ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1999, p. 2236–2239 Vol. 43, No. 9
0066-4804/99/$04.00+0

In Vitro Activities of BMS-207147 against Over 600 Contemporary Clinical Bloodstream Isolates of *Candida* Species from the SENTRY Antimicrobial Surveillance Program in North America and Latin America

D. J. DIEKEMA,* M. A. PFALLER, S. A. MESSER, A. HOUSTON, R. J. HOLLIS, G. V. DOERN, R. N. JONES, AND THE SENTRY PARTICIPANTS GROUP

Medical Microbiology Division, Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa

Received 14 May 1999/Returned for modification 25 June 1999/Accepted 15 July 1999

We compared the in vitro activity of BMS-207147, an investigational triazole, with those of itraconazole and fluconazole against 613 clinical bloodstream isolates of *Candida* spp. collected from SENTRY participating hospitals during 1997 and 1998. Overall, BMS-207147 was the most active azole against all *Candida* spp. While both BMS-207147 and itraconazole displayed a stepwise decrease in activity against isolates for which the fluconazole MICs were elevated, BMS-207147 had two- to fourfold greater activity than itraconazole both against *Candida* spp. that were dose-dependently fluconazole susceptible and against those that were fluconazole resistant.

BMS-207147 (ER-30346) is a novel investigational triazole antifungal agent (1, 12) with a broad spectrum of in vitro activity against *Candida*, *Aspergillus*, and *Cryptococcus* spp. (2–6, 8, 9, 11). BMS-207147 has recently been demonstrated to be two- to fourfold more active than itraconazole against bloodstream isolates of *Candida* spp. collected from U.S. hospitals between 1992 and 1997 (8). In this study, we compared the activity of BMS-207147 with those of itraconazole and fluconazole against over 600 bloodstream isolates of *Candida* spp. collected from medical centers in Canada, the United States, and Latin America during 1997 and 1998. This represents the first evaluation of the in vitro activity of BMS-207147 against recently collected isolates of *Candida* spp. from outside the United States. Special attention was given to a comparison of BMS-207147 versus itraconazole against *Candida* sp. isolates for which the fluconazole MICs are elevated.

MATERIALS AND METHODS

Organisms. The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals distributed by geographic location and size. The organisms tested in this study represented all of the isolates of *Candida* sp. causing bloodstream infections at SENTRY centers in the western hemisphere during 1997 and 1998. *Candida* sp. isolates were collected from 22 centers in the United States, 6 in Canada, and 7 in Latin America. Most of the centers were tertiary-care hospitals.

Each participating center contributed results on consecutive blood culture isolates of *Candida* spp. judged to be clinically significant by local criteria. All isolates were saved on agar slants and sent on a weekly basis to the University of Iowa College of Medicine (Iowa City) for storage and further characterization by reference identification and susceptibility testing methods.

Organism identification. All fungal blood culture isolates were identified at the participating institution by the routine method in use at each laboratory. Upon receipt at the University of Iowa, the isolates were subcultured onto potato dextrose agar (Remel, Lenexa, Kans.) and CHROMagar Candida medium (Hardy Laboratories, Santa Maria, Calif.) to ensure viability and purity. Confirmation of species identification was performed with Vitek and API products (bioMerieux, St. Louis, Mo.) or by conventional methods, as required. Isolates were stored as suspensions in water or on agar slants at ambient temperature until needed.

Susceptibility testing. Antifungal susceptibility testing was performed by the reference broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS) (7). Reference powders of fluconazole (Pfizer), itraconazole (Janssen), and BMS-207147 (Bristol-Meyers Squibb) were obtained from the respective manufacturers. Stock solutions were prepared in dimethyl sulfoxide (BMS-207147 and fluconazole) or polyethylene glycol (itraconazole). Serial twofold dilutions were prepared as outlined by the NCCLS (7), and final dilutions were made in RPMI 1640 medium buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (Sigma). Aliquots (0.1 ml) of each antifungal agent at a 2× final concentration were dispensed into the wells of plastic microdilution trays by using a Quick Spense II system (Dynatech Laboratories, Chantilly, Va.). The trays were sealed and frozen at −70°C until needed.

A 0.1-ml yeast inoculum (concentration of 1.0×10^3 to 5.0×10^3 cells/ml) was added to each well of the microdilution trays (final concentration of 0.5×10^3 to 2.5×10^3 cells/ml). The final concentrations of the antifungal agents were 0.007 to 8 μg/ml for BMS-207147 and itraconazole and 0.12 to 128 μg/ml for fluconazole. The BMS-207147 concentrations were chosen based upon previous studies of the in vitro activity (3, 4) and pharmacokinetic profile (6) of the drug (i.e., to ensure that on-scale and clinically relevant concentrations were tested). The trays were incubated in air at 35°C, and MIC endpoints were read after 48 h of incubation. Drug-free and yeast-free controls were included on each tray. Following incubation, the broth microdilution trays were examined with a reading mirror and the growth in each well was compared with that in the growth control well. The MIC of each triazole was defined as the lowest concentration resulting in 80% inhibition of growth compared to the growth control (7). The data reported are the MICs of each antifungal agent necessary to inhibit 50% (MIC_{50}) and 90% (MIC_{90}) of the isolates tested.

Interpretive susceptibility criteria for fluconazole and itraconazole were those published by Rex et al. (10) and the NCCLS (7). Isolates for which the fluconazole MICs were ≤8 μg/ml were considered susceptible (S), those for which the MICs were 16 to 32 μg/ml were considered susceptible dependent upon dose (S-DD), and those for which the MICs were ≥64 μg/ml were considered resistant (R). For itraconazole, interpretative breakpoints were as follows: S, ≤0.12 μg/ml; S-DD, 0.25 to 0.5 μg/ml; R, ≥1 μg/ml.

Quality control. Quality control was performed by testing *Candida parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258.

RESULTS

A total of 634 bloodstream isolates of *Candida* spp. were reported by SENTRY centers in the United States, Canada, and Latin America during 1997 and 1998. Of these, 613 were

* Corresponding author. Mailing address: Medical Microbiology Division, C606 GH, Department of Pathology, University of Iowa College of Medicine, Iowa City, IA 52242. Phone: (319) 384-9951. Fax: (319) 356-4916. E-mail: daniel-diekema@uiowa.edu.

TABLE 1. Species distribution of *Candida* bloodstream isolates in the SENTRY program in 1997 and 1998

Organism	% of isolates by geographic area							
	United States		Canada		Latin America		Total	
	1997 (203)[a]	1998 (206)	1997 (61)	1998 (57)	1997 (42)	1998 (65)	1997 (306)	1998 (328)
C. albicans	56.2	54.4	52.5	70.1	40.5	44.6	53.3	55.2
C. glabrata	18.7	21.8	11.5	12.3	2.4	9.2	15.0	17.7
C. parapsilosis	8.9	15.0	22.9	7.0	38.1	18.5	15.7	14.3
C. tropicalis	6.9	5.8	8.2	5.2	11.9	20.0	7.8	8.5
C. krusei	2.5	1.0	1.6	1.8		1.5	2.0	1.2
C. guilliermondii	0.5	1.0		1.8	2.4	6.2	0.7	2.1
Candida sp.	6.4	1.0	3.3	1.8	4.7		5.8	1.0

[a] The values in parentheses are the numbers of isolates tested.

contained within the six most common species groups (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. guilliermondii*). The frequency of isolation of each *Candida* sp. by year and region is presented in Table 1.

Table 2 summarizes the in vitro susceptibilities of the 613 bloodstream isolates of *Candida* spp. tested against BMS-207147, itraconazole, and fluconazole. Overall, the fluconazole resistance of *C. albicans* was extremely low (0.9%) and, in particular, no resistance was detected in *C. parapsilosis* and *C. tropicalis*. Of 106 *C. glabrata* bloodstream isolates tested, 5.7% were fluconazole resistant (MIC, ≥64 μg/ml). For each species of *Candida* tested, the MIC_{50} and MIC_{90} of BMS-207147 were two- to fourfold lower than those of itraconazole.

TABLE 2. In vitro susceptibilities to fluconazole, itraconazole, and BMS-207147 of bloodstream isolates of *Candida* spp. from 1997 and 1998

Species (no. of isolates tested) and antifungal agent	MIC (μg/ml)		% R[c]
	50%[a]	90%[b]	
C. albicans (341)			
Fluconazole	0.25	0.5	0.9
Itraconazole	0.03	0.12	1.5
BMS-207147	0.007	0.03	
C. glabrata (106)			
Fluconazole	8	16	5.7
Itraconazole	0.5	2	34.9
BMS-207147	0.25	1	
C. parapsilosis (97)			
Fluconazole	0.5	2	0
Itraconazole	0.12	0.25	0
BMS-207147	0.03	0.06	
C. tropicalis (49)			
Fluconazole	0.5	2	0
Itraconazole	0.12	0.25	4.1
BMS-207147	0.03	0.12	
C. guilliermondii (10)			
Fluconazole	2	4	0
Itraconazole	0.25	1	20
BMS-207147	0.12	0.25	
C. krusei (10)			
Fluconazole	32	64	100
Itraconazole	0.5	2	40
BMS-207147	0.25	0.5	
Total (613)			
Fluconazole	0.5	8	1.8
Itraconazole	0.06	0.5	8.2
BMS-207147	0.015	0.25	

[a] 50%, MIC_{50}.
[b] 90%, MIC_{90}.
[c] Based on NCCLS breakpoints (7). All *C. krusei* isolates are considered fluconazole R.

BMS-207147 and itraconazole were compared with respect to the fluconazole susceptibility categories. These data are presented in Table 3. As the fluconazole MIC increased (categorized as S, S-DD, or R), stepwise increases in the MIC_{50}s and MIC_{90}s of both BMS-207147 and itraconazole were also noted. However, within each fluconazole susceptibility category, BMS-207147 still displayed two- to fourfold greater activity than itraconazole. For example, when all 42 fluconazole S-DD isolates were combined for analysis, BMS-207147 had twofold greater activity than itraconazole (MIC_{50}/MIC_{90}, 0.5/1.0 versus 1.0/2.0 μg/ml, respectively).

Eleven *Candida* sp. isolates were fluconazole R (MIC, ≥64 μg/ml). The BMS-207147 and itraconazole MICs for these strains are listed in Table 4. For eight of these isolates, the BMS-207147 MIC was two- to eightfold lower than the itraconazole MIC. Notably, against the two *C. krusei* isolates for which the fluconazole MICs were ≥64 μg/ml, the BMS-207147 MICs were 0.25 and 0.5 μg/ml, compared to 2.0 μg/ml for itraconazole. For three fluconazole-R strains (two of *C. albicans* and one of *C. glabrata*), the BMS-207147 MIC was equal to or higher than the itraconazole MIC.

DISCUSSION

These results demonstrate that BMS-207147 has a broader spectrum of in vitro activity against invasive (bloodstream) isolates of *Candida* spp. than either itraconazole or fluconazole. Based upon MIC_{50}s and MIC_{90}s, BMS-207147 consistently demonstrated 2- to 4-fold greater potency than itraconazole and 16- to 32-fold greater potency than fluconazole against all of the *Candida* spp. tested, including *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. guilliermondii*. Furthermore, we found that BMS-207147 retained twofold greater activity than itraconazole against *Candida* sp. bloodstream isolates for which the fluconazole MICs were elevated. Other investigators have demonstrated the excellent in vitro activity of BMS-207147 against *Candida* spp. (3, 4, 6, 8, 9) and other fungal pathogens, including *Aspergillus* spp. (2, 3, 6) and cryptococci (4, 6).

BMS-207147 has also been evaluated in vivo in murine models of disseminated candidiasis (6), pulmonary candidiasis (5), and oral candidiasis (5). These studies demonstrated BMS-207147 to be more effective than itraconazole and comparable in efficacy to fluconazole. Also of interest is that BMS-207147

TABLE 3. In vitro susceptibilities of bloodstream isolates of various species of *Candida* tested against BMS-207147 and itraconazole and stratified by fluconazole susceptibility category

Species and fluconazole susceptibility category (no. of isolates tested)[a]	MIC (μg/ml)					
	BMS-207147			Itraconazole		
	Range	50%[b]	90%[c]	Range	50%	90%
C. albicans						
S (334)	0.007–1.0	0.007	0.03	0.007–1.0	0.03	0.12
S-DD (1)	2.0	2.0	2.0	4.0	4.0	4.0
R (3)	0.06–16	16	16	1.0–16	16	16
All (338)	0.007–16	0.007	0.03	0.007–16	0.03	0.12
C. glabrata						
S (66)	0.015–2.0	0.25	0.5	0.06–2.0	0.25	1.0
S-DD (34)	0.007–8.0	0.5	1.0	0.25–16	1.0	2.0
R (6)	0.5–8.0	4.0	8.0	2.0–16	16	16
All (106)	0.007–8.0	0.25	1.0	0.06–16	0.5	2.0
C. parapsilosis, S (97)	0.007–0.12	0.03	0.06	0.015–0.5	0.12	0.25
C. tropicalis, S (49)	0.007–0.5	0.03	0.12	0.015–1.0	0.12	0.25
C. krusei						
S (1)	0.25	0.25	0.25	0.12	0.12	0.12
S-DD (7)	0.06–2.0	0.25	2.0	0.12–1.0	0.5	1.0
R (2)	0.25–0.5	0.25	0.5	2.0	2.0	2.0
All (10)	0.06–2.0	0.25	0.5	0.12–2.0	0.5	2.0
C. guilliemondii, S (10)	0.03–2.0	0.12	0.25	0.12–1.0	0.25	1.0
C. lusitaniae, S (2)	0.015–0.03	0.015	0.03	0.06–0.25	0.06	0.25
All *Candida* spp.						
S (559)	0.007–2.0	0.015	0.12	0.007–2.0	0.06	0.5
S-DD (42)	0.007–8.0	0.5	1.0	0.12–16	1.0	2.0
R (11)	0.06–16	4.0	16	1.0–16	16	16
All (613)	0.007–16	0.015	0.25	0.007–16	0.06	0.5

[a] Fluconazole susceptibility categories according to NCCLS M27-A (7): S, ≤8.0 μg/ml; S-DD, 16 to 32 μg/ml; R, ≥64 μg/ml.
[b] 50%, MIC_{50}.
[c] 90%, MIC_{90}.

appeared to have greater activity than itraconazole or fluconazole against an experimental model of pulmonary infection due to fluconazole-resistant *C. albicans* (5). In these studies and in other experimental models (11), BMS-207147 was administered orally. Hata et al. found the absorption of BMS-207147 in the mouse to be comparable to that of itraconazole at an equivalent oral dose (maximum drug concentration in serum, 1.0 μg/ml after administration of a 10-mg/kg dose) but found the half-life of BMS-207147 (4.0 h) to be about three times longer than that of itraconazole (6).

TABLE 4. Activities of BMS-207147 and itraconazole against *Candida* species resistant to fluconazole[a]

Organism and strain no.	MIC (μg/ml) of:	
	BSM-207147	Itraconazole
C. albicans		
6-2733	16	16
10-2139	0.06	1.0
10-7387	16	16
C. glabrata		
16-5789	4.0	2.0
36-8868	4.0	16
27-1281	8.0	16
2-1797	4.0	8.0
17-6580	8.0	16
41-6251	0.5	16
C. krusei		
25-2562	0.5	2.0
2-4227	0.25	2.0

[a] Fluconazole resistance is defined, according to NCCLS-recommended criteria (7), as a MIC of ≥64 μg/ml.

The in vitro data we present suggest that BMS-207147 may be a promising alternative to currently available triazoles for the treatment of infections due to *Candida* spp., including those due to organisms for which the fluconazole MICs are elevated. Further study of the safety and pharmacokinetic profiles of BMS-207147 in humans is warranted.

ACKNOWLEDGMENTS

We thank Kay Meyer for her assistance in the preparation of the manuscript. We appreciate the contributions of all SENTRY site participants. The following participants contributed data or isolates to the study: The Medical Center of Delaware, Wilmington (L. Steele-Moore); Clarion Health Methodist Hospital, Indianapolis, Ind. (G. Denys); Henry Ford Hospital (C. Staley); Summa Health System, Akron, Ohio (J. R. Dipersio); Good Samaritan Regional Medical Center (M. Saubolle); Denver General Hospital, Denver, Colo. (M. L. Wilson); University of New Mexico Hospital, Albuquerque, (G. D. Overturf); University of Illinois at Chicago, (P. C. Schreckenberger); University of Iowa Hospitals and Clinics, Iowa City (R. N. Jones); Creighton University, Omaha, Nebr. (S. Cavalieri); Froedtert Memorial Lutheran Hospital-East, Milwaukee, Wis. (S. Kehl); Boston VAMC, Boston, Mass. (S. Brecher); Columbia Presbyterian Medical

Center, New York, N.Y. (P. Della-Latta); Long Island Jewish Medical Center, New Hyde Park, N.Y. (H. Isenberg); Strong Memorial Hospital, Rochester, N.Y. (D. Hardy); Kaiser Regional Laboratory, Berkeley, Calif. (J. Fusco); Sacred Heart Medical Center, Spokane, Wash. (M. Hoffmann); University of Washington Medical Center, Seattle (S. Swanzy); Barnes-Jewish Hospital, St. Louis, Mo. (P. R. Murray); Parkland Health & Hospital System, Dallas, Tex. (P. Southern); The University of Texas Medical School, Houston (A. Wanger); University of Texas Medical Branch at Galveston (B. Reisner); University of Louisville Hospital, Louisville, Ky. (J. Snyder); University of Mississippi Medical Center, Jackson (J. Humphries); Carolinas Medical Center, Charlotte, N.C. (S. Jenkins); University of Virginia Medical Center, Charlottesville (K. Hazen); University of Alberta Hospital, Edmonton, Alberta, Canada (R. Rennie); Health Sciences Centre, Winnipeg, Manitoba, Canada (D. Hoban); Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada (K. Forward); Ottawa General Hospital, Ottawa, Ontario, Canada (B. Toye); Royal Victoria Hospital, Montreal, Quebec, Canada (H. Robson); Microbiology Laboratory C.E.M.I.C., Buenos Aires, Argentina (J. Smayvsky); Hospital San Lucas and Olivos Community Hospital, Buenos Aires, Argentina (J. M. Casellas and G. Tome); Lamina LTDA, Rio de Janeiro, Brazil (J. L. M. Sampaio); Unidad de Microbiología Oriente, Santiago, Chile (V. Prado); Hospital Clinico Universidad Católica, Santiago, Chile (E. Palavecino); Corporación para Investigaciónes Biológicas, Medellín, Colombia, (J. A. Robledo); Instituto Nacional de la Nutrición, Mexico City, Mexico (J. S. Osornio); Laboratorio Medico Santa Luzia, Florianopolis, Brazil (C. Zoccoli); Instituto DE Doencas Infecciosas-IDIPA, Sao Paulo, Brazil (H. S. Sader); Centro Medico de Caracas, San Bernadino, Caracas, Venezuela (M. Guzman); and the Hospital Maciel, Montevideo, Uruguay (H. Bagnulo).

This study was supported by a research and educational grant from Bristol-Myers Squibb Company.

REFERENCES

1. **Bartroli, J., E. Turmo, and M. Alguero.** 1998. New azole antifungals. 3. Synthesis and antifungal activity of 3-substituted-4(3H)-quinozolinones. J. Med. Chem. **41:**1868–1882.
2. **Espinel-Ingroff, A.** 1998. Evaluation of antifungal susceptibility testing parameters for amphotericin B, itraconazole, voriconazole, SCH56592, and BMS-207147 against *Aspergillus* spp., abstr. J-7, p. 452. *In* Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
3. **Espinel-Ingroff, A., A. Palacio, and A. Carrillo-Munoz.** 1998. In vitro activity of the new triazole BMS-207147 against *Aspergillus* spp., *Candida* spp., and emerging mold pathogens: a comparative study, abstr. F-154, p. 271. *In* Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
4. **Fung-Tomc, J. C., E. Huczko, B. Minassian, and D. P. Bonner.** 1998. In vitro activity of a new oral triazole, BMS-207147 (ER-30346). Antimicrob. Agents Chemother. **42:**313–318.
5. **Hata, K., J. Kimura, H. Miki, T. Toyosawa, M. Moriyama, and K. Katsu.** 1996. Efficacy of ER-30346, a novel oral triazole antifungal agent, in experimental models of aspergillosis, candidiasis, and cryptococcosis. Antimicrob. Agents Chemother. **40:**2243–2247.
6. **Hata, K., J. Kimura, H. Miki, T. Toyosawa, T. Nakamura, and K. Katsu.** 1996. In vitro and in vivo antifungal activities of ER-30346, a novel oral triazole with a broad antifungal spectrum. Antimicrob. Agents Chemother. **40:**2237–2242.
7. **National Committee for Clinical Laboratory Standards.** 1997. Reference method for broth dilution antifungal susceptibility testing of yeast. Approved standard M27-A. National Committee for Clinical Laboratory Standards, Wayne, Pa.
8. **Pfaller, M. A., S. A. Messer, R. J. Hollis, R. N. Jones, G. V. Doern, M. E. Brandt, and R. A. Hajjeh.** 1998. In vitro susceptibilities of *Candida* bloodstream isolates to the new triazole antifungal agents BMS-207147, Sch 56592, and voriconazole. Antimicrob. Agents Chemother. **42:**3242–3244.
9. **Pfaller, M. A., S. A. Messer, S. Gee, S. Joly, C. Pujol, D. J. Sullivan, D. C. Coleman, and D. R. Soll.** 1999. In vitro susceptibilities of *Candida dubliniensis* isolates tested against the new triazole and echinocandin antifungal agents. J. Clin. Microbiol. **37:**870–872.
10. **Rex, J. H., M. A. Pfaller, J. N. Galgiani, M. S. Bartlett, A. Espinel-Ingroff, M. A. Ghannoum, M. Lancaster, F. C. Odds, M. G. Rinaldi, T. J. Walsh, and A. L. Barry for The Subcommittee on Antifungal Susceptibility Testing of The National Committee for Clinical Microbiology Standards.** 1997. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and *Candida* infections. Clin. Infect. Dis. **24:**235–247.
11. **Shock, K., S. Marino, T. Baumgartner, and V. Andriole.** 1998. Efficacy of a new triazole, BMS-207147, in a model of invasive aspergillosis in immunosuppressed, neutropenic rabbits, abstr. J-54, p. 466. *In* Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
12. **Tsuruoka, A., Y. Kaku, H. Kakinuma, M. Yanagisawa, K. Nara, and T. Naito.** 1998. Synthesis and antifungal activity of novel thiazole-containing triazole antifungals. II. Optically active ER-30346 and its derivatives. Chem. Pharm. Bull. **46:**623–630.