Sarecycline Demonstrated Reduced Activity Against Representative Bacterial and Fungal Microflora Commonly Present in the Human Gastrointestinal Tract

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Objective

Evaluate the effect of sarecycline, a narrow spectrum antibiotic, compared to minocycline, a broad-spectrum antibiotic, against a panel of microorganisms that reflect the diversity of the gut microbiome using *in vitro* minimum inhibitory concentration (MIC) testing and time-kill kinetic assays.

Methods

1. Chose representative bacterial and fungal strains found in the Healthy Gut

2. Perform Antimicrobial Susceptibility Testing

Minimum inhibitory concentration (MIC) testing was performed using modified Clinical Laboratory Standards Institute methodology

3. Establish Growth Curves

E. coli and *Candida tropicalis* were selected as representative of aerobic bacteria and yeast, respectively. While *Lactobacillus paracasei* and *Bifidobacterium adolescentis* were selected as representative of anaerobic bacteria that colonize the gut.

Table 1. Susceptibility Testing Results for sarecycline and minocycline Against Healthy Gut Microbes (µg/mL, n=28)

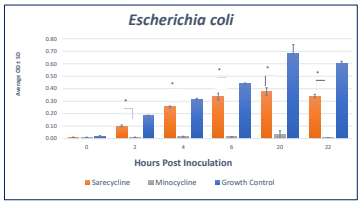
Phylum	Genus	Species	Sarecycline	Minocycline	Fold Difference in MIC
Actinobacteria	*Bifidobacterium*	*Bifidobacterium adolescentis*	1	1	1
Actinobacteria	*Collinsella*	*Collinsella aerofaciens*	1	0.5	2
Actinobacteria	*Eggerthella*	*Eggerthella lenta*	1	0.5	2
Actinobacteria	*Actinomycetales*	*Propionibacterium freudenreichii*	8	1	8
Bacteroidetes	*Bacteroides*	*Bacteroides caccae*	8	0.25	32
Bacteroidetes	*Bacteroides*	*Bacteroides fragilis enterotoxigenic (ET)*	2	4	0.5
Bacteroidetes	*Bacteroides*	*Bacteroides fragilis nontoxigenic*	1	0.25	4
Bacteroidetes	*Bacteroides*	*Bacteroides ovatus*	0.5	0.5	1
Bacteroidetes	*Bacteroides*	*Bacteroides thetaiotaomicron*	0.25	0.125	2
Bacteroidetes	*Bacteroides*	*Bacteroides uniformis*	2	0.5	4
Bacteroidetes	*Bacteroides*	*Bacteroides vulgatus*	0.125	0.016	7.8
Bacteroidetes	*Bacteroides*	*Bacteroides xylanisolvens*	1	0.25	4
Bacteroidetes	*Bacteroides*	*Bifidobacterium subtile Biavati*	>8	8	Not Determined
Bacteroidetes	*Odoribacter*	*Odoribacter splanchnicus*	8	4	2
Bacteroidetes	*Parabacteroides*	*Parabacteroides distasonis*	8	2	4
Bacteroidetes	*Parabacteroides*	*Parabacteroides merdae*	0.06	0.016	3.8
Firmicutes	*Blautia*	*Blautia obeum*	1	0.5	2
Firmicutes	*Clostridium*	*Clostridium bolteae*	4	0.5	8
Firmicutes	*Clostridium*	*Clostridium ramosum*	2	0.06	33.3
Firmicutes	*Clostridium*	*Clostridium saccharolyticum*	2	2	1
Firmicutes	*Dorea*	*Dorea formicigenerans*	0.25	0.06	4.2
Firmicutes	*Eubacterium*	*Eubacterium eligens*	>8	4	Not Determined
Firmicutes	*Lactobacillus*	*Lactobacillus paracasei*	1	0.25	4
Proteobacteria	*Escherichia*	*Escherichia coli IAI1*	16	8	2
Sac fungi	*Candida*	*Candida albicans*	32	16	2
Sac fungi	*Candida*	*Candida glabrata*	32	32	1
Sac fungi	*Candida*	*Candida parapsilosis*	32	16	2
Sac fungi	*Candida*	*Candida tropicalis*	16	16	1

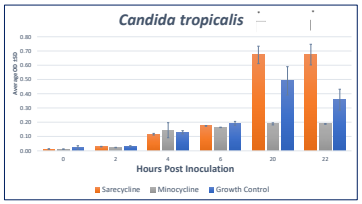
Higher fold difference indicates lower sarecycline activity

Compared to minocycline, sarecycline showed significantly less antimicrobial activity against:

- **10 of 12 isolates from the *Bacteroidetes* phylum**
- **3 out of 4 isolates from *Actinobacteria* phylum**
- **5 of 7 isolates from the *Firmicutes* phylum, *E. coli***
- ***Propionibacterium freudenreichii* (≥ 3 dilutions)**
- **Sarecycline also showed less activity against 2 *Candida* species**

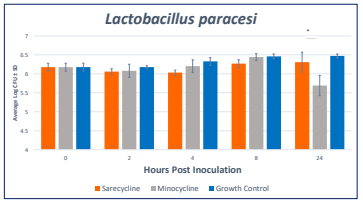
Figure 1. and 2. Effect of sarecycline vs. minocycline on the growth rates of Aerobic Microorganisms

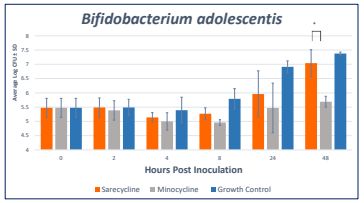




- Sarecycline showed significantly **less activity against *E. coli*** compared to minocycline at all time points (*P*-values <0.05)
- Sarecycline was significantly **less active against *C. tropicalis*** compared to minocycline at 20 and 22 hours post exposure (*P*-values <0.05)
- Time kill study shows that with longer time exposure sarecycline has **less inhibitory activity against *Candida***

Figure 3. and 4. Effect of sarecycline vs. minocycline on the growth rates of Anaerobic Microorganisms





- Sarecycline showed significantly less activity against ***L. paracasei*** compared to minocycline after 24 hours of growth (P-value of 0.002)
- Sarecycline showed significantly less activity against ***B. adolescentis*** compared to minocycline after 48 hours of growth (P-value of 0.042)

- In this study, **sarecycline demonstrated less activity against 79% of the microorganisms** normally found in a healthy human gut, **when compared to minocycline**
- Sarecycline is a **narrow-spectrum** antibiotic
- Our data suggests that sarecycline may have less impact on disrupting commensal and symbiotic organisms residing in the gut and is less likely to promote dysbiosis. *In vivo* evaluation is ongoing

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