New Developments in Pediatric Antifungal Pharmacology

Andreas H. Groll, MD, Emmanuel Roilides, MD, PhD,† and Thomas J. Walsh, MD‡§*

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From the *Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital, Muenster, Germany; †Infectious Diseases Unit, 3rd Department of Pediatrics, School of Medicine, Faculty of Health Sciences, Aristotle University and Hippokration General Hospital, Thessaloniki, Greece; ‡Center for Innovative Therapeutics and Diagnostics, Richmond, Virginia; and §University of Maryland School of Medicine, Baltimore, Maryland.

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Address for correspondence: Andreas H. Groll, MD, Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, Children's University Hospital, Albert-Schweitzer-Campus 1, 48129 Muenster, Germany. Email: andreas.groll@ukmuenster.de.

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The past 2 decades have seen a considerable increase in both the number and relevance of invasive fungal diseases in immunocompromised and critically ill pediatric patients of all age groups. At the same time, major advances have been made in our knowledge of the biology of fungal diseases, the recognition of patients at risk, the microbiological detection, and imaging modalities, the algorithms of antifungal interventions, and the design and implementation of clinical trials. Most importantly, however, several new antifungal agents of different classes have become available for children and have made antifungal therapy safer and more effective but also more complicated.[1,2] Consequently, a thorough updated understanding of the available antifungal armamentarium is essential for its judicious use and the successful management of individual patients. This article reviews the clinical trials that led to the recent pediatric approval of anidulafungin and posaconazole and their respective indications, provides an update on the pediatric development of isavuconazole and very briefly presents 4 new antifungal agents that are in clinical development.

ANTIFUNGAL TRIAZOLES

The antifungal triazoles have become an essential component of the antifungal armamentarium. They are acceptably well tolerated, possess a broad spectrum of activity and have demonstrated clinical efficacy under many circumstances. The triazoles function by inhibiting the cytochrome P450 dependent conversion of lanosterol to ergosterol, which leads to altered membrane properties and inhibition of cell growth and replication. Whereas fluconazole, itraconazole and voriconazole have been available to pediatric patients for most of the past 2 decades, posaconazole has been approved for children only in the past year, and the pediatric development of isavuconazole is still ongoing.[2]

Posaconazole

Posaconazole is a lipophilic antifungal triazole with potent and broad-spectrum activity against opportunistic, endemic and dermatophytic fungi in vitro. The compound has a large volume of distribution in the order of 5 L/kg and a prolonged elimination half-life of approximately 20 hours. Posaconazole is not metabolized through the cytochrome P450 enzyme system but primarily excreted in unchanged form in the feces. It is inhibitory against cytochrome P3A4 but has no effects on 1A2, 2C8, 2C9, 2C19, 2D6 and 2E1 isoenzymes, and therefore, a limited spectrum of drug-drug interactions. The compound is overall well tolerated, with gastrointestinal disturbances, headaches and elevated hepatic transaminases being the most frequently reported adverse events (AEs).[2] Important indications approved for adults include antifungal prophylaxis in high-risk patients with hematologic malignancies and patients with graft versus host disease post allogeneic hematopoietic cell transplantation and, since 2021, the use for first-line treatment of invasive aspergillosis. Posaconazole is available as an intravenous (i.v.) solution in sulfobutylether-β-cyclodextrin and 3 different oral formulations (oral suspension, gastro-resistant/delayed release tablets and a

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novel gastro-resistant/delayed-release powder for oral suspension [PFS]).

Posaconazole was first approved in adults in 2006 in the form of the oral suspension. In 2007, a pediatric multicenter sequential dose-escalation trial of the pharmacokinetics (PKs) and safety of the oral suspension was initiated. Enrolled subjects were divided into 3 age groups and 3 dosage cohorts and received 7–28 days of posaconazole with systematic PK sampling. The dosing target was predefined as ~90% of subjects with mean steady state plasma concentrations (Cavg; area under the concentration [AUC]/dosing interval) between 500 and 2500 ng/mL, with an anticipated Cavg of ~1200 ng/mL. Unfortunately, despite dosages as much as 18 mg/kg/d 3 times daily, the percentage of subjects meeting the PK target was <90% across all age groups and dosage cohorts (range: 31–80%). The study was discontinued after 8 years in 2015. The lack of a dose-exposure relationship and high variability in exposures were likely because of absorption properties of the oral suspension.[3]

After the introduction of the i.v. solution and the gastro-resistant/delayed-release tablets with improved oral bioavailability in adults, a novel pediatric gastro-resistant/delayed-release PFS was developed and subsequently investigated with the i.v. solution in an open-label, sequential dose-escalation, phase 1b trial in children 2–17 years of age with documented or expected neutropenia.[4] Participants received posaconazole i.v. at 3.5, 4.5 or 6.0 mg/kg/d for ≥10 days, with an option to switch to posaconazole PFS at the identical dose for ≤ 18 days. In this study, i.v. dosages of 4.5 and 6.0 mg/kg/d achieved the target exposure of ~90% of participants with a Cavg ≥ 500 ng/mL and Cavg of ~1200 ng/mL. Both posaconazole i.v. and PFS were well tolerated and had safety profiles similar to those reported for adults: 4 of 115 evaluable patients (3.5%) discontinued the study drug because of drug-related AEs; no correlation between drug-related AEs and exposure were observed.[4]

Based on the results of this pivotal dose-finding trial, posaconazole was approved by both Food and Drug Administration and European Medicines Agency in 2021 for pediatric patients 2 years and older for prophylaxis of invasive fungal diseases in high-risk patient populations (Table 1). Of note, pending completion of a phase II clinical trial in pediatric patients >2 years, approval for first-line treatment of invasive aspergillosis has been deferred. In addition, a phase I/II trial of safety and PKs of i.v. and PFS in neonates, infants and young children <2 years with proven/probable IFDs is part of the agreed commitments of the pediatric investigation plan (PIP), and pending its completion, approval of the compound in this population may be expected at some point in the future.

Isavuconazole

Isavuconazole, administered as the water-soluble prodrug isavuconazo-nium sulfate, is an i.v. and oral antifungal triazole approved since 2015 in adults for first-line treatment of invasive aspergillosis and treatment of mucormycosis. The compound has a broad spectrum of antifungal activity, linear PKs, a long half-life and high oral bioavailability. Its interaction and safety profile are similar to those of other triazoles with advantages in reduced hepatotoxicity, visual effects and neurotoxicity in direct comparison with voriconazole.[2]

Based on a population PK model developed in adults, allometric scaling and Monte-Carlo simulations, a dosage of 10 mg/kg isavuconazonium sulfate (maximum 372 mg), administered i.v. every 8 hours for the first 2 days (loading doses) and once daily thereafter (maintenance dose), was predicted to likely result in adequate steady/state exposures in pediatric patients 2–17 years of age.[5] The PKs and safety of this dosage regimen were subsequently studied in an age-stratified phase 1 clinical trial in 46 immunocompromised pediatric patients after either i.v. or oral dosing. Using population PK and stepwise covariate modeling, no covariates with significant effects on PK parameters could be identified. Prediction of the AUC time curve at steady state by Monte Carlo simulations and assessment of the probability of target attainment (AUC time curve at steady state range, 60–233 ug·h/mL) revealed predicted plasma drug exposures within the target range observed in adults for >80% and >76% of simulated pediatric patients after i.v. or oral administration, respectively. Administration of isavuconazonium sulfate at the studied dosage of 10 mg/kg was well tolerated with AEs leading to study drug discontinuation in 5 patients.[5]

A phase 2 multicenter study is currently under way to evaluate the safety, efficacy and PKs of isavuconazonium sulfate for treatment of invasive aspergillosis or mucormycosis in pediatric subjects ≥1 years of age (9766-CL-0107) as part of the agreed commitments of the PIP of the compound. Development in patients from birth to less than 1 year of age has been waived on the grounds that the compound may not represent a significant therapeutic benefit over existing treatments in this population.

ECHINOCANDIN LIPOPEPTIDES

The echinocandins are a distinct class of semisynthetic amphiphilic lipopeptides that act by inhibiting the synthesis of (1→3)-β-D-glucan of the cell wall of pathogenic fungi. This homopolysaccharide provides osmotic stability and is important for cell growth and cell division. Currently, 3 i.v. echinocandins with extended antifungal spectrum against *Candida* and *Aspergillus* spp., very favorable safety profile and PK characteristics are available: anidulafungin, caspofungin and micafungin. The accumulated data indicate that these agents are not fundamentally different from each other with respect to their antifungal or pharmacodynamic properties. However, they are distinct in their metabolism and excretion. Apart from invasive candidiasis, they also have slightly different indications.[2] Whereas caspofungin and micafungin are approved in pediatric patients of all age groups for several years, the pediatric development of anidulafungin has been completed only recently.

Anidulafungin

Anidulafungin has been licensed in the United States and in the European Union since 2006 in patients ≥18 years of age for primary therapy of candidemia, other forms of invasive *Candida* infections and for esophageal candidiasis. The compound has linear and stable PKs, a long half-life allowing for once daily dosing, is eliminated by slow chemical degradation in plasma, does not interact to a relevant extent with CYP450 isoenzymes and is generally very well tolerated without specific safety concerns.

Data from early studies in pediatric patients revealed that after body weight-based dosing, PK parameters are similar across age groups and dosage cohorts and similar relative to adult subjects. In a phase I/II multicenter sequential dose escalation study of the PKs and safety of anidulafungin in 19 granulocytopenic children of 2 age cohorts (2–11 and 12–17 years), no drug-related serious AEs were recorded. After single and multiple daily doses of 0.75 and 1.5 mg/kg, plasma concentration data corresponded to those in adults following a daily 50 and 100 mg dose, respectively.[6] In a second phase I/II study, i.v. anidulafungin was administered to 15 infants and neonates over 3–5 days. Neonates and infants receiving 1.5 mg/kg/d had similar exposure levels with children receiving similar weight-based dosing and adult patients receiving 100 mg/d. No drug-related serious AEs were observed.[7] In a subsequent pooled population, PK analysis including data from these and 2 further studies across a full range of adult and pediatric ages estimated systemic anidulafungin exposures were similar across age groups (neonates to adults) at the weight-based doses studied in pediatric patients. No clear associations were identified between anidulafungin exposure and efficacy or safety end points.[8]

The efficacy and safety of i.v. anidulafungin were later studied in a prospective, noncomparative multicenter study of first-line therapy of invasive candidiasis including

TABLE 1. Compounds, Formulations, Dosages and Clinical Indications Approved or Targeted for Approval in Pediatric Patients

Antifungal Agent (Brand Name)	Formulation	Adult Dose	Pediatric Dosage	Approved or Targeted Pediatric Indications
Posaconazole (Noxafil®)	Posaconazole intravenous solution delayed-release tablets oral suspension powder for delayed release oral suspension	300 mg once daily (day 1: twice daily) 300 mg once daily (day 1: twice daily) 200 mg three times daily (≥ 13 yr [FDA]) Not approved	≥ 2 yr old: 6 mg/kg once daily (maximum 300 mg; day 1: twice daily) >40 kg: 300 mg once daily (day 1: twice daily) Not approved (EMA) ≤40 kg: weight-based once daily dosing (day 1: twice daily). For details, see SPC.	Prophylaxis in high-risk patients receiving remission-induction chemotherapy for AML or MDS expected to result in prolonged neutropenia, and HSCT recipients who are undergoing high-dose immunosuppressive therapy for GVHD (EMA)/Prophylaxis of invasive Aspergillus and Candida infections in high risk patients including HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy (FDA). Treatment of invasive aspergillosis (EMA/FDA; targeted).
Anidulafungin (U.S.: Eraxis®; E.U.: Ecalta®)	Anidulafungin intravenous solution	100 mg once daily (day 1: 200 mg)	≥ 1 mo old: 1.5 mg/kg (not to exceed 100 mg) of anidulafungin once daily (day 1: 3.0 mg/kg; not to exceed 200 mg)	Treatment of invasive candidiasis (EMA)/Treatment of candidemia and other forms of Candida infections (intra-abdominal abscess and peritonitis) (FDA).
Investigational: Isavuconazole (Cresemba®)	Isavuconazonium sulfate oral capsules intravenous solution	372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily (days 1 and 2: three times daily)	≥ 1 yr old: 10 mg/kg of isavuconazonium sulfate once daily (days 1 and 2: three times daily); investigational	Treatment of invasive aspergillosis (EMA/FDA); targeted. Treatment of invasive mucormycosis (FDA) in patients for whom amphotericin B is inappropriate (EMA); targeted.

AML indicates acute myelogenous leukemia; EMA, European Medicines Agency; FDA, Food and Drug Administration; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndromes; SPC, summary of product characteristics.

candidemia in 49 pediatric patients 2 to <18 years old. Patients received anidulafungin for 10–35 days at a dosage of 1.5 mg/kg (day 1: 3 mg/kg). Efficacy, measured by global (clinical and microbiologic) response, was assessed at end of i.v. treatment (EOIVT), end of treatment, weeks 2 and 6 follow-up, while safety was measured through week 6 follow-up. All patients reported ≥1 treatment-emergent AE, with gastrointestinal disturbances and pyrexia being most frequent. Four patients discontinued treatment because of AEs considered related to anidulafungin. All-cause mortality was 8.2% by EOIVT and 14.3% by week 6 follow-up. None of the 7 deaths during the study period was considered treatment related. Global response success rate was 70.8% at EOIVT.[9] In 19 additional patients (1 month to <2 years of age with [= 16] or at high risk of [n = 3]) with invasive candidiasis who were enrolled in the same trial but published separately, most treatment-emergent AEs were mild or moderate, and no treatment-related deaths occurred. EOIVT global response rate was 68.8%.[10]

Based on these data, anidulafungin was approved in 2020 by both Food and Drug Administration and European Medicines Agency for treatment of invasive candidiasis in pediatric patients aged 1 month to <18 years. A waiver has been issued to study neonates because of need for 2–3 times increased dosages to cover hematogenous *Candida* meningoencephalitis and the potential toxicity of the polysorbate-80 solvent in this population.

NEW ANTIFUNGAL AGENTS IN DEVELOPMENT

New populations at risk, the emergence of resistance and limitations of existing antifungal agents warrant a continuous search for more antifungal drug options. Whereas no new class has been licensed during the last 2 decades, and only 1 single new agent from a known antifungal class has been approved in the last decade, several new antifungal compounds are currently in late-stage clinical development. These include rezafungin (a stabilized form of anidulafungin with an extended half-life dosed once weekly), ibrexafungerp (a first-in-class oral and i.v. triterpenoid targeting (1→3)-β-D-glucan synthesis with limited cross-resistance to echinocandins), fosmanogepix (a novel oral and i.v. Gwt1 enzyme/glycosylphosphatidylinositol anchor protein inhibitor with broad antifungal spectrum) and olorofim (a novel oral and i.v. inhibitor of dihydroorotate dehydrogenase involved in pyrimidine synthesis with broad activity against filamentous and dimorphic fungi).[11,12] PIPs exist for all of these compounds, and pediatric phase I/II clinical trials are in advanced stages of planning. One may therefore expect that these compounds may complement our antifungal armamentarium within the next 5–10 years.

CONCLUSIONS

Over the past 3 decades, major advances have been made in the field of medical mycology. Most importantly, an array of new antifungal agents has entered the clinical arena. While the pediatric development of some of these agents was tedious, all except isavuconazole now have a pediatric label. As invasive fungal diseases remain important causes for morbidity and mortality in immunocompromised and critically ill pediatric patients, the availability of alternative therapeutic options is essential for improving outcome. At the same time, however, antifungal management has become increasingly complex and calls for comprehensive antifungal stewardship programs in pediatric centers that provide care for patients at risk.

REFERENCES

1. Pana ZD, Roilides E, Warris A, et al. Epidemiology of invasive fungal disease in children. *J Pediatric Infect Dis Soc*. 2017;6(suppl_1):S3–S11.
2. Downes KJ, Fisher BT, Zane NR. Administration and dosing of systemic antifungal agents in pediatric patients. *Paediatr Drugs*. 2020;22:165–188.
3. Arrieta AC, Sung L, Bradley JS, et al. A non-randomized trial to assess the safety, tolerability, and pharmacokinetics of posaconazole oral suspension in immunocompromised children with neutropenia. *PLoS One*. 2019;14:e0212837.
4. Groll AH, Abdel-Azim H, Lehrnbecher T, et al. Pharmacokinetics and safety of posaconazole intravenous solution and powder for oral suspension in children with neutropenia: an open-label, sequential dose-escalation trial. *Int J Antimicrob Agents*. 2020;56:106084.
5. Arrieta AC, Neely M, Day JC, et al. Safety, tolerability, and population pharmacokinetics of intravenous and oral isavuconazonium sulfate in pediatric patients. *Antimicrob Agents Chemother*. 2021;65:e0029021.
6. Benjamin DK Jr, Driscoll T, Seibel NL, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high

risk for invasive fungal infections. *Antimicrob Agents Chemother*. 2006;50:632–638.

7. Cohen-Wolkowiez M, Benjamin DK Jr, Piper L, et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. *Clin Pharmacol Ther*. 2011;89:702–707.
8. Xie R, McFadyen L, Raber S, et al. Population analysis of anidulafungin in infants to older adults with confirmed or suspected invasive candidiasis. *Clin Pharmacol Ther*. 2020;108:316–325.
9. Roilides E, Carlesse F, Leister-Tebbe H, et al; Anidulafungin A8851008 Pediatric Study Group. A prospective, open-label study to assess the safety, tolerability and efficacy of anidulafungin in the treatment of invasive candidiasis in children 2 to <18 years of age. *Pediatr Infect Dis J*. 2019;38:275–279.
10. Roilides E, Carlesse F, Tawadrous M, et al; Anidulafungin A8851008 Pediatric Study Group. Safety, efficacy and pharmacokinetics of anidulafungin in patients 1 month to <2 years of age with invasive candidiasis, including candidemia. *Pediatr Infect Dis J*. 2020;39:305–309.
11. Hoenigl M, Sprute R, Egger M, et al. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs*. 2021;81:1703–1729.
12. Jacobs SE, Zagaliotis P, Walsh TJ. Novel antifungal agents in clinical trials. *F1000Res*. 2021;10:507.