Subantimicrobial Dose Doxycycline for Acne and Rosacea

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Acne vulgaris and rosacea present therapeutic challenges due to their chronicity, potential for disfigurement, and psychosocial impact. Although pathophysiologically distinct, both conditions have major inflammatory components. Consequently, topical and systemic antimicrobial agents are routinely prescribed for extended periods. Emergence of resistant strains of Propionibacterium acnes, adverse events, and compliance issues associated with chronic systemic tetracycline use have led to new treatment approaches. At subantimicrobial doses, tetracyclines reduce inflammation via anti-collagenolytic, antimatrix-degrading metalloproteinase, and cytokine down-regulating properties. Subantimicrobial dose (SD) doxycycline (Periostat 20 mg) has clinical utility in periodontitis and has been investigated in a double-blind, placebo-controlled trial in the treatment of moderate facial acne as well as in an open label study in the treatment of rosacea. The results of subantimicrobial dose doxycycline treatment in early trials support its benefits and further investigation in acne and rosacea. (SKINmed. 2003;2:234–245)

Acne vulgaris is the most common chronic skin disorder in the United States, affecting approximately 80% of persons at some point between 11 and 30 years of age.[1] In 1996 in the United States, the National Health Interview Survey reported the prevalence of acne was 26/1000 in persons <45 years of age.[2] Although the data in adults are sparse, one community-based study in England found the prevalence of clinical acne in women >25 years was 12% and in men it was 3%.[3] In addition to the economic costs of physician visits,[4] medications, and over-the-counter treatments,[5] the disfigurement and permanent scarring can have significant impact on psychosocial development and the quality of life of those who suffer from it.[1]

Rosacea is also a common, chronic dermatosis estimated to affect at least 1 in 20 people in the United States.[6] The majority are fair-skinned, Caucasian women, aged 30–50 years old.[7] One community study found 10% of those examined had rosacea (14% were women, 5% were men).[8] Similar to acne, rosacea has a significant economic cost[6] and psychosocial impact. Because the features of rosacea are so visible, people with rosacea are often distressed and embarrassed about their appearance and may exhibit low self-esteem.[9]

The Pathogenesis of Acne

Acne, the major disorder of the pilosebaceous unit, presents as noninflammatory (closed and open comedones) and inflammatory (papules, pustules, nodules) lesions. Several factors contribute to the pathogenesis of acne including androgens (testosterone and DHEA-S), increased sebum production, *P. acnes*-driven inflammation, and abnormal follicular epithelial differentiation. Desquamated cornified cells of the upper canal of the follicle become abnormally adherent. Instead of undergoing normal shedding and discharge through the follicular opening, the cells form a microscopic hyperkeratotic plug (the microcomedo) in the follicular canal, which enlarges and becomes a visible comedo. Inflammation (and subsequently, inflammatory acne) is a direct or indirect result of the proliferation of *P. acnes*. Overgrowth of this anaerobic organism, which is otherwise a normal constituent of the skin flora, occurs in the lipid-rich environment of the pilosebaceous units containing microcomedones. The host

damage to and rupture of the follicular wall which extends the inflammatory process into the surrounding dermis, resulting in the formation of the inflammatory lesions (papules, pustules, and nodules) and ultimately, destruction of the collagen matrix in the skin and cyst formation. Each of these pathogenic processes is a potential target for treatment.[1,10]

The Pathogenesis of Rosacea

Rosacea is a chronic, cutaneous vascular disorder. The earliest manifestations are increased and prolonged flushing, erythema, and sensitive skin. Although the etiology of rosacea remains unclear, local irritants (e.g., certain topical medications, astringents), wind, temperature extremes, hot and/or spicy foods and beverages, and alcohol can precipitate vasodilation (flushing) and inflammation (papules, pustules), the clinical signs of rosacea.[11] In addition, the erythema of rosacea is apparently aggravated by chronic sun exposure and photo damage. Exposing facial skin to sources of radiant heat, such as from a fireplace, reproduces the erythema.[12]

Extravascular fluid from the flushing reaction accumulates in the superficial dermis faster than the lymphatic vessels can remove it, leading to edema and damage to the lymphatic vessels. Elastin degeneration due to actinic exposure is probably a common cause of lymphatic failure. The upregulation of proteolytic activity during inflammation, along with neutrophil infiltration, exacerbates the degradation of elastin. Neutrophil elastase and gelatinase, from a variety of cellular sources, are capable of degrading the type IV collegen in the extracellular matrix on which the integrity of the capillary cell wall depends.

Lymphatic failure results in a sustained inflammatory response. In a later vascular stage, telangiectasias commonly develop on the nose, nasolabial folds, and cheeks. The condition progresses to an inflammatory stage characterized by erythematous papules and pustules on the cheeks, forehead, nose, and chin. The final stage is the development of large inflammatory nodules and connective tissue hypertrophy and fibroplasia (a result of the accumulation of plasma proteins). Finally, the fibroplasia may lead to the development of rhinophyma (predominantly in men).[11]

Commonly Used Therapy for Acne and Rosacea

Treatment for acne focuses on the resolution of inflammation, downregulation of sebum production, and elimination of the noninflammatory lesions manifested as microcomedo and comedones. In rosacea, therapy is typically anti-inflammatory in nature. For acne, the choice of therapy usually depends on the grade and severity. Rosacea therapy is determined by the stage.[11]

Mechanism of Action of Antimicrobials in Acne. The multifactorial nature of acne ideally requires an agent with a variety of mechanisms, exerting an effect not only on the bacteria but also on the inflammatory host response induced by the bacteria.[1] Certain antimicrobials exhibit these pleiotropic effects both reducing the numbers of bacteria and suppressing the host's inflammatory response. For example, tetracyclines have been shown to: diminish polymorphonuclear neutrophil (PMN) chemotaxis (possibly by inhibiting PMN chemotactic factor); reduce lipase production in *P. acnes*, resulting in a reduction of fatty acids in sebum on the skin surface;[13,14] affect complement pathways; down-regulate inflammatory cytokine production; and inhibit host collagenolytic activity. These pleiotropic properties have led to the widespread use of tetracyclines for the treatment of acne.

> ***"Tetracyclines diminish PMN chemotaxis, reduce lipase production in P. acnes, down-regulate inflammatory cytokine production, and inhibit host collagenolytic activity"***

Systemic Antimicrobial Therapy

Systemic antimicrobial therapy is generally more effective than topical therapy presumably because the drugs penetrate the follicle more readily. Oral antimicrobials are indicated for persons with moderate-to-severe acne, persons with inflammatory acne in whom topical antimicrobials have failed or are not tolerated, persons with involvement of the skin of the shoulders, back, or chest (where it is difficult to apply topical therapy), and persons with mild-to-moderate acne who have a potential for substantial scarring or pigmentary changes (post inflammatory hyperpigmentation).[10]

The most common oral antimicrobials used are tetracycline HCl, doxycycline, and minocycline. The selection of an antimicrobial is typically

guided by the drug's efficacy, safety, convenience of use, and cost. The pharmacologic properties of doxycycline and minocycline are improved over tetracycline HCl. They both have improved absorption from the gastrointestinal (GI) tract along with increased lipophilicity resulting in better uptake by the pilosebaceous unit, and thus better tissue penetration than tetracycline HCl. In addition, their increased half-life allows once- or twice-daily dosing, potentially facilitating patient adherence to the dosing regimen.[15]

Efficacy of the Tetracyclines in Acne Vulgaris

There are few well done, placebo-controlled clinical trials evaluating the systemic use of tetracyclines (especially doxycycline) for the treatment of acne. Many studies lack objective descriptions of baseline disease severity and consistent measures of efficacy and outcome between studies, thus making the assessment of the relative efficacy of the study drugs even more difficult. Despite limitations, overall study results and numerous case reports support the use of the tetracycline family of drugs in the treatment of acne. These studies are summarized in Tables I and II.

Efficacy of Tetracyclines in Rosacea

Therapy for rosacea usually consists of a combination of topical and oral antimicrobials.[11] Papules and pustules in rosacea are generally eliminated with systemic antimicrobials, such as tetracycline HCl, and remission can be maintained to some extent with topical treatment, such as metronidazole.[16] Approximately 25% of patients relapse within 1 month after discontinuation of active therapy, approximately 50% to 60% at 6 months, and approximately 70% by 1–4 years in the absence of maintenance therapy.[16,17] The literature concerning rosacea is even more sparse than that of acne, but Table III summarizes some of the few comparative studies that have been done with tetracyclines in rosacea.

Drawbacks of Long-Term Standard Dose Therapy

The Problem of Resistance. The widespread use of oral antimicrobials for long-term acne therapy has resulted in the development of resistant strains of *P. acnes*. There is a clear association between the emergence of resistant *P. acnes* and the therapeutic use of these antimicrobials.[18,19] Resistance of *P. acnes* to tetracyclines increased tion,[20] demonstrating the effect of an antimicrobial regimen of tetracycline use in acne therapy on bacterial resistance.[21]

Overall resistance of *P. acnes* to antibiotics had increased from 20% in 1978 to 62% in 1996.[22,23] Levels of resistance to specific antibiotics vary widely, but strains resistant to erythromycin, clindamycin, tetracycline HCl, doxycycline, and trimethoprim are the most common.[18] The Minimum Inhibitory Concentrations (MICs) of tetracycline required to kill 50% of a population of *P. acnes* (MIC_{50}) are typically higher than MIC_{50} for doxycycline, which are typically higher than those of minocycline. Eady et al.[24] found that tetracycline-resistant organisms were cross resistant to doxycycline but susceptible to minocycline. Because resistance to minocycline was rarely observed, minocycline has been the preferred tetracycline for use in acne.[25] More recently, high-level resistance to minocycline (MIC_{50}, 4–16 μg/mL) has been found in populations in the United States.[26] While *P. acnes* resistance per se is not a major public health concern, the ability of microbes to pass resistance from one to another is well known, and even more important is the observation that resistance determinants can co-travel, resulting in the potential for spread of multiantibiotic resistance with potentially devastating effects in clinical practice.[12,27]

One strategy designed to minimize the development of resistance is to use a combination of topical and systemic therapies with regimens that incorporate agents with complementary mechanisms of action. Another innovative approach is to use a subantimicrobial dose (SD) of the antibiotic. As the predominant mechanism for the development of microbial resistance is selection of resistant strains over susceptible strains, a dose could be administered low enough that even susceptible strains remained unaffected. The exploitation of the anti-inflammatory properties of certain antibiotics might be sufficient to elicit a meaningful clinical response, and the administration of SDs may provide effective therapy without the risk of soliciting alterations in microbial susceptibility.

Other Adverse Consequences of Long-Term Tetracycline Therapy. Based on available information, there are more reports of serious adverse events associated with the use of minocycline than with tetracycline HCl or doxycycline. It is speculated that the difference is related to the

Table I. Efficacy of Tetracyclines in Acne Vulgaris—Minocycline vs. Placebo and/or Tetracycline

Study	Design	Efficacy Measures	Results
Hersle, 1976 Minocycline vs. placebo; 43 pts (acne severity not specified)	DB, CO Minocycline (n=18), 200 mg × 7 days; then 100 mg × 5 wk vs. Placebo (n=25) × 5 wk; then placebo group given minocycline and minocycline group given placebo × 5 wk	↓ Total acne load Lesions counted and graded (slightly modified) as in Juhlin study (Table II) After each period, new evaluation and new score expressed as % of original value	After 5 wks: ↓ total acne l Minocycline ↓ 40%; Placebo ↓ 16% ($p<0.05$) After 2nd stage: Minocycline (CO) ↓ 379 Placebo group ↓ 15% (p
Hubbell, 1982 Minocycline vs. tetracycline; 49 pts, grade 2 or 3 pustular acne (Pillsbury system)	DB, 6-mo study Minocycline (n=25) 50 mg b.i.d. vs. Tetracycline (n=24) 250 mg b.i.d.	Conversion to grade 1 acne Grade 1=occasional profuse comedones, no inflammation Grade 2=comedones, small superficial pustules and inflammation Grade 3=comedones, small pustules, deeper inflammatory lesions	After 6 months: Reached and maintaine Minocycline: 23/25 (92 Tetracycline: 18/24 (75
Leyden, 1982 Minocycline vs. tetracycline; 15 pts, moderately severe inflammatory acne	CO, 15 wk All pts tetracycline 500 mg b.i.d. × 6 wk; then 3 wk wash-out; then minocycline 100 mg b.i.d. × 6 wk	Effects of tetracycline and minocycline on *P. acnes* and skin-surface lipid levels: Complete count inflammatory lesions (face and trunk) Quantitative measure *P. acnes* on forehead and cheek (log mean *P. acnes*/cm^2) Skin surface lipid levels (ratio FFA/trigly)	After 6 wks of tetracycline Inflammatory lesions ↓ *P. acnes* on forehead ↓ Skin surface lipids on fo (p <0.0001 for both) After 2nd stage: Inflammatory lesions ↓ *P. acnes* on forehead ↓ cheek ↓ 30% (p <0.001 Skin surface lipids on fo cheek ↓ 62% (p <0.001
Eady, 1990 Minocycline vs. tetracycline 25 pts (severity not specified)	6-mo study Tetracycline (n=12) 500 mg b.i.d. vs. Minocycline (n=13) 50 mg b.i.d.	Changes in numbers of *P. acnes* on skin surface (↓ $\log_{10}$ cfu/cm^2 skin); Resistance to both tetracycline and minocycline; Clinical improvement (mean % ↓ acne grade, Leeds technique)	After 12 wks: Minocycline ↓ *P. acnes* After 24 wks: Minocycline ↓ *P. acnes* No resistant *P. acnes* After 24 wks: Minocycline 56% ↓ acn Tetracycline 65.5% ↓ a

pts=patients; DB=double-blind; CO=crossover; FFA=free fatty acids; trigly=triglyceride; sxs=symptoms; ↓=decrease.

Table II. Efficacy of Tetracyclines in Acne Vulgaris—Tetracycline vs. Doxycycline and Doxycycline vs. Placebo or Minocycline

STUDY	DESIGN	EFFICACY MEASURES	RESULTS
Juhlin, 1969 Tetracycline vs. doxycycline; 28 pts, moderate to severe acne	DB, CO T group: Oxytetracycline 250 mg t.i.d. × 4 wk, then 250 q.d. × 4 wk, then doxycycline 100 mg every third day vs. D group: Doxycycline 100 mg q.d. × 4 wk, then 100 every third day × 4 wk, then oxytetracycline 250 q.d.	↓ Total acne load Lesions graded I–III: I=noninflammatory, pustule <double pinhead; II=pustules >grade I with inflammation; III=deep-seated, large infiltrates; Lesions on face, neck, trunk, back counted/graded, given points; grade I=1 point; II=2 points; III=4 points	After 4 wk: ↓ Total acne load; Both gro After 12 wk: T group ↓ of 81%; D group
Plewig, 1970 Doxycycline vs. placebo; 62 pts, inflammatory acne	DB, CO Phase I: Doxycycline 100 mg q.d. or placebo × 4 wk, then 4-wk wash-out Phase II: Placebo and doxycycline switched for final 4 wk	Total counts of erythematous papules, pustules, and cysts % ↓ of lesions measured Response scores: Excellent: >75% ↓ lesions Good: 50%–74.9% ↓ Fair: 25%–49.9% ↓ Poor: no change–24.9% ↓ Worsening: ↑ lesions	Phase I: Doxycycline 36% ↓ (p<.00 Phase II: Doxycycline 24% ↓ (p <.05 Individual lesion response: Comedones Doxycycline & placebo 76% Papules Doxycycline 43% good/exce Pustules Doxycycline 39% good/exce Cysts Doxycycline 25% good/exce
Smit, 1978 Doxycycline vs. minocycline; 16 pts, severe acne	DB, 12 wk Doxycycline (n=8) 100 mg q.d. vs. Minocycline (n=8) 100 mg q.d. Also 5% salicylic acid and 5% resorcinol b.i.d.	↓ in lesion score based on: • Extension of sxs (grades 1–5, E) • Seborrhea (grades 0–4,S) • Comedones (grades 0–4,C) • Papules & pustules (grades 0–4,P) • Infiltration (grades 0–4,I) • Abscess (grades 0–4,A) (grades not described) Score= E × (S+C+P+I+A); Max=5 × (4+4+4+4+4)=100; Min= 0 × (0+0+0+0+0)=0	Doxycycline mean score diffe Minocycline mean score diffe not statistically significant
Harrison, 1988 Doxycycline vs. minocycline; 34 acne pts (severity not specified)	Observer-B, 12-wk Doxycycline (n = 15) 50 mg q.d. vs Minocycline (n = 19) 50 mg b.i.d. Also 4% chlorhexidine and 5% benzoyl peroxide	Change in no. of nodules, pustules, papules on face and back; Weighted scores for active and less active papules=1, pustules=4, nodules=10, cysts=15; Patient assessed severity as a score out of 100 on a 10 cm analog scale; Tolerance of treatment and treatment effect scores 4=excellent, 3=good, 2=fair, 1=poor	↓ Mean total lesion score (ad Doxycycline 66%; minocyc Patient assessment efficacy s Doxycycline good/excellen Minocycline good/excellen Patient tolerance scores: Doxycycline excellent 53%
Olaffson, 1989 Doxycycline vs. minocycline; 64 pts, moderate to moderately severe acne	DB, 12-wk Doxycycline (n=33) 50 mg b.i.d. × 4 wk vs. Minocycline (n= 1) 50 mg b.i.d. × 4 wk, then both q.d. × 8 wk	Lesion counts on head, neck, trunk (papules, pustules, and open comedones [OC] and closed comedones [CC]); Patient and physician assessment of treatment efficacy	% ↓ LESIONS* All lesions Papules Pustules OC CC Doxy: 85% MDs and pts sai Mino: 87% MDs, 90% pts sa

* P*Percentages based on interpretation of line graphs, exact numbers not given.
DB=double-blind; CO=crossover; P=placebo; sxs=symptoms; chlorhex=; B= blind; rx= therapy

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