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JOURNAL SCAN

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Exploring the Role of Modified-Release Doxycycline in Rosacea

Introduction by Brian Berman, MD, PhD

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Exploring the Role of Modified-Release Doxycycline in Rosacea

INTRODUCTION BY BRIAN BERMAN, MD, PHD

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Rosacea, a common dermatologic disorder that affects the central part of the face, is most prevalent in pale-skinned individuals of Celtic, Northern, or Eastern European background. The disorder is estimated to affect more than 16 million Americans. Among the factors contributing to the disease are a genetic predisposition, increasing age, emotional stress, alcohol, menopause, weather, UV radiation, and vasodilating medication. The disorder can present as persistent redness of the facial skin, dome-shaped red papules with or without pustules, and telangiectasia. In addition, because of its red-faced, acne-like effects on personal appearance, it can cause significant psychological, social, and occupational problems if left untreated.[1]

Although the etiology of rosacea remains unknown, inflammation is known to play a prominent role in its pathophysiology. According to Del Rosso et al,[2] collagen-degrading matrix metalloproteinases (MMPs) and proteases may be responsible for the inflammation occurring in rosacea, and drugs in the tetracycline family have been shown to inhibit MMPs, as well as reduce cytokine expression and inhibit serine proteases—two additional mechanisms that have been implicated in the disease.

Doxycycline, a member of the tetracycline family, has been proven effective in the treatment of rosacea because of its anti-inflammatory effects.[2] Unfortunately, doses of doxycycline 50 mg or above have also been shown to increase antibiotic resistance and alter the normal intestinal flora. A randomized double-blind trial in which 100 mg of oral doxycycline was given to healthy adults, for instance, found that at this dose, the drug increases the concentration of doxycycline-resistant nasopharyngeal flora in as little as 7 days.[3] Long-term administration of 40 mg of modified-release doxycycline, on the other hand, did not affect bacterial susceptibility over a 9-month period.[4,5]

In his review on antibiotic resistance as it applies to dermatologic practice, Rosen[6] further emphasizes the need for caution in prescribing

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long-term antimicrobial agents. He points out that "widespread antibiotic use for acne and rosacea has been implicated in the conversion of normal cutaneous saprophytes into drug-resistant pathogens." As an example, the author cites the fact that tetracycline-resistant *Micrococcus luteus* has been implicated as a cause of bacterial endocarditis.

By way of contrast, a subantimicrobial-dose (40 mg) modified-release formulation that combined 30 mg of immediate-release and 10 mg of modified-release doxycycline (Oracea®) has been proven effective in reduction of the total inflammatory lesions of rosacea.

Del Rosso et al,[2] for instance, found that 40 mg of modified-release doxycycline is just as efficacious as 100 mg of doxycycline during a 16-week trial and was less likely to produce adverse effects. Similarly, a community-based open label trial by Webster[7] has found that at 12 weeks on 40 mg of modified-release doxycycline, nearly 75% of the patients were clear or near clear, based on the 5-point Investigator's Global Assessment scale. This same open-label trial also demonstrated that a subantimicrobial dose of doxycycline improves patients' quality of life, as measured by a rosacea-specific quality-of-life questionnaire.[8]

To test the effects of modified-release oral doxycycline in combination with a topical agent, Fowler[9] administered 40 mg of modified-release doxycycline capsules (Oracea®) once daily with topical metronidazole 1% (MetroGel®). The combination was compared to placebo plus MetroGel in a double-blind fashion. Combining Oracea and MetroGel was found to be more effective than was placebo plus MetroGel, and combination therapy resulted in faster and greater reduction of inflammatory lesions than did MetroGel monotherapy.

This *Journal Scan* supplement to FAMILY PRACTICE NEWS summarizes some of the recent studies that have investigated the use of subantimicrobial-dose modified-release oral doxycycline. Our goal is to provide clinicians with a therapeutic tool for rosacea that is both effective and potentially more tolerable than other treatment options.

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9. Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, USP monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol*. 2007;6:641-645.

Comparing Antimicrobial and Anti-Inflammatory Doses of Oral Doxycycline in the Treatment of Rosacea

Some of the strongest evidence supporting the value of subantimicrobial-dose, modified-release doxycycline in the treatment of rosacea comes from a randomized double-blind trial that compared 100 mg of oral doxycycline to a 40-mg formulation containing 30 mg of immediate-release doxycycline and 10 mg of delayed-release doxycycline in the treatment of moderate to severe rosacea.

Del Rosso and associates recruited 91 subjects in this multicenter, outpatient noninferiority study and administered standard-dose doxycycline plus topical metronidazole 1% to one group and the modified-release formulation plus topical metronidazole 1% to the other group over a 16-week period. The patient population comprised 89 men and women more than 18 years of age who had been diagnosed with inflammatory papulopustular rosacea. All patients were classified as scoring between 2 and 5 on the Investigator's Global Assessment (IGA) scale. The IGA scale starts at 0, representing completely clear skin, and extends to 5, representing very severe disease with more than 25 papules and pustules, as well as the presence of nodules, perilesional redness, and edema.

Patients were excluded from the trial if they were taking clinically significant concomitant medications, including vasodilatory drugs and corticosteroids. The primary therapeutic end point measured was an observed change in papules, pustules, and nodules from baseline to week 16.

Both treatment groups experienced a similar onset of action at week 4 when compared to baseline, with no statistically significant difference in therapeutic response (P=0.61). At week 16, the investigators observed that both groups experienced significant improvements in inflammatory lesion counts with no significant differences between the two groups (P=0.83). There were, however, noticeable differences in adverse effects (AEs): 26 patients in the antimicrobial-dose (doxycycline 100-mg) group experienced one or more of the 10 most frequent AEs, including nausea, headache, influenza, nasopharyngitis, urticaria, diarrhea, esophageal pain, vomiting, abdominal pain, and upper abdominal pain. In the anti-inflammatory–dose (doxycycline 40-mg) group, only six patients experienced any of these reactions. As the authors point out, "Both the number of AEs and the number of subjects with AEs were greater in the 100-mg group."

Most of the AEs were gastrointestinal (GI) in nature, with nausea topping the list. Eight patients in the 100-mg group complained of this AE; whereas, none in the subantimicrobial-dose, modified-release formulation group mentioned it. Similarly, patients in the 100-mg group complained of diarrhea, esophageal pain, vomiting, and abdominal pain; whereas, these GI reactions were not reported by any patients in the subantimicrobial-dose, modified-release formulation group.

The researchers reached several conclusions after analyzing their data.

- Antimicrobial and anti-inflammatory doses of doxycycline are equally effective when used as a once-daily treatment for moderate to severe rosacea.
- Antimicrobial doses (100 mg) of doxycycline do not have a more rapid onset of action than do doses of anti-inflammatory (40-mg) modified-release doxycycline.
- Doses of 100 mg doxycycline are more likely to cause AEs than are doses of anti-inflammatory (40 mg) modified-release doxycycline.

Based on Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol.* 2008;7:573-576.

Commentary by Brian Berman, MD, PhD

The Del Rosso trial confirms what other investigators have observed, namely that 40 mg of modified-release doxycycline is as effective as an antimicrobial (100-mg) oral dose of the drug, but with fewer AEs. In that respect, it is useful to compare doxycycline to aspirin. In high doses, aspirin has an analgesic effect, but along with that therapeutic effect comes the risk of GI bleeding and other adverse reactions. However, at a much lower dose, namely 81 mg, aspirin has anticoagulant effects and a lower risk of GI complications.

So, too, does subantimicrobial-dose 40 mg doxycycline benefit patients with inflammatory lesions of rosacea with lower reported side effects in clinical studies. In one study, for instance, there were five times the number of GI AEs in patients on the 100-mg antimicrobial oral dose. In addition, photosensitivity and fungal overgrowth can occur with the antimicrobial doses of doxycycline, but, in controlled clinical trials, there were no reports of vaginal candidiasis or photosensitivity with the subantimicrobial, anti-inflammatory dose of doxycycline.

Impact of Antibiotic Resistance on Dermatologic Practice

Antibiotic resistance has become a major concern to both health professionals and the general public in recent years. That has not always been the case. When penicillin became commercially available in the 1940s, many looked on it as a "wonder drug," and, in fact, it had a profound effect on *Streptococcus pneumoniae*, the leading cause of infectious disease and death worldwide at the time. Unfortunately, within a relatively short time, bacteria found "creative" ways to resist the drug's effects, and now many clinicians worry that they may soon run out of therapeutic agents to treat infections that were once considered relatively minor inconveniences in the developed world.

Mechanism of Action

Rosen points out that some bacterial species are inherently resistant to certain classes of antibiotic agents, whereas others acquire resistance through a variety of mechanisms. For example, as an antibiotic destroys the vast majority of organisms in a given host, there is less competition for available nutrients and water, which gives surviving organisms an opportunity to thrive.

Some resistant organisms also have the ability to pass on their genetic material to their neighbors, thereby spreading resistance to a much larger community of microbes. Such genetic exchange usually takes two pathways. During *vertical evolution*, microbes develop advantageous chromosomal mutations that they pass on to their progeny. During *horizontal evolution*, one species passes on new genetic material to unrelated species or groups. During the process of transduction, for instance, genetic material is transferred from one bacterial species to another via viruses called bacteriophages, a phenomenon that specifically contributes to *S. aureus* resistance to antibiotics.

Implications for Dermatologists

In 2009 alone, dermatologists wrote about 9.5 million prescriptions for oral antibiotics, with tetracycline derivatives topping the list (68.6%). In fact, doxycycline, tetracycline HCl, and minocycline are the three oral antibiotics most frequently given to patients with acne vulgaris and rosacea. But as Rosen points out, the need for relatively high doses of these agents for rosacea is probably unjustified because the disease is likely the result of inflammatory mediators rather than infectious agents.

With these concerns in mind, Rosen concludes that "systemic use of antibiotics in the treatment of rosacea might be minimized or completely avoided, by prescribing an FDA-approved subantimicobial dose (SD) of doxycycline (40 mg controlled released doxycycline once daily). Using this anti-inflammatory dose of antibiotics may avoid the side effects associated with the long-term use of tetracyclines…and reduce the potential for developing antibiotic resistance."

In addition to avoiding unnecessary long-term antibiotic therapy, other important measures that can help reduce the risk of antibiotic resistance include strict adherence to an infection-control protocol, including thorough hand washing and topical antiseptics; avoiding broad-spectrum antimicrobials, when possible; and patient education that encourages patients to take the full course of antibiotic treatment.

Based on Rosen T. Antibiotic resistance: An editorial review with recommendations. *J Drugs Dermatol.* 2011;10:724-733.

Commentary by Brian Berman, MD, PhD

In the vast majority of patients with rosacea, the disease is the result of an inflammatory process, not an infectious process. It is, therefore, important to avoid the use of antimicrobial dosing of doxycycline in cases like this for at least two reasons: (1) these higher doses are associated with more side effects, including gastrointestinal distress, photosensitivity, and vertigo, and (2) equally important, at higher doses, the drug can contribute to antibiotic resistance. By way of contrast, a modified-release 40-mg doxycycline formulation has been given to patients with rosacea for up to 9 months with no evidence of antibiotic resistance and no reported abnormalities in intestinal flora. Given the availability of a subantimicrobial, anti-inflammatory oral therapy, a shift in the rosacea treatment regimen must be considered. With equivalent efficacy to antibiotic doses of doxycycline, but with lower reported side effects and no evidence of resistance concerns, subantimicrobial-dose doxycycline may warrant placement as the preferred first treatment option for patients with papulopustular rosacea.

The Effects of Modified-Release Doxycycline on Quality of Life

In order to evaluate the effects of a 40-mg subantimicrobial formulation of doxycycline (30-mg immediate-release and 10-mg delayed-release beads; Oracea®) in everyday clinical practice, investigators conducted an open-label phase IV trial among adults with mild to severe papulopustular rosacea with moderate to severe perilesional redness. The Oracea for Rosacea: A Community-Based Assessment (ORCA) study enlisted 1,421 patients from 271 community-based investigational sites and evaluated the benefits—both physical and psychological—and the side effects profile of the medication over a 12-week period.

The researchers used the 5-point Investigator's Global Assessment (IGA) score as their primary end point, which consists of clear, near clear, mild, moderate, and severe ratings. In addition to measuring physiologic parameters, investigators also looked at the effects of the medication on quality of life (QoL) and patient satisfaction. A 21-question rosacea-specific survey called RosaQoL was given to patients at the beginning of the trial and at week 12, or at the time of early termination.

Baldwin summarizes the effects of the 40-mg subantimicrobial doxycycline formulation as monotherapy and as add-on therapy on QoL and patient satisfaction; 966 patients completed the trial without deviating significantly from the treatment regimen, including 826 patients on monotherapy and 140 who received 40-mg subantimicrobial doxycycline as an add-on to topical medication.

When patients initially enrolled in the study, QoL scores averaged 3.3 (**Table**). By the time they finished, the scores had dropped to 2.8, indicating a statistically significant improvement ($P<0.0001$). Similarly, by the time the trial was completed, about 80% of the patients in both groups said they were very satisfied or satisfied with doxycycline. And most patients also said they were very likely or likely to continue taking the medication.

Based on Baldwin HE. A community-based study of the effectiveness of doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) on quality of life and satisfaction with treatment in participants with rosacea. *Cutis*. 2010;86(5 suppl):26-36.

Table. Changes in mean RosaQoL scores after 12 weeks of treatment with subantimicrobial formulation of doxycycline monotherapy or add-on therapy

	Monotherapy Patients	Add-On Patients	Overall
Baseline RosaQoL scores	**3.3**	**3.2**	**3.3**
12-week RosaQoL scores	**2.8**	**2.8**	**2.8***

*$P<0.0001$ versus baseline

Rosacea-specific quality of life questions 5pt. scale: 1=never; 5=all the time

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The ORCA study looked at the real-world use of oral doxycycline, as opposed to controlled randomized trials in which the use of the drug is closely monitored and subjects are often paid for their involvement; both factors encourage better-than-average compliance with therapy. With that in mind, it is important to see how modified-release doxycycline monotherapy would work in community practice, where no one is standing over patients counting pills and watching them very closely.

We know that rosacea has a significant negative impact on patients' well-being. In surveys by the National Rosacea Society, more than 76% of the patients with rosacea said that their condition had lowered their self-confidence and self-esteem, and 41% reported that it had caused them to avoid public contact or cancel social engagements.[1] Among patients with rosacea with severe symptoms, 88% said that the disorder had adversely affected their professional interactions, and 51% said that they had even missed work because of their condition. As the summary above mentions, patients taking doxycycline as monotherapy or taking the drug in combination with topical medication reported that their quality of life improved, suggesting that the oral medication may benefit patients' self-image and their overall emotional state. This is the first study to report that oral therapy with 40 mg of modified-release doxycycline for 3 months can significantly improve this psychological parameter, regardless of whether patients are taking it with topicals.

Reference

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Combining Anti-Inflammatory–Dose Doxycycline With Topical Metronidazole

To determine what benefits might incur from combining subantimicrobial, modified-release oral doxycycline with topical metronidazole 1%, Fowler enlisted 72 patients in a 16-week double-blind randomized trial. The design consisted of two groups: one that received anti-inflammatory–dose doxycycline (30 mg of immediate-release and 10 mg of delayed-release doxycycline) plus metronidazole gel (group 1) and one receiving placebo plus metronidazole gel (group 2). At week 12, the topical gel was discontinued, at which point group 1 continued on anti-inflammatory–dose doxycycline and group 2 continued on placebo alone.

The Fowler study's primary end point was the mean change in inflammatory lesion count, which included papules, pustules, and nodules. On average, patients had between eight and 40 lesions entering the study, two or fewer nodules, an Investigator's Global Assessment (IGA) score of 2 or higher, moderate to severe erythema, and telangiectasia. IGA score was rated on a scale from 0 to 5, with 0 representing skin that was completely clear of inflammatory lesions and 5 representing a very serious state in which patients had more than 25 papules and pustules, the presence of nodules, accompanied by perilesional redness and edema.

Among the 64 patients who completed the trial, the reduction in inflammatory lesions was significantly better in those on the combination of anti-inflammatory–dose doxycycline and metronidazole than in those on placebo plus the topical gel. The difference in therapeutic response was seen as early as 4 weeks into the experiment, at which point the doxycycline plus metronidazole gel group's change in lesions was -9.69, compared to only -2.86 in the placebo plus topical gel group (P=0.0008) (**Table**). By week 12, just before discontinuing the topical gel, the respective scores were -13.86 vs -8.47 (P=0.002). As expected, the placebo group's improvement declined by week 16.

IGA scores improved in patients taking both anti-inflammatory–dose doxycycline and metronidazole at each clinic visit, but the difference between this group and the group taking placebo and the topical gel only became statistically significant at weeks 12 and 16. By week 12, the mean percent change in IGA scores for group 1 was -66.4%, compared to -48.2% in the group 2 (P=0.008).

It is significant to note that between weeks 12 and 16, patients who were taking doxycycline without the topical gel "maintained the results of the combined therapy with regard to inflammatory lesions and IGA scores," prompting the author to conclude that maintenance therapy consisting of low-dose doxycycline monotherapy "is an option that avoids long-term use of topical or systemic antimicrobials."

Finally, the study confirmed that the adverse effects profile of subantimicrobial-dose, modified-release doxycycline plus metronidazole gel was similar to that seen in patients on placebo and metronidazole gel.

Table. Mean Change in Inflammatory Lesion Count

	Group 1[a]	Group 2[b]
Baseline	0	0
Week 4	-9.69	-2.86
Week 8	-11.86	-7.52
Week 12[c]	-13.86	-8.47
Week 16	-13.44	-6.5

[a] Group 1—40 mg modified-release doxycycline plus metronidazole 1%.
[b] Group 2—metronidazole 1% plus placebo.
[c] Patients in groups 1 and 2 stopped taking metronidazole.

Based on Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, USP monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol*. 2007;6:641-645.

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Combination therapy using both oral doxycycline and topical metronidazole for rosacea is routinely used among dermatologists. However, one unresolved issue is which agent is doing the "heavy lifting" in a situation like this. Fowler has addressed that issue by comparing anti-inflammatory–dose doxycycline plus topical metronidazole to placebo plus topical metronidazole. Although he found that patients in both groups benefited, the reduction in inflammatory lesions was 3 to 4 times greater when the oral medication was taken with the topical gel. In fact, the improvement among patients on the combination at week 4 was slightly better than what was achieved by the topical gel alone at week 12. That suggests that the "heavy lifting" was, in fact, done by the oral medication. That suggestion is further supported by the results that Fowler observed between weeks 12 and 16, when the topical gel was discontinued in both groups. By week 16, patients on the modified-release oral doxycycline monotherapy maintained the benefits obtained by week 12, despite the fact that they were no longer on the topical gel. Beginning with the anti-inflammatory dose, doxycycline appears to result in faster and greater reduction of inflammatory lesions. This also suggests that overall patient outcomes may be improved.