Recently Approved Systemic Therapies for Acne Vulgaris and Rosacea

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Until recently, with the exception of oral isotretinoin for the treatment of severe recalcitrant nodular acne, systemic therapy for acne vulgaris and rosacea has been based on anecdotal support, clinical experience, and small clinical trials. Tetracycline derivatives are the predominant systemic agents that have been used for both disease states, prescribed in dose ranges that produce antibiotic activity. Anti-inflammatory dose doxycycline, a controlled-release (CR) 40-mg capsule formulation of doxycycline that is devoid of antibiotic activity when administered once daily, was US Food and Drug Administration (FDA)–approved for the treatment of inflammatory lesions (papules and pustules) of rosacea, based on large-scale phase 3 pivotal trials and long-term microbiologic and safety data. Also, an extended-release (ER) tablet formulation of minocycline was approved by the FDA for the treatment of inflammatory lesions of moderate to severe acne vulgaris in patients 12 years and older based on large-scale phase 3 clinical trials that evaluated efficacy and safety, dose-response analysis, and long-term data. This article discusses the studies and clinical applications related to the use of these agents.

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With the exception of oral isotretinoin, which is approved by the US Food and Drug Administration (FDA) for the treatment of severe recalcitrant nodular acne, use of systemic agents for the treatment of inflammatory acne vulgaris and inflammatory (papulopustular) rosacea has been based on anecdotal observation, clinical experience, and a sparse collection of clinical data.[1-4] Released in 2006, anti-inflammatory dose doxycycline (40-mg capsule containing 30-mg immediate-release [IR] and 10-mg delayed-release beads) administered once daily was FDA-approved for the treatment of inflammatory lesions (papules and pustules) of rosacea in adults based on pivotal phase 3 trials and is the first oral agent approved for this indication. Also released in 2006, an extended-release (ER) minocycline tablet, administered based on a dosage of 1 mg/kg daily, was FDA-approved to treat inflammatory lesions of moderate to severe acne vulgaris in patients 12 years and older and represents the first oral antibiotic approved for the treatment of acne vulgaris based on large-scale phase 3 clinical studies.

The tetracycline derivatives doxycycline and minocycline exhibit both dose-related antibiotic activity and biologic effects unrelated to their antibiotic properties.[5-10] At present, doxycycline is the only available tetracycline agent for which dosing and formulation have been delineated based on pharmacokinetic and microbiologic studies that allow for anti-inflammatory activity without antibiotic effects.[9] In the case of acne vulgaris, in which a bacterium (*Propionibacterium acnes*) is involved in the underlying pathogenic process, there is justification for the use of oral antibiotic agents such as ER minocycline tablets to suppress the colony counts and proliferation of the organism.[11,12] Additionally, the efficacy of tetracycline derivatives in acne vulgaris, including doxycycline and minocycline, is believed to be related at least partially to anti-inflammatory effects.[8-10,13,14] With rosacea, there is

no definitive evidence that a bacterium is involved in the underlying pathogenesis of the disorder.[7,9,15-17] As a result, as achieved with anti-inflammatory dose doxycycline, anti-inflammatory activity devoid of antibiotic effects is well-justified based on our current understanding of the underlying mechanisms involved in the pathogenesis of rosacea.[9]

This article discusses the anti-inflammatory effects associated with tetracycline derivatives, followed by a review of data and clinical application related to anti-inflammatory dose doxycycline for inflammatory rosacea and ER minocycline for inflammatory acne vulgaris.

What are the anti-inflammatory effects associated with the use of tetracycline derivatives?

The anti-inflammatory effects of tetracyclines are multiple and varied and have been extensively reviewed.[5,6,8] Although a clear correlation between individual anti-inflammatory effects and therapeutic response for specific disease states is not always apparent or established, many of the anti-inflammatory effects associated with the use of doxycycline and minocycline appear to at least partially explain their therapeutic activity in acne vulgaris and rosacea.[4-10]

Inhibitory effects on inflammation associated with tetracycline derivatives related to T-lymphocyte functions include inhibition of mitogen-induced human lymphocytic proliferation by blockage of blast transformation, inhibition of transmigration of T lymphocytes, inhibition of T-lymphocyte activation, and resultant inhibition of T-cell proliferation.[5] Biologic and anti-inflammatory effects reported in association with tetracycline derivatives include decreased expression of cytokines, which modulates innate immune response (eg, tumor necrosis factor α, interleukin 1β); reduced activity of reactive oxygen species; inhibition of the expression of nitric oxide synthetase (NOS); accelerated degradation of NOS; suppression of neutrophilic migration and chemotaxis; up-regulation of anti-inflammatory cytokine interleukin 10; inhibition of phospholipase A_2; inhibition of protein kinase C activity; and down-regulation of several matrix metalloproteinase (MMP) enzymes, including collagenase I (MMP-1), collagenase II (MMP-8), collagenase III (MMP-13), gelatinase A (MMP-2), gelatinase B (MMP-9), and macrophage metalloelastase (MMP-12).[5-10]

It has not been completely established how the specific biologic, immunomodulatory, and anti-inflammatory effects of tetracycline agents correlate with therapeutic activity for acne vulgaris and rosacea; however, some mechanisms appear to be operative.[5,7-10,18,19] For example, decreased expression of cytokines associated with innate immune response and suppression of both neutrophilic migration and chemotaxis appear to correlate with clinical benefit in acne treatment.[8,18-22] Additionally, reduced activity of reactive oxygen species, inhibition of the expression of NOS, degradation of NOS, suppression of both neutrophilic migration and chemotaxis, and down-regulation of several MMPs have been associated with therapeutic benefit for rosacea.[7-10]

ANTI-INFLAMMATORY DOSE DOXYCYCLINE (CONTROLLED-RELEASE 40-MG CAPSULE)

What is anti-inflammatory dose doxycycline?

Anti-inflammatory dose doxycycline refers to a specific 40-mg capsule formulation of doxycycline monohydrate containing 30-mg IR and 10-mg delayed-release beads (controlled-release [CR] doxycycline 40 mg).[9] Anti-inflammatory dose doxycycline administered once daily is devoid of antibiotic activity.[6,9,23-26] Below is an outline of the pharmacokinetic studies performed after single-dose and steady-state administration, dose-response analysis, and long-term microbiologic studies performed initially from subgingival cultures but also from the skin, vaginal tract, and gastrointestinal tract.[6,9,23-26]

How was the efficacy of anti-inflammatory dose doxycycline established for the treatment of rosacea in the pivotal trials?

Two phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel-group monotherapy trials were completed with adults receiving either one capsule daily of anti-inflammatory dose doxycycline (n=269), also referred to as CR doxycycline 40 mg, or placebo (n=268) for 16 weeks to treat inflammatory rosacea.[9] The mean total inflammatory lesion count at baseline in both studies was approximately 20 lesions (range, 19.5−21.2) in all 4 study arms. Importantly, the inclusion criteria for inflammatory lesions was defined as 10 to 40 superficial inflammatory lesions (papules and/or pustules) and 2 or less nodules, indicating that the study allowed for subjects who demonstrated a broad range of rosacea severity. The primary efficacy end point was mean change from baseline in inflammatory lesion count, which was −11.8 and −9.5 in actively treated subjects and −5.9 and −4.3 in placebo-treated subjects in the 2 trials, respectively. These results were statistically significant in both studies ($P<.001$) and correlated with mean percentage inflammatory lesion reductions of 61% and 46% in subjects receiving anti-inflammatory dose doxycycline and 29% and 20% in subjects receiving placebo, respectively.[9]

Inclusion criteria in the pivotal phase 3 trials also required the presence of moderate to severe facial erythema.[9] Assessment of change in facial erythema, a secondary efficacy end point, was evaluated as a decrease in the mean total erythema score from baseline and demonstrated a statistically significant greater reduction in actively treated compared with placebo-treated subjects in one pivotal study (P=.017). In the second study, although a decrease in erythema was observed in both study arms, the results did not achieve statistical significance.[9]

Are any data available on the use of anti-inflammatory dose doxycycline in combination with other therapies for rosacea?

The combined effect of anti-inflammatory dose doxycycline (CR doxycycline 40 mg once daily) and metronidazole gel 1% once daily (n=36) versus metronidazole gel 1% and placebo capsule once daily (n=36) was evaluated in a randomized, multicenter, double-blind, placebo-controlled, 16-week trial in adults with inflammatory rosacea.[27] After 12 weeks, metronidazole was discontinued, allowing for comparison of anti-inflammatory dose doxycycline versus placebo capsule from weeks 12 through 16. The primary efficacy parameter was the mean change in total inflammatory lesion count from baseline to end points at weeks 4, 8, 12, and 16.[27]

As early as 4 weeks, and at all subsequent time points, the mean change in inflammatory lesions was markedly superior in the treatment group receiving the combination of anti-inflammatory dose doxycycline and metronidazole.[27] The mean inflammatory lesion reduction from baseline to week 4 was −9.69 in the active combination treatment group and −2.86 in the metronidazole and placebo treatment arm, with the difference being statistically significant (P=.008). At week 12, subjects treated with metronidazole and placebo demonstrated a mean inflammatory lesion reduction of −8.70 versus −13.86 in the study arm treated with anti-inflammatory dose doxycycline and metronidazole, thus demonstrating a statistically significant difference (P=.002).[27]

The results of this study indicate that concurrent use of anti-inflammatory dose doxycycline and metronidazole once daily produces a faster onset and greater magnitude of inflammatory lesion reduction than metronidazole alone.[27] With combined use of anti-inflammatory dose doxycycline and metronidazole, the mean inflammatory lesion reduction from baseline to week 4 (−9.69) was comparable with, and even slightly greater than, the mean inflammatory lesion reduction noted at week 12 (−8.70) in the group treated actively with only metronidazole and placebo. From weeks 12 through 16, after discontinuation of metronidazole in both study arms, the improvement noted in the first 12 weeks receded in subjects who received only placebo compared with those subjects receiving only anti-inflammatory dose doxycycline.[27]

What is the overall safety profile of anti-inflammatory dose doxycycline?

In both pivotal phase 3 trials, inclusive of 269 actively treated subjects, anti-inflammatory dose doxycycline was well-tolerated, with a side effect profile similar to placebo. No reports of photosensitivity were observed in subjects who were actively treated, and none of the women treated with anti-inflammatory dose doxycycline (n=185) experienced vaginal candidiasis in both pivotal studies.[9] In the combination therapy trial inclusive of 36 actively treated subjects, anti-inflammatory dose doxycycline was well-tolerated.[27]

In a randomized, multicenter, double-blind, placebo-controlled, 9-month study of subjects with periodontitis, the adverse reaction profiles of anti-inflammatory dose doxycycline (n=133) and placebo (n=133) were compared.[23] In a subset of subjects, microbiologic profiles were determined in both actively treated (n=34) and placebo-treated (n=36) subjects for 9 months. The number and type of adverse events were similar in the active and placebo groups. Microbiologic testing obtained from multiple subgingival sites demonstrated no evidence of antimicrobial selection pressure associated with the use of anti-inflammatory dose doxycycline during the entire course of the trial. Anti-inflammatory dose doxycycline did not alter antibiotic susceptibility of subgingival microflora during 9 months of continuous administration, with no previously susceptible bacteria developing doxycycline resistance. Additionally, cross-resistance or multiantibiotic resistance was not observed.[23]

How do the anti-inflammatory and therapeutic activities of anti-inflammatory dose doxycycline compare with results achieved with doxycycline administered at higher doses in the treatment of rosacea?

At present, there are no direct head-to-head data comparing the efficacy of anti-inflammatory dose doxycycline, which is devoid of antibiotic activity, and higher doses of doxycycline, which exhibit antibiotic activity, in the treatment of rosacea or other disorders. Anti-inflammatory dose doxycycline, the only FDA-approved oral therapy for the treatment

of rosacea, is supported by efficacy and safety data from large-scale pivotal phase 3 trials as well as additional studies that evaluated safety and microbiologic profiles.[9,23-27] Because other formulations and doses of doxycycline have not been assessed in large-scale controlled trials or pivotal phase 3 studies assessing efficacy and safety for rosacea, and because other formulations of doxycycline have not been FDA-approved for rosacea, there are no data that could potentially allow comparative analyses or meta-analysis of similarly performed studies.

An evaluation using a model that quantified levels of neutrophil-generated MMP-8 demonstrated a dose-response breakpoint with regard to anti-inflammatory activity.[6] Within the range of subantimicrobial doses of doxycycline, 20 mg daily produced markedly less down-regulation of MMP-8 expression compared with doxycycline 40 mg daily. However, at a higher dosage of doxycycline (80 mg daily) that is within the antibiotic level, the down-regulation of MMP-8 expression was comparable with the level achieved with doxycycline 40 mg daily. These data suggest that there may be a dosage ceiling for at least some of the anti-inflammatory effects of doxycycline that is independent of the dose-response patterns related to its antibiotic activity.[6]

Because of the absence of studies comparing anti-inflammatory dose doxycycline with higher antibiotic-level dosages of doxycycline, investigators completed specific subanalyses of anti-inflammatory dose doxycycline.[28] These evaluations included standard parametric regression analyses to estimate the correlation of dosage adjusted for body weight (milligram per kilogram) and overall drug exposure based on area under the curve (AUC), and correlations between dosage adjusted for body weight (milligram per kilogram) and efficacy based on the 2 pivotal phase 3 trials. In the pharmacokinetic and efficacy trials, all subjects received one doxycycline CR 40-mg capsule daily (anti-inflammatory dose doxycycline).[28]

In the subanalysis evaluating clinical efficacy based on the 16-week pivotal phase 3 trials, subjects were grouped based on their weight, which resulted in 3 mean-dose groups: 0.37 mg/kg (range, 0.23−0.44 mg/kg; n=90), 0.49 mg/kg (range, 0.44−0.55 mg/kg; n=90), and 0.65 mg/kg (range, 0.55−0.89 mg/kg; n=89).[28] The analysis indicated that there was no significant difference in reductions in inflammatory lesions from baseline to week 16 between the 3 mean-dose groups. Using inflammatory lesion reductions as the parameter for efficacy evaluation, body weight differences did not affect clinical efficacy at week 3 (P=.85), week 6 (P=.53), week 12 (P=.98), and week 16 (P=.98). The mean reductions in lesion counts were −11.3, −10.7, and −9.8 in the subjects receiving a mean dose of 0.37 mg/kg, 0.49 mg/kg, and 0.65 mg/kg, respectively. In the subanalysis correlating the dosage adjusted for body weight (milligram per kilogram) and overall drug exposure calculated as the AUC, the investigators found a highly significant correlation between the dose adjusted for body weight and AUC (milligram per kilogram)(P=.006). The results from these subanalyses indicated that higher milligram per kilogram–dose exposures correlated with higher plasma concentrations of doxycycline but not with increased clinical efficacy based on inflammatory lesion reductions. The investigators concluded that anti-inflammatory dose doxycycline conferred peak anti-inflammatory activity in the treatment of inflammatory rosacea and that increased doses of doxycycline would not be expected to provide additional anti-inflammatory benefit.[28]

How was it determined that anti-inflammatory dose doxycycline is devoid of antibiotic activity and does not produce antibiotic selection pressure?

Importantly, available formulations of doxycycline 50 mg once daily, and higher daily dosages, produce antibiotic selection pressure. A doxycycline dose of 50 mg produces selection pressure for a minimum of 2 to 4 hours as serum levels rise above the minimum inhibitory concentration of at least some doxycycline-sensitive bacteria, an antimicrobial threshold defined as 1 μg/mL.[9,23,24] With anti-inflammatory dose doxycycline, subantimicrobial dosing and lack of antibiotic activity were established based on pharmacokinetic studies performed after single-dose and steady-state administration, dose-response analysis, and long-term microbiologic studies performed initially from subgingival cultures but also from the skin, vaginal tract, and gastrointestinal tract.[6,9,23-26] Longitudinal and cross-sectional microbiologic analyses of specimens obtained repeatedly from subgingival sites performed for 9 months and up to 18 months in some subjects treated with either subantimicrobial dosing regimens of doxycycline or placebo confirmed no statistically significant differences in the proportion of doxycycline-resistant bacterial strains, no changes in antibiograms, no evidence of antibiotic cross-resistance or multidrug resistance, and no growth of opportunistic pathogens.[23-26] It is recognized in FDA-approved product labeling that properly prescribed anti-inflammatory dose doxycycline is devoid of antibiotic activity, it is not classified as an antibiotic, and it is not recommended to be used as an antibiotic in clinical practice.[29]

EXTENDED-RELEASE MINOCYCLINE TABLETS

What is extended-release minocycline?

ER minocycline is an oral tetracycline agent formulated as a tablet that produces a slower release of active drug. Unlike anti-inflammatory dose doxycycline, ER minocycline is an antibiotic. ER minocycline differs from IR minocycline formulations because of its unique pharmacokinetic properties.[1,30] This formulation was developed to reduce the risk of unwanted side effects believed to be associated with the rate of rise to and/or magnitude of the maximum plasma minocycline concentration and/or the overall exposure to minocycline (AUC) measured against time.[1,30] The pharmacokinetic profile of ER minocycline was not modified by concurrent ingestion with food, including dairy products.[30] The ER formulation of minocycline exhibits a pharmacokinetic profile characterized by approximately a 1-hour delay in time of maximum concentration (T_{max}), a lower maximum concentration (C_{max}), and a 28% lower overall drug exposure (AUC).[1,30] ER minocycline is the first oral antibiotic approved for the treatment of inflammatory acne vulgaris based on pivotal phase 3 efficacy and safety trials.[1]

What was the rationale for the development of an extended-release formulation of minocycline?

The basis for the development of an ER minocycline tablet was the desire for a formulation associated with a decreased risk of acute vestibular adverse reactions, including nausea, vomiting, vertigo, dizziness, and tinnitus. It previously has been observed that acute vestibular adverse reactions associated with ingestion of IR formulations of minocycline, primarily vertigo and dizziness, were more common in patients of smaller body size.[31] In addition, IR minocycline formulations characterized by a rapid dissolution rate and quick rise to peak serum level had been associated with a greater risk of acute vestibular adverse reactions such as vertigo and dizziness.[30,32]

In a blinded crossover study of women (N=32) receiving generic and brand-name formulations of IR minocycline, with dosage based on weight (once daily for 4 days followed by a 2-week washout period), differences were noted between the formulations for vestibular adverse reactions.[30] During ingestion of the generic formulation, 27 of 32 subjects experienced vestibular side effects compared with 5 of 32 subjects during ingestion of the brand-name formulation. Interestingly, the more rapid dissolution rate of the generic formulation released 100% of minocycline within 15 minutes; the brand-name formulation released 90% of the active drug within 45 minutes. Differences in the dissolution rate and release time of minocycline, and the rate of rise in serum levels, appeared to correlate with the higher rate of reported vestibular reactions occurring during the period of ingestion of the generic formulation.[30]

An ER minocycline tablet also was developed based on the belief that efficacy of an oral antibiotic in acne vulgaris is correlated more directly with follicular concentration of the drug as opposed to serum concentration.[1] Unfortunately, methodology is not available to directly measure drug concentration within the follicle. Minocycline exhibits greater lipophilicity than other tetracyclines; thus, based on measurements of octanol-water partition coefficients, it is believed that minocycline exhibits high tissue penetration, including permeation into the lipid-rich follicle.[33] The clinical development and pivotal phase 3 trials performed with ER minocycline tablets evaluated clinical efficacy and safety in subjects with acne vulgaris for weight-based dosing (milligram per kilogram daily).[1] Clinical efficacy, defined primarily as a reduction in inflammatory lesions, was comparable among subjects receiving either a once daily dosage of 1 mg/kg, 2 mg/kg, or 3 mg/kg.[34,35] However, a dose-response correlation with acute vestibular adverse events was observed, with higher rates occurring in subjects receiving 2 mg/kg daily (n=59) or 3 mg/kg daily (n=60), and lower rates observed in subjects using 1 mg/kg daily (n=59) or placebo (n=55).[34]

What is the efficacy of extended-release minocycline tablets for the treatment of acne vulgaris based on dose-response and pivotal phase 3 trials?

A randomized, multicenter, double-blind, placebo-controlled, dose-ranging, 12-week, monotherapy study of subjects (N=233) with moderate to severe facial acne vulgaris was designed to delineate the lowest effective and safe once-daily dosage of ER minocycline.[34] Results were similar among subjects receiving once-daily dosages of 1 mg/kg (range, 0.66–1.32 mg/kg; n=59), 2 mg/kg (range, 1.60–2.38 mg/kg; n=59), and 3 mg/kg (range, 2.52–3.47 mg/kg; n=60), with an approximate 50% reduction in inflammatory lesion counts observed in all 3 groups by study end point. These results indicated that the percentage decrease in inflammatory lesion counts in the 1 mg/kg once daily treatment group was equal to or greater than the decreases achieved in the higher dose treatment groups, with 1 mg/kg once daily being significantly superior to treatment with placebo (n=55)(P=.015).[34]

The efficacy profile of ER minocycline tablets was shown in data collected during the phase 2 dose-finding study and 2 phase 3 pivotal trials, all of which used similar protocol designs (randomized, multicenter, double-blind, placebo-controlled, prospective trials) and subject populations.[34,35] All subjects (N=1038) included in the pooled analysis demonstrated moderate or severe acne vulgaris and were treated for 12 weeks with ER minocycline 1 mg/kg or placebo once daily.[35] In all 3 studies, the nominal and percentage reduction in inflammatory lesions was greater in subjects treated with active drug compared with placebo. At week 12, the mean nominal reduction in inflammatory lesions was 17.3 and 12.6 and the mean percentage change was 45.5% and 32.4% in subjects treated with ER minocycline 1 mg/kg once daily and placebo, respectively. These differences were statistically significant ($P<.001$).[35]

What is the overall safety profile of anti-inflammatory dose doxycycline?

As with the discussion of efficacy above, the safety analysis of ER minocycline 1 mg/kg once daily versus placebo was pooled from the similarly performed phase 2 dose-finding study and pivotal phase 3 trials completed over 12 weeks.[35] Adverse events were similar in type and frequency between subjects who were actively treated (n=674) and placebo treated (n=364), with most adverse events graded as mild in severity. The most commonly noted adverse events were cephalalgia, nausea, fatigue, dizziness, diarrhea, and pruritus. In all 3 trials, no cases of cutaneous dyschromia or hyperpigmentation were observed.[35]

The study protocols defined acute vestibular adverse events as vertigo, dizziness, tinnitus, nausea, and vomiting.[34,35] Most vestibular adverse events occurred within the first 5 days of therapy in all 3 studies. Pooled analysis of the 3 trials demonstrated that acute vestibular adverse events occurred in 7.9% to 16.4% of subjects treated with placebo and 9.0% to 10.5% of subjects treated with ER minocycline 1 mg/kg once daily.[35]

Laboratory evaluations, including complete blood cell counts, serum chemistry panels, and urinalysis, were performed as part of the safety evaluation, with no clinically important abnormalities observed based on comparisons with baseline indices.[35] Importantly, no treatment-associated effects on liver panel or thyroid panel parameters were observed. One subject in each phase 3 trial developed weak antinuclear antibody positivity. In one case, the subject also experienced flulike symptoms, and in the other case, the subject was asymptomatic, with antinuclear antibody positivity noted during follow-up after completion of treatment with ER minocycline.[35]

COMMENT

This article discusses 2 new formulations, anti-inflammatory dose doxycycline capsules, which are FDA-approved for the treatment of inflammatory rosacea, and ER minocycline tablets, which are FDA-approved for the treatment of inflammatory acne vulgaris. Both of these tetracycline derivatives have been available collectively for approximately 7 decades. What are the similarities and differences between these agents?

These agents are similar in that they represent the first systemic agents that are FDA-approved for their respective disease state indications (with the exception of oral isotretinoin, which is approved for the treatment of severe recalcitrant nodular acne) based on phase 3 clinical trials. These large-scale trials were performed based on FDA-approved protocols that were randomized, multicenter, double-blind, placebo-controlled, prospective studies that were adequately powered for statistical analysis using recognized methodologies.

Another similarity between these agents is that their formulations are uniquely designed and are not bioequivalent with other doxycycline or minocycline formulations. More importantly, the pharmacokinetic properties of both anti-inflammatory dose doxycycline and ER minocycline have been correlated with clinically relevant properties based on the available studies reviewed in this article. In the case of anti-inflammatory dose doxycycline, the CR formulation administered once daily provides anti-inflammatory activity proven to be effective for inflammatory rosacea without emergence of antibiotic-resistant bacterial strains and with an apparent reduction in the potential for adverse reactions such as gastrointestinal tract upset, photosensitivity, and vaginal candidiasis. ER minocycline allows for effective treatment of inflammatory acne vulgaris using a weight-based dosing regimen (1 mg/kg once daily) that decreases both the potential for acute vestibular adverse reactions and cumulative drug exposure with time. Therefore, these agents should not be substituted with other generic or brand-name formulations of doxycycline or minocycline.

Anti-inflammatory dose doxycycline and ER minocycline differ in several ways. First, the former is FDA-approved for inflammatory rosacea and the latter is approved for inflammatory acne vulgaris. Second, anti-inflammatory dose doxycycline is not an antibiotic and ER minocycline does exhibit antibiotic activity. This is an important differentiation

because effective treatment of rosacea is not dependent on the need for antibiotic activity, and there is no definitive evidence that a bacterium is involved in the pathogenesis of rosacea. Additionally, because rosacea is a chronic disease that warrants long-term therapy, avoidance of both antibiotic selection pressure and emergence of antibiotic-resistant organisms are major benefits of anti-inflammatory dose doxycycline, especially with long-term administration.

In the case of acne vulgaris, therapeutic benefit has been correlated with reduction in *P acnes* colony counts after oral antibiotic use. The high lipophilicity of minocycline is believed to enhance follicular penetration, a factor that appears to account for the clinical efficacy of weight-based dosing of ER minocycline, despite lower peak serum levels and decreased overall drug exposure with time. The antibiotic effects of minocycline, coupled with its inherent anti-inflammatory properties, explain its therapeutic role in acne vulgaris. ER minocycline provides an approach to treatment of acne vulgaris that was proven to be effective in large-scale controlled studies for both moderate and severe acne vulgaris and by its ability to reduce vestibular side effects and overall drug exposure with time. The latter factor may explain the absence of reports of hyperpigmentation with the use of ER minocycline, including some subjects who have been followed for several months beyond the completion of the clinical trials discussed in this article. This does not indicate definitively that hyperpigmentation will not occur in the future in some patients treated with ER minocycline, though a reduction in cumulative drug exposure may reduce the risk. At present, there is no formulation or dosage regimen of minocycline that has been shown to be subantimicrobial after short-course or long-term administration, including ER minocycline.

Because the phase 2 and phase 3 clinical trials of anti-inflammatory dose doxycycline and ER minocycline were completed in preparation for submission to the FDA for drug approval, the results reflected responses achieved with monotherapy. In real-world clinical practice, it is important that ER minocycline be used in combination with topical therapy for acne vulgaris. It is rational to include a benzoyl peroxide–containing product as a component of the treatment regimen to reduce the emergence of *P acnes* strains that are less sensitive to antibiotic therapy. Combination use with topical retinoid therapy also is suggested to optimize therapeutic results. In patients with inflammatory rosacea, anti-inflammatory dose doxycycline may be used as monotherapy based on the results achieved in phase 3 clinical trials. However, prescription data and postmarketing surveys indicate that many dermatologists use an oral agent, including anti-inflammatory dose doxycycline, in combination with topical therapy for rosacea. The results of the study evaluating the concurrent use of anti-inflammatory dose doxycycline and topical metronidazole demonstrated the superiority of this combination compared with the topical agent alone in terms of both speed of onset of clinical effectiveness and the magnitude of therapeutic response.[27]

It is important that large-scale clinical research is performed on agents that have been used for several years, primarily based on anecdotal evidence and clinical experience. Important observations, advancements in our fundamental knowledge, and the uncovering of findings that may effectively challenge long-standing beliefs and recycled dogma sometimes can be achieved only through carefully performed well-controlled prospective trials. There is always more to learn about our existing therapies. New information gleaned from research may help to improve efficacy and/or reduce untoward effects of treatment.

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