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SUSCEPTIBILITY

Low *In Vitro* Antifungal Activity of Tavaborole against Yeasts and Molds from Onychomycosis

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ABSTRACT The *in vitro* activity of tavaborole, an FDA-approved antifungal drug, was compared to that of four antifungal agents against 170 clinical fungal isolates originating from patients with onychomycosis. Tavaborole had low activity against all isolates compared to itraconazole, terbinafine, and fluconazole, the principal choices for treatment of onychomycosis. Thus, it appears that tavaborole is not a candidate for the treatment of onychomycosis due to *Candida* species, *Aspergillus* species, and dermatophytes.

KEYWORDS tavaborole, antifungal, onychomycosis

Fungal nail infections are common and recurrent problems caused predominantly by different species of dermatophytes, *Candida*, and filamentous fungi. The distribution pattern has been reported to be variable in different geographic regions (1–3). Whereas most reports indicate that *Trichophyton rubrum* and *Trichophyton interdigitale* are the most common agents of onychomycosis, several fungal genera, such as *Candida*, *Aspergillus*, *Fusarium*, *Scopulariopsis*, *Acremonium*, *Onychocola*, and *Penicillium*, have been isolated from nail samples (4–9). Estimates of the prevalence rate of onychomycosis in the different communities range from 0.5% to 30% (6, 10, 11). It may affect patients with advanced age, distorted nails, hyperhidrosis, diabetes, psoriasis, peripheral vascular disease, genetic predisposition, and immunosuppression (8, 9). Currently, the preferred treatments for onychomycosis include itraconazole, terbinafine, and fluconazole combined with topical nail formulations, such as luliconazole 1% (12, 13), efinaconazole 10% (14), amorolfine 5%, and ciclopirox 8% (15). Despite the introduction of new generations of antimycotics, as well as laser and photodynamic therapy, achievement of complete cure is challenging (16, 17). Tavaborole (5%), a boronic acid quinolone compound, received FDA approval in 2014 for use in the topical treatment of onychomycosis (17). This drug has a unique mechanism of inhibition among antifungals, targeting the leucyl-tRNA synthetase enzyme and thus preventing protein synthesis (18, 19). Tavaborole, due to its small molecular weight, demonstrated appropriate safety with excellent nail penetration through keratin layers (20). Previous limited studies using a few strains showed that tavaborole had *in vitro* activity against *Trichophyton*, *Candida*, *Aspergillus*, and *Fusarium* (21, 22), although no antifungal susceptibility data of tavaborole against a large

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collection of clinical fungi from onychomycosis cases have been published. Therefore, we used a panel of isolates of different species of dermatophytes, molds, and yeasts from patients with onychomycosis to evaluate the *in vitro* activity of this novel drug and four comparator agents, i.e., voriconazole, itraconazole, fluconazole, and terbinafine.

A total of 170 clinical nail isolates were included in this study. Fifty-one yeasts, consisting of *Candida parapsilosis* ($n = 27$), *Candida tropicalis* ($n = 10$), *Candida albicans* ($n = 7$), *Candida krusei* ($n = 4$), *Candida orthopsilosis* ($n = 2$), *Candida guilliermondii* ($n = 1$), and *Candida glabrata* ($n = 1$); as well as 88 molds, including *Aspergillus flavus* ($n = 36$), *Aspergillus terreus* ($n = 21$), *Aspergillus niger* ($n = 17$), *Aspergillus tubingensis* ($n = 8$), *Fusarium proliferatum* ($n = 8$), *Trichophyton interdigitale* ($n = 8$), *Trichophyton rubrum* ($n = 5$), *Aspergillus oryzae* ($n = 3$), *Aspergillus fumigatus* ($n = 2$), *Fusarium solani* ($n = 2$), *Fusarium verticillioides* ($n = 2$), *Fusarium* sp. ($n = 2$), *Aspergillus uvarum* ($n = 1$), and *Trichophyton tonsurans* ($n = 1$), were recovered from patients suffering from fingernail ($n = 70$) and toenail ($n = 100$) infections. Isolates were cultured on Sabouraud dextrose agar (Difco) supplemented with chloramphenicol for 2 to 7 days at 30°C and identified to the species level by PCR restriction fragment length polymorphism and DNA sequencing as previously described (23–25, 33–36). *In vitro* antifungal susceptibility testing for filamentous fungi and yeast were performed according to Clinical and Laboratory Standards Institute (CLSI) documents M38-A2 and M27-A3, respectively (26, 27). Concentration ranges used were 0.016 to 16 μg/ml for tavaborole (Sigma-Aldrich, Germany), itraconazole (Janssen Research Foundation, Beerse, Belgium), and voriconazole (Pfizer, Central Research, Sandwich, United Kingdom); 0.004 to 4 μg/ml for terbinafine (Novartis Research Institute, Vienna, Austria); and 0.063 to 64 μg/ml for fluconazole (Pfizer). The maximal final concentration of dimethyl sulfoxide in the test wells was $<$1%. Trays were stored at -80°C until the day of testing. Briefly, conidial suspensions of filamentous fungi were obtained by scraping the mature colonies on potato dextrose agar (Difco) with a moistened swab. The turbidity was measured spectrophotometrically at a wavelength of 530 nm. Transmission was adjusted to 65% to 70% for dermatophytes, 80% to 82% for *Aspergillus* spp., and 69% to 70% for *Fusarium* isolates. To obtain the final inoculum, suspensions were diluted 1:50 in RPMI 1640 medium. Microdilution plates were incubated at 35°C for 48 h for *Aspergillus* and *Fusarium*, but trays were incubated at 35°C for 96 h for *Trichophyton*. MIC endpoints were defined as the lowest concentration that caused complete inhibition of growth. In contrast, yeast suspensions were adjusted spectrophotometrically at a wavelength of 530 nm to a transmission in the 75% to 77% range and diluted in RPMI 1640 medium to yield final inocula of 0.5 to 5×10^3 cells/ml. The microdilution trays were incubated at 35°C for 24 h. The MIC values were determined visually and were defined as the lowest concentration of drug that caused $\geq$50% growth inhibition for all drugs. *C. krusei* (ATCC 6258) and *Paecilomyces variotii* (ATCC 3630) were used as quality controls. All tests were performed in duplicate, and differences of the mean values were determined by Student's *t* test with the statistical SPSS package (version 7.0). *P* values of <0.05 were considered statistically significant.

Table 1 summarizes the *in vitro* susceptibility pattern of 170 clinical nail isolates as the MIC range, MIC mode, MIC_{50}, and, when appropriate, the MIC_{90} for the five tested antifungal drugs. Tavaborole demonstrated consistently very high MIC values against all filamentous fungi and yeast isolates, compared to those of the other antifungal drugs. Tavaborole showed high MICs for most of the *Candida* isolates (MIC_{50} and MIC_{90}, 16 μg/ml), whereas the MIC_{90}s of voriconazole, itraconazole, and terbinafine were lowest for this genus, at 0.25, 4, and 4 μg/ml, respectively (Table 1). Unlike the study by Mao et al. (22), which reported MICs ranging from 0.5 to 1 μg/ml for *Candida* spp. and 0.125 to 4 μg/ml for the other yeasts, this study showed lower activity, with MIC ranges of 2 to 16 μg/ml. For *Aspergillus* strains, all antifungal agents except fluconazole demonstrated better activity than tavaborole. As presented in Table 1, MIC_{50} values of fluconazole and tavaborole were 64 and 2 μg/ml, respectively, whereas all *Aspergillus* strains showed MIC_{50} values of $\leq$1 μg/ml for the remaining drugs. The MICs for

TABLE 1 *In vitro* susceptibilities of five antifungal drugs against different fungal isolates from patients with onychomycosis[a]

Genus	Species (no. of isolates)	MIC parameter	MIC (μg/ml) for:				
			Tavaborole	Voriconazole	Itraconazole	Fluconazole	Terbinafine
Candida	*C. parapsilosis* (27)	Range	2 to >16	0.008 to >16	0.125 to >16	0.0625 to >64	4 to >4
		MIC_{50}	16	0.016	1	0.5	4
		MIC_{90}	16	0.25	2	8	4
		GM	14.49	0.06	2.46	1.71	4
	C. tropicalis (10)	Range	8 to >16	0.0625 to >0.5	1 to >8	0.25 to >64	4 to >4
		MIC_{50}	16	0.032	2	2	4
		MIC_{90}	16	0.25	4	16	4
		GM	14.49	0.06	2.46	1.71	4
	C. albicans (7)	Range	4 to >16	0.008 to >0.016	0.25 to 16	0.125 to >4	4 to >4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	C. krusei (4)	Range	8 to 16	0.0625 to 0.016	0.5 to 1	0.5 to 16	4 to >4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	C. orthopsilosis (2)	Range	16	0.016	1	0.25 to 1	4 to >4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	C. guilliermondii (1)	Range	16	0.125	4	4	>4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	C. glabrata (1)	Range	16	0.125	4	2	>4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	All *Candida* strains (52)	Range	2 to >16	0.008 to >16	0.125 to >16	0.0625 to >16	4 to >4
		MIC_{50}	16	0.032	1	1	4
		MIC_{90}	16	0.25	4	8	4
		GM	12.58	0.03	0.77	0.74	4
Aspergillus	*A. flavus* (36)	Range	0.5 to 16	0.0625 to 0.5	0.0625 to 1	16 to >64	0.032 to 8
		MIC_{50}	2	0.25	0.125	64	0.5
		MIC_{90}	4	0.5	0.25	64	4
		GM	1.8	0.21	0.13	45.25	0.59
	A. terreus (21)	Range	1 to 4	0.125 to 1	0.0625 to 0.25	64	0.032 to 8
		MIC_{50}	2	0.25	0.016	64	4
		MIC_{90}	4	1	0.125	64	8
		GM	2.4	0.33	0.03	64	1.8
	A. niger (17)	Range	0.5 to 16	0.0625 to 2	0.0625 to >16	32 to >64	0.125 to 8
		MIC_{50}	1	0.25	0.032	32	0.5
		MIC_{90}	16	0.5	1	64	4
		GM	1.92	0.25	0.2	42.25	0.81
	A. tubingensis (8)	Range	1 to 8	0.125 to 1	0.25 to 1	64	0.25 to 8
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	A. oryzae (3)	Range	1 to 8	0.0625 to 0.125	0.032 to 0.125	32 to 64	0.0625 to 1
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	A. fumigatus (2)	Range	2 to 16	0.0625 to 0.25	0.0625 to 0.5	64 to >64	4 to >4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	A. uvarum (1)	Range	0.5	0.125	0.016	>64	4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	All *Aspergillus* strains (88)	Range	0.5 to 16	0.0625 to 2	0.016 to >16	0.5 to >64	0.032 to >4
		MIC_{50}	2	0.25	0.125	64	1

(Continued on next page)

TABLE 1 (Continued)

Genus	Species (no. of isolates)	MIC parameter	MIC (μg/ml) for: Tavaborole	Voriconazole	Itraconazole	Fluconazole	Terbinafine
		MIC_{90}	4	0.5	0.5	64	4
		GM	2	0.24	0.1	50.79	0.92
Dermatophytes	*T. interdigitale* (8)	Range	4 to 16	0.016 to 0.0625	0.0625 to 0.125	16 to 32	0.008 to 4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	T. rubrum (5)	Range	8 to 16	0.016 to >16	0.016 to >16	2 to 16	0.008 to >4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	T. tonsurans (1)	Range	8	0.032	0.032	16	0.004
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	All dermatophyte strains (14)	Range	4 to 16	0.016 to >16	0.016 to >16	2 to 32	0.004 to >4
		MIC_{50}	8	0.032	0.0625	16	0.004
		MIC_{90}	16	0.032	0.0625	32	0.008
		GM	9.28	0.02	0.03	10.24	0.007
Fusarium	*F. proliferatum* (8)	Range	16 to >16	1 to 4	>16	64 to >64	>4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	F. verticillioides (2)	Range	8-16	1->16	8->16	>64	0.032- >4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	F. solani (2)	Range	16 to >16	0.5 to 2	>16	>64	>4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	Fusarium sp. (2)	Range	16	2	>16	>64	>4
		MIC_{50}	ND	ND	ND	ND	ND
		MIC_{90}	ND	ND	ND	ND	ND
		GM	ND	ND	ND	ND	ND
	All *Fusarium* strains (14)	Range	8 to >16	0.5 to >16	8 to >16	64 to >64	0.032 to >4
		MIC_{50}	16	2	8	64	4
		MIC_{90}	16	4	8	64	4
		GM	14.67	2	8	64	4

[a]GM, geometric mean; MIC_{50}, concentration at which 50% of the isolates were inhibited; MIC_{90}, concentration at which 90% of the isolates were inhibited; ND, not determined.

tavaborole against all dermatophyte isolates ranged from 4 to 16 μg/ml, compared to 0.016 to >16 μg/ml for voriconazole, 0.016 to >16 μg/ml for itraconazole, 2 to 32 μg/ml for fluconazole, and 0.004 to >4 μg/ml for terbinafine. Overall, MIC_{50} and MIC_{90} values of tavaborole (8 and 16 μg/ml) had low activities compared to those of itraconazole (both 0.0625 μg/ml) and terbinafine (0.004 and 0.008 μg/ml) used for treatment of onychomycosis due to dermatophytes. Remarkably, *Fusarium* sp. demonstrated extremely high MICs to tavaborole (8 to >16 μg/ml); however, the lowest MIC ranges were found with terbinafine (0.032 to >4 μg/ml). Tavaborole MIC_{50} and MIC_{90} values of all isolates were 4 and 16 μg/ml, respectively, whereas those of the other agents were, respectively, 0.125 and 1 μg/ml for voriconazole, 0.25 and 2 μg/ml for itraconazole, 4 and 64 μg/ml for fluconazole, and 2 and 4 μg/ml for terbinafine. Furthermore, MIC_{90} values of tavaborole against all isolates were 2 and 3 log2 dilutions higher than terbinafine and itraconazole, respectively. Tavaborole inhibited only 14.7% ($n = 25$) of all isolates at a concentration of ≤1 μg/ml, whereas itraconazole and terbinafine inhibited 78.82% ($n = 134$) and 40% ($n = 69$) of isolates with this MIC value, respectively. Mao et al. (22) examined tavaborole MIC values (0.5 μg/ml) for only 1 isolate of *A. fumigatus*. Among 88 *Aspergillus* strains in the current study, just 5 isolates,

TABLE 2 *In vitro* susceptibilities of 5 antifungal drugs against 170 fungal isolates from different patients with onychomycosis[b]

	MIC (μg/ml)[a]																	
Antifungal drug	0.004	0.008	0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	>64	MIC range	MIC_{50}	MIC_{90}	GM
Tavaborole								5	20	45	18	19	**63**			0.5 to 16	4	16	4.44
Voriconazole		4	27	14	16	**30**	30	25	8	9	4		3			0.008 to >16	0.125	1	0.13
Itraconazole			19	10	18	23	20	20	**24**	7	8	2	19			0.016 to >16	0.25	2	0.2
Fluconazole					1	7	5	11	7	10	5	2	12	8	**102**	0.0625 to >64	4	64	3.67
Terbinafine	10	9		3	1	12	10	13	11	11	**89**	1				0.004 to >4	2	4	0.74

[a]Numbers in boldface are modal values.
[b]GM, geometric mean; MIC_{50}, concentration at which 50% of the isolates were inhibited; MIC_{90}, concentration at which 90% of the isolates were inhibited.

including 2 *A. flavus*, 2 *A. niger,* and 1 *A. uvarum*, were inhibited at an MIC of 0.5 μg/ml, and 28.4% ($n = 25$) of all isolates were inhibited at ≤1 μg/ml of tavaborole (Tables 1 and 2).

Tavaborole, in contrast to other recently FDA-approved topical antifungal agents for onychomycosis, including efinaconazole (28) and luliconazole (29), demonstrated lower activity against *Aspergillus* spp. Luliconazole showed excellent activity against susceptible and resistant *A. fumigatus* isolates, with MIC ranges of <0.001 to 0.016 μg/ml (30). Also, Siu et al. (14) found that efinaconazole had geometric mean MICs of 0.089 μg/ml for *A. fumigatus* and 0.11 μg/ml for *A. flavus* from onychomycosis.

MICs of tavaborole for dermatophyte isolates were similar to those reported by Mao et al. (22) but different from the those in the FDA study. MIC ranges in our study were 4 to 16 μg/ml, Mao et al. (22) reported MICs of 1 to 8 μg/ml, and the FDA evaluation demonstrated MIC ranges of 0.5 to 2 μg/ml. Based on the MIC_{90} value (16 μg/ml), tavaborole showed low activity, which was not comparable to the MIC_{90} of terbinafine (0.008 μg/ml) and itraconazole with (0.0625 μg/ml). Almost all dermatophyte isolates (92%) were inhibited at ≥8 μg/ml of tavaborole, except for a single isolate with an MIC of 4 μg/ml (Table 1). Finally, tavaborole MICs of *Fusarium* isolates in this study (8 to 16 μg/ml) were higher than those found in other reports (<0.5 μg/ml) (22). With the exception of a single isolate of *F. verticillioides* which had an MIC of 8 μg/ml, all had MICs of 16 μg/ml (Table 1). These results concur with previously published data on azoles versus *Fusarium* sp., with MICs of ≥8 for itraconazole (31, 32). In conclusion, we found that the *in vitro* antifungal activity of tavaborole against a panel of different agents of onychomycosis is inferior to those of terbinafine and azoles, except for fluconazole.

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We have no other conflicts of interest to declare.

We alone are responsible for the content and writing of the paper.

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