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Evaluation of the antimicrobial activity of ridinilazole and six comparators against Chinese, Japanese and South Korean strains of *Clostridioides difficile*

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Background: *Clostridioides difficile* is the most common cause of antimicrobial-associated diarrhoea in high-income countries. Fluoroquinolone resistance enabled the emergence and intercontinental spread of the epidemic ribotype (RT) 027 strain of *C. difficile* in the early 2000s. Despite frequent inappropriate antimicrobial use in Asia, RT 027 is rarely isolated in the region, but the often fluoroquinolone- and clindamycin-resistant RT 017 strain predominates.

Objectives: This study evaluated the antimicrobial activity of ridinilazole, a novel antimicrobial agent with highly specific activity for *C. difficile*, against clinical strains of *C. difficile* from Asia.

Methods: *C. difficile* strains from Japan ($n = 64$), South Korea ($n = 32$) and China ($n = 44$) were tested by the agar dilution method for susceptibility to ridinilazole, metronidazole, vancomycin, clindamycin, moxifloxacin, rifaximin and fidaxomicin.

Results: All strains were susceptible to ridinilazole, with low MICs (0.03–0.25 mg/L). Several strains showed multiresistance profiles, particularly RT 017 (100% clindamycin resistant, 91.3% moxifloxacin resistant, 82.6% rifaximin resistant) and RT 369 (94.4% clindamycin resistant, 100% moxifloxacin resistant). Rifaximin resistance was absent in all strains from Japan. Multiresistance to clindamycin, moxifloxacin and rifaximin was found in 19 RT 017 strains (from China and South Korea), 2 RT 001 strains (South Korea) and 1 RT 046 strain (South Korea).

Conclusions: Ridinilazole showed potent activity against a range of Asian *C. difficile* strains, which otherwise frequently displayed resistance to several comparator antimicrobial agents. Ongoing surveillance of antimicrobial resistance profiles is required to monitor and control the spread of resistant strains.

Introduction

Clostridioides difficile has emerged in the 21st century as the most common cause of healthcare-associated diarrhoea in high-income countries.[1] Outbreaks of *C. difficile* infection (CDI) in the early 2000s brought increased mortality across North America and Europe, driving researchers to investigate CDI epidemiology and *C. difficile* virulence further to determine how best to control its spread. In the ensuing years, infection prevention and control measures, including enhanced disinfection and antimicrobial stewardship, have had mixed results in curbing the transmission of *C. difficile* within hospitals, while a growing body of evidence is showing community-based transmission is increasing.[2]

C. difficile causes diarrhoea via production of three different toxins, toxin A, toxin B and binary toxin (CDT), in several combinations, the most common being A+ B+ CDT−, followed by A− B+ CDT− and A+ B+ CDT+, while A− B− CDT− strains are incapable of causing disease but can colonize the gut. Other combinations of toxin profiles are rare.

Another key virulence factor of *C. difficile* is intrinsic and acquired resistance to an array of antimicrobial agents, which has helped drive expansion of *C. difficile* around the globe in recent decades, influenced by overuse of antimicrobials in both healthcare and agriculture.[2] In particular, unprecedented outbreaks of CDI were caused by the epidemic RT 027 strain (A+ B+ CDT+). RT 027 spread globally from North America in the early 2000s, due in part to acquired resistance to fluoroquinolones via a Thr82Ile mutation (*gyrA* gene).[3]

C. difficile RT 027 has rarely been isolated in Asia-Pacific countries,[4] but several other fluoroquinolone-resistant strains are prominent in the region. The most common strain of *C. difficile* circulating in Asia is RT 017, an A− B+ CDT− strain that is particularly prevalent in East and South-East Asia and is frequently reported as fluoroquinolone resistant and clindamycin resistant.[5,6] *C. difficile* RT 017 notably caused outbreaks of CDI in Canada and Europe in the late 1990s and early 2000s.[6] Another A− B+ CDT− strain, RT 369, is currently one of the most common circulating strains in Japan and China and shows high rates of resistance to clindamycin and moxifloxacin.[4,7] *C. difficile* RT 018 (A+ B+ CDT−), another frequently fluoroquinolone-resistant strain,[8] predominates in northern Asia, particularly in Japan and South Korea where, to some extent, it has replaced RT 017.[4,5]

Recurrent CDI (rCDI) is a frequent and serious outcome of CDI, due to slow recovery of host gut microbiota following treatment with broad-spectrum antimicrobials. Recurrence rates reach as high as 20% in North America and Europe.[9,10] In Asia, rCDI rates appear to be somewhat lower overall at 5%–10%;[4,11] however, a general lack of awareness and underdiagnosis of CDI in Asia[5] may mean that reported recurrence rates are underestimated.

The heavy burden that rCDI places on healthcare systems has driven exploratory research to develop therapeutic agents that will eliminate *C. difficile* while preserving the gut microflora, to reduce the likelihood of recurrence. One promising candidate therapeutic agent is ridinilazole/SMT19969 [2,2′-bis(4-pyridyl)3H,3′H 5,5′-bibenzimidazole] (Summit Therapeutics Inc.), which has shown highly specific inhibitory activity against *C. difficile*.[12]

The aim of this study was to evaluate the antimicrobial activity of ridinilazole and six comparator antimicrobials against a collection of common *C. difficile* strains from northern Asia.

Methods

Study strain collection

A total of 140 *C. difficile* strains from clinical cases of CDI were selected for testing from collections from Japan ($n = 64$, isolated in 2010), South Korea ($n = 32$, isolated 2005–12) and China ($n = 44$, isolated 2010–11). Strains were selected to represent the most common *C. difficile* strains circulating in Asia, which included RTs 017, 369, 012, 014/020, 002, 046, 018, 001, 070, 127 and QX 029 (Table 1). In the case of RT 127, the only A+ B+ CDT+ strain included, a single strain was tested since it had caused a ward-based CDI outbreak in a Tokyo hospital in 2010.[13]

Susceptibility testing by agar incorporation

Agar dilution susceptibility testing for ridinilazole, fidaxomicin, metronidazole, vancomycin, clindamycin, moxifloxacin and rifaximin was performed according to the CLSI guidelines.[14] Strains were recorded as susceptible to fidaxomicin for MIC <1 mg/L[8] and susceptible to metronidazole, vancomycin, clindamycin and moxifloxacin for MICs of ≤2 mg/L.[8,14] Resistance to metronidazole was recorded for MIC >2 mg/L, to vancomycin for MIC >8 mg/L, to clindamycin and moxifloxacin for MICs ≥8 mg/L[8] and to rifaximin for MIC ≥32 mg/L.[15] Assays were performed a minimum of twice for each strain; for all results presented, resistance profiles matched for each iteration of the study. Resistance rates, MIC_{50} and MIC_{90} and geometric mean MICs were calculated for each RT.

Results

MICs for ridinilazole ranged from 0.03 to 0.25 mg/L, with an MIC_{50} of 0.125 mg/L (Table 1) and geometric mean MIC of 0.12 mg/L overall. Similar MICs were recorded for fidaxomicin (range 0.015–0.25 mg/L) with an MIC_{50} of 0.125 mg/L but lower geometric mean MIC of 0.07 mg/L. All strains were susceptible to metronidazole and vancomycin; one strain from China (RT 001) displayed intermediate vancomycin resistance (MIC 4 mg/L) while all other vancomycin MICs were recorded as ≤2 mg/L.

Resistance to clindamycin was widespread (70.7% overall, MIC_{50} of >32 mg/L, MIC_{90} of >32 mg/L and geometric mean MIC of 13.03 mg/L; Table 1), found in all RT 017 strains (geometric mean MIC 30.62 mg/L) and in >80% of RT 369 (94.4%), RT 012 (92.3%), RT 046 (81.8%), RT 018 (83.3%) and RT 001 (81.3%) (all MIC_{50}s and MIC_{90}s >32 mg/L) strains. Clindamycin resistance was most frequently found in strains from South Korea (80.9%), then China (73.0%), then Japan (64.1%; Table 2).

Overall, 61.4% of strains were resistant to moxifloxacin, with an MIC_{50} of 16 mg/L, MIC_{90} of 32 mg/L and geometric mean of 7.96 mg/L. Moxifloxacin resistance was present in all RT 369 strains, 91.3% of RT 017, 94.1% of RT 002 and 83.3% of RT 018 (Table 1). Resistance to moxifloxacin was rare in China (36.0% of strains), found in 69.5% of strains from Japan and was widespread among strains from South Korea (82.4%); all RT 017, RT 002, RT 001 and RT 018 strains from South Korea were moxifloxacin resistant (Table 2).

Rifaximin resistance was rarer overall (16.4%, MIC_{50} of 0.03 mg/L, MIC_{90} of >32 mg/L, geometric mean MIC of 0.08 mg/L; Table 1), found most frequently in RT 017 strains (82.6%) and among some strains of RT 001 (12.5%), RT 070 (20.0%), RT 046 (9.1%) and RT 014/020 (5.3%). Rifaximin resistance was most commonly found in strains from South Korea (33.8%); all RT 017 strains from South Korea and 91.7% of RT 017 from China were resistant to rifaximin; however, no rifaximin resistance was detected in any strains from Japan (Table 2).

Multiresistance to clindamycin, moxifloxacin and rifaximin was found in 22 strains. These were mainly RT 017 strains from China and South Korea ($n = 19$), plus two RT 001 strains (South Korea) and one RT 046 strain (South Korea).

Discussion

The collection of Asian strains of *C. difficile* tested here showed diverse antimicrobial susceptibility profiles, with high rates of resistance to clindamycin and moxifloxacin. In particular, strains of *C. difficile* RT 017, the predominant strain circulating in Asia, were almost all multiresistant to clindamycin, moxifloxacin and rifaximin. *C. difficile* RTs 369 and 018 also showed high resistance rates and high geometric mean MICs for clindamycin and moxifloxacin (Table 1). While the strains tested here were collected prior to 2013, more recent reports from the region show similar resistance

Table 1. Overall susceptibility testing results

RT	Agent	Resistant *n* (%)	MIC range	MIC_{50}	MIC_{90}	Geometric mean
			(mg/L)			
All (*n* = 140)	RDZ	0	0.03–0.25	0.125	0.25	0.12
	MTZ	0	0.06–0.5	0.25	0.25	0.18
	VAN	0	0.06-4	1	2	1.13
	CLI	99 (70.7)	0.125 to >32	>32	>32	13.03
	MOX	86 (61.4)	1 to >32	16	32	7.96
	RFX	23 (16.4)	0.002 to >32	0.03	>32	0.08
	FDX	0	0.015–0.25	0.125	0.25	0.07
RT 017 (*n* = 23)	RDZ	0	0.03–0.125	0.125	0.25	0.11
	MTZ	0	0.06–0.25	0.125	0.25	0.16
	VAN	0	0.06–2	1	2	0.86
	CLI	23 (100.0)	8 to >32	>32	>32	30.62
	MOX	21 (91.3)	1 to >32	32	32	21.81
	RFX	19 (82.6)	0.008 to >32	>32	>32	7.63
	FDX	0	0.015–0.125	0.06	0.125	0.06
RT 014/020 (*n* = 19)	RDZ	0	0.06–0.25	0.125	0.125	0.11
	MTZ	0	0.06–0.25	0.25	0.25	0.20
	VAN	0	0.5–2	1	2	1.36
	CLI	4 (21.1)	0.25 to >32	4	16	2.83
	MOX	4 (21.1)	1–32	2	16	3.39
	RFX	1 (5.3)	0.005–32	0.015	0.03	0.02
	FDX	0	0.03–0.25	0.125	0.125	0.08
RT 369 (*n* = 18)	RDZ	0	0.06–0.25	0.125	0.25	0.16
	MTZ	0	0.125–0.25	0.25	0.25	0.18
	VAN	0	0.5–2	1	1	1.00
	CLI	17 (94.4)	0.25 to >32	>32	>32	26.40
	MOX	18 (100.0)	8 to >32	16	16	13.45
	RFX	0	0.015–0.03	0.03	0.03	0.02
	FDX	0	0.03–0.25	0.125	0.25	0.09
RT 002 (*n* = 17)	RDZ	0	0.03–0.25	0.125	0.25	0.12
	MTZ	0	0.125–0.5	0.25	0.25	0.20
	VAN	0	0.125–2	1	2	1.17
	CLI	10 (58.8)	0.25 to >32	>32	>32	8.16
	MXF	16 (94.1)	1 to >32	32	>32	19.89
	RFX	0	0.008–0.03	0.015	0.03	0.02
	FDX	0	0.015–0.25	0.06	0.125	0.08
RT 001 (*n* = 16)	RDZ	0	0.06–0.125	0.125	0.125	0.09
	MTZ	0	0.125–0.25	0.25	0.25	0.18
	VAN	0	0.06–4	1	2	0.94
	CLI	13 (81.3)	0.25 to >32	>32	>32	19.03
	MOX	11 (68.8)	1 to >32	8	16	6.11
	RFX	2 (12.5)	0.008 to >32	0.03	>32	0.24
	FDX	0	0.015–0.25	0.03	0.06	0.04
RT 012 (*n* = 13)	RDZ	0	0.06–0.25	0.125	0.125	0.11
	MTZ	0	0.125–0.5	0.25	0.25	0.23
	VAN	0	1–2	2	2	1.57
	CLI	12 (92.3)	4 to >32	>32	>32	27.27
	MOX	0	2	2	2	2.00
	RFX	0	0.008–0.03	0.015	0.03	0.02
	FDX	0	0.03–0.25	0.125	0.25	0.10
RT 018 (*n* = 12)	RDZ	0	0.06–0.125	0.125	0.125	0.11
	MTZ	0	0.125–0.25	0.125	0.25	0.17

Continued

Table 1. *Continued*

RT	Agent	Resistant *n* (%)	MIC range	MIC_{50}	MIC_{90}	Geometric mean
			(mg/L)			
	VAN	0	0.25–2	1	2	1.14
	CLI	10 (83.3)	0.25 to >32	>32	>32	18.28
	MOX	10 (83.3)	2–32	32	32	16.88
	RFX	0	0.008–16	0.015	0.03	0.02
	FDX	0	0.03–0.125	0.06	0.125	0.06
RT 046 (*n* = 11)	RDZ	0	0.06–0.25	0.125	0.125	0.12
	MTZ	0	0.125–0.25	0.25	0.25	0.19
	VAN	0	0.06–2	2	2	1.50
	CLI	9 (81.8)	0.125 to >32	>32	>32	18.15
	MOX	2 (18.2)	1–16	2	16	2.27
	RFX	1 (9.1)	0.008 to >32	0.015	0.03	0.03
	FDX	0	0.06–0.25	0.125	0.125	0.09
QX 029 (*n* = 6)	RDZ	0	0.06–0.25	0.125		0.12
	MTZ	0	0.125–0.25	0.25		0.19
	VAN	0	0.25–2	1		0.84
	CLI	1 (16.7)	0.25 to >32	4		2.24
	MOX	4 (66.7)	1–32	16		10.08
	RFX	0	0.008–0.03	0.03		0.02
	FDX	0	0.06–0.25	0.125		0.10
RT 070 (*n* = 4)	RDZ	0	0.125	0.125		0.13
	MTZ	0	0.06–0.25	0.25		0.18
	VAN	0	2	2		2.00
	CLI	0	0.5–4	2		2.00
	MOX	0	2	2		2.00
	RFX	1 (20.0)	0.015–0.03	0.03		0.02
	FDX	0	0.06–0.125	0.06		0.09
RT 127 (*n* = 1)	RDZ	0	0.25			
	MTZ	0	0.25			
	VAN	0	1			
	CLI	0	8			
	MOX	0	1			
	RFX	0	0.03			
	FDX	0	0.06			

RDZ, ridinilazole; MTZ, metronidazole; VAN, vancomycin; CLI, clindamycin; MOX, moxifloxacin; RFX, rifaximin; FDX, fidaxomicin.

patterns.[16] The circulation of strains with enhanced resistance profiles warrants regular surveillance and stewardship of prescribing practices.

Ridinilazole and fidaxomicin were both potently active against *C. difficile*. The low MICs found here agreed with previous reports.[12] Fidaxomicin is already in therapeutic use in several countries and fidaxomicin-resistant *C. difficile* strains have been reported in rare cases.[17] Ridinilazole is currently in Phase III clinical trials; to date, no resistance to ridinilazole has been reported.

No resistance to metronidazole or vancomycin was found. One strain (an RT 001 strain from China) showed borderline resistance to vancomycin (4 mg/L) according to EUCAST epidemiological cut-off values (>2 mg/L, www.eucast.org), but was considered as intermediately resistant according to Freeman *et al.*[8] (breakpoint >8 mg/L). Increased MICs implying intermediate or complete resistance to vancomycin have been reported previously,[8] as have increased MICs to metronidazole, including among A− B− CDT− *C. difficile* strains,[18] which circulate widely in Asia. These findings highlight a need for continuing surveillance for changes in susceptibility of *C. difficile* to metronidazole and vancomycin worldwide.

Notably, no rifaximin resistance was detected in strains from Japan, compared with the high rates seen among RT 017 strains from China and South Korea (Table 2). Rifaximin was only introduced in Japan in November 2016, after the strains tested here were collected.[19] Rifaximin resistance may now emerge among *C. difficile* strains in Japan, as rapid emergence of rifaximin/rifampin resistance following treatment with rifaximin has been demonstrated in *Staphylococcus aureus* and in *C. difficile*.[15,20] The fact that *C. difficile* strains from neighbouring China and/or South Korea had comparatively high rates of resistance to rifaximin

Table 2. Summary of percentage of resistant strains and geometric mean MICs by country and RT

			Percentage resistant (geometric mean MIC, mg/L)						
Country	RT	*n*	RDZ	MTZ	VAN	CLI	MOX	RFX	FDX
China	RT 017	12	0 (0.14)	0 (0.17)	0 (1)	100 (32)	91.7 (20.53)	91.7 (13.48)	0 (0.05)
	RT 014/020	4	0 (0.1)	0 (0.18)	0 (1.41)	25.0 (4.36)	25.0 (2.83)	0 (0.02)	0 (0.09)
	RT 002	3	0 (0.16)	0 (0.25)	0 (1.59)	100.0 (32)	100.0 (16)	0 (0.02)	0 (0.14)
	RT 001	4	0 (0.13)	0 (0.21)	0 (2.18)	50.0 (8)	0 (1.83)	0 (0.02)	0 (0.04)
	RT 012	10	0 (0.12)	0 (0.24)	0 (1.68)	90.0 (25.99)	0 (2)	0 (0.02)	0 (0.1)
	RT 046	5	0 (0.12)	0 (0.22)	0 (1.87)	100.0 (32)	0 (2.3)	0 (0.02)	0 (0.11)
	QX 029	2	0 (0.13)	0 (0.21)	0 (1.68)	0 (2)	0 (1.68)	0 (0.02)	0 (0.09)
	RT 070	4	0 (0.13)	0 (0.18)	0 (0.38)	0 (7.34)	0 (12.34)	0 (0.03)	0 (0.04)
	Overall	44	0 (0.13)	0 (0.20)	0 (1.50)	73.0 (15.51)	36.0 (4.57)	24.7 (0.12)	0 (0.08)
South Korea	RT 017	8	0 (0.09)	0 (0.15)	0 (0.77)	100.0 (32)	100.0 (32)	100.0 (32)	0 (0.06)
	RT 014/020	6	0 (0.1)	0 (0.22)	0 (1.5)	50.0 (4.24)	33.3 (3.78)	16.7 (0.02)	0 (0.06)
	RT 002	3	0 (0.11)	0 (0.22)	0 (1.26)	33.3 (5.04)	100.0 (20.16)	0 (0.02)	0 (0.05)
	RT 001	11	0 (0.08)	0 (0.17)	0 (0.72)	100.0 (31.16)	100.0 (10.17)	18.1 (0.63)	0 (0.04)
	RT 018	1	0 (0.09)	0 (0.25)	0 (1.41)	100.0 (32)	100.0 (32)	0 (0.49)	0 (0.03)
	RT 046	3	0 (0.11)	0 (0.18)	0 (0.99)	66.7 (8.98)	33.3 (4)	33.3 (0.2)	0 (0.05)
	Overall	32	0 (0.09)	0 (0.18)	0 (0.92)	80.9 (16.84)	82.4 (11.31)	33.8 (0.58)	0 (0.05)
Japan	RT 017	3	0 (0.11)	0 (0.12)	0 (0.63)	100.0 (22.63)	33.3 (10.08)	0 (0.02)	0 (0.08)
	RT 014/020	9	0 (0.11)	0 (0.19)	0 (1.26)	0 (1.78)	11.1 (3.43)	0 (0.02)	0 (0.09)
	RT 369	18	0 (0.16)	0 (0.18)	0 (1)	94.4 (26.4)	100.0 (13.45)	0 (0.02)	0 (0.09)
	RT 002	11	0 (0.12)	0 (0.18)	0 (1.06)	54.5 (6.42)	90.9 (20.99)	0 (0.02)	0 (0.08)
	RT 001	1	0 (0.09)	0 (0.18)	0 (1)	0 (1)	50.0 (1)	0 (0.02)	0 (0.06)
	RT 012	3	0 (0.1)	0 (0.2)	0 (1.26)	100.0 (32)	0 (2)	0 (0.02)	0 (0.11)
	RT 018	11	0 (0.12)	0 (0.17)	0 (1.12)	81.8 (17.45)	81.8 (16)	0 (0.02)	0 (0.06)
	RT 046	3	0 (0.14)	0 (0.16)	0 (1.59)	66.7 (14.25)	0 (1.26)	0 (0.02)	0 (0.12)
	QX 029	4	0 (0.12)	0 (0.18)	0 (0.59)	25.0 (2.38)	25.0 (24.68)	0 (0.02)	0 (0.1)
	RT 127	1	0 (0.09)	0 (0.13)	0 (1)	0 (1.41)	0 (1)	0 (0.02)	1 (0.04)
	Overall	64	0 (0.13)	0 (0.18)	0 (1.04)	64.1 (10.12)	69.5 (9.68)	0.0 (0.02)	0 (0.08)

RDZ, ridinilazole; MTZ, metronidazole; VAN, vancomycin; CLI, clindamycin; MOX, moxifloxacin; RFX, rifaximin; FDX, fidaxomicin.

implies there is little movement of *C. difficile* strains between the countries, at least into Japan.

In conclusion, ridinilazole showed excellent activity against a range of *C. difficile* strains from Asian countries, which were frequently multiresistant to clindamycin, moxifloxacin and rifaximin. Dependent on the outcome of Phase III trials that are currently underway, ridinilazole appears to be a strong candidate for first-line therapy for CDI not only in Asia but elsewhere; however, cost-effectiveness of treatment with ridinilazole versus other antimicrobials must be considered, especially in lower-income Asian countries.

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Transparency declarations

R. Vickers was formerly an employee of Summit Therapeutics plc (now Summit Therapeutics Inc.). All other authors have no conflicts to declare in relation to this work.

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