

Sarecycline Demonstrates Narrow-spectrum Antibacterial Activity and Anti-inflammatory

Effect in Animal Models

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Introduction

- Sarecycline is an FDA-approved tetracycline-class oral antibiotic specifically developed for the treatment of moderate-to-severe acne vulgaris.
- In vitro* studies demonstrated a narrow-spectrum antibacterial activity, targeting clinically relevant Gram-positive bacteria while showing reduced activity against Gram-negative bacteria commonly found in the human gastrointestinal tract.
- Here we report results of *In vivo* antibacterial and anti-inflammatory studies in mouse and rat models.

Methods

In vivo antibacterial activity

Table 1. A murine systemic (intraperitoneal) infection model was utilized to assess the *in vivo* efficacies of sarecycline, doxycycline, and minocycline against *S. aureus* RN450-1 and *E. coli* PBS1478.

Table 2. A murine neutropenic thigh wound infection model was utilized to represent a tissue-based infection to assess the comparative efficacies of sarecycline and doxycycline against *S. aureus* RN450-1.

Anti-inflammatory effect *In vivo*

Table 3. To evaluate the anti-inflammatory effects of sarecycline, a carrageenan-induced rat footpad edema model was utilized. Male, Sprague Dawley rats were intraperitoneally injected with saline, sarecycline, or a positive control (doxycycline or minocycline) and inflammation was determined as change in paw volume. Percent inflammation was calculated as $100 \times [(post\ paw\ volume\ at\ 3\ hours - pre\ paw\ volume\ at\ 0\ hours) / pre\ paw\ volume\ at\ 0\ hours]$.

Results - Table 1. Efficacy of sarecycline and comparators against *S. aureus* and *E. coli* in mice

Antibacterial agent	<i>S. aureus</i> RN450-1		<i>E. coli</i> PBS1478	
	MIC (µg/mL)	PD ₅₀ (mg/kg)	MIC (µg/mL)	PD ₅₀ (mg/kg)
Sarecycline	≤ 0.06	0.25	4	> 40
Doxycycline	≤ 0.06	0.3	0.5	5.72
Minocycline	≤ 0.06	0.03	1	6.95

MIC – minimum inhibitory concentration; PD₅₀ – protective dose required to achieve 50% survival
Murine systemic infection model at 48 h post-infection.

Results - Table 2. Efficacy of sarecycline and doxycycline against *S. aureus* tissue infection

Agent	MIC (µg/mL)	ED ₅₀ (mg/kg)
Sarecycline	≤ 0.06	8.23
Doxycycline	≤ 0.06	8.31

MIC – minimum inhibitory concentration; ED₅₀ – effective dose required to achieve a 50%, or 2-log₁₀, reduction in bacterial burden

Murine neutropenic thigh wound infection model to represent tissue-based infection with *S. aureus* RN450-1.

References

Zhanel G, et al. Microbiological Profile of Sarecycline, a Novel Targeted Spectrum Tetracycline for the Treatment of Acne Vulgaris. *Antimicrob Agents Chemother*. 2018 Dec;63(12):e01297-18.
Carrageenan-induced rat footpad edema model experiments performed by Paratek Pharmaceuticals. Data on file with Almirall.

Results - Table 3. Anti-inflammatory effect of sarecycline and comparators in rat footpad model

Compound	Mean % inflammation compared to untreated controls							
	150 mg/kg	100 mg/kg	75 mg/kg	50 mg/kg	25 mg/kg	10 mg/kg	5 mg/kg	1 mg/kg
Sarecycline	25.8	53.1	55.7	52	59	65.2	77.8	103.3
Doxycycline	-	36	67.6	-	-	-	-	-
Minocycline	-	20.5	53.9	32.9	47.2	-	-	-

Carrageenan-induced rat footpad edema model

Discussion

- Sarecycline is the first narrow-spectrum tetracycline-class antibiotic to be developed for the treatment of acne vulgaris.
- Sarecycline proved effective against *S. aureus* (G+ Bacteria) in both systemic and tissue-based infection models in mice. However, low efficacy was demonstrated vs. *E. coli* (G- enteric bacteria).
- The reduced activity of sarecycline against bacteria commonly found in the gut suggests reduced risk of antibiotic resistance within the GI tract microbiome.
- The anti-inflammatory effect of sarecycline in rats is similar to doxycycline and minocycline, and in agreement with sarecycline being efficacious for inflammatory moderate-to-severe acne lesions in humans.

Conclusions

- Sarecycline demonstrated *in vivo* efficacy against *S. aureus* but not *E. coli* in animal models of infection, in agreement with the narrower-spectrum of activity observed in *in vitro* studies.
- Sarecycline showed anti-inflammatory effect comparable to doxycycline and minocycline in the rat footpad edema model.