REVIEW ARTICLE

Drugs 2001; 61 Suppl. 1: 39-47
0012-6667/01/0001-0039/$27.50/0

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Clinical Experience with Itraconazole in Systemic Fungal Infections

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Abstract

The broad spectrum antifungal itraconazole is an effective and well tolerated agent for the prophylaxis and treatment of systemic fungal infections. The recent development of an itraconazole oral solution and an intravenous itraconazole solution has increased the options for the use of this drug and increased the oral bioavailability in a variety of at-risk patients. Reliable absorption of the itraconazole oral solution has been demonstrated in patients with HIV infection, neutropenic patients with haematological malignancy, bone marrow transplant recipients and neutropenic children. In clinical trials, itraconazole oral solution (5 mg/kg/day) was more effective at preventing systemic fungal infection in patients with haematological malignancy than placebo, fluconazole suspension (100 mg/day) or oral amphotericin-B (2 g/kg/day) and was highly effective at preventing fungal infections in liver transplant recipients. There were no unexpected adverse events with the itraconazole oral solution in any of these trials. In addition, intravenous itraconazole solution is at least as effective as intravenous amphotericin-B in the empirical treatment of neutropenic patients with systemic fungal infections, and drug-related adverse events are more frequent in patients treated with amphotericin-B. A large proportion of patients with confirmed aspergillosis also respond to treatment with intravenous itraconazole followed by oral itraconazole. The new formulations of itraconazole are therefore effective agents for prophylaxis and treatment of most systemic fungal infections in patients with haematological malignancy.

Itraconazole is a triazole antifungal (fig. 1) with a broad spectrum of activity against *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, dermatophytes, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, phaeohyphomycetes, *Sporothrix schenckii* and a variety of other fungi.[1] When first introduced approximately 10 years ago, itraconazole was formulated as a capsule only. This formulation is widely used for the treatment of onychomycosis, other superficial fungal infections, endemic systemic infections, systemic *Aspergillus* infections and to a lesser extent systemic *Candida* infections in immunocompromised and non-immunocompromised patients.

The prophylactic efficacy of itraconazole capsules has been demonstrated in a number of trials. In neutropenic patients with haematological malignancy, itraconazole prophylaxis at doses of 200 mg/day[2] or 400 to 600 mg/day[3] halved the number of proven systemic fungal infections and significantly decreased mortality from systemic fungal infections, particularly yeast infections, compared with placebo. In another trial comparing a historical untreated control group with a group

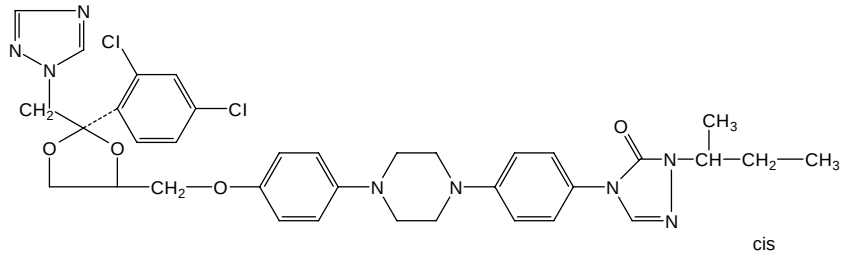

Fig. 1. Structural formula of itraconazole.

given prophylaxis with itraconazole capsules 400 to 600 mg/day, itraconazole significantly decreased mortality from invasive fungal infections.[4] In addition, prophylaxis with itraconazole capsules (200 or 400 mg/day) is at least as effective as prophylaxis with oral amphotericin-B (historical controls)[5] or fluconazole capsules (100 mg/day; randomised) in patients with haematological malignancy.[6] Other patient groups who have been shown to benefit from prophylaxis with itraconazole capsules are selected patients with advanced HIV infection (200 mg/day; placebo-controlled),[7] patients with solid tumours (100 mg/day; open trial),[8] lung transplant recipients (case report),[9] and patients with chronic granulomatous disease (5 to 10 mg/kg/day; historical controls).[10] However, it should be noted that long term prophylaxis with azoles in patients with HIV is generally avoided because of the cost of long term drug use, the potential for drug resistance and the lack of overall survival benefit in this patient group.

Itraconazole capsules alone or in combination with amphotericin-B have been used successfully to treat confirmed aspergillosis.[11-15] However, in practice, systemic fungal infections are difficult to diagnose and many patients are treated empirically; until recently, intravenous (IV) amphotericin-B was considered the 'gold standard' of empirical therapy. In a small study, itraconazole capsules (400 mg/day) were as effective as IV amphotericin-B (0.6 mg/kg/day) for the empirical therapy of systemic fungal infections in neutropenic patients.[16]

The absorption of the itraconazole capsule can be variable in patients with damage to the intestinal epithelium or with reduced gastric acidity.[17,18] Novel formulations of itraconazole, containing the solubilising excipient hydroxypropyl-β-cyclodextrin (HP-β-CD), have therefore been developed. When the capsules and oral solution of itraconazole are compared, the bioavailability of the oral solution, which contains HP-β-CD, is approximately 60% greater than that of the capsules.[19-21] This value was obtained in healthy volunteers but the absorption of the itraconazole oral solution has been shown to be reliable in patients with HIV infections, with or without AIDS,[22,23] in neutropenic patients with acute leukaemia,[24] in neutropenic children and children who receive liver transplants,[25,26] in autologous[27] and allogeneic[28] bone marrow transplant recipients, and in patients receiving omeprazole.[29] No adverse events attributable to the HP-β-CD were reported in these studies.

An IV formulation of itraconazole has also been introduced recently. In patients with haematological malignancy,[30] patients with advanced HIV infection[31] or those in intensive care units,[32] high and steady-state plasma concentrations can be achieved within 2 to 3 days using IV itraconazole 400 mg/day for 2 days followed by 200 mg/day for 5 days. Subsequent administration of itraconazole oral solution or capsules 400 mg/day will maintain these high plasma concentrations in all patient groups. These studies confirmed the safety of the IV formulation and the HP-β-CD vehicle;[31,32] HP-β-CD was essentially eliminated through the kidney and no accumulation in the body was observed.

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The re-formulation of itraconazole has clearly improved the pharmacokinetics of this drug in patients at risk of systemic fungal infection. The corresponding clinical efficacy and safety of these new formulations are discussed in this chapter.

1. Patients with Haematological Malignancy

Patients with haematological malignancy are at risk of systemic fungal infections because many have neutropenia induced by the disease or by intensive chemotherapy, or are immunosuppressed to facilitate stem cell transplantation. In addition, the natural host defence mechanisms and anatomical barriers to infection may be compromised in these patients by catheters, mucositis induced by radiotherapy or chemotherapy, steroid treatment or graft-versus-host disease (GVHD) after allogeneic transplantation.

1.1 Chemoprophylaxis

Recent data suggest that itraconazole oral solution is an effective prophylactic agent in neutropenic patients with haematological malignancies (mostly patients with acute leukaemia; table I). The incidence of proven and suspected systemic fungal infection combined was significantly lower in patients treated with itraconazole oral solution (5 mg/kg/day) than in patients receiving placebo (24% and 33%, respectively).[33] The authors concluded that treatment of 11 patients with itraconazole oral solution would prevent one case of proven or suspected systemic fungal infection. In common with other trials of itraconazole oral solution, the death rate with proven fungal infection was very low in itraconazole-treated patients. On average, patients received itraconazole oral solution for 20 days, and tolerability was excellent; adverse events causing interruption of the drug dosage regimen occurred in 18% of recipients of itraconazole oral solution and 13% of recipients of placebo (nonsignificant difference), which also contained the HP-β-CD vehicle.[33]

The efficacy of chemoprophylaxis with itraconazole oral solution in patients with haematological malignancy was confirmed in an open-label comparative trial with fluconazole 100 mg/day; table I). Significantly fewer systemic fungal infections and deaths of presumed fungal origin occurred in the itraconazole-treated group than in the fluconazole-treated group.[34] However, significance was only achieved after inclusion of 2 cases of invasive aspergillosis that occurred outside the study period. The relatively narrow spectrum of activity of fluconazole was reflected in the fungal infections that occurred in fluconazole-treated patients (4 cases of *Aspergillus* infection, and 1 case each of *Candida tropicalis* and *C. krusei* infection). Treatment with itraconazole oral solution was associated with more gastrointestinal adverse events, except for constipation, which occurred more frequently in the fluconazole-treated group. However, neither azole was associated with seri-

Table I. Summary of efficacy results from itraconazole oral solution prophylaxis trials[a]

Variable	Trial 1[33]		Trial 2[34]		Trial 3[37]	
	itraconazole (5 mg/kg/day)	placebo	itraconazole (5 mg/kg/day)	fluconazole (100 mg/day)	itraconazole (5 mg/kg/day)	amphotericin-B (2 g/day)
No. of patients	201	204	288	293	281	276
Proven SFI	5 (2.5)	9 (4.4)	0 (0.0)*[b]	6 (2.0)*[b]	8 (2.8)	13 (4.7)
Proven + suspected SFI	48 (23.9)*	68 (33.3)*	10 (3.5)	13 (4.4)	91 (32.4)	93 (33.7)
Proven aspergillosis	4 (2.0)	1 (0.5)	0 (0.0)*	6 (2.0)*	5 (1.8)	9 (3.3)
Death with SFI	1 (0.5)	5 (2.5)	0 (0.0)*	7 (2.4)*	1 (0.4)	5 (1.8)
Proven superficial fungal infection	11 (5.5)	13 (6.4)	4 (1.4)	11 (3.8)	2 (0.7)	13 (4.7)

a Where appropriate, values are shown as no. of cases (%).

b First study episodes only.

SFI = systemic fungal infection. Statistically significant difference: * $p < 0.05$.

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ous unexpected adverse events.[34] It has been suggested that the osmotic activity of the HP-β-CD excipient in itraconazole oral solution can loosen stools, which may explain the greater number of gastrointestinal adverse events with itraconazole oral solution in this trial. However, chemotherapy for haematological malignancy often causes gastrointestinal adverse events and it is therefore difficult to attribute such events to a given antifungal regimen. Many previous studies have used higher doses of fluconazole – 400 mg/day – for prophylaxis (for example, see Rotstein et al.[35]). These higher doses tend to be favoured in the USA, whereas in Europe doses of 50 to 100 mg/day are preferred. However, there is no conclusive evidence to suggest that high doses of fluconazole are more effective than doses of 50 to 100 mg/day, and in Europe 50 mg/day has been recommended.[36]

Itraconazole oral solution (5 mg/kg/day) was also shown to be more effective than oral amphotericin-B (2 g/day) in preventing superficial fungal infections in neutropenic patients. There was also a nonsignificant trend towards a reduction in proven systemic fungal infections and death with fungal infection with itraconazole oral solution (table I).[37] These two prophylactic agents were shown to be equivalent in a second comparative trial (unpublished data), probably because a lower dosage of itraconazole oral solution (200 mg/day) was used.

On the basis of results of a noncomparative study, itraconazole oral solution may also be an effective agent for antifungal prophylaxis in children with haematological malignancy. Of 103 neutropenic children with haematological malignancy (90% undergoing transplantation) given itraconazole oral solution (5 mg/kg/day) as prophylaxis, none developed a proven systemic fungal infection.[38] One patient received amphotericin-B rescue therapy for mycologically confirmed oesophageal candidiasis and 26 patients received amphotericin-B rescue therapy for fever of unknown origin. There were no unexpected problems with the tolerability of itraconazole oral solution (the most frequent drug-related adverse event was vomiting) and compliance was good with this formulation.[38]

Taken together, these trial data suggest that itraconazole oral solution (5 mg/kg/day) is an effective prophylactic agent. Fluconazole has also been effective for prophylaxis in clinical trials[35] but the narrower spectrum of antifungal activity of fluconazole makes itraconazole oral solution an attractive prophylactic option. Further trials of itraconazole oral solution and IV itraconazole for the prophylaxis of systemic fungal infections in patients with haematological malignancy, recipients of bone marrow transplants, and patients with GVHD are ongoing.

1.2 Treatment

The therapeutic plasma concentrations of itraconazole that are rapidly achieved with the IV formulation make it ideal for the treatment of confirmed systemic fungal infection or empirical treatment. In addition, these high plasma concentrations can be maintained, after 5 to 10 days of IV treatment, with itraconazole oral solution 400 mg/day.[30,32] The availability of the three itraconazole formulations potentiates switching from IV to oral therapy, which provides the flexibility and convenience needed to treat the different groups of patients susceptible to systemic fungal infection.[39]

A recent trial compared a regimen of IV itraconazole (400 mg/day for 2 days then 200 mg/day for 12 days) followed by itraconazole oral solution (400 mg/day) for 14 days with IV amphotericin-B (0.7 to 1.0 mg/kg/day) for up to 28 days as empirical therapy in 384 patients with haematological malignancy. In the itraconazole-treated group, 48% of patients responded to treatment and, in the amphotericin-B-treated group, 38% responded.[40] In addition, patients receiving itraconazole experienced significantly fewer drug-related adverse events than patients receiving amphotericin-B. The liposomal formulation of amphotericin-B is also as effective as, and has a better safety profile than, conventional amphotericin-B,[41] but it is less cost effective than IV itraconazole.[42]

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These results suggest that IV itraconazole and lipid-associated formulations of amphotericin-B are valuable options for empirical therapy in persistently febrile neutropenic patients. A randomised trial comparing IV itraconazole with liposomal amphotericin-B for empirical therapy is needed.

The itraconazole capsule formulation may be as effective as IV amphotericin-B for empirical therapy and is possibly more effective against *Aspergillus* infections.[16] The IV formulation of itraconazole has therefore been investigated for the treatment of confirmed aspergillosis.[43] The same IV itraconazole regimen was used as for empirical therapy (400 mg/day for 2 days then 200 mg/day for 12 days), but was followed by 12 weeks of treatment with itraconazole capsules (400 mg/day). Of 31 patients treated, 15 (48%) responded to treatment with IV itraconazole. It is unlikely that the response rate would have been influenced by the oral formulation of itraconazole used, because plasma concentrations of itraconazole remained high throughout the study.[43] Most of the patients in this trial had haematological malignancy but patients with AIDS and chronic granulomatous disease were also included. The response rate of 48% with IV itraconazole followed by capsules may be similar to response rates with itraconazole capsules alone[14] and may be higher than that reported with amphotericin-B in similar populations.[44,45]

Most of the patients included in this trial of IV itraconazole for the treatment of aspergillosis had previously failed therapy with IV amphotericin-B, but this did not affect the efficacy of itraconazole therapy.[43,46] Other studies have found no evidence of reduced efficacy in patients who have previously received amphotericin-B;[12,14,15] amphotericin-B and itraconazole are therefore not clinically antagonistic when used sequentially in this order. However, studies are needed to determine whether or not initial therapy with itraconazole followed by therapy with amphotericin-B is clinically antagonistic, as suggested in one *in vitro* study.[47]

Interactions between itraconazole and other drugs used in haematology have been reported. Interaction with the immunosuppressive agent cyclosporin can result in an elevation of cyclosporin levels.[48,49] Routine monitoring of cyclosporin is sufficient to warn of any complications, which can be managed by reducing the cyclosporin dosage. A similar interaction may be seen between itraconazole and tacrolimus, and this can be managed in a similar manner.[48,50] Sporadic cases of interaction between itraconazole and the antineoplastic agent vincristine, resulting in an aggravation of vincristine-induced neurotoxicity, have also been reported.[51]

2. Other Patient Groups

2.1 Patients with HIV Infection

Initially, the itraconazole oral solution was tested and found to be effective for the treatment of oropharyngeal candidiasis in patients with HIV infection. Itraconazole oral solution 200 mg/day for 14 days is at least as effective as fluconazole 100 mg/day for 14 days for the treatment of oropharyngeal candidiasis,[52] and most patients with fluconazole-refractory *Candida* infections respond to treatment with itraconazole oral solution.[53-55] Longer term treatment of oesophageal candidiasis for up to 8 weeks with fluconazole or itraconazole oral solution was also effective.[56] In all of these trials, the adverse event profile for itraconazole oral solution was as expected (nausea was generally the most frequent adverse event) and the tolerabilities of fluconazole and itraconazole oral solution were equivalent.

The broad spectrum of activity of itraconazole makes it ideal for the treatment of rare endemic mycoses that also affect patients with HIV in some parts of the world. Itraconazole is therefore recommended as first-line or maintenance therapy for many endemic mycoses, such as *Penicillium marneffei* infection, paracoccidioidomycosis, coccidioidomycosis, blastomycosis and histoplasmosis.[57-61] In addition, itraconazole is an alternative to fluconazole for the treatment of cryp-

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tococcosis and coccidioidal meningitis,[62,63] and the two drugs are equivalent for consolidation therapy of cryptococcal meningitis.[64]

The IV formulation was shown to be well tolerated in patients with advanced HIV infection and most adverse events reported were infusion-related.[31] In addition, target plasma concentrations of itraconazole were achieved quickly and maintained with itraconazole oral solution.

Protease inhibitors used to treat HIV infection are metabolised by P450-dependent cytochrome 3A. These agents can therefore potentially interact with itraconazole, or any other azole, and dosage reduction and blood concentration monitoring may be advisable when these agents are used concurrently.[65]

2.2 Solid Organ Transplant Recipients

Solid organ transplant recipients, such as liver, lung or heart transplant recipients, are given immunosuppressive therapy to reduce the risk of transplant rejection, and are therefore at risk of systemic fungal infections. As in other immunocompromised groups, infections by *Aspergillus* spp. and *Candida* spp. are the most frequent, but histoplasmosis, coccidioidomycosis and cryptococcosis have been reported.[9,66-68] In general, because mortality from systemic fungal infections in solid organ transplant recipients is high and treatment is often unsuccessful,[67,69,70] antifungal prophylaxis may be warranted in patients at high risk.

Prophylaxis with oral itraconazole has recently been assessed in liver transplant and heart transplant patients. In heart transplant recipients, primary prophylaxis with itraconazole capsules reduced the incidence of invasive aspergillosis from 9.6% in a historical control group to an incidence of 2%.[71] Treatment with itraconazole capsules was well tolerated despite relatively long term treatment (median of 135 days). However, because of the episodic nature of aspergillosis in many institutions, the use of historical controls is inadequate.

A placebo-controlled trial demonstrated the efficacy and safety of prophylaxis with itraconazole oral solution (5 mg/kg/day) in liver transplant recipients. Significantly more patients in the placebo-treated group than in the itraconazole-treated group developed a fungal infection: 9 patients and 1 patient, respectively.[72] In addition, itraconazole oral solution caused no more adverse events than placebo in this patient group.[73] These initial results indicate that prophylaxis with itraconazole oral solution in liver transplant recipients may be effective.

2.3 Miscellaneous

The IV or oral solution formulations of itraconazole may also be effective treatment for systemic candidiasis in non-neutropenic patients; this includes many patients in intensive care units, such as neonates, patients recovering from surgery and people with severe burns. Oral formulations of itraconazole have been used successfully to treat *Candida* septicaemia and systemic candidiasis in neonates.[74-76] However, at present there is an absence of published reports on the use of these new formulations for treating systemic candidiasis.

3. Conclusions

Since its launch approximately 10 years ago, the efficacy of itraconazole has been demonstrated in a number of different clinical settings. Use of the capsule formulation for the management of systemic fungal infections in immunocompromised patients has been limited by the variable absorption of the drug in some patient groups. The new formulations of itraconazole containing HP-β-CD have not only improved oral absorption of the drug in these patient groups but have also facilitated the use of itraconazole intravenously. The IV itraconazole formulation introduces more flexibility in the use of itraconazole and rapidly achieves high plasma concentrations of itraconazole when needed. The available clinical data for the oral solution and IV formulations are for the prophylaxis and treatment of systemic fungal infections in neutropenic patients with haematological malignancies. These data suggest that the broad spectrum of itraconazole oral solution is an important advantage in

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prophylaxis over the widely used fluconazole, and the safety of both itraconazole formulations (when used sequentially) make itraconazole an attractive choice of agent in empirical therapy. Initial data also support the use of itraconazole oral solution in preventing fungal infections in solid organ transplant patients and emphasise the value of itraconazole in a wide variety of patient groups at risk of fungal infection.

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