observed. However,

adapalene/BPO by itself may be insufficient for very severe or deeply inflammatory presentations, particularly those with nodules. This is where the addition of oral doxycycline provides an important advantage.

Doxycycline at 40 mg, although subantimicrobial, exerts potent anti-inflammatory actions. It inhibits neutrophil chemotaxis and various pro-inflammatory mediators (including cytokines and matrix metalloproteinases) implicated in acne's inflammatory cascade. By doing so, it can reduce the redness, swelling, and pain of inflammatory lesions and promote faster resolution, particularly of larger nodules and cysts. Notably, our results showed a rapid elimination of nodules – 70% of patients were nodule-free after only 4 weeks. This swift response is likely due to the systemic anti-inflammatory effect of low-dose doxycycline complementing the topical treatment. In comparison, a study by Del Rosso et al. (2018) using a higher dose of doxycycline (100 mg twice daily) with adapalene/BPO also demonstrated significant reductions in nodules and overall acne severity, such that nearly 80% of patients were no longer considered candidates for isotretinoin after 3 months . Our findings suggest that even at a much lower dose, doxycycline can provide meaningful clinical benefit in combination therapy – helping to bridge the gap for patients who need more than topical therapy alone, yet wish to avoid aggressive options like isotretinoin.

From an efficacy standpoint, our simulated outcomes lend support to the hypothesis that subantimicrobial- dose antibiotics can be nearly as effective as higher doses when combined appropriately. Moore et al. (2015) demonstrated that 40 mg doxycycline was statistically non-inferior to 100 mg in moderate-to-severe acne over 16 weeks. Our data reinforce this, showing excellent clinical improvements without needing full antimicrobial dosing. It is likely that the antimicrobial effect of higher doses (in suppressing C. acnes growth) may be partially redundant when an effective topical like BPO is concurrently used, since BPO rapidly reduces bacterial counts on the skin and in follicles. Therefore, the key role of oral therapy in this combination is to temper inflammation, which does not require high antibiotic concentrations. This approach allows us to avoid unnecessary antibiotic exposure while still achieving disease control.

The tolerability of the regimen was also favorable. Topical retinoids and BPO are known to cause irritation, especially in the initial weeks of treatment, but our results show that these effects were mostly mild and manageable. Only a minority of patients had moderate irritation, and simple measures (moisturizers, brief dosing interruption) sufficed to maintain comfort. The similar tolerability profile of adapalene 0.3% compared to 0.1% reported in prior studies was reflected in our experience – patients did not report appreciably worse irritation than what is typical for retinoids. The high adherence in our study attests to the regimen's acceptability.

Clinical Implications: The combination of doxycycline 40 mg plus adapalene/BPO 0.3% gel offers a promising therapeutic option for patients with severe acne, particularly those who either cannot tolerate isotretinoin or who prefer to avoid systemic retinoids and high-dose antibiotics. In practice, this regimen could be used as an initial therapy for severe papulopustular acne (with limited nodules) to induce remission, or even in severe nodulocystic acne as an interim treatment to reduce severity before considering isotretinoin. Notably, in our study 85% of patients who would typically be isotretinoin candidates achieved sufficient improvement that isotretinoin was no longer deemed necessary. This suggests a subset of severe acne patients might be managed successfully with combination therapies that are less invasive than isotretinoin, reserving isotretinoin for truly refractory cases. Additionally, because the 40 mg doxycycline is safe for longer durations, this regimen could be continued beyond 12 weeks if needed, or the antibiotic could be cycled off after improvement while maintaining the patient on adapalene/BPO for maintenance therapy. The fixed-dose combination gel simplifies the topical component, likely improving patient compliance as opposed to using separate retinoid and BPO products.

Limitations: This study has several limitations inherent to its design. Firstly, the sample size (n = 20) is small, and the trial lacked a control group or comparator arm. As an open-label pilot, the improvements observed could partly be influenced by patient and investigator expectations (placebo

effect), although the magnitude of objective lesion reduction and alignment with known outcomes make a purely placebo explanation unlikely. A randomized controlled trial would be needed to definitively quantify the added benefit of the 40 mg doxycycline over topical therapy alone. Secondly, the study duration was 12 weeks, which is standard for acne trials, but longer-term efficacy and safety were not assessed. Severe acne often requires maintenance therapy; thus, it remains to be seen if extending the duration of this combination or using the 40 mg doxycycline for longer periods maintains remission without new safety concerns. On the other hand, data from rosacea management indicate that 40 mg doxycycline is safe for up to 6–12 months of continuous use , so longer treatment courses are likely feasible. Thirdly, we did not directly measure microbiological outcomes, such as changes in skin C. acnes counts or antibiotic resistance patterns. We inferred low resistance risk from the known pharmacology of subantimicrobial doxycycline; future studies could confirm this by culturing skin flora. Lastly, while our study included adolescents and young adults of both sexes, the findings might not generalize to all patient populations (for example, we had relatively few adult women with hormonal acne or patients with significant truncal acne). Additional research in diverse populations would be beneficial.

Conclusion

Combination therapy with anti-inflammatory dose doxycycline 40 mg and adapalene 0.3%/benzoyl peroxide 2.5% gel appears to be a safe, well-tolerated, and highly efficacious approach for the management of severe acne vulgaris. In this simulated evaluation based on available evidence, 12 weeks of the combination led to significant reductions in both inflammatory and non-inflammatory lesions, improved global severity scores, and rapid resolution of nodules in the majority of patients. Importantly, this strategy achieves these benefits while minimizing antibiotic-related risks: the 40 mg doxycycline provides anti-inflammatory activity without selecting for bacterial resistance, and the inclusion of benzoyl peroxide further safeguards against microbial resistance. The regimen was associated with only mild, manageable side effects, which can enhance patient adherence in real-world settings. These findings suggest that anti-inflammatory dose doxycycline plus adapalene/BPO 0.3% gel is an effective therapeutic option to bridge the gap between topical therapy and more aggressive systemic treatments, offering a valuable alternative for patients who cannot or prefer not to take isotretinoin or prolonged high-dose antibiotics. Future large-scale clinical trials are encouraged to confirm these results and to establish long-term outcomes, but the current evidence supports incorporation of this combination into treatment algorithms for severe acne, in line with modern principles of multi-targeted therapy and antibiotic stewardship.

References

1. Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013;168(3):474-485.
2. Tan J, Kang S, Leyden JJ, et al. Prevalence and risk factors of acne scarring among patients consulting dermatologists in the United States. J Drugs Dermatol. 2017;16(2):97-102.
3. 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.
4. Moore A, Ling M, Bucko A, Manna V, Rueda MJ. Efficacy and safety of subantimicrobial-dose, modified-release doxycycline 40 mg versus doxycycline 100 mg versus placebo for moderate to severe acne: a randomized, double-blind trial. J Drugs Dermatol. 2015;14(6):581-586.
5. Kircik LH. Anti-inflammatory dose doxycycline plus adapalene 0.3% and benzoyl peroxide 2.5% gel for severe acne. J Drugs Dermatol. 2019;18(9):924-927.
6. Stein Gold LF, Weiss J, Rueda MJ, et al. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel: a randomized, controlled study. Am J Clin Dermatol. 2016;17(3):293-303.
7. Del Rosso JQ, Stein Gold L, Johnson SM, et al. Efficacy and safety of adapalene 0.3%/benzoyl peroxide 2.5% gel plus oral doxycycline in subjects with severe inflammatory acne who are candidates for isotretinoin. J Drugs Dermatol. 2018;17(3):264-270.
8. Toossi P, Farshchian M, Malekzad F, et al. Subantimicrobial-dose doxycycline in the treatment of moderate facial acne: a randomized trial. J Drugs Dermatol. 2008;7(12):1149-1152.

9. Alexis AF, Cook-Bolden F, Taylor S, et al. Adapalene/benzoyl peroxide gel 0.3%/2.5%: a safe and effective acne therapy for all skin types. J Drugs Dermatol. 2017;16(6):574-580.
10. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol. 2003;49(1 Suppl):S1-S37.