Optimizing outcomes and enhancing adherence through formulation advancements.

Leon H. Kircik, MD
Joseph B. Bikowski, MD

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This third edition of *Vehicles Matter* provides an in-depth look at the unique features of oral formulations of antibiotics frequently used in clinical dermatology and discusses the pertinent data demonstrating the benefits associated with these formulations. Characteristics of oral formulations may either minimize common adverse events or reduce risk of resistance while optimizing efficacy. It is important that prescribers understand the rationale and science behind formulation advancements, identify the advantages of these unique formulations, and utilize them when appropriate for the clinical benefit of the patient.

Previous editions of *Vehicles Matter* are available online at VehiclesMatter.com. This edition can also be accessed at the site.

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**About the Authors**

**Leon H. Kircik, MD, Chair**
Clinical Associate Professor of Dermatology
Mount Sinai Medical Center
Indiana University School of Medicine
Physicians Skin Care, PLLC
DermResearch, PLLC
Louisville, KY

**Joseph B. Bikowski, MD**
Clinical Assistant Professor of Dermatology
Ohio State University
Bikowski Skin Care Center
Sewickley, PA

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Dermatologists prescribe antibiotics for a range of infectious and non-infectious diseases. Perhaps surprisingly, their rate of prescribing for oral antibiotics—eight to nine million prescriptions in 2003—outpaces the rate for topical antibiotics at three to four million. The most commonly prescribed antibiotics in dermatology are the tetracyclines, of which second-generation molecules doxycycline and minocycline are most prominent. Within dermatology, the main uses of oral tetracyclines are for the management of moderate to severe acne or rosacea. Other important uses include management of pyoderma gangrenosum and bullous pemphigoid (BP), most tick-borne illnesses, and community-acquired methicillin-resistant Staphylococcus aureus infections (MRSA). Minocycline is being studied for the treatment of vitiligo with early promising results.

All agents in the tetracycline class are bacteriostatic; their method of action involves inhibition of bacterial protein synthesis. These drugs have been shown active against gram-negative bacteria, Chlamydia trachomatis, mycoplasma, and ureaplasma. However, doxycycline and minocycline are used as much or more for their anti-inflammatory properties as for their antimicrobial effects. For example, neither rosacea, BP, or vitiligo have primarily infectious etiologies. Even in diseases such as acne, that involve microbial mediators, there is a significant element of inflammation. Tetracyclines are shown to regulate inflammatory cytokines and to inhibit matrix metalloproteinases (MMPs), leukocyte chemotaxis and activation, and oxidation.

Compared to tetracycline, doxycycline and minocycline provide important benefits, including less frequent dosing and improved safety. However, certain potential side effects of this class, including GI concerns, staining of developing teeth in children, candidiasis, and photosensitivity, are still a concern. 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. 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.

While serious side effects associated with second generation tetracyclines are rare, they warrant consideration by the prescriber. All tetracyclines 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 AEs of 13 per million new prescriptions for doxycycline and 72 per million new prescriptions for minocycline.1

Minocycline may be associated with more significant adverse events than doxycycline, such as CNS side effects, including dizziness and vertigo not seen with doxycycline, and rare but serious drug reactions.8 Minocycline is also associated with potentially fatal hypersensitivity syndrome or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).11,12 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 experience 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.11 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.12

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 epidermidis14,16 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.17

Given their utility for the management of a range of dermatologic diseases, doxycycline and minocycline are invaluable therapeutic agents. Due to the increased incidence of side effects associated with minocycline relative to doxycycline, this publication will focus primarily on unique formulation advancements associated with doxycycline. In order to enhance their utility, drug formulators have employed novel approaches to either minimize common adverse events or reduce risk of resistance while optimizing efficacy. It is important that prescribers understand the rationale and science behind these advancements in formulation and recognize the advantages of these unique formulations over standard formulations of the same active drug and utilize them for their patients’ benefit.
One of the most common adverse events associated with standard doxycycline formulations is gastrointestinal upset which is not considered a serious AE, but can significantly diminish patient compliance and thus compromise therapeutic outcomes. Historic data suggest that the incidence of nausea and vomiting associated with doxycycline can be up to three-fold higher than that reported with other antibiotics. Experience of nausea and vomiting contributes to patient discontinuation of therapy or non-adherence with prescribed dosing and thus suboptimal therapeutic outcomes. Furthermore, due to concerns about impaired absorption of drug from standard formulations, patients prescribed these formulations are often advised to avoid taking medication with food. By requiring the patient to modify their daily routine, such limitations can also negatively impact adherence.

When dermatologists were surveyed about their perceptions of teenage patient adherence in oral antibiotic therapy, almost half said that GI side effects were the most significant contributor to non-adherence. Twice-a-day dosing was the second most frequently cited factor. Another survey of dermatologists revealed that the vast majority believe that once-daily dosing is more likely to encourage adherence among adolescent acne patients than is twice-a-day dosing. (See Fig. 1)

Enteric-coating of drugs emerged in the middle part of the last century as a method to improve the tolerability of oral drugs. Enteric coating protects a drug from the acidic pH of the stomach, delaying release until the drug reaches the more alkaline small intestine. This reduces the rate of nausea and vomiting and also protects the stomach from exposure to potentially harmful drugs (such as in the case of aspirin). In addition to these protective effects, enteric coating can be employed as a method for delayed release or controlled release of a drug, as well.

A unique formulation of enteric-coated doxycycline hyclate pellets in a pressed powder tablet (Doryx, Warner-Chilcott) has been linked to a decrease in GI side effects. Available in 50mg, 75mg, and 150mg dosage strengths, Doryx tablets can be cut or crushed without diminishing their therapeutic efficacy or the GI tolerability of doxycycline. This is made possible by the fact that the individual

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**Enteric-Coated Doxycycline Pellets, Delayed Release, in Tablets**

**Fig. 1. Dermatologists’ Perceptions of Teenage Patient Adherence: Oral Therapy**

<table>
<thead>
<tr>
<th>Dosing Frequency</th>
<th>Reasons for Non-adherence</th>
</tr>
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<tbody>
<tr>
<td>BID</td>
<td>GI Side Effects</td>
</tr>
<tr>
<td>QD</td>
<td>BID Dosing</td>
</tr>
<tr>
<td>94</td>
<td>Dosing restrictions</td>
</tr>
<tr>
<td>19</td>
<td>CNS Side effects</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
</tr>
</tbody>
</table>

Most dermatologists believe QD dosing promotes adherence. Dermatologists cite several factors that reduce adherence.
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Doxycycline pellets—not the finished tablet—are enteric-coated.

Background and Rationale

Current guidelines from the Global Alliance to Improve Outcomes in Acne Therapy emphasize the nature of acne as a chronic disease, characterized by a prolonged course, a pattern of recurrence or relapse, acute outbreaks or slow onset, and a psychologic and/or social impact. As such, treatment should be instituted as early as possible within the disease course with a drug regimen selected based on the specific presentation, its severity, and extent of involvement. The guidelines affirm the role of oral antibiotics in the management of moderate to severe acne vulgaris.

The recent guidelines also highlight new findings regarding the pathogenesis of acne, particularly the inflammatory component of the disease. It has now been shown that immune changes and inflammatory responses precede comedogenesis. This inflammatory response was thought to follow other acne pathogenic steps such as hyperkeratinization, increased sebum production, and the presence of P. acnes within the pilosebaceous unit. 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-κB signaling pathways. The same study found significant increases in IL-8 and IL-10. In addition to NF-κB, Activator Protein-1 (AP)-1 is also elevated in acne lesions, leading to elevated matrix metalloproteinases, which degrade collagen—up to 2.5-fold compared to normal skin.

Clearly, then, acne vulgaris is a disease mediated not only by bacteria but also by inflammatory processes. The fact that tetracycline antibiotics confer both antimicrobial and anti-inflammatory effects accounts for their utili-
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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. 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, 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.

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-inflammatory hyperpigmentation.

Published results of comparative trials of minocycline and doxycycline in conditions other than acne are limited.

The Novel Formulation of Doryx

The incidence of side effects associated with doxycycline may vary based on the formulation of the drug. Doxycycline is available in two different forms: doxycycline hyclate and doxycycline monohydrate. Doxycycline hyclate, which is more acidic than doxycycline monohydrate, may be associated with higher risk of esophageal ulceration when the drug is not taken without sufficient water. However, the risk of ulceration is notably decreased when the formulation is taken with adequate fluid. Concomitant intake of food and dairy products does not significantly influence absorption of either form of doxycycline; consumption of antacids and iron may decrease absorption.

To reduce the incidence of GI effects associated with doxycycline hyclate, enteric-coated, delayed-release pellets were formulated into pressed powder tablets (Doryx). These tablets have been associated with a decrease in doxycycline-induced GI effects. A crossover-design double-blinded study involving 102 healthy volunteers compared GI complaints associated with doxycycline hyclate capsules, doxycycline hyclate enteric-coated pellets, and placebo. Twice on the first day of the study the subjects took either a 100mg tablet of Doryx (enteric-coated DH) and placebo Vibramycin (non-enteric-coated doxycycline hyclate) capsule, Vibramycin and a placebo Doryx tablet, or a placebo Doryx and placebo Vibramycin after an overnight fast of at least 10 hours. Subjects received the same regimen once daily in the morning on days 2, 3, and 4. Every subject had 180mL of water administered with the treatment, which was given at least one hour before eating. There was also a three-day washout period between each
A total of 98 subjects completed the trial, which found that the mean symptom scores for vomiting, nausea, stomach/abdominal discomfort, and decreased appetite with enteric-coated pellets were statistically-significantly lower compared to mean scores for standard doxycycline capsules. Mean nausea scores were lower for enteric-coated pellets compared to standard capsules (1.6 versus 3.2, reported by 36 percent and 66 percent of subjects, respectively), and only slightly higher than for placebo (0.7, reported by 21 percent of subjects). Moderate to severe nausea was reported by 40 percent of the subjects receiving non-enteric coated doxycycline hyclate, 18 percent of the subjects receiving enteric-coated doxycycline hyclate, and three percent of subjects receiving placebo.

A second study of similar design found that among subjects taking doxycycline monohydrate, 66 percent reported adverse events, versus 43 percent of those taking enteric-coated doxycycline hyclate, and 30 percent of controls, which was also statistically significant. Nausea was significantly more common with doxycycline monohydrate (59 of 111 subjects) than with doxycycline hyclate (21 of 111 subjects). (Fig. 2) Vomiting and abdominal pain were also significantly more common with doxycycline monohydrate than with enteric-coated doxycycline hyclate or placebo. Rates of vomiting and abdominal pain were similar for enteric-coated doxycycline hyclate and placebo.

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Conclusion: Vehicle Benefits
Although minocycline and doxycycline have equivalent efficacy in the treatment of acne vulgaris, doxycycline has a more favorable safety profile overall. If doxycycline is appropriate for the management of acne vulgaris, the selection of Doryx may provide additional benefits in terms of treatment tolerability and reduced incidence of adverse events. Doryx has no warnings or reports of CNS (vestibular) effects, drug-induced lupus-like syndrome or skin hyperpigmentation. Doryx may also provide benefits for patients when used for the management of rickettsial infections and sexually transmitted infections.

Doryx is the only formulation on the market that features the unique delivery system of delayed-release, enteric-coated pellets of doxycycline hyclate in 150mg QD dosing. Although 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.

In addition to the reduced incidence of GI side effects, which is expected to improve therapeutic adherence, Doryx allows once-daily dosing. Once-daily dosing of medication is also associated with improved therapeutic adherence. 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 tablet does not interfere with the release of active drug. Therefore, tablets may be crushed and the contents sprinkled on apple sauce to facilitate dosing.

Clinical Pearl
Scored tablets may be broken to permit dosing flexibility. This flexibility may also be cost-efficient. Consider that if a clinician prescribes a 90-day supply of Doryx 150QD, the pharmacy is likely to dispense just a 30 day supply. For each additional month of therapy, the patient would have to pay an additional co-pay. However, if the patient achieves significant clearance by the end of month one, he or she can taper the daily dose to 75mg. Upon receiving the second 30-day supply of tablet, he/she may divide the tablets and take one-half pill per day. In this way, the patient receives two months of therapy with one co-pay.
Anti-inflammatory Dose Doxycycline

Although the problem of antibiotic resistance continues to generate concern among clinicians and public health officials, prescribing for oral tetracyclines among both dermatologists and non-dermatologists has increased over the last decade. 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. Importantly, the sub-MIC dose is not simply a low dose; any antibiotic currently marketed as a “low-dose” formulation is indicated for the management of infectious etiologies and will when properly administered achieve plasma levels above the MIC. Continuous use of low-dose antibiotics contributes to development of resistance.

Doxycycline is available on the market in a sub-MIC dose in the form of Oracea (Galderma). The novel formulation of Oracea features a unique combination of 30mg doxycycline monohydrate immediate-release beads and 10mg anhydrous doxycycline monohydrate delayed-release beads in a capsule administered once-daily. The unique formulation of both immediate and delayed release (DR) doxycycline enables plasma concentrations of doxycycline to peak well below the MIC for the drug. Therefore, the formulation confers no antimicrobial effect and is not shown to encourage the development of bacterial resistance, even with nine months of continuous use. Importantly, the unique formulation of Oracea has a pharmacokinetic profile that differs significantly from that of standard low-dose (50mg) doxycycline. Oracea confers anti-inflammatory effects, as demonstrated by the reduction in inflammatory lesions of rosacea. Oracea is the only FDA-approved oral agent approved for the management of inflammatory lesions of rosacea.

Background and Rationale

Rosacea is an inflammatory skin disease with a high prevalence, affecting an estimated 14 million Americans. The condition is associated with a significant impact on the individual’s quality of life (QoL), much of which can be linked to feelings of embarrassment or effects of the disease on self-esteem, emotions, and personal/social and professional relationships. Additionally, rosacea is associated with physical discomfort, due to sensations of stinging, burning, itching, etc. While the pathogenesis of rosacea is not entirely understood, current conceptions of the disease emphasize the significant influence of inflammatory mediators in driving the disease process and producing associated symptoms. Rosacea is an inflammatory rather than infectious disease; any infectious etiologies that had been considered in the past have all been disproven.

Histological evidence has confirmed the perivascular and perifollicular infiltration of inflammatory lymphocytes and neutrophils in the cutaneous lesions of rosacea. Recent evidence has further implicated neutrophils in the development and persistence of rosacea. For example, nitric oxide is thought to mediate the dilatation of dermal capillaries in rosacea, while increased levels of matrix metalloproteases are also evident. Additionally, high levels of reactive oxygen species, also shown to activate matrix metalloproteases, have been associated with the disease.

The erythema that is characteristic of rosacea is directly mediated by inflammatory compounds, such as prostacyclin, prostaglandin-E2, nitric oxide (NO), or other vasoactive com-
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pounds. Dilation initiates a cycle of events that contribute to worsening of symptoms and persistence of the disease. With time, dilation leads to weakening of the capillary walls and accumulation of extravascular fluid, producing edema. Neutrophils and proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1 and IL-6), leak into the dermis creating inflammation in the surrounding dermis. In response to increased inflammation, additional neutrophils are recruited, including matrix metalloproteinases (MMPs), reactive oxygen species (ROS), nitric oxide (NO), and other degradative or proinflammatory compounds.

The course of rosacea is known to wax and wane, though the inciting factors remain unknown. With repeated episodes of neutrophil-mediated tissue injury, progressive damage to skin structure occurs and may lead to the development of telangiectases.

Another recently identified contributor to the disease process are cathelicidins, a family of antimicrobial peptides. Cathelicidins are directly antimicrobial, and they initiate additional host immune responses. Cathelicidins at increased levels have been shown to promote tissue responses that resemble the histopathologic features of rosacea, including increased leukocyte infiltration and angiogenesis. When cathelicidin peptides were injected into the skin of mice, a dose-related inflammatory response, including erythema, vascularization, and neutrophil infiltration was observed.

Benefits of Anti-inflammatory Dose Therapy

The use of oral antibiotics to treat rosacea dates to at least the 1960s. It has been proposed that tetracyclines were first used in rosacea on the assumption that an infectious etiology caused the disease. However, an article published in 1966 acknowledged that the mechanism of action of tetracycline in rosacea was unknown but was not thought to be associated with anti-infective properties. Over the ensuing four decades, 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.

Doxycycline and other tetracyclines have been shown to reduce the production of interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) and may reduce neutrophil chemotaxis. Tetracyclines also reduce the activity of phospholipase A2, a family of inflammatory enzymes.

Doxycycline reduces the generation of neutrophil-derived toxic reactive oxygen species, including superoxide anion, hydrogen peroxide, and the hydroxyl ion. In vitro studies show that doxycycline can reduce the production of nitric oxide by epithelial cells at concentrations as low as 3 µg/ml. 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. The anti-inflammatory effects of the tetracyclines are thought to produce their efficacy in rosacea therapy.

The Novel Formulation of Oracea
Based on the evidence that CMTs confer anti-inflammatory benefits even when no antibiotic effect is possible, researchers investigated subantimicrobial dose doxycycline (SDD), now commonly called anti-inflammatory dose doxycycline, for the management of periodontal disease, which was shown to involve an increase in matrix metalloproteinases. A 20mg dose of doxycycline hyclate is below the minimum inhibitory concentration; there is no antibiotic action. Twice-daily Periostat (20mg doxycycline hyclate, CollaGenex) received FDA approval in 1998 for treatment of adult periodontitis and has been widely used for that indication. Long-term use (up to 18 months) produced no changes in antimicrobial susceptibility in patients during the treatment period or up to six months post-treatment.

As the evidence shows, “subantimicrobial” does not mean “subtherapeutic.” The efficacy of subantimicrobial dose doxycycline in reducing the inflammation of periodontitis without simultaneously providing an antibacterial effect prompted interest in the potential for SDD to treat rosacea. The ability to reduce inflammatory lesions and target the inflammatory component of the disease without the side effects of standard dose antibiotics or risk of resistance would be clearly beneficial.

Oracea (doxycycline capsules 40mg, Galderma), is the first and only oral therapy approved for rosacea. 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.

This unique 40mg capsule is not formulated in the same manner as Periostat. Periostat is prescribed for BID dosing, delivering a total 40mg dose in a day.

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/
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sinusitis). Although it has not been definitely established, it is believed that Oracea, by delivering a constant dose of sub-antimicrobial dose doxycycline, provides only the anti-inflammatory effects of doxycycline. A review of the study data follows.

Two parallel, 16-week, randomized, double-blind, placebo-controlled phase 3 clinical trials were conducted to evaluate the efficacy and safety of Oracea for the treatment of moderate-to-severe rosacea (Fig. 4). Study 1 enrolled 251 patients. Study 2 enrolled 286 patients. Study 2 included a post-therapy assessment of efficacy and safety parameters four weeks after discontinuation of study medication.

Subjects with moderate-to-severe rosacea (defined as the presence of 10 to 40 papules and pustules and two or fewer nodules) and a score greater than 2 on an Investigator’s Global Assessment of rosacea severity (rated on a scale from 0 (no signs or symptoms present) to 4 (severe disease)) were also required to have telangiectasia with moderate-to-severe erythema at baseline. All patients were randomized to receive Oracea capsules or placebo once daily every morning for 16 weeks. In Study 2, patients were instructed to use no rosacea or acne therapies until the 20-week assessment.

Of note, in dose-ranging studies, 30mg immediate release plus 10mg delayed release doxycycline provided a similar reduction in inflammatory lesions regardless of the subject’s body mass or the associated dose in mg/kg. (Fig. 5)

Importantly, 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. In the study, which involved 32 healthy adult subjects...
randomized to receive standard doxycycline 50mg QD or Oracea once-daily (16 subjects per arm), the plasma concentration of doxycycline remained well below the antimicrobial threshold over 24 hours in the anti-inflammatory dose group, while the 50mg dose group exceeded the antimicrobial threshold over a period of several hours. Mean subject weight was 75kg. Plasma concentration measurement was conducted on day 7 of use.

Of note, the plasma concentrations in the anti-inflammatory dose group remained more consistent over time, fluctuating no more than 300 units from baseline to peak. The plasma concentration approached 400ng/mL at one hour and at 75 minutes it neared its peak at roughly half the 1000ng/mL threshold for antimicrobial effect. The concentration remained in the 500ng/mL range through hour 4, then gradually declined to 200ng/mL at hour 12.

By contrast, the standard dose group showed an 800-unit fluctuation from drug administration to plasma concentration peak. The peak, at 1200ng/mL was well above the antimicrobial threshold. At about 105 minutes, the plasma concentration reached 1000ng/mL and remained at or above this level through hour 6 (Fig. 6).

Data show that sub-antimicrobial dose doxycycline does not induce resistance in organisms after treatment for up to 9 months. In trials, the percent change in doxycycline resistance was equivalent in SDD-treated patients and controls. These data contrast with those for standard dose doxycycline, which is associated with the development of bacterial resistance with just two weeks of continuous therapy. A 14 day, prospective, placebo-controlled, randomized, double-blind study of 29 healthy male and female subjects sought to determine the effect of a typical 2-week course of oral doxycycline on the proportion of resident nasopharyngeal flora expressing resistance to doxycycline and on the minimal inhibitory concentrations (MICs) of resistant flora. Subjects aged 21-60 years (mean 39 years, median 35 years; 11 men, 18 women) received oral doxycycline 100mg once-daily for 14 days. Analyzable data obtained from 26 subjects (14 in the doxycycline group and 12 in the placebo group) showed a significant increase in the percentage of culturable nasopharyngeal flora expressing resistance to doxycycline 4µg/mL. The greatest increase occurred within the first seven days of doxycycline administration with a minor increase seen between days 7 and 14. On Day 28, two weeks after cessation of antibiotic administration, resistance remained high.

There is evidence to support the combination of SDD with topical therapy, with the oral agent enhancing the efficacy or the topical treatment. A double-blind, randomized, placebo-controlled study involving 40 patients with rosacea with eight to 30 total inflammatory lesions compared SDD plus topical metronidazole lotion 0.75% to placebo plus topical metronidazole lotion 0.75%. The results document clinically significant differences in Clinician’s Global Severity Scores between individuals in the SDD/topical metronidazole group and those in the placebo/topical metronidazole group by week four of treatment. These differences became statistically significant by week 12, at which time the topical agent was withdrawn and patients continued either oral therapy or placebo treatment. SDD-treated patients maintained changes through monotherapy.

Conclusion: Vehicle Benefits

The unique formulation of 30mg immediate-release and 10mg delayed-release doxycycline in an anhydrous capsule produces a predictable and relatively stable plasma concentration of doxycycline that remains well below the antimicrobial threshold. The ability of Oracea to provide improvement in the inflammatory lesions of rosacea is directly linked to this novel design; Standard doxycycline in a similar dose quickly achieves plasma concentrations above the antimicrobial threshold. The low dose of doxycycline in Oracea coupled with its delayed release is thought to account for its favorable tolerability profile.
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.

In a multicenter, 12-week, double-blinded, placebo-controlled, dose-ranging study, 233 subjects with moderate to severe facial acne vulgaris were randomized to receive once-daily treatment with ER minocycline 1mg/kg, 2mg/kg, 3mg/kg or placebo. Patients in the active treatment groups had approximately a 50 percent reduction from baseline in the number of inflammatory lesions. While the difference in the percentage reduction in inflammatory lesions was statistically significant between the 1mg/kg group and controls, there was no statistically significant difference in the percent reduction between any of the dosage groups. The rate of AVAEs in the 1mg/kg dosing group was 24 percent, compared to 26 percent in the placebo group.

Individual and pooled analysis of data from phase 2 and 3 trials of ER minocycline 1mg/kg confirm its safety and efficacy. 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 1mg/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. According to the reported data, at steady state (Day 6), the ER minocycline formulation had a 0- to 24-hour area under the curve (AUC(0-24)) and cmax of 33.32 microg x h/mL and 2.63 microg/mL, respectively, compared with 46.35 microg x h/mL and 2.92 microg/mL, respectively, for the nonmodified-release minocycline.

Concomitant food intake, including dairy, did not alter the pharmacokinetic profile of the ER minocycline tablets. Tablets are available in 45, 65, 90, 115, and 135mg doses.

Conclusion

Systemic antibiotics are important therapeutic agents with a wide range of uses in dermatology, and second-generation tetracyclines are among the most commonly prescribed antibiotics in dermatology. These drugs have overall been associated with therapeutic outcomes.

However, certain side effects are historically associated with therapy and may limit patient adherence and therapeutic outcomes. Furthermore, ongoing concerns about the growing problem of bacterial resistance are causing clinicians to reconsider the ways they prescribe antibiotics.

Advancements in formulation have produced oral therapies that address these important concerns. Importantly, the formulations discussed in these pages do not have generic equivalents, nor is it possible to approximate their benefits by modifying the dosage or administration of other formulations containing the same active drugs. The benefits of these formulations in terms of patient adherence, associated treatment success, lack of common adverse events such as nausea, and overall patient satisfaction may well outweigh apparent cost-savings associated with alternative therapies.


