

An Update on the Use of Minocycline for the Treatment of Acne



Advances in formulation technology have led to the development of a stable topical minocycline that recently received FDA approval.

Here's what you should know.

BY JOSHUA ZEICHNER, MD

>> Antibiotics are a mainstay of treatment for acne vulgaris for their direct anti-inflammatory effects and indirect anti-inflammatory effects by lowering *C. acnes* levels in the skin. Oral tetracyclines, such as minocycline and doxycycline, are considered first line for moderate to severe acne. Best practice is to limit the duration of use of antibiotics and combine with benzoyl peroxide-containing agents to minimize the risk of bacterial resistance.¹ Topical antibiotics, like clindamycin and erythromycin, are an attractive option because of limited systemic exposure. They are commonly used in regimens along with other actives or as part of fixed-dose combination drugs. With the emergence of bacterial resistance, the utility of these topical antibiotics has decreased.² For this reason, effective topical antibiotic options to treat acne remain an unmet need.

UP TO DATE: AN OVERVIEW OF TETRACYCLINES FOR ACNE

Tetracycline antibiotics exert a variety of anti-inflammatory effects in the skin, which is why they are beneficial in treating acne. They downregulate production of proinflammatory

cytokines (eg. TNF- α , IL-1 β) and *C. acnes* lipase enzymes.³ Tetracyclines suppress neutrophil chemotaxis and subsequent production of reactive oxygen species.³ Finally, they decrease matrix metalloproteinase and nitric oxide activity⁴ and reduce arachidonic acid metabolites by inhibition of phospholipase A2.^{3,5}

The structure of minocycline offers specific advantages over other tetracyclines. It is highly lipophilic, enhancing high penetration into sebum and resulting in high follicular concentrations. Systemic absorption is virtually unaffected by stomach contents, including dairy. Of the tetracyclines, minocycline has been shown to have the lowest level of *C. acnes* resistance based on mean inhibitory concentrations (MICs).⁶ It has also been shown to have the largest log reductions in *C. acnes* counts, as compared to doxycycline, tetracycline, trimethoprim-sulfamethoxazole, and erythromycin.⁷

Minocycline has been available in the United States since 1971. Minocycline, particularly in immediate-release systemic formulas, has been associated with several potential adverse events.

Extended-release formulations were subsequently brought to the market in an attempt to limit potential adverse events. The extended-release formula allows for maintained efficacy despite lower doses. Lower maximum plasma concentration resulted in reductions in acute vestibular side effects. In 2006, extended-release minocycline became the first minocycline formula that was FDA approved for the treatment of inflammatory and non-nodular moderate to severe acne.⁸

Vestibular side effects, such as dizziness, may occur with immediate-release systemic formulas, but are less likely with longer-acting formulations. Idiosyncratic hypersensitivity reactions, DRESS syndrome, pneumonitis, and minocycline-induced lupus-like reactions are rare.⁹ Finally, minocycline-related hyperpigmentation may occur. This is most common with long-term exposure. All of the reported cases of pigmentation occurred after a minimum treatment of eight months and a cumulative dose of at least 70g of the drug.¹⁰

Topical application of minocycline has the advantage of limiting both

systemic exposure and potential serious adverse events. Despite its introduction to the market more than 40 years ago, the structure of minocycline made it difficult to stabilize in a topical preparation. However, advances in formulation technology have led to the development of a stable topical minocycline that recently received FDA approval. Amzeeq (FMX-101), a novel lipophilic topical minocycline 4% foam from Foamix, is now approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients down to the age of 9.¹¹

In Phase 2 and 3 clinical trials, the drug was found to be safe and effective. A pharmacokinetic study evaluating once-daily topical application of Amzeeq foam 4% for up to 21 days did not demonstrate any significant systemic exposure.¹² In its Phase 3 clinical trials, the drug met both of its co-primary endpoints, with statistically significant reductions in inflammatory lesion counts at week 12 compared to baseline, as well as week 12 treatment success, defined as clear or almost-clear with a 2-point reduction in global assessment score.¹³

The drug was safe and well tolerated, with no serious treatment-related adverse events. The most common treatment emergent adverse events (occurring in at least one percent of patients) were upper respiratory tract infections, worsening acne, headache, elevated CK, and influenza. The majority of these events were mild to moderate in severity. Notably, hyperpigmentation was only observed in one patient out of 1,488 and deemed to be post-inflammatory. The drug was found to be non-irritating and not associated with photosensitivity.^{13,14}

Despite high levels of bacterial resistance to both topical and systemic antibiotics, in vitro data evaluating

Amzeeq shows that it maintains its potency with a low rate of promoting bacterial resistance. In vitro studies comparing the Amzeeq formulation to several other antibiotics showed that Amzeeq had the lowest mean inhibitory concentration against *C. acnes*. Amzeeq was found to be four times more potent than tetracycline, eight times more potent than clindamycin, and more than 32 times more potent than erythromycin against *C. acnes*. Moreover, after 15 repeated exposures, Amzeeq maintained its antibacterial activity against *C. acnes*, while high levels of resistance developed with exposure to clindamycin.¹⁵

MINIMIZING RESISTANCE

While effective in treating acne, the major concern with use of antibiotics is the development of resistant organisms. Topical application is beneficial in that it limits systemic exposure and disruption of the gut microbiome. However, the potential for local resistance of both *C. acnes* and commensal organisms may occur. One strategy to minimize the development of bacterial resistance is to deliver high enough drug concentrations to kill all susceptible organisms and prevent growth of mutants.

The term “mutant selection window” refers to the concentration of antibiotics that kills bacteria, but may still allow for growth of mutant organisms and can thus result in bacterial resistance. Antibiotic doses high above the mean inhibitory concentration may be needed to keep drug levels outside this window and prevent bacterial resistance. However, it may be impractical or impossible to dose many systemic antibiotics this way because of potential side effects. Notably, as these adverse events do not exist with the use of topical antibiotics, it is possible to deliver concentrations of topical antibiotics outside of the mutant

selection window.^{16,17} This alone may prevent the development of bacterial resistance and circumvent the need for concurrent use of benzoyl peroxide alongside the topical antibiotic.

More data are needed to fully evaluate this concept with respect to this novel topical formulation of minocycline. ■

Author Disclosures: Dr. Zeichner is a consultant for Almirall, Burt's Bees, Dermavant, Dermira, Galderma, Johnson and Johnson, L'Oreal, LEO Pharma, Menlo Therapeutics, Ortho Dermatologics, Pfizer, Sanofi/Regeneron, Sun Pharma, and Unilever.

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