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Response to Antifungal Therapy by Human Immunodeficiency Virus-Infected Patients with Disseminated *Penicillium marneffei* Infections and In Vitro Susceptibilities of Isolates from Clinical Specimens

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Eighty-six patients with laboratory evidence of human immunodeficiency virus infection presented to Chiang Mai University Hospital in Chiang Mai, Thailand, between 1 June 1990 and 30 June 1992 with systemic infection caused by the dimorphic fungus *Penicillium marneffei*. Thirty isolates of *P. marneffei* from clinical specimens from these patients were tested for their in vitro susceptibilities to amphotericin B, 5-fluorocytosine, miconazole, ketoconazole, itraconazole, and fluconazole. *P. marneffei* was highly susceptible to miconazole, itraconazole, ketoconazole, and 5-fluorocytosine. Amphotericin B showed intermediate antifungal activity, while fluconazole was the least active; some strains of the fungus were resistant to fluconazole. The clinical and microbiological responses correlated with the overall patterns of in vitro susceptibility to the azoles, whereas results with amphotericin B were more difficult to assess. Antibiotic failures of initial therapy occurred in 8 of 35 (22.8%) patients treated with amphotericin B, 3 of 12 (25%) patients treated with itraconazole, and 7 of 11 (63.6%) patients treated with fluconazole. Itraconazole or ketoconazole should be considered to be the drug of first choice in the treatment of mild to moderately severe *P. marneffei* infection. Parenteral therapy with amphotericin B may be required for seriously ill patients. Since at least 12 patients who responded to initial therapy relapsed within 6 months regardless of initial antifungal therapy, maintenance oral therapy with itraconazole or ketoconazole may be necessary.

Penicillium marneffei has been a rare fungal pathogen of humans, responsible for disseminated opportunistic infection in patients. Infections with this organism have recently been reported for patients infected with the human immunodeficiency virus (HIV), especially in Southeast Asia and Southern China (15–18). The number of patients with this systemic mycosis presenting to hospitals or clinics in areas in which this organism is endemic has increased dramatically in recent years (5, 8–10, 15–18). Data on the in vitro susceptibility of *P. marneffei* to antifungal agents and clinical or microbiological responses to therapy are very limited. In one study, 10 stock strains from a repository culture collection were tested for their in vitro sensitivities to antifungal agents (11). These strains were most sensitive to itraconazole (ITZ) and miconazole (MCZ) and had intermediate sensitivities to amphotericin B (AMB) and 5-fluorocytosine (5FC). In this communication, we report the in vitro susceptibility test results for 30 *P. marneffei* isolates from HIV-infected patients who presented with disseminated *P. marneffei* infections. In addition, we describe the clinical and microbiological responses to antifungal therapy of 80 consecutive patients with disseminated *P. marneffei* infections in order to provide a clinical correlation to the in vitro data.

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MATERIALS AND METHODS

Patients. All HIV-infected patients seen at Chiang Mai University Hospital between 1 June 1990 and 30 June 1992 who presented with culture-proven disseminated *P. marneffei* infections were included in this study. The diagnosis of HIV infection was made if the patient was repeatedly reactive to HIV by enzyme-linked immunosorbent assay (ELISA) and gel particle agglutination tests. Western blot (immunoblot) assays were not done routinely on these patients. However, each patient was repeatedly reactive to ELISAs for HIV antibody with commercially available reagents from at least two different manufacturers. *P. marneffei* infection was diagnosed by isolation of the fungus from a clinical specimen from a patient with clinical evidence of an infection.

Isolation of *P. marneffei*. Isolation of *P. marneffei* was done by incubating the clinical specimen at 25°C on Sabouraud dextrose agar. The isolate, which was the mycelial form of the organism, was subcultured on brain heart infusion agar and incubated at 37°C to yield the yeast phase. Characterization of *P. marneffei* was determined by the appearance of the fungal colonies and microscopic examination (15). In its mycelial form, the colony was downy and grayish pink and produced a soluble red pigment that diffused into the medium. Seen under a microscope, the conidiophores consisted of basal stripes with terminal verticils of three to five metulae. Some metulae bore four to seven phialides that produced conidia in chains. The colony

of its yeast form appeared white to tan and soft or convoluted. Yeast cells characteristic of *P. marneffei* were unicellular, pleomorphic, and ellipsoidal to rectangular. They divided by binary fission and not by budding.

Susceptibility tests. (i) Preparation of inocula. *Candida albicans* Squibb 1539 served as the control strain for bioassays involving AMB and 5FC, whereas *Torulopsis glabrata* M128-85 served as the control strain for bioassays involving azoles. For each susceptibility assay, control cultures of *C. albicans* were grown for 48 h at 37°C on P-K fungal agar (tryptone [Difco, Detroit, Mich.], 5 g; yeast extract [Difco], 3 g; malt extract [Difco], 3 g; glucose [Difco], 10 g; agar [Difco], 15 g; distilled water, 1.0 liter) slants, whereas control cultures of *T. glabrata* were grown on yeast morphology agar (Difco) slants. The drug susceptibilities of the *P. marneffei* isolates were determined from cultures grown for 3 to 7 days on cornmeal agar (Difco) slants containing 1% (vol/vol) Tween 80 (Difco). Inocula were prepared by gently resuspending the growth from one agar slant in sterile 0.85% saline contained in a round glass cuvette (19 by 150 mm; Fisher Scientific, Pittsburgh, Pa.). The turbidity of the suspension was adjusted with a Spectronic 21 (Bausch and Lomb, Rochester, N.Y.) spectrophotometer as follows: for AMB bioassays, 50% transmission at 650 nm (approximately 4×10^6 CFU of *C. albicans* per ml); for 5FC bioassays, 85% transmission at 530 nm (approximately 1.8×10^5 CFU of *C. albicans* per ml); and for azole bioassays, 85% transmission at 530 nm with a subsequent dilution by 1:20 (approximately 2.4×10^4 CFU of *T. glabrata* per ml).

(ii) In vitro bioassay for antifungal activity of AMB. The MIC of AMB for a particular isolate was determined with a modification (2, 19) of the macrobroth dilution bioassay described by Littman et al. (7). Briefly, AMB powder (Squibb Institute for Medical Research, Princeton, N.J.) was dissolved in dimethyl sulfoxide to an initial concentration of 2,000 μg/ml and then diluted in Penassay broth (Difco) to make a working stock solution containing 4 μg of AMB per ml. For each isolate to be assayed, serial twofold dilutions were made in Penassay broth with 1 ml of stock solution. This resulted in a series of tubes containing 1 ml of test medium ranging in AMB concentration from 4 to 0.0019 μg/ml. To each tube, including a growth (no drug) control, 50 μl of inoculum was added. An uninoculated tube containing drug and test medium was also included as a sterility control. All assay tubes were incubated at 37°C until the growth control exhibited significant growth. For the control isolate, *C. albicans* Squibb 1539, this occurred at 18 to 24 h following inoculation, whereas *P. marneffei* isolates exhibited significant growth after 3 to 6 days of incubation. The MIC was determined as the lowest concentration of AMB that completely inhibited growth, i.e., no turbidity observed. An isolate for which the MIC was ≥2 μg/ml was considered resistant to AMB.

(iii) In vitro bioassay for antifungal activity of 5FC. The MIC of 5FC for a particular isolate was determined with a modification of the macrobroth dilution bioassay described by Shadomy (12). Briefly, 5FC (Hoffmann-La Roche, Nutley, N.J.) was dissolved in sterile 0.85% saline to a concentration of 10,000 μg/ml and then filter sterilized. This stock solution was further diluted in a modified yeast nitrogen base (YNB) medium to a working concentration of 250 μg/ml. A 10× solution of YNB contains YNB (67.0 g/liter; Difco), L-asparagine (15.0 g/liter; Difco), and Bacto Dextrose (100.0 g/liter; Difco), adjusted to pH 7.2. For each isolate to be assayed, serial twofold dilutions were made in 1× YNB with 1 ml from the working drug solution. This resulted in a series of tubes containing 1 ml of test medium ranging in 5FC concentration from 250 to 0.015 μg/ml. To each tube, including a growth (no drug) control, 50 μl of inoculum was added. An uninoculated tube containing drug and test medium was also included as a sterility control. All assay tubes were incubated at 37°C until the growth control exhibited significant growth. For the control isolate, *C. albicans* Squibb 1539, this was 36 to 48 h following inoculation, whereas *P. marneffei* isolates exhibited significant growth after 3 to 6 days of incubation. The MIC was determined as the lowest concentration of 5FC that completely inhibited growth, i.e., no turbidity observed. An isolate for which the MIC was ≥62.5 μg/ml was considered resistant to 5FC.

(iv) In vitro bioassay for antifungal activity of azoles. The MIC of an azole compound was determined with the bioassay described by Gordon et al. (3). This assay employs a semisolid growth medium distributed in 24-well microtiter plates. Briefly, the imidazoles, ketoconazole (KTZ) and MCZ (Janssen Pharmaceutica, Beerse, Belgium), and the triazoles, ITZ (Janssen Pharmaceutica) and fluconazole (FLZ; Pfizer Central Research, Sandwich, England), were dissolved in dimethyl sulfoxide to a concentration of 4,000 μg/ml. Each stock solution was further diluted 1:10 in sterile water, and this dilution was followed by serial twofold dilutions in water to provide concentrations from 400 to 0.02 μg/ml. A total of 1 ml of these stock solutions was mixed with 9 ml of molten semisolid agar base medium and then distributed in 1-ml portions to wells in a 24-well microtiter plate and allowed to solidify. The final drug concentrations ranged from 40 to 0.002 μg/ml. The semisolid agar base medium consists of 15 ml of 10× YNB, 135 ml of 0.01 M sodium phosphate buffer (pH 7.0), and 50 ml of molten 2% Bacto Agar (Difco). To each well, including a growth (no drug) control, 10 μl of inoculum was added. The assay plates were incubated at 37°C until the growth control exhibited significant growth. For the control isolate, *T. glabrata* M128-85, this was 18 to 24 h following inoculation, whereas *P. marneffei* isolates exhibited significant growth after 3 to 6 days of incubation. The MIC was defined as the lowest concentration of azole that completely inhibited growth, i.e., no colonies observed. An isolate for which the MIC was ≥10 μg/ml was considered resistant to the azole being studied.

Treatment and outcome of patients. Patients whose diagnosis was made before their death or discharge from the hospital were treated with AMB, ITZ, or FLZ. Selection of an antifungal agent for therapy was based on the decision of the attending physician and infectious disease consultant. The results of susceptibility tests were not available at the time of the onset of treatment. AMB was given at a dose of 0.3 to 0.6 mg/kg of body weight intravenously daily for 6 to 8 weeks. ITZ was given in a daily dose of 400 mg orally in two divided doses for 8 to 12 weeks. FLZ was given as 400 mg orally daily in two divided doses for 8 weeks. Evaluation of clinical improvement was performed at regular intervals. Blood cultures were taken intermittently every 1 to 2 weeks until the patient was culture negative or until the end of treatment.

The patients in this series presented with systemic signs and symptoms of disseminated infection. Most were febrile and had papulonecrotic skin lesions. All were culture positive for *P. marneffei*. Blood cultures were positive for 59 (75.6%) of the 78 patients who were cultured prior to antifungal therapy; several of those without positive blood cultures had bacteremia which could have obscured a positive culture for *P. marneffei*. Others had positive cultures from bone marrow, skin, or other sites. A detailed descrip-

TABLE 1. Clinical and microbiological responses to antifungal therapeutic agents for 80 patients with disseminated *P. marneffei* infections in Chiang Mai, Thailand[a]

Treatment	No. of patients	No. of patients with clinical and microbiological outcome[b]:		
		Response	Failure	Unknown
None	12	0	9 (100%)	3
AMB	39	27 (77.2%)	8 (22.8%)	4
ITZ	16	9 (75%)	3 (25%)	4
FLZ	13	4 (36.4%)	7 (63.6%)	2

[a] For the outcome of FLZ versus either AMB or ITZ, Fisher's exact two-tailed *P* value = 0.02.

[b] Percentages of the total are shown in parentheses for responses among patients whose outcomes could be determined.

tion of the clinical features of these patients will be reported elsewhere.

The outcome of treatment was classified as follows: (i) response, which was defined as resolution of fever, skin lesions, and other symptoms and signs of *P. marneffei* infection and absence of fungal growth in the follow-up blood cultures; (ii) failure, which was defined as no clinical improvement or deterioration of symptoms and signs of *P. marneffei* infection and/or persistence of fungemia during the course of treatment; and (iii) relapse, which was defined as recurrence of symptoms and signs of *P. marneffei* infection with isolation of the fungus after an initial clinical and microbiological response.

RESULTS

Clinical and microbiological response to treatment. Eighty-seven patients with *P. marneffei* infection were diagnosed at Chiang Mai University Hospital in the interval from 1 June 1990 to 30 June 1992. All except one of these patients were HIV type 1 (HIV-1) antibody positive. Six HIV-1-infected patients had incomplete medical records, and so their responses could not be evaluated. In this communication, we are reporting the clinical and microbiological responses to therapy of the 80 HIV-1-infected patients with *P. marneffei* infections who were evaluable (Table 1).

Of 12 patients who had not received antifungal therapy, 9 were known to have died soon after the diagnosis of *P. marneffei* infection was made. The other three left the hospital prior to therapy, and the final outcome is unknown.

AMB therapy was given to 39 patients. Of patients who received 4 weeks or more of AMB therapy, 27 (69%) responded with both resolution of clinical symptoms and sterilization of fungal blood cultures. Isolates from seven patients who responded to AMB were tested for their in vitro susceptibilities to the drug; two strains required MICs of 1.0 μg/ml, three required MICs of 2.0 μg/ml, and two required MICs of 4.0 μg/ml. Six patients who received AMB died during their hospitalizations; five of them died with active *P. marneffei* infection during AMB treatment, and one died from another cause after an initial response to treatment. For one of the patients who failed AMB therapy, the MIC for the isolate was 2.0 μg/ml. Among those patients who initially responded to AMB, four relapsed with active *P. marneffei* infection at 1, 3, 4, and 6 months after completion of therapy. Among three AMB-treated patients who relapsed, the MICs of AMB were 0.5, 2.0, and 4.0 μg/ml. The long-term status of the other patients who responded is not known. None of those originally treated with AMB were also treated with other antifungal agents during their initial hospitalizations or after their discharge.

ITZ was used for the initial therapy of 16 patients. Of these, nine (56%) patients responded clinically and microbiologically; five died, three of whom still had active *P. marneffei* infections at the time of their deaths. One patient who died had been switched to AMB because he developed cryptococcal meningitis. Another patient developed cerebral toxoplasmosis and was started on pyrimethamine and sulfadiazine. He subsequently died; at the time of his death, there was no evidence of active *P. marneffei* infection. Among those who responded to ITZ therapy, five relapses occurred; two patients relapsed after 1 month, two relapsed after 3 months, and one relapsed at 4 months after the completion of treatment.

Among the 13 patients treated with FLZ, 4 (31%) had clinical and microbiological responses. Four patients had resolution of their fever and skin lesions despite continued positivity of their fungal blood cultures while on FLZ. Five patients died with active *P. marneffei* infections; one of these had been treated for only 3 days, and the other four had received at least 2 weeks of therapy at the time of their deaths. The MICs of FLZ for two of those who died were 5.0 and 10.0 μg/ml. Among those responding initially, three relapsed, one each after 3 months, 5 months, and 6 months. Two patients left the hospital shortly after therapy was started and were unavailable for follow-up.

Follow-up after hospital discharge was successful in only some of the 40 patients who responded to the initial therapy with antifungal agents. Of those for whom follow-up information was available, 12 are known to have relapsed; 4 of these had been treated with AMB, 5 had been treated with ITZ, and 3 had been treated with FLZ.

In vitro susceptibility data. The results of the in vitro susceptibility tests of the 30 isolates of *P. marneffei* are presented in Table 2. With the azole antifungal agents, all isolates were highly susceptible to ITZ, KTZ, and MCZ within very narrow ranges of MICs. FLZ was not as active; 73% of the strains were either borderline susceptible or resistant, with a range of MICs from 0.313 to 20 μg/ml. Although many strains (59%) were sensitive to AMB, 41% were only moderately sensitive or could be considered resistant. All isolates were highly susceptible to 5FC, with a range of MICs from ≤0.015 to 0.9 μg/ml.

For the control strain of *C. albicans* (Squibb 1539), the MIC of AMB was 0.0625 μg/ml and that of 5FC was 0.12 μg/ml. The MICs of MCZ, KTZ, ITZ, and FLZ for *T. glabrata* (M128-85) were 0.625, 0.625, 2.5, and 40 μg/ml, respectively. The MICs for the control strains were measured in order to standardize the in vitro assay system. The MICs for these control strains have been consistent for over 2,000 collective assays during the past 20 years and have been used for comparison of susceptibilities of a variety of other fungal species. Fungi often considered to be resistant to certain antifungal agents (e.g., *Aspergillus* spp. and FLZ and *Pseudallescheria boydii* and AMB) consistently required MICs far greater than those for the control isolates noted above. Conversely, susceptible isolates (e.g., *Aspergillus* spp. and ITZ) typically required MICs nearly equal to or less than those for the control isolates.

DISCUSSION

There is very little information on the in vitro susceptibility and the clinical and microbiological responses to therapy of *P. marneffei*, since until recently disseminated infections

TABLE 2. In vitro susceptibility of *P. marneffei* isolates

Antifungal agent	No. of isolates tested	MIC (μg/ml)	No. of isolates with that MIC	MIC geometric mean (μg/ml)
FLZ	30	≤0.313	1	7.937
		5	7	
		10	20	
		20	2	
ITZ	28	≤0.002	1	0.009
		0.004	5	
		0.009	18	
		0.019	2	
		0.039	1	
		0.078	1	
KTZ	29	≤0.002	7	0.027
		0.004	1	
		0.009	0	
		0.019	1	
		0.039	1	
		0.078	19	
MCZ	29	≤0.002	27	0.001
		0.004	1	
		0.156	1	
AMB	29	0.25	4	0.976
		0.5	8	
		1.0	5	
		2.0	9	
		4.0	3	
5FC	29	≤0.015	1	0.248
		0.12	3	
		0.23	16	
		0.46	8	
		0.9	1	

with this organism have been very rare. In the first reported case of natural human infection caused by *P. marneffei*, the MIC of AMB was 0.78 μg/ml (1). Jayanetra et al. studied the in vitro sensitivities of three isolates from Thailand and found that the MICs of AMB were 1.56, 0.78, and 3.12 μg/ml and that those of 5FC were 12.5, 12.5, and 6.25 μg/ml (6). So et al. reported the MIC of KTZ for their one isolate to be 1 μg/ml (14). Sekhon et al. tested 10 strains of *P. marneffei* from a repository collection at the Centers for Disease Control for their sensitivities to various antifungal agents (11). MCZ and ITZ had good activity against the fungus, with MICs of less than 0.195 μg/ml for all these isolates. The MICs of KTZ ranged from less than 0.195 to 0.39 mg/ml. The MICs of AMB ranged from less than 0.195 to 1.56 μg/ml, while those of FLZ varied from 0.195 to 100 μg/ml.

The results of in vitro susceptibility tests of the 30 *P. marneffei* isolates from our patients indicate that *P. marneffei* was highly sensitive to the azole compounds, i.e., MCZ, ITZ, and KTZ. However, 73% of strains were resistant to FLZ. AMB had an intermediate activity against the organism. The median MIC of AMB was 1.0 μg/ml, with a range of 0.25 to 4.0 μg/ml. For three of our isolates, the MICs were above 2.5 μg/ml, which suggests that the isolates might not be inhibited readily by therapy with this drug (13).

Our study is the first report of the in vitro susceptibilities and clinical and microbiological responses to therapy with several antifungal agents of a large number of patients with *P. marneffei* infection in northern Thailand. Patients treated with ITZ or AMB responded somewhat better than those treated with FLZ, particularly in their success in resolving positive blood cultures. Despite the intermediate inhibitory activity of AMB for some strains of *P. marneffei*, patients improved when treated with high doses of the drug administered intravenously. Some disparity between in vitro susceptibilities and in vivo responses to AMB has been reported previously for other fungal pathogens (13). Also, treatment of patients with oral FLZ in doses of 400 mg/day has yielded peak concentrations in plasma of 18.9 μg/ml (4). These data may help to explain the satisfactory responses to therapy in some of our patients, despite only moderate in vitro sensitivities. While only a few of our patients had infections of the central nervous system with *P. marneffei*, treatment with AMB for such infections would be indicated. Patients who also have cryptococcal infections of the nervous system should probably be treated with AMB. However, for mild to moderate infections with *P. marneffei* in patients who could be given oral therapy, the use of KTZ and ITZ would seem to be preferable. Our data on clinical responses should be interpreted with caution, however. Patients were not randomly assigned to receive therapy with the various antimicrobial agents being reported. Since the decisions for therapy were made by several clinicians on the basis of their clinical judgment, those receiving intravenous treatment with AMB could have been more seriously ill. However, none of our patients were treated with multiple antifungal antibiotics. Therefore, the microbiological and clinical responses to therapy observed likely signify some therapeutic efficacy of the drug being given. It seems likely that the degree of compromise of the immune system of the patient may have had some effect on the success of antifungal therapy, as well as on the risk of infection and later relapse with *P. marneffei* after therapy.

For patients who are seriously ill, therapy could be started with intravenous AMB. This could be followed by oral therapy with ITZ or KTZ until cultures are negative and clinical findings have resolved. Since several patients relapsed within weeks to months after the cessation of antifungal therapy, it would appear likely that long-term secondary prophylaxis might be needed to prevent reoccurrence of *P. marneffei* infection, especially in patients with HIV infection.

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