Comparative Antimicrobial Activity of Mul-1867, a Novel Antimicrobial Compound and Amikacin, Against New Clinically Important Airway Pathogens In Cystic Fibrosis: *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Mycobacterium abscessus*

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Abstract

As a result of treatment of "classic" bacterial infections in cystic fibrosis (CF), there are now increasing problems with innately resistant new airway pathogens such as *S.maltophilia*, *A.xylosoxidans, M.abscessus*. These bacteria are associated with higher morbidity among CF patients and display high resistance to antimicrobials. The aim of the present study was to compare selected antimicrobials against these planktonic and sessile pathogens.

We used:

Mul-1867[1] - a first-in class, novel, broad-spectrum inhaled antimicrobial.

Amikacin - aminoglycoside antibiotic

Methods

Clinical isolates of *S.maltophilia* and *A.xylosoxidans* from cystic fibrosis patients and a clinical isolate of *M.abscessus*

The anti-biofilm activity against 48-h-old *S.maltophilia* and *A.xylosoxidans* biofilms was evaluated as minimum biofilm eliminating concentration that completely eradicated mature biofilms (MBEC100). MBEC sensitivities were determined using the 2012 Clinical and Laboratory Standards Institute guidelines for interpretation. Biofilms were exposed for 24 h containing antibacterial at 1 - 64× the MIC. All assays were repeated in triplicate.

Mechanism of action

MOA Mul-1867

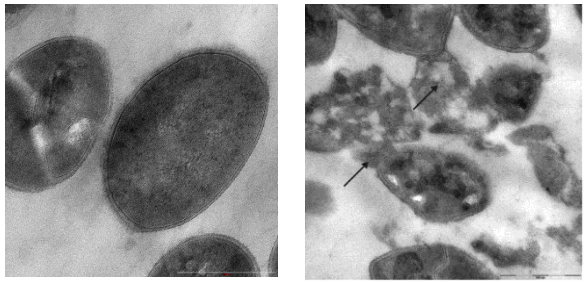

Fig.1 TEM micrographs of reference microorganisms (a) untreated S. aureus (b) incubation with a 0.05 % Mul-1867 for 30 s shows some completely lysed cells

Results

MICs of Mul-1867 and Amikacin against *M. abscessus*

Bacterial strain	Day 5 incubation MIC (mg/L)		Day 15 incubation MIC (mg/L)	
	Mul-1867	Amikacin	Mul-1867	Amikacin
M.abscessus BB2	2	4	2-4	8-16

MICs of Mul-1867 and Amikacin against *S.maltophilia and A.xylosoxidans*

Bacterial strain	MIC (mg/L)	
	Mul-1867	Amikacin
S.maltophilia	0.125	128
A.xylosoxidans	0.25	25

MBEC100 of Mul-1867 and Amikacin against *S.maltophilia and A.xylosoxidans*

Bacterial strain	MBEC100 (mg/L)	
	Mul-1867	Amikacin
S.maltophilia	**0.25**	**> 2048**
A.xylosoxidans	**2.0**	**1600**

Antibiofilm activity of Mul-1867 and Amikacin against *S.maltophilia and A.xylosoxidans*

Bacterial strain	Times MIC	
	Mul-1867	Amikacin
S.maltophilia	2x MIC	> 20 x MIC
A.xylosoxidans	4x MIC	> 64 x MIC

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Conclusion

Our study demonstrated that a nanoglobular antimicrobial Mul-1867 possesses great in vivo activity against *A.xylosoxidans*, *S.maltophilia, M. abscessus* isolates from CF patients and patients with other respiratory tract infections. Mul-1867 is an original, first-in-class, small molecular entity and is not relative to existing antibiotics.

In the current study, we found that a novel drug candidate, Mul-1867, exhibits a high level of antimicrobial activity against *S.maltophilia, A.xylosoxidans* and *M. abscessus*. We revealed that Mul-1867 was more active than amikacin against selected clinical isolates, displayed lower MICs and possessed low MBEC100/MIC. Bacterial biofilms respond poorly to treatment with existing medicines due to the presence of additional barriers including a surface film or extracellular polymeric substances that reduce antibiotic penetration. Biofilms formed by A.*xylosoxidans, S.maltophilia*, are almost completely insensitive to treatment with antibiotics used for the patients with Cystic fibrosis with MBEC values that can not be achieved at the site of infection using currently recommended dosages, or even with local administration directly to the site of infection.

The MBEC100/MIC ratio is an important parameter for choosing the best antibacterial to treat biofilm-associated infections (lower is better). Our studies revealed that Mul-1867 possessed low MBEC100/MIC ratios from 2 to 4. Biofilms formed by *A.xylosoxidans* or *S.maltophilia* were totally eradicated with Mul-1867 at concentrations that can easily be achieved at the site of infection in cystic fibrosis patients.

The efficacy of Mul-1867 raises the possibility that it may serve as a locally acting antimicrobial compound in CF patients.

Further studies are required for the development of Mul-1867 as an inhaled antimicrobial.

References

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