Evaluating the Activity of SPR719, a Novel Aminobenzimidazole, against Nontuberculous Mycobacteria

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ABSTRACT

Background: Pulmonary infections caused by Nontuberculous Mycobacteria (NTM) are increasing in prevalence and are associated with high mortality and morbidity. Members of the *Mycobacterium avium* complex (MAC; primarily *M. avium* and *M. intracellulare*) and *M. abscessus* are most commonly associated with NTM pulmonary disease. Treatment options are limited and new agents with potent activity are needed. In this study, the activity of SPR719, a novel aminobenzimidazole, against NTM is reported.

Methods: The susceptibility of 58 non-consecutive, non-duplicate clinical NTM isolates was determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) standard M24. Isolates included 20 rapidly-growing mycobacteria (10 *M. abscessus/chelonae* Group, 6 *M. fortuitum* Group, and 4 *M. mucogenicum* Group) and 38 slow-growing mycobacteria (28 MAC and 10 *M. kansasii*). SPR719 and comparators clarithromycin (CLA), amikacin (AMK), moxifloxacin (MXF), rifabutin (RFB), minocycline (MIN), and imipenem (IPM) were evaluated. Minimum bactericidal concentrations (MBC) for SPR719, CLA, and AMK were determined in accordance with CLSI M26.

Results: The activity of SPR719 and comparators by MIC range and $MIC_{50/90}$ (µg/mL) is summarized in **Table 1**. SPR719 activity was not affected by resistance to CLA, AMK, or MXF. MBC:MIC ratios for SPR719 and CLA were typically >8 which indicates a bacteriostatic mode of action **(Table 2);** AMK MBC:MIC ratios were typically ≤ 4 indicative of bactericidal activity **(Table 2).**

Conclusion: SPR719 had potent activity by both $MIC_{50/90}$ and MIC range across the evaluated NTM species. The SPR719 activity against clinically relevant MAC and M. *abcessus/chelonae* Group isolates was comparable or superior to the evaluated comparators, and SPR719 was active against isolates resistant to currently utilized agents. These results highlight the potential of SPR719 in the treatment of NTM pulmonary disease.

BACKGROUND

- Although the true prevalence of NTM infections is difficult to determine, recent reports indicate that NTM pulmonary disease is on the rise.[1-3]
- MAC and *M. abscessus* account for up to 95% of NTM pulmonary infections.[4]
- Treatment involves a lengthy multi-drug regimen tailored to the patient and disease state.
- For initial nodular/bronchiectatic disease a combination of a macrolide, ethambutol, and rifampin are recommended; for advanced disease (cavitary) or disease refractory to treatment, more frequent dosing is recommended and the addition of an aminoglycoside and/or substitution of rifampin with RFB is an option; other agents used with limited data on efficacy include isoniazid, MXF, clofazimine and linezolid.[5]
- Given the poor outcomes associated with these infections, new therapies are desperately needed.
- SPR719, a novel aminobenzimidazole, is currently undergoing development as a potential treatment for NTM pulmonary disease.

METHODS

- The susceptibility of 58 clinical NTM isolates to SPR719, AMK, CLA, MXF, RFB, MIN, and IPM was determined by broth microdilution in accordance with the CLSI M24 standard and M62 supplement.
- The test media consisted of cation-adjusted Mueller-Hinton broth (CAMHB) which for slow-growing mycobacteria (SGM) was supplemented with oleic acid albumin dextrose catalase complex (OADC).
- The inoculum density for each isolate was determined by serial dilution and plating on Middlebrook 7H10 agar.
- The MBC was determined in accordance with CLSI document M26-A; viable counts in the MIC well and three wells above the MIC were assessed by plating duplicate 10 µL spots; the MBC was defined as the lowest concentration resulting in a 3-log_{10} decrease relative to the initial inoculum.

RESULTS

Table 1. MIC range, MIC_{50}, and MIC_{90} (µg/mL) of SPR719 and comparators against NTM

Organism (N)		SPR719	CLA	AMK	MXF	RFB	MIN	IPM
MAC (28*)	Range	0.25-4	0.25->32	4->256	0.25-8	≤0.008-2	2->32	2-128
	$MIC_{50/90}$	1/2	2/8	16/32	1/4	0.25/1	16/>32	32/128
M. kansasii (10)	Range	0.03-0.06	0.12-0.5	2-8	0.06-2	≤0.008-0.06	0.5-8	1-64
	$MIC_{50/90}$	0.03/0.06	0.5/0.5	8/8	0.25/0.5	≤0.008/0.06	4/8	16/64
M. abscessus/ chelonae Group (10)	Range	1-16	0.12->32	2->256	1->8	0.12-4	8->32	8-64
	$MIC_{50/90}$	2/4	0.5/1	4/16	8/>8	2/4	32/>32	8/16
M. fortuitum Group (6)	Range	0.5-2	1-16	0.5-2	0.03-0.5	0.5-2	0.05-8	0.015-4
	$MIC_{50/90}$	0.5/-	4/-	0.5/-	0.06/-	0.5/-	0.5/-	2/-
M. mucogenicum Group (4)	Range	0.12-2	≤0.03-0.25	≤0.25-1	0.25-1	0.5-1	≤0.03-4	0.25-2
	$MIC_{50/90}$	-/-	-/-	-/-	-/-	-/-	-/-	-/-

*N=27 for SPR719 & CLA against MAC; SPR719 & CLA MIC could not be determined for 1 MAC due wells drying out during prolonged incubation

Table 2. SPR719 MIC distribution against NTM

SPR719 MIC (µg/mL):		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
MAC (27)	n				4	9	7	6	1		
	%				14.8	33.3	25.9	22.2	3.7		
	cum.%				14.8	48.1	74.1	96.3	100		
M. kansasii (10)	n	7	3								
	%	70.0	30.0								
	cum.%	70.0	100								
M. abcessus/ chelonae Group (10)	n						3	4	2		1
	%						30.0	40.0	20.0		10.0
	cum.%						30.0	70.0	90.0		100
M. fortuitum Group (6)	n					4	1	1			
	%					66.7	16.7	16.7			
	cum.%					66.7	83.3	100			
M. mucogenicum Group (4)	n			2	1			1			
	%			50.0	25.0			25.0			
	cum.%			50.0	75.0			100			

n, number of isolates at MIC; %, percent of isolates at MIC; cum.%, cumulative percent (percentage of isolates at and below MIC)

Table 3. Summary of MBC:MIC ratio of SPR719, CLA, and AMK against NTM

Organism	Test agent	N evaluable	MBC:MIC ratio (n [%])						
			1	2	4	8	>8	≤4	≥8
MAC	SPR719	26		1 (3.8)		2 (7.7)	23 (88.4)	1 (3.8)	25 (96.2)
	CLA	25		4 (16.0)	4 (16.0)	4 (16.0)	13 (52.0)	8 (32.0)	17 (68.0)
	AMK	27	7 (25.9)	6 (22.2)	6 (22.2)	2 (7.4)	6 (22.2)	19 (70.4)	8 (29.6)
M. kansasii	SPR719	2	1 (50.0)	1 (50.0)				2 (100)	
	CLA	2	2 (100)					2 (100)	
	AMK	2		2 (100)				2 (100)	
M. abscessus/ chelonae Group	SPR719	7			1 (14.3)	1 (14.3)	5 (71.4)	1 (14.3)	6 (85.7)
	CLA	8		1 (12.5)			7 (87.5)	1 (12.5)	7 (87.5)
	AMK	8	1 (12.5)	3 (37.5)	2 (25.0)	2 (25.0)		6 (75.0)	2 (25.0)
M. fortuitum Group	SPR719	6	1 (16.7)		2 (33.3)		3 (50.0)	3 (50.0)	3 (50.0)
	CLA	6		3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.3)
	AMK	6	1 (16.7)	4 (66.7)	1 (16.7)			6 (100)	
M. mucogenicum Group	SPR719	4	3 (75.0)		1 (25.0)			4 (100)	
	CLA	3			1 (33.3)		2 (66.7)	1 (33.3)	2 (66.7)
	AMK	3	2 (66.7)	1 (33.3)				3 (100)	

N evaluable = number of isolates where the indicated MBC:MIC ratios could be determined
MBC:MIC ratios of ≤ 4 are indicative of bactericidal activity; MBC:MIC ratios of ≥ 8 are indicative of bacteriostatic activity

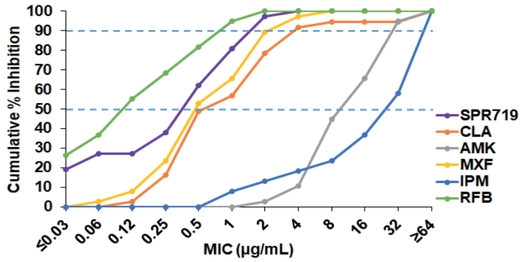

Figure 1. Cumulative susceptibility of SGM (N=38) to SPR719 and comparators

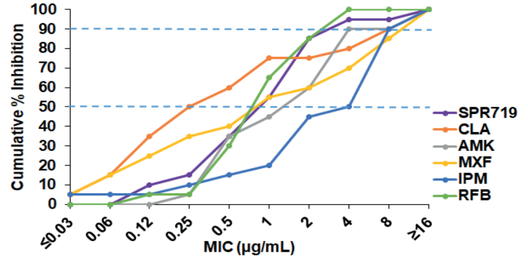

Figure 2. Cumulative susceptibility of RGM (N=20) to SPR719 and comparators

- SPR719 was active against both rapidly-growing mycobacteria (RGM) and SGM, with $MIC_{50/90}$ values of 2/4 µg/mL against the *M. abcessus/chelonae* Group and 1/2 µg/mL against MAC (**Tables 1 and 2**).
- SPR719 had potent MIC values against *M fortuitum* Group (0.5 to 2 µg/mL), *M. mucogenicum* Group (0.12 to 2 µg/mL), and *M. kansasii* (0.03 to 0.06 µg/mL) (**Tables 1 and 2**).
- Consistent with a prior report[6], SPR719 and RFB had the most potent activity against the evaluated NTM followed by CLA and MXF as shown by $MIC_{50/90}$ and cumulative susceptibility of SGM and RGM (**Table 1**, **Figures 1 and 2**).
- SPR719 maintained potent activity against resistant NTM with MIC values of 1 µg/mL against two CLA-resistant and one CLA-intermediate MAC and 2 µg/mL against a CLA-resistant *M. abcessus*, 0.25 and 2 µg/mL against two AMK-resistant MAC and 2 µg/mL against an AMK-resistant *M. abcessus*, and 0.5, 1, and 2 µg/mL against three MXF-resistant MAC.
- Based on MBC:MIC ratio, SPR719 and CLA were bacteriostatic for MAC and *M. abcessus/chelonae* Group while AMK was typically bactericidal (**Table 2**).

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CONCLUSIONS

- SPR719 had potent activity in vitro against clinically important NTM including *M. abscessus/chelonae* Group and MAC isolates which are responsible for the vast majority of NTM infections.
- SPR719 and CLA were bacteriostatic against MAC and *M. abscessus/chelonae* Group
- These results highlight the potential of SPR719 as a therapeutic for NTM infections