Oral and Intravenous Itraconazole for Systemic Fungal Infections in Neutropenic Haematological Patients: Meeting Report

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Key Words

Bone marrow transplantation · Fungal infection, systemic · Itraconazole · Malignancy, haematological · Neutropenia

Abstract

Effective prevention, or treatment, of invasive fungal infection in the neutropenic patient has hitherto been unsatisfactory because of either an inadequate anti-fungal spectrum of the agent or important toxicity. Itraconazole is effective against a broad spectrum of the opportunistic pathogens seen in Europe and North America. Prior problems with absorption, e.g. in the marrow transplant recipient, have been overcome with the introduction of an oral solution and an i.v. preparation. The deliberations of an expert meeting held in June, 1998 include recommendations on which patient requires one of these new preparations based on clinical trials, the dose and route. Important drug interactions are also detailed.

This is an expert report of a meeting held in London on 20 June 1998 on itraconazole. The meeting was supported by an unrestricted educational grant from Janssen-Pharmaceutica and Janssen Research Foundation, Beerse, Belgium.

Introduction

Systemic fungal infection is an increasing problem in patients receiving immunosuppressive chemotherapy for haematological malignancies and in bone marrow transplant recipients. Contributory factors include the use of broad-spectrum antibiotics, corticosteroids, central venous catheters, profoundly immunosuppressive chemotherapy, intensive irradiation protocols and mismatched or unrelated donor transplants, despite the increasing use of rooms with high-efficiency particulate air filtration.

Previously, most infections were by *Candida* species. Although infection by *Candida albicans* is decreasing, the incidence of non-*C. albicans* isolates is increasing [1]. In Europe, *Aspergillus* species are now the most frequently identified invasive pathogens. Mucorales are seen occasionally and any of a wide range of emerging fungi, such as *Fusarium*, *Scedosporium* and *Trichosporon*, may be involved [2, 3]. Broad-spectrum antifungal therapy is therefore required.

Many fungal infections are diagnosed only at autopsy [4] because current diagnostic tools are largely inadequate; as a result, prophylaxis and empirical therapy play a key role in patient management. The agents used most frequently are amphotericin B (the treatment of choice for many years), fluconazole and itraconazole.

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Amphotericin B has a broad spectrum of activity (including against *Candida* and *Aspergillus* species) [5], but conventional formulations are associated with acute toxic reactions and nephrotoxicity [2]. New lipid-based preparations of amphotericin B are now available; each is likely to be at least as effective as and less nephrotoxic than the conventional formulations [6, 7], but optimum therapeutic dosages require clarification.

Fluconazole is used extensively [8–12], particularly as prophylaxis, but it has a limited spectrum of activity (it is ineffective against *Aspergillus* and some non-*C. albicans* species, such as *Candida krusei*) and the emergence of drug resistance has been reported [13–16].

Itraconazole is active against a wide range of dermatophytes, yeasts and fungi (including *Candida* and *Aspergillus* species) [17], but the standard capsule formulation is less suitable for use in some patients because absorption from the capsules is impaired in patients with gastrointestinal epithelial damage [18]; in addition, because absorption depends on gastric acidity, the capsules must be taken with food to achieve optimum bioavailability; they may therefore be absorbed suboptimally by patients with restricted oral food intake [19–21].

The use of hydroxypropyl- β -cyclodextrin has enabled the development of two new itraconazole formulations (an oral solution and an intravenous preparation), which provide higher, more consistent plasma concentrations of itraconazole than the capsule formulation does [22–27] and should facilitate the effective use of this agent in a wider range of patients.

A meeting was held in London, UK, on 20 June 1998, to discuss the use of the itraconazole oral solution and intravenous formulations in neutropenic or otherwise immunosuppressed patients. Specific questions were addressed in a round-table discussion and pharmacokinetic and efficacy data were presented to facilitate informed debate. This publication is a summary of the practical recommendations made at the meeting regarding the use of the new itraconazole formulations in this patient population.

Prophylaxis

Which Patients Require Prophylaxis?

Prophylaxis with itraconazole was recommended for patients who are expected to have neutropenia (neutrophil count $0.1\text{--}0.5 \times 10^9/\text{l}$) for at least 2 weeks or profound neutropenia (neutrophil count $<0.1 \times 10^9/\text{l}$) for more than 1 week. Prophylaxis may not be required for

patients receiving autologous peripheral stem cell transplants because they have a relatively short period of neutropenia (compared with bone marrow transplant recipients).

The incidence of systemic fungal infection depends not only on the severity of neutropenia but also on the underlying disease. Lower rates of infection (4–5%) occur in patients undergoing autologous bone marrow transplantation, especially those with solid tumours receiving a colony-stimulating factor [28]; intermediate rates (8%) are documented in patients with acute leukaemia [11, 12] and higher rates (16–18%) are reported in patients undergoing allogeneic bone marrow transplantation for haematological malignancies [9,10]. The risk of *Aspergillus* infection in allogeneic bone marrow transplant recipients is higher if the patient is older, has acute myelogenous leukaemia beyond first remission, has graft-versus-host disease treated with high-dose steroids or is not treated in a laminar airflow room with high-efficiency particulate air filtration or when unrelated donors are used. In addition, the risk of *Aspergillus* infection is higher in patients with relapsing or progressive acute myelogenous leukaemia or other haematological malignancies if they receive high doses of gut-damaging chemotherapy, fludarabine or powerful immunosuppressive agents such as steroids.

Have the New Itraconazole Formulations Been Evaluated in the Prophylactic Setting?

The itraconazole oral solution (5 mg/kg/day) has been evaluated as prophylaxis during neutropenic episodes in three major studies; results are summarized in table 1. Study 1 was a double-blind, placebo-controlled trial with blinded review and standard antibiotics ($n = 405$) [29]. Prophylaxis was started at the same time as chemotherapy. Patients undergoing allogeneic bone marrow transplantation or receiving high-dose cytosine arabinoside were excluded. Study 2 and study 3 used similar patient populations, but allogeneic bone marrow transplant recipients were included in study 2. Study 2 was an open, randomized comparison with fluconazole 100 mg/day ($n = 445$) [30]. Study 3 was a double-blind, double-dummy comparison with oral amphotericin B 2 g/day ($n = 557$), with blinded review and an interim analysis [31]; this trial was stopped prematurely because the anticipated incidence of aspergillosis was not reached in either arm.

Fewer fungal infections occurred in the itraconazole groups than in the comparison groups in all three studies (significant difference vs. placebo in study 1). Consequently, the use of intravenous amphotericin B therapy was also lower in the itraconazole group in all three stud-

Table 1. Summary of data from three major prophylactic studies evaluating itraconazole oral solution

	Study 1 [29]		Study 2 [30]		Study 3 [31]	
	itraconazole (n = 201)	placebo (n = 204)	itraconazole (n = 288)	fluconazole (n = 293)	itraconazole (n = 281)	amphotericin B (n = 276)
All fungal infections	48*, ^a	68*, ^a	67	82	93	103
Deep aspergillosis	4	1	0	4	5	9
Use of i.v. amphotericin B	43**	59**	39*	58*	90	102
Death with proven deep fungal infection	1	5	0*	4*	1	5

*p ≤ 0.05 (statistical significance); 0.05 < **p ≤ 0.1 (statistical trend). n = Number of patients.
^a Proven deep fungal infections (itraconazole n = 5, placebo n = 9) plus suspected deep fungal infections requiring empirical amphotericin B (itraconazole n = 43, placebo n = 59).

ies (significant difference vs. fluconazole in study 2; trend towards significant difference vs. placebo in study 1). This observation is of particular clinical relevance because of the risk of severe nephrotoxicity with intravenous amphotericin B. The incidence of deep aspergillosis was consistently low across the studies; indeed, the overall incidence of mould infection was low in all three studies, which may explain the lack of statistical difference between groups. Additionally, in study 1, significantly lower incidences of candidaemia (itraconazole n = 1, placebo n = 8; p < 0.05) and fewer deaths related to *Candida* infection (itraconazole n = 0, placebo n = 4) were seen in the itraconazole group than in the placebo group. Fewer deaths with proven deep fungal infection occurred in the itraconazole groups in all three studies (table 1).

The itraconazole intravenous formulation is currently under evaluation as prophylaxis for allogeneic bone marrow transplant recipients.

Which Itraconazole Formulations Should Be Used for Prophylaxis?

The itraconazole oral solution was considered to be appropriate for prophylaxis, starting from day 1 of chemotherapy. One week of the intravenous formulation and the oral solution thereafter was considered to be an appropriate prophylactic regimen for high-risk patients, such as allogeneic bone marrow transplant recipients. The intravenous formulation was considered to be appropriate for patients unable to take oral medication (i.e. those with chemotherapy-induced, severe, oral and intestinal mucositis). Further information is needed to assess the potential impact of interactions between azole antifungals and chemotherapeutic agents on multidrug resistance and the timing of prophylaxis.

Which Patients May Require Long-Term Prophylaxis?

Patients receiving corticosteroids, patients undergoing mismatched bone marrow transplantation, patients with graft-versus-host disease, patients who have received profoundly immunosuppressive chemotherapy (such as combinations containing fludarabine) or durable semi-intensive chemotherapy for acute lymphoblastic leukaemia and patients undergoing another course of myeloablative chemotherapy who have had a previous invasive fungal infection (such as aspergillosis) were considered to require long-term prophylaxis beyond the period of neutropenia.

What Factors May Affect the Long-Term Administration of the Itraconazole Oral Solution?

Some patients receiving the itraconazole oral solution may experience cyclodextrin-associated diarrhoea, which is usually well tolerated; however, if the diarrhoea becomes problematic and gastrointestinal absorption is unimpaired, a switch from the oral solution during neutropenia to capsules after neutrophils have recovered was proposed. (Neutrophils are used as a marker of mucosal repair, except in graft-versus-host disease affecting the gastrointestinal tract.) Intermittent monitoring of the plasma concentration of itraconazole is advised if the capsule formulation is used in the long term.

Empirical and Definitive Therapy

Have the New Itraconazole Formulations Been Evaluated in the Treatment Setting?

The efficacy of the itraconazole oral solution in oral candidiasis [32–34] and oesophageal candidiasis [35] has been compared with that of fluconazole in HIV-positive

individuals. In all four studies, the response rates were equivalent. In most cases, the causative organism was *C. albicans*.

The itraconazole intravenous formulation is under evaluation as definitive treatment for aspergillosis and candidiasis and as empirical therapy for fever that is unresponsive to antibiotics in patients with persistent neutropenia.

Which Itraconazole Formulations Should Be Used for Treatment?

One week of the itraconazole intravenous formulation and the oral solution thereafter were considered to be an acceptable regimen for empirical treatment.

An earlier switch to the itraconazole oral solution was also considered to be a viable option, given that an adequate plasma concentration of itraconazole is achieved after 2 days of treatment with the intravenous formulation [27]. Because the two new formulations have equivalent spectra of activity and bioavailability, only a patient's inability to take oral medication should delay a switch from intravenous itraconazole to the oral solution.

A longer overall period of treatment was considered to be required for aspergillosis than for candidiasis (non-*C. albicans*) but a precise duration could not be agreed. Treatment for 1 week beyond resolution of all diagnostic features of infection (fever, computed tomography scan) was considered the minimum requirement in patients whose neutrophils have recovered.

For patients who do not respond to itraconazole, a switch to amphotericin B was recommended (the choice of amphotericin B formulation should be made according to local practice and taking specific indication, renal function and concomitant use of other nephrotoxic drugs into consideration); no data are currently available on switching back to intravenous itraconazole in this setting.

Have the New Itraconazole Formulations Been Evaluated in Patients with Fluconazole-Resistant Infections?

At present, no data are available for neutropenic patients, but the itraconazole oral solution has been evaluated in three open trials in HIV-positive individuals with fluconazole-resistant or fluconazole-refractory oropharyngeal candidiasis [36–38]. Responses ranged from 60 to 80%. Causative agents were *C. albicans* (75.4% of cases), *Candida glabrata* (17.4%) and *C. krusei* (5.9%). Response was achieved in 23 of 25 patients with a fluconazole-resistant *C. glabrata* infection.

General Considerations

What Is the Target Plasma Concentration of Itraconazole?

Tentative interpretive minimal inhibitory concentration breakpoints for itraconazole have been established for mucosal candidal infections: susceptible 100–250 ng/ml, susceptible dependent on dose 250–500 ng/ml, and resistant $\geq 1,000$ ng/ml [39]. A plasma concentration of itraconazole of at least 250–500 ng/ml was therefore considered to be desirable.

Early pharmacokinetic data from autologous bone marrow transplant recipients show that use of the itraconazole oral solution 5 mg/kg once daily during remission-induction treatment produced serum concentrations of itraconazole that reached (and exceeded) 500 ng/ml from day 8 onwards [22]. When itraconazole was given prophylactically, 86–100% of patients reached adequate levels after 12 days [29].

In patients who received a loading dose of intravenous itraconazole 200 mg twice daily for 2 days followed by 200 mg once daily from day 3 to day 7, steady-state plasma concentrations of itraconazole of 250 ng/ml were achieved by day 1 and 500 ng/ml by day 2. In addition, a plasma concentration of at least 500 ng/ml was maintained after a switch to the oral solution 200 mg twice daily at day 7 [27].

Both new itraconazole formulations therefore rapidly produce target plasma concentrations of the drug. (Itraconazole concentrations were obtained by high-performance liquid chromatography.)

Is Monitoring Required?

For both the oral solution and the intravenous formulation of itraconazole, monitoring of the plasma drug concentration was considered to be unnecessary (given the reliable pharmacokinetic profiles) [40] and impractical (given the short anticipated duration of neutropenia). Monitoring plasma itraconazole concentrations may be useful when the oral solution or the intravenous formulation is used for treatment of documented infection.

How Should the Itraconazole Oral Solution Be Taken to Achieve Optimum Bioavailability?

In healthy volunteers, the relative bioavailability of the itraconazole oral solution exceeds that of the capsule formulation when both are taken with food [31]. In addition, unlike the capsule formulation, bioavailability is increased with the oral solution under fasting conditions (fig. 1) [41, 42].

Fig. 1. Itraconazole capsules and oral solution in healthy volunteers: effect of food on oral bioavailability at steady state

Can the New Itraconazole Formulations Be Used in Patients with Impaired Gastrointestinal Absorption?

The itraconazole oral solution was considered to be appropriate for allogeneic bone marrow transplant recipients with impaired gastrointestinal absorption, including that caused by severe graft-versus-host disease of the intestine. However, the intravenous formulation was recommended for patients with severe mucositis.

What Other Factors Might Influence the Choice of Itraconazole Formulation?

If a patient is unconscious or intubated, oral administration of any antifungal agent is not always appropriate.

The recommendation was made to switch patients to the itraconazole intravenous formulation if they experience unacceptable gastrointestinal upset with the oral solution and do not require long-term treatment. A trial is in progress in the UK to examine the pharmacokinetics of switching from the itraconazole oral solution to the intravenous formulation, to determine whether a loading dose is still appropriate in this setting.

Which Drugs Should Not Be Given with Itraconazole or Require Special Precautions?

The following drugs should not be given concurrently with itraconazole: terfenadine, astemizole, cisapride, pimozide, HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam or triazolam.

Inhibition of cytochrome P450 by itraconazole may lead to reduced clearance of oral anticoagulants, digoxin, cyclosporin A, systemic methylprednisolone, vinca alkaloids [43, 44], dihydropyridine calcium channel blockers,

quinidine, intravenous midazolam, clarithromycin, phenytoin, tacrolimus and busulphan [45]. These drugs require monitoring and may require dose reductions. Other drugs may increase the elimination of itraconazole (rifampicin, carbamazepine and isoniazid) and may lead to sub-therapeutic blood levels of itraconazole.

Which Drugs Are Not Affected by Itraconazole?

In vitro studies have shown that no interactions on plasma protein binding occur between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide or sulphamethazine.

No interaction between itraconazole and zidovudine or omeprazole and no inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone have been observed.

How Will the New Itraconazole Formulations Contribute to the Management of Systemic Fungal Infections?

The new formulations of itraconazole are expected to play an important role in the management of systemic fungal infection for several reasons. First, they provide high, consistent plasma concentrations of itraconazole. With the intravenous formulation, adequate plasma concentrations of itraconazole are achieved rapidly (in 2 days). With the oral solution, optimum bioavailability is achieved under fasting conditions (whereas the capsule formulation must be taken with food). For both the oral solution and the intravenous formulation, monitoring of the plasma concentration of itraconazole is unnecessary. Furthermore, allogeneic bone marrow transplant recipients with impaired gastrointestinal absorption caused by severe graft-versus-host disease can still receive the itraconazole oral solution, whereas patients who cannot swallow or tolerate the oral solution can receive itraconazole by intravenous infusion.

Overall, therefore, the new itraconazole formulations should provide clinicians with greater flexibility in the management of systemic fungal infection in neutropenic haematological patients and they are expected to reduce the use of intravenous amphotericin B, with resultant patient benefit.

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