Efficacy and safety of itraconazole use in infants

Shuang Chen, Kai-Yi Sun, Xiao-Wei Feng, Xin Ran, Jebina Lama, Yu-Ping Ran
Chengdu, China

Background: **Itraconazole has been used to treat fungal infections, in particular invasive fungal infections in infants or neonates in many countries.**

Data sources: **Literature search was conducted through Ovid EMBASE, PubMed, ISI Web of Science, CNKI and Google scholarship using the following key words: "pediatric" or "infant" or "neonate" and "fungal infection" in combination with "itraconazole". Based on the literature and our clinical experience, we outline the administration of itraconazole in infants in order to develop evidence-based pharmacotherapy.**

Results: **Of 45 articles on the use of itraconazole in infancy, 13 are related to superficial fungal infections including tinea capitis, sporotrichosis, mucosal fungal infections and opportunistic infections. The other 32 articles are related to systemic fungal infections including candidiasis, aspergillosis, histoplasmosis, zygomycosis, trichosporonosis and opportunistic infections as caused by *Myceliophthora thermophila*.**

Conclusions: **Itraconazole is safe and effective at a dose of 5 mg/kg per day in a short duration of therapy for superficial fungal infections and 10 mg/kg per day for systemic fungal infections in infants. With a good compliance, it is cost-effective in treating infantile fungal infections. The profiles of adverse events induced by itraconazole in infants are similar to those in adults and children.**

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Author Affiliations: Department of Dermatovenereology, West China Hospital, Sichuan University, Chengdu, China (Chen S, Sun KY, Feng XW, Ran X, Lama J, Ran YP)

Corresponding Author: Yu-Ping Ran, MD, PhD, Department of Dermatovenereology, West China Hospital, Sichuan University, Chengdu 610041, China (Tel: +86-18980601697; Fax: +86-028-85422560; Email: ranyuping@vip.sina.com)

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Introduction

Fungal infections account for 9% episodes of late onset sepsis in neonatal infections.[1] Four classes of antifungal agents are commonly used in the treatment of fungal infections in pediatric patients: polyene macrolides, fluorinated pyrimidines, triazoles, and echinocandins. Among them, liposomal and lipid complex preparations of amphotericin B and fluconazole are very effective for the treatment of fungal infections; however, the optimal dosage and duration of therapy is difficult to establish.[2] Itraconazole (ITR) has a broader spectrum of activity than fluconazole,[3] which has been approved by the United States Food and Drug Administration for the treatment of fungal infections in adults. ITR is well tolerated and effective in adults with superficial and systemic fungal infections, but no recommendation has been established for pediatric use. There are limited data concerning the use of ITR to treat fungal infections in infants, although fungal infections are common in infants. This review focuses on the use of ITR in the treatment of mycotic infections in infants. Literature search was conducted through Ovid EMBASE, PubMed, ISI Web of Science, CNKI and Google scholarship in July 2013 using the following key words: "pediatric" or "infant" or "neonate" and "fungal infection" in combination with "itraconazole".

Pharmacokinetics

ITR is a lipophilic compound which exerts its effects on fungi by interfering with synthesis of the cytochrome P450-dependent enzyme lanosterold 14-α-emethylase, an ergosterol precursor that is an essential component of fungal cell membranes.[1-3] The drug concentrations of ITR in all the target organs are 2 to 20 times higher than that in the serum, and are especially high in nails, skin and adipose tissue. However, penetration into the cerebrospinal fluid is poor.[4]

When the trough blood level of ITR ranges from 250 to 500 ng/mL, ITR may be effective in patients with suspected fungal infection.[5] The rate or extent of absorption from itraconazole oral solution (ITR-OS) was found to be greater than that from capsules in 49 pediatric patients, and twice-daily dosing rather than once-daily dosing improves the maintenance of trough

concentrations above the recommended minimum of 500 ng/mL.[6] The bioavailability (60%) of ITR-OS administered after fasting is higher than that of capsules administered immediately after meals.[7] Approximately 30% of the patients who were given ITR capsules 5 mg/kg per day had levels less than 250 ng/mL at which the prophylaxis was considered to be ineffective.[8] In the dosing range of 7.6-10 mg/kg per day, protective trough concentrations were reached in most patients no matter what oral formulation had been used.[9] Another study indicated a trend toward higher concentrations of ITR in plasma in older children.[10] However, the single-dose pharmacokinetics of ITR and hydroxyitraconazole after intravenous administration to children was evaluated, and no relationship was found between age and maximum plasma concentrations or total body clearance.[11] Repeated-dose pharmacokinetics of ITR-OS at a dose of 5 mg/kg per day for 2 weeks in infants and children showed that the potentially therapeutic plasma concentrations were lower in infants aged 6 months to 2 years than those in children aged 2 to 12 years on day 1, but comparable on day 14. The study also indicated that severe infections might need higher doses. Pharmacokinetic data in healthy volunteers from infants are lacking.[12]

Superficial fungal infections

Tinea capitis

Although less frequent than in children, tinea capitis has also been seen in infants and toddlers, even in neonates.[13,14] Seven infants with tinea capitis caused by *Microsporum canis* received ITR 5 mg/kg per day in a continuous regimen, and they were cured clinically and mycologically after 3 to 6 weeks.[15] It is worth noting that ITR at a dose of 100 mg/d for 4 weeks was only effective in less than half of children with *Trichophyton tonsurans* caused tinea capitis.[16] A regimen of ITR for infantile tinea capitis may be needed for additional 14-day courses after a 4-week continuous course.[17,18] Oral ITR was also administrated either as a capsule for older children (116 patients) or an oral suspension for infants (47 patients). Afterward, 88% of the children after 6 weeks of therapy and all the infants after 12 weeks achieved a clinical cure. Mycological examinations were negative although 55 of all patients showed failure of treatment with terbinafine.[19] In a large open, nonrandomized, clinical study, ITR oral pulse regimen, each of 1-week duration with an interval of 2 weeks, provided another ideal alternative to griseofulvin. The number of pulses should be administered according to the clinical response.[20] Infantile tinea capitis, whatever they were caused by *Mirosporum canis* or *Trichophyton rubrum*, was successfully treated with only 2-3 pulses of oral ITR in both formulations.[21,22]

Sporotrichosis

Sporotrichosis is caused by the dimorphic fungus sporothrix complex as a result of implantation into the subcutaneous tissue by contaminated organic material.[23] Sporotrichosis during infancy is rare. Infant sporotrichosis usually presents as a solitary lesion on the face.[24] Oral potassium iodide has been the treatment of choice for childhood sporotrichosis for many years, but it is easy to induce gastrointestinal side effects.[25,26] ITR is the most promising one among newer antimycotic agents. The minimal inhibitory concentration of ITR, ranging from 0.1 to 1.0 mg/L, for the yeast form of *S. schenckii* is well within the therapeutic range. In a previous study, 15 cases of sporotrichosis in Chinese infants aged <10 months were diagnosed, and three of them were treated with oral ITR at a dose of 3 mg/kg per day and was cured in 2.5-4 months (mean: 3.2 months) with neither recurrence nor adverse effects in a follow-up period of 4 to 24 months.[27] Another two infants with sporotrichosis were cured with ITR at a dose of 3 mg/kg or 5 mg/kg per day separately.[28,29]

Mucosal fungal infections

ITR is widely used in the treatment of mucosal fungal infections in children, which are frequently caused by *Candida* or *Aspergillus* species. An ITR-OS given at a dose of 5 mg/kg per day showed potentially therapeutic concentrations in plasma for infants with mucosal fungal infections or at risk for the development of invasive fungal disease.[12] Intravenous ITR given at a dose of 2.5 mg/kg per day was well tolerated in children including 6 infants and afforded the ability to rapidly achieve the therapeutic concentrations of ITR in plasma.[10]

Other cutaneous infections

Children with onychomycosis aged less than 3 years are rarely reported.[30] Topical antifungal agents with lacquers such as amorolfine and ciclopirox and occlusive ointment bifonazole urea, are primarily used for infantile onychomycosis.[26] However, ITR-OS, which facilitates proper administration and dosing, has been introduced.[31,32]

An 18-month-old boy with acute and severe inflammation around his left eyelid caused by a rare opportunistic pathogenic fungi *Chaetomium atrobrunneum* and *Clavispora lusitaniae* was cured with oral ITR capsules in half a month.[33]

Table 1 shows the detailed information on itaconazole use for superficial fungal infections in infants.

Systemic fungal infections

Candidiasis

Fungal infections especially Candida may be responsible for serious diseases in infants. The predominant role of *C. albicans* as a cause of candidemia in hospitalized children has changed in contrast to previous reports.[34,35] Hospital candidemia due to non-albicans *Candida*, such as *C. parapsilosis*, *C. krusei*, *C. pelliculosa*, *C. tropicalis*, and *C. glabrata* are increasing, and *C. parapsilosis* as a significant neonatal pathogen comprises a third of all *Candida* infections and is associated with a mortality of 10%.[35] Bhandari et al[36,37] used oral ITR successfully at a dose of 10 mg/kg per day for 3 to 4 weeks for the treatment of systemic candidiasis in 3 very low birth weight neonates. ITR was associated with good clinical and mycological responses and no significant toxicities were found in a neonate with hepatic candidiasis.[38] ITR at a dose of 10 mg/kg per day for only 6-14 days was effective in the treatment of infants with nosocomial candidemia.[39] In another study, oral ITR was continued 1 week after the blood culture turned to negative, with a minimum duration of 2 weeks, which was also effective in treatment of candidemia in children.[40] A preliminary randomized controlled study including 43 children, 76% of whom had protein energy malnutrition, demonstrated that ITR at a dose of 10 mg/kg per day was as effective as fluconazole in the treatment of children with nosocomial candidiasis receiving intensive care.[41]

Aspergillosis

An immunocompetent infant was treated successfully with amphotericin B (AMB) followed by prolonged ITR therapy for cerebellar aspergillosis as an adjunct to aggressive surgical debridement.[42] The same results were obtained in a preterm neonate with cutaneous disseminated aspergillosis and in another infant with pulmonary aspergillosis.[43,44] However, an infant diagnosed with allergic bronchopulmonary aspergillosis and cystic fibrosis was unsuccessfully treated with oral prednisone and ITR.[45] Despite the dose of oral ITR increased up to 120 mg/kg per day, no effective serum concentrations could be achieved for invasive Aspergillus infection of a two-year-old boy with mild diarrhea at the same time.[46] A large cohort study showed a poor response rate for patients receiving AMB, The patients who achieved complete response accounted for 25% and those who died due to aspergillosis accounted for 65%. By contrast, patients who had received ITR alone or following AMB died of *Aspergillus* accounted for 26% and 36%, respectively.[47]

Histoplasmosis

Histoplasmosis is endemic in Americans, especially in children, the elderly, and immunosuppressed patients.[48] ITR was used in children with disseminated histoplasmosis preliminarily, and a patient had improvement after 1 month of treatment with ITR but died because his guardian refused further treatment.[49] A 4-month-old human immunodeficiency virus (HIV)-negative infant with disseminated histoplasmosis showed good results after treatment with AMB followed by ITR-OS, which was given at a dose of 2.5 mg/kg twice a day for 6 months.[50] Similar result was found in one of dizygotic twins.[51] An 11-month-old infant with acute disseminated histoplasmosis was also successfully treated with ITR at a dose of 10 mg/kg per day for 6 months.[48] In a cohort study of 42 children, 24 who were subjected to antifungal treatment with ITR, AMB or in combination separately had significant improvement. Exceptions included one child with AIDS who relapsed and another child with chronic meningitis who suffered from cerebral sequelae.[52]

Zygomycosis

Zygomycosis is a chronic infection caused by fungus of the order entomophthorales. Robertson et al[53] reported a case of fibrosing mediastinitis secondary to zygomycosis in an immunocompetent 22-month-old infant successfully treated with AMB and ITR for 20 weeks, who was well at follow-up 17 months later. Few infants with gastrointestinal zygomycosis diagnosed by histopathologic findings responded favorably to the treatment including surgical resection of the infected portion of the bowel and administration of ITR.[54,55] A 9-month-old baby, with a rapidly expanding malignant presentation of basidiobolomycosis with non-healing ulcers and spread to underlying muscles mimicking lymphoma, responded poorly to ITR at a dose of 5 mg/kg per day but showed marked improvement after combined therapy of ITR and potassium iodide.[56]

Trichosporonosis

Trichosporon spp. are emerging as opportunistic agents that cause systemic diseases in immunocompromised hosts.[57] *T. asahii*, which had high minimal inhibitory concentration for ITR, was isolated from the throat, feces and urine of a bone-marrow-transplanted infant, who finally died after combined therapy of liposomal AMB (LAMB), fluconazole and ITR.[58] Since *Trichosporon spp.* are difficult to isolate, clinical suspicion is essential for early antifungal therapy to improve the outcome.

Fungal suppuration by *Myceliophthora thermophila*

A 21-month-old male infant developed a gas-containing left parietal brain abscess caused by *Clostridium*

Table 1. Itaconazole for superficial fungal infections in infants

Diagnosis	Study	Age (y)	Sample size	Treatment regimen	Pharmaceutical dosage forms	Efficacy of treatment	Side effects	Drug interactions
Tinea capitis	Binder, 2009[15]	<1	7	Continuous regimen: 5 mg/kg/d for 3-6 wk	Capsule or ITR-OS	7/7 complete cure	No	No
	Koumantaki-Mathioudaki, 2005[20]	0.5-14	Unclear	Pulse regimen: 81 with 5 mg/kg/d 1-7 pulses, 1 pulse every 4 wk	Capsule	60/60 complete cure, 21 lost follow-up for long time	Mild to moderate diarrhea in 2 in continuous regimen	No
			Unclear	Continuous regimen: 30 with 5 mg/kg/d for 12 wk	ITR-OS	31/31 complete cure		
	Ginter-hanselmayer, 2004[19]	0.9-12.5	Unclear	Continuous regimen: 5 mg/kg/d for 10-77 d	Capsule or ITR-OS	163 complete cure	Diarrhea in 5, cutaneous eruption in 4, abdominal pain in 2	No
	Chang, 2002[21]	0.1	1	Pulse regimen: 25 mg/2.5 mL/d for 3 pulse, each pulse lasting 1 wk, with 2 wk off drug between the first and second pulses and 3 wk off between the second and third pulses	ITR-OS	1/1 complete cure	No	No
	Koumantaki, 2001[22]	0.8	1	Pulse regimen: 50 mg/d for 2 pulse as the last study	Capsule	1/1 complete cure	No	No
	Möhrenschlager, 2000[17]	1-12	Unclear	Continuous regimen: 50-100 mg/d for 4 wk	Capsule	34/42 complete cure	Reversibility of indigestion in 2	No
	Gupta, 1998[18]	1-12	10 (1-12 y)	Continuous regimen: 3 mg/kg/d for 4-8 wk	Capsule	8/10 complete cure	No	No
	Abdel-Rahman, 1998[16]	1.5-11	25 (1.5-11 y)	Continuous regimen: 100 mg/d for 4-8 wk	Capsule	10/25 complete cure	Headache in 1, vomiting in 3, diarrhea in 1, epistaxis in 1, seizures in 1	No
Sporotrichosis	Song, 2011[27]	0.4,0.3,0.5	3	Continuous regimen: 3 mg/kg/d for 2-4 mon	Oral	3/3 complete cure	No	No
	Mahajan, 2005[29]	1.6	1	Continuous regimen: 5 mg/kg/d for 60-90 d	Capsule	1/1 complete cure	No	No
	Kwon, 1998[28]	1.4	1	Continuous regimen: 3 mg/kg/d for 8 wk		1/1 complete cure	No	No
Cutaneous infection	Zhang, 2010[33]	1.6	1	50 mg/d for 7 days, then 50 mg every other d for 8 d	Capsule	1/1 complete cure	No	No
Mucosal fungal infections	Abdel-Rahman, 2007[11]	0.6-2	6	Single dose: 2.5 mg/kg/d	Intravenous ITR	6/6 achieved therapeutic concentrations of ITR in plasma	No	No
	de Repentigny, 1998[12]	<2	3	Continuous regimen: 50 mg/d for 7 d, then 50 mg every other day for 8 d	Solution	3/3 complete cure	Gastrointestinal system and general disorders	No

ITR: itraconazole; AMB: amphotericin B; OS: oral solution.

Table 2. Itaconazole for systemic fungal infections in infants

Diagnosis	Study	Age (y)	Sample size	Treatment regimen	Pharmaceutical dosage forms	Efficacy of treatment	Side effects	Drug interactions
Candidiasis	Singhi, 2004[40]	0-12	64 (<12 y)	10 mg/kg/d for 21-42 d in 35 patients	Capsule	30/35 complete cure	None had any major side effect	No
	Mondal, 2004[41]	0-12	21 (10, <2 y)	10 mg/kg/d for 2 wk or until 1 wk more than negative result	Capsule	17/21 complete cure	Nausea and vomiting in 1	No
	Hiranandani, 1995[39]	0-3	6 (4, <0.2 y)	10 mg/kg/d for 21-28 d	Capsule	5/5 complete cure	No	No
	Bhandari, 1992[36]	0	2	10 mg/kg/d for 3-4 wk	Capsule	1/2 complete cure, 1/2 improved	No	No
	Bhandari, 1992[37]	0	1	10 mg/kg per d for 4 wk	Capsule	1/1 complete cure	No	No
	Sciacca, 1995[38]	0	1	Unclear	Oral	1/1 complete cure	No	No
Aspergillosis	Manzoni, 2012[43]	0	1	AMB 3 mg/kg/d for 28 days followed by ITR 1 mg/kg/d for 30 d	Oral	1/1 complete cure	No	No
	Mohindra, 2006[42]	3	1	AMB, followed by ITR 200 mg/d for 6 mon in adjunct to aggressive surgical debridement	Oral	1/1 complete cure	No	No
	Thomson, 2006[45]	1.6	1	Oral prednisone and ITR	Unclear	1/1 dead	No	No
	Zhao, 2005[44]	1.5	1	Unclear dose for 1 y	Oral	1/1 improved	No	No
	Roesler, 1990[46]	2	1	16-120 mg/kg/d	Capsule	0/1 complete cure	Mild diarrhea became moderate in 1	No
	Patterson, 2000[47]	0-86	187	ITR	Capsule	25% complete cure, 36% dead with *Aspergillus*	No	No
			58	AMB		26% complete cure, 65% dead with *Aspergillus*		

Table 2. Itaconazole for systemic fungal infections in infants (continued)

Diagnosis	Study	Age (y)	Sample size	Treatment regimen	Pharmaceutical dosage forms	Efficacy of treatment	Side effects	Drug interactions
Histoplasmosis	Mata-Essayag, 2008[52]	0-83	158 (42, <18 y; 15, <2 y)	12/24 (5%) received only ITR 7 mg/kg/d	Oral	All in 3 groups improved exceptions for 2 patients, 1 with HIV replased and the other with meningitis had sequelae	No	No
				9/24 (37.5%) with AMB followed by ITR 3/24 (12.5%) were treated with AMB	Oral			
	Kristien, 2002[48]	0.9	1	10 mg/kg for 6 mon	Oral	1/1 complete cure	No	No
	Tobón, 1996[49]	1-14	7 (4, <3 y)	6-16 mg/kg/d for 1-12 mon	Capsule	3/4 complete cure	Elevated serum bilirubin, alkaline phosphatase and amino-transferase in 1	No
	Troillet, 1996[50]	0.3	1	5 mg/kg/d for 6 mon	Capsule	1/1 complete cure	No	No
	Quilter, 2012[51]	0.5	1	AMB for 3 wk followed by ITR for 4 mon	Unclear	1/1 complete cure	No	No
Zygomycosis	Mendiratta, 2012[56]	0.8	1	ITR 5 mg/kg/d for 4 wk	Oral	No resolution with ITR alone	No	No
				Followed by saturated solution of potassium iodide, up to a maximum of dose 40 mg/kg/d for 3 mon	Oral	1/1 complete cure with combination therapy		
	Robertson, 2002[53]	1.8	1	Combined with AMB for 20 wk	Unclear	1/1 complete cure	No	No
	Geramizadeh, 2007[54]	2.5, 2	2	5-10 mg/kg/d	Unclear	2/2 complete cure	No	No
	Fahimzad, 2006[55]	1.5	1	AMB for 1 wk followed by ITR for 9 mon	Oral	1/1 complete cure	No	No
Trichosporonosis	Ağirbasli, 2008[58]	1.9	1	LAMB (4 mg/kg)+ITR (100 mg)+fluconazole (400 mg) each day for 11 mon	Oral	Death without Trichosporon asahii isolation	No	No
Fungal suppuration	Tekkök, 1996[59]	1.8	1	8 mg/kg/d for 4 mon	Unclear	1/1 complete cure	No	No
Prophylaxis for IFI	Kobayashi, 2010[62]	0-14	22 (10, <5 y)	5 mg (0.5 mL) /kg/d for 19-183 d	Solution	18/18 without fungal infections, 4 lost to follow-up	No	Non-alcoholic steato-hepatitis in 2 vincristine sulfate, syndrome of inappropriate anti-diuretic hormone secretion and liver dysfunction in 1 irinotecan-hydrochloride Noseperately
	Lehrnbecher, 2007[61]	0.1-17	<9	6 mg/kg/d	Oral	7/8 without fungal infections	No	No
	de Repentigny, 1998[12]	<2	5	5 mg/kg/d for 14 d	solution	5/5 complete cure	Gastrointestinal system and general disorders	No
	Foot, 1999[64]	0-14	103 (0-14 y)	5 mg/kg/d for 1-265 d	Solution	No proven systemic fungal infections occurred during the study except for 3 suspected oral candidiasis	Vomiting in 12, abnormal liver function in 5, rash in 1, abdominal pain in 3, convulsions in 3	4 withdrawn in vincristine
	Grigull, 2007[63]	0.4-18.3	53 (<18 y)	10 mg/kg/d first 2 d followed by 5 mg/kg/d for 98 d	Intravenous followed by solution	2 new IFI, 11/53 discontinued for unknown fever	Abnormal results of laboratory investigations in 21 of 53 (40%) of the children, Predominantly including elevated transaminases in 10 and veno-occlusive disease in 5	No
	Simon, 2007[9]	0.7-11.5	<39	Median dose of 8 (3.5-16.0) mg/kg/d for 6-246 d	Capsule or solution	No fungal infections were found	Nausea, vomiting, constipation, abdominal pain, fever, diarrhea and abnormal liver function	No
	Cale, 2000[66]	0.3-13	21 (12, <5 y)	3-5 mg/kg/d	Oral	Unclear	No	No
	Beauté, 2011[67]	2.6-18.2	155	Unclear	Unclear	127/155 complete cure	No	No
	Mouy, 1994[8]	<18	30	5-10 mg/kg/d	Capsule	27/30 complete cure	Elevated serum liver enzyme levels in 4, mild hypokalemia in 3	No
	Soler-Palacín, 2007[65]	0.2-11	13 (12, <6 y; 6, <3 y)	Unclear	Unclear	9/13 complete cure, 1/13 was dead for fungal infections	No	No

ITR: itraconazole; AMB: amphotericin B; LAMB: liposomal amphotericin B; HIV: human immunodeficiency virus; IFI: invasive fungal infections.

perfringens with unique simultaneous fungal suppuration by *Myceliophthora thermophila* after sustaining a penetrating head injury in a barnyard. He presented with high fever, galeal swelling, and seizure. Antifungal treatment consisted of the administration of LAMB for 6 weeks and ITR at a dose of 8 mg/kg per day for 4 months. Six months after the excision of the abscess, the infant was well and neurologically intact.[59]

Table 2 shows the detailed information on itaconazole use for systemic fungal infections in infants.

The efficacy of prophylaxis with ITR

The incidence of invasive fungal infection (IFI) in children with hematological malignancies was reported to be 6.9% and the mortality rate of IFI children was as high as 48.2%.[60] In children with hematological malignancies and solid tumor who received chemotherapy, the prophylactic effects of either intravenous or oral ITR were confirmed.[61-63] One hundred and three neutropenic children were given ITR-OS as antifungal prophylaxis either at the start of conditioning 9 days before transplantation or longer, they had no systemic fungal infections during the study.[64] Prophylactic treatment with ITR also proved to be effective in preventing serious infections in pediatric patients with chronic granulomatous disease.[12,65,66] ITR at a median dose of 8 mg/kg per day, in capsules or oral solution, is feasible and inexpensive for antifungal prophylaxis in children with malignant diseases.[9] In 30 patients who received ITR prophylaxis, 3 developed fungal lung infection, giving an incidence 10% in the ITR group infected with *Aspergillus* versus 34.4% in an untreated group (P=0.013).[8] Similar results were obtained in a multicenter study from France, which also indicated that ketoconazole prophylaxis reduced IFI.[67]

Safety

In infants ITR has demonstrated an excellent safety profile as in children. ITR was once used in 16001 patients, of whom 1106 ranged in age from 0 to 19 years. The incidence of serious, adverse liver events was approximately 3.2/100 000 prescriptions of ITR, which proved that ITR rarely induces serious effect on the liver, kidneys, skin, or blood.[68,69]

In 45 reports we reviewed, 23 were case reports on 42 infants, and the remaining were cohort or control studies of infants (the number was not clear). No adverse events were described in the case reports except mild diarrhea became moderate in one infant.[12,15,21,22,27-29,33,36-38,42-46,48,50,51,53,54,56,58,59] There were mild to moderate gastrointestinal diseases (nausea, vomiting, diarrhea, and constipation), elevated transaminases, headache, abdominal pain, fever, rash, and epistaxis.[8,9,12,41,46,49,63,64] Convulsions as serious adverse events were observed in 7 patients, but none of them was definitely or probably related to ITR except for 3 cases.[64] The side-effects may be not related to drug administration since there was no control group in most studies. In addition, the administration of ITR was discontinued in 8 patients with unknown reason in four, syndrome of inappropriate anti-diuretic hormone secretion in one, non-alcoholic steatohepatitis in two, and liver dysfunction in one, who had received vincristine sulfate (VCR) or irinotecan hydrochloride with ITR.[62,64]

In the 45 reports, 13 mentioned superficial fungal infections including tinea capitis, sporotrichosis, mucosal fungal infections and opportunistic infections.[12,15-22,27-29,33] The remaining 32 had systemic fungal infections including candidiasis, aspergillosis, histoplasmosis, zygomycosis, trichosporonosis, and opportunistic infections caused by *Myceliophthora thermophila*.[8,9,12,36-56,58,59,61-67] The mortality rates of the infections were high in untreated immunocompromised infants who had risk factors for systemic fungal infections, such as low birth weight, HIV infection, broad-spectrum antibiotic therapy, prolonged indwelling catheters, malnutrition, and disruption of gastrointestinal mucosa. Thus, recognizing fungal infections is important in infants, especially those caused by uncommon pathogens including Basidiobolus ranarum, the zygomycetes class of fungi, *Trichosporon asahii*, *Clavispora lusitaniae*, and *Chaetomium atrobrunneum*.[33,53-56,58,59]

Conclusions

Superficial fungal infections

Tinea capitis is a common superficial fungal infection in children. Traditional treatment for tinea capitis is griseofulvin, but its usefulness may be restricted for its long-term dose, side effects, increased resistance and limited spectrum of activity, which does not include *Candida* species.[70-72] ITR is effective in treating tinea capitis when used as continuous or pulse therapy, which is better tolerated than griseofulvin.[18,31,73] It is necessary to individualize the duration of therapy administered according to the clinical response. The advantages of pulse therapy are better compliance than continuous therapy. Tinea capitis caused by *Microsporum* species or *Trichophyton tonsurans* may be cured with a longer duration of ITR.[15,16] Although no ITR dosage is available for infants, 5 mg/kg per day is used for infantile superficial fungal infections within 3 to 6 weeks.[12,15,19,20,39] ITR pulse therapy seems to be an ideal regimen for infantile superficial fungal infections as it

has a good safety profile, high efficacy and low cost.[20-22]

Systemic fungal infections

Aspergillosis and candidiasis are the most common systematic fungal infections in infants and children. AMB, followed by prolonged ITR therapy is a "gold standard" modality for severe systematic fungal infections.[42,51,52,55,58] The IFI incidence was significantly lower after prophylaxis using ITR, and few serious side effects were noted, even if it continued for several months up to 1 year.[16,18,42,44,48,51,53,55] Systematic fungal infections were treated with ITR at a dose of 5-10 mg/kg per day for 2 to 6 months according to the clinical response.[9,34-67] In 252 neonates with invasive candidiasis in Tunisian Hospital, there was a low resistance rate (5.6%) of ITR for *Candida albicans* in vitro.[74] However, resistant strains of *C. krusei*, *C. glabrata*, *C. albicans*, *C. haemulonii* and *C. tropicalis* to ITR were observed in neonates who had not received antifungal therapy.[75-78] Triazoles, namely, voriconazole, posaconazole, and ravuconazole, had a notable *in vitro* activity against all Candida species.[77,79]

ITR is safe and effective in the treatment of fungal infections in infants who have normal liver function and are not given ITR concomitantly with agents that will result in side effects, such as vincristine sulfate and irinotecan hydrochloride.[69] Therefore, it is important to monitor liver function for infants before and during the treatment with ITR as in adults. Weight-based doses of ITR can be used in spite of age of infants, children and adolescents. ITR at the dose of 5 mg/kg per day is suggested for the treatment of superficial fungal infections in infants, and the dose can increase to 10 mg/kg per day for systemic fungal infections. ITR is available in different dosage forms including capsules, oral solution and parenteral solution. ITR-OS facilitates proper administration and dosing for infants. Compliance with treatment instructions of ITR in infants has been judged good.

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