

A CONTROLLED TRIAL OF ITRACONAZOLE TO PREVENT RELAPSE OF *PENICILLIUM MARNEFFEI* INFECTION IN PATIENTS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

KHUANCHAI SUPPARATPINYO, M.D., JOSEPH PERRIENS, M.D., KENRAD E. NELSON, M.D., AND THIRA SIRISANTHANA, M.D.

ABSTRACT

Background In Southeast Asia, disseminated infection with *Penicillium marneffeii* is common among patients with human immunodeficiency virus (HIV) infection. Even after successful primary treatment, the relapse rate for this potentially fatal systemic fungal infection is about 50 percent.

Methods We conducted a double-blind trial in Thailand to evaluate itraconazole as secondary prophylaxis against *P. marneffeii* infection in patients with the acquired immunodeficiency syndrome (AIDS) who were in complete remission after treatment for culture-proved *P. marneffeii* infection. The patients were randomly assigned to receive either oral itraconazole (200 mg daily) or placebo as maintenance therapy.

Results Of the 72 HIV-infected patients who completed initial treatment for *P. marneffeii* infection, 71 were enrolled in the maintenance study. None of the 36 patients assigned to itraconazole had a relapse of *P. marneffeii* infection within one year, whereas 20 of the 35 patients assigned to placebo (57 percent) had relapses ($P < 0.001$). Among the 20 patients who had relapses, *P. marneffeii* was cultured from blood (15 patients), lymph-node tissue (3 patients), skin (3 patients), and sputum (1 patient). The median time to relapse was 24 weeks after the completion of the initial treatment (95 percent confidence interval, 19.0 to 36.1). Survival and toxic effects were similar in the two groups.

Conclusions In patients infected with HIV who have completed successful primary treatment of *P. marneffeii* infection, secondary prophylaxis with oral itraconazole is well tolerated and prevents relapses of this opportunistic infection. (N Engl J Med 1998;339:1739-43.)

©1998, Massachusetts Medical Society.

PENICILLIUM MARNEFFEII is a dimorphic fungus that can produce systemic mycosis in humans. This fungal infection is most commonly found in Southeast Asian countries and Hong Kong and other parts of southern China.¹ The recent increase in the number of cases, particularly in Thailand, has occurred exclusively in patients infected with the human immunodeficiency virus (HIV).² In northern Thailand, this potentially fatal fungal infection is the third most common opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS), accounting for 15 to 20 percent of all AIDS-related illness. Tuberculosis is the most prevalent infection,

followed by cryptococcosis.³ *P. marneffeii* infection in HIV-infected patients is a serious systemic disease, with fever, anemia, weight loss, and skin lesions as the major manifestations.² With the further spread of HIV in Asia, disseminated *P. marneffeii* infection is likely to increase in importance.

A previous study in Chiang Mai, Thailand, showed that 50 percent of patients with AIDS who had been successfully treated for *P. marneffeii* infection had a relapse within six months after the discontinuation of antifungal therapy.⁴ There has been no study of maintenance treatment to prevent relapse in patients with AIDS who have *P. marneffeii* infection. We conducted a study to evaluate the efficacy and safety of maintenance therapy with itraconazole in patients with HIV infection who had been successfully treated for disseminated *P. marneffeii* infection.

METHODS

Study Design

A placebo-controlled, double-blind, randomized trial was conducted to evaluate the efficacy and safety of oral itraconazole at a dose of 200 mg once daily after the successful completion of standard antifungal therapy for disseminated, culture-proved *P. marneffeii* infection. A placebo capsule, which was identical in appearance to the study drug, was used as a control. The study design was reviewed by the World Health Organization Global Program on AIDS and was approved by the Human Experimentation Committee of Chiang Mai University before the start of the trial. All patients enrolled in the study gave their written informed consent. All were adults with documented HIV infection who had completed a standard course of treatment for an episode of culture-proved *P. marneffeii* infection and who had Karnofsky scores above 70 (normal activity possible with effort).

The standard antifungal therapy consisted of 2 weeks of parenteral amphotericin B at a dose of 0.6 mg per kilogram of body weight per day; this was followed by oral itraconazole at a dose of 200 mg twice daily for 10 weeks. Success of the primary treatment was confirmed by complete resolution of clinical symptoms and signs of disseminated *P. marneffeii* infection and negative blood cultures for *P. marneffeii* at the end of the 2nd, 6th, 10th, and 12th weeks of therapy. Randomization was performed after the success of the initial treatment had been confirmed.

Conditions that made patients ineligible for the study were pregnancy or breast-feeding; a history of another systemic mycosis; a malignant neoplastic disease; a history of intolerance to triazole compounds; concurrent treatment with other systemic antifungal agents (ketoconazole, fluconazole, amphotericin B, or

From the Department of Medicine, Chiang Mai University, Chiang Mai, Thailand (K.S., T.S.); the Joint United Nations Program on HIV/AIDS, Geneva (J.P.); and the Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore (K.E.N.). Address reprint requests to Dr. Sirisanthana at the Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

flucytosine); concurrent treatment with phenytoin, barbiturates, carbamazepine, rifampin, rifabutin, histamine H₂-receptor blockers, antacids, corticosteroids, cytotoxic chemotherapeutic agents, or investigational drugs; serum creatinine levels above 2.0 mg per deciliter (176.8 μmol per liter); and serum aminotransferase levels more than five times the upper limit of normal.

The patients were randomly assigned to receive itraconazole or placebo in a 1:1 ratio. Randomization was performed by the drug manufacturer in Belgium with a computerized randomization list based on a block size of 10. The medication was packaged in sequentially numbered boxes that were dispensed to successive patients. All the patients in both study groups received two single-strength tablets of trimethoprim-sulfamethoxazole orally once daily for prophylaxis against *Pneumocystis carinii* pneumonia throughout the study period. The study medications were continued until the end point, which was defined as the completion of 44 weeks of follow-up, a relapse of *P. marneffei* infection at any site, the occurrence of any mycosis that required systemic use of antifungal agents, serious adverse events due to the study drug, death, or withdrawal of consent. Topical therapy for cutaneous or mucosal fungal infection was permitted.

Evaluation of Patients

The patients were scheduled for follow-up visits every four weeks. At each visit, all the patients were evaluated by a history taking and complete physical examination, complete blood counts and blood chemical studies, and blood cultures for fungus. Blood culture was performed by incubating 5 ml of blood in 50 ml of trypticase soy broth at 37°C. The broth was subcultured on Sabouraud's dextrose agar at 25°C on the 3rd, 7th, and 14th days. The isolate that was visible within two to three days of incubation was, in turn, subcultured on brain-heart infusion agar and incubated at 37°C. Positive cultures for *P. marneffei* were characterized by a dimorphic penicillium species that grew as a mold at 25°C and as a yeast at 37°C. Other mycologic characteristics of *P. marneffei* have been described previously.⁵ Cultures of other specimens, such as sputum, cerebrospinal fluid, and lymph-node tissue, were performed if there was any clinical indication. The titer of cryptococcal antigen was determined whenever a sample of cerebrospinal fluid was obtained for culture.

None of the patients or study personnel were aware of the treatment assignments of the patients. Patients who had relapses of *P. marneffei* infection were treated with standard antifungal therapy, followed by open-label itraconazole for secondary prophylaxis. Abnormal laboratory values were defined as follows: a hemoglobin level of 10.5 g per deciliter (6.52 mmol per liter) or less; a white-cell count of less than 4000 per cubic millimeter; and alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase values more than two times the upper limit of normal.

Compliance with study treatment was evaluated by comparing the number of tablets returned at each visit with the number given out at the previous visit. If a patient missed a follow-up visit, one of the study personnel visited the patient at home and scheduled a new visit. Patients who missed two consecutive appointments were considered lost to follow-up.

Statistical Analysis

We determined that with 32 subjects in each treatment group, the study would have an 80 percent power to detect a 70 percent reduction in the risk of relapse in the active-treatment group (corresponding to a 15 percent rate of relapse within six months, assuming that the placebo group had a 50 percent rate of relapse within six months), with a two-sided significance level of 0.05. To account for a projected 20 percent loss to follow-up, we planned to enroll 80 patients in the study. We planned to have an interim analysis by a data and safety monitoring board of the World Health Organization Global Program on AIDS when 32 patient-years of follow-up were reached. The study was to be stopped if the difference in relapse rates between the study groups was significant at a P value of 0.01 or less.

The analysis was performed on an intention-to-treat basis. Comparison of base-line demographic and clinical data was made with Student's t-test or Fisher's exact test, as appropriate. The end points (time to relapse and time to death) were analyzed with a Kaplan-Meier life-table method and compared by a log-rank test. The incidence of adverse events was calculated as the number of events divided by the person-time, with each patient contributing to the person-time until a first event or last observation. The distribution of the natural log of the rate ratio (relative risk) was assumed to be normal and was used to compare treatment groups and estimate corresponding 95 percent confidence intervals.⁶ The P values used in all analyses were two-sided.

RESULTS

Patients

From October 1993 to January 1996, 74 HIV-infected patients were given a diagnosis of disseminated *P. marneffei* infection at Chiang Mai University Hospital and received the standard primary antifungal treatment. One patient was lost to follow-up before the end of the 12-week period of primary therapy, and one patient died of sepsis at week 10. Of the 72 patients who successfully completed the primary treatment, 71 were enrolled in the maintenance-treatment study. One patient was not enrolled because of poor compliance during the initial treatment period. Randomization began in January 1994. The study was discontinued on August 1, 1996, at the recommendation of the data and safety monitoring board after the interim analysis.

Of the 71 patients enrolled, 36 were randomly assigned to receive itraconazole, and 35 to receive placebo. All patients were included in the analysis. The overall rate of compliance with study treatment at each visit among those who returned for follow-up ranged from 93.5 percent to 100 percent in the itraconazole group and from 96.7 percent to 100 percent in the placebo group. Three patients in the itraconazole group stopped taking the medication before the study end points were reached. One was lost to follow-up after the 12th week, and another after the 28th week. In the third patient, pulmonary tuberculosis that required treatment with rifampin developed after the 20th week, and the patient was lost to follow-up after the 28th week.

Treatment with study drugs was stopped in six patients assigned to itraconazole and four assigned to placebo when the study was discontinued after the interim analysis. The six patients in the itraconazole group had been followed for 16, 20, 32, 36, 40, and 40 weeks after randomization. Those in the placebo group had been followed for 20, 20, 24, and 24 weeks. They were then treated with open-label itraconazole.

The clinical characteristics of patients in both treatment groups were similar at base line, except that those in the placebo group had a lower mean hemoglobin level (Table 1). At the start of induction therapy, *P. marneffei* was isolated from cultures of blood from 31 of 36 itraconazole recipients (86 per-

TABLE 1. CLINICAL CHARACTERISTICS OF 71 ENROLLED PATIENTS AT BASE LINE.*

| CHARACTERISTIC | ITRACONAZOLE (N=36) | PLACEBO (N=35) | P VALUE |
|--|---------------------|----------------|---------|
| Sex (M/F) | 33/3 | 28/7 | |
| Age (yr) | | | 0.72 |
| Mean | 29.7 | 29.5 | |
| Range | 19–49 | 19–49 | |
| Hemoglobin (g/dl) | | | 0.01 |
| Mean | 11.6 | 10.4 | |
| Range | 8.6–15.2 | 5.4–15.7 | |
| White-cell count (per mm ³) | | | 0.63 |
| Mean | 4586 | 4851 | |
| Range | 1400–9800 | 2200–11,200 | |
| Platelet count (×10 ⁻³ /mm ³) | | | 0.96 |
| Mean | 247 | 230 | |
| Range | 122–940 | 107–408 | |
| Creatinine (mg/dl) | | | 0.30 |
| Mean | 0.99 | 0.94 | |
| Range | 0.5–1.7 | 0.5–1.4 | |
| Aspartate aminotransferase (U/liter) | | | 0.51 |
| Mean | 43.8 | 51.1 | |
| Range | 12–157 | 14–191 | |
| Alanine aminotransferase (U/liter) | | | 0.77 |
| Mean | 42.3 | 41.6 | |
| Range | 9–213 | 9–112 | |
| Alkaline phosphatase (U/liter) | | | 0.26 |
| Mean | 115.4 | 152.7 | |
| Range | 60–205 | 47–617 | |
| Bilirubin (mg/dl) | | | 0.40 |
| Mean | 0.61 | 0.55 | |
| Range | 0.4–1.7 | 0.3–1.0 | |
| CD4+ cells (per mm ³) | | | 0.89 |
| Mean | 71.3 | 64.8 | |
| Range | 1–350 | 6–180 | |
| CD8+ cells (per mm ³) | | | 0.28 |
| Mean | 766.0 | 985.9 | |
| Range | 67–2120 | 143–3650 | |

*To convert values for hemoglobin to millimoles per liter, multiply by 0.6206. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

cent) and 32 of 35 placebo recipients (91 percent). *P. marneffeii* was isolated from cultures of skin from 21 itraconazole recipients (58 percent) and 18 placebo recipients (51 percent). All 71 patients had had successful induction therapy at the time of randomization. None of the patients in either group were receiving antiretroviral therapy at enrollment, and none were given antiretroviral therapy during the study.

Risk of Relapse

There were 20 relapses of *P. marneffeii* infection, all in the placebo group. Among the patients who had relapses, *P. marneffeii* was recovered from cultures of blood (15 patients), lymph node (3 patients), skin (3 patients), and sputum (1 patient). In two patients, the organism was isolated from cultures of both blood and skin. The median time to relapse was 24 weeks (95 percent confidence interval, 19.0

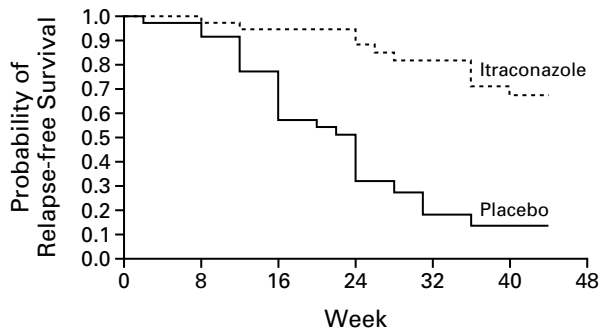


Figure 1. Proportion of Patients Who Survived and Remained Free from Relapse during Secondary Prophylaxis against Disseminated *Penicillium marneffeii* Infection.

to 36.1). The total number of person-weeks of follow-up was 1256 for the itraconazole group and 753.3 for the placebo group. The relapse rate in the placebo group was 2.6 per 100 person-weeks. Kaplan–Meier curves demonstrating the probability of relapse-free survival in the treatment groups are shown in Figure 1. The difference between the two groups was statistically significant (P<0.001).

Mortality and Incidence of Other Systemic Mycoses

Cryptococcosis developed in two patients, one in each treatment group. No other systemic fungal infections were reported.

Eleven patients (31 percent) in the itraconazole group and 15 (43 percent) in the placebo group died during the study. Three patients in the placebo group died while receiving antifungal therapy for a relapse of *P. marneffeii* infection. They died 3, 8, and 11 weeks after the relapse. The primary cause of death in these patients was believed to be *P. marneffeii* infection. One patient each from the placebo group died from tuberculous meningitis, disseminated cytomegalovirus infection, pneumocystis pneumonia, and bacterial sepsis. In the itraconazole group, one patient each died from cryptococcal meningitis, salmonella sepsis, bacterial pneumonia, bacterial sepsis, disseminated cytomegalovirus infection, lymphoma, and Guillain–Barré syndrome. The causes of death for the remaining eight patients in the placebo group and the four in the itraconazole group are not definitely known. None of these 12 patients had clinical evidence of *P. marneffeii* infection, and blood cultures performed before death were negative for *P. marneffeii*. Figure 2 shows the Kaplan–Meier survival curves. There was no significant difference between the two groups (P=0.27).

Adverse Events

Table 2 shows the incidence of adverse events in the itraconazole and placebo groups. The common

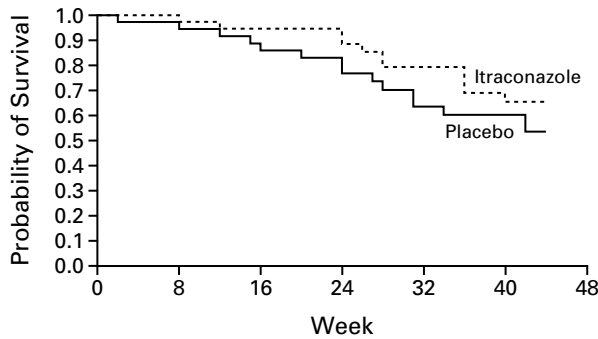


Figure 2. Proportion of Patients Who Survived during Secondary Prophylaxis against Disseminated *Penicillium marneffei* Infection.

adverse events included elevated alanine and aspartate aminotransferase and alkaline phosphatase levels, anemia, and leukopenia. The greatest difference between the groups was in elevated aspartate aminotransferase levels (4.5 per 100 person-weeks in the placebo group as compared with 2.1 per 100 person-weeks in the itraconazole group, $P=0.03$). However, given the numerous comparisons made, this difference may well be due to chance. There was no significant difference between the two groups in the incidence of other adverse events.

DISCUSSION

Disseminated *P. marneffei* infection is one of the most common opportunistic infections in HIV-infected patients in Southeast Asian countries and the southern part of China.¹ The incidence of this systemic mycosis continues to increase in parallel with the increasing number of cases of HIV infection in these areas.^{1-3,7-10} Many cases of *P. marneffei* mycosis have also been reported among visitors to Southeast

Asia from countries outside the region.¹¹⁻¹⁵ Patients infected with *P. marneffei* have a poor prognosis without treatment.² Although treatment with antifungal agents has improved the prognosis, the mortality rate from disseminated *P. marneffei* infection in patients with AIDS is still about 20 percent.¹⁶ In a study from Chiang Mai, the rate of relapse of *P. marneffei* was reported to be approximately 50 percent after the discontinuation of successful initial therapy.⁴

This controlled study demonstrates the efficacy and safety of secondary antifungal prophylaxis in patients who have been effectively treated for disseminated *P. marneffei* infection. To be certain that those in the study were both clinically and microbiologically free of the disease, we enrolled only patients who had received a standard regimen, and we used strict criteria for response to the primary treatment. Among candidate antifungal agents for maintenance therapy, parenteral amphotericin B is relatively toxic and inconvenient for long-term administration. A study of the in vitro sensitivity of *P. marneffei* isolates showed that the organism is sensitive to miconazole, itraconazole, and ketoconazole, whereas fluconazole is less active.¹⁶ Miconazole is available only in an intravenous preparation, and its toxicity is high. Itraconazole is a triazole compound with a broad antifungal spectrum, good pharmacokinetic properties, and relatively low toxicity. In our experience, this agent is effective and safe for the treatment of patients infected with HIV and *P. marneffei*.⁴ Although ketoconazole was found to be active in vitro, our clinical experience has shown that it is less active than itraconazole both for treatment and for the prevention of relapse. Furthermore, endocrinologic abnormalities and hepatotoxicity have been observed more frequently with ketoconazole.¹⁷ Therefore, we decided to conduct the trial with itraconazole. However, because ketoconazole is much less expensive

TABLE 2. ADVERSE EFFECTS DURING TREATMENT WITH ITRACONAZOLE OR PLACEBO.

| VARIABLE | ITRACONAZOLE | | PLACEBO | | P VALUE |
|-------------------------------------|----------------------------------|---------------------------------|----------------------------------|---------------------------------|---------|
| | EVENTS/ PATIENTS OBSERVED* | INCIDENCE/ 100 PERSON- WK | EVENTS/ PATIENTS OBSERVED* | INCIDENCE/ 100 PERSON- WK | |
| Clinical effects | | | | | |
| Rash | 1/36 | 0.0 | 1/35 | 0.1 | 0.70 |
| Exfoliative dermatitis | 1/36 | 0.1 | 2/35 | 0.3 | 0.33 |
| Effects on laboratory values | | | | | |
| Anemia | 17/30 | 2.0 | 10/28 | 2.2 | 0.82 |
| Elevated alanine aminotransferase | 17/33 | 2.1 | 12/29 | 2.5 | 0.59 |
| Elevated aspartate aminotransferase | 12/26 | 2.1 | 19/28 | 4.5 | 0.03 |
| Elevated alkaline phosphatase | 15/30 | 1.6 | 13/31 | 2.4 | 0.30 |
| Leukopenia | 16/28 | 2.8 | 10/28 | 2.4 | 0.70 |

*For laboratory values, the number of patients observed is the number whose test results were normal at the beginning of the study.

than itraconazole, we plan to conduct a second study comparing itraconazole and ketoconazole.

The study was terminated after the interim analysis, because antifungal prophylaxis with itraconazole was highly effective. All 20 relapses occurred in the placebo group. The incidence rate was 2.6 per 100 person-weeks of follow-up. No relapses occurred in the itraconazole group, resulting in a significant difference between the treatment groups. The median time from the discontinuation of initial treatment to relapse was 24 weeks. This result is similar to our previous observation of a 50 percent relapse rate within six months.⁴

Cryptococcosis developed in only two patients, one receiving itraconazole and the other receiving placebo. These data do not permit us to estimate the efficacy of itraconazole for the prevention of opportunistic fungal infections other than *P. marneffeii*. The rates of mortality and of adverse events were similar in the two groups.

Although a survival benefit could not be demonstrated, secondary prophylaxis with itraconazole can substantially decrease morbidity by preventing relapse of *P. marneffeii* infection. *P. marneffeii* infection is serious and potentially fatal.² The mortality rate is high when physicians fail to make a rapid diagnosis and give appropriate and prompt therapy.¹⁶ In our study, all relapses were diagnosed and treated promptly. Intensive follow-up, as in our study, is not always possible in the public health systems of the developing countries of Southeast Asia.

Our study was designed to have the power to detect a difference in the rate of relapse from *P. marneffeii* infection, and not to detect a difference in mortality. Nevertheless, 3 of the 20 patients who had a relapse died — a mortality rate of 15 percent. This suggests that some relapses will not be effectively treated even when the patients are under active and frequent surveillance. We therefore believe that prevention of relapse is a better strategy than treatment of patients after relapse has been detected. In addition, itraconazole was well tolerated. The rates of adverse clinical effects and effects on laboratory values in the two treatment groups were similar.

We suggest that patients infected with HIV who are successfully treated for disseminated *P. marneffeii* infection should receive long-term maintenance therapy. Treatment with oral itraconazole at a dose of 200 mg once daily is highly effective in preventing relapses. The regimen is well tolerated and

should be the standard of care for patients with AIDS and *P. marneffeii* infection.

Supported by a grant from Janssen Research Foundation, Belgium.

We are indebted to the Global Program on AIDS of the World Health Organization for data management and analysis and for the services of its data and safety monitoring board; to Dr. Naronk Tonkul of the Janssen Research Council, Thailand; to Dr. J.M.A. Lange and Mr. L.G. Dally of the Global Program on AIDS; and to Dr. Suwat Chariyalertsak, Dr. Chartichai Kwangsukstith, Dr. Sirinet Kitiyawongs, Dr. Worapol Buranachokpaisal, Dr. Tosapol Limpjarnkij, Ms. Chantana Khamwan, and Ms. Jutharat Praparatanapan of the Faculty of Medicine, Chiang Mai University.

REFERENCES

1. Duong TA. Infection due to *Penicillium marneffeii*, an emerging pathogen: review of 155 reported cases. *Clin Infect Dis* 1996;23:125-30.
2. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffeii* infection in southeast Asia. *Lancet* 1994;344:110-3.
3. Supparatpinyo K, Sirisanthana T. New fungal infections in the Western Pacific. *JAMA Southeast Asia* 1994;10:Suppl 3:208-9.
4. Supparatpinyo K, Chiewchanvit S, Hirunsi P, et al. An efficacy study of itraconazole in the treatment of *Penicillium marneffeii* infection. *J Med Assoc Thai* 1992;75:688-91.
5. Supparatpinyo K, Chiewchanvit S, Hirunsi P, Uthammachai C, Nelson KE, Sirisanthana T. *Penicillium marneffeii* infection in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1992;14:871-4.
6. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown, 1986:170-5.
7. Lee SS, Lo YC, Wong KH. The first one hundred AIDS cases in Hong Kong. *Chin Med J (Engl)* 1996;109:70-6.
8. Chang CC, Liao ST, Huang WS, Liu JD, Shih LS. Disseminated *Penicillium marneffeii* infection in a patient with acquired immunodeficiency syndrome. *J Formos Med Assoc* 1995;94:572-5.
9. Leung R, Sung JY, Chow J, Lai CK. Unusual cause of fever and diarrhea in a patient with AIDS: *Penicillium marneffeii* infection. *Dig Dis Sci* 1996;41:1212-5.
10. Rokiah I, Ng KP, Soo-Hoo TS. *Penicillium marneffeii* infection in an AIDS patient — a first case report from Malaysia. *Med J Malaysia* 1995;50:101-4.
11. Sobottka I, Albrecht H, Mack D, et al. Systemic *Penicillium marneffeii* infection in a German AIDS patient. *Eur J Clin Microbiol Infect Dis* 1996;15:256-9.
12. Remadi S, Lotfi C, Finci V, et al. *Penicillium marneffeii* infection in patients infected with the human immunodeficiency virus: a report of two cases. *Acta Cytol* 1995;39:798-802.
13. Hilmarsdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated *Penicillium marneffeii* infection in a patient with AIDS. *Clin Infect Dis* 1994;19:357-8.
14. Borradori L, Schmit JC, Stetzkowski M, Dussoix P, Saurat JH, Filt-huth I. *Penicilliosis marneffeii* infection in AIDS. *J Am Acad Dermatol* 1994;31:843-6.
15. Kok I, Veenstra J, Rietra PJ, Dirks-Go S, Blaauwgeers JL, Weigel HM. Disseminated *Penicillium marneffeii* infection as an imported disease in HIV-1 infected patients: description of two cases and a review of the literature. *Neth J Med* 1994;44:18-22.
16. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated *Penicillium marneffeii* infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother* 1993;37:2407-11.
17. Bennett JE. Antimicrobial agents: antifungal agents. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's the pharmacological basis of therapeutics*. 8th ed. New York: Pergamon Press, 1990:1165-81.