Acne and rosacea are chronic inflammatory disorders long thought to be primarily infectious. However, evidence in recent years indicates that far more than microorganisms inflammation plays a key role in the pathogenesis of these disorders.\textsuperscript{1} Coinciding with recent emphasis on inflammation has been an increased reliance on antibiotic agents, which we now know to confer anti-inflammatory effects. In the last 10 years, prescriptions for oral antibiotics by both dermatologists and non-dermatologists have continued to rise. The most commonly prescribed antibiotics in dermatology are the tetracyclines, of which second-generation molecules doxycycline and minocycline are most prominent. While antibiotics can be used in a variety of dermatologic conditions, doxycycline and minocycline are likely used as much or more for their anti-inflammatory properties as for their antimicrobial effects.

As researchers strive to learn more about the specific role of inflammation in the etiology of acne and rosacea, clinicians should be aware of new developments and prepare to adapt to changing therapeutic conditions. Ahead, I will provide an update of research on antibiotics in acne and rosacea care with a particular focus on the anti-inflammatory effects of antibiotics. I will also discuss novel formulations that may be particularly beneficial for patients.

**Antibiotics: How and Why They Benefit Acne and Rosacea Care**

Scientific inquiries increasingly articulate the importance of systemic antibiotics as therapeutic agents in the treatment of both conditions.

By Leon H. Kirck, MD

**Take-Home Tips.** Despite concerns of resistance and adverse effects, antibiotics have proven most useful for the anti-inflammatory effects associated with their use. Given the equivalent efficacy of doxycycline and minocycline, selection of an agent often depends on the specific patient and the prescriber’s assessment of the relative risks for development of therapy-associated adverse events. As advancements in formulation are undoubtedly paving the way for more efficacious antibiotic agents to play an increased role in acne and rosacea therapy, clinicians’ abilities to understand and manage these conditions will continue to evolve.

**Therapeutic Challenges and Resistance Concerns**

Compared to tetracycline, doxycycline and minocycline provide important benefits, including less frequent dosing and improved safety.\textsuperscript{2} However, certain potential side effects of this class, including GI concerns, staining of developing teeth in children, candidiasis, and photosensitivity, are still a concern.\textsuperscript{2,3,4} Probably one of the major disadvantages of the use of minocycline is the potential for blue/grey staining of the skin, sclera, teeth, and nails.\textsuperscript{5} Increasingly, there has been more attention paid to the risk for development of autoantibodies, including antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and antiphospholipid antibodies, associated with minocycline, with or without associated clinical symptoms.\textsuperscript{4}
While serious side effects associated with second-generation tetracyclines are rare, they warrant consideration. All tetracyclines—but especially minocycline—may be associated with benign intracranial hypertension with dizziness, lethargy, headaches, nausea and vomiting associated with photophobia, diplopia, and papilledema. Staining of the teeth can occur with these agents, and they are not recommended in children under the age of eight years.

Although the rates of adverse events were perceived to be similar between doxycycline and minocycline, a review of the published data shows a disadvantage for minocycline. In data from clinical trials published from 1966 to 2003, rates of reported adverse events ranged from 0 to 61 percent for doxycycline and 11.7 to 83.3 percent for minocycline. The majority of AEs associated with doxycycline were related to GI complaints, while minocycline had primarily CNS or GI complaints. Similarly, evaluation of FDA MedWatch reports from 1998 to 2003 found a rate of adverse events of 13 per million new prescriptions for doxycycline and 72 per million new prescriptions for minocycline.

Minocycline is associated with potentially fatal hypersensitivity syndrome or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). A retrospective analysis of 15 ICU-admitted cases of DRESS in France found that minocycline was causative in three cases. All three of those patients experienced renal failure, and two of those three patients died. Based on their analysis of these cases and other databases, the authors recommend that minocycline be considered a “higher risk” medication. Although predictive and prognostic factors are not well-defined, evidence from another recent review of hypersensitivity reactions in African and African-American patients suggests that the risk for DRESS may be associated with prolonged exposure to minocycline and subsequent accumulation of the drug in plasma and skin.

Antibiotic Resistance. In addition to treatment-associated adverse events, use of topical and oral antibiotics at standard doses (at or above minimal inhibitory concentration) is associated with the risk of antibiotic resistance. The problem of resistance has been especially well documented in the management of acne and has been linked to resultant treatment failure. However, resistance is not limited to Propionibacterium acnes (P acnes). Researchers have identified resistant strains of Staphylococcus epidermidis among acne patients treated with oral erythromycin. Another study of acne patients showed that systemic antibiotic therapy was associated with Streptococcus pyogenes colonization and resistance in the oropharynx. While only 20 percent of S pyogenes cultures from individuals not treated with antibiotics were resistant to at least one tetracycline, 85 percent of cultures from antibiotic-treated patients demonstrated resistance.

 Proposed strategies to reduce the risk of resistance are to limit the use of oral and topical antibiotics, to use these agents in combination with adjunctive antimicrobial agents, such as benzoyl peroxide, or to administer antibiotics at levels below the minimal inhibitory concentration or MIC. The MIC is the plasma concentration that must be achieved in order for an antibiotic agent to inhibit or kill bacteria. The MIC is specific to each antibiotic agent. Continuous use of low-dose antibiotics contributes to development of resistance.

Anti-Inflammatory Effects

Despite concerns of resistance and adverse effects, antibiotics have proven most useful for the anti-inflammatory effects associated with their use. Guidelines from the Global Alliance to Improve Outcomes in Acne Therapy highlight findings the inflammatory component of acne. It has now been shown that immune changes and inflammatory responses precede comedogenesis. Recent in vivo research into the pathophysiology of acne and associated scarring found a marked increase in inflammatory cytokine gene transcripts in active acne lesions, including TNF-α and IL-1β. These pro-inflammatory cytokines amplify NF-κβ signaling pathways. These reports suggest that acne is a disease mediated not only by bacteria but also by inflammatory processes.
Table 1. Antibiotic Formulations to Consider

**Doryx.** A unique formulation of doxycycline (Doryx, Warner Chilcott) may provide benefits in terms of treatment tolerability and reduced incidence of adverse events. Doryx has been linked to a decrease in GI side effects.\textsuperscript{31,32} Available in 50mg, 75mg, and 150mg QD dosage strengths, Doryx capsules can be cut or crushed without diminishing their therapeutic efficacy or the GI tolerability of doxycycline.

Doryx features a unique delivery system of delayed-release, enteric-coated pellets of doxycycline hyclate. The pressed powder tablet dissolves in the stomach, releasing the enteric-coated pellets. The pH-sensitive enteric coating remains intact in the acidic environment of the stomach. When the pellets reach the more alkaline small intestine, the enteric coating dissolves, and the active drug is released and absorbed. This unique design minimizes exposure of the stomach to doxycycline.

Once-daily dosing of medication is also associated with improved therapeutic adherence.\textsuperscript{33,34} To further assure tolerability, doxycycline may be taken with food, which is not shown to reduce absorption of the drug. Because the individual doxycycline pellets are enteric-coated, crushing the capsule does not interfere with the release of active drug. Therefore, capsules may be crushed and the contents sprinkled on food to facilitate dosing, which may also be cost-efficient.

**Oracea.** Oracea (doxycycline capsules 40mg, Galderma), the once-daily 40mg doxycycline anhydrous capsule, formulated with a mixture of immediate-release and delayed-release beads is designed to provide an anti-inflammatory dose of doxycycline. Randomized controlled clinical trials demonstrate the efficacy of Oracea for treatment of the inflammatory lesions of rosacea and demonstrate a favorable adverse event profile, similar to placebo (most common AEs associated with treatment are nausea, gastrointestinal upset, nasopharyngitis/pain and nasal congestion/sinusitis).\textsuperscript{35}

Anti-inflammatory dose doxycycline is distinct from low-dose doxycycline because of its specific formulation of 40mg active drug. *In vitro* plasma concentration data demonstrate the unique pharmacokinetic profile of the sub-antimicrobial dose formulation. Data show that sub-antimicrobial dose doxycycline does not induce resistance in organisms after treatment for up to nine months. In trials, the percent change in doxycycline resistance was equivalent in SDD-treated patients and controls.\textsuperscript{36}

In addition, the low dose of doxycycline in Oracea coupled with its delayed release is thought to account for its favorable tolerability profile.

**Solodyn.** Efforts to reduce the incidence of acute vestibular adverse events (AVAEs) associated with minocycline have resulted in a novel, once-daily extended release oral formulation for the management of acne vulgaris. In trials, the rate of AVAEs associated with extended-release (ER) minocycline hydrochloride (Solodyn, Medicis) 1mg/kg was similar to the rate seen among placebo controls. The low rate of AVAEs is thought to result from a combination of the low dose and its extended release.

Individual and pooled analysis of data from phase II and III trials of ER minocycline 1mg/kg confirm its safety and efficacy.\textsuperscript{37} The studies were prospective, multicenter, randomized, double-blinded, and placebo-controlled, involving a total of 1,038 subjects with moderate to severe acne. Treatment was associated with statistically significant reduction in inflammatory lesions and improvement in the Evaluator’s Global Assessment scores. The percentage of subjects reporting AVAEs was about 10 percent in those receiving ER-minocycline 1-mg/kg and in those receiving placebo. Based on the data, researchers concluded that the once-daily ER formulation delivers consistent levels of drug.

Studies of the bioavailability of the formulation show that the extended-release (ER) minocycline hydrochloride tablet formulation demonstrates delayed time of maximum concentration (tmax, 3.5-4 hours) compared with a nonmodified-release minocycline (tmax, 2.25-3 hours), and a lower maximum concentration of drug (cmax) in the blood (90 percent) compared with nonmodified-release “formulations.”\textsuperscript{38}
The fact that tetracycline antibiotics confer both antimicrobial and anti-inflammatory effects accounts for their utility in acne management. Both minocycline and doxycycline are lipophilic agents that demonstrate better tissue permeability than tetracycline, adding to their therapeutic benefit.16

Minocycline and doxycycline appear to offer similar efficacy in the management of acne. A systematic review of clinical trials from 1962 to 2006 failed to identify a significant difference in reduction of inflammatory or non-inflammatory lesions between patients treated with doxycycline and those treated with minocycline.17 In a head-to-head study in which 64 patients were randomized to receive either doxycycline or minocycline 50mg twice daily for four weeks and then once daily for the next eight weeks,18 the two agents had equivalent efficacy. In another comparative trial, this one involving 34 patients randomized to treatment with doxycycline 50mg once daily or minocycline 50mg twice daily, the agents again had similar efficacy.19

Given their equivalent efficacy, selection of an agent often depends on the specific patient and the prescriber’s assessment of the relative risks for development of therapy-associated adverse events. For patients with moderate to severe inflammatory acne, initiation of appropriate systemic therapy should not be delayed. Treatment aimed at reducing inflammation can reduce the risk of scarring and post-inflammantory hyperpigmentation.20

Oral antibiotics have also been used effectively in the treatment of rosacea since the 1960s.21 Doxycycline and other tetracyclines have been shown to produce a number of anti-inflammatory effects that may contribute to their beneficial effects in patients with rosacea. The tetracyclines, generally classified as antibiotics, have a range of therapeutic effects that are independent of antimicrobial mechanisms. In fact, tetracyclines have current or theoretical applications in periodontitis, arthritis, osteoporosis, and cancer.22-24

Doxycycline and other tetracyclines have been shown to reduce the production of interleukin-1 beta (IL-1β) (p <0.05) and tumor necrosis factor alpha (TNF-α)25 and may reduce neutrophil chemotaxis.26 Tetracyclines also reduce the activity of phospholipase A2, a family of inflammatory enzymes.27 Doxycycline reduces the generation of neutrophil-derived toxic reactive oxygen species, including superoxide anion, hydrogen peroxide, and the hydroxyl ion.28 In vitro studies show that doxycycline can reduce the production of nitric oxide by epithelial cells at concentrations as low as 3µg/ml.29 Doxycycline has also been shown to reduce angiogenesis in animal models.

Appreciation of the anti-inflammatory effects of tetracyclines may be attributed to research with chemically-modified tetracycline (CMT) analogues. There are at least 10 CMTs, modified so that the dimethylamino group from carbon-4 position (the side-chain required for antimicrobial activity) is removed. These analogues provide no antimicrobial effect, but they inhibit synthesis of collagenase and other matrix metalloproteinases and down regulate cytokines in animal models.22-25

**Conclusion**

While the pathogeneses of acne and rosacea are not

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**Table 2. Tips for Responsible Antibiotic Use and Improved Adherence in Acne**

- Choose a formulation for tolerability and to match patient needs/preferences.
- Prescribe oral antibiotics for an appropriate course. Do not prolong therapy unnecessarily.
- If using conventional systemic antibiotics, prescribe concomitant topical benzoyl peroxide to reduce resistance risk.
- Recognize and capitalize on the multiple actions of antibiotics.
- Educate patients regarding the multiple actions of antibiotic agents and your rationale for prescribing them.
- Educate patients about the basis for combination approaches in acne//rosacea treatment.
- Emphasize adherence to optimize systemic therapy efficacy and reduce the risk of resistance.

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fully understood, scientific inquiries increasingly articulate the importance of systemic antibiotics as therapeutic agents in the treatment of both conditions. In addition, new data indicate that the widespread use of oral antibiotics is associated with a significant decrease in total annual prescription spending. As advancements in formulation are undoubtedly paving the way for more efficacious antibiotic agents to play an increased role in acne and rosacea therapy (Table 1), clinicians’ abilities to understand and manage these conditions will continue to evolve.

Dr. Kircik has served as a researcher, consultant, or speaker for Allergan, Coria, Dermik, Galderma, Stiefel/GSK, Intendis, Medisic, Obagi, OrthoDermatologics, and Triax.

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