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An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia

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***Objectives*: This trial studied the efficacy and safety of itraconazole and fluconazole in the prevention of invasive fungal infections in neutropenic patients with haematological malignancies.**

***Patients and methods*: An 8 week, open-label, randomized, parallel-group, multicentre trial comparing itraconazole oral solution (2.5 mg/kg twice daily; *N* = 248) with fluconazole oral solution or capsules (400 mg daily; *N* = 246) in 494 patients with anticipated profound neutropenia (i.e. neutrophil count expected to be <500 cells/mm^3 for at least 10 days) from tertiary care centres.**

***Results*: Invasive fungal infections were reported for 4 out of 248 patients (1.6%) in the itraconazole group and 5 out of 246 patients (2.0%) in the fluconazole group. Invasive *Aspergillus* infections were proven for 2 out of 248 patients (0.8%) in the itraconazole group and 3 out of 246 patients (1.2%) in the fluconazole group. For both the ITT and profoundly neutropenic populations, no differences were detected between treatment groups in proven or suspected invasive fungal infections or other endpoints. The mortality rates owing to proven invasive fungal infections were 2 out of 248 patients (0.8%) for the itraconazole group and 3 out of 246 patients (1.2%) for the fluconazole group. There was also no difference between treatment groups in the number of patients who recovered from neutropenia or in the duration of neutropenia. More discontinuation of drug intake owing to nausea and more hypokalaemia occurred in the itraconazole group, other adverse events and the total number of adverse events were similar in both groups.**

***Conclusions*: In this study there were no differences in the efficacy and safety of itraconazole and fluconazole prophylaxis in neutropenic patients with haematological malignancies.**

Keywords: invasive fungal infections, candidiasis, antifungal prophylaxis, aspergillosis, survival

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Introduction

Invasive fungal infections are a leading cause of mortality and morbidity in neutropenic patients with haematological malignancies and profound neutropenia. The prevalence of invasive fungal infections is from 2 to 40% depending upon a variety of factors, including the underlying disease and required treatment.[1] The predominant causative fungi in Europe and North America are *Aspergillus* and *Candida* species. Invasive *Aspergillus* infections have a mortality rate of at least 50% in patients with neutropenia alone and 86% in those who have had a stem cell transplant.[2] Invasive non-*albicans Candida* infections are now responsible for almost half of all nosocomial invasive *Candida* infections, with a case fatality rate between 20 and 40%, depending on the species,[3] and in one transplant centre, these species are responsible for >90% of all *Candida* infections.[4] In response to these findings, we sought to confirm that antifungal prophylaxis may reduce the morbidity and mortality associated with invasive fungal infections in patients with haematological malignancy and profound neutropenia.

The primary objective of this study was to compare the efficacy of itraconazole oral solution with fluconazole oral solution for the prevention of invasive fungal infections, particularly invasive *Aspergillus* infections, in patients with haematological malignancy and anticipated profound neutropenia (neutrophil count expected to be <500 cells/mm^3 for at least 10 days). The secondary objectives were the incidence of superficial fungal infections, the incidence of and time to initiation of intravenous amphotericin B, the evolution of colonization and the safety in the two prophylactic groups. Other analyses included comparisons between treatment groups of mortality rates from invasive fungal infections and the duration of neutropenia.

Patients and methods

Study design

This was an open-label, randomized, parallel-group, comparative study of itraconazole and fluconazole, conducted between 18 March 1996 and 4 September 1999. The maximum duration of treatment scheduled was 56 days (8 weeks). The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed by an independent institutional review board or ethics committee at each of the 34 participating centres at University and State hospitals in Germany. Prior to any study activities, written informed consent was obtained from each patient or his/her legal representative. An independent expert committee, consisting of the principal investigators, a non-participating haematologist, an independent statistician and radiologist, evaluated all fungal endpoints and made the final decisions. The Janssen-Cilag GmbH study coordinator functioned as an observer.

Patients

Eligibility requirements included hospitalized male or female patients with neutrophil counts expected to be <500 cells/mm^3 for at least 10 days owing to acute leukaemia who were scheduled for remission/induction or consolidation/re-induction chemotherapy, autologous bone marrow transplantation (no autologous blood stem cell transplantation), chemotherapy for the blast crisis of chronic myeloid leukaemia, or lymphoma or myeloma undergoing aggressive chemotherapy. Patients had to have a life expectancy of ≥14 days and had to have no signs or symptoms of fungal infection (such as proven or suspected invasive fungal infection, positive chest X-ray, or fever of unknown origin). However, patients with fungal colonization were allowed to enrol.

Investigators enrolled patients using a centralized randomization schedule generated by a contract research organization (i.e. International Institute for Drug Development S.A., Brussels). Patients were randomized so that each centre had balance between the treatment groups. The randomization was also to be stratified for underlying disease (transplant, acute leukaemia and other subjects); however, owing to administrative reasons, this stratification was not performed at randomization. Instead, the analysis was stratified by acute leukaemia versus all others.

Study treatment

Itraconazole oral solution (supplied by Janssen-Cilag GmbH, Beerse, Belgium) was administered on a 5 mg/kg body weight basis (0.25 mL/kg body weight). The total daily dose was divided equally between a morning and evening dose and was preferably administered without a meal. The dose was adjusted if a patient's body weight changed >10% compared with baseline. Fluconazole oral solution was provided by Janssen-Cilag GmbH from commercial sources and was administered as a single daily dose of 400 mg (four cups of 20 mL each) shortly before or with a meal. In an amendment to the study protocol (dated 15 May 1996), if patients could not tolerate the taste of fluconazole oral solution, the single daily dose was administered as two 200 mg capsules. Prophylaxis was started on the first day of treatment of the underlying disease and continued until the neutrophil count was ≥1000 neutrophils/mm^3. Dosing could be extended up to a maximum of 2 days following the end of neutropenia, unless a study endpoint was reached earlier. Blood sampling for itraconazole levels was done but no analysis occurred.

Concomitant medication

Systemic antifungal agents, other than study treatments, were not allowed. Topical antifungal agents (i.e. applied to the skin or vagina) were allowed during the study. Mouthwash products containing non-absorbable amphotericin B, nystatin or chlorhexidine were allowed provided patients did not swallow the rinse. Drugs with known significant interaction with azole antifungals were not permitted during the study, including astemizole, cisapride, oral midazolam, triazolam, HMG-CoA reductase inhibitors, rifampicin, rifabutin, phenobarbital, carbamazepine, isoniazid, ritonavir, clarithromycin and pimozide.

Endpoints

The primary study endpoint was the incidence of invasive *Aspergillus* infections in neutropenic patients treated prophylactically with itraconazole or fluconazole. Secondary endpoints were the incidence of proven invasive, suspected invasive and superficial fungal infections; the incidence of fever of unknown origin; the incidence of recovery from neutropenia; the duration of neutropenia; the mortality rate; and the probability of survival from invasive fungal infections.

Proven invasive fungal infections were defined by any of the three criteria. The first criterion was a positive histology on biopsy from deep tissue. The second criterion was at least one positive blood culture for yeasts to be further specified into three categories (i) no clinical signs and symptoms except fever, (ii) clinical signs and symptoms in addition to fever, or (iii) sepsis. Moreover, candidaemia was also further specified as (i) not catheter related, (ii) catheter related, (iii) acute disseminated candidiasis, or (iv) chronic disseminated candidiasis. The third criterion was the presence of clinical signs and radiological lesions typical for invasive fungal infections in combination with presence of *Aspergillus* spp. or other filamentous fungi in bronchoalveolar fluid.

Suspected invasive infections were also defined by any of the three criteria. The first criterion was the clinical signs and symptoms (with or without radiological lesions) with fever of unknown origin, which was unresponsive to broad-spectrum antibacterials. The second criterion was highly suggestive radiological lesions (e.g. X-ray or CT scan, with halo or air-crescent sign) for invasive fungal infection without mycological evidence by culture or histology (e.g. hepatosplenic candidiasis and some types of pulmonary invasive *Aspergillus* infections). The third criterion was the clinical signs and symptoms (with or without radiological lesions) that were not highly suggestive of fungal infection but associated with suggestive fungal isolation (e.g. from sputum or nasal cavities for *Aspergillus* infections).

Statistical analysis

At least 670 patients were anticipated to provide the 608 evaluable patients (304 patients per treatment group) required to achieve a two-sided 5% significance level with 80% power to detect a difference between treatments of 1 versus 5%.

Statistical analyses were conducted on each of the two analysis samples: all randomized patients who had at least one administration of the trial medication and who had post-baseline efficacy data (modified ITT population), and ITT patients whose neutrophil count was <500 cells/mm^3 for a period of at least 10 consecutive days anytime during the study (profoundly neutropenic population). Although statistical tests were conducted, interpretation of the *P*-values was descriptive.

Comparisons of the incidence rates between treatment groups at endpoints were performed using the Cochran–Mantel–Haenszel test with a controlling factor of underlying disease (acute leukaemia versus all others). The endpoints included proven invasive fungal infections (*Candida* spp., *Aspergillus* spp. and other), suspected invasive fungal infections (*Candida* spp., *Aspergillus* spp. and others), superficial fungal infections (oral candidiasis, oesophageal candidiasis, vaginal candidiasis, superficial skin infection and others), fever of unknown origin, recovery from neutropenia and duration of neutropenia >56 days. The same statistical test was used to compare the mortality rates (owing to proven invasive fungal infections and owing to any cause) between the two treatment groups. Additionally, 95% confidence intervals (CIs) were constructed on the difference in incidence rates and mortality rates between the two treatment groups under the assumption of normality. Differences in frequencies were calculated with Fisher's exact test. Survival probability by days was plotted using the Kaplan–Meier method. In addition, the log-rank test stratified by underlying disease was conducted to assess the difference in survival rates between the treatment groups. Differences in the duration of neutropenia between the two groups were also evaluated using a two-way analysis of variance, with treatment group and underlying disease as the main effects.

Results

Patient population

This study was terminated early owing to the slow enrolment of patients necessary to reach a target population of 670 patients. From 18 March 1996 to 23 July 1999, 508 patients were eligible and entered into the study. One patient was not randomized or treated because the patient withdrew consent. The remaining 507 patients were randomly assigned to receive either itraconazole or fluconazole oral solution (Figure 1). Thirteen patients were randomized to treatment groups (eight in the itraconazole group and five in the fluconazole group), but were not treated (primarily because they withdrew consent before treatment). These patients were excluded from all analyses.

Four hundred ninety-four patients received treatment (248 patients received itraconazole therapy twice daily and 246 patients

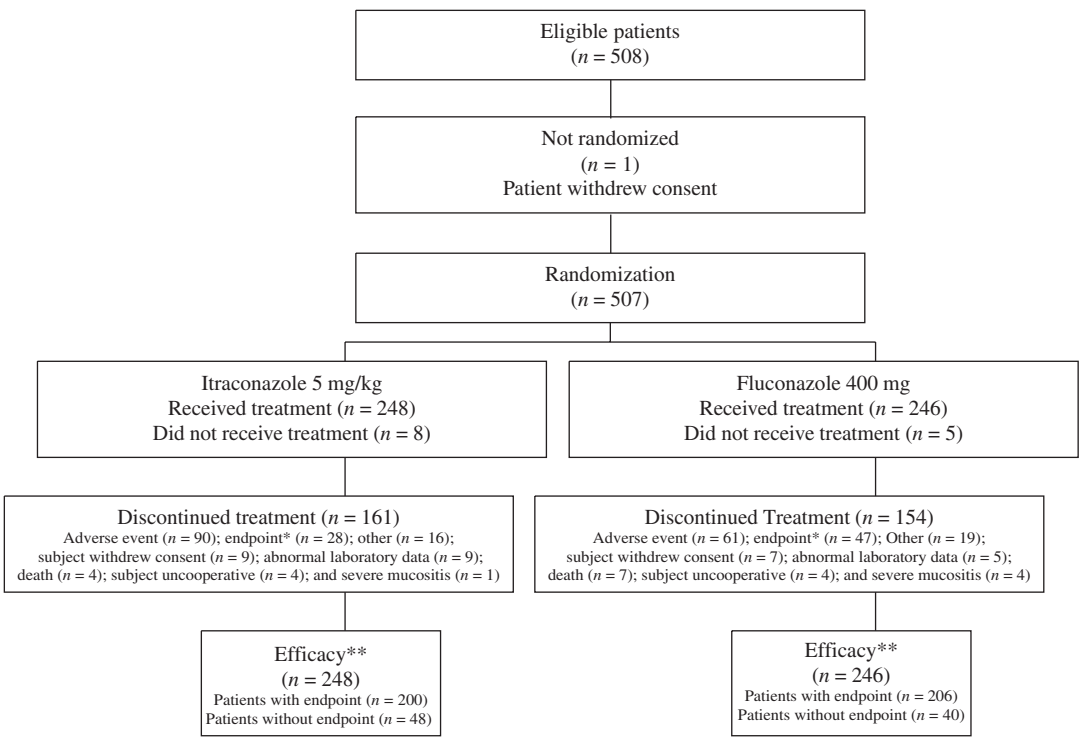

Figure 1. Study flow chart. Single asterisk represents discontinued treatment due to occurrence of an endpoint other than neutrophil recovery or neutropenia >56 days. Double asterisks represent as assessed by an independent expert committee.

Table 1. Demographic and baseline characteristics

	Itraconazole 5 mg/kg (n = 248)	Fluconazole 400 mg (n = 246)
Sex, n (%)		
male	140 (56.5)	141 (57.3)
female	108 (43.5)	105 (42.7)
Age (years), n (%)		
16 to <21	10 (4.0)	10 (4.1)
21 to <65	207 (83.5)	195 (79.3)
≥65	31 (12.5)	41 (16.7)
Underlying disease		
acute lymphoblastic leukaemia	34 (13.7)	26 (10.6)
acute myelogenous leukaemia	171 (69.0)	189 (76.8)
chronic myeloid leukaemia (blast crisis)	11 (4.4)	7 (2.8)
lymphoma	25 (10.1)	14 (5.7)
myeloma	–	2 (0.81)
others	7 (2.8)	8 (3.3)
First treatment[a]		
induction	163	157
consolidation	49	52
Relapse/refractory[a]		
induction	24	26
consolidation	19	12
Neutropenia		
duration of neutropenia (days), median (min–max)	18.0 (1–63)	17.0 (1–52)
profound neutropenia, n (%)	73 (29.4)	91 (37.0)
Concomitant topical antifungal agents		
amphotericin B	92 (37.1)	84 (34.1)
nystatin	9 (3.6)	7 (2.8)

Min, minimum; max, maximum.
[a]Type of treatment is reported for all assessed subjects (itraconazole, n = 255; fluconazole, n = 247).

received fluconazole therapy once daily). One hundred fifty-three patients (62.2%) changed from the oral solution of fluconazole to fluconazole capsules. Baseline demographic characteristics were similar for both treatment groups (e.g. 56.5% of the itraconazole patients were men with a mean age of 47.7 years, and 57.3% of fluconazole patients were men with a mean age of 50.2 years) (Table 1). One patient with lymphoma and autologous stem cell transplantation was treated with itraconazole.

The mean total daily dose and mean duration of treatment was 375.7 mg (range 230–800 mg) and 18.2 days (range 1–57 days) for patients in the itraconazole treatment group, and 396.0 mg (range 200–690 mg) and 20.6 days (range 1–64 days) for patients in the fluconazole treatment group, respectively. A few protocol deviations did occur during the study, including concomitant intake of a contraindicated medication (phenytoin) in one subject treated with fluconazole, and the concomitant administration of one or two fluconazole doses in two subjects treated with itraconazole (one subject inadvertently received a prescription by a non-study physician, and the reason for the other subject is unknown). None of the protocol violations adversely affected the efficacy or safety results.

Approximately 39% of the patient population received additional topical antifungal agents for oral rinses (mostly amphotericin B; Table 1). There was no significant difference between the two arms in the use of these agents (P = 0.407).

Efficacy

A total of 494 patients were in the ITT population (248 patients in the itraconazole group and 246 patients in the fluconazole group), and 164 patients were in the profoundly neutropenic population (73 patients in the itraconazole group and 91 patients in the fluconazole group), defined as those who had documented neutrophil counts <500 cells/mm^3 for at least 10 consecutive days.

Invasive fungal infections and invasive Aspergillus infections

Proven invasive fungal infections were reported for 4 out of 248 patients (1.6%) in the itraconazole group and 5 out of 246 patients (2.0%) in the fluconazole group. Invasive *Aspergillus* infections were confirmed for 2 out of 248 patients (0.8%) in the itraconazole group and 3 out of 246 patients (1.2%) in the fluconazole group.

For the ITT population, no differences in proven or suspected invasive fungal infection endpoints were detected between the itraconazole and fluconazole groups. Differences between the two groups for other endpoints (i.e. superficial fungal infections, fever of unknown origin and >56 days neutropenia) were also not detected (Table 2). Patients with profound neutropenia showed similar results (Table 3). Owing to the small sample size, some of the 95% CIs were generally not informative.

Mortality

Overall, five of the nine patients with proven invasive fungal infections died during the study. The mortality rates owing to proven invasive fungal infections were 0.8% (2 out of 248; one *Aspergillus* spp., one *Candida* spp.) for patients in the itraconazole group and 1.2% (3 out of 246; one *Aspergillus* spp., one *Candida* spp. and one unspecified fungus) for patients in the fluconazole group. Of the two patients who died from invasive fungal infections in the itraconazole group, the final cause of death was pulmonary haemorrhage (with additional Gram-negative pneumonia) in one patient and to gastrointestinal bleeding in the other patient. Of the three patients who died from proven invasive fungal infections in the fluconazole group, one succumbed to circulatory failure, a second to septic shock and multiple organ failure, and a third patient to pneumonia with fungal sepsis.

A Kaplan–Meier analysis showed that there was no statistically significant difference in the time of survival between the itraconazole and fluconazole treatment groups (P = 0.775). For the ITT population, mortality rates owing to any cause between the itraconazole and fluconazole treatment groups were comparable [25 out of 248 (10.1%) and 28 out of 246 (11.4%), respectively; 95% CI, –6.8% to 4.2%; P = 0.678] (Table 4). Patients with profound neutropenia showed similar results, although there was a trend towards a lower mortality rate in the itraconazole treatment group compared with fluconazole treatment group (P = 0.131). The mortality rate owing to any cause for patients with profound neutropenia was 5 out of 73 (6.8%) for the itraconazole treatment group and 13 out of 91 (14.3%) for the fluconazole treatment group (95% CI, –16.7 to 1.8%; P = 0.128) (Table 4).

Duration and recovery from neutropenia

For patients treated with itraconazole or fluconazole, there was no difference in the number of patients who recovered from

Table 2. Summary of endpoints—intent-to-treat population

Endpoint[a]	Itraconazole 5 mg/kg (N_1 = 248) n_1 (%)	Fluconazole 400 mg (N_2 = 246) n_2 (%)	Total (N = 494) n (%)	P-value[b]	Difference in proportion (%)	95% CI[c] (%)
Proven invasive fungal infection	4 (1.6)	5 (2.0)	9 (1.8)	0.694	–0.4	–2.8 to 1.9
candidiasis	1 (0.4)	1 (0.4)	2 (0.4)	0.984	0	–1.1 to 1.1
aspergillosis	2 (0.8)	3 (1.2)	5 (1.0)	0.581	–0.4	–2.2 to 1.4
others[d]	1 (0.4)	1 (0.4)	2 (0.4)	0.984	0	–1.1 to 1.1
Suspected invasive fungal infection	22 (8.9)	28 (11.4)	50 (10.1)	0.379	–2.5	–7.8 to 2.8
candidiasis	0	2 (0.8)	2 (0.4)	0.166	–0.8	–1.9 to 0.3
aspergillosis	12 (4.8)	12 (4.9)	24 (4.9)	0.981	0	–3.8 to 3.8
others	6 (2.4)	13 (5.3)	19 (3.8)	0.122	–2.9	–6.3 to 0.5
not specified	4 (1.6)	1 (0.4)	5 (1.0)	NA	1.2	–0.6 to 3.0
Superficial fungal infection[e]	1 (0.4)	1 (0.4)	2 (0.4)	0.932	0	–1.1 to 1.1
vaginal candidiasis	1 (0.4)	0	1 (0.2)	0.382	0.4	–0.4 to 1.2
not specified	0	1 (0.4)	1 (0.2)	NA	–0.4	–1.2 to 0.4
Fever of unknown origin[e]	24 (9.7)	23 (9.3)	47 (9.5)	0.889	0.3	–4.8 to 5.5
Recovery from neutropenia	146 (58.9)	144 (58.5)	290 (58.7)	0.948	0.3	–8.3 to 9.0
>56 days neutropenia	3 (1.2)	5 (2.0)	8 (1.6)	0.501	–0.8	–3.1 to 1.4
No endpoint	48 (19.4)	40 (16.3)	88 (17.8)	0.381	3.1	–3.6 to 9.8

CI, confidence interval; NA, not applicable.
[a]Endpoints were based on a review by an expert panel.
[b]Between-treatment P value from Cochran–Mantel–Haenszel test controlling for underlying disease (acute leukaemia and others).
[c]95% CI of the difference in proportion = difference in proportion $\pm 1.96 * [p_1 * (1 - p_1)/N_1 + p_2 * (1 - p_2)/N_2]^{1/2}$, where $p_1 = n_1/N_1$ and $p_2 = n_2/N_2$.
[d]Other proven fungal infections included *Cryptococcus* and not otherwise specified.
[e]Requiring systemic antifungal therapy.

Table 3. Summary of endpoints—profoundly neutropenic population[a]

Endpoint[b]	Itraconazole 5 mg/kg (N_1 = 73) n_1 (%)	Fluconazole 400 mg (N_2 = 91) n_2 (%)	Total (N = 164) n (%)	P-value[c]	Difference in Proportion (%)	95% CI[d] (%)
Proven invasive fungal infection	2 (2.7)	3 (3.3)	5 (3.0)	0.839	–0.6	–5.8 to 4.7
candidiasis	0	1 (1.1)	1 (0.6)	0.371	–1.1	–3.2 to 1.0
aspergillosis	1 (1.4)	1 (1.1)	2 (1.2)	0.874	0.3	–3.1 to 3.7
others	1 (1.4)	1 (1.1)	2 (1.2)	0.874	0.3	–3.1 to 3.7
Suspected invasive fungal infection	11 (15.1)	14 (15.4)	25 (15.2)	0.955	–0.3	–11.4 to 10.7
candidiasis	0	1 (1.1)	1 (0.6)	0.375	–1.1	–3.2 to 1.0
aspergillosis	6 (8.2)	8 (8.8)	14 (8.5)	0.916	–0.6	–9.1 to 8.0
others	3 (4.1)	4 (4.4)	7 (4.3)	0.950	–0.3	–6.5 to 5.9
not specified	2 (2.7)	1 (1.1)	3 (1.8)	NA	1.6	–2.7 to 6.0
Superficial fungal infection[e]	0	1 (1.1)	1 (0.6)	0.371	–1.1	–3.2 to 1.0
not specified	0	1 (1.1)	1 (0.6)	NA	–1.1	–3.2 to 1.0
Fever of unknown origin[e]	11 (15.1)	7 (7.7)	18 (11.0)	0.137	7.4	–2.5 to 17.2
Recovery from neutropenia	38 (52.1)	55 (60.4)	93 (56.7)	0.285	–8.4	–23.6 to 6.9
>56 days neutropenia	3 (4.1)	4 (4.4)	7 (4.3)	0.931	–0.3	–6.5 to 5.9
No endpoint	8 (11.0)	7 (7.7)	15 (9.1)	[f]	3.3	–5.8 to 12.3

CI, confidence interval; NA, not applicable.
[a]Intent-to-treat patients with neutrophil count less than 500 cells/mm^3 for at least 10 consecutive days.
[b]Endpoints were based on a review by an expert panel.
[c]Between-treatment P value from Cochran–Mantel–Haenszel test controlling for underlying disease (acute leukaemia and others).
[d]95% CI of the difference in proportion = difference in proportion $\pm 1.96 * [p_1 * (1 - p_1)/N_1 + p_2 * (1 - p_2)/N_2]^{1/2}$, where $p_1 = n_1/N_1$ and $p_2 = n_2/N_2$.
[e]Requiring systemic antifungal therapy.
[f]P-value for 'no endpoint' not available because Breslow-Day test for homogeneity of the odds ratio was significant.

Table 4. Summary of mortality

	Itraconazole 5 mg/kg	Fluconazole 400 mg	Total	*P*-value[a]	Difference in proportion (%)	95% CI[b] (%)
	(N_1 = 248) n_1 (%)	(N_2 = 246) n_2 (%)	(N = 494) n (%)			
Intent-to-treat population						
Mortality from proven invasive fungal infection	2 (0.8)	3 (1.2)	5 (1.0)	0.628	–0.4	–2.2 to 1.4
Mortality from any cause	25 (10.1)	28 (11.4)	53 (10.7)	0.678	–1.3	–6.8 to 4.2
	(N_1 = 73) n_1 (%)	(N_2 = 91) n_2 (%)	(N = 164) n (%)			
Profoundly neutropenic population[c]						
Mortality from proven invasive fungal infection	0	3 (3.3)	3 (1.8)	0.119	–3.3	–7.0 to 0.4
Mortality from any cause	5 (6.8)	13 (14.3)	18 (11.0)	0.128	–7.4	–16.7 to 1.8

CI, confidence interval.
[a]Between-treatment *P* value from Cochran–Mantel–Haenszel test controlling for underlying disease (acute leukaemia and others).
[b]95% confidence interval of the difference in proportion = difference in proportion ± $1.96 * [p_1 * (1 - p_1)/N_1 + p_2*(1 - p_2)/N_2]^{1/2}$, where $p_1 = n_1/N_1$, and $p_2 = n_2/N_2$.
[c]Intent-to-treat patients with neutrophil count <500 cells/mm^3 for a period of at least 10 consecutive days.

neutropenia prior to reaching other endpoints (Tables 2 and 3) or in the duration of neutropenia (Table 1) in either the ITT or profoundly neutropenic populations.

For the ITT population, the number of patients who recovered from neutropenia prior to other endpoints was 146 out of 248 (58.9%) in the itraconazole treatment group and 144 out of 246 (58.5%) in the fluconazole treatment group (95% CI, –8.3 to 9.0%; $P = 0.948$). For the profoundly neutropenic population, the number of patients who recovered from neutropenia prior to other endpoints was 38 out of 73 (52.1%) in the itraconazole treatment group and was 55 out of 91 (60.4%) in the fluconazole treatment group (95% CI, –23.6 to 6.9%; $P = 0.285$).

The mean duration of neutropenia in days (±SE) for patients in the ITT population was 19.2 ± 0.83 days (95% CI, 17.6–20.9) in the itraconazole treatment group and 18.6 ± 0.73 days (95% CI, 17.1–20.0) in the fluconazole treatment group ($P = 0.511$). For patients who were profoundly neutropenic, the duration of neutropenia in days (±SE) was 26.5 ± 1.51 days (95% CI, 23.6–29.5) in the itraconazole treatment group and 23.3 ± 1.07 days (95% CI, 21.2–25.4) in the fluconazole treatment group ($P = 0.077$).

Safety and tolerability

All but 10 patients who received at least one dose of study treatment experienced adverse events. Both the investigators and the expert committee considered most of these events not to be treatment related. A total of 90 out of 248 patients (36%) in the itraconazole group and 61 out of 246 patients (28%) in the fluconazole group discontinued treatment owing to adverse events ($P = 0.0062$). Table 5 lists adverse events leading to discontinuation of the trial medication, adverse events related to the trial medication and severe adverse events (Grades III and IV). Fifty-three patients (25 patients in the itraconazole group and 28 patients in the fluconazole group) died during the study. All deaths were attributed to the underlying disease and were not considered by the investigators or the expert committee to be related to either study medication. Serious adverse events were reported by 47 out of 248 patients (19%) in the itraconazole group and 48 out of 246 patients (20%)

Table 5. Adverse events and serious adverse events

	Itraconazole 5 mg/kg (N = 248)	Fluconazole 400 mg (N = 246)
Adverse events leading to discontinuation of trial medication (in ≥10 patients), *n* (%)		
nausea	45 (18.1)	23 (9.3)
vomiting	25 (10.1)	24 (9.8)
diarrhoea	9 (3.6)	2 (0.8)
fever	27 (10.9)	31 (12.6)
hepatotoxicity	12 (4.8)	7 (2.8)
pneumonia	7 (2.8)	11 (4.5)
Adverse events related to trial medication (in ≥10 patients), *n* (%)		
nausea	74 (29.8)	71 (28.9)
diarrhoea	57 (23.0)	24 (9.8)
vomiting	34 (13.7)	45 (18.3)
abdominal pain	20 (8.1)	8 (3.3)
constipation	6 (2.4)	17 (6.9)
fever	8 (3.2)	6 (2.4)
hypokalaemia	24 (9.7)	19 (7.7)
hyperkalaemia	8 (3.2)	6 (2.4)
hyponatraemia	9 (3.6)	3 (1.2)
skin	11 (4.4)	14 (5.7)
headache	8 (3.2)	7 (2.8)
hepatotoxicity	30 (12.1)	25 (10.2)
Serious adverse events (in ≥4 patients), *n* (%)		
sepsis	11 (4.4)	15 (6.1)
increase of hepatic enzymes	10 (4.0)	6 (2.4)
pneumonia	8 (3.2)	8 (3.3)
respiratory insufficiency	7 (2.8)	6 (2.4)
fever	5 (2.0)	3 (1.2)
cardiac failure	4 (1.6)	4 (1.6)
circulatory failure	4 (1.6)	2 (0.8)
GI haemorrhage	4 (1.6)	0

in the fluconazole group. Of these, the events for 15 out of 248 patients (6%) in the itraconazole group and 12 out of 246 patients (5%) in the fluconazole group were considered by the investigators and the expert committee to be possibly related to the study medication.

The most common treatment-related adverse events were nausea, diarrhoea, vomiting, constipation, hypokalaemia and abdominal pain. Although the overall rate was similar, moderate to severe hypokalaemia was reported more often for patients in the itraconazole group than for patients in the fluconazole group [total rates: 30 out of 248 (12.1%) and 21 out of 246 (8.5%), respectively; for rates related to trial medication see Table 5]. Hypokalaemia did not lead to discontinuation of trial medication. Although rates of treatment-related nausea were similar, twice as many patients in the itraconazole group than in the fluconazole group discontinued treatment owing to nausea [45 out of 248 (18.1%) and 23 out of 246 (9.3%), respectively]. There were four events with cardiac failure in each arm, no cardiac adverse events were related to itraconazole (Table 5).

Discussion

This study demonstrated that differences in efficacy and serious adverse events between itraconazole and fluconazole were not discernible in this patient population with haematological malignancies and profound neutropenia. A larger proportion of patients stopped taking itraconazole oral solution (where a switch to capsules was not allowed) than fluconazole (where patients could switch from oral solution to capsules).

Relatively low rates of proven invasive fungal infections were observed in both treatment arms (1.6 and 2.0%). The reason for this lower incidence remains unclear, as the patient group in this study was severely immunosuppressed as shown by the high proportion (87%) of patients with acute leukaemia or the long duration of neutropenia (median 21–22 days). A possible explanation could be that the lack of confirmation of a suspected diagnosis resulted in the low rate of proven invasive infections. Galactomannan antigen testing[5] and high-resolution CT scan[6] were not regularly available or used in all centres during the time of the study when prophylaxis and empirical antifungal therapy were considered to be the main weapons against fungal infections. It should also be noted that the EORTC/MSG criteria[7] were not yet established at the time the study was planned and conducted.

Furthermore, the study was terminated early, which further reduced its statistical power to detect differences between the two treatment arms. However, considering the low rate of proven infections, accrual of the planned number of patients would probably not have made a difference. The trial's patient population, however, was a group with considerable risk to develop invasive fungal infections. They would be classified as high risk according to the Infectious Diseases Working Party of the German Society of Haematology and Oncology or as intermediate high risk according to Prentice *et al.*[1,8] The later classification has been validated recently by McLintock *et al.*[9] and a rate of ~10% proven and probable (according to the EORTC/MSG criteria) invasive fungal infections could be expected in this population. Studies on antifungal prophylaxis should be very careful to include only patients with a sufficient risk of invasive fungal infections.

A meta-analysis on antifungal prophylaxis in neutropenic patients, which included the data from this trial, demonstrated that itraconazole solution reduced the relative risk of proven invasive fungal infections by 49% and of proven invasive *Aspergillus* infections by 48%.[10] Also, itraconazole was superior in the subset of six trials, including this study, which compared itraconazole with fluconazole (1769 patients, relative risk reduction of proven invasive fungal infection 40%, $P = 0.04$).[11–15] The dose of fluconazole in these trials ranged between 100 mg/day (two trials),[12,13] 300 mg/day (one trial)[11] and 400 mg/day (three trials).[14,15] In this meta-analysis a number-needed-to-treat (NNT) was calculated as 1 : 13 to prevent one invasive fungal infection in a patient population with an incidence of these infections of 15%.[10] Lower or higher incidence rates would lead to different NNTs as these highly depend on the baseline risk. We have discussed the evidence for antifungal prophylaxis in detail elsewhere.[16]

The incidence of proven invasive fungal infections in control arms without systemic antifungals in studies of antifungal prophylaxis was ~5.5%.[17–21] In the meta-analysis the rate of proven invasive fungal infections in patients with itraconazole prophylaxis was 3.3%, when trials using itraconazole solution and itraconazole capsules were combined, and 2.7%, when only trials with itraconazole solution were analysed.[10] The rate of proven invasive fungal infection in systematic reviews of antifungal prophylaxis with fluconazole was 3.1[10] and 2.1%,[22] respectively.

Another notable result from this study was that there was no difference in the duration of neutropenia (Table 5) in patients receiving itraconazole or fluconazole. As a drug–drug interaction has been demonstrated with vincristine[23–25] and high-dose cyclophosphamide[26] and cytarabine[27] owing to itraconazole's inhibition of cytochrome P450 isoenzyme 3A4, it is important to confirm that the myelosuppressive effects of antileukaemia drugs, are not enhanced.

Adverse events did not differ in the total rate but were different in only two aspects related to the application of itraconazole. (i) Hypokalaemia was more often moderate or severe in the itraconazole arm although the reported overall rates were the same. Thus, monitoring is advisable in patients receiving itraconazole. (ii) The rates of treatment-related nausea were comparable for both solutions, even though patients given fluconazole were permitted to switch to fluconazole capsules which occurred in a large proportion of patients. Patients given itraconazole were not allowed to switch to itraconazole capsules in this study. The discontinuation rate was considerably higher than in other comparable trials where the rate of discontinuation was lower in patients receiving itraconazole capsules than in their controls (2.5 versus 2.8%)[11,12,17,28] and highest in patients receiving itraconazole solution (23 versus 13%).[13,19,29] A trial that compared itraconazole solution with a placebo containing cyclodextrin found comparable rates of discontinuation in both arms (27 versus 28%).[18] The rate of discontinuation was much higher in this trial (itraconazole 36%, fluconazole 25%) for unknown reasons.

Excessive renal or liver toxicity was not observed in the itraconazole arm of this study and this corresponds to results in most studies of prophylaxis with itraconazole. However, a recently published trial of antifungal prophylaxis in patients after allogeneic stem cell transplantation found an excess of renal and liver toxicity in the itraconazole arm compared with fluconazole.[15] There, itraconazole was given at high doses in this trial concomitantly with conditioning chemotherapy. Thus, the observation was most probably owing to an interaction of itraconazole and high-dose cyclophosphamide or busulfan treatment.[30,31] The toxicity was comparable in both arms after the protocol was changed and itraconazole was applied only after the conditioning chemotherapy.[15]

Similarly, another clinical trial which compared fluconazole and itraconazole after the conditioning chemotherapy in patients after allogeneic stem cell transplantation found no difference in renal and hepatic toxicity between the two arms.[14] These experiences emphasize the need to pay close attention to drug–drug interactions in the clinical use of azoles.[32]

Several studies that analysed itraconazole pharmacokinetics have confirmed that the oral solution of itraconazole is much more bioavailable than the capsules.[10,32–35] Also, a clear dose–response relationship could be established in the meta-analysis and in retrospective analyses of patient cohorts.[10,36,37] These concentrations (a target trough concentration of >500 ng/mL was recommended) can only be reached by application of the oral solution of itraconazole.[35] Another alternative is to use intravenous itraconazole as it has been successfully done in two studies in allogeneic stem cell transplantation.[14,15] Further research on this problem is clearly needed, unfortunately, pharmacokinetic samples have not been analysed in this study. Pharmacokinetic studies have shown that the use of a loading dose with either oral or intravenous itraconazole achieves effective plasma concentrations faster and more reliably.[33–35]

No drug-related congestive heart failure or an increase in the rate of sepsis was observed in either arm of this trial, which confirms the results of other clinical studies with itraconazole and fluconazole.[10,38]

In conclusion, owing to the low number of proven invasive fungal infections, the sensitivity of this study was not sufficient to demonstrate a difference between itraconazole and fluconazole in the antifungal prophylaxis in neutropenic patients. Additionally, this trial provides evidence for the equivalent safety of itraconazole and fluconazole in this indication.

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