

ORIGINAL ARTICLE

Itraconazole to Prevent Fungal Infections in Chronic Granulomatous Disease

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ABSTRACT

BACKGROUND

Chronic granulomatous disease is a rare disorder in which the phagocytes fail to produce hydrogen peroxide. The patients are predisposed to bacterial and fungal infections. Prophylactic antibiotics and interferon gamma have reduced bacterial infections, but there is also the danger of life-threatening fungal infections. We assessed the efficacy of itraconazole as prophylaxis against serious fungal infections in chronic granulomatous disease.

METHODS

Thirty-nine patients at least 5 years old (6 female and 33 male; mean age, 14.9 years) were enrolled in a randomized, double-blind, placebo-controlled study. After the initially assigned treatment, each patient alternated between itraconazole and placebo annually. Patients 13 years of age or older and all patients weighing at least 50 kg received a single dose of 200 mg of itraconazole per day; those less than 13 years old or weighing less than 50 kg received a single dose of 100 mg per day. The primary end point was severe fungal infection, as determined by histologic results or culture.

RESULTS

One patient (who had not been compliant with the treatment) had a serious fungal infection while receiving itraconazole, as compared with seven who had a serious fungal infection while receiving placebo ($P=0.10$). No patient receiving itraconazole but five patients receiving placebo had a superficial fungal infection. No serious toxic effects were noted, although one patient had a rash and another had elevated results on liver-function tests; both of these effects resolved with the discontinuation of itraconazole.

CONCLUSIONS

Itraconazole prophylaxis appears to be an effective and well-tolerated treatment that reduces the frequency of fungal infections in chronic granulomatous disease, but monitoring for long-term toxic effects is warranted.

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CHRONIC GRANULOMATOUS DISEASE of childhood is a rare group of inherited disorders of phagocytic cells characterized clinically by recurrent life-threatening infections and excessive granuloma formation.¹ Phagocyte migration and phagocytosis are normal, but killing of microorganisms is impaired because of defective production of hydrogen peroxide and related products of oxygen metabolism. A variety of biochemical defects lead to the disorder.

The current mortality rate is 2 to 5 percent per year.² In the absence of prophylaxis with antibiotics or interferon gamma, patients with chronic granulomatous disease have severe infections due to catalase-positive bacteria and fungi about once a year. Prophylaxis with the combination antibiotic trimethoprim-sulfamethoxazole has reduced the incidence of serious bacterial infections to about one every four years.^{3,4} Interferon gamma prophylaxis has reduced bacterial infections by an additional 70 percent.⁵ Despite these reductions in the incidence of bacterial infections with antibiotics and interferon gamma, fungal infections remain a difficult problem, with an incidence of approximately 0.1 infection per patient per year.^{2,6} We performed a study of the use of prophylactic oral itraconazole to reduce the incidence of fungal infections in chronic granulomatous disease.

METHODS

PATIENTS

Patients with chronic granulomatous disease were followed at the National Institutes of Health Clinical Center from 1991 through 2001. All patients or their parents gave written informed consent, and written assent was obtained from minors. The diagnosis of chronic granulomatous disease was based on an abnormal nitroblue tetrazolium reduction test on phagocytes from the patient, less than 10 percent of normal neutrophil and macrophage oxidative metabolism (abnormal superoxide or hydrogen peroxide production), or both. The patients were at least five years old and had not been taking itraconazole or other systemic antifungal agents for three months before entry into the study.

The patients had no evidence of active infection at the time of enrollment. They had normal blood counts, normal or stable results on chest radiography, normal liver-function results and urinalysis, and no signs of infection on physical examination.

Patients with confirmed fungal infection within the preceding 12 months were ineligible.

The patients could elect to receive interferon gamma, but those just initiating interferon gamma were required to wait 30 days before they became eligible for randomization. No patients began to take interferon gamma during the study. Patients with long-term granulomatous complications of chronic granulomatous disease who were taking low-dose corticosteroids (up to 5 mg of prednisone every other day) at the time of enrollment continued to take them throughout the study; patients receiving higher doses of corticosteroids were excluded.

STUDY MEDICATION

Itraconazole and placebo were provided by Janssen Pharmaceutica under investigational-new-drug application 36148; the company had no other involvement in the study. The elimination half-life of itraconazole in healthy adult volunteers is approximately 20 hours after a single dose and 30 hours after multiple doses.^{7,8} For patients younger than 13 years and weighing less than 50 kg, a single daily dose of 100 mg was given with food or a carbonated beverage. For all other patients, a single daily dose of 200 mg was given.

Before this study was initiated, the pharmacokinetics and tolerability of itraconazole in children with chronic granulomatous disease were assessed in five boys with chronic granulomatous disease who were between five and eight years of age and weighed 20 to 35 kg. Itraconazole was administered orally as a 100-mg capsule (3 to 5 mg per kilogram per dose) once per day for two weeks. Each daily dose was given with food to maximize absorption.⁸⁻¹⁰ The mean plasma level of itraconazole plus its biologically active metabolite, hydroxyitraconazole, in the children was 0.373 μg per milliliter after 14 days. No toxic effects were noted. On the basis of these studies, a single daily dose of 100 mg was used for children less than 13 years of age and weighing less than 50 kg.

Once the study was initiated, plasma drug levels were determined on samples obtained two to four hours after the dose at periodic study evaluations and frozen at -80°C in 1-ml aliquots until use. The levels of itraconazole and hydroxyitraconazole were measured after completion of the study by commercial high-performance liquid chromatography (Mayo Medical Laboratories). The limit of detection with this assay was 0.3 μg per milliliter. For the

purposes of plotting and computing means and standard deviations, values below the detectable level of 0.3 µg per milliliter were considered to be 0.15 µg per milliliter.

STUDY DESIGN

This was a double-blind study with sequential monitoring, and only the pharmacy department held the code. The patients were randomly assigned at the time of enrollment to receive either itraconazole or placebo. The patients were switched to the other therapy at annual clinic visits. The randomization was stratified according to whether the patient also received interferon gamma; at the time of randomization, 34 patients were taking interferon gamma. All patients received antibacterial prophylaxis with trimethoprim-sulfamethoxazole, or with trimethoprim alone or dicloxacillin alone if they could not tolerate sulfa drugs.¹¹ The patients were evaluated at entry and at week 1 and week 2. They were then monitored for any problems or any signs of hepatotoxicity. Thorough evaluations were conducted at the National Institutes of Health every three to six months, and all infections were recorded. Toxic effects and other adverse events were scored according to protocol-specified criteria.

MONITORING OF EFFICACY

A serious fungal infection was defined as an invasive infection of the lung, bone, blood, or soft tissue, with clear evidence of a fungal cause from histologic studies or culture. Symptomatic superficial dermatophyte infections involving only the skin or nails that were not serious enough to warrant systemic therapy with amphotericin B were identified clinically by inspection. These infections were not included in the primary analysis but were considered separately at the conclusion of the study to determine the difference in their incidence between the drug and placebo groups.

When a serious fungal infection was diagnosed by histopathological or microbiologic techniques, the treatment was recorded as a failure. The patient's participation in the study then ended, and the patient received all appropriate therapy, including amphotericin B, surgery, or both, as clinically indicated. If the study physicians determined that in order to provide optimal care, it was necessary to know whether a patient with a confirmed fungal infection had received itraconazole or placebo, this

information was provided by the data monitor, and the patient's participation in the study ended. Otherwise, neither the patient nor the study physician knew when a patient received active drug until the end of the study.

STATISTICAL ANALYSIS

A power calculation in the protocol specified that the study would require approximately 100 patient-years of follow-up. This was based on a historical rate of serious fungal infection in patients with chronic granulomatous disease of approximately 0.1 infection per patient per year, which would suggest approximately five treatment failures in the placebo group. At approximately one-year intervals, each patient whose treatment had not yet failed was switched to the other study treatment (multiple crossover study). The sequential stopping and analysis rule, mandated by the protocol and originally described by Frank et al.,¹² stated that if the first five, or seven of the first eight, serious fungal infections were found in patients who received placebo, it would have been shown that significantly fewer serious fungal infections occurred in the itraconazole group, and the study would be terminated. Conversely, should two serious fungal infections be found in the itraconazole-treated patients, no conclusion concerning efficacy would be possible, and the study would be terminated.¹² For this sequential design, the calculated exact one-sided P value, if itraconazole were demonstrated to be superior, would be 0.051. In conformity with the *Journal's* practice of reporting two-sided P values, this has been converted to a two-sided P value of 0.102.

A critical assumption in the design and analytic approach was that the exposure of patients in the placebo and itraconazole groups to possible fungal infection was approximately equal. Two approaches were used to ensure that this criterion was met. First, Efron's biased-coin design was used to keep the randomization tightly balanced.¹³ Using Efron's approach helped ensure that the number of patients whose first course of study treatment was itraconazole was very close to the number of patients whose first course was placebo, while making it difficult for either selection bias or accidental bias to affect the validity of the trial results adversely. Second, the difference between treatment groups in the rate of patient dropout was assessed throughout the study by the data-monitoring statistician.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Thirty-nine patients with chronic granulomatous disease were enrolled in the study. Accrual lasted from October 1991 to March 2000. There were 6 female patients (15 percent) and 33 male patients (85 percent). The mean (\pm SD) age at the time of enrollment was 14.9 ± 10.4 years (range, 5.0 to 56.7), with a median of 11.5 years. The disease was autosomally inherited in 13 patients (33 percent) and X-linked in 26 patients (67 percent).

PLASMA LEVELS OF ITRACONAZOLE

Thirty blood samples obtained from 11 courses of treatment in patients receiving 100 mg of itraconazole per day and 65 samples obtained from 32 courses of treatment in patients receiving 200 mg per day were available for study. Of the 95 samples, 50 had no detectable levels of itraconazole (less than $0.3 \mu\text{g}$ per milliliter), and 39 had no detectable levels of the principal metabolite, hydroxyitraconazole (less than $0.3 \mu\text{g}$ per milliliter), a result consistent with the findings in previous studies of patients receiving these doses.¹⁴ The plasma levels of itraconazole and hydroxyitraconazole were higher when the subjects were taking the drug than when they were taking placebo (the median total drug levels were $0.7 \mu\text{g}$ per milliliter [interquartile range, 0.3 to 1.3] for those taking 200 mg of itraconazole per day, $0.4 \mu\text{g}$ per milliliter [interquartile range, 0.3 to 0.8] for those taking 100 mg of itraconazole per day, and less than $0.3 \mu\text{g}$ per milliliter for those taking placebo). Fifty-six of 95 samples obtained while patients were taking the drug (59 percent) had detectable levels of itraconazole, hydroxyitraconazole, or both, as compared with only 2 (from one patient) of the 102 samples from patients taking placebo (2 percent); the 2 samples with low levels of itraconazole ($0.6 \mu\text{g}$ and $0.5 \mu\text{g}$ per milliliter) from one patient taking placebo were probably due to either carryover drug from a prior cycle or lack of adherence to the treatment regimen. There was no significant difference in the plasma levels of itraconazole or hydroxyitraconazole between patients taking 200 mg of itraconazole per day and those taking 100 mg per day.

The 39 patients enrolled in the study received 61 courses of itraconazole and 63 courses of placebo. Eight patients (seven receiving placebo and one receiving itraconazole) were withdrawn from the

Table 1. Serious Fungal Infections.

Patient No.	Age (yr)	Sex	Time from Randomization (yr)	Genotype	Infection
Itraconazole					
3*	19	M	3.7	p47 ^{phox}	<i>Aspergillus fumigatus</i> pneumonia
Placebo					
7	16	M	5.1	gp91 ^{phox}	<i>A. fumigatus</i> pneumonia
13	5	M	0.1	gp91 ^{phox}	<i>Aspergillus</i> species pneumonia
15	16	M	5.9	gp91 ^{phox}	<i>A. nidulans</i> pneumonia
28	7	M	0.3	gp91 ^{phox}	<i>A. nidulans</i> pneumonia
32	10	M	3.7	gp91 ^{phox}	<i>Paecilomyces lilacinus</i> soft-tissue abscess
34	25	M	4.3	gp91 ^{phox}	Fungal pneumonia†
37	16	M	0.4	gp91 ^{phox}	<i>Aspergillus</i> species pneumonia

* Itraconazole therapy failed in Patient 3, but the return of unused medication indicated that he probably was not taking the drug.

† Fungal elements were identified on lung biopsy, with no growth in culture.

study because of serious fungal infections (Table 1), and three were withdrawn because of adverse events (Table 2). Other patients were withdrawn because of death from a bacterial infection (Table 3), transition to another protocol, pregnancy, or noncompliance (8 receiving placebo and 10 receiving itraconazole). No patients were lost to follow-up or unaccounted for at the termination of the study. The study reached a prespecified termination point for a one-sided type I error of 0.05 when the eighth therapy failure due to serious fungal infection occurred; seven of the eight fungal infections occurred in patients receiving placebo. Thus, at the termination of the study there had been one serious fungal infection for 61 courses of itraconazole and seven serious fungal infections for 63 courses of placebo (Table 1) ($P=0.10$). Seven patients had serious fungal infections in the lungs, and one patient had a serious fungal infection in the soft tissue (Table 1). Of the seven patients in the placebo group who had a serious fungal infection, only one was over 18 years old. There was no significant difference in the number of fungal infections between patients receiving in-

Table 2. Adverse Events.*

Event	Itraconazole no. of events (no. of patients)	Placebo no. of events (no. of patients)	P Value†
Headache	5 (4)‡	4 (3)	0.96
Fever	0	3 (3)	0.26
Rash	4 (3)‡	2 (2)	0.65
Fatigue	0	1	1.00
Diarrhea	0	1	1.00
Vomiting	0	1	1.00
Weight loss	1	0	0.98
Increased liver-function values	1‡	0	0.98
Abdominal pain	1	3 (2)	0.64
Inflammatory process requiring corticosteroids	0	4 (3)§	0.13
Superficial dermatophyte infection	0	5 (5)	0.06
Serious bacterial infection	10 (7)	9 (8)¶	0.94

* Thirty-nine patients were treated with 61 courses of itraconazole and 63 courses of placebo.

† P values were calculated with the use of a two-sided Fisher's exact test.

‡ One patient with headache, one with rash, and one with increased liver-function values were withdrawn from the study.

§ In the placebo group, the four inflammatory processes in three patients were granulomatous colitis (two episodes, one patient), bladder granuloma, and gastric granuloma.

¶ One patient died from disseminated *Chromobacterium violaceum* infection.

interferon gamma and those not receiving it (six infections in 34 patients receiving interferon gamma, and two infections in 5 patients not receiving interferon gamma). The itraconazole group also had fewer clinically diagnosed superficial fungal infections. No such infections were observed in 61 courses of itraconazole, as compared with five infections in 63 courses of placebo ($P=0.06$).

To assess whether the results could have been substantially affected by any difference between the itraconazole and placebo groups in exposure to possible fungal infection, the total number of patient-days for itraconazole and placebo was calculated from actual drug-dispensing information from the pharmacy department of the National Institutes of Health Clinical Center. Patient exposure in the two courses was in close balance, with 20,000 days for patients receiving itraconazole and 21,253 days for those receiving placebo (an overall difference of 6 percent). Thus, whereas the power analysis at study design anticipated 100 patient-

years, the total patient follow-up under both treatment regimens at completion of the study was approximately 113 patient-years.

ADVERSE EVENTS

Few major toxic effects were attributed to itraconazole (Table 2). A rash in one patient receiving itraconazole required discontinuation of the drug and removal of the patient from the study; the rash cleared when the drug was stopped. One patient receiving itraconazole had increased liver-function values (133 IU of alanine aminotransferase per liter, 155 IU of aspartate aminotransferase per liter, 247 IU of alkaline phosphatase per liter, and 690 IU of lactate dehydrogenase per liter), requiring discontinuation of the drug and removal from the study; the values returned to normal eight weeks after discontinuation of the drug. In one patient receiving itraconazole, the drug was discontinued because of headache, which resolved after discontinuation. There was no relation between high plasma drug levels and toxicity in the three patients with itraconazole-related adverse events. In addition, there was no apparent association between granulomata and fungal infection; in the three patients who had granulomatous complications requiring corticosteroids, one had an associated fungal infection and two did not.

Itraconazole had no effect on serious bacterial infections. There were 10 serious bacterial infections in seven patients receiving itraconazole and 9 serious bacterial infections in eight patients receiving placebo ($P=0.94$) (Table 3). One patient receiving placebo died from disseminated *Chromobacterium violaceum* infection.

DISCUSSION

Although prophylactic trimethoprim-sulfamethoxazole reduces the incidence of life-threatening bacterial infections in patients with chronic granulomatous disease from about one per year to about one every four years,^{3,4} and interferon gamma further reduces the incidence of such infections by about 70 percent,⁵ fungal infections remain a major problem for these patients.² The well-tolerated oral antifungal agent itraconazole has been shown to be useful in treating superficial fungal infections¹⁵ and in treating invasive pulmonary aspergillosis in patients with hematologic cancers, chronic granulomatous disease, and the acquired immunodeficiency syndrome.¹⁶⁻¹⁸ Prophylactic it-

Table 3. Serious Bacterial Infections.

Itraconazole				Placebo			
Patient No.	Sex	Genotype	Infection	Patient No.	Sex	Genotype	Infection
5	M	gp91 ^{phox}	Pneumonia*	6	M	gp91 ^{phox}	Pneumonia (nocardia)
10	M	gp91 ^{phox}	Rectal abscess*	7	M	gp91 ^{phox}	Pneumonia*
10	M	gp91 ^{phox}	Adenitis*	10	M	gp91 ^{phox}	Orbital cellulitis*
10	M	gp91 ^{phox}	<i>Clostridium difficile</i> diarrhea	10	M	gp91 ^{phox}	<i>C. difficile</i> diarrhea
11	M	gp91 ^{phox}	Pneumonia*	11	M	gp91 ^{phox}	Cellulitis*
18	F	p47 ^{phox}	Soft-tissue abscess (thigh)*	12	F	p47 ^{phox}	Pneumonia*
18	F	p47 ^{phox}	Soft-tissue abscess (breast)*	17	M	p47 ^{phox}	Sepsis (<i>Chromobacterium violaceum</i>)†
23	F	p47 ^{phox}	Soft-tissue abscess*	31	M	gp91 ^{phox}	Pneumonia*
26	M	pp91 ^{phox}	Soft-tissue abscess*	38	M	gp91 ^{phox}	Liver abscess (<i>Staphylococcus aureus</i>)
31	M	gp91 ^{phox}	Pneumonia (<i>Serratia marcescens</i>)				

* The diagnoses of infections without organisms listed were based on radiographic and clinical findings, with negative cultures and no organisms seen microscopically.

† The infection was fatal.

itraconazole also reduces the incidence of invasive pulmonary aspergillosis in high-risk patients with neutropenia.¹⁹

The findings in our double-blinded, randomized, placebo-controlled study suggest that itraconazole is highly effective in preventing both serious and superficial fungal infections in patients with chronic granulomatous disease and that its long-term use is well tolerated, with minimal side effects. Indeed, the only serious fungal infection in patients taking itraconazole occurred in a patient who had probably stopped taking the medication, as judged by the return of unused medication and by careful review of his adherence to the treatment regimen. This case was included as a treatment failure in the intention-to-treat analysis, but if the patient had adhered to the regimen, it is possible that there would have been no serious fungal infections in patients taking itraconazole. Despite the inclusion of this patient in the final analysis, the study's one-sided stopping criterion to show that itraconazole significantly reduces fungal infections in chronic granulomatous disease was just met ($P=0.051$).

The minor toxic effects of rash, increased liver-function values, and headache (each in one patient) were reversed on discontinuation of the drug. Con-

gestive heart failure has occurred in patients taking itraconazole,²⁰ but it did not occur in any of the patients in this study. As expected, itraconazole prophylaxis had no benefit in reducing bacterial infections in patients with chronic granulomatous disease.

Although 50 of 95 plasma samples had no detectable levels of itraconazole and 39 had no detectable levels of hydroxyitraconazole, a clinical benefit was still demonstrated. A similar beneficial effect, despite low plasma levels, was observed in patients with neutropenia and acute leukemia who were treated with itraconazole to prevent invasive gingival aspergillosis.¹⁴ The clinical efficacy of itraconazole, despite the absence of detectable plasma levels in many patients, is not surprising, since the high lipophilicity of itraconazole results in extensive tissue distribution, with levels many times higher in the tissues than in plasma.⁸ The strong clinical efficacy, with no detectable plasma levels in nearly half the patients, suggests that monitoring of plasma drug levels is not routinely indicated.

This prospective trial of antifungal prophylaxis in patients with a primary immunodeficiency shows that itraconazole therapy is effective and safe in children and adults and does not result in the development of clinically significant resistance when

used for a prolonged period. When added to antibiotics and interferon gamma, itraconazole should markedly reduce the greatest remaining cause of mortality in chronic granulomatous disease. We suggest that itraconazole prophylaxis should be added to the treatment regimens for all patients over five years of age who have chronic granulomatous disease. However, since our study patients received itraconazole continuously for only one year, rigorous monitoring for itraconazole toxicity is warranted for patients receiving long-term, continuous therapy.

REFERENCES

1. Lekstrom-Himes JA, Gallin JI. Immunodeficiency diseases caused by defects in phagocytes. *N Engl J Med* 2000;343:1703-14.
2. Winkelstein JA, Marino MC, Johnston RB, et al. Chronic granulomatous disease: report on a national registry of 368 patients. *Medicine (Baltimore)* 2000;79:155-69.
3. Margolis DH, Melnick DA, Alling DW, Gallin JI. Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. *J Infect Dis* 1990; 162:723-6.
4. Weening RS, Kabel P, Pijman P, Roos D. Continuous therapy with trimethoprim-sulfamethoxazole in patients with chronic granulomatous disease. *J Pediatr* 1983;103:127-30.
5. The International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. *N Engl J Med* 1991;324:509-16.
6. Cohen MS, Isturiz RE, Malech HL, et al. Fungal infection in chronic granulomatous disease: the importance of the phagocyte in defense against fungi. *Am J Med* 1981;71: 59-66.
7. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrob Agents Chemother* 1988;32: 1310-3.
8. Heykants J, Van Peer A, Van de Velde V, et al. The clinical pharmacokinetics of itraconazole: an overview. *Mycoses* 1989;32: Suppl 1:67-87.
9. Van Peer A, Woestenborghs R, Heykants J, Gasparini R, Gauwenbergh G. The effects of food and dose on the oral systemic availability of itraconazole in healthy subjects. *Eur J Clin Pharmacol* 1989;36:423-6.
10. Van Cauteren H, Heykants J, De Coster R, Cauwenbergh G. Itraconazole: pharmacologic studies in humans and animals. *Rev Infect Dis* 1987;9:Suppl 1:S43-S46.
11. Gallin JI, Buescher ES, Seligmann BE, Nath J, Gaither T, Katz P. NIH conference: recent advances in chronic granulomatous disease. *Ann Intern Med* 1983;99:657-74.
12. Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. *N Engl J Med* 1972;286:808-12.
13. Efron B. Forcing a sequential experiment to be balanced. *Biometrika* 1971;58: 403-17.
14. Myoken Y, Sugata T, Kyo T, Fujihara M, Mikami Y. Itraconazole prophylaxis for invasive gingival aspergillosis in neutropenic patients with acute leukemia. *J Periodontol* 2002;73:33-8.
15. Gupta AK, De Doncker P, Scher RK, et al. Itraconazole for the treatment of onychomycosis. *Int J Dermatol* 1998;37: 303-8.
16. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. *Clin Infect Dis* 2001; 33:e83-e90.
17. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clin Infect Dis* 2002; 34:277-84.
18. Smith DE, Bell J, Johnson M, et al. A randomized, double-blind, placebo-controlled study of itraconazole capsules in the prevention of deep fungal infections in immunodeficient patients with HIV infection. *HIV Med* 2001;2:78-83.
19. Lamy T, Bernard M, Courtois A, et al. Prophylactic use of itraconazole for the prevention of invasive pulmonary aspergillosis in high risk neutropenic patients. *Leuk Lymphoma* 1998;30:163-74.
20. Ahmad S, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. *Lancet* 2001;357:1766-7.

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