High-dose posaconazole for azole-resistant aspergillosis and other difficult-to-treat mould infections

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There is nothing more deceptive than an obvious fact. (Arthur C Doyle)

ABSTRACT

Background

Oral follow-up therapy is problematic in moulds with reduced azole-susceptibility, such as azole-resistant *A. fumigatus* infection. Currently only intravenous liposomal amphotericin B (L-AmB) is advocated by guidelines for the treatment of azole-resistant aspergillosis infections. Preclinical research indicates that high-dose posaconazole (HD-POS) might be a feasible option provided that high drug exposure (i.e. POS serum through levels >3 mg/L) can be achieved and is safe.

Objectives

To describe our experience with the use of oral HD-POS as a treatment strategies for patients infected with pathogens with a POS MIC close to the clinical breakpoint.

Patients/Methods

We review evidence supporting the use of HD-POS and describe our experience on safety and efficacy in 16 patients. In addition, we describe the adverse events (AE) observed in 25 patients with POS concentrations at the higher end of the population distribution during treatment with the licensed dose.

Results

Sixteen patients were treated intentionally with HD-POS for voriconazole-resistant invasive aspergillosis (7/16), mucormycosis (4/16), salvage therapy for IA (4/16) and IA at a sanctuary site (spondylodiscitis) in 1. Grade 3-4 AEs were observed in 6 and all of them were considered at least possibly related. Grade 3-4 AEs were observed in 5 of the 25 patients with spontaneous high POS serum through levels considered at least possibly related using Naranjo scale.

Conclusions

HD-POS is a treatment option if strict monitoring for both exposure and for AE is possible.

INTRODUCTION

Invasive aspergillosis (IA) in patients with haematological malignancies is associated with a mortality of 20-30%. (1, 2) Triazole resistance is increasingly reported in different countries through culture-based surveillance studies, (3) and is associated with a much higher mortality of 50-88%. (4, 5) In 2015, a consensus meeting on the management of azole-resistant IA was organized (6) and liposomal-amphotericin B (L-AmB) was advocated as the preferred therapy but has obvious toxicity limitations and can only be administered intravenously. Treatment of IA has to be continued for a minimum of 6–12 weeks but occasionally much longer. (7) Other treatment options are therefore urgently needed. Phase II studies on new antifungals are just about to start and subsequent phase III studies typically take 3 or 4 years to complete. Therefore, these drugs will not provide a short term solution. Targeting high-exposure posaconazole (POS) may be a potential oral step-down treatment option for azole-resistant IA and other difficult-to-treat mould infections.

POS is approved in patients with haematological malignancies both for prophylaxis and treatment of refractory IA or when intolerance to first-line agents occurs. (8, 9) The agent is available as oral suspension, a delayed-release tablet and an intravenous formulation. Oral absorption of POS oral suspension is affected by food and gastric pH. In contrast, POS-tablets contains the active drug mixed with a pH-sensitive polymer (10) and this polymer releases the drug in the intestines, causing three-fold increased exposures compared to POS oral suspension. (11)

Therapeutic drug monitoring (TDM) has been widely implemented to assess therapeutic efficacy of POS oral suspension but its usefulness is in a state of flux following the introduction of the new POS formulations specifically in the setting of prophylaxis. (12-14) Current guidelines recommend a Ctrough concentration of ≥0.7 mg/L for prophylaxis and >1.0 mg/L for primary and >1.25 mg/L for salvage therapy, (15) although these concentrations were determined independent of the susceptibility of the infecting pathogen. (13)

These targets have been derived for susceptible pathogens and are not valid for pathogens with attenuated susceptibilities. A different approach is needed to optimize treatment in case of reduced susceptibility.

Preclinical research indicates that high-dose posaconazole (HD-POS) might be a feasible option provided that high drug exposure (i.e. POS serum through levels >3 mg/L) can be achieved and is safe. Hence, we argued that oral high-dose treatment strategies might be feasible to treat pathogens with relatively low MICs/MICs just above the clinical breakpoint (low-resistant). Human data on the treatment of pathogens with reduced susceptibility as well as safety of POS Ctrough concentrations of >3 mg/L are sparse.

Here, we review the evidence supporting the use of HD-POS and describe our experience on safety and efficacy in 16 patients. In addition, we describe the adverse events (AE) observed in 25 patients with POS concentrations at the higher end of the population distribution during treatment with the licensed dose.

Patients / Methods

We set out to explore safety of HD-POS and retrospectively collected clinical and laboratory data of patients from 2 Dutch academic medical centres (Erasmus University Medical Centre, Rotterdam and Radboud University Medical Centre, Nijmegen) in which POS Ctrough concentrations >3 mg/L had been documented in two different populations. All patients were in care by one of the authors of this paper. Data were extracted and reviewed by J.B. and A.S. Group 1 consisted of patients intentionally treated with HD-POS targeting POS Ctrough concentrations >3 mg/L and Group 2 were patients that reached POS Ctrough concentrations >3 mg/L with the licensed dose. We focused on AEs (related or unrelated to POS) described in the patient files and laboratory data. Data from these patients were reviewed for toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. An AE was defined as unfavourable or unintended sign or symptom while the patient was treated with POS, whether or not the sign or symptom was related to POS. The Naranjo scale was used to determine for the assessment of causality of potential AE with POS. This is a questionnaire for determining a potential likelihood that an adverse drug reaction is actually linked to a drug. Probability is assigned using a scoring system with the following possible results: definite, probable, possible of doubtful. (16) Medians and 25th to 75th inter-quartile ranges were used for statistic descriptions. This type of research does not fall under the Dutch law of research on human subjects. However, to safeguard the privacy of the patients, the data were stored anonymously after data extraction.□

RESULTS

Group 1

Sixteen patients were treated intentionally with HD-POS for voriconazole-resistant IA (7/16), mucormycosis (4/16), salvage therapy for IA (4/16) and IA at a sanctuary site (spondylodiscitis) in 1. The median POS dose given was 600 (IQR 400,750) mg daily when the POS Ctrough concentrations of >3 mg/L was reached after a median of 8 (IQR 6,40) days. Ten patients had significantly higher Ctrough concentration (above 4 mg/L) and 6 patients had Ctrough concentrations between 3.0 and 4.0 mg/L and on average patients had these concentrations for a median 76 days (IQR 20,162). Thirteen patients received POS-tablet, 1 patient posaconazole-oral suspension (POS-OS) and 2 patients a combina-

tion of formulations. AEs are described in table 1. Grade 3-4 AEs were observed in 6 patients and all of them were considered at least possibly related using Naranjo scale. In 3 out of16 patients the treatment was stopped following an AE: arterial hypertension (grade 2), QTc prolongation, cardiac troponin T increased and left ventricular failure (grade 3) and leukocytopenia (grade 4).

Efficacy

Of the 7 patients with azole-resistant IA treated with HD-POS, 4 survived while 3 died from their underlying disease but unrelated to the IA. In 2 patients HD-POS was used as salvage therapy. One patient with IA caused by *A. terreus* was treated with HD-POS because serum galactomannan levels increased under conventional dosage which is a predictor of poor outcome (table 3). All patients with mucormycosis survived.

Group 2

This group consisted of 25 patients. The median POS Ctrough concentration was 4.3 mg/L (IQR 3.5-6.0). 19, 5 and 1 patient received POS-tablet, POS-OS and the IV formulation respectively. Posaconazole was given to 18 and 7 patients for prophylaxis and treatment, respectively. All observed AEs are described in table 2. The most frequently

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	1				
Nausea		1			
Vomiting	3				
Increased hepatic enzymes	4	1	1[(3)]	2[(5|7)]	
Cardiac troponin T increased			1[(6)]		
Electrocardiogram QTc corrected interval prolonged	1	1	1[(6)]		
Leukopenia				1[(4)]	
Hypokalaemia	3	3			
Hyperkalaemia	1				
Headache		1			
Delirium	1		1[(2)]		
Alopecia	1				
Hypertension		2			
Heart failure			1[(5)]		
Rash	1				

Table 1: Adverse events of 16 patients receiving intentionally HD-POS graded accordingly to the Common Terminology Criteria for Adverse Events (version 4.03). Digits refer to the number of patients in whom these AEs have been documented. Prolongation in the QTc interval was assessed by comparing electrocardiograms obtained at baseline and during HD-POS treatment, if available. [(*)] Naranjo adverse drug reaction probability scale: >9: definite, 5 to 8: probable, 1-4: possible. -3 to 0: doubtful.

observed AE were hypokalaemia in 8 patients and neurological in 6 patients (headache, convulsions). Grade 3-4 AEs were observed in 5 and all of them were considered at least possibly related using Naranjo scale. In 8 of the 25 patients the dosage was reduced. Follow-up Ctrough concentrations were between 1.1 and 4.3 mg/L after dosage reduction.

DISCUSSION

Little is known about the toxicity of patients attaining high POS Ctrough of >3 mg/L. The upper boundary level of average POS serum concentrations of 3.75 mg/L is set by the European Medicines Agency based on experience with the POS-OS and preclinical toxicology findings (17). In this study, we reviewed the safety and tolerability of HD-POS. In both group 1 and group 2, three patients were seen with a combination of hypertension and hypokalaemia that required antihypertensive therapy and potassium supplementation. The most striking case was a child treated with POS, L-AmB and micafungin for a proven aspergillosis following surgical removal of *Aspergillus* lesions in the

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adverse event					
Diarrhoea	4				
Nausea	4				
Vomiting	2				
Increased hepatic enzymes	2	3	1[(4)]		
Electrocardiogram QT corrected interval prolonged	2	1			
GGT increased		1			
Anorexia	5	1			
Hyponatremia	2		1[(1)]		
Hypokalaemia	7	1			
Headache	5				
Seizure		1			
Alopecia	2				
Hypertension		2	1[(7)]	1[(4)]	
Hypotension					1[(#)(7)]
Rash	3				

Table 2: Adverse events of 25 patients receiving POS with high spontaneous concentration graded accordingly to the Common Terminology Criteria for Adverse Events(version 4.03). Digits refer to the number of patients in whom these AEs have been documented. [(*)]These grade 3 or 4 AE were considered at least possible related to POS.[(#)] Refractory shock, rapidly fatal. Distributive shock most likely according to treating physician.[(*)] Naranjo adverse drug reaction probability scale: >9: definite, 5 to 8: probable, 1-4: possible. -3 to 0: doubtful.

Patient	Age (years)	Underlying disease	IFD, classification	Reason HD-POS	Sample with culture	Aspergillus PCR result	MIC(mg/L)*				POS concentration: calculated target		Outcome
							ITZ	VCZ	POS	ISA	Highest C	Calculated Target	
1	69	Mixed dust pneumoconiosis	CPA	Resistant strain	Sputum: *A. fumigatus*	TR_{46}/ Y121F/ T289A	>16	8	1	4	3.8	6.18-6.66	Alive
2	51	AML, AlloTx	IPA, probable	Resistant strain	No positive culture	Y121F/ T289A in BAL					6.1		Dead
3	18	ALL	IPA, proven (cerebral)	Resistant strain	Sputum: *A. fumigatus*	TR_{34}/L98H	16	8	2	8	6	>10	Alive
4	46	SOT (kidney), PTLD	IPA, probable	Resistant strain	BAL: *A. fumigatus*	TR_{34}/L98H	>16	4	0.5	8	0.2[b]	3.09-3.33	Dead
5	69	AML	IPA, probable	Resistant strain	No positive culture	TR_{34}/L98H in BAL					4		Dead
6	61	No relevant	CPA	Resistant strain	BAL: *A. fumigatus*		>16	8	1	8	6.6	6.18-6.66	Alive
7	32	SOT (lung)	Pulmonary mucormycosis, proven	Mucormycosis	Lung: *Rhizopus* species		1	8	0.25	1	3.8	1.44-1.55	Alive
8	17	ALL	IPA, probable	Mixed infection (R/S)	BAL: *A. fumigatus* R and S		>16	4	0.5	8	5.6	3.09-3.33	Alive
9	50	AML, AlloTx	Mucormycosis, probable	Mucormycosis	No positive culture						5.2		Alive
10	58	SLE with pancytopenia	Mucormycosis, proven	Mucormycosis	Liver biopsy: microscopy: hyphy. No positive culture. Spleen biopsy PCR positive	*PCR: Rizomucor pussilus*					5.0		Alive
11	67	DM type II	Mucormycosis, probable (skin)	Mucormycosis	Tissue sample wound: *Rhizopus oryzae*		0.25	8	0.25	1	3.5	1.44-1.55	Alive
12	2	ALL	Mucormycosis, proven	Mucormycosis	Multiple skin biopsies: *Lichtheimia corymbifera*		0.5	16	0.5	>16	6.6	3.09-3.33	Alive

Patient	Age (years)	Underlying disease	IFD, classification	Reason HD-POS	Sample with culture	Aspergillus PCR result	MIC(mg/L)*				POS concentration: calculated target		Outcome
13	50	No relevant	IA, proven	Sanctionary site infection	Spinal biopsy: *A. fumigatus*		0.25[a]	0.25[a]	0.063[a]	0.5[a]	3.6		Alive
14	68	AML	IPA, probable	Salvage	No positive culture						3.8		Dead
15	65	AML	IPA, probable	Salvage	Sputum: *A. nidulans*	Wild-type *A. fumigatus* in BAL	0.25	0.25	0.25	0.5	3.1	1.44-1.55	Dead
16	8	ALL	IPA, proven	Salvage *A. terreus*	Lobectomy, lung tissue: *A. terreus*	Lung biopsy: *Aspergillus* Species	0.125	1	0.031	1	4.7		Alive

Table 3: Underlying condition, IFD, *A. fumigatus* genotype and phenotype, and outcome in 16 patients treated with high-dose posaconazole (HD-POS). *MIC was determined according to the EUCAST method for susceptibility testing of moulds (version 9.2). Patients were classified following the revised definitions of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG). (42)

[a]MIC was determined according to the CLSI method for susceptibility testing of moulds(M38-A2); [b]This patient was included because the patient was treated with POS 400mg BID despite the low Ctrough level.

Abbreviations: C concentration, HD-POS high-dose posaconazole, SOT solid organ transplantation, AlloTx allogeneic stem cell transplant, R: resistant, S: Susceptible, IPA Invasive pulmonary aspergillosis, CPA chronic pulmonary aspergillosis, IA invasive aspergillosis, IFD invasive fungal diseases, PTLD post-transplant lymphoproliferative disease, ITZ Itraconazole, VCZ voriconazole, POS posaconazole and ISA isavuconazole. Calculated target Ctrough based on the MIC is taken from Seyedmousavi et al. (28)

spleen, left lung and right kidney. This patient developed several hypertensive crises and developed hypokalaemia for which oral supplementation was needed. 8 months after POS treatment, the patient died due to a vasopressor refractory shock. During these hypertensive crises, aldosterone could not be measured (<50 pmol/L) and renine was within normal range. In retrospect, POS may have caused the hypertension, and hypokalaemia. Recently, a case of POS induced heart failure, hypertension and hypokalaemia was described with low renin and aldosterone levels. The inhibition of the enzyme 11-beta-hydroxysteroid dehydrogenase 2 is suggested as the potential mechanism causing apparent mineralocorticoid excess. (18-20) This enzyme is homeostatic regulator and damps mineralocorticoid activity by converting cortisol to cortisone.

The AE of HD-POS observed in this study are in line with previous reports of AE due to POS. A phase III study assessing PK and safety of POS-tablet demonstrated that nausea and diarrhoea were the most common treatment-related AEs leading to POS discontinuation in 2% and 1%, respectively. (21) Only 9 patients (10%) in this study attained an average Ctrough concentration between 2.5 and 3.75 mg/L and six patients (3%) reached Ctrough concentrations ≥3.75 mg/L. No increase of AEs in patients with higher POS serum concentrations was observed but the study was not powered to detect such a relation. Very recently, PK and safety results from a phase 3 study of IV POS in patients at risk for invasive fungal disease were published. Six percent of the patients had a steady-state concentration between >2.5 and ≤3.65 mg/L without signs of toxicity. (22) In a retrospective analysis of 64 patients receiving POS-tablet as prophylaxis, median POS steady state concentrations of 1.67 mg/L (0.52-3.83 mg/L) were documented. In 21% of the patients a QT_c prolongation was observed and the median steady state concentration was 2.04 mg/L. (23) In a single-centre study, 343 courses of POS prophylaxis (IV or tablet) were assessed for safety and effectiveness. 20% of these patients developed liver injury, mostly hyperbilirubinemia but this is often multifactorial. More importantly, grade 3-4 elevations in hepatic enzymes were only observed in 2% of the patients without pre-existing liver injury with mostly spontaneous resolution despite treatment continuation. (24) Thus, in the current literature, information about the toxicity of high POS serum concentrations is limited but no increase in the number of AEs was observed in patients with higher than average serum concentrations.

Azole-resistant IA

The large majority of azole-resistant *A. fumigatus* isolates harbour TR_{34}/L98H or TR_{46}/Y121F/T289A mutations in the *cyp*51A gene, (25, 26) encoding the cytochrome p450 sterol 14α-demethylase, the target of azoles. *A. fumigatus* isolates carrying resistance associated mutations have high minimal inhibitory concentrations (MICs) for itraconazole and/or voriconazole as well as isavuconazole. (27) The MIC of POS often remains close to the susceptible population (i.e. MIC ≤0.5 to 1 mg/L). (28) MIC levels of POS

>0.25 mg/L are considered resistant according to the EUCAST breakpoint, but this is based on population susceptibility and on concentrations achieved with the POS-OS at licensed dose. Indeed, drug exposure with POS-OS will marginally cover the *A. fumigatus* wild-type population, let alone low-level POS-resistant isolates. Higher exposures can be achieved with the newer formulations. (13) The pharmacodynamic-pharmacokinetic (PK-PD) relationships of POS have been studied *in vivo*. A murine model of IA indicated that low-level POS-resistant isolates can be treated when the POS exposure is increased. Two *in vivo* studies demonstrated that POS retains efficacy against *A. fumigatus* isolates with POS-MIC of 0.5 mg/L as long as POS exposure is sufficiently high. (29, 30) Based on these experiments, the required POS exposure (area-under-the concentration time curve (AUC)) in patients can be calculated for isolates with an increased MIC. The probability of target attainment for treatment of IA using standard dosing of POS-tablet is estimated to be ~80 % for isolates with POS-MIC of 0.25 mg/L and >90% for isolates with a POS-MIC of 0.125 mg/L. (28) The probability of target attainment for a POS-MIC of 0.5 mg/L was 24% and for a POS-MIC ≥ 0.5 mg/L it was 0%.

As determination of the AUC requires multiple sampling moments, and this AUC is linear correlated to Ctrough concentrations, quite often the Ctrough concentrations are used in daily practice as surrogate markers. (13, 28) Monte Carlo simulations estimated that the POS Ctrough concentrations needed to be 1.44-1.55 mg/L for isolates with a POS-MIC of 0.25 mg/L and 3.09-3.33 mg/L for isolates with a POS-MIC of 0.5 mg/L. (28)

As the aforementioned *in vivo* experiments indicated that *A. fumigatus* with a POS-MIC of 0.5 mg/L can be treated with elevated POS dosing, we hypothesized that targeting high exposure with HD-POS is an oral step-down treatment option for azole-resistant IA. Although clinical evidence supporting HD-POS has not been described, preclinical animal studies and experience in veterinary medicine provided proof-of-principle for its efficiency. (28, 29)

Mucormycosis

Limited *in vivo* models are available that assess POS for the treatment of mucormycosis. A neutropenic mouse model indicated similar pharmacodynamics for mucormycosis compared to *A. fumigatus* infections. An AUC/MIC of 87 was needed to treat *Rhizopus oryzae* infection, which was comparable to the target needed for IA (AUC/MIC of 76). (31) Efficacy of POS showed a dose-response relationship in another *in vivo* model of experimental mucormycosis in which a dose of 100mg/kg/day showed significant reduction of mortality of *Lichtheimia corymbifera* infection. (32) Similar dose-response relationships were seen for *Mucor* species and *R. oryzae*. (33, 34) Compared to *A. fumigatus* isolates, the MICs of Mucorales are often higher with a geometric mean CLSI MIC of 0.39 mg/L (35) and an epidemiological cut-off value of 1 mg/L for *L. corymbifera*, *R. oryzae*, and *R. microspores* and 4 mg/L for *M. circinelloides* (Figure 1). (36) Furthermore, the

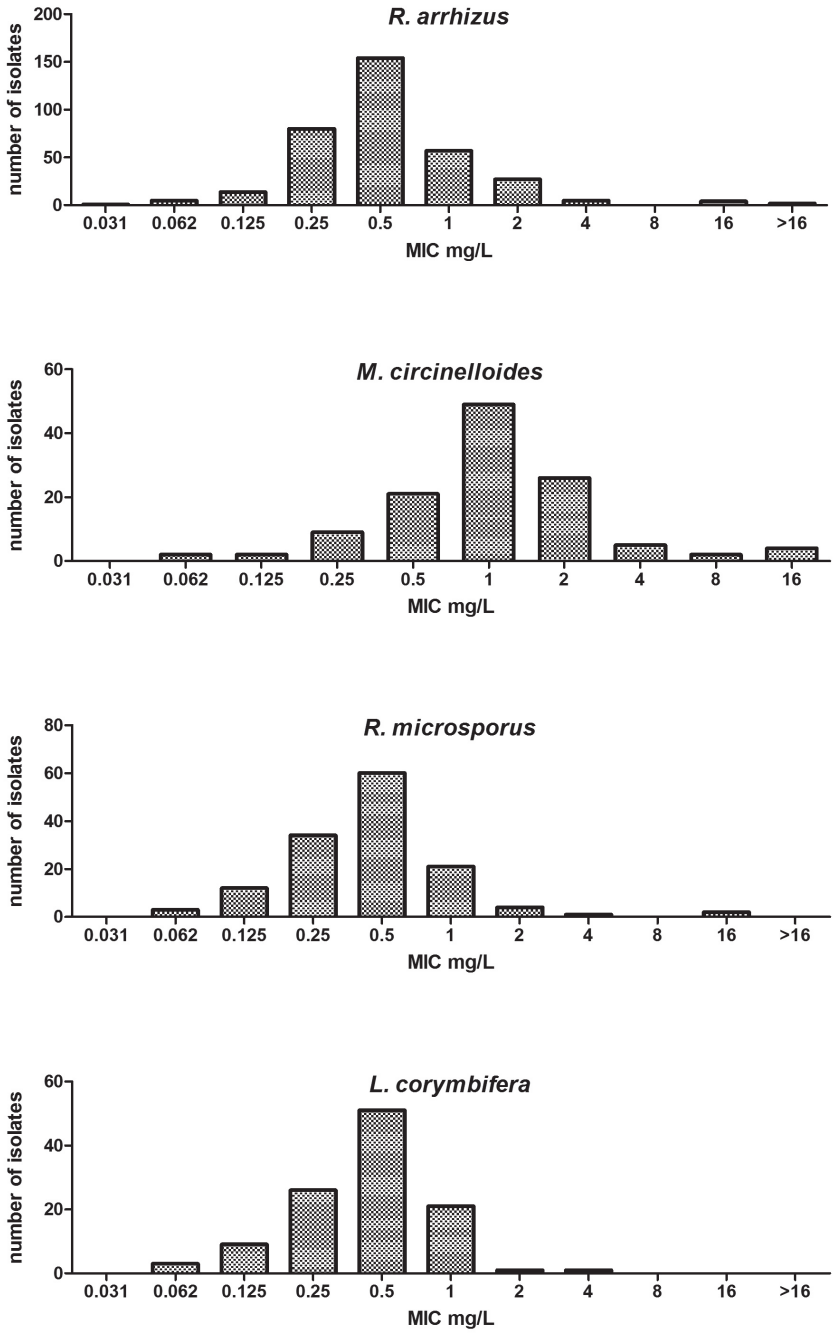

Figure 1: Posaconazole MIC distributions of most common Mucorales species: *Rhizopus oryzae*, *Mucor circinelloides*, *Rhizopus microspores and Lichtheimia corymbifera*
MICs were extracted from Espinel-Ingroff et al. (36) MICs were determined according to the CLSI method for susceptibility testing of molds (M38-A2).

EUCAST MICs for Mucorales are higher than CLSI MICs for most species. (37) Taken into account the similar target AUC/MIC for Mucorales as *A. fumigatus*, but higher MICs for Mucorales isolates compared to *A. fumigatus*, it seems reasonable to pursue higher than normal POS serum concentrations for the treatment of mucormycosis as long as this is not associated with toxicity. (13)

POS-OS has been used as salvage therapy for mucormycosis with a success rate of approximately 60-80%. (38) A recently published matched-paired analysis assessed the clinical effectiveness and safety of POS tablets and intravenous formulation in comparison with amphotericin B as first-line treatment and with POS-OS as salvage treatment for invasive mucormycosis. POS tablets and intravenous formulation were effective in terms of treatment response and associated mortality. However, these observations should be interpreted with caution given the small sample size in this study (43). Clinical data on PK/PD are lacking due to limited susceptibility data from clinical studies. (38)

Dosing and TDM

The pharmacokinetics of posaconazole tablets are best described by a one-compartment pharmacokinetic model with sequential zero-order and first-order absorption and a first-order disposition from the central compartment. Recently, several covariates were identified influencing bioavailability (like disease state, body weight, formulation), adsorption rate (food status) and clearance (dosing regimen) of POS tablets. Only body weight was considered clinically relevant. (39) Knowledge on the PK of POS helps to identify the optimal dose when targeting high exposure. Subsequently, an infrastructure is needed where one can quickly assess drug concentrations to deploy an adaptive approach in terms of dosing. With the new formulations of POS a loading dose is given, which enables early assessment, typically by day 3, of POS concentrations. Follow-up samples are measured again before the 5th dose of every changed dosage.

The pharmacokinetics described above translate into an expected doubling of the Ctrough concentration when the dose of POS-tablet or IV formulation is doubled. For example, when the Cthrough concentration is 1.5 mg/L, increasing the dose from 300 mg once daily to 300mg twice daily can be expected to lead to a serum concentration of 3 mg/L. For safety reasons, we advise to increase the dose with no more than 200 mg per step.

Inhibitory potential of HD-POS

POS is a strong CYP3A4 inhibitor and the clinician should therefore also remain vigilant for drug interactions. In our case series, we had two patients with significant interactions. Toxicity of HD-POS in combination with vincristine was seen in a child with ALL, resulting in hepatotoxicity, convulsions and hypertension which might be attributed to

the inhibition of CYP3A4 as well as P-gp resulting in increased levels of vincristine. (40) Another allogeneic stem cell transplant patient developed IA despite prophylaxis with voriconazole. Treatment with L-AmB was started but switched to HD-POS for progressive renal impairment. POS Ctrough concentration was 5.2 mg/L. After the patient was treated with panobinostat, a histone deacetylase (HDAC) inhibitor, grade 4 leukopenia developed. After 4 weeks of persisting grade 4 leukopenia, POS treatment was stopped as presumed culprit and leukopenia improved. This interaction could have been predicted based on the interaction of panobinostat with ketoconazole where panobinostat maximum serum concentrations were increased by an average of 1.6-fold. (41)

Safety monitoring for HD-POS

We propose that the following safety measures are taken if HD-POS is used as a treatment strategy. At least the following laboratory tests should be performed twice weekly during the first 2 weeks and as long as the POS dosage is being increased: electrolytes, renal clearance, haemoglobin, leukocyte differentiation, thrombocytes and liver enzymes. Posaconazole, may cause QT prolongation. Therefore, an ECG should be recorded before the start of HD-POS as well as during treatment. If no lab abnormalities possibly related to POS are observed the monitoring interval can be increased.

In conclusion, registration of new antifungals with efficacy against azole-resistant *A. fumigatus* is expected to take several more years. Therefore, targeting high serum concentrations of POS using the tablet or IV formulation is, in our point of view, a possible step-down option in patients with azole-resistant IA as long as the POS-MIC is <1 mg/L and for patients treated for mucormycosis with L-AmB. It should only be used when close monitoring for AE is implemented as described above in conjunction with TDM and when the benefits are likely to outweigh the risks.

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Author Contributions

A.F.A.D.S. and J.B.B. collected the clinical data. A.F.A.D.S., J.B.B., R.J.B. and B.J.A.R. analyzed the data. A.F.A.D.S., J.B.B., R.J.B. and B.J.A.R. wrote the initial draft. All authors critically revised the initial draft and final manuscript.

Ethics statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this type of research does not fall under the Dutch law of research on human subjects.

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