Comparison of Amphotericin B, Flucytosine and Itraconazole with Amphotericin B and Flucytosine in the Treatment of Cryptococcal Meningitis in AIDS

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Abstract

We compared amphotericin B (0.3 mg/kg/d) plus flucytosine (150 mg/kg/d) plus itraconazole (400 mg/d) (study group) with amphotericin B plus flucytosine (control group) by an open-randomized trial. In the study group, after CSF mycological cultures disclosed nothing, itraconazole was administrated alone through six weeks of treatment. Treatment was considered successful if the patient had two consecutive negative CSF cultures by the end of the 6-week treatment period. Fifty patients were enrolled in each group. There were significant differences between the study group and the control group in the successful treatment (100% *vs* 90 %; P = 0.03), the mean length of time until normal body temperature after treatment (5.9 ± 3.7 days *vs* 8.8 ± 5.1 days; P = 0.02) and the adverse effects. The mean length of time to the first negative CSF culture was 13.9 ± 6.1 days in the study group and 13.3 ± 6.5 days in the control group (P = 0.66). Relapse rate with itraconazole 200 mg/day was higher in the study group.

Cryptococcal meningitis, a serious neurological disease in patients infected with the human immunodeficiency virus, occurs in approximately 10 per cent of patients with the acquired immunodeficiency syndrome (AIDS)[1-4]. Amphotericin B with or without flucytosine, the standard therapeutic regimen for this disease[5,6], has been less effective among patients with AIDS, in whom success rates are about 50 per cent and drug intolerance is common, especially when flucytosine is used[1,7]. Itraconazole, a triazole antifungal drug, is promising for the treatment of cryptococcal meningitis in patients with AIDS with minimal side effects[8]. However, these regimens have failed to treat some patients with cryptococcal meningitis. Also, certain patients who had failed with conven-

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tional treatment, responded to itraconazole and vice versa[8-11]. Interestingly, we experienced a good result of an open study concerning treatment in non-AIDS patients with cryptococcal meningitis with triple combination of amphotericin B, flucytosine and itraconazole[12].

Accordingly, we initiated an open-randomized, controlled, prospective clinical trial to compare the efficacy and tolerability of amphotericin B, flucytosine and itraconazole with amphotericin B and flucytosine as an initial therapy for cryptococcal meningitis in patients with AIDS. The results of this clinical trial are reported here.

MATERIAL AND METHOD

Study Population

The criteria for enrollment included HIV infection documented by a positive test for the HIV antibody, age of at least 16 years, and a positive cerebrospinal fluid (CSF) culture for *Cryptococcus neoformans*. The episode of cryptococcal meningitis that we studied may have been an initial episode or represented a relapse after an initial treatment or unsuccessful therapies from other regimens if the patients had received no therapy for at least one week before entry.

Patients were excluded if they had a known allergy to either drug, died within 3 days after the initial treatment, a white cell count under 1,500 per cubic millimeter, a platelet count under 30,000 per cubic millimeter, significant impairment of liver (more than 3 x normal), and renal function (creatinine more than 3 microgram per cubic millimeter), another concurrent central nervous system infection (for example, toxoplasmosis), or pregnancy. Concomitant therapy with anticoagulants, oral hypoglycemic agents, barbiturates, phenytoins, immunostimulants, rifampin, lymphocytic replacement therapy was not allowed. The study protocol was reviewed and approved by the institutional review board.

The severity of the disease was classified as the following criteria.

Stage 1: The patients were well conscious and rational with meningism or only headache, but no focal neurological signs or signs of hydrocephalus.

Stage 2: The patients were confused or had focal neurological signs such as squint, hemiparesis or signs of hydrocephalus.

Stage 3: The patients's mental state could not be assessed because of stupor or delirium, complete hemiplegia or paraplegia.

Sample size and Power

The estimated number of subjects was 40 in each group according to the successful treatment in the study group of 80 per cent and in the control group of 50 per cent with type I error 5 per cent and type II error 20 per cent.

Randomization and Treatment

The patient was stratified according to the staging of the disease and randomly assigned to the treatment by block size of 4. Amphotericin B was given intravenously in a dose of 0.3 mg per kilogram body weight daily and oral flucytosine 150 mg per kilogram body weight in four divided doses, after meals. Patients in the study group were given 400 mg of itraconazole per day in 100 mg capsules orally twice a day after meals until mycological cultures disclosed nothing. Then itraconazole 400 mg per day was administrated alone through six weeks of treatment. Patients who received the standard treatment (control group), amphotericin B and flucytosine, were given through six weeks of treatment. Oral itraconazole 200 mg once daily was given for secondary prophylaxis after completion of treatment in both groups. Zidovudine use and prophylactic therapy for *Pneumocystis carinii* were also permitted.

Studies to Monitor Efficacy and Toxicity

Before treatment, the following studies were performed: complete blood count, Venereal Disease Research Laboratory (VDRL) and *Treponema pallidium* hemagglutination assay (TPHA), HIV serology (ELISA and Western Blot), CD_4 count, toxoplasma titer, blood glucose, electrolytes, serum BUN, creatinine, liver function test, a test for serum cryptococcal antigen titer, cultures of blood and urine for bacteria and fungi, CSF for an India ink preparation and a fungal culture, determination of the opening pressure, total cell counts with differential cell counts, levels of glucose and protein, and the cryptococcal antigen titer and chest roentgenography. Cultures of fungi were carried out and held for 30 days before being rejected as negative culture. All pretreatment studies were repeated weekly during therapy and every 3rd, 6th, 9th and 12th month after therapy.

CSF cultures for fungi were also performed at the third, seventh, tenth, fourteenth day and weekly till there was negative culture. A repeated chest roentgenogram was obtained if the first was abnormal.

On each occasion, the CSF pressure was measured after the patients were fully relaxed. Patients with a high CSF pressure (more than 300 mm H_2O) were relieved by repeated lumbar puncture.

Evaluation

After a base-line evaluation, patients were evaluated every week until the 6-week study period was completed, and at 3rd, 6th, 9th and 12th month after therapy. At each visit, a physical examination was performed and any adverse events were assessed and recorded.

Treatment was considered successful if the patient had clinical improvement or complete resolution of symptoms together with two consecutive negative cultures of CSF samples, obtained at least one week apart, the second of which was obtained at the end of an initial therapy. Treatment was considered to have failed if the patient had quiescent disease, defined as clinically stable, progressive improvement or resolution of symptoms but persistently positive cultures of CSF or only one negative CSF culture by the end of the 6-week treatment period; had progressive disease, defined as progressive clinical deterioration in the presense of persistently positive cultures; or died of progressive cryptococcal meningitis.

During a period of follow-up after successful treatment, a relapse of cryptococcal meningitis documented by positive CSF culture for *C. neoformans*.

Study Design and Statistical Analysis

The primary efficacy analysis in this study compared the rates of successful treatment in the two groups. Information obtained from the subjects and laboratories were recorded in case record forms. The data were analysed by descriptive statistics, student *t*-test, Chi-square test, Fisher's exact probability test and survival analysis where appropriate.

RESULTS

Study Population

From April 1994 through January 1996, 100 patients were enrolled in this study and completed the course. Fifty patients were studied in each group. The clinical presentations and staging were similar in both groups at randomization (Table 1-2). Associated infections were observed in 5 patients of the study group (*Salmonella* bacteremia 2 cases, PCP 2 cases and *Rhodococcus* pneumonia 1 case) and in 4 patients of the control group (*Salmonella* bacteremia 1 case, PCP 1 case and *Enterobactor* bacteremia 2 cases). There were 2 patients in each group who died within 1 day after treatment who were not included in this study.

Outcome

During the period of an initial treatment, 1 patient in each group developed cranial nerve palsy (unilateral CN 7th palsy at the 12th day of treatment and unilateral CN 6th palsy at the 4th week of treatment in the study and control group respectively) which recovered when the treatment was continued. The mean duration of therapy with amphotericin B and flucytosine in the study group was 2.4 ± 0.6 weeks.

As shown in Table 3, treatment was successful in 50 of the 50 patients in the study group, as compared with 45 of the 50 patients in the control group ($P = 0.03$). The mean length of time until normal body temperature after treatment were statistically significantly different between the two treatment groups ($P = 0.02$). There was no significant difference in the persistence of high CSF pressure and India ink preparation after completion of the initial treatment and time to the conversion of fungal culture from positive to negative (Fig. 1). Of the 5 patients who died in the control group; 1 was in stage 1, 3 were in stage 2 and 1 was in stage 3.

Toxicity

As shown in Table 4, more adverse events occurred in the control group than in the study group (21 patients *vs* 32 patients, $P = 0.045$) with the statistically significant difference between the two groups in the adverse effect of metabolic acidosis. Hepatotoxicity was not observed in the study group.

Follow - up

Of the remaining 95 patients after completion of the initial treatment, 9 patients successfully completed one year of maintenance therapy and an additional 26 patients who were treated for less than one year were receiving the medication when the study was stopped (January 1996). The remaining 60 patients left the study prematurely. Twenty-

Table 1. Comparison of initial clinical features between the treatment and control groups.

	Treatment group (n = 50)	Control group (n = 50)	P value
Age (mean) , years	29.0 ± 6.1	28.6 ± 7.1	0.78
range	19-46	18-51	
Sex (males) , n	46	46	1.00
Recurrent of cryptococcal meningitis	3	2	1.00
Signs or symptoms			
Headache , n	48	49	1.00
duration of headache , days			
mean	23.2 ± 21.0	27.0 ± 31.7	0.97
range	3-90	1-20	
< 7 days	9	8	
Fever (T ≥ 38.0°C), n	31	26	0.42
duration of fever , days			
mean	25.3 ± 31.4	43.4 ± 44.7	0.08
range	2-150	5-180	
< 7 days	8	3	
Stiffneck , n	40	37	0.63
Mental impairment , n	11	10	1.0
drowsiness , n	3	5	
confusion , n	7	4	
stuporous , n	1	1	
Papilledema , n	4	4	1.0
6 th nerve palsy , n	5	3	0.71
unilateral , n	5	2	
bilateral , n	0	1	
8 th nerve palsy , n	0	1	1.0
Decreased vision , n	0	3	0.24
Convulsion , n	1	3	0.62
Vomitus	30	27	0.75
Cervical lymphadenopathy , n	36	31	0.39
Skin cryptococcosis , n	6	2	0.27
Hepatomegaly , n	7	5	0.76
Splenomegaly , n	2	1	1.0
Staging			1.0
1 , n	36	36	
2 , n	13	13	
3 , n	1	1	

seven of these were lost to follow-up at various times; 2 patients were excluded from the study (1 case had a relapse of *Rhodococcus* pneumonia and 1 case developed pulmonary tuberculosis for which both required rifampin therapy); 1 patient died from pancytopenia for with sepsis; 18 patients had relapses of cryptococcal meningitis and 12 patients just completed the initial treatment.

During the period of follow-up, other infections were developed in 3 patients (PCP 1 case, cerebral toxoplasmosis 1 case and CMV retinitis 1 case). Newly developed neurological complications occurred in 3 patients (optic atrophy with blindness secondary to long-standing increased intracranial pressure 2 cases and hemiparesis secondary to lacunar infarction 1 case).

Table 2. Comparison of initial laboratory features between the treatment and control groups.

	Treatment group (n = 50)	Control group (n = 50)	P value
Complete blood count			
Hematocrit, %			
mean	33.4 ± 5.8	32.9 ± 5.5	0.65
range	20-45	19-44	
White blood cell, cells/mm^3			
mean	6,421 ± 2,173.3	6,697 ± 4,244.1	0.77
range	1,600-10,500	1,600-28,400	
Blood culture positive for *C. neoformans*, n	15	14	1.00
Hyponatremia (Na < 125 mEq/L), n	7	4	0.52
CD4 , cells / mm^3			
mean	22.3 ± 27.6	27.4 ± 30.0	0.52
range	0-124	0-130	
Abnormal CXR , n	6	8	0.80
Bilateral interstitial infiltration	3	2	
Miliary pattern	0	1	
Mass or nodule	1	0	
Bronchopneumonia	1	5	
Cavitary lesion	1	0	
CSF abnormalities			
High opening pressure (≥ 300 mmH_2O), n	23	23	0.84
White blood cell, cells/mm^3			
mean	55.4 ± 103.9	50.0 ± 108.6	0.80
range	0-610	0-550	
≤ 5 cells / mm^3, n	20	26	
Protein content, mg/dl			
mean	105.7 ± 103.5	87.2 ± 59.2	0.71
range	5-570	17-267	
≤ 45 mg / dl , n	12	12	
Glucose ratio (CSF / blood), %			
mean	34.4 ± 12.5	35.6 ± 14.3	0.66
range	10-59	10-80	
normal ratio (≥ 50 %), n	6	6	
Positive India ink preparation , n	47	46	1.0
Cryptococcal antigen titer*			0.68
negative , n	0	0	
1:1 , n	0	2	
1:10 , n	2	4	
1:100 , n	5	5	
1:1,000 , n	12	9	
1:10,000 , n	3	3	
>1:10,000 , n	28	26	
Serum cryptococcal antigen titer*			0.65
negative , n	0	2	
1:1 , n	0	1	
1:10 , n	2	2	
1:100 , n	7	8	
1:1,000 , n	9	10	
1:10,000 , n	2	0	
>1:10,000 , n	28	24	

* Cryptococcal antigen titer were not done in certain patients.
CXR = Chest X-ray

Table 3. Comparison of clinical outcomes after initial treatment.

	Treatment group (n = 50)	Control group (n = 50)	P value
Successful	50	45	0.03
Treatment failure, n	0	5	
Quiescent disease, n	0	0	
Disease progression, n	0	0	
Death, n	0	5	
early (≤ 2 wk), n	0	4	
late (≥ 2 wk), n	0	1	
Time until normal body temperature after treatment, days			
mean	5.9 ± 3.7	8.8 ± 5.1	0.02
range	1-16	2-22	
CSF responses after initial treatment			
Persistence of high CSF pressure, n	7	8	1.0
Time to the conversion of fungal culture from positive to negative			
mean, days	13.9 ± 6.1	13.3 ± 6.5	0.66
range	3-28	3-35	
early (≤ 2 wk), n	34	37	
Persistence of India ink preparation, n	31	30	0.89

Table 4. Laboratory abnormalities during the initial treatment.

	Treatment group (n = 50)	Control group (n = 50)	P value
Abnormal	21	32	0.045
Fall in hematocrit (> 5%), n	6	13	0.13
Neutropenia (< 1,500/mm^3), n	0	4	0.12
Thrombocytopenia (< 100,000/mm^3), n	2	4	0.68
Rise in serum creatinine (> 2mg/dl), n	1	2	1.00
Hypokalemia (< 3.5 mEq/L), n	15	14	1.00
Metabolic acidosis (Hco3 < 18 mEq/L), n	1	8	0.02

Fig. 2 demonstrates the survival curve of patients who remained free of cryptococcal meningitis. Of the 18 patients who had relapses of meningitis, the mean duration of the relapse of cryptococcal meningitis that occurred after completion of acute treatment was 102.4 ± 71.4 days (range; 25-315 days). Clinical manifestation of hepatitis from drug toxicity was not observed.

DISCUSSION

Currently, an initial therapy for cryptococcal meningitis in AIDS patients is the combination of amphotericin B and flucytosine[13,14]. Two studies[15,16] found a significantly better outcome of amphotericin B regimens than the triazole group. Larsen et al and colleagues[15] compared amphotericin B (0.7 mg/kg per day) plus flucytosine (150 mg/kg per day) with fluconazole (400 mg per day), 8 of 14 in the fluconazole group did not respond to therapy compared with none of the 6 receiving amphotericin B plus flucytosine and a more rapid clearance of CSF was also noted in the amphotericin B group (the mean duration of positive CSF cultures was 15.6 days and 40.6 days in the ampho-

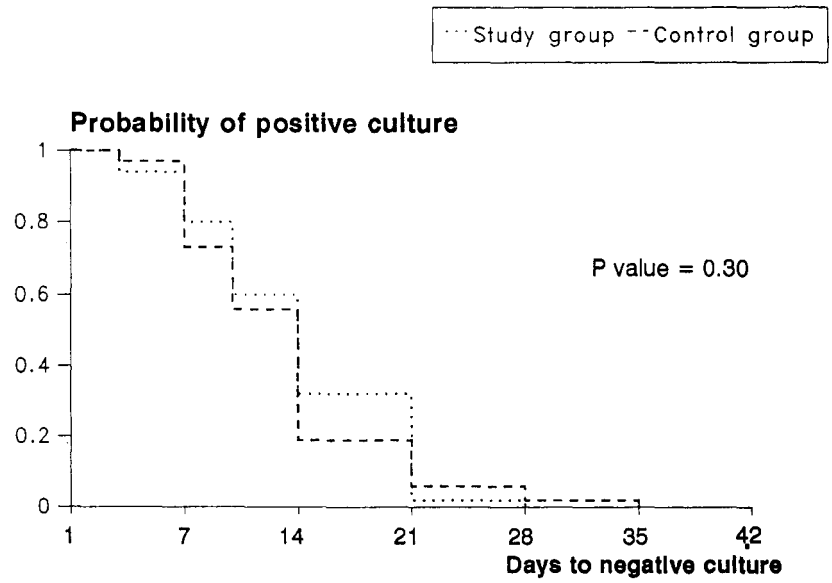

Fig. 1. Survival curve of the length of time to the first negative CSF culture.

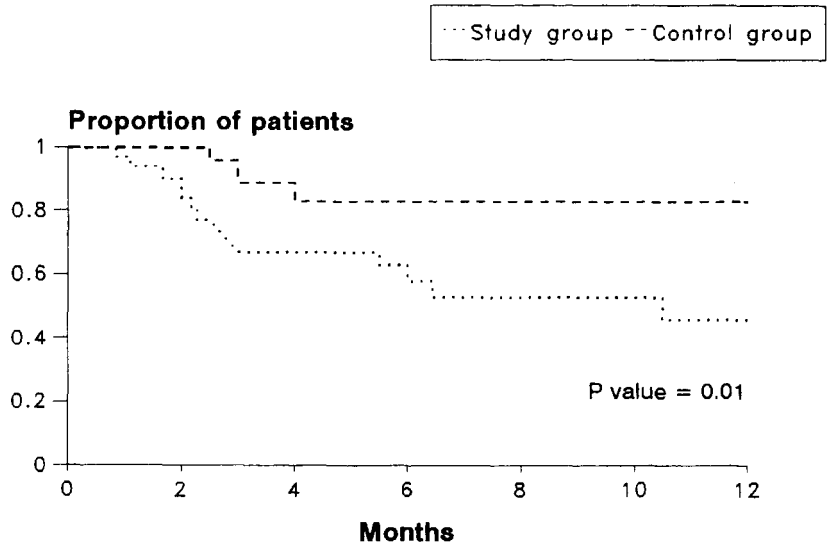

Fig. 2. Survival curve of patients remaining free of cryptococcal meningitis during 1 year follow-up.

tericin B group and fluconazole group respectively). De Gans et al[16] demonstrated that a complete response was observed in 5 out of the 12 patients who were treated with itraconazole (400 mg per day) and all 10 patients who completed treatment with amphotericin B (0.3 mg/kg per day) plus flucytosine (150 mg/kg per day).

However, the optimal duration of the initial therapy with amphotericin B plus flucytosine is not established. Nowadays, the 6-week course[6] is not suitable because of the long hospital-days and more side effects. Recently, the results of treatment regimen of cryptococcal meningitis in AIDS patients with amphotericin B (0.7 mg/kg/day) with or with-

out flucytosine (100 mg/kg/day) for 14 days (step 1), followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for 8 weeks (step 2) were reported[17,18]. The results after the initial 2 weeks were CSF culture negativity 59 per cent *vs* 50 per cent and death 5 per cent *vs* 5 per cent in amphotericin B plus flucytosine and amphotericin B alone respectively. In step 2, CSF culture negativity was 67 per cent and 61 per cent in the fluconazole and itraconazole respectively. This result demonstrated that certain patients still had persistent positive fungal cultures after completion of the acute treatment.

The efficacy of intensive treatment with the combination of amphotericin B, flucytosine and itraconazole has been studied in 9 non-AIDS patients[12]. Interestingly, almost of them responded to this regimen and rate of negative India ink staining and CSF fungal culture was rapid (within 2 weeks of treatment) with minimal side effects.

The present study has documented the efficacy of intensive treatment with the combination of triple drugs in AIDS patients with cryptococcal meningitis. The advantages of the combination regimen are a reduction of the hospital-days and the serious side effects and a rapid clearance of the organism in the CSF. From these clinical data we suggest that this intensive regimen is highly effective in the initial treatment of cryptococcal meningitis in AIDS patients.

After completion of the initial therapy, the potential for relapse needs long-term use of antifungal agents, such as amphotericin B, fluconazole and itraconazole. Comparison of fluconazole (200 mg per day) with weekly amphotericin B (1 mg/kg)[19] revealed that relapse rates were 2 per cent and 18 per cent for fluconazole and amphotericin B respectively. Relapse rate was about 20 per cent for itraconazole (200 mg daily)[16]. Recent data demonstrated that the relapse rates were 3.8 per cent and 23.6 per cent in fluconazole (200 mg/day) and itraconazole (200 mg/day) respectively[20]. The relapse rate in our study was also high with itraconazole 200 mg/day and we could not explain why the relapse rate was higher in the study group than the control group. It may be explained that the maintenance dose of itraconazole 200 mg/day was too low to prevent a relapse of disease and/or the total dose of amphotericin B in the control group was higher than the study group, causing more effective fungal clearance. Further studies are needed to assess the effectiveness of itraconazole 400 mg/day for prevention of this setting.

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เปรียบเทียบประสิทธิผลการรักษาเยื่อหุ้มสมองอักเสบจากเชื้อรา คริบโตคอคคัส นีโอฟอร์แมน ในผู้ป่วยโรคเอดส์ ระหว่างยา แอมโฟเทอริซิน บี + ฟลูซัยโตซีน + อิทราโคนาโซล กับ แอมโฟเทอริซิน บี + ฟลูซัยโตซีน

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วิสุทธิ์ สุขีไพศาลเจริญ, พ.บ., ยุพา ถาวรพิทักษ์, วท.ม.***

รายงานผลการศึกษาเปรียบเทียบประสิทธิผลการรักษาเยื่อหุ้มสมองอักเสบจากเชื้อรา คริบโตคอคคัส นีโอฟอร์แมน ในผู้ป่วยโรคเอดส์ ระหว่างยา แอมโฟเทอริซิน บี + ฟลูซัยโตซีน + อิทราโคนาโซล กับ แอมโฟเทอริซิน บี + ฟลูซัยโตซีน ด้วยวิธี open-randomized controlled ขนาดของยาที่ใช้ ได้แก่ แอมโฟเทอริซิน บี 0.3 มก.ต่อกก.ต่อวัน ฟลูซัยโตซีน 150 มก.ต่อกก.ต่อวัน และอิทราโคนาโซล 400 มก.ต่อวัน ระยะเวลาที่ให้ยานาน 6 สัปดาห์ โดยผู้ป่วยที่ได้รับยา 3 ชนิด เมื่อผลการเพาะเชื้อราในน้ำไขสันหลังได้ผลลบ จะลดยาเหลือแต่อิทราโคนาโซล จนครบ 6 สัปดาห์

มีผู้ป่วยที่ศึกษากลุ่มละ 50 ราย ผลการศึกษาพบว่าระหว่างผู้ป่วยที่ได้รับยา 3 ชนิด และ 2 ชนิด มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในเรื่องของอัตราของความสำเร็จของการรักษา (ร้อยละ 100 ต่อ ร้อยละ 90 ; P = 0.03) เวลาเฉลี่ยที่ไข้ลดลงหลังการรักษา (5.9 $\pm$ 3.7 วัน ต่อ 8.8 $\pm$ 5.1 วัน; P = 0.02) และผลข้างเคียงของยา โดยเฉพาะภาวะเป็นกรดในร่างกาย ส่วนเวลาเฉลี่ยที่ผลการเพาะเชื้อในน้ำไขสันหลังให้ผลลบหลังการรักษา ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (13.9 $\pm$ 6.1 ต่อ 13.3 $\pm$ 6.5 วัน; P = 0.66) ผลการป้องกันการกลับเป็นโรคอีกด้วยยาอิทราโคนาโซล ขนาด 200 มก.ต่อวัน พบอัตราการกลับเป็นโรคอีกสูงกว่าในกลุ่มผู้ป่วยที่ได้รับยา 3 ชนิด

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