A Status Report on the Use of Subantimicrobial-Dose Doxycycline: A Review of the Biologic and Antimicrobial Effects of the Tetracyclines

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Acne vulgaris and rosacea are among the most common inflammatory dermatoses involving the face, with acne vulgaris occurring in more than 35 million people and rosacea occurring in 14 million people. Perioral dermatitis, another common facial dermatosis, typically affects women. Since tetracycline became available in 1953, followed by doxycycline in 1967 and minocycline in 1972, dermatologists have frequently used oral tetracyclines for the treatment of acne vulgaris, rosacea, and perioral dermatitis. In the treatment of acne vulgaris, the major mechanism focus has been the reduction of *Propionibacterium acnes* organism counts, which correlates with reduction in inflammatory lesions. For rosacea and perioral dermatitis, disorders that are not definitively associated with bacterial pathogenesis, direct anti-inflammatory effects, such as inhibition of neutrophil chemotaxis, have been suggested as mechanisms related to clinical efficacy. For acne vulgaris, rosacea, and perioral dermatitis, recommended regimens with oral tetracyclines have primarily used dosing schedules capable of inducing both antibiotic (antimicrobial) and anti-inflammatory effects.

Enhanced understanding of inflammatory pathways in epithelial and mesenchymal tissues has revealed that the use of subantimicrobial doses of doxycycline initiates anti-inflammatory activity that correlates with clinical efficacy. Doxycycline at subantimicrobial doses has induced clinical responses in disorders such as acne vulgaris and rosacea, without antibiotic activity against *P acnes* and other commensal organisms and without emergence of antibiotic resistance.

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What has been the conventional use of oral antibiotic agents for the treatment of acne vulgaris and rosacea?

The oral tetracycline agents (tetracycline, doxycycline, and minocycline) and the oral macrolide erythromycin have been the predominant oral antibiotics used for acne vulgaris, rosacea, and perioral dermatitis for several decades. Owing to their overall efficacy and favorable safety profiles (even when used for the chronic therapy often required for management of dermatologic disease), collectively these agents have been used for more than 172 years.[1] A recent article reviewed published comparative and placebo-controlled trials of tetracycline, doxycycline, and minocycline that included 321 patients with acne vulgaris and 130 patients with rosacea.[2] A common approach to the use of oral antibiotics in acne vulgaris and rosacea is to achieve control initially with the use of a high daily dosage, tapering to a lower dose for maintenance treatment.[3-5] The clinician may initiate therapy with a lower daily dosage because some patients require it (eg, patients with less than average body weight) or because short-term studies

have demonstrated efficacy with lower doses.[1,3] A common finding noted by clinicians is that oral antibiotics at lower doses have often maintained control of both acne vulgaris and rosacea; this observation is believed to be related to the anti-inflammatory effects of some antibiotics (such as tetracyclines) rather than to their antimicrobial effects.[6,7]

How have emerging trends related to bacterial resistance to antibiotics influenced dermatologic practice?

Overall concerns related to increased bacterial resistance to antibiotics have had an impact on all disciplines of medicine, including dermatology. Several antibiotic resistance issues have emerged in common pathogens of dermatologic infections and inflammatory disorders. Examples include macrolide-resistant *Streptococcus pyogenes* and *Staphylococcus aureus;* methicillin-resistant *S aureus;* mupirocin-resistant *S aureus;* vancomycin-resistant *S aureus;* quinolone-resistant *S aureus*, *Pseudomonas aeruginosa*, and mycobacteria; and *P acnes* resistant to tetracyclines, macrolides, and lincosamides (eg, clindamycin).[4,8]

As a result of these emerging concerns, the US Food and Drug Administration issued a warning notification in February 2003 urging caution in prescribing systemic antibiotic therapy.[9] In addition, the issue of *P acnes* resistance to both topical and oral antibiotics has been addressed in the literature over the past several years.[4,10] How these warnings, recommendations, and educational initiatives will affect antibiotic prescribing patterns by dermatologists for disease states such as acne vulgaris, rosacea, perioral dermatitis, and clinically suspected cutaneous infections remains to be determined.

In the United Kingdom, concerns regarding overall antibiotic use have reduced prescribing patterns. The use of systemic antibiotics for all indications decreased by 23.1% between the periods of 1995 to 1996 and 1999 to 2000, dropping from 44.5 million to 34.2 million prescriptions.[4,11] In 1995, general practitioners wrote 1.6 million prescriptions for tetracycline agents and 0.8 million for topical antibiotics for the treatment of acne. By 2000, the number of prescriptions written had dropped significantly, to 1 million for tetracycline agents and 0.7 million for topical antibiotics. The overall reduction in antibiotic prescriptions for acne in the second half of the 1990s was 33%, including a 37.5% drop in prescriptions for tetracycline agents and a 12.5% drop in prescriptions for topical antibiotics.[4]

What is the prevalence of antibiotic-resistant *P acnes?*

Although earlier isolated cases of erythromycin-resistant strains of *P acnes* were observed in 1971 and tetracycline-resistant strains were observed in 1975, the initial observations of *P acnes* antibiotic resistance in patients with acne were reported in 1979.[4,12,13] Over time, data collected from acne patients in several countries revealed an increased emergence of antibiotic-resistant isolates of *P acnes*. A review of several reports indicated a prevalence rate of 20% in 1978, rising to 62% in 1996.[14] Overall, the prevalence rates of *P acnes* resistance to erythromycin and clindamycin have outpaced trends observed for resistance to tetracyclines; this trend may reflect the widespread prescribing of topical erythromycin and clindamycin for acne over the past 3 decades and their common usage without concurrent therapy with benzoyl peroxide.[4] In Europe, approximately 50% of acne patients appear to be colonized by *P acnes* strains that are resistant to erythromycin or clindamycin, with up to 20% of patients demonstrating tetracycline-resistant isolates.[4,15] Nevertheless, studies completed over the past decade in several countries have confirmed the definite trend of increased prevalence of *P acnes* resistance to several antibiotics used to treat acne, including the tetracycline agents, erythromycin and clindamycin.[14-18]

Cross-resistance between antibiotics in similar structural classes (eg, tetracycline and doxycycline, erythromycin and clindamycin) has been reported frequently.[4,12,14,17,18] However, differences in antibiotic penetration into affected follicles and variable antibiotic cross-resistance related to differences in minimum inhibitory concentrations (MICs) may alter the clinical outcome in individual patients.[4,14,17,18] Although *P acnes* is the predominant *Propionibacterium* species present on skin, other species, such as *Propionibacterium granulosum*, have been ignored in most evaluations. These other species may be operative in the pathogenesis of acne.[4]

What is the impact of antibiotic-resistant *P acnes* on treatment outcomes in patients with acne vulgaris?

It is important to recognize that resistance of *P acnes* to antibiotics is not an all or nothing phenomenon. In patients with acne vulgaris, up to 20% of nonlesional follicles are colonized with *P acnes*, with fewer than 1% of follicles involved in lesional activity at any given point.[4,19] In acne patients evaluated for the presence of antibiotic-resistant

P acnes isolates, patients with positive test results for these organisms are not exclusively colonized with antibiotic-resistant strains. The relative distribution of antibiotic-resistant and antibiotic-susceptible *P acnes* strains demonstrates interpatient variability related to factors such as previous antibiotic use and origin of colonization (eg, person-to-person spread).[4]

Several factors are involved in the pathogenesis of acne vulgaris and clinical response to treatment. The pathogenic influence of *P acnes* is one of several components involved in the development of acne. As a result, patients colonized with a significant number of *P acnes* strains that are resistant to a given oral antibiotic most commonly demonstrate a limited response to that antibiotic or to similar agents owing to "true" (ie, microbiologic and clinical) cross-resistance.[4] If a significant number of *P acnes* strains resistant to a prescribed oral antibiotic emerge over time (usually ≥6 months), the response to treatment frequently diminishes.

It is important to recognize that microbiologic resistance and clinical resistance (ie, treatment failure) are not always synonymous, because reduction in *P acnes* with antibiotic therapy is dependent on achieving follicular drug levels in excess of the MIC.[14] Ultimately, clinical response may vary from follicle to follicle because the concentration of antibiotic within individual follicles may vary owing to physical factors such as sebum excretion rate and extent of hyperkeratosis.[10] Nevertheless, a major underlying consideration regarding antibiotic resistance is that "the harder the organisms are hit, the more they fight back, driving the MICs higher and higher."[4]

What is the effect of systemic antibiotic use on commensal organisms?

Oral antibiotic agents prescribed for dermatologic disease are distributed to other tissues. As a result, commensal organisms (ie, normal flora) present at other sites, including oral cavity, nares, pharynx, conjunctiva, vaginal tract, respiratory tract, and gastrointestinal tract also are exposed to the inhibitory effects of the antibiotic.[10] Antibiotic selection pressure may alter the nature and distribution of commensal flora and can promote the proliferation of antibiotic-resistant isolates, especially after prolonged antibiotic administration. In addition, antibiotic therapy for acne enhances resistance in the normal flora of close personal contacts; affected organisms may include *P acnes* and coagulase-negative staphylococci.[10] This phenomenon is believed to occur via direct interpersonal contact.[4] Coagulase-negative staphylococci may behave as nosocomial pathogens and may provide a pool of antibiotic resistance genes shared with other staphylococci, such as *S aureus*.[10]

A recent study compared patients using oral or topical antibiotics for acne with a control group not treated with antibiotic therapy.[20] A 3-fold increase in oropharyngeal *S pyogenes* was demonstrated in the group using antibiotics. The incidence of *S pyogenes* resistance to at least one tetracycline antibiotic was 85% in the group receiving antibiotics versus 20% in the control group.

What is the separation of biologic and antimicrobial effects related to tetracycline agents?

It is important to recognize that the term *antibiotic* is more a reference to an effect rather than a true description of a drug class or category. There is evidence that tetracycline agents exhibit several intracellular and extracellular biologic activities unrelated to antimicrobial effects.[21] These activities result in reduced inflammation, decreased collagenolysis, reduced degradation of matrix components, and cytokine inhibition.[2,21] The properties of tetracyclines include inhibition of polymorphonuclear leukocyte migration, reduction in generation of reactive oxygen species from polymorphonuclear leukocytes, inhibition of several proteolytic matrix metalloproteinases produced by infiltrating inflammatory cells and connective tissue cells, down-regulation of certain proinflammatory cytokines such as interleukin 1 and tumor necrosis factor-α, inhibition of *P acnes*–derived lipase with reduction of follicular free fatty acids, and blocking of arachidonic acid metabolism by inhibition of phospholipase A_2.[2,7,21-23]

Several biologic activities of tetracyclines that are unrelated to antimicrobial activity may be correlated with therapeutic mechanisms involved in treating inflammatory skin disorders such as acne vulgaris, rosacea, and perioral dermatitis.[2,4,22] Several biologic activities and therapeutic effects are achieved with doxycycline using doses below those needed for antibiotic activity. Subantimicrobial-dose doxycycline hyclate 20 mg twice daily was approved by the US Food and Drug Administration for the treatment of adult periodontitis based on research confirming reductions in collagen and matrix degradation and decreased inflammation in gingival tissue.[21,23-25] Similarities between periodontitis and acne vulgaris have been observed: the pathogenesis of both disorders involves induction of an inflammatory response by commensal bacteria, with *P acnes* operative in acne vulgaris

and *Porphyromonas gingivalis* operative in periodontitis.[2] Clinical trials and case reports have confirmed effective treatment of acne vulgaris, rosacea, and perioral dermatitis using doxycycline hyclate 20 mg twice daily.[2,23,26]

What data are available documenting a separation of the biologic and antimicrobial effects of doxycycline based on dosage?

As mentioned previously, treatment with subantimicrobial-dose doxycycline hyclate 20 mg twice daily has been shown to be effective for acne vulgaris, rosacea, perioral dermatitis, and periodontitis. The mechanism of action of subantimicrobial-dose doxycycline involves biologic effects other than antimicrobial activity.[2,21-25] Studies have demonstrated that doxycycline hyclate 20 mg administered twice daily for up to 18 months does not alter or promote antibiotic susceptibility patterns of normal flora or opportunistic periodontal pathogens and does not create cross-sectional or longitudinal differences in doxycycline-resistant bacteria. These effects also have been documented for up to 9 months after therapy.[27-29] In acne patients treated over a 6-month period, doxycycline hyclate 20 mg twice daily had no effect on *P acnes* or other cutaneous commensal bacteria; did not alter microflora composition; and did not induce the emergence of organisms resistant to doxycycline, minocycline, tetracycline, erythromycin, clindamycin, or vancomycin.[23] Results of studies conducted over 6 to 18 months comparing subantimicrobial-dose doxycycline with placebo indicated no effect on microbial flora of the gastrointestinal and genitourinary tracts and no emergence of isolates resistant to tetracyclines and several other commonly prescribed antibiotics.[23,25,29] Analysis of mean and steady state plasma concentrations of doxycycline over 24 hours demonstrated that administration of 20 mg twice daily produced maximal levels significantly lower than the MIC required to produce an antimicrobial effect at all points in time.[23,25] Administration of doxycycline 50 mg once daily has been shown to produce plasma concentrations that exceed the MIC for approximately 2 to 3 hours.[23]

What data are available on the clinical efficacy of subantimicrobial-dose doxycycline for the treatment of common facial dermatoses?

In a multicenter, double-blind, randomized, parallel-group trial involving adult patients with acne vulgaris, subjects were treated with either doxycycline hyclate 20 mg twice daily (n=21) or placebo (n=19).[23] Compared to the placebo group, the group treated with doxycycline exhibited significantly greater percentage reductions in total inflammatory lesions, comedonal (noninflammatory) lesions, and combined inflammatory and noninflammatory lesions and greater clinical improvement based on investigator global assessment. At study endpoint (month 6), inflammatory lesion counts were reduced by 50.1%, comedonal lesion counts were reduced by 53.6%, and total lesion counts were reduced by 52.3% in the patients treated with doxycycline hyclate 20 mg twice daily. The corresponding reductions observed in the study population treated with placebo were 30.2% for inflammatory lesions, 10.6% for comedonal lesions, and 17.5% for total lesions. As had been noted in periodontitis trials, adverse reaction rates were similar in groups receiving doxycycline and placebo.[23,25]

An open-label study involving adult patients with all stages of rosacea (n=50) evaluated doxycycline hyclate 20 mg twice daily as monotherapy.[2] Study parameters included inflammatory lesions, erythema, and telangiectasia evaluated at baseline and again at 2 to 8 weeks. After an average duration of 4 weeks, an 80% to 100% reduction in inflammatory lesions and a 50% reduction in erythema were reported. Findings also included decreased size and diameter of telangiectasia. Treatment was well tolerated.

Analysis of a double-blind randomized trial (n=36) comparing the combination of metronidazole 0.75% lotion and oral doxycycline hyclate 20 mg twice daily versus metronidazole 0.75% lotion alone (administered with oral placebo) demonstrated that the active combination regimen provided greater reduction in both inflammatory lesions and erythema.[26] After 12 weeks of treatment, the mean percentage reduction in total inflammatory lesions was 64% in the group receiving the combination treatment and 44% in the group receiving topical metronidazole monotherapy. From week 12 through week 16, monotherapy with subantimicrobial-dose doxycycline alone (with topical placebo lotion) provided continued reduction in both erythema and inflammatory lesions, indicating persistence of efficacy and lack of a plateau effect over 16 weeks of use. These findings suggested a potential value for subantimicrobial-dose doxycycline as maintenance therapy. Other cases of effective therapy for perioral dermatitis using subantimicrobial-dose doxycycline have been reported.[2]

REFERENCES

1. Del Rosso JQ. Systemic therapy for rosacea: focus on oral antibiotic therapy and safety. *Cutis*. 2000;66(suppl 4):7-13.

2. Bikowski JB. Subantimicrobial dose doxycycline for acne and rosacea. *Skinmed*. July/August 2003:1-12.
3. Maibach H. Second-generation tetracyclines, a dermatologic overview: clinical uses and pharmacology. *Cutis*. 1991;48:411-417.
4. Eady AH, Cove JH, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant?: implications of resistance for acne patients and prescribers. *Am J Clin Dermatol*. 2003;4:813-831.
5. Bikowski JB. Rosacea: a tiered approach to therapy. *Cutis*. 2000;66(suppl 4):3-6.
6. Meynadier J, Alirezai M. Systemic antibiotics for acne. *Dermatology*. 1998;196:135-139.
7. Webster GF, Leyden JJ, McGinley KJ, et al. Suppression of polymorphonuclear leukocyte chemotactic factor production in *Propionibacterium acnes* by subminimal inhibitory concentrations of tetracycline, ampicillin, minocycline and erythromycin. *Antimicrob Agents Chemother*. 1982;21:770-772.
8. Guay DRP. Treatment of bacterial skin and skin structure infections. *Expert Opin Pharmacother*. 2003;4:1259-1275.
9. FDA to require warning labels on antibiotics. *Health Care Business Daily*. February 6, 2003.
10. Eady EA. Bacterial resistance in acne. *Dermatology*. 1998;196:59-66.
11. Ferguson J. Recent trends in prescribing of antibiotics. *Prescriber*. 2001;12:59-62.
12. Crawford WW, Crawford IP, Stoughton RB, et al. Laboratory induction and clinical occurrence of combined clindamycin and erythromycin resistance in *Corynebacterium acnes*. *J Invest Dermatol*. 1979;72:187-190.
13. Guin JD, Huber DS, Gierlerak PL. Antibiotic susceptibility of comedonal *Propionibacterium acnes*. *Acta Derm Venereol*. 1979;59:552-554.
14. Cooper AJ. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. *Med J Aust*. 1998;169:259-261.
15. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant acne: lessons from Europe. *Br J Dermatol*. 2003;148:467-478.
16. Jones CF, Vyakrnam S, Eady EA, et al. Antibiotic resistant *Propionibacteria* and acne: crisis or conundrum [abstract]? *J Invest Dermatol*. 1997;108:381.
17. Coates P, Vyakrnam S, Eady EA, et al. Prevalence of antibiotic-resistant *Propionibacteria* on the skin of acne patients: 10-year surveillance data and a snapshot distribution study. *Br J Dermatol*. 2002;146:840-848.
18. Ross JI, Snelling AM, Eady EA, et al. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the U.S.A., Japan and Australia. *Br J Dermatol*. 2001;144:339-346.
19. Leeming JP, Holland KT, Cunliffe WJ. The microbial ecology of inflamed acne vulgaris lesions. *Br J Dermatol*. 1988;118:203-208.
20. Levy RM, Huang EY, Roling D, et al. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol*. 2003;139:467-471.
21. Golub LM, Lee HM, Ryan ME, et al. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res*. 1998;12:12-26.
22. Miyachi Y, Yoshioka A, Imamura S, et al. Effect of antibiotics on the generation of reactive oxygen species. *J Invest Dermatol*. 1986;86:449-453.
23. Skidmore R, Kovach R, Walker C, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol*. 2003;139:459-464.
24. Golub LM, Ciancio S, Rhamamamurthy NS, et al. Low-dose doxycycline therapy: effect on gingival and crevicular fluid collagenase activity in humans. *J Periodontal Res*. 1990;25:321-330.
25. Periostat [package insert]. Newton, Pa: CollaGenex Pharmaceuticals, Inc; 2003.
26. Sanchez J. Single-center, randomized, double-blind study of subantimicrobial-dose doxycycline and metronidazole 0.75% lotion for moderate rosacea. Paper presented at: Caribbean Dermatology Meeting; January 2003; San Juan, Puerto Rico.
27. Thomas J, Walker C, Bradshaw M. Long-term use of subantimicrobial-dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol*. 2000;71:1472-1483.
28. Walker C, Thomas J, Nango S, et al. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on subgingival microflora associated with adult periodontitis. *J Periodontol*. 2000;71:1465-1471.
29. Walker C, Nango S, Lennon J, et al. Effect of subantimicrobial dose doxycycline (SDD) on intestinal and vaginal flora. Poster presented at: International Association of Dental Research; 2000; Alexandria, Va.