



Review

Current and future use of isavuconazole in children and adolescents

Natalia Mendoza-Palomar, Pere Soler-Palacín *



Paediatric Infectious Diseases and Immunodeficiencies Unit, Children's Hospital, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

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ABSTRACT

Invasive fungal infections (IFI) present significant challenges in newborn, children and adolescents, particularly in immunocompromised patients, such as those with some primary immunodeficiencies or hematologic malignancies, and those who undergo hematopoietic stem cell transplantation. Isavuconazole (ISA), a broad-spectrum triazole antifungal, has emerged as an effective alternative for treating IFI in adults, especially those caused by *Aspergillus* and Mucorales. Recent approvals by the Food and Drug Administration (2023) and the European Medicines Agency (2024) have extended the use of ISA to paediatric populations, offering an important addition to the current treatment options. Two clinical trials have assessed ISA in paediatric patients, showing it is generally well tolerated, with an acceptable safety profile. While adverse events are primarily gastrointestinal and hepatic, they are less frequent than those associated with voriconazole or liposomal amphotericin B. According to pharmacokinetic studies, drug clearance is faster in children, particularly in those under 35 kg; thus, doses require careful modification.

ISA may represent a crucial advancement in the treatment of paediatric IFIs, but therapeutic drug monitoring remains essential due to variability in drug concentrations.

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Uso actual y futuro del isavuconazol en niños y adolescentes

RESUMEN

Las infecciones fúngicas invasoras (IFI) plantean importantes retos en recién nacidos, niños y adolescentes, sobre todo en los pacientes inmunodeprimidos, como aquellos que padecen algunas inmunodeficiencias primarias o neoplasias hematológicas, y los sometidos a trasplante de células madre hematopoyéticas. El isavuconazol (ISA), un antifúngico triazólico de amplio espectro, se ha revelado como una alternativa eficaz para el tratamiento de las IFI en adultos, especialmente para aquellas causadas por especies del género *Aspergillus* y Mucorales. Las recientes aprobaciones de la *Food and Drug Administration* (2023) y la *European Medicines Agency* (2024) han extendido el uso de ISA a poblaciones pediátricas, ofreciendo una importante opción de tratamiento a las actuales disponibles. Dos ensayos clínicos han revelado que el ISA es generalmente bien tolerado por los pacientes pediátricos, y su perfil de seguridad es aceptable. Aunque los acontecimientos adversos son principalmente gastrointestinales y hepáticos, son menos frecuentes que los asociados al voriconazol o a la anfotericina B liposomal. Los estudios farmacocinéticos indican un aclaramiento más rápido del fármaco en niños, sobre todo entre los que pesan menos de 35 kg, lo que requiere ajustes cuidadosos de la dosis.

El ISA puede representar un avance crucial en el tratamiento de las IFI pediátricas, pero la monitorización terapéutica del fármaco sigue siendo esencial debido a la variabilidad en las concentraciones del mismo.

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Peculiarities of invasive fungal infection in paediatrics

Invasive fungal infections (IFIs) in paediatric patients, though rare, carry significant morbidity and mortality, especially among immunocompromised children.¹⁵

* Corresponding author.

E-mail address: psoler@vhebron.net (P. Soler-Palacín).

Invasive candidiasis is the predominant cause of IFI in this population. Its incidence is higher in neonates, especially preterm babies, and in children with underlying conditions such as cancer or prolonged hospitalization. *Candida albicans* keeps being the most common species globally, though non-*C. albicans Candida* species are also emerging. Starting antifungal therapy early improves clinical outcome significantly, underscoring the importance of monitoring in at-risk paediatric populations. Fluconazole or echinocandins are, typically, the antifungals of choice due to their efficacy and safety profile, but depending on the *Candida* species and susceptibility patterns amphotericin B is also used.^{12,22}

Among the filamentous fungi, *Aspergillus* species and Mucorales are the main causative agents. Children with hematologic malignancies, particularly those undergoing allogeneic hematopoietic stem cell transplantation (HSCT), and children with some inborn errors of immunity, like chronic granulomatous disease, are at highest risk. The case fatality rate in these patients reaches 50%, with poor prognosis in those with disseminated fungal infections. A study based on two large international registries (Zygomycos-net and FungiScope TM) described the epidemiology of mucormycosis in paediatric population.^{16,17} Among 63 cases (44 proven and 19 probable), 38.1% had disseminated infection and overall mortality reached 33.3%.^{11,18,25}

Diagnostic challenges in paediatric IFIs arise due to less specific radiological signs and the limited use of biomarkers, which remain underexplored in children despite advances in the last years. In addition, the approval of many antifungal drugs for paediatric use, including those used in adults, is often lagged behind, limiting the available treatment options. Pharmacokinetic differences between children and adults further complicate the treatment, necessitating dose adjustments and close monitoring of drug concentrations to ensure efficacy and minimize toxicity.^{23,24}

Isavuconazole

Isavuconazole (ISA) is a broad-spectrum triazole antifungal initially approved for the treatment of invasive aspergillosis (IA) and mucormycosis (IM) in adults. Its spectrum of activity includes the genus *Aspergillus*, Mucorales, and *Candida* species, offering a potent alternative to voriconazole and liposomal amphotericin B. The use of the intravenous formulation of ISA was approved by both the Food and Drug Administration – FDA (December 2023) and the European Medicines Agency – EMA (August 2024) for children aged 1 year and up, while the oral formulation is recommended for individuals aged 6 years and above.^{7,8} The safety profile of ISA is generally favourable, with fewer drug-drug interactions and adverse events compared to voriconazole and liposomal amphotericin B, thus being included among the antifungal therapy options for paediatric invasive fungal infections.¹⁵

Isavuconazole in children and adolescents

The FDA and EMA recent approval of ISA for children was based on two paediatric clinical trials. In the first phase 1 study, 46 immunocompromised children aged 1–18 years received ISA, and 41% suffered drug-related adverse reactions. The treatment was discontinued in five patients due to significant adverse events, such as elevated liver enzymes and QT prolongation.¹ A subsequent phase 2 open-label, non-comparative, multicentre study (NCT03816176) evaluated the safety, efficacy and pharmacokinetics of ISA for up to 180 days in 31 paediatric patients (1–17 years of age) with IA or IM. The satisfactory clinical response rate was 54.8% at the end of treatment, with acceptable safety (29% of patients experienced drug-related adverse events).²¹ Retrospective studies have also shown ISA is a proper salvage treatment in paediatric IFIs,

especially for children with cancer and those who undergo HSCT. Table 1 summarizes the most relevant findings in these trials and other previously published studies; the off-label use of ISA as IFI treatment and prophylaxis in children and adolescents is described. The variability in drug concentration among children, particularly those under 35 kg, and dose adjustments to reach adult-equivalent therapeutic concentrations is highlighted.^{1–6,9,10,13,20,26}

Safety data

ISA has demonstrated a favourable safety profile in paediatric patients, similar to its adult counterparts. In paediatric clinical trials, common adverse events included gastrointestinal disturbances, infusion reactions and hepatic enzyme elevations, consistent with the safety data reported in adult studies. In the phase 1 paediatric study adverse events were observed in 93.5% of the patients, although there were considered ISA-related in 41%. These events were primarily gastrointestinal, similar in both the oral-formulation and the intravenous-formulation group, and were solved with supportive care. Serious adverse events appeared in 43.5% of the patients, although only two were drug-related.¹ In the phase 2 trial, 93.5% of the patients experienced treatment-emergent adverse events, with 29% attributable to ISA. Serious adverse events occurred in 58.1% of the patients, though only one was directly attributed to ISA. Liver toxicity was the most common serious adverse event, although the rates were lower than those seen with voriconazole or liposomal amphotericin B.²¹ It is important to point out that ISA did not show significant drug-drug interactions, which is a key advantage for patients undergoing complex, multi-drug therapies. The long half-life of ISA and its pharmacokinetic stability further contribute to its safety profile.

Efficacy

The efficacy of ISA in paediatric patients mirrors the results observed in adult populations, with positive outcomes reported in several case series and clinical studies. In the previously mentioned phase 2 trial involving 31 paediatric patients with IA or IM, successful responses were observed in approximately 55% of the patients by the end of the treatment, with a 6.5% all-cause fatality rate by day 42, and a 9.7% rate by day 84. Most fatalities were attributed to underlying conditions rather than to ISA-related factors. ISA was often used as second-line treatment in these cases, sometimes in combination with other antifungal agents, which may have influenced outcome variability.²¹ Despite these complexities, ISA showed significant potential as salvage therapy for children with advanced or disseminated infections. Importantly, the efficacy of ISA in children is contingent upon achieving adequate drug exposure, which varies significantly depending on patient weight and disease severity. Furthermore, the use of ISA in critically ill children, including those requiring extracorporeal membrane oxygenation (ECMO), has highlighted the need for individualized dosing strategies to optimize drug concentration.^{1–6,9,10,20,26}

Therapeutic drug monitoring

As with triazole antifungals, therapeutic drug monitoring (TDM) seems necessary for optimizing ISA therapy in paediatric patients due to the higher variability in pharmacokinetics across different age groups when compared with adults. While ISA exhibits linear pharmacokinetics in adults, paediatric studies suggest that children, particularly those weighting less than 35 kg, may clear the drug more rapidly, leading to subtherapeutic plasma concentrations. In these patients, higher or more frequent dosing may be required to achieve effective drug exposure.^{5,6,20,26} Furthermore,

Table 1
Main results of studies describing isavuconazole usage in children.

Author, year	Study type	Patients (number)	Median age (years)	Isavuconazole initial dosages, route	Median Ctrough	Patients with TDM	Clinical outcomes
Barg et al., 2018 ³	Case series	3	5	<30 kg: 100 mg/day >30 kg: 200 mg/day, OR and IV Loading dose first 48 h	2.32 µg/mL	3	AE: NR Efficacy: complete response 3/3
Decembrino et al., 2020 ⁵	Retrospective	29 (24 treatment, 5 prophylaxis)	14.5	<30 kg: 100 mg/24 h >30 kg: 200 mg/24 h OR and IV Loading dose first 48 h	4.91 µg/mL	17	AE: 6 patients (transaminase or serum creatinine elevation) No drug-to-drug interactions Efficacy: 15/24 success rate
Ross et al., 2020 ²⁰	Retrospective	18 (11 treatment, 7 prophylaxis)	12.5	5.4 mg/kg/day (MD 200 mg) OR and IV Loading dose first 48 h	3.6 µg/mL	11	AE: 4 patients (transaminase increase) Efficacy: success rate at 90 days of proven and probable IFI 54%
Ashkenazi-Hoffnung 2020 ²	Retrospective	4 (4 treatment)	10.5	Median dose 5 mg/kg/day OR and IV	NR	NR	AE: none Efficacy: 4/4 complete response
Arrieta et al., 2021 ¹	Prospective (Phase 1)	46 (prophylaxis)	10 iv, 12 or	5.4 mg/kg/day (MD 200 mg) OR and IV Loading dose first 48 h	NR	45	AE: 20 patients (pyrexia and gastrointestinal symptoms) Efficacy: no breakthrough IFD
Gatti et al., 2022 ¹⁰	Retrospective	6 (prophylaxis)	9.1	5.4 mg/kg/day (MD 200 mg) OR and IV Loading dose first 48 h	2.9 µg/mL	16	AE: 1 patient (leukopenia) Efficacy: no breakthrough IFI reported
Elhence et al., 2022 ⁵	Retrospective	26 (treatment)	12.7	5.4 mg/kg/day (MD 200 mg), OR and IV Loading dose first 48 h	3 µg/ml	26	AE: 5 patients (transaminase increase) Efficacy: 5 IFD-related mortality
Zimmerman et al., 2022 ²⁶	Retrospective	15 (9 treatment, 6 prophylaxis)	9	<30 kg: 100 mg/day >30 kg: 200 mg/day, OR and IV Loading dose first 48 h	3.19 µg/mL	14	AE: 6 patients (transaminase or serum creatinine elevation) Efficacy: 6/9 complete response, 3/9 partial response
Fernández Ledesma et al., 2023 ⁹	Retrospective	15 (treatment)	12	<35 kg: 5.4 mg/kg/day >35 kg: 200 mg/day, OR and IV Loading dose first 48 h	3.1 µg/mL	15	AE: 1 patient (transaminase increase) Efficacy: 4/8 favourable response
Bury et al., 2023 ⁴	Prospective, observational	17 (treatment)	9	5.4 mg/kg/day (MD 200 mg), OR, IV and NGT Loading dose first 48 h	NR (range 1.08–11.6 µg/dL)	17	AE: NR Efficacy: NR
Kunvarjee et al., 2024 ¹³	Retrospective	26 (6 treatment, 20 prophylaxis)	14.8	5.4 mg/kg/day (MD 200 mg) OR and IV	NR	NR	AE: 6 patients (transaminase increase) Efficacy: 3 breakthrough IFD (prophylaxis group), treatment response NR

AE, adverse events; IFD; invasive fungal disease; IV, intravenous; MD, maximum dose; NGT, nasogastric tube; NR, not reported; OR, oral; TDM, therapeutic drug monitoring.

critically ill paediatric patients, such as those on ECMO, show even greater variability in drug clearance, necessitating individualized dosing and frequent TDM.⁹ Retrospective studies have supported this approach, especially for children with severe underlying conditions or those receiving ISA as salvage therapy.^{5,9} Despite the variability in drug exposure, ISA has been well-tolerated, even in cases where plasma concentrations fell outside the typical adult therapeutic range. This suggests that the safety margin of ISA might provide dosage flexibility; nonetheless, more investigation is required to develop guidelines for paediatric TDM of

ISA in clinical practice.^{4,9} In general, studies in paediatrics have used concentrations between 2.5 and 5 µg/ml as the therapeutic range, extrapolated from adult data.¹⁹ A recent unicentric study including 26 children found a statistically significant association between IFI-attributable mortality and ISA steady-state daily AUC < 60 mg h/L, as well as higher transaminases concentration with Ctrough > 5 µg/mL.⁶ Although these findings need to be confirmed in more powerful studies, they support the recommendation of TDM in children, as proposed in the recently published TDM consensus of the Spanish Society of Hospital Pharmacy

(SEFH) and the Spanish Society of Pediatric Infectious Diseases (SEIP).¹⁴.

Our center's experience

We conducted a retrospective observational study in the children's hospital at Vall d'Hebron Barcelona Hospital Campus, a tertiary-care referral medical centre in Barcelona (Catalonia, Spain). During the study period, 15 patients received treatment with ISA for suspected fungal infections. Median (interquartile range [IQR]) age was 13 (6–14) years. Proven and probable IFI were diagnosed in five and three patients, respectively, and *Aspergillus* spp. was the main causative pathogen (6/8). ISA was given as second-line or salvage therapy in most cases (10/15). The main reasons for ISA indication were toxicity to previous antifungals (9/15) and a better safety profile as first-line treatment (4/15). Most patients (13/15) received ISA as a part of a combined antifungal therapy. TDM was performed in all patients, obtaining 111 ISA Ctrough concentrations. Overall, 52/111 (46.8%) Ctrough determinations were outside the therapeutic range (34/111 [30.6%] below therapeutic concentrations, and 18/111 [16.2%] above). However, the median ISA Ctrough was within the therapeutic range: 3.1 µg/mL (IQR 2.4–4.5). The differences between median Ctrough values of intravenous and oral administration (3 µg/mL [IQR 2.4–4.2] versus 3.6 µg/mL [IQR 2.5–4.6], $p = 0.406$) were not significant. Throughout the study period, only one patient had an adverse event attributed to ISA: mildly increased liver enzymes (grade 1 AE) leading to ISA withdrawal, being Ctrough concentrations subtherapeutic. This patient had previously experienced severe liver graft-versus-host disease. At the end of the treatment, there was a favourable clinical response in 4/8 patients with proven or probable IFI; four patients died, two of them due to IFI progression.⁹

A still unpublished Spanish multicentric study has collected data from nine paediatric hospitals, focusing on ISA usage, outcomes and TDM practices, and it is currently under peer review.

Which the role of isavuconazole in Paediatrics will be?

ISA holds significant promise as both first line and salvage therapy for IFI in paediatric patients. While ISA has shown efficacy and safety in paediatric trials, its role in clinical practice is not yet fully defined. At present, ISA is recommended as second-line agent for treating children with IA or IM in whom conventional treatments, like voriconazole or liposomal amphotericin B, have failed or cannot be tolerated. With further research, ISA may also find utility in combination antifungal therapies, particularly for children with advanced or refractory fungal infections. Given the variability in pharmacokinetics seen in younger patients, TDM will remain an important tool for optimizing ISA therapy in this age group. Moving forward, ISA could play a key role in the management of IFI in paediatrics, with ongoing studies that may help supporting the role of ISA in treatment protocols.

Conclusions

In conclusion, ISA represents a promising alternative for the management of invasive fungal infections in paediatric populations, particularly those with hematologic malignancies or post-HSCT. Its safety and efficacy profiles, combined with the ability to use both intravenous and oral formulations, make ISA a versatile tool in the paediatric antifungal arsenal. However, due to the pharmacokinetic variability in children, further research is needed to refine dosing strategies and optimize therapeutic outcomes.

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Conflict of interest

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