How many patients come to the office asking, “Do I have rosacea?” Patients often expect that diagnosis because their faces are always red, or because they blush often, or simply because a friend told them so. In any case, making the correct diagnosis with the patient’s understanding of the process is the first step in addressing rosacea management strategies. More importantly, those who truly have rosacea are concerned about the severity of their flares as well as the consequences of not treating aggressively enough or at all. According to the National Rosacea Society, there are an estimated 16 million Americans with rosacea.1 Compared to other common diseases in the United States, rosacea is slightly less prevalent than diabetes and approximately twice as common as psoriasis.1

Even though papulopustular rosacea is traditionally considered a disease of the dermis with little epidermal component due to the lack of scale or other epidermal changes, there is growing evidence that stratum corneum impairment results in variations in permeability as well as overall breakdown in barrier functions. As a result, symptoms of hyperirritability may impact the irritation potential of cleansing, moisturizing and applying conventional therapies resulting in limitations of a topical approach to management.7

The psychosocial impact of rosacea is significant, as patients tend to be highly self-conscious, even to the point of withdrawing from both work and social activities. A study from the National Rosacea Society (NRS) revealed that 76% of surveyed patients reported low self-confidence and self-esteem, causing almost half (41%) to avoid public contact or cancel social engagements. Results from another survey suggest severe rosacea adversely affected professional interactions for 88% of patients, and half missed work because of the disease.2

Clinical features of rosacea

Other than a biopsy, there is no one confirmatory laboratory test for making the diagnosis of rosacea, which means it is important to have uniform criteria to classify the stages and morphologic variants. These include flushing (transient erythema), presence of nontransient erythema, telangiectasia, papules and pustules.3

In addition, a high proportion of patients experience ocular involvement. These manifestations of rosacea, such as conjunctivitis, keratitis, episcleritis and posterior blepharitis, often go undiagnosed or are not connected to the overall presentation of rosacea. While less common in patients of darker skin types, it has been estimated that about 4% of cases of rosacea occur in darker-skinned patients with non-caucasian ethnic backgrounds. Since the cutaneous signs may be obscured by cutaneous pigmentation in darker-skinned patients, ocular manifestations in this group may be the first evidence that a patient has rosacea.4,5

Histological features and concerns for disease progression

Histologically, early changes parallel those of a chronic dermatosis with actinic injury (solar elastosis), including venular and lymphatic ectasia, mild edema and a lymphocytic perivascular infil-
and NO. Telangiectasias develop from these ongoing vascular alterations.

• Eventually, the extended dilation deteriorates the capillary walls, resulting in edema from the accumulation of extravascular fluid.

• A cycle of continued dermal stroma breakdown leads to chemotaxis, recruitment of neutrophil–mediators inducing tissue injury and further progressive damage.9

The role of cathelicidins

Understanding what cathelicidins are and how they impact the pathogenesis and progression of rosacea is important. To avoid confusion, remember that cathelicidins are antimicrobial peptides (AMPs) that the innate immune system recruits during times of alteration or injury to the skin. They do not circulate like cytokines or interleukins and do not need a receptor. In short, cathelicidins provide direct protection against microorganisms and indirect promotion of host immune responses via cytokine release, angiogenesis, and re-epithelialization at sites of injury. Finally, abnormal production of AMPs creates inflammation that is harmful to skin.10

There is a human cathelicidin proprotein called hCAP18. When necessary, it is converted to active cathelicidin peptides, such as RK 31, KS 30, inactive LL–25 and LL–37 (2 leucines, 37 amino acids long), which are the most abundant. The conversion is mediated by a stratum corneum trypsin enzyme known as KLK5, or kallikrein-related peptidase. Under normal functional circumstances, cathelicidins are recruited to perform functions that protect host immunity. The presence of cathelicidin correlates with the ability of a host to mount a defense against infection.11 Cathelicidins at increased levels have been shown to promote tissue responses that resemble the histopathologic features of rosacea, including increased leukocyte infiltration and angiogenesis. Angiogenesis clearly plays a role in the development and progression of erythema and leukocytes are integral to the formation of papules and pustules.10,11

Matching mechanisms of diseases and therapies

Independent of antimicrobial activity, the tetracycline antibiotics can exert significant anti-inflammatory effects. Relevant to what has been described in rosacea, these include:

• Down-regulation of proinflammatory cytokines (TNF–α, IL–1β)

• Inhibition of angiogenesis

• Suppression of neutrophil–derived production of ROS

• Inhibition of leukocyte–derived matrix metalloproteinases, including collagenases (MMP–8, -13), gelatinase (MMP–2, -9), elastase (MMP–12)

• Reduction of serine protease–related activation of cathelicidin precursors8,12,13

Correlation to the effects of doxycycline on the cascade of MMP activation and cathelicidin expression are demonstrated in Figure 2. The sequence of events downstream is demonstrated through a series of enzymatic reactions. MMPs cleave pro–KLK5 to the active enzyme KLK5, which is autocatalytic, enhancing cleavage of pro–KLK5 and also converting cathelicidin to the active LL–37 peptide. Elevated and unregulated levels of LL–37 are implicated in the pathogenesis of rosacea.

Using this model, it can be hypothesized that doxycycline reduces inflammation associated with rosacea by blocking cathelicidin proteolysis initiated upstream by MMPs. As a
result, doxycycline could reduce inflammation by suppressing the subsequent steps leading to cathelicidin proteolysis and therefore decreasing LL-37 production.14,15

More does not always mean better

There are many disease states where only enough active medication is necessary to accomplish the goal of treatment and higher doses are not only unessential, but may also be harmful. For example, we prescribe only 81 mg of aspirin for cardioprotection while a full dose of 325 mg can result in excessive anticoagulation. When patients have colds, they take only 1 gram of vitamin C because any more would just go to waste. Dermatologists treat androgenetic alopecia with 1 mg of finasteride even though there is a 5 mg preparation available for treating prostate disease. These examples are similar to the use of Oracea in the treatment of rosacea in that this dose impacts the inflammatory mechanisms and, more importantly, because any additional doxycycline above the anti-inflammatory dose becomes an antibiotic and introduces antibiotic side effects.

Clinical importance of doxycycline at anti-inflammatory doses

As evidenced in Figure 3, the subantimicrobial dose formulation of Oracea with 30 mg immediate and 10 mg delayed release of doxycycline monohydrate maintains its action below the antimicrobial curve and does not function as an antibiotic at that dose. This is in sharp contrast to the spike above the plasma level curve with the 50 mg generic doxycycline hydolate dosage, which brings along potential side effects of an antibiotic dose along with potential induction of resistance mechanisms.16 As there is no evidence of a bacterial target in rosacea, the question of the need for antibiotic doses of doxycycline arises when data presented over several years strongly suggest that the application of doxycycline’s mechanisms of action are directed against the inflammatory cascades previously described here.

One of the early studies of Oracea 40 mg capsules, which contain 30 mg immediate release and 10 mg delayed release beads, suggested a safe and effective approach to the treatment of papulopustular rosacea with results seen as early as 3 weeks into therapy (Figure 4). In this study, patients who received Oracea demonstrated greater reduction ($P < .001$) of total inflammatory lesions at Week 16 compared with patients who received placebo. The design was a comparison of two Phase III clinical trials (16-week, randomized, double-blind, placebo-controlled studies), which were conducted in parallel: 251 patients were enrolled in study 1 and 286 patients in study 2.17

Another important study exposed the challenge facing dermatologists that more is not better in the case of rosacea, where enough active ingredients impact the process of the disease without increasing risks of adverse events and contributing to antibiotic resistance. The primary efficacy end point was the reduction from baseline in the number of inflammatory lesions (papules, pustules and nodules) after 16 weeks. An end-point analysis was conducted using a last observation carried forward (LOCF) approach to account for missing data for patients who discontinued early.18

Patients entered the study with between 8 and 40 inflammatory lesions (papules or pustules). The mean number of inflammatory lesions decreased from baseline in both groups (Figure 5). There were no significant differences between the Oracea group and the doxycycline 100 mg group at any evaluation throughout the 16-week study or at end point using the LOCF approach to include patients who stopped treatment before the end of 16 weeks. Both arms of the study showed efficacy in the reduction of total number of inflammatory lesions. Use of the 100 mg dose of doxycycline did not appear to produce a more rapid onset of effect than the Oracea dose. In addition, there was a notable absence in the adverse events reported that are associated with higher doses of doxycycline in this study. These include nausea, vomiting, GI distress, photosensitivity and vaginal candidiasis.19 It is worth noting that in pivotal clinical studies, the most common treatment-related adverse events (>2%) were nasopharyngitis, diarrhea, hypertension, sinusitis and aspartate aminotransferase increase.

One of the important premises of this study was that the 100 mg once daily dose represents the most commonly prescribed dose for rosacea. Though sometimes substituted at the pharmacy for the modified-release dose of 40 mg, there is no additional benefit in the higher dose. Oracea 40 mg capsules is still the only FDA approved oral therapy for the inflammatory lesions of rosacea.8,18

Two other important post-hoc analyses of the pivotal clinical data examined the issues of patient weight and severity in terms of the bias that prescribers may have when encountering patients who might be heavier or have more severe disease.19 These presentations might motivate the dermatologist to prescribe a higher dose out of concern for absorption in a weight-based scenario, or out of concern for insufficient dosage where
Figure 6. Oracea had no reported effects on antimicrobial resistance in a study of 266 patients with periodontal disease. The study was conducted to investigate the potential resistance mechanisms of Oracea on oral mucosal isolates in 70/266 subjects in a long-term safety study. The development of resistant strains of oral flora was compared between Oracea and a placebo over 9 months.

Antibacterial resistance

Antibiotics are used to treat various inflammatory disorders as well as cutaneous infections, but a result of this practice has been a significant resistance to tetracyclines over the past 3 decades. In particular, during the year 2009, dermatologists prescribed 9.5 million oral antibiotics, 6.5 million of which were for tetracycline derivatives. The progressive emergence of bacterial strains less sensitive to commonly used antibiotics, as well as cutaneous infections, but a result of this practice has been a significant resistance to tetracyclines over the past 3 decades. In particular, during the year 2009, dermatologists prescribed 9.5 million oral antibiotics, 6.5 million of which were for tetracycline derivatives. The progressive emergence of bacterial strains less sensitive to commonly used antibiotics, such as MRSA and macrolide-resistant gram positive bacteria, in conjunction with the slow development of new antibiotics, have compounded the problems due to resistance.20,21

A study of 266 patients with periodontal disease was conducted. A subset of 70 subjects was evaluated microbiologically to investigate the potential resistance mechanisms of Oracea on oral mucosal isolates over a 9-month course (Figure 6). After 9 months, doxycycline resistance was noted in 17.7% from Oracea-treated patients and 9.3% of patients who were treated with placebo. This represents an increase of 5.1% in the proportion of resistant strains for patients in the Oracea group versus 5.3% for patients in the placebo group after 9 months.22

By contrast, a smaller study of 29 healthy male and female subjects examined the effect of a typical 2-week course of oral doxycycline on the proportion of resident nasopharyngeal flora.23

Figure 7. A small study of 29 healthy male and female subjects examined the effect of a typical 2-week course of oral doxycycline on the proportion of resident nasopharyngeal flora.23

In a 9-month study, Oracea® demonstrated a mean change from baseline in doxycycline-resistant flora that was similar to placebo (5.09% and 5.38%).

Conclusions

Oracea capsules represent the appropriate dose for the effective treatment of papulopustular rosacea. This is based on the impact on the disease process and the amount of active therapy necessary without the increase of side effects and consequences. Clinical data from researchers across multiple specialties demonstrate that increasing the doses to antibiotic levels does not provide additional benefit in the acute and chronic phases of rosacea or with variation in body weight or severity of presentation. More importantly, the rising issues of bacterial resistance based on prescribing habits raise the need for increasing awareness among dermatologists that, in a condition not linked to bacteria, there is no indication to use antimicrobial doses of doxycycline to treat the process involved.

Oracea is the only FDA-approved oral treatment of inflammatory lesions (papules and pustules of rosacea), and, based on extensive research and clinical experience, dermatologists have a strong, safe weapon for managing this difficult chronic disease.■

References

23. Data on file, Galderma Laboratories, LP.