Clinical Implications of Minocycline Use in Acne Vulgaris: Focus on Antimicrobial and Anti-inflammatory Properties

James Q. Del Rosso, DO

The decreased sensitivity of *Propionibacterium acnes* to commonly used oral antibiotics has increased worldwide during the last 20 to 30 years. Depending on the country involved and the specific antibiotic in question, the prevalence of *P acnes* resistance ranges from 20% to higher than 90%. Studies with *P acnes* isolates, which measure minimum inhibitory concentrations (MICs) and degrees of prevalence of decreased antibiotic sensitivity, demonstrate that among all the antibiotics tested, resistance to minocycline has been low. In addition, as with other tetracycline agents, minocycline exhibits multiple anti-inflammatory properties, which, in addition to its antibiotic activity, appear to contribute to clinical efficacy in the treatment of acne vulgaris.

In many countries, the most commonly used systemic antibiotic treatments for acne vulgaris have been erythromycin, clindamycin, tetracycline, doxycycline, minocycline, and trimethoprim. During the last 20 to 30 years, there has been a growing recognition within the dermatologic community that patterns of *P acnes* resistance to systemic antibiotic treatment are emerging and increasing worldwide. This perspective is based in part on studies showing that the prevalence of *P acnes* resistance ranges, depending on the antibiotic and the country, from as low as less than 5% for minocycline to 20% or higher (>90%) for many other antibiotics.[1-3] It is further supported by studies reporting decreased therapeutic responses and a greater recognition of treatment failures among patients identified with antibiotic-resistant *P acnes* strains.[4-8]

Literature review of the prevalence of antibiotic-resistant *P acnes* and evaluation of MIC data for multiple oral antibiotics indicate that *P acnes* resistance has continued to be lowest overall with minocycline. Additionally, the therapeutic benefit of minocycline and other tetracycline derivatives when used to treat inflammatory dermatoses such as acne vulgaris appears to relate also to anti-inflammatory properties that are unrelated to antimicrobial activity. This article provides a historical review of *P acnes* antibiotic resistance and discusses anti-inflammatory properties of minocycline that appear to be of therapeutic benefit in acne vulgaris.

Historical Review of *P acnes* Resistance to Antibiotics Used to Treat Acne

In 1979, Crawford et al[1] were the first to report *P acnes* resistance to erythromycin and clindamycin, averaging approximately 20% in 43 evaluated patients. Subsequently, in 1983, Leyden et al[9] published findings from 75 patients with nonresponding or worsening acne receiving long-term antibiotic treatment and concluded that *P acnes* resistance to tetracycline and erythromycin was readily apparent.

In 1988, Kurokawa et al[10] evaluated 46 patients with acne who were treated with different antibiotics and compared those results to historical observations for other individuals spanning a 15-year period. Using MIC data from different strains of *P acnes*, they determined that *P acnes* resistance to erythromycin, tetracycline, and clindamycin was evident, whereas resistance to minocycline was not. The widespread topical use of erythromycin may be a factor in the marked progressive emergence of decreased sensitivity of *P acnes* strains to this agent.

Eady et al[11] showed in 1993 that 178 patients with acne harbored *P acnes* strains that were resistant to most

Dr. Del Rosso is Clinical Associate Professor, Dermatology, University of Nevada School of Medicine, Las Vegas; Clinical Associate Professor, Dermatology, Touro University Nevada College of Osteopathic Medicine, Henderson; and Dermatology Residency Director, Valley Hospital Medical Center, Las Vegas.

Dr. Del Rosso is a consultant, speaker, and researcher for Allergan, Inc; Coria Laboratories; Galderma Laboratories, LP; Intendis GmbH; Medicis Pharmaceutical Corporation; OrthoNeutrogena; QLT Inc; Ranbaxy Pharmaceuticals Inc; SkinMedica, Inc; Stiefel Laboratories, Inc; Triax Pharmaceuticals, LLC; and Warner Chilcott.

commonly used antibiotics. Altogether, 153 patients (86%) demonstrated resistance to erythromycin or trimethoprim. In addition, 61 of 178 patients (34%) harbored strains of *P acnes* that were resistant to tetracycline and cross-resistant to doxycycline, whereas all patients were sensitive to minocycline. In the same year, Eady et al[12] evaluated MICs for 46 resistant strains and 19 sensitive strains of *P acnes* isolated from patients with nonresponding acne who were treated with tetracyclines. MIC data obtained for the resistant *P acnes* isolates showed that minocycline was more active than tetracycline or doxycycline.

In 1995, Cunliffe[5] reported that levels of *P acnes* resistance to erythromycin and clindamycin were 72.5%; to trimethoprim, 17.5%; to doxycycline and tetracycline, 35.6%; and to minocycline less than 1%. In 1998, Cooper[4] published his findings after reviewing 12 manuscripts that discussed *P acnes* antibiotic resistance. It was concluded that the prevalence of *P acnes* resistance had increased from 20% in 1978 to 62% in 1996 and that resistance of *P acnes* to several commonly prescribed antibiotics such as erythromycin, clindamycin, tetracycline, and doxycycline was common, with a low prevalence of *P acnes* resistance to minocycline.

In 1998, Eady[13] described a 6-year study with 2853 outpatients, during which antibiotic resistance in patients with acne was evaluated. Based on MIC evaluations for erythromycin, clindamycin, and tetracycline, it was concluded that the prevalence of antibiotic-resistant propionibacteria to these 3 antibiotics progressively rose from 5% during 1991 to 60% in 1996.

One year later in 1999, Kurokawa et al[14] reported on the effects of various antimicrobial agents versus resistant *P acnes* isolated from acne lesions. Results showed that resistance to erythromycin, clindamycin, tetracycline, and doxycycline could be observed for several strains of *P acnes*, whereas no strains were resistant to minocycline.

In 1998, Ross et al[15] obtained 21 clinically resistant isolates of *P acnes* from the skin of patients with acne. Respective MIC ranges for tetracycline, doxycycline, and minocycline were 2 to 64 µg/mL, 1 to 32 µg/mL, and 0.25 to 4 µg/mL, respectively. Among the major agents used to treat acne vulgaris from the tetracycline antibiotic category, minocycline was shown to be the most active against resistant *P acnes* strains.

In 2001, Tan et al[16] reported the MICs of resistant *P acnes* strains isolated from 150 patients. The profile of resistant strains was highest with erythromycin (11/13 [85%]), followed by clindamycin (10/13 [77%]), tetracycline (1/13 [.08%]), and doxycycline (1/13 [.08%]). No resistance was observed with minocycline (0/13 [0%]).

That same year, Ross et al[17] published an evaluation of 73 different antibiotic-resistant *P acnes* strains isolated from patients in the United Kingdom, United States, France, Germany, Australia, and Japan. Using break-point antibiotic concentrations for the initial screen with erythromycin and tetracycline, resistance was demonstrated for 35 of 73 strains (48%) and for 15 of 73 strains (21%) for erythromycin and tetracycline, respectively. Using these same isolates, the average MIC_{90} for minocycline (4 µg/mL) was half than that observed for doxycycline (8 µg/mL); 8 times lower than that observed for tetracycline (32 µg/mL); 16 times lower than that observed for clindamycin (64 µg/mL); and at least 128 times less than that observed for erythromycin (~512 µg/mL).

Mechanisms of Antibiotic Resistance

On a cellular level, erythromycin, clindamycin, and tetracycline bind to the ribosomal RNA (rRNA) of *P acnes*, blocking protein synthesis and disrupting crucial cellular processes.[16] Resistance to these agents develops when point mutations take place within the bacterial rRNA, most likely interfering with or compromising attachment of these drugs to *P acnes* ribosomal subunits.[16] It has also been suggested that *tet* gene products cause ribosomal conformational changes, which may interfere with or cause dissociation of drug binding to ribosomes.[18,19] Employing tetracycline as a model, it has been shown that a point mutation in 16S rRNA of the small ribosomal subunit is responsible for resistance with *P acnes*.[15,17]

The reason that minocycline has demonstrated over time the lowest level of *P acnes* resistance based on evaluation of MICs and prevalence data is not completely understood. Assuming that an attachment to the ribosomal subunit of *P acnes* is necessary for inhibition of protein synthesis, minocycline may possess molecular structural properties that are less susceptible to the *P acnes* resistance response. Comparative preferential binding studies with tetracycline, doxycycline, and minocycline to ribosomes from resistant *P acnes* could shed more understanding on differences in resistance patterns.

Anti-inflammatory Properties of Minocycline

The lipophilic nature of minocycline is believed to result in its propensity for accumulation within the sebaceous follicle.[20-24] As a result, the drug is capable of exerting its antimicrobial effect against *P acnes* by reaching the target site of the disease. However, reduction of *P acnes* does not explain all of the mechanisms whereby minocycline and other tetracycline agents improve acne vulgaris. The anti-inflammatory properties of tetracyclines appear to play an important role in their efficacy for treatment of acne vulgaris.

In addition to its antibacterial effect, minocycline has been shown to inhibit inflammatory mechanisms that appear to be operative in acne vulgaris. Minocycline blocks the production of interleukin (IL)-like cytokines and inhibits *P acnes* lipase enzyme, thus preventing the release of follicular-free fatty acids.[25-28] Additional properties reported with minocycline include suppression of production of chemotactic factors that attract neutrophils to the follicular site; inhibition of phagocytosis and subsequent release of proinflammatory enzymes; inhibition of neutrophil migration to the site of inflammation; activation of superoxide dismutase, which reduces the adverse impact of reactive oxygen species; inhibition of several cytokines, such as IL-1, IL-6; tumor necrosis factor-α; and inhibition of protein kinase C, which is associated with granuloma formation.[30-39]

Other Clinically Relevant Properties of Minocycline

Extended-release minocycline is the only oral antibiotic approved by the US Food and Drug Administration for treatment of acne vulgaris based on large-scale phase 3 clinical trials and is the only oral antibiotic used for the treatment of acne vulgaris that has been evaluated in dose-response trials.[40] It has been determined in subjects with acne vulgaris that extended-release minocycline, when properly dosed based on the weight of the patient, is equally effective at a dose of 1 mg/kg once daily, when compared to 2 mg/kg once daily and 3 mg/kg once daily.[40-42] Despite lower cumulative exposure to minocycline at 1 mg/kg once daily, its marked lipophilicity is believed to result in facile penetration into sebum, which produces high follicular concentrations.[42-44]

Conclusion

Tetracycline has been used during the last 40 to 50 years for the treatment of acne vulgaris, and its congeners, doxycycline and minocycline, during the last 30 to 40 years. The efficacy of these agents appears to relate to a combination of antimicrobial effects, defined as the ability to reduce *P acnes* counts and multiple anti-inflammatory properties. Several microbiologic studies have demonstrated that minocycline exhibits superior *P acnes* reduction as compared to tetracycline and doxycycline. Because of its high lipophilicity, minocycline is believed to achieve high follicular concentrations, which may account for more favorable *P acnes* reduction than that of other tetracyclines. Minocycline has also been shown to exhibit multiple anti-inflammatory properties, many of which are unrelated to its antimicrobial properties.

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