AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Short Form

Isavuconazole use and TDM in real-world pediatric practice

Berta Fernández Ledesma,[1] Natalia Mendoza-Palomar,[1] Susana Melendo Pérez,[1] Aurora Fernández-Polo,[2] Berta Renedo Miró,[2] Alba Pau Parra,[2] Sonia Luque Pardos,[3] Santiago Grau Cerrato,[3] Jaume Vima Bofarull,[4] María Teresa Martín-Gómez,[5] Montserrat Pujol Jover,[6] Maria Isabel Benítez-Carbante,[7] Cristina Díaz de Heredia,[7] Pere Soler-Palacin[8]

AUTHOR AFFILIATIONS See affiliation list on p. 7.

ABSTRACT Isavuconazole (ISA) is approved for treating invasive aspergillosis and mucormycosis in adults, but its use in children remains off-label. We report on the use of ISA in real-world pediatric practice with 15 patients receiving ISA for treatment of invasive fungal infections. Therapeutic drug monitoring (TDM) was performed in all patients, with 52/111 (46.8%) C_{trough} determinations out of range, thus supporting the need for TDM in children, especially those receiving extracorporeal membrane oxygenation (ECMO).

KEYWORDS isavuconazole, targeted drug monitoring, children, ECMO, invasive fungal infection

Invasive fungal infections (IFI) mainly affect immunocompromised or critically ill children, especially patients with hematological malignancies or who have received a stem cell transplant (SCT) or solid organ transplant (SOT). Despite the latest medical advances in the field, it is still an important cause of morbidity and mortality in this population, and its diagnosis and treatment remain challenging (1–3).

Isavuconazole (ISA) is a broad-spectrum triazole antifungal approved for the treatment of invasive aspergillosis and mucormycosis in adult patients (4, 5). Its safety profile and risk for pharmacological interactions seem to be better than with L-amphotericin B (L-Amb) and voriconazole (VRC), respectively, making it an interesting alternative for the treatment of IFI (4–6). Routine therapeutic drug monitoring (TDM) may not be necessary for ISA in most instances, as ISA presents a linear pharmacokinetic profile in adult studies (4, 5, 7). Nevertheless, subsequent studies have found disparities in drug levels in critically ill patients, obese patients, children, or patients with moderate liver failure (8–10).

To date, the use of ISA in children remains off-label, as there are only a few observational studies in pediatrics, and optimal dosing and the need for TDM in children are unclear (11). At the time of writing, a clinical trial on the use of ISA in pediatric patients is ongoing with recruitment completed; however, the results are still pending publication (ClinicalTrials.gov identifier: NCT03241550; available at https://clinicaltrials.gov/ct2/show/NCT03241550. Accessed 30 January 2023).

This study aimed to describe the use of ISA and the usefulness of TDM in a real-world pediatric setting in a tertiary-care pediatric hospital.

We conducted a retrospective observational study in the Children's Hospital at the Vall d'Hebron Barcelona Hospital Campus, a tertiary-care referral center in Barcelona (Catalonia, Spain). The local Clinical Research Ethics Committee approved the study in October 2021 [EOM(AG)056/2021(5887)].

All pediatric (≤18 years) patients who received intravenous or oral ISA for IFI treatment from June 2018 to August 2021 were included.

ISA was indicated as off-label use according to the treating physician's criteria. ISA dosages were adjusted according to patient weight: patients weighing 35 kg or less

Editor Helen Boucher, Tufts University - New England Medical Center, Boston, Massachusetts, USA

Address correspondence to Natalia Mendoza-Palomar, nataliaana.mendoza@vallhebron.cat.

The authors declare no conflict of interest.

Received 28 June 2023
Accepted 28 September 2023
Published 14 November 2023

received initial doses of 5.4 mg/kg/day (up to a maximum of 200 mg) of ISA, whereas patients weighing more than 35 kg received initial doses of 200 mg/24 h of ISA (12). All patients received a loading dose, which consisted of a target dose every 8 h during the first 48 h of treatment, followed by a maintenance dose once daily. The same dosages were maintained when patients were switched from intravenous to oral route.

Initial plasma trough levels (C_{trough}) were measured just before the next infusion/intake and after at least 5 days of treatment, with weekly monitoring recommended thereafter (13). These levels were determined by ultrahigh-performance liquid chromatography (Nexera X2, Shimadzu Corporation, Tokyo, Japan) with a fluorescence detector. The target for ISA plasma C_{trough} was 2.5–5 mcg/mL (14), and recommendations for dose adjustment were provided by the pharmacy department assuming linear pharmacokinetics (PK). Due to the limited data in clinical practice, dose escalations or dose decreases were only performed successively and modified individually as analyzed by continuous drug monitoring.

IFI classification and response to treatment were defined according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) 2019 definitions (15). Clinical and radiological response to treatment was evaluated only in proven and probable IFI at 6 and 12 weeks and end of treatment, irrespective of the first antifungal choice (15). We considered complete, partial, or stable response to be successful, as stabilization of fungal disease during periods of severe immunocompromise may provide evidence of treatment efficacy (16). The final outcome was defined for all patients as vital status (death or alive) at IFI resolution or at the end of the study period, whichever occurred first. Adverse events (AEs) were collected from medical records, reviewing possible liver, skin, and cardiovascular toxicities as well as infusion-related reactions attributed to ISA as per the treating physician's evaluation and classified according to the Common Terminology Criteria for Adverse Events v5.0 (17).

The statistical analysis was performed by the Statistics and Bioinformatics Unit at the Vall d'Hebron Research Institute. All analyses were performed using the statistical software "R" (R version 4.2.0 [2022-04-22 ucrt], R Foundation for Statistical Computing).

During the study period, 15 patients (15 IFI episodes) received treatment with ISA for suspected fungal infections. Median (interquartile range [IQR]) age and weight were 13 (6–14) years and 35 (22–57.6) kg, respectively.

Proven and probable IFI were diagnosed in five and three patients, respectively, and *Aspergillus* spp. was the main causative pathogen (6/8). Complete information on patient and IFI characteristics is shown in Table 1.

Isavuconazole was indicated 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. The median total duration of ISA treatment was 51 days (IQR 14–219). Two patients received ISA for more than 2 years (until complete IFI resolution and lung retransplant, respectively). All patients but one initiated treatment with ISA intravenously, and six were switched to the oral route during treatment.

The median daily dose in non-ECMO patients was 5.7 mg/kg/day (IQR 5.45–6.56 mg/kg/day) in those weighing ≤35 kg and 200 mg/day in those weighing >35 kg. Individual daily dosages are shown in Table 2.

TDM was performed in all patients (median two levels/patient, range 1–30), obtaining 111 ISA C_{trough} levels. The median time to the first ISA C_{trough} sampling was 9 days (IQR 7–11). Overall, 52/111 (46.8%) C_{trough} determinations were outside the therapeutic range (34/111 [30.6%] subtherapeutic and 18/111 [16.2%] supratherapeutic). The median ISA C_{trough} was 3.1 mcg/mL (IQR 2.4–4.5).

Overall, 9/15 initial ISA C_{trough} measurements were out of therapeutic range (6/15 subtherapeutic and 3/15 supratherapeutic) as reported in Table 2. The differences between median C_{trough} during intravenous and oral administration (3.0 mcg/mL [IQR 2.4–4.2] versus 3.6 mcg/mL [IQR 2.5–4.6], $P = 0.406$) were not significant, with both within the therapeutic range.

TABLE 1 Invasive fungal infection and treatment characteristics of the study cohort[a]

Age (y), sex, weight (kg)	Underlying condition	IFI definition	Microorganism	ISA susceptibility	IFI location	Concomitant antifungals	ISA use	ISA indication	Total duration of ISA treatment (days)	Adverse events	Response to treatment at 6w[b]	Response to treatment at 12 w[b]	Final response to treatment[b]	Reason for ISA withdrawal	Outcome at end of follow-up	Cause of death
9, F, 25	Influenza + ECMO	Proven	*Aspergillus fumigatus*	Yes	Disseminated	Yes	Firstline	Better pharmacokinetic profile	Ongoing	No	Progression	Partial response	Partial response	N/A (ongoing)	Alive and well	N/A
16, M, 70	SCT (B-ALL)	Possible	N/A	N/A	Lung	No	Second line	Toxicity of previous antifungals	48	No	N/A	N/A	N/A	Cure	Alive and well	N/A
13, F, 28	SCT (AML)	Proven	*Fusarium solani*	No	Disseminated	Yes	Second line	Toxicity of previous antifungals	9	Grade one elevated liver enzymes	Stable	N/A (death)	N/A (death)	Toxicity	Death	Underlying disease
6, M, 22	SCT	Possible	N/A	N/A	Lung	No	Second line	Toxicity of previous antifungals	14	No	N/A	N/A	N/A	No improvement in IFI	Death	Underlying condition in the presence of IFI
14, M, 33	Lung transplant + ECMO	Probable	*Aspergillus fumigatus*, *Aspergillus terreus*	Yes	Disseminated	Yes	First line	Better pharmacokinetic profile	7	No	Death	N/A (death)	N/A (death)	Death	Death	Related to IFI
5, M, 18	B-ALL	Proven	*Lichtheimia corymbifera*	N/A (molecular diagnosis)	Disseminated	Yes	Second line	Previous treatment failure	747	No	Stable	Partial	Complete response	Cure	Alive and well	N/A
17, M, 51	SCT	Possible	N/A	N/A	Lung	No	First line	Better safety profile	36	No	N/A	N/A	N/A	Cure	Alive and well	N/A
9, M, 35	Relapsed B-ALL	Possible	N/A	N/A	Lung	Yes	Second line	Toxicity of previous antifungals	51	No	N/A	N/A	N/A	Death	Death	Underlying condition in the presence of IFI
18, M, 58	SCT	Possible	N/A	N/A	Brain	No	Second line	Toxicity of previous antifungals	26	No	N/A	N/A	N/A	Death	Death	Underlying condition in the

(*Continued on next page*)

TABLE 1 Invasive fungal infection and treatment characteristics of the study cohort[a] (*Continued*)

Age (y), sex, weight (kg)	Underlying condition	IFI definition	Microorganism	ISA susceptibility	IFI location	Concomitant antifungals	ISA use	ISA indication	Total duration of ISA treatment (days)	Adverse events	Response to treatment at 6w[b]	Response to treatment at 12 w[b]	Final response to treatment[b]	Reason for ISA withdrawal	Outcome at end of follow-up	Cause of death
																presence of IFI
14, M, 53	SCT	Possible	N/A	N/A	Brain	No	Second line	Toxicity of previous antifungals	137	No	N/A	N/A	N/A	Cure	Alive and well	N/A
14, M, 58	B-ALL	Possible	N/A	N/A	Lung	No	Second line	Toxicity of previous antifungals	51	No	N/A	N/A	N/A	Cure	Alive and well	N/A
10, F, 60	SCT	Proven	*Scopulariopsis* spp.	No	Disseminated	Yes	Second line	Toxicity of previous antifungals	14	No	Death	N/A	Death	Death	Death	Related to IFI
3, M, 17	SCT	Probable	No	N/A	Lung	No	First line	Better safety profile	94	No	Partial response	Stable	Death	Death	Death	Underlying condition in the presence of IFI
4, M, 13	Lung transplant + ECMO	Probable	*Aspergillus flavus*	Yes	Lung	No	First line	Better safety profile	Ongoing	No	Partial response	Partial response	Partial response	Ongoing	Alive and well	N/A
	IEI under study	Proven	*Aspergillus niger*	N/A (molecular diagnosis)	Lung	No	Second line	Toxicity of previous antifungals	219	No	Stable	Stable	Complete response	Cure	Alive and well	N/A

[a]AML, acute myeloblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; ECMO, extracorporeal membrane oxygenation; F, female; IEI, inborn error of immunity; IFI, invasive fungal infection; 77 ISA, isavuconazole; M,78 male; N/A, not applicable; SCT, stem cell transplant; w, weeks; y, years.
[b]response to treatment was only evaluated in proven or probable IFI.

TABLE 2 Isavuconazole therapeutic drug monitoring and weighted dosing per patient[a]

Patient no.	Total no. of C_{trough} determinations	Initial C_{trough} (mcg/mL)	In range	Supratherapeutic	Subtherapeutic	Number of dosage adjustments	Median C_{trough} (mcg/mL)[b]	Daily dose[c]
1	29	2.33	15	9	5	8	4.4 (3.1–5.8)	During ECMO: 9.56 mg/kg Out of ECMO: 5.93 mg/kg
2	2	2.40	0	0	2	0	–	200 mg
3	1	2.44	0	0	1	0	–	7 mg/kg
4	1	2.05	0	0	1	0	–	5.7 mg/kg
5	1	6.04	0	1	0	0	–	6.1 mg/kg
6	15	1.00	6	1	8	8	2.3 (1.4–4.3)	7.4 mg/kg
7	2	3.50	2	0	0	2	–	133.3 mg
8	3	6.40	2	1	0	1	3.3 (3.1–4.8)	4.3 mg/kg
9	1	2.79	1	0	0	0	–	200 mg
10	1	2.66	1	0	0	0	–	200 mg
11	6	2.43	2	0	4	0	2.5 (2.4–2.5)	200 mg
12	2	3.38	2	0	0	0	–	200 mg
13	7	4.19	6	0	1	0	3 (2.8–3.8)	7 mg/kg
14	30	6.50	17	4	9	12	2.9 (2.4–4)	During ECMO: 14.5 mg/kg Out of ECMO: 5.4 mg/kg
15	10	2.82	5	2	3	1	3.5 (2.2–4.8)	272 mg

[a]The target for ISA plasma C_{trough} was 2.5–5 mcg/mL.
[b]Median C_{trough} and coefficient of variation were only determined in patients with more than two plasma levels.
[c]Doses per day were expressed in mg/kg in patients dosed by kg and in total mg in patients receiving adult dosages. ECMO, extracorporeal membrane oxygenation; N/A, not applicable.

Age or weight were not related to overall C_{trough} levels (Pearson's correlation coefficient for overall C_{trough} 0.067 [95%CI –0.12 to 0.25] for age and –0.039 [95%CI –0.22 to 0.149] for weight).

TDM led to dosage adjustments in 6/15 patients (four of them more than once), with 32 total dosage adjustments during the study period.

In the case of ISA TDM in patients receiving ECMO, a total of 29 C_{trough} determinations were performed in three patients (patients 1, 5, and 14) during ECMO support. Patient 1 was initially on ECMO for 73 days, and ISA was initiated on day +15 due to disseminated aspergillosis (18). She needed higher dosages during ECMO to maintain the levels in range (median dose of 9.5 mg/kg/day during ECMO compared to 5.9 mg/kg/day without ECMO), with similar median C_{trough} during ECMO compared to after ECMO support (3.1 mcg/dL [IQR 2.3–8.1] versus 4.4 mcg/dL [IQR 3.6–5.6], P = 0.333). Similarly, patient 15 needed higher dosages during ECMO (14.5 mg/kg/day with ECMO versus 5.4 mg/kg/day without ECMO) to maintain similar levels (median C_{trough} 2.8 mcg/dL before ECMO, IQR 2.4–3.3 mcg/dL, and 3 mcg/dL [IQR 2.7–5.3] during ECMO; P = 0.377). Patient 5 only received ISA for 1 week after lung transplantation that required ECMO support after surgery. TDM was performed just once as the patient unfortunately died due to IFI progression and massive bleeding. Complete TDM data are presented in Table 2.

Treatment response was favorable in 4/8 patients with proven or probable IFI at the end of treatment (the other four patients died, and two of them attributed to IFI progression). Two patients (patients 14 and 15) received ISA as monotherapy throughout the entire study period: one presented a partial response at the end of the study period, and the other died due to his underlying disease.

Throughout the study period, only one patient (patient 3) had an adverse event attributed to ISA: mildly increased liver enzymes (grade 1 AE, peak levels of aspartate aminotransferase 100 IU/L, and alanine aminotransferase 213 IU/L) leading to ISA withdrawal although the C_{trough} levels were subtherapeutic. This patient had previously experienced severe liver graft-versus-host disease.

The present study reports on our experience with ISA use in a real-world setting in a tertiary-care children's hospital. This study is the first to include pediatric patients with nonhematological conditions, some receiving ECMO.

Our data support the need for TDM in pediatric settings, as half the C_{trough} determinations were outside of the therapeutic range, especially initial C_{trough}, even though all patients had initial C_{trough} determinations after 5 days of treatment once a steady state had been reached. However, the median C_{trough} was within the therapeutic range (3.1 mcg/mL), probably due, at least in part, to dosage adjustments following TDM.

Throughout the study period (including TDM-guided changes), the median ISA dose in patients < 35 kg (excluding patients under ECMO support) was similar to the initial doses established in all patients, suggesting that initial doses of 5.4 mg/kg/day may usually be adequate to attain therapeutic levels. Some studies used 100 mg/day in patients < 30 kg and 200 mg/day in patients > 30 kg (11, 19). But our results suggest that younger patients may be dosed by kg as higher doses may be needed.

Overall, we found no relationship between ISA C_{trough} and weight or age in our group, in contrast with Decembrino et al. (19) who found that younger patients had high drug clearance and, therefore, proposed higher dosages in younger patients.

In our cohort, ISA was switched to the oral route in six patients who continued with similar C_{trough} levels, consistent with previous data demonstrating a very high oral bioavailability in both adults and children (20–22).

Patients receiving ECMO therapy were analyzed separately. Interestingly, patients 1 and 14 were receiving ECMO support only for part of the time they were receiving ISA treatment, allowing us to demonstrate the need for higher dosages under ECMO support to attain levels within range. This could be explained by previously described PK changes during ECMO support, mainly due to an increased volume of distribution (more accentuated in children), variations in drug clearance, and drug sequestration within the ECMO circuit and components. While ECMO significantly affects the VRC plasma levels and strict TDM is required (23), there are scant data on ISA during ECMO to suggest the need for increased dosages during ECMO (7, 18, 24–26). Hence, ISA TDM in this setting is generally recommended (8), as we saw in our cohort, in which patients receiving ECMO support were those who required more dosage adjustments.

Favorable ISA response to treatment (4/8) was similar to that observed in other pediatric studies (11, 19, 27). However, because ISA was administered as a second-line treatment or in combination with other antifungals in many cases, efficacy cannot be properly evaluated in our study. Our results showed very few ISA-related adverse events, providing evidence of the drug's good safety profile in children similar to previous pediatric studies (11, 19, 22). However, we only reported AEs that clinicians attributed directly to ISA, thus potentially underestimating mild-to-moderate AEs. Another limitation is that we were unable to retrospectively collect data on possible drug interactions, major organ failure, ECMO circuit changes, or renal replacement therapy.

In conclusion, our data present the use of ISA in a real-world pediatric setting. Our results corroborate the proposed initial dosages of 5.4 mg/kg/day in patients who weigh less than 35 kg and adult dosages of 200 mg/day in patients who weigh more than 35 kg, with oral dosage forms being a good option for stable patients. Additionally, our data support that children, especially those receiving ECMO, could benefit from early and systematic TDM, as the initial dosage is not well defined and a high proportion of C_{trough} results, especially initial C_{trough}, were outside the therapeutic range. Moreover, pediatric patients receiving ECMO would probably require higher dosages and strict TDM. Nevertheless, further studies are needed to evaluate ISA efficacy and safety and to evaluate TDM in pediatric settings.

ACKNOWLEDGMENTS

We would like to thank the Statistics and Bioinformatics Unit of the Vall d'Hebron Hospital Research Institute for the statistical analysis. We also thank Helen Casas and Laura Casas for their English language support. Finally, we would especially like to thank all participating patients and their families.

AUTHOR AFFILIATIONS

[1]Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Infantil. Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Barcelona, Catalonia, Spain
[2]Pharmacy Department, Hospital Infantil, Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Barcelona, Catalonia, Spain
[3]Pharmacy Department, Hospital del Mar, Barcelona, Catalonia, Spain
[4]Department of Clinical Biochemistry, Central Clinical Laboratories, Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Barcelona, Catalonia, Spain
[5]Microbiology Department, Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain
[6]Pediatric Intensive Care Unit, Hospital Infantil, Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Barcelona, Catalonia, Spain
[7]Pediatric Oncology and Hematology Department, Hospital Infantil. Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Barcelona, Catalonia, Spain
[8]Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Infantil. Vall d'Hebron Barcelona Hospital Campus, Institut de Recerca Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

AUTHOR ORCIDs

Berta Fernández Ledesma http://orcid.org/0000-0003-2919-3144
Natalia Mendoza-Palomar http://orcid.org/0000-0002-2035-8291

AUTHOR CONTRIBUTIONS

Berta Fernández Ledesma, Investigation, Methodology, Writing – original draft, Writing – review and editing | Natalia Mendoza-Palomar, Writing – review and editing | Susana Melendo Pérez, Investigation, Methodology, Writing – review and editing | Berta Renedo Miró, Writing – review and editing.

REFERENCES

1. Al-Rezqi A, Hawkes M, Doyle J, Richardson SE, Allen U. 2009. Invasive mold infections in iatrogenically immunocompromised children: an eight-yr review. Pediatr Transplant 13:545–552. https://doi.org/10.1111/j.1399-3046.2008.01056.x
2. Burgos A, Zaoutis TE, Dvorak CC, Hoffman JA, Knapp KM, Nania JJ, Prasad P, Steinbach WJ. 2008. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics 121:e1286–e1294. https://doi.org/10.1542/peds.2007-2117
3. Dornbusch HJ, Manzoni P, Roilides E, Walsh TJ, Groll AH. 2009. Invasive fungal infections in children. Pediatr Infect Dis J 28:734–737. https://doi.org/10.1097/INF.0b013e3181b076b1
4. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW, Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee D-G, Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson GR, Lee M, Maher RM, Schmitt-Hoffmann A-H, Zeiher B, Ullmann AJ. 2016. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. The Lancet 387:760–769. https://doi.org/10.1016/S0140-6736(15)01159-9
5. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, Alangaden GJ, Brown JM, Fredricks DN, Heinz WJ, Herbrecht R, Klimko N, Klyasova G, Maertens JA, Melinkeri SR, Oren I, Pappas PG, Ráčil Z, Rahav G, Santos R, Schwartz S, Vehreschild JJ, Young J-A, Chetchotisakd P, Jaruratanasirikul S, Kanj SS, Engelhardt M, Kaufhold A, Ito M, Lee M, Sasse C, Maher RM, Zeiher B, Vehreschild M, VITAL and FungiScope Mucormycosis Investigators. 2016. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 16:828–837. https://doi.org/10.1016/S1473-3099(16)00071-2
6. Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. 2018. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther 12:1033–1044. https://doi.org/10.2147/DDDT.S145545
7. Andes D, Kovanda L, Desai A, Kitt T, Zhao M, Walsh TJ. 2018. Isavuconazole concentration in real-world practice: consistency with results from clinical trials. Antimicrob Agents Chemother 62:1–4. https://doi.org/10.1128/AAC.00585-18
8. Zurl C, Waller M, Schwameis F, Muhr T, Bauer N, Zollner-Schwetz I, Valentin T, Meinitzer A, Ullrich E, Wunsch S, Hoenigl M, Grinschgl Y, Prattes J, Oulhaj A, Krause R. 2020. Isavuconazole treatment in a mixed patient cohort with invasive fungal infections: outcome, tolerability and clinical implications of isavuconazole plasma concentrations. J Fungi (Basel) 6:90. https://doi.org/10.3390/jof6020090

9. Höhl R, Bertram R, Kinzig M, Haarmeyer G-S, Baumgärtel M, Geise A, Muschner D, Prosch D, Reger M, Naumann H-T, Ficker JH, Kubitz J, Steinmann J, Sörgel F. 2022. Isavuconazole therapeutic drug monitoring in critically ill ICU patients: a monocentric retrospective analysis. Mycoses 65:747–752. https://doi.org/10.1111/myc.13469
10. Borman AM, Hughes JM, Oliver D, Fraser M, Sunderland J, Noel AR, Johnson EM. 2020. Lessons from isavuconazole therapeutic drug monitoring at a United Kingdom reference center. Med Mycol 58:996–999. https://doi.org/10.1093/mmy/myaa022
11. Zimmermann P, Brethon B, Roupret-Serzec J, Caseris M, Goldwirt L, Baruchel A, de Tersant M. 2022. Isavuconazole treatment for invasive fungal infections in pediatric patients. Pharmaceuticals (Basel) 15:375. https://doi.org/10.3390/ph15030375
12. Arrieta AC, Neely M, Day JC, Rheingold SR, Sue PK, Muller WJ, Danziger-Isakov LA, Chu J, Yildirim I, McComsey GA, Frangoul HA, Chen TK, Statler VA, Steinbach WJ, Yin DE, Hamed K, Jones ME, Lademacher C, Desai A, Micklus K, Phillips DL, Kovanda LL, Walsh TJ. 2021. Safety, tolerability, and population pharmacokinetics of intravenous and oral isavuconazonium sulfate in pediatric patients. Antimicrob Agents Chemother 65:e0029021. https://doi.org/10.1128/AAC.00290-21
13. Livermore J, Hope W. 2012. Evaluation of the pharmacokinetics and clinical utility of isavuconazole for treatment of invasive fungal infections. Expert Opin Drug Metab Toxicol 8:759–765. https://doi.org/10.1517/17425255.2012.683859
14. Risum M, Vestergaard M-B, Weinreich UM, Helleberg M, Vissing NH, Jørgensen R. 2021. Therapeutic drug monitoring of isavuconazole: serum concentration variability and success rates for reaching target in comparison with voriconazole. Antibiotics (Basel) 10:487. https://doi.org/10.3390/antibiotics10050487
15. De PauwB, Walsh TJ, Donnelly JP, StevensDA, Edwards JE, CalandraT, Pappas PG, MaertensJ, Lortholary O, KauffmanCA, et al. 2008. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive. Clin Infect Dis 46:1813–1821. https://doi.org/10.1086/588660
16. Segal BH, Herbrecht R, Stevens DA, Ostrosky-Zeichner L, Sobel J, Viscoli C, Walsh TJ, Maertens J, Patterson TF, Perfect JR, Dupont B, Wingard JR, Calandra T, Kauffman CA, Graybill JR, Baden LR, Pappas PG, Bennett JE, Kontoyiannis DP, Cordonnier C, Viviani MA, Bille J, Almyroudis NG, Wheat LJ, Graninger W, Bow EJ, Holland SM, Kullberg B-J, Dismukes WE, De Pauw BE. 2008. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: mycoses study group and European organization for research and treatment of cancer consensus criteria. Clin Infect Dis 47:674–683. https://doi.org/10.1086/590566
17. U.S. Department of Health and Human Services. 2017. Common terminology criteria for adverse events (CTCAE).V.5.0. Cancer Ther Eval Progr. Available from: http://upen.terengganu.gov.my/index.php/2017
18. Mendoza-Palomar N, Melendo-Pérez S, Balcells J, Izquierdo-Blasco J, Martín-Gómez MT, Velasco-Nuño M, Rivière JG, Soler-Palacin P. 2021. Influenza-associated disseminated aspergillosis in a 9-year-old girl requiring ECMO support. J Fungi (Basel) 7:726. https://doi.org/10.3390/jof7090726
19. Decembrino N, Perruccio K, Zecca M, Colombini A, Calore E, Muggeo P, Soncini E, Comelli A, Molinaro M, Goffredo BM, De Gregori S, Giardini I, Scudeller L, Cesaro S. 2020. A case series and literature review of isavuconazole use in pediatric patients with hemato-oncologic diseases and hematopoietic stem cell transplantation. Antimicrob Agents Chemother 64:e01783-19. https://doi.org/10.1128/AAC.01783-19
20. Schmitt-Hoffmann A, Roos B, Heep M, Schleimer M, Weidekamm E, Brown T, Roehrle M, Beglinger C. 2006. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers. Antimicrob Agents Chemother 50:279–285. https://doi.org/10.1128/AAC.50.1.279-285.2006
21. Desai A, Helmick M, Heo N, Moy S, Stanhope S, Goldwater R, Martin N. 2021. Pharmacokinetics and bioequivalence of isavuconazole administered as isavuconazonium sulfate intravenous solution via nasogastric tube or orally in healthy subjects. Antimicrob Agents Chemother 65:e0044221. https://doi.org/10.1128/AAC.00442-21
22. Garner LM, Echols CD, Wilson WS. 2021. Enteral tube administration of Isavuconazole in a pediatric patient. Pediatr Blood Cancer 68:e29108. https://doi.org/10.1002/pbc.29108
23. Ye Q, Yu X, Chen W, Li M, Gu S, Huang L, Zhan Q, Wang C. 2022. Impact of extracorporeal membrane oxygenation on voriconazole plasma concentrations: a retrospective study. Front Pharmacol 13:972585. https://doi.org/10.3389/fphar.2022.972585
24. Hatzl S, Schilcher G, Hoenigl M, Kriegl L, Krause R. 2022. Isavuconazole plasma concentrations in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother 77:2500–2505. https://doi.org/10.1093/jac/dkac357
25. Zhao Y, Seelhammer TG, Barreto EF, Wilson JW. 2020. Altered pharmacokinetics and dosing of liposomal amphotericin B and isavuconazole during extracorporeal membrane oxygenation. Pharmacotherapy 40:89–95. https://doi.org/10.1002/phar.2348
26. Miller M, Kludjian G, Mohrien K, Morita K. 2022. Decreased isavuconazole trough concentrations in the treatment of invasive aspergillosis in an adult patient receiving extracorporeal membrane oxygenation support. Am J Health Syst Pharm 79:1245–1249. https://doi.org/10.1093/ajhp/zxac043
27. Ross JA, Karras NA, Tegtmeier B, Yamada C, Chen J, Sun W, Pawlowska A, Rosenthal J, Zaia J, Dadwal S. 2020. Safety of isavuconazonium sulfate in pediatrics patients with hematologic malignancies and hematopoietic cell transplantation with invasive fungal infections: a real world experience. J Pediatr Hematol Oncol 42:261–265. https://doi.org/10.1097/MPH.0000000000001787