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 ORIGINAL ARTICLE

Fifty Years of Minocycline and Its Evolution: A Dermatological Perspective

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ABSTRACT

2021 is the 50th anniversary of the FDA approval of minocycline (MCN). While many other antibiotics have become obsolete during this time, MCN continues to be quite useful. In dermatology, MCN is used prominently in acne vulgaris, and is also employed in many other dermatological conditions because of its molecular and pharmacological properties. In this article, we review the history of minocycline, and outline the evolution of the drug since its inception. Based on its existing longstanding utility and continued innovations in formulation and delivery systems, we postulate that it will continue to have a prominent position in the dermatologist's armamentarium.

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INTRODUCTION

This year, 2021, is the 50th anniversary since the 1971 FDA approval of minocycline (MCN) and its introduction into the dermatologist's toolbox. Over those same 50 years, multiple antibiotics have proceeded from auspicious launch to functional obsolescence,[1] while MCN continues to be an integral dermatological therapeutic. Its inherent favorable molecular characteristics and pharmacokinetics have been complemented by an evolution of incremental improvements in dosing, formulation, and delivery systems that have led to its ongoing, longstanding utility. Whereas it was originally approved for systemic infections such as pneumonia and those of the genitourinary tract,[2] in dermatology MCN has been employed for a whole host of cutaneous conditions ranging from rosacea to confluent and reticulated papillomatosis,[3] central centrifugal cicatricial alopecia,[4] pyoderma gangrenosum,[5] methicillin-resistant *Staphylococcus aureus,*[6,7] and many others. Most notably however, its lipophilicity as well as anti-microbial and anti-inflammatory properties have made it particularly suitable for the predominant therapeutic use in dermatology, acne vulgaris.

The Tetracycline Class of Antibiotics

Tetracycline (TCN) itself was discovered in the 1940's, and FDA-approved in 1953. Although effective in the treatment of acne, TCN required frequent (QID) dosing, and had a prominent side effect profile, including common gastrointestinal (GI) disturbances, and photosensitivity. Also, it was vulnerable to antibiotic resistance, and therefore is no longer a standard treatment option. The TCN derivatives: doxycycline (1967), minocycline (1971), and sarecycline (2018), were chemically adapted (primarily via modifications on carbons 7–9 on the D ring) to reduce side effects and provide additional therapeutic benefits.[8-10]

These derivatives share common mechanisms of action in the treatment of acne. They are transported into bacterial cells where they bind to the 30S unit of the ribosome, and subsequently inhibit protein synthesis, thereby suppressing the proliferation of *Cutibacterium acnes.* A Gram-positive anaerobic rod, *C. acnes,* is the primary bacterium in acne vulgaris.[11-14] In addition to its antibacterial action, the TCN class also exhibits a variety of anti-inflammatory properties. It has been shown to suppress neutrophil chemotaxis, inhibit pro-inflammatory cytokines such as TNF-α and IL-1β, reduce *C. acnes* lipase enzymes, decrease matrix metalloproteinases, and reduce arachidonic acid metabolites.[15,16] These anti-inflammatory actions may be particularly important considering increasing evidence that acne is primarily an inflammatory disorder with inflammation preceding the development of clinically recognizable lesions.[17,18]

Together, the TCN class makes up approximately three-quarters of all antibiotics prescribed in dermatology.[19] The class is considered first-line for acne except where it is contraindicated,[20] whereas the macrolides and trimethoprim sulfamethoxazole are secondary alternatives.[20,21] Hydrophilic antibiotics such as penicillin and the cephalosporins are thought to be less effective because a lack of lipophilicity prevents adequate distribution into the pilosebaceous unit,[22] although there is limited evidence showing some efficacy.[23]

Although oral antibiotics are highly effective in the treatment of acne, concerns regarding their overuse contributing to the global incidence of antibiotic resistance are valid. Responsible

use of the TCN agents includes: limiting indiscriminate and long term use, having an exit strategy, and concomitant use of a topical agent such as benzoyl peroxide (BP) to optimize therapeutic efficacy and help prevent *C. acnes* resistance.[19,24] Oral antibiotics are not to be used as monotherapy in acne vulgaris,[20,25] and the addition of topicals such as a retinoid or retinoid plus BP may help to successfully limit antibiotic use to 3–4 months or less.[20]

Among the TCN derivatives with available clinical trials and data, there is no evidence of clinical superiority of one drug over the other. However, there is considerable difference between the agents in terms of tolerability and safety, development of resistance, delivery systems, and administration recommendations. Knowledge of all these agents is required to make the best choice for each individual patient.

Doxycycline

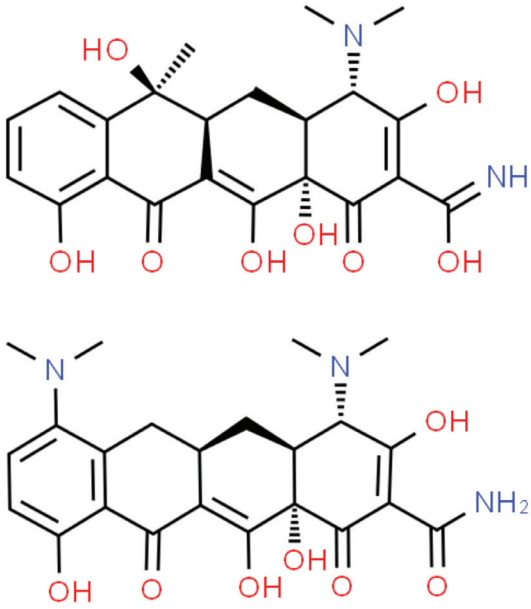
Doxycycline was the first TCN derivative to come to market in 1967 and is most commonly prescribed for acne vulgaris. Relative to TCN, it is more lipophilic and better able to penetrate and accumulate in the sebaceous glands. It is available in two formulations that are both salt forms of the same drug: hyclate and monohydrate. In general, doxycycline hyclate is more likely to cause GI side effects, but these effects can be mitigated by buffering.[26,27] Doxycycline is dosed once or twice daily, and absorption is decreased by co-administration with food (especially dairy), although the clinical significance of this characteristic in acne is unknown.[28]

The side effect profile of doxycycline is improved compared to its parent TCN. However, there are still several potential adverse reactions, most of which can be minimized with proper precautions. GI distress is common, but is lessened with buffered formulations, delayed-release formulations, and administration with food. Pill esophagitis can be avoided by taking with a large glass of water and remaining in the upright position for 30–60 minutes.[29] Photosensitivity is common, particularly with higher daily doses, but is preventable with the use of photoprotection.

Sarecycline

New to the TCN class is sarecycline, which was approved by the FDA in 2018 for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris.[30] Compared to minocycline and doxycycline, sarecycline has been shown to have 16–32 fold less activity against anaerobic gram-negative gut flora including *E. coli, K. pneumoniae* and *E. cloacae*.[32] As a result, it may cause less emergence of antibiotic resistance than other tetracyclines.[31] Recently, it was shown that *C. acnes* strains displayed a low propensity for the development of resistance to sarecycline, with spontaneous mutation frequency being 10^{-10} at 4–8 X MIC. The clinical relevance of this finding has yet to be explored.[32]

FIGURE 1. Tetracycline chemical structure[33] and its derivative minocycline (below).[34] *Images courtesy of ChemSpider.*



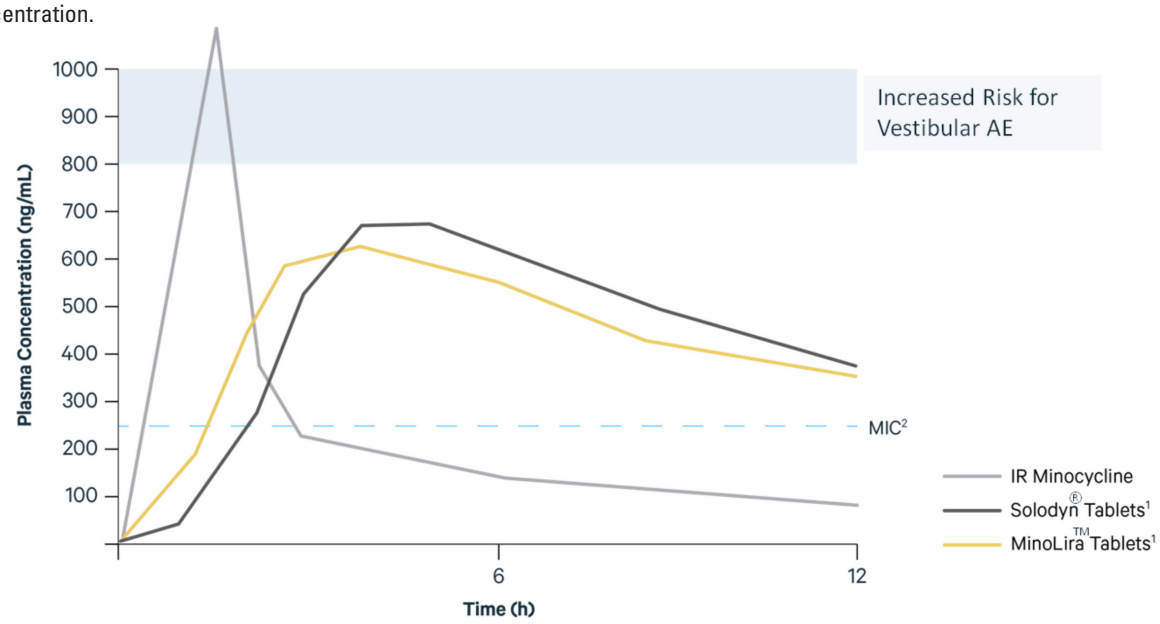
Sarecycline is weight-based, aiming for 1.5 mg/kg/day. It is dosed once daily, can be taken with or without food, and is the only oral tetracycline derivative FDA-approved down to 9 years of age. In its clinical trials, GI side effects were uncommon, and photosensitivity, drug hypersensitivity syndromes, and esophagitis were not reported.[31,32] It must be noted, however, that the drug is in its infancy compared to the other TCN derivatives.

Minocycline

7-dimethylamino-6-demethyl-6-deoxytetracycline (MCN)[35] is a semi-synthetic, second-generation of the TCN class,[36] and is the most lipophilic of the TCN derivatives.[37] This lipophilicity affords high concentrations within the lipid-filled pilosebaceous unit, the anatomical location for acne pathophysiology.[20] In addition to being strongly anti-microbial against *C. acnes,* numerous anti-inflammatory mechanisms address the inflammatory nature of the disease.[38,39] These mechanisms include reducing lipid peroxidation and proinflammatory cytokines, decreasing neutrophil chemotaxis, and resulting reactive oxygen species, inhibition of phospholipase A2 and subsequent arachidonic acid metabolites, as well as suppressing matrix metalloproteinases and nitric oxide.[16,40-42]

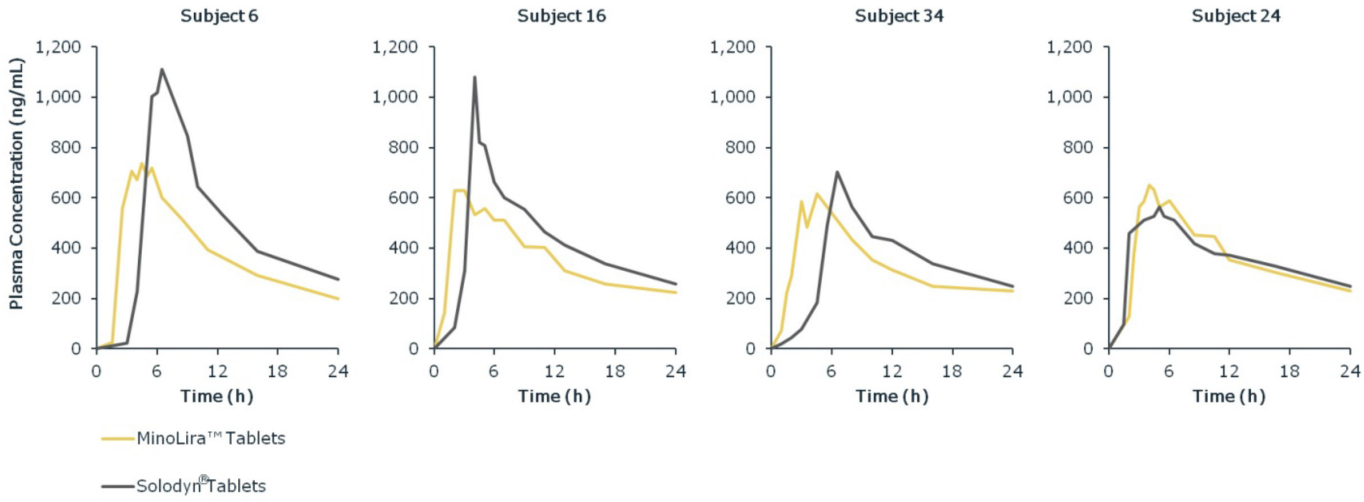
MCN has a long half-life, and excellent absorption that is not substantially impaired by food (dairy included).[28] It is dosed once daily, with or without meals. These two factors may increase the likelihood of compliance in acne vulgaris, a disease whose treatment is commonly fraught with adherence difficulties.[43]

FIGURE 2. Mean pharmacokinetic curves of MCN IR, MCN ER (Solodyn®), and Biphasic MCN ER (MinoLira™). AE = adverse event; MIC = minimal inhibitory concentration.



1. Celerion Clinical Study Report No. CA16742, Contained in MinoLira™ NDA 209269 2. Linuma K, et al. *Clin Cosmet Investig Dermatol.* 2011;4:161-165.

FIGURE 3. Pharmacokinetic curves of individual patients with Solodyn® and Minolira™.



Data is from the Celerion Clinical Study Report No. CA16742, contained in MinoLira™ NDA 209269. Note the unpredictable serum concentration spikes with Solodyn® while MinoLira™ remained consistent across the same subjects.

Based on mean inhibitory concentration testing with *C. acnes,* some evidence has shown MCN to have the lowest resistance susceptibility and lowest cross resistance,[44-47] as well as the largest log reductions in *C. acnes*, when compared to doxycycline and multiple other antibiotics.[40,48] Although oral MCN has a low propensity for antibiotic resistance,[49] which has contributed to its longevity, resistance following antibiotic use is always a concern. Therefore, good antibiotic stewardship and judicious use is important to preserve an antibiotic's utility.[19]

Because of its lipophilicity, MCN more easily crosses the blood brain barrier, and vestibular adverse events (AEs) are the most common side effects seen with MCN. These types of AEs are minimized when weight-based dosing and an extended release formulation (MCN ER) are employed.[50] There is negligible phototoxicity seen with MCN.[22] Hyperpigmentation can occur in patients taking higher doses of MCN for longer periods of time, but has rarely been seen with extended-release formulations, presumably because cumulative doses are so low. Serious idiosyncratic hypersensitivity or autoimmune reaction AEs have been reported but are rare, on the order of 1 in a million. Overall, MCN generally has a good safety record.[51]

Topical Minocycline

New to the class is MCN topical foam, 4% which was approved in October, 2019 to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.[52] Previously, the MCN molecular structure made stability a challenge so that a topical formulation was elusive, until a lipid-rich, hydrophobic formulation was developed.[53] In the 12-week, phase III clinical trials, once-daily MCN topical foam, 4% demonstrated a significant improvement in both inflammatory and non-inflammatory lesions as well as the investigators global assessment. MCN topical foam, 4% was generally well tolerated, and related AEs were reported in less than 1% of subjects treated.[54,55]

Due to the relative infancy of this product, longer term data in regard to resistance are needed. Topical antibiotics such as erythromycin and clindamycin were also previously effective long-term acne treatments, but are not recommended any longer as monotherapy because of bacterial resistance.[20] According to the current American Academy of Dermatology acne guidelines, the long term use of a topical antibiotic without benzoyl peroxide (BP) could be a concern for developing resistance, and for this same reason the use of BP is also recommended for patients on systemic antibiotic therapy as well.[20] However, recently data has been presented that *C. acnes* displays a low propensity for resistance to MCN topical foam, 4%. Spontaneous resistance frequencies were determined to be low at $<1\times10^{-8.56}$ Also, systemic exposure is 730–765X lower than that on the skin, theoretically reducing the risk of systemic resistance.[57]

Advances in Minocycline Dosing and Formulation

Initially, and for many years subsequently, MCN dosing recommendations in dermatology mimicked those for systemic infectious disease where high doses of immediate release MCN (MCN IR) were prescribed to produce the fast Tmax and high Cmax necessary for serious infections. However, fast dissolution and high serum concentrations are not needed in acne vulgaris, and can correlate with adverse events.[50,58] With profound serum concentration spikes, its characteristic lipophilicity can in turn enable the molecule to cross the blood-brain barrier, affecting the vestibular apparatus. Predictably, unnecessarily high MCN IR doses in acne lead to excessive drug exposure and predictable side effects, with doses 2–3 times the optimal range.

In 2006, a landmark MCN extended release (MCN ER) phase II dose ranging study demonstrated an optimal dose at 1 mg/kg in acne vulgaris where higher doses were no more efficacious but risked vestibular side effects.[50,58] The extended release formulation and optimal weight-based dosing regimen afforded slower drug release and less systemic drug exposure, with steady accumulation in the lipid-filled follicle over time. Ultimately, MCN ER with weight based dosing at 1 mg/kg study was a critical advancement, because high efficacy was complemented by a side effect profile more similar to placebo.[50,58] The extended release formulation, Solodyn®, was the first MCN to be FDA approved for acne vulgaris.[59] All preceding tetracyclines had been "grandfathered" into use for adjunctive therapy in the absence of formal phase III testing in acne.

Advances In Delivery Systems

The introduction of Solodyn® substantially changed the use of MCN in acne vulgaris. It enabled the drug to maintain high efficacy with a significantly reduced dose, leading to markedly decreased vestibular side effects and other dose-related AEs. Building on the progress of the extended-release formulation, additional delivery systems have continued to evolve.

In 2012, a MCN ER formulation named Ximino® was released with an eye to improving the patient experience. The drug was formulated in small, 45 mg pellets placed within a gelatin capsule (Capsular Minotab Technology). Capsules are thought by some to be easier to swallow than tablets. Conversely, the small pellets within the capsule shell can be taken individually by those who find larger units difficult to swallow.

The most recent advancement in extended-release formulations was seen with the 2017 introduction of MinoLira™, a biphasic MCN (25% MCN IR/75% MCN ER) indicated to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.[60] Although the extended release formulation of MCN combined with weight-based dosing was a landmark improvement, MCR ER did not utilize a delivery system for absorption. Leyden and Del Rosso reported that MCN absorption is variable from subject to subject and designated some patients as "high GI absorbers" and others as "low GI absorbers." Accordingly, high absorbers may experience adverse events, and low absorbers may experience a lack of efficacy.[28] Without delivery systems, pharmaceutical tablets are conventionally matrix-based, essentially the active pharmaceutical ingredient within a "cake" of binders held together until the gastrointestinal tract indiscriminately breaks it down for absorption.

The delivery system in Biphasic MCN ER is termed the Multiple Unit Pellet System (MUPS), and is designed to promote more uniform drug release, with predictable gastric emptying, and less risk of dose dumping (an immediate release of all the active pharmaceutical ingredient in an uncontrolled manner).[61,62] MUPS distributes the dosage over multiple units with coated and uncoated pellets in a complex matrix reservoir, for controlled delivery.[61] The potential advantage of the MUPS delivery system was indeed noted during the regulatory bioequivalence study designed to demonstrate close similarity of Biphasic MCN ER to MCN ER. Thirty-six patients participated in the pharmacokinetic comparative study. Although the composite results supported bioequivalence, there were some profound

individual differences. Several of the 36 patients in the study had notable serum concentration spikes with MCN ER, while Biphasic MCN ER remained pharmacokinetically consistent.[63] Additional, larger studies may be warranted to analyze the clinical and pharmacokinetic differences of MCN ER and Biphasic MCN ER to ascertain if MUPS technology is promoting a more reliable and consistent drug release. Biphasic MCN ER also employs true "functional scoring," in adherence to strict FDA guidelines, ensuring even distribution of MCN across the tablet, which enables accurate dosing when using whole, as well as manually or mechanically split tablets,[64] so that 1 mg/kg dosing may be closely followed.

The Future of MCN

Similar to the 40th anniversary of topical tretinoin in 2013,[65] 2021 marks the 50th anniversary of another longstanding dermatological therapeutic, minocycline. It remains central in our armamentarium for multiple reasons. Inherent characteristics such as excellent absorption, long half-life, high lipophilicity, and marked anti-inflammatory properties complement its continued efficacy against *C. acnes.* Now, with a half century track record of beneficial utility, new formulations and delivery systems continue to point to a bright foreseeable future for MCN.

DISCLOSURES

Drs. Baldwin and Ward are consultants for EPI Health, Charleston S.C. who owns and markets Minolira™ (Biphasic MCN ER).

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