The emergence on the market of two new formulations of tetracycline antibiotics has engendered some confusion among clinicians regarding low-dose versus anti-inflammatory/sub-antimicrobial dose agents. In simplest terms, a low-dose formulation of an antibiotic, such as once-daily minocycline 1mg/kg (Solodyn, Medicis) or doxycycline 50mg QD, provides antimicrobial effects. Upon administration, plasma levels will rise above the minimal inhibitory concentration or MIC—the concentration at which an agent becomes antibiotic. An anti-inflammatory dose formulation produces plasma levels below the MIC and will not meet or exceed that level. Importantly, there is no standard anti-inflammatory/sub-antimicrobial dose across antibiotics; the dose varies based on pharmacokinetics from one particular agent to another. Hence, 40mg QD doxycycline is subantimicrobial, while 45mg QD minocycline in a patient weighing 125lbs., for example, is not.

Evidence for Anti-Inflammatory Dose Doxycycline
Relatively new to the market, Oracea (doxycycline monohydrate 40mg, CollaGenex)—provided in a single capsule containing 30mg immediate-release and 10mg delayed-release beads—is approved for management of inflammatory lesions of rosacea. The 40mg total dose is sub-antimicrobial/anti-inflammatory. Note that sub-antimicrobial does not mean sub-therapeutic. The antimicrobial threshold plasma concentration for doxycycline is 1.0µg/mL. The combination of immediate- and delayed-release doxycycline beads was selected so that once-daily administration could provide a therapeutic level in terms of area under the concentration-by-time curve without surpassing the antimicrobial plasma concentration.

Various trials involving anti-inflammatory dose doxycycline have shown there is no detectable antimicrobial effect on skin flora or increase in the number or severity of resistant organisms. In acne trials, there was no decrease in P. acnes counts from the start of the study through its conclusion.2

Early studies showing efficacy of anti-inflammatory dose doxycycline for rosacea involved a 20mg formulation of doxycycline hyclate (Periostat, CollaGenex) administered twice daily. Twice-daily dosing of 20mg doxycycline is widely and effectively used for the management of periodontitis. Its action is exclusively anti-inflammatory and long-term anti-inflammatory dose doxycycline therapy (up to 18 months) produced no changes in antimicrobial susceptibility in patients during the treatment period or up to six months post-treatment.3,4 Results of an open-label study involving 50 patients with all stages of rosacea receiving 20mg doxycycline BID showed a 80 to 100 percent reduction in inflammatory lesions and a 50 percent reduction in erythema after an average duration of four weeks of therapy.1

The once-daily 40mg capsule appears to offer enhanced efficacy for rosacea versus 20mg BID. Although the two formulations have not been studied in a head-to-head trial, results from trials of each formulation, all with similar designs and patient characteristics, allow comparison. Patients (n=537) treated with doxycycline 40mg QD in phase III clinical trials5,6 for rosacea demonstrated more significant clearance in inflammatory lesions from baseline than did those (n=134) receiving...
The reduction on inflammatory lesions, the main outcome measure, was about three times greater than for 20mg BID. One possible contributing factor is that patients were presumably more compliant with the QD regimen, though this would not appear to sufficiently explain the enhanced efficacy.

Treatment with anti-inflammatory dose doxycycline did not significantly improve erythema compared to placebo in phase III trials, prompting study of the agent in conjunction with traditional topical rosacea therapies.

Findings presented this year at the AAD Annual Meeting by Fowler et al. support combination therapy. Seventy-two patients were randomized to receive doxycycline 40mg plus topical metronidazole 1% once daily or placebo plus topical metronidazole 1% once daily for 12 weeks. At the close of the study, the dual therapy group had a mean reduction in inflammatory lesions of 13.9 versus 8.5 in the monotherapy group. The mean percent reduction in inflammatory lesions was 66.4 percent in the dual therapy group compared to 48.2 percent in the group receiving topical therapy alone.

**Shifting Perspectives**

An assessment of contemporary rosacea management reveals a paradigm shift in the clinical approach to management of the disease. Sub-antimicrobial dose—more accurately described as anti-inflammatory dose—antibiotics represent a novel approach to disease management that contrasts with other available interventions. Clinicians must recognize the differences between anti-inflammatory dose and low-dose antibiotics and their respective roles in patient care. Combined use of anti-inflammatory dose doxycycline with standard topical rosacea therapies is safe and effective and obviates concerns about antibiotic resistance.

9. Comparison data and analysis reported via personal communication by CollaGenex. Also presented: Del Rosso J. South Beach Symposium, Miami, Fl, February 2007.