[LITERATURE REVIEW]

Extended-release Formulation of Minocycline in the Treatment of Moderate-to-severe Acne Vulgaris in Patients Over the Age of 12 Years

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ABSTRACT

Oral antibiotics continue to play an important role in the treatment of moderate-to-severe acne. Minocycline is widely used in moderate-to-severe acne. Minocycline has anti-inflammatory properties, activity against *Propionibacterium acnes* and lipophilicity. An extended-release formulation of minocycline has been introduced. Extended-release minocycline is not bioequivalent to nonmodified release minocycline products and exhibits dose-proportional pharmacokinetics. Food or dairy products did not influence absorption. Efficacy is not dose-dependent, while the incidence of acute vestibular adverse events increases with dose suggesting an optimal dose of 1mg/kg. In two Phase 3 clinical trials, mean percent improvement in inflammatory lesions after 12 weeks of treatment with extended-release minocycline was 43.1 and 45.8 percent compared to 31.7 and 30.8 percent with placebo (P=0.001 and P<0.001, respectively) while the incidence of acute vestibular adverse events was comparable to placebo. (*J Clin Aesthet Dermatol.* 2013;6(7):19–22.)

Oral antibiotics are recommended for the treatment of moderate-to-severe acne vulgaris,[1] and tetracyclines are the most frequently prescribed antibiotic class among dermatologists.[2] Tetracyclines are bacteriostatic, having a dual mechanism of action by inhibiting *Propionibacterium acnes* proliferation within the sebaceous follicles, and having intrinsic anti-inflammatory effects.[3–6]

Minocycline is lipid soluble and distributes into the skin and sebum.[7] Its lipophilicity also enhances its absorption, making it less affected by food or dairy intake.[8]

Minocycline's lipophilicity profile plays a role in its ability to cross the blood–brain barrier, which may lead to acute vestibular adverse events (AVAEs), such as dizziness, vertigo, and ataxia.[9]

THE DEVELOPMENT OF AN EXTENDED-RELEASE MINOCYCLINE

Formulation differences may alter treatment outcomes. Specifically, rapid absorption and/or high-peak concentrations of a medication may induce or exacerbate adverse events such as AVAEs.[10]

An extended-release (ER) formulation of minocycline hydrochloride (Solodyn®, Medicis [a division of Valeant Pharmaceuticals], Scottsdale, Arizona) with weight-based dosing was developed in an attempt to lower the systemic effects associated with minocycline administration without compromising efficacy.

The bioavailability of ER-minocycline was studied in 24 healthy volunteers using a randomized, single-dose (dose adjusted to135mg), 2-way crossover design and found not to be influenced by food intake.[7] T_{max} was 3.52h and 3.69h in fed and fasted subjects, respectively. Other bioavailability studies showed a T_{max} of 3.5 to 4h for ER-minocycline compared to 2.25 to 3h for a nonmodified-release minocycline.[11]

The relative steady state systemic exposure of ER-minocycline and immediate-release (IR) minocycline was compared in 28 healthy volunteers using a 2-way crossover design. Subjects were given ER-minocycline tablets (135mg once-daily) and IR-minocycline capsules (100mg twice daily) for six days.[7] Based on dose adjusted to 135mg

DISCLOSURE: Dr. Torok was an investigator in the Medicis-sponsored Solodyn Phase 2 and 3 studies. Medicis, a division of Valeant Pharmaceuticals, funded Inergy's activities pertaining to this manuscript.
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TABLE 1. Baseline demographics and subject disposition (intention-to-treat population), ER-minocycline and placebo

	STUDY 1		STUDY 2	
	ER-MINOCYCLINE (N=300)	PLACEBO (N=151)	ER-MINOCYCLINE (N=315)	PLACEBO (N=158)
Age, y (mean)	19.2	21.3	20.0	19.6
Gender (N, %)				
Male	171 (57.0%)	85 (56.3%)	182 (57.8)	88 (55.7%)
Female	129 (43.0%)	66 (43.7%)	133 (42.2%)	70 (44.3%)
Race (N, %)				
Caucasian	214 (71.3%)	97 (64.2%)	237 (75.2%)	121 (76.6%)
African American	26 (8.7%)	22 (14.6%)	37 (11.7%)	17 (10.8%)
Hispanic	51 (17.0%)	29 (19.2%)	26 (8.3%)	11 (7.0%)
Other	9 (3.0%)	3 (2.0%)	15 (4.8%)	9 (5.6%)
Inflammatory lesions (mean)	39.1	38.7	38.9	38.4

per day for both products, at steady state (Day 6) mean AUC0-24 and C_{max} were 33.32µgxh/mL and 2.63µg/mL compared to 46.35µgxh/mL and 2.92µg/mL, respectively, with IR-minocycline. The ratio of average exposure to minocycline over 24h (ER:IR) was 72 percent. Also, the average peak blood level after ER-minocycline administration was 90 percent that seen with IR-minocycline, suggesting ER-minocycline is absorbed more slowly and yields a lower dose-adjusted systemic exposure.[7]

A multicenter, 12-week, randomized, double-blind, placebo-controlled, Phase 2 dose-ranging study was conducted in 233 patients with moderate-to-severe acne.[12] Patients were randomly treated with 1, 2, or 3mg/kg ER-minocycline or placebo daily for 12 weeks. At the end of the study, inflammatory lesions had decreased by 46.6 to 56.8 percent in the active treatment groups with no dose-dependent effect being noted.[12] Improvement in the 1mg/kg group was significant compared to placebo (P=0.015). AVAEs appeared to be dose-dependent and more common during the first five days of treatment, with the lowest incidence in the 1mg/kg group (24%) being comparable to placebo (26%), although overall differences among the groups was not statistically significant.[12]

EFFICACY AND TOLERABILITY IN PATIENTS WITH MODERATE-TO-SEVERE ACNE VULGARIS

The safety and efficacy of ER-minocycline in the treatment of inflammatory lesions of non-nodular moderate-to-severe acne was assessed in two identical 12-week, multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies in 924 patients aged 12 years or

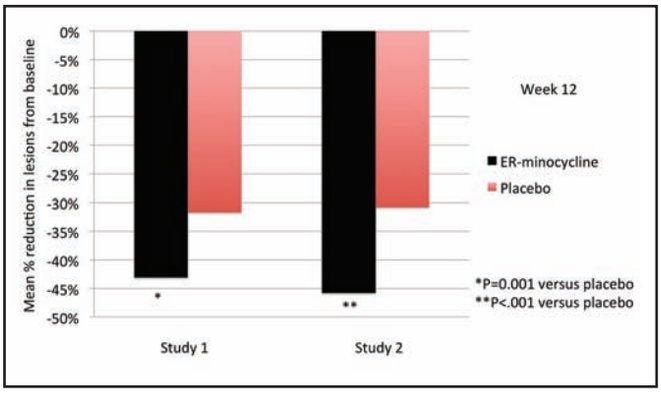

Figure 1. Mean percent reduction in inflammatory lesions from baseline to Week 12, ER-minocycline, and placebo (intention-to-treat population)

older.[9] The studies were conducted across 30 centers in the United States and patients received ER-minocycline 1mg/kg once daily (determined by body weight and available tablet strength). Primary efficacy assessments were the reduction in inflammatory lesion counts from baseline and an Evaluator Global Severity Assessment (EGSA) defined as the proportion of patients who were clear (score of 0) or almost clear (score of 1) at Week 12. The mean age of patients was 20 years and the majority (73%) were Caucasian (Table 1).

Mean inflammatory lesion counts at baseline were similar across the two studies, and both the absolute and percentage changes in the ER-minocycline treatment group were significantly greater than the placebo group. Mean percent reduction in inflammatory lesions at Week 12 was 43.1 percent (Study 1) and 45.8 percent (Study 2) with ER-minocycline and 31.7 percent and 30.8 percent with placebo (P=0.001 and P<0.001, respectively, Figure 1).[1]

The proportion of patients judged as "treatment successes" with ER-minocycline increased over the course of both studies and was significantly greater than placebo from Week 4 in Study 1 and Week 8 in Study 2 (Figure 2). At Week 12, 17.3 and 15.9 percent of patients treated with ER-minocycline were "treatment successes" compared to 7.9 and 9.5 percent on placebo (P=0.006 and P=0.018, respectively).

Consistent with the Phase 2 study, AVAEs were reported more frequently during the first five days of treatment. The percentage of patients reporting AVAEs over this period was comparable between those receiving ER-minocycline (9.0 and 10.5%) and placebo (7.9 and 10.8%). Analysis of the pooled adverse events (AEs) across the Phase 2 and 3 studies in 1,038 patients showed treatment-emergent AEs to be similar between ER-minocycline and placebo (Table 2).

COMMENT

ER-minocycline was specifically formulated to have a low potential for AVAEs (by reducing both the amount and rate of drug crossing the blood-brain barrier) while maintaining efficacy. Two Phase 3 studies showed that ER-

TABLE 2. Selected treatment-emergent adverse reactions in at least one percent of clinical trial subjects, ER-minocycline and placebo

ADVERSE REACTIONS	ER-MINOCYCLINE (1MG/KG) N=674 (%)	PLACEBO N=364 (%)
At least one treatment-emergent event	379 (56)	197 (54)
Headache	152 (23)	83 (23)
Fatigue	62 (9)	24 (7)
Dizziness	59 (9)	17 (5)
Pruritis	31 (5)	16 (4)
Malaise	26 (4)	9 (3)
Mood alteration	17 (3)	9 (3)
Somnolence	13 (2)	3 (1)
Uticaria	10 (2)	1 (0)
Tinnitus	10 (2)	5 (1)
Arthralgia	9 (1)	2 (0)
Vertigo	8 (1)	3 (1)
Dry mouth	7 (1)	5 (1)
Myalgia	7 (1)	4 (1)

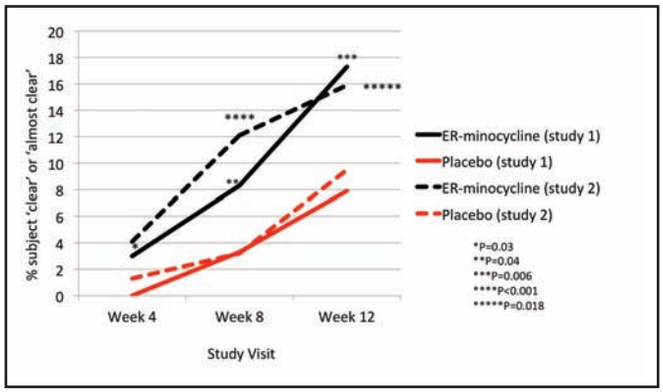

Figure 2. Treatment success (% subjects "clear" or "almost clear") by study visit, ER-minocycline, and placebo (Study 1 and Study 2).

minocycline (1mg/kg) administered once daily for 12 weeks was safe and effective in the treatment of inflammatory lesions in moderate-to-severe acne vulgaris. ER-minocycline resulted in both significant reductions in lesion counts and improvement in acne compared to placebo. AVAEs reported with ER-minocycline were similar to those seen with placebo. ER-minocycline (1mg/kg) is prescribed based on a subject's weight without need for a loading dose.

ACKNOWLEDGMENT

I thank Brian Bulley, MSc (Inergy Limited, UK) for assistance with the preparation of the manuscript. Medicis, a division of Valeant Pharmaceuticals, funded Inergy's activities pertaining to this manuscript. I also would like to thank Dr. Christina Smith of Medicis for her review of the manuscript.

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