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Optimizing antifungal treatment through pharmacometrics: dosing considerations to enhance outcome

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Chapter 2

Pharmacokinetics and pharmacodynamics of posaconazole

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Abstract

Posaconazole is typically used for preventing invasive yeast and mold infections such as invasive aspergillosis in high risk immunocompromised patients. The oral suspension was the first released formulation and many pharmacokinetic and pharmacodynamic studies of this formulation have been published. Erratic absorption profiles associated with this formulation were widely reported. Posaconazole exposure was found to be significantly influenced by food and many gastrointestinal conditions, including pH and motility. As a result, low posaconazole plasma concentrations were obtained in large groups of patients. These issues of erratic absorption urged the development of the subsequently marketed delayed-release tablet, which proved to be associated with higher and more stable exposure profiles. Shortly thereafter, an intravenous formulation was released for patients who are not able to take oral formulations.

Both new formulations require a loading dose on day one, to achieve high posaconazole concentrations more quickly, which was not possible with the oral suspension. So far, there appears to be no evidence of increased toxicity correlated to the higher posaconazole exposure achieved with the regimen for these formulations. The higher systemic availability of posaconazole for the delayed-release tablet and intravenous formulation caused these two formulations to be preferable for both prophylaxis and treatment of invasive fungal disease.

This review aims to integrate the current knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, clinical experience in special populations, and new therapeutic strategies in order to get a clear understanding of the clinical use of this drug.

Key words Posaconazole Pharmacokinetics Pharmacodynamics

2.1 Introduction

Posaconazole (Noxafil®) is a systemic triazole antifungal drug derived from itraconazole and exerts the same antifungal mechanism of action as other azole derivatives [1]. Three formulations are currently available, namely an oral suspension (40 mg/ml), a delayed-release tablet (100 mg) and an intravenous formulation (18 mg/ml). The posaconazole oral suspension and delayed-release tablet are approved for patients of 13 years and older (USA) or adults of 18 years and older (Europe), while the intravenous formulation is licensed only in patients of 18 years and older. Posaconazole is mainly licensed for prophylaxis of invasive fungal diseases (IFD) in: 1) patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) which are expected to result in prolonged neutropenia and who are at high risk of developing IFD; 2) hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing IFD [2]. Additionally, it is approved for treatment of oropharyngeal candidiasis, for the treatment of patients with IFD that are intolerant to first line therapy, and as salvage treatment of IFD caused by rare pathogens, such as fusariosis, chromoblastomycosis, mycetoma and coccidioidomycosis [3].

2.1.1 Dosing

The posaconazole suspension is indicated to be dosed as 200 mg TID for prophylaxis or as 400 mg BID or 200 mg QID for treatment of refractory IFDs or for treatment of patients with IFD who are intolerant to first line therapy. The delayed-release tablet and intravenous formulation are indicated to be given as a loading dose at 300 mg BID on the first day and a maintenance dose at 300 mg QD thereafter.

2.1.2 Mechanism of Action

Similar to other azole derivatives, posaconazole inhibits the enzyme lanosterol 14 α -demethylase and consequently inhibits the biosynthesis of ergosterol which is an essential component of fungal cell membrane (see in Fig. 1). This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thereby weakening the structure and function of the fungal cell membrane, which is considered to be responsible for the antifungal activity of posaconazole [2].

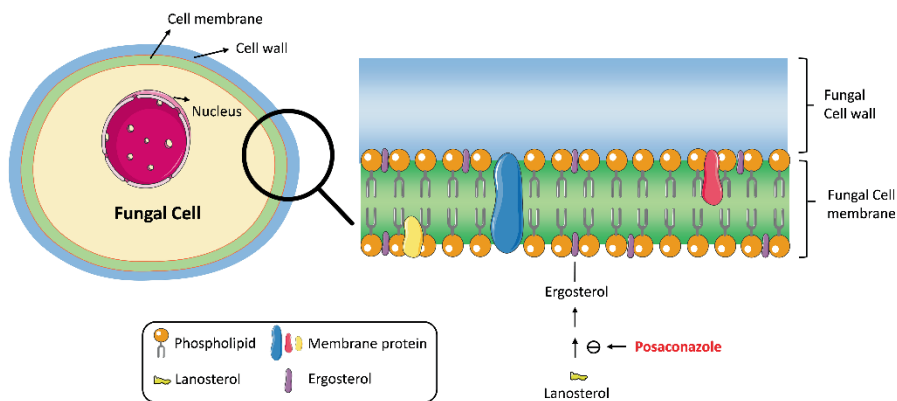


Fig. 1 Antifungal mechanism of action of posaconazole.

2.1.3 In Vitro Antifungal Activity

Posaconazole shows a wide spectrum activity against the majority of opportunistic pathogenic yeasts and molds in vitro, including the common pathogenic fungal species, such as *Candida* and *Aspergillus* species, but also against less common pathogens such as Mucorales and some *Fusarium* species [3]. According to European Committee on Antimicrobial Susceptibility Testing (EUCAST), the minimum inhibitory concentration (MIC) breakpoints for *A. fumigatus* are ≤ 0.12 mg/L for susceptible and >0.25 mg/L for resistant strains, 0.25 mg/L for *A. terreus* and 0.5 mg/L for *A. flavus*, *A. nidulans*, and *A. niger* [4]. The breakpoints of posaconazole against *C. albicans*, *C. dubliniensis*, *C. parapsilosis*, *C. tropicalis* are all defined as ≤ 0.06 mg/L for susceptible and >0.06 mg/L for resistant substrains. Higher resistant breakpoints of 0.25, 0.5 and 1.0 mg/L were demonstrated in *C. guilliermondii*, *C. krusei*, and *C. glabrata*, respectively [4].

2.1.4 *Aspergillus* resistance

Posaconazole showed potent dose-dependent in vivo antifungal activity in many animal studies on prophylaxis and treatment against *C. albicans*, *A. fumigatus*, and other uncommon fungal infections [5-13]. The area under the concentration-time curve (AUC) versus MIC, i.e. AUC/MIC, showed the strongest correlation with therapeutic success. Despite the dose-dependent killing, some strains of *A. fumigatus* have become fully resistant against azoles and this resistance has become of increasing clinical concern.

Acquired azole resistance in *A. fumigatus* is emerging globally and poses a therapeutic challenge [14, 15]. The majority of isolates with azole resistant phenotypes harbor mutations in the *cyp51A* gene, which codes for the enzyme lanosterol 14 α -demethylase, or in the promotor region of this gene. Two routes of resistance

development have been proposed [16]. Azole resistance can develop in-host during treatment (patient route) or alternatively through exposure to azole fungicides in the environment (environmental route). Generally, the resistant mutations associated with these routes are different, as point mutations in locus G54, M220, G448, P216 in the *cyp51A* gene and non-*cyp51A* mediated mechanisms are mostly associated with in-host resistance development, while the L98H mutations in combination with a 34 base pair tandem repeat in the promoter region (TR₃₄/L98H) or Y121F/T289A in combination with a TR₄₆ (TR₄₆/Y121F/T289A) are associated with the environmental route. Importantly, resistant isolates with environmental mutations have been found in patients without prior antifungal exposure. Exceptions to the categorization in resistance development routes were recently described as isolates with *cyp51A* point mutations have been recovered from the environment and azole-naïve patients [17]. In addition, an isolate harboring a tandem repeat in the promoter region (TR120) was shown to have developed in-host through azole therapy [17, 18].

Case series indicate that azole resistance in *A. fumigatus* is associated with increased mortality rates [19-21]. Most resistance mutations affect the azole susceptibility of all the triazoles. But, as the triazoles are structurally different (e.g. long tailed and short tailed triazoles), different mutations may have various effects on the target binding of triazoles and thus mutations may have distinct effects on MIC values [22]. For example, TR₃₄/L98H often results in high itraconazole resistance with voriconazole, isavuconazole and posaconazole MICs being variable, while isolates with TR₄₆/Y121F/T289A have high resistance to voriconazole and isavuconazole with itraconazole and posaconazole being less affected. In most azole-resistant isolates, posaconazole retains the greatest *in vitro* activity, with MICs that are close to the resistance breakpoint. *In vivo* studies indicate that isolates with increased posaconazole MICs may still be treated with increased posaconazole exposure [7, 9]. As the azoles are the only drug class with activity against *Aspergillus* that can be administered orally, strategies are explored using higher than standard dosing to overcome resistance in selected patients and in infections by azole low-resistant isolates [23]. An increasing number of studies on different formulations, together with an extended clinical use of posaconazole, enriched our understanding regarding the pharmacology of this drug, but some discrepancies and controversial issues have also arisen. This review aims to integrate the current knowledge on posaconazole pharmacokinetics, pharmacodynamics, major toxicity, existing resistance, new therapeutic strategies, and clinical experience in special populations, in order to get a clear understanding of the clinical use of this drug.

2.2 Clinical Pharmacokinetics

The posaconazole oral tablet - not the marketed delayed-release tablet, but a premarketing formulation used before the oral suspension - showed dose-linearity in exposure up to a single dose of 800 mg, with saturation of absorption occurring above 800 mg in healthy volunteers [24]. Using simulation-based approaches it has

been proposed that the non-linear absorption might be attributable to the extensive precipitation of posaconazole in the small intestine due to the incomplete gastric dissolution in the pH shift from stomach to the intestine, caused by its high lipophilicity and weakly basic property [25, 26]. Hence, development of this oral tablet was not pursued and an oral suspension was brought to the market. Unfortunately, this suspension also demonstrated high inter-individual variability as typically patients that received the suspension did demonstrate dose-limited absorption above a daily dose of 800 mg with a highly variable and erratic absorption [27].

A gastric-resistant tablet formulation was subsequently designed for releasing posaconazole in the small intestine, in order to avoid the erratic absorption caused by the gastric conditions and to improve the systemic absorption. The systemic exposure after administration of this delayed-release tablet showed dose-linearity between 200 mg to 400 mg, while higher doses were not explored [28]. Finally, an intravenous formulation was designed for patients who do not tolerate oral medication. Dose-linearity was observed between doses of 200 mg and 300 mg whereas non-linearities were observed below 200 mg [29, 30]. Intravenous doses above 300 mg were not investigated. The exposure of these two new formulations still shows substantial interpatient variability [31-34].

The published population pharmacokinetic findings on posaconazole are discussed below and are summarized in Table 1. Model-independent findings on the clinical pharmacokinetics of posaconazole in healthy volunteers and patients are also discussed and are summarized in Table 2 and Table 3, respectively.

Table 1 Summary of population pharmacokinetic parameter values for posaconazole.

Authors	AbuTarif <i>et al.</i> [38]	Kohl <i>et al.</i> [35]	Storzinger <i>et al.</i> [36]	Vehreschild <i>et al.</i> [37]	Dolton <i>et al.</i> [39]	Petticollin <i>et al.</i> [40]	Iersel <i>et al.</i> [41]	Boonsathorn <i>et al.</i> [52]	Merk <i>et al.</i> [30]
Year	2010	2010	2012	2012	2014	2017	2018	2019	NA
Formulations	Sus	Sus	Sus	Sus	Sus	DR-tab ^a	DR-tab ^b	Sus and DR-tab ^a	Inj
Populations	AML/MDS	allogeneic HSCT	SICU	AML/MDS	HV, IMD (48%HSCT)	HM	HV, AML/MDS/ HSCT	IMD	HV, AML/MDS/ HSCT, clinical trials
Number of individuals	215	32	15	84	102 (20 HV and 82 patients)	49	335 (104 HV and 231 patients)	117 (children aged 5m-18y)	HV (67), AML/ MDS (166), HSCT (73)
Number of samples	702	149	270	643	905	205	5756	338 (96.4% Sus)	2322
Sample type	plasma	serum	serum	serum	plasma	NA	plasma	plasma	plasma
Absorption	NA	first-order	NA	first-order	first-order oral absorption with ALAG	first-order	sequential zero first-order	first-order	NA
k_a (h ⁻¹) estimate (%RSE)	0.040	0.40 fixed	0.77 (35.6)	0.40 fixed	1.3	0.59 (15.0)	0.85 (7.8)	Sus 0.20 (fixed); DR-tab, 0.59 (fixed)	—
Number of compartments	one	one	one	one	one	one	one	one	two
V/F (L) estimate (%RSE)	3290.0 (24.9)	2250 (6.9)	5280.0 (29.5)	2770.0 (6.6)	1100.0	420.0 (10.0)	393.0 (2.8), V only	201.7 (38.8)	V =61.6 (6.8), V _r =181.0 (4.5), absolute V
Elimination	NA	first-order	NA	first-order	first-order	first-order	first-order	NA	first-order
CL/F (L/h) estimate (%RSE)	65.1	67.0 (5.9)	195.0 (16.7)	42.5 (5.2)	30.2	7.3 (5.0)	9.7 (5.0)	15.0 (34.5)	7.8 (3.0), absolute CL
Others parameters	k_e (h ⁻¹)=0.020 fixed	—	—	—	ALAG (h)=1.8	—	D1 (h)=2.5 (3.5)	$\beta_{0.98}$ =99.0 (44.4)	Q=93.5 (9.3)

Authors	AbuTarif <i>et al.</i> [38]	Kohl <i>et al.</i> [35]	Storzinger <i>et al.</i> [36]	Vehreschild <i>et al.</i> [37]	Dolton <i>et al.</i> [39]	Petitcollin <i>et al.</i> [40]	Iersel <i>et al.</i> [41]	Boonsathorn <i>et al.</i> [52]	Merk <i>et al.</i> [30]
IIV, %CV (%RSE)									
CL/F	—	26.9 (13.2)	51.8 (39.9)	25.3 (10.9)	46.4	24.2 (30.0)	37.9 (13.1), CL only	63.0 (23.9)	43.9 (11.2)
V/F	41.1 (9.01)	—	52.0 (53.3)	—	30.2	28.2 (32.0)	—	—	$V_e=51.9$ (72.5), $V_p=22.0$ (29.5),
k_a	—	—	—	—	53.4	—	57.5 (29.3)	—	—
Others	$k_e=49.7$ (10.8)	—	—	—	—	—	relative F=24.2 (26.7)	—	Q=35.2 (49.8)
IOV, %CV (%RSE)									
Relative F	—	—	—	—	23.6 (HV vs. patients)	—	21.4 (23.3)	—	—
Others	—	—	—	—	—	CL/F=31.9 (14.0)	$k_e=71.1$ (17.0); D1=48.6 (9.8)	—	$V_e=47.2$ (75.8)
Residual error, %CV (%RSE)									
Proportional	—	—	—	—	6.8 in HV, 53.8 in patients	14.8 (4.0)	—	47.3 (0.2)	—
Additive	—	—	—	—	—	—	0.42 (8.7) in phase 1 studies; 0.32 (10.3) in phase 3 study	0.02 mg/L (82.7)	—
Exponential	32.1 (8.74)	—	—	—	—	—	—	—	—
Unknown	—	42.0 (8.7)	11.6 (53.2), 2.8 (32.1)	23.2 (5.1)	—	—	—	—	0.39 (5.9) in HV, 0.47 (6.1) in patients

Authors	AbuTarif <i>et al.</i> [38]	Kohl <i>et al.</i> [35]	Storzinger <i>et al.</i> [36]	Vehreschild <i>et al.</i> [37]	Dolton <i>et al.</i> [39]	Petitcollin <i>et al.</i> [40]	Iersel <i>et al.</i> [41]	Boonsathorn <i>et al.</i> [52]	Merk <i>et al.</i> [30]
Covariates (increase)	race (nonwhite vs. white), diarrhea, PPI use, GGT levels $\geq 2 \times$ ULN, bilirubin levels $\geq 2 \times$ ULN on V/F	diarrhea on V/F and CL/F	none	body weight on V/F, diarrhea and PPI use on CL/F	coadministration of phenytoin/ rifampin and fosamprenavir on CL/F, nutritional supplement on relative F (HV vs. patients)	none	dosing regimen (single dose vs. multiple dose) on CL/F, food intake on k_a , formulation (tablet A/B vs. tablet C/D) on relative F	none	body weight on V_p , disease status (patients vs. HV) on V_c and V_p
Covariates (decrease)	none	age on V/F	none	coadministration of chemotherapy on V/F	coadministration of metoclopramide, PPI, concurrent mucositis and diarrhea on relative F (HV vs. patients)	none	concurrent of AML/MDS and body weight on relative F	coadministration of PPI on relative F (Sus vs. DR-tab)	none

*the marketed delayed-release tablet; *four trial delayed-release tablet formulations, including tablet A, tablet B, tablet C and tablet D (tablet D is the marked image); ALAG, absorption lag time; AML, acute myelogenous leukemia; CL, clearance; CL/F, apparent clearance; CV, coefficient variability; D1, duration of zero-order absorption into the depot compartment; DR-tab, delayed-release tablet; F, bioavailability; GGT, gamma-glutamyl transpeptidase; HM, hematological malignancy; HSCT, hematopoietic stem cell transplant; HV, healthy volunteers; IV, inter-individual variability; IMD, immunodeficiency; inj, injection; IOV, inter-occasion variability; k_a , absorption rate constant; k_e , elimination rate constant; MDS, myelodysplastic syndrome; NA, not available; PPI, proton-pump inhibitors; Q, intercompartment clearance; RSE, relative standard error; SICU, surgical intensive care unit; Sus, suspension; ULN, upper limit of normal; V_c , volume of distribution; V/F, apparent volume of distribution; V_p , central volume; V_p , peripheral volume; β_{obs} , estimated dose in mg/m^2 for suspension bioavailability to drop to half that of the delayed-release tablet;

Table 2 Summary of pharmacokinetic characteristics of posaconazole in healthy volunteers using model-independent methods.

Authors	Year	Posaconazole formulation	No. of subjects	Dosage (mg)	Single or multiple dose	Food status	AUC ₀₋₂₄ (mg·h/L), mean (%CV)	T _{max} (h), median (%CV/range)	t _{1/2} (h), mean (%CV)	C _{max} (mg/L), mean (%CV)	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv	AR
Courtney et al.[24]	2003	Tab ^a	6	50	single	fed	2.3 (50.0)	6.3 (51.0), mean	15.9 (18.0)	0.11 (46.0)	23.3 (40.0)	511.0 (32.0)	—
			6	100	single	fed	6.1 (28.0)	7.3 (36.0), mean	18.3 (13.0)	0.24 (26.0)	16.5 (21.0)	431.0 (20.0)	—
			6	200	single	fed	10.4 (30.0)	5.8 (35.0), mean	24.5 (22.0)	0.33 (21.0)	20.5 (40.0)	674.0 (18.0)	—
			6	400	single	fed	19.4 (33.0)	6.3 (44.0), mean	24.1 (24.0)	0.61 (31.0)	21.8 (35.0)	781.0 (49.0)	—
			6	800	single	fed	47.0 (40.0)	6.2 (46.0), mean	24.4 (33.0)	1.3 (26.0)	19.2 (48.0)	594.0 (19.0)	—
			6	1200	single	fed	41.8 (42.0)	8.8 (85.0), mean	28.5 (26.0)	0.93 (28.0)	35.1 (73.0)	1341.0 (58.0)	—
			9	50 BID	multiple	fed	8.3 (36.0), AUC ₀₋₂₄	T _{max} 1=5.0 (12.0), T _{max} 2=9.0 (34.0)	19.2 (16.0)	C _{max} 1=0.46 (38.0), C _{max} 2=0.37 (30.0)	13.5 (34.0)	365.0 (29.0)	6.6 (29.0)
			9	100 BID	multiple	fed	21.8 (40.0), AUC ₀₋₂₄	T _{max} 1=6.0 (40.0), T _{max} 2=11.0 (16.0)	24.1 (20.0)	C _{max} 1=1.1 (37.0), C _{max} 2=1.0 (42.0)	10.3 (32.0)	343.0 (24.0)	6.9 (27.0)
			9	200 BID	multiple	fed	31.1 (26.0), AUC ₀₋₂₄	T _{max} 1=4.0 (12.0), T _{max} 2=10.0 (19.0)	23.9 (26.0)	C _{max} 1=1.8 (27.0), C _{max} 2=1.4 (27.0)	13.9 (34.0)	467.0 (32.0)	7.6 (37.0)
			9	400 BID	multiple	fed	73.1 (20.0), AUC ₀₋₂₄	T _{max} 1=5.0 (12.0), T _{max} 2=9.0 (32.0)	31.0 (46.0)	C _{max} 1=4.2 (20.0), C _{max} 2=3.2 (19.0)	11.5 (25.0)	486.0 (34.0)	8.3 (32.0)
Krishna et al.[50]	2012	Sus	15	100	single	fed	8.5 (25.0)	6.0 (5.0-12.0)	25.1 (35.0)	0.24 (18.0)	12.1 (26.0)	4 2 7 . 0 (39.0)	—
			15	100	single	fasted	3.0 (50.0)	4.0 (2.0-8.0)	29.2 (31.0)	0.084 (62.0)	34.0 (38.0)	1 4 5 0 . 0 (54.0)	—
P07691_EMA [42]	NA	Sus	23	100	single	fed	8.0 (32.0)	5.0 (4.0-12.0)	26.2 (26.0)	0.25 (25.0)	12.9 (31.0)	468.0 (26.0)	—
P07691_EMA [42]	NA	DR-tab ^b	22	100	single	fasted	8.3 (33.0)	5.0 (3.0-12.0)	27.0 (27.0)	0.29 (40.0)	12.7 (37.0)	467.0 (25.0)	—
Krishna et al.[28]	2012	DR-tab ^c	10	200	single	fasted	23.0 (23.0)	4.0 (3.0-8.0)	25.1 (20.0)	0.78 (29.0)	8.8 (26.0)	NA	—
			9	400	single	fasted	42.8 (35.0)	5.0 (3.0-8.0)	26.1 (22.0)	1.3 (29.0)	9.6 (34.0)	NA	—

Authors	Year	Posaconazole formulation	No. of subjects	Dosage (mg)	Single or multiple dose	Food status	AUC _{0-24h} (mg·h/L), mean (%CV)	T _{max} (h), median (%CV/range)	t _{1/2} (h), mean (%CV)	C _{max} (mg/L), mean (%CV)	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv	AR
			8	200 QD	multiple	fasted	31.4 (32.0), AUC _{0-24h}	5.0 (2.0-8.0)	NA	1.8 (31.0)	NA	NA	3.14 (24.0)
			8	200 BID	multiple	fasted	30.6 (38.0), AUC _{0-24h}	4.0 (2.0-8.0)	NA	3.0 (38.0)	NA	NA	4.75 (28.0)
			8	400 QD	multiple	fasted	56.6 (54.0), AUC _{0-24h}	5.0 (0-12.0)	NA	2.9 (46.0)	NA	NA	3.16 (57.0)
Kraft et al.[48]	2014	DR-tab ^b	20	400	single	fasted	41.0 (47.0)	4.0 (2.0-8.0)	27.3 (37.0)	1.1 (43.0)	NA	NA	—
P07783_EMA [30]	NA	DR-tab ^b	13	300	single	NA	22.7 (46.0)	5.0 (3.0-6.0)	28.1 (25.6)	0.61 (37.9)	15.4 (45.8)	583.3 (36.0)	—
Kersemaekers et al.[29]	2015	Inj	9	50	single	NA	4.6 (31.0)	0.6 (0.5-0.7)	18.7 (34.0)	0.31 (30.0)	10.9 (25.0)	294.0 (39.0)	—
			9	100	single	NA	10.8 (27.0)	0.5 (0.5-0.5)	19.6 (16.0)	1.3 (27.0)	9.4 (23.0)	262.0 (22.0)	—
			9	200	single	NA	34.6 (52.0)	0.5 (0.5-24.0)	23.6 (23.0)	2.3 (29.0)	6.5 (32.0)	226.0 (38.0)	—
			9	250	single	NA	40.6 (39.0)	0.5 (0.5-0.5)	26.0 (23.0)	2.3 (26.0)	6.7 (29.0)	245.0 (33.0)	—
			9	300	single	NA	45.5 (26.0)	0.5 (0.5-1.0)	24.6 (20.0)	2.8 (30.0)	6.9 (27.0)	236.0 (17.0)	—
P07783_EMA [30]	NA	Inj	13	300	single	NA	42.9 (30.7)	0.5 (0.25-0.5)	28.8 (27.8)	4.3 (19.1)	7.6 (41.4)	294.6 (24.8)	—

^aan unmarketed tablet formulation before releasing oral suspension, not a delayed-release formulation; ^btablet D, the marketed delayed-release tablet; ^ctablet C, an unmarketed trial delayed-release tablet formulation; AR, accumulation ratio; AUC_{0-24h}, the area under the concentration-time curve from time zero (0 h) to the time of recovery of the final sample with a quantifiable concentration; AUC_{0-12h}, the area under the concentration-time curve during the dosing interval; BID, twice a day; CL, clearance; CL/F, apparent clearance; C_{max}, maximum concentration; CV, coefficient variability; DR-tab, delayed-release tablet; EMA, European Medicines Agency; F, oral bioavailability; Inj, injection; NA, not available; QD, once a day; Sus, suspension; T_{1/2}^a, terminal-phase half-life; Tab, tablet; T_{max}^a, the time to peak concentration; V, apparent volume of distribution; V/F, apparent volume of distribution;

Table 3 The summary of pharmacokinetic characteristics of posaconazole in patients using model-independent method.

Authors	Year	Posaconazole formulation	Diseases	No. of patients	Dosage (mg)	Sample day	AUC ₀₋₂₄ (ng·h/L), mean (%CV)	T _{max} (h), median (%CV), range	t _{1/2} (h), mean (%CV)	C _{max} (mg/L), mean (%CV)	C _{min} (mg/L), mean (%CV)	AR	CL/F (L/h) for oral, CL V for iv	V/F (L) for oral, CL V for iv
Ullmann <i>et al.</i> [27]	2006	Sus	FN&IFD	24	400 BID	10	8.6 (86.0)	3.0 (0-12.5)	11.9 (3.0)	0.64 (98.0)	0.72 (86.0)	NA	283.0 (354.0)	2447.0 (421.0)
				19	600 BID	10	5.8 (71.0)	3.8 (0-10)	12.0 (3.0)	0.39 (64.0)	0.49 (71.0)	NA	179.0 (82.0)	4984.0 (919.0)
				18	800 QD	10	6.2 (71.0)	4.0 (2.4-12.5)	24.0 (2.0)	0.25 (100.0)	0.26 (72.0)	NA	215.0 (81.0)	5061.0 (903.0)
Gubbins <i>et al.</i> [53]	2006	Sus	autologous HSCT	7	200 QD	1	2.0 (56.1)	8.0 (4.0-12.5)	NA	NA	NA	—	NA	NA
				15	400 QD	1	3.0 (67.6)	8.0 (3.0-24.0)	NA	NA	NA	—	NA	NA
				7	200 QID	1	3.0 (37.3), AUC ₀₋₂₄	4.5 (2.0-6.0)	NA	NA	NA	—	NA	NA
				7	200 QD	14.0 (42.9)	4.5 (64.4)	4.0 (1.0-6.0)	NA	NA	NA	2.7	59.4 (52.1)	NA
				14	400 QD	9.9 (23.2)	6.4 (50.0)	7.0 (3.0-12.0)	NA	NA	NA	2.4	90.4 (79.8)	NA
				7	200 QID	8.1 (13.6)	8.7 (37.9), AUC ₀₋₂₄	10.3 (1.0-24.0)	NA	NA	NA	3.9	89.1 (58.8)	NA
Zhang <i>et al.</i> [54]	2016	Sus	LT-CF	7	829/day	≥5d	5.8 (0.25-15.8), AUC ₀₋₂₄ , median (range)	4.4 (0-7.8)	NA	0.19 (0-0.62), median (range)	0.23 (0.01-0.77), median (range)	NA	143.2 (32.3-3278.7)	NA
			LT-non-CF	12	862/day	≥5d	17.2 (4.3-63.8), AUC ₀₋₂₄ , median (range)	4.0 (0-11.8)	NA	0.47 (0.12-2.1), median (range)	0.59 (0.15-2.5), median (range)	NA	51.8 (13.6-216.3)	NA
Duarte <i>et al.</i> [31]	2014	DR-tab ^a	AML/MDS	20	200 BID	1	4.6 (34.0)	3.1 (1.9-4.1)	NA	0.16-0.88, range	NA	—	NA	NA
				33	300 BID	1	6.2 (28.0)	4.0 (1.8-8.1)	NA	0.44-1.6, range	NA	—	NA	NA

Authors	Year	Posaconazole formulation	Diseases	No. of patients	Dosage (mg)	Sample day	AUC ₀₋₂₄ (mg·h/L), mean (%CV)	T _{max} (h), median (%CV/ range)	t _{1/2} (h), mean (%CV)	C _{min} (mg/L), mean (%CV)	C _{avg} (mg/L), mean (%CV)	C _{max} (mg/L), mean (%CV)	AR	CL/F (L/h) for oral, CL for iv	V/F (L) for oral, V for iv
				19	200 QD	8	22.7 (51.0)	4.9 (2.0-9.2)	NA	0.19-1.7, range	0.95 (50.0)	1.3 (49.0)	2.2 (60.0)	NA	NA
				32	300 QD	8	35.0 (41.0)	2.2 (1.3-8.1)	NA	0.34-2.6, range	1.5 (38.0)	2.0 (33.0)	2.5 (37.0)	NA	NA
Cornely <i>et al.</i> [32]	2016	DR-tab ^a	AML/MDS/ HSCt	50	300 QD	8	37.9 (42.0), AUC ₀₋₂₄	4.0 (1.3-8.3)	NA	1.3 (50.0)	1.6 (42.0)	2.1 (38.0)	NA	9.4 (45.0)	NA
			HSCt	17	300 QD	8	44.8 (45.0), AUC ₀₋₂₄	4.1 (2.0-8.3)	NA	1.5 (49.0)	1.9 (45.0)	2.4 (43.0)	NA	8.1 (46.0)	NA
			AML/MDS	33	300 QD	8	34.3 (36.0), AUC ₀₋₂₄	2.2 (1.3-8.1)	NA	1.2 (47.0)	1.4 (36.0)	1.9 (32.0)	NA	10.1 (43.0)	NA
Maertens <i>et al.</i> [33]	2014	Inj	AML/MDS	20	200 BID	1	5.4 (29.0)	1.5 (1.0-4.0)	NA	—	—	0.99 (47.0)	—	NA	NA
				22	300 BID	1	8.2 (26.0)	1.5 (1.0-2.0)	NA	—	—	1.6 (61.0)	—	NA	NA
				15	200 QD	14	28.2 (51.0)	1.0 (1.0-4.0)	NA	0.96 (63.0)	1.2 (51.0)	2.0 (50.0)	3.6 (44.0)	NA	NA
				19	300 QD	14	34.3 (42.0)	1.5 (0.98-4.0)	NA	1.1 (50.0)	1.4 (42.0)	2.6 (39.0)	2.8 (31.0)	NA	NA
Cornely <i>et al.</i> [34]	2017	Inj	AML/MDS/ HSCt	49	300 QD	10	36.1 (35.0)	1.5 (0.98-4.0)	NA	1.1 (44.0)	1.5 (35.0)	3.3 (74.0)	NA	NA	NA
Sime <i>et al.</i> [55]	2018	Inj	ICU	8	300 QD	1	11.6, AUC ₀₋₂₄	NA	23.0	0.22	—	1.7	—	16.8	529.1

^atablet D, the marked delayed-release tablet;

AR, accumulation ratio; AUC₀₋₂₄, the area under the concentration-time curve during the dosing interval; AML, acute myelogenous leukemia; AUC₀₋₁₂, the area under the concentration-time curve from 0 to 12 h; AUC₀₋₂₄, the area under the concentration-time curve from 0 to 24 h; AUC₀₋₆, the area under the concentration-time curve from time zero (0 h) to the time of recovery of the final sample with a quantifiable concentration; BID, twice a day; C_{avg}, average concentration; CF, cystic fibrosis; CL, clearance; CL/F, apparent clearance; C_{max}, maximum concentration; C_{min}, trough concentration; CV, coefficient variability; DR-tab, delayed-release tablet; FW, IFD, persistent febrile neutropenia or cradomy invasive fungal infection; HSCt, hematopoietic stem cell transplantation; Inj, injection; LT, lung transplantation; MDS, myelodysplastic syndrome; NA, not available; QD, once a day; QID, four times a day; Sus, suspension; T_{1/2}, terminal-phase half-life; T_{max}, the time to peak concentration; V, apparent volume of distribution; V/F, apparent volume of distribution;

2.2.1 Absorption

The two relevant parameters for oral absorption are the absorption rate constant (k_a), describing the rate of absorption, and bioavailability (F), describing the extent of absorption. The k_a of the suspension was reported to be different in different patient groups and mostly ranged from 0.40 to 0.77 h⁻¹, which corresponds to an absorption half-life ($t_{1/2}$) between 0.90 and 1.7 h [35-37]. Both a slower absorption (absorption $t_{1/2}$ of 17.5 h) as well as a faster absorption (absorption $t_{1/2}$ of 0.55 h) with a delayed onset of absorption have been reported [38, 39]. High inter-individual variability (53.4%) was reported for the k_a upon administration of the posaconazole suspension [39]. For the delayed-release tablet, similar k_a values were reported (0.59 h⁻¹ and 0.85 h⁻¹) [40, 41] with inter-individual variability in k_a (57.5%) being as high as for the oral suspension [41]. Food intake proved to be associated with an increase in k_a , but was not expected to have a clinically relevant influence, because it had no impact on bioavailability or steady-state exposure parameters [41].

The mean value for F for the posaconazole suspension and delayed-release tablet were reported to be around 50% in healthy volunteers [42, 43], but was found to be about 2.6 times lower in patients receiving the posaconazole suspension [39]. It has been shown that food intake and nutritional supplements increase the F by improving solubility and delaying gastric emptying, thereby enhancing posaconazole exposure. Higher gastric pH and gastrointestinal motility decrease F of the oral suspension by reducing the solubility and shortening gastric residence time [44-47]. Additionally, administering the posaconazole suspension via nasogastric tube showed approximately 20% decreases in exposure compared to oral administration in healthy volunteers [47]. In immunocompromised patients, coadministration of proton pump inhibitors (PPI) or metoclopramide, or the occurrence of mucositis or diarrhea were proven to reduce the F of posaconazole by 45%, 35%, 58%, and 45%, respectively, while administration with nutritional supplements could increase F by 129% [39].

The systemic exposure of posaconazole upon dosing of the delayed-release tablet formulation is less susceptible to the aforementioned gastric conditions than the suspension. Coadministration with antacids, PPIs, H₂ receptor functional antagonists, or metoclopramide proved to have a non-clinically relevant impact on the F of posaconazole in a healthy population receiving the delayed-release tablet [48]. A high-fat meal could only modestly increase the posaconazole AUC by 50%, in contrast to a 400% increase in similar conditions for the suspension, even though the high-fat meal postpones the median time to peak concentration (t_{max}) with one hour [49, 50].

The posaconazole suspension exhibits a dose-dependent and saturable absorption profile, with more frequent dosing leading to higher exposure when the total daily dose is lower than 800 mg [46, 51]. This pattern was not observed in the delayed-

release tablet [28], due to the distinct differences in the gastrointestinal drug delivery features between these two oral formulations.

2.2.2 Distribution

Figure 2 shows posaconazole distribution in various human tissues and fluids after systemic administration [56-65]. This figure shows that posaconazole accumulates in peripheral tissues, especially in lungs, kidneys, liver, and heart [56, 66]. For instance, exposure in alveolar cells is about 32-fold higher than in plasma, although the exposure in the pulmonary epithelial lining fluid (ELF) is slightly lower than in plasma in health volunteers receiving the posaconazole suspension of 400 mg twice daily [58]. The concentrations in skin are similar to blood [59]. Posaconazole showed inconsistent distribution profiles in the cerebral spinal fluid (CSF) with CSF/serum levels ranging from 0.4% to 237% [62, 63]. It is unclear how cerebral inflammation impacts the permeability of the blood-brain barrier to further influence posaconazole exposure in CSF [62, 63]. Posaconazole concentrations in brain tissue have not been reported in humans, but in two murine models these concentrations were reported to be about half of serum concentrations [67, 68]. Based on the current evidence of posaconazole distribution in the central nervous system, there is no clear pharmacokinetic evidence to prioritize posaconazole in the treatment of cerebral infections.

Posaconazole is bound to the plasma proteins for more than 98%, predominantly to albumin [42], yet this does not limit extravascular distribution of posaconazole. With values of 61.6 L and 181 L for the central and peripheral volume of distribution (V_d) respectively, the V_d of posaconazole is relatively large [30]. When posaconazole is only administered orally, F cannot be estimated. In such studies apparent V_d (V_d/F) will be reported, which is inversely proportional to the value of F . Thus, the inter-individual variability in apparent V_d observed in patients receiving oral posaconazole is significantly affected by the F . In healthy volunteers, the V_d/F of the posaconazole suspension and the delayed-release tablet are about twice as high as the absolute V_d that was determined upon intravenous injection [29], which could be explained by the reported value of 50% for F . A compartmental pharmacokinetic model developed for patients with persistent febrile neutropenia or refractory IFD showed that the V_d/F of posaconazole suspension is 2447 L [27], which indicates a remarkably larger V_d/F than for the healthy population (427 L under fed and 1450 L under fasted conditions) [50]. Four population pharmacokinetic studies using non-linear mixed effect modeling confirmed this finding in other hematological patients receiving posaconazole suspension [35, 37-39]. The markedly larger V_d/F in the patient population might be in part due to the lower F caused by concomitant medication and multiple clinical factors. Patients from the surgical intensive care unit (SICU) exhibited the largest V_d/F (5280 L, compared to 1100 - 2770 L in hematological patients), which might be mainly caused by poor absorption resulting from the application of nasogastric tubes and/or by increased distribution to peripheral tissue due to capillary leakage

tissue due to capillary leakage and edema [36].

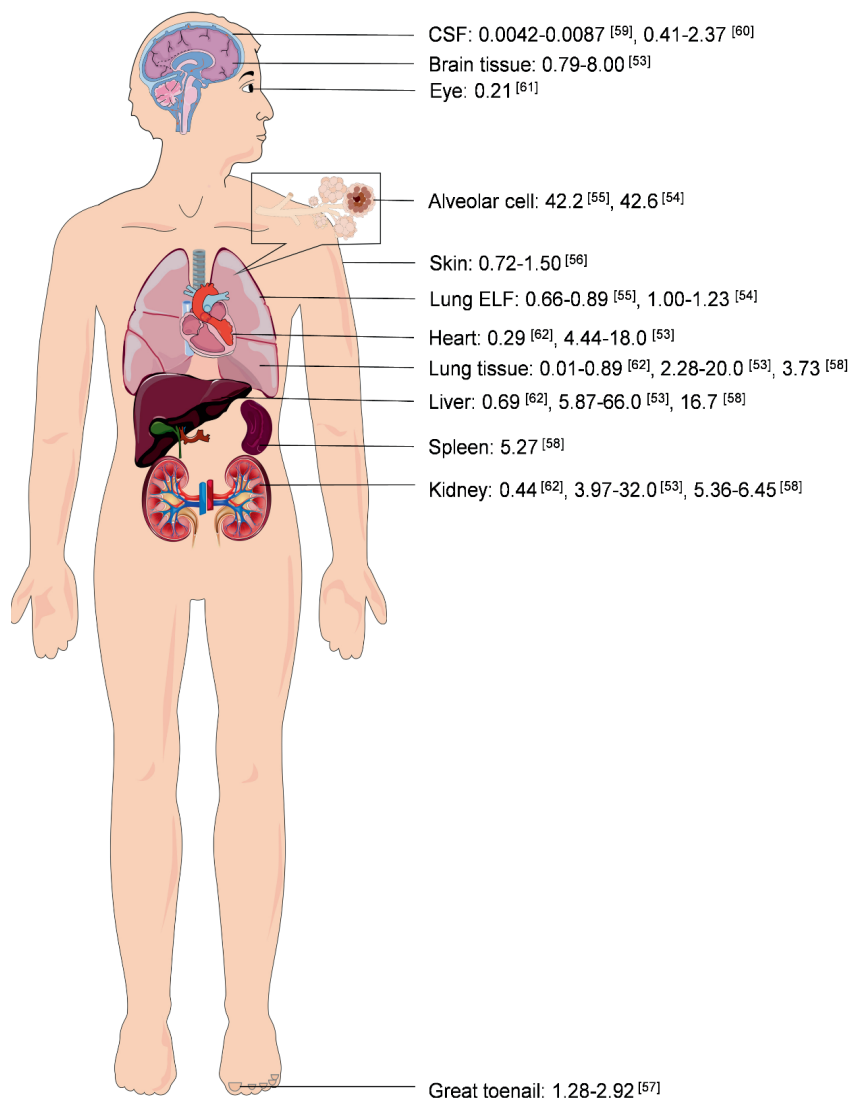


Fig. 2 Posaconazole distribution depicted as the ratios of tissue or fluid concentrations versus simultaneously measured plasma concentrations in different organs and tissues (tissue concentration unit: ng/g, fluid or plasma concentration unit: ng/mL). CSF = cerebrospinal fluid; ELF = pulmonary epithelial lining fluid

Inter-individual variability in posaconazole V_d was reported to be high among AML/MDS/HSCT patients [30]. Disease status (patients vs. healthy volunteers) proved to increase both central and peripheral V_d , moreover peripheral V_d was found to

increase with increasing body weight [30].

The delayed-release tablet formulation was found to exhibit a lower V_d/F than the suspension based on population pharmacokinetic analyses [35-41], but this is likely driven by the difference in F rather than by a true difference in V_d . In patients with AML/MDS receiving the oral suspension, ethnicity (non-white vs. white), higher weight, PPI use, occurrence of diarrhea, and high gamma-glutamyl transpeptidase or bilirubin levels (≥ 2 times the upper limit of normal) proved to significantly increase the V_d/F [37, 38], among which the impact of diarrhea and PPI use are likely driven by the decrease in F . In contrast, coadministration of chemotherapy has shown to decrease the V_d/F [37]. In patients receiving allogeneic HSCT, increasing age proved to be associated with decreases in V_d/F [35]. No variable was associated inter-individual variability in V_d/F for the delayed-release tablet [40, 41], which might be partly due to the weak influence from gastric condition on the extent of absorption.

2.2.3 Biotransformation and elimination

After administration of the posaconazole suspension, 77% of the dose is excreted by feces of which $>66\%$ is unchanged, while 13% of the doses is eliminated in urine of which $<0.2\%$ is unchanged [2]. Unlike other triazole antifungal agents, posaconazole is barely metabolized by cytochrome P450 (CYP). About 17% is glucuronidated by UGT1A4 and the remainder is eliminated unchanged [69, 70]. There are no major circulating metabolites. Nevertheless, posaconazole may still be impacted as victim drug by interactions with drugs that interact with UGT enzymes, like phenytoin, rifampin, and fosamprenavir [2]. Besides that, posaconazole is a potent inhibitor of CYP3A4 [2]. Clinicians and pharmacists should remember that the inhibitory potency of posaconazole is concentration, and thus formulation, dependent [71]. Several clinically relevant drug-drug interactions have been identified that require substantial empirical dose reductions of victim drugs (i.e. 30 - 50%), like cyclosporine A or tacrolimus. Adding to these examples are the interactions of posaconazole with new targeted therapies such as ibrutinib, venetoclax and ruxolitinib that make optimal management with these combinations challenging [72].

The posaconazole intravenous injection showed a decrease in clearance when increasing a single dose from 50 mg to 200 mg and this remained stable for doses of 200 mg and 300 mg [29]. which may be attributable to saturation of for instance enzyme or transporter involved in the elimination of posaconazole, which leads to the observed more-than-dose-proportional increase in exposure. Posaconazole clearance (CL) reported in a population pharmacokinetic analysis using combined data from both healthy volunteers and patients with AML/MDS/HSCT receiving an intravenous infusion appeared to be in line with these results reported from a clinical pharmacokinetic study in healthy volunteers (7.8 vs. 6.5 - 6.9 L/h) [29, 30]. The apparent clearance (CL/F) observed upon administration of the posaconazole suspension in patients is significantly higher than in healthy volunteers and differs among different

patient populations. Patients with persistent febrile neutropenia or refractory IFD, patients from SICU, and cystic fibrosis patients after lung transplantation appear to have high CL/F values (283.0, 195.0 and 143.2 L/h, respectively) [27, 36, 54], compared with those suffering from AML/MDS/HSCT (42.5 - 67.0 L/h) [35, 37, 38]. In general, the difference in F plays an important role in the substantial differences of posaconazole reported absolute clearance with intravenous formulation and apparent clearance with the oral suspension.

The posaconazole clearance upon administration of the delayed-release tablet showed a similar clearance profile in both healthy volunteers and patient populations [28, 40, 41]. The CL/F observed for the delayed-release tablet is twice as high as the CL of the intravenous formulation in healthy volunteers (15.4 vs. 7.6 L/h), which is also in line with F being estimated around 50% [30]. Two population pharmacokinetic models developed on data upon administration of the posaconazole delayed-release tablet demonstrated that CL/F is slightly lower, with values of 7.3 and 9.7 L/h in patients with hematological malignancies [40, 41]. Generally, the CL/F after administration of the oral suspension is higher than CL/F after administration of the delayed-release tablet, which could be explained by the lower F caused by the lower F of the suspension.

In patients receiving the posaconazole suspension, occurrence of diarrhea and coadministration of PPI or phenytoin/rifampin was associated with increases in posaconazole CL/F [35, 37, 39]. No clinically relevant covariate was identified with significant impact on CL/F or CL of posaconazole delayed-release tablet or iv formulation [30, 40, 41, 52].

Since posaconazole is metabolised by UGT and is a substrate for P-glycoprotein, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g. rifampicin, rifabutin, certain anticonvulsants, etc.) of these proteins may increase or decrease posaconazole plasma concentrations, respectively [3]. On the other hand, as a potent CYP3A4 inhibitor, posaconazole can induce large increases in exposure of CYP3A4 substrates as exemplified before. More details about drug-drug interactions for posaconazole can be found in previously published reviews [73-76].

2.2.4 Posaconazole descriptive pharmacokinetics

The AUC and peak concentration (C_{max}) after a single 100 mg dose of the posaconazole delayed-release tablet to healthy volunteers under fasting conditions were found to be similar compared to the oral suspension under fed conditions using the same dosage. This concentration is three times higher compared to the suspension under fasted conditions [42], which could be explained by the great impact of food and formulation on F for the oral suspension. The AUC and C_{max} of posaconazole upon intravenous administration are 2-fold and 7-fold higher, respectively compared to the delayed-release tablet after a single dose of 300 mg [30]. Posaconazole exposure

after administration of the oral suspension in healthy volunteers is about 2 - 3 times higher compared to hematological patients [42]. The steady-state exposures to posaconazole after administration of the delayed-release tablet or intravenous formulation are similar in patients with AML/MDS/HSCT, but are significantly higher than the suspension [32, 34, 77-79]. The variability in posaconazole average concentration (C_{avg}) upon administration of the oral suspension in patients with AML/MDS/HSCT is relatively high, ranging from 57 - 68% [77, 78]. As the variability in exposure (i.e. AUC or C_{avg}) upon dosing with the posaconazole delayed-release tablet and intravenous formulation in patients with AML/MDS/HSCT is smaller, i.e. 40% and 35% respectively [32, 34], it seems that absorption-related factors are attributable to the variation. A higher steady-state concentration was reported in HSCT patients compared to AML/MDS patients receiving posaconazole suspension and delayed-release tablet (1.47 vs. 0.58 mg/L for suspension, 1.87 vs. 1.44 mg/L for delayed-release tablet) [32, 77, 78], but not for the intravenous administration (1.56 vs. 1.47 mg/L) [34]. The accumulation ratio of upon dosing of the posaconazole suspension in patients is similar to the other two formulations (2.4 - 3.9 for suspension, 2.2 - 2.5 for delayed-release tablet, 2.8 - 3.6 for iv solution) based on the magnitude of AUC [31, 33, 53].

The mean t_{max} observed after administration of the posaconazole suspension ranged from 5.0 to 6.0 h in healthy subjects under fed conditions and 4.0 h under fasted conditions [50], which is similar to the value of delayed-release tablet (4.0 - 5.0 h) under fasted condition [24, 48]. The t_{max} of an intravenous dose is attained around the time of termination of infusion [28, 29, 32, 34]. The mean elimination $t_{1/2}$ of the posaconazole suspension is (25.1 - 29.2 h), which is also comparable to the delayed-release tablet (27.0 - 28.1 h) in healthy volunteers [48, 50]. However, the mean $t_{1/2}$ of the intravenous injection in healthy volunteers showed a dose-dependent prolongation from a single dose of 50 mg (18.7 h) to 200 mg (23.6 h), which can be explained by the aforementioned decreased clearance [29]. When giving a single dose from 250 - 300 mg, the elimination $t_{1/2}$ of posaconazole intravenous formulation is similar to the other two oral formulations (24.6 - 28.8 h) [29].

2.3 Pharmacodynamics

Since neither one single dose nor one target concentration may be appropriate for all patients, researchers integrate the *in vivo* drug exposure and the *in vitro* susceptibility of pathogen against antimicrobial drugs, normally quantified as MIC, as a pharmacokinetic/pharmacodynamic (PK/PD) predictor for the *in vivo* antimicrobial efficacy. The relationship between the exposure to posaconazole and the corresponding antifungal response (PD) in relation to the pathogen susceptibility (MIC) has been verified in many preclinical studies.

2.3.1 Posaconazole PK/PD in preclinical studies

Prophylaxis

Posaconazole given as prophylactic therapy against pulmonary aspergillosis showed a dose-(and concentration)-dependent response in a neutropenic rabbit model and a neutropenic murine model [6, 11]. In the rabbit model, posaconazole was administered orally with 3 dosing levels of 2, 6, and 20 mg/kg/day 4 h before endotracheal inoculation with *A. fumigatus*. Rabbits receiving prophylactic posaconazole at all dosages showed a significant reduction in infarct scores, total lung weights, and organism clearance from lung tissue in comparison to those of untreated controls. A dose-dependent microbiological clearance of *A. fumigatus* from lung tissue in response to posaconazole was observed [6]. In the murine model, oral posaconazole was administered once daily with 5 dosing levels of 1, 4, 8, 16, and 32 mg/kg and mice were infected through instillation of the inoculum in the nares. A 24h-AUC/MIC ratio (AUC_{0-24}/MIC) of 37.4 (95% confidence interval, 7.1 - 196) was able to achieve half-maximal survival for preventing the pulmonary IFD caused by azole-resistant *A. fumigatus* for which the MIC against posaconazole was 0.5 mg/L [11]. Table 4 shows the posaconazole exposure-response relationships in various murine mode

Treatment

In addition to prophylaxis models, many preclinical PK/PD models have been established for the treatment of invasive candidiasis and aspergillosis [5-10]. The posaconazole exposure-response relationship was described using an inhibitory sigmoid E_{max} model based on an in vitro human alveolus model consisting of a bilayer of human alveolar epithelial and endothelial cells [8, 80]. EC_{50} with an AUC/MIC ratio of 2.2 and 11.6 was observed in endothelial and alveolar compartments of an in vitro model infected with *A. fumigatus*, respectively, and an AUC/MIC ratio of 100 was able to achieve near maximal decrease of galactomannan concentrations in both endothelial and alveolar compartments [8].

The relationship between AUC/MIC and the antifungal response to posaconazole were confirmed in three neutropenic murine models of invasive pulmonary aspergillosis and one non-neutropenic murine model of disseminated aspergillosis, all infected with *A. fumigatus* strains [7-10]. The AUC_{0-24}/MIC target associated with half-maximal antifungal response differs from model to model, with a ratio of the AUC/MIC of 321 when using mice mortality as endpoints [7] versus an AUC/MIC ratio of 167 when using the decline in serum galactomannan concentrations as end point [8], or an AUC/MIC of 179 and 53 when models using the fungal burden in the mouse lung are used as PD endpoint [9, 10]. The difference in pharmacodynamic endpoints, number and variety of fungal strains, inoculum size, and data analysis method, as well as drug source might contribute to the difference among these PK/PD targets. EUCAST accepted a PK/PD target of 167 - 178 AUC_{0-24}/MIC for infections

with *Aspergillus*. Using the licensed dose of 400 mg BID of the posaconazole oral suspension an AUC_{0-24} of 17.2 ± 14.8 mg·h/L (mean $\pm$ standard deviation [SD]) was achieved [27], suggesting 98% probability of target attainment for aspergillosis when $MIC \leq 0.015$ mg/L [4]. If the delayed-release tablet or intravenous formulation is used in the licensed dose of 300 mg QD, an AUC_{0-24} of 34.3 ± 12.4 mg·h/L [31] and of 34.3 ± 14.4 mg·h/L (mean $\pm$ SD) [33] are achieved respectively, yielding 100% probability of target aggainment for a pathogen with a $MIC \leq 0.06$ mg/L [4].

Table 4 Posaconazole AUC/MIC threshold corresponding to the EC_{50} for prophylaxis or treatment of IFD caused by different pathogenic fungi in murine models.

Model type	Year	Authors	Pathogens	Immune state	Infection type	No. of Strains	MIC (mg/L)	AUC_{0-24}/MIC	Pharmacodynamic endpoints	R^2
Prophylaxis	2015	Seyedmousavi <i>et al.</i> [11]	<i>A. fumigatus</i>	neutropenic	pulmonary	4	0.063 - >16	37	Survival rate	0.77
Treatment	2004	Andes <i>et al.</i> [5]	<i>C. albicans</i>	neutropenic	disseminated	12	0.015 - 0.12	169	Log_{10} CFU/ml of kidney homogenate	0.70
	2010	Mavridou <i>et al.</i> [7]	<i>A. fumigatus</i>	nonneutropenic	disseminated	4	0.031 - >16	321	Survival rate	0.89
	2011	Howard <i>et al.</i> [8]	<i>A. fumigatus</i>	neutropenic	pulmonary	4	0.12 - >8	167	Galactomannan index	NA
	2013	Lepak <i>et al.</i> [9]	<i>A. fumigatus</i>	neutropenic	pulmonary	10	0.25 - 8	179	Log_{10} CE/ml of lung homogenate	0.79
	2014	Lewis <i>et al.</i> [10]	<i>A. fumigatus</i>	neutropenic	pulmonary	1	0.5	53	Log_{10} CE/ml of lung homogenate	0.80
			^a <i>R. oryzae</i>	neutropenic	pulmonary	1	2	63	Log_{10} CE/ml of lung homogenate	0.83

^anow named *R. arrhizus*; AUC_{0-24} : area under the 24h-concentration time curve; CFU, colony-forming unit; CE, conidial equivalents of fungal DNA; MIC, minimum inhibitory concentration; NA, not available; R^2 , correlation coefficient

Posaconazole PK/PD in treating mucormycosis

Apart from the promising in vitro activity against Mucorales species, posaconazole also showed potential for preventing neutropenic mice from pulmonary mucormycosis by *Rhizopus delemar* [81], and disseminated mucormycosis by *Absidia corymbifera* (now *Lichtheimia corymbifera*) or *R. oryzae* (now *R. arrhizus*) [82]. When posaconazole is used for treatment of mucormycosis, an AUC₀₋₂₄/MIC ratio of 63 proved to be the target that was associated with half-maximal effect of lung fungal burden based on a neutropenic murine model of pulmonary mucormycosis infected with *R. oryzae* [10]. Unfortunately, no controlled, adequately powered clinical efficacy trial is available to confirm this finding in humans. In clinical practice, the posaconazole suspension has been used as salvage therapy of mucormycosis and showed satisfactory efficacy in many cases [83, 84], which also indicates an encouraging prospect of the new formulation with higher drug exposure in this respect [85, 86]. Much like treatment of aspergillosis, for mucormycosis the delayed-release tablet or intravenous formulation are preferred due to the more favorable exposure attained with these formulations.

2.3.2 Posaconazole PK/PD in clinical studies

Although controversial, some studies suggest an exposure-response relationship for both prophylaxis and treatment of IFD in patients. As a certain amount of patients receiving the oral suspension showed low plasma concentrations [2, 79, 87-90], this indicates that therapeutic drug monitoring (TDM) may be needed to ensure adequate exposure [88, 89, 91-93].

Prophylaxis

In general it can be stated that target concentrations for posaconazole prophylaxis are still under debate [87, 94]. A lower boundary of steady-state C_{avg} of 0.7 mg/L for posaconazole is accepted as a target for prophylaxis by the FDA and in European guidelines [95, 96], which was supported by the analysis from two randomized, active-controlled clinical studies [87]. Posaconazole trough concentrations (C_{min}) proved to be well correlated with C_{avg} or AUC₀₋₂₄ [32, 97]. Thus, C_{min} is also frequently used for TDM measures in practice and considered as a more conservative and practicable index [30, 98]. A recent meta-analysis indicated that a C_{min} of 0.5 mg/L could represent a clear margin separating successful from failed prophylaxis [99].

Treatment

For treatment purposes, posaconazole plasma $C_{avg} \geq 1.25$ mg/L at steady-state proved to be associated with 75% successful response rates in patients with invasive aspergillosis and other mycoses, and therefore was considered as a cut-off value for IFD treatment [79]. The 2017 ESCMID-ECMM-ERS guidelines for management of *Aspergillus* disease recommends a slightly lower target trough concentration of 1.0 mg/L for treatment [100]. Both targets lack validation in a larger cohort.

2.3.3 Challenges of conventional PK/PD indices

Although PK/PD indices based on MIC are widely used for target exposures, there are some inherent drawbacks of these indices. Firstly, the PK/PD indices are mostly based on animal studies, but the species differences in pharmacokinetics are not taken into account. Secondly, the *in vitro* MIC is a static threshold value often established with poor precision, that is obtained in experiments with static antifungal concentrations, while it is not known how fungal susceptibility towards the antifungals is impacted by the dynamics in the exposure *in vivo*, nor how this impacts the development of resistance. By not considering the concentration-time course in a dosing interval, these indices are basically assumed to be independent of the drug pharmacokinetics. Finally, the indices do not take the hosts' immune response to the fungal infection into account, which may decrease the required *in vivo* drug exposure needed to obtain the same antifungal effect as in an *in vitro* setting.

Figure 3 illustrates how the currently applied PK/PD indices for antifungals relate to the pharmacological and physiological processes that occur *in vivo*. Upon antifungal administration a dynamic concentration-effect profile is obtained. Subsequently, it is the combination of the antifungal effect of the dynamic drug exposure as well as the immune system of the host that will determine the fungal burden. The fungal burden then drives the responses that are observed in preclinical or clinical studies. The PK/PD indices ignore most of this mechanistic information by summarizing the dynamic exposure into a single value and empirically establishing which of the available exposure metrics best correlates with the observed responses, using the MIC value obtained in *in vitro* experiments with static exposure and in the absence of host immune response. In the field of antibacterial drugs, more mechanism-based PK/PD models that do take this mechanistic information into account have been established to overcome the weaknesses associated with the use of the PK/PD indices [101-104]. Unfortunately, this approach has not yet been applied in the antifungal field. This should yield better target exposure values as well as improved between-species scaling of findings.

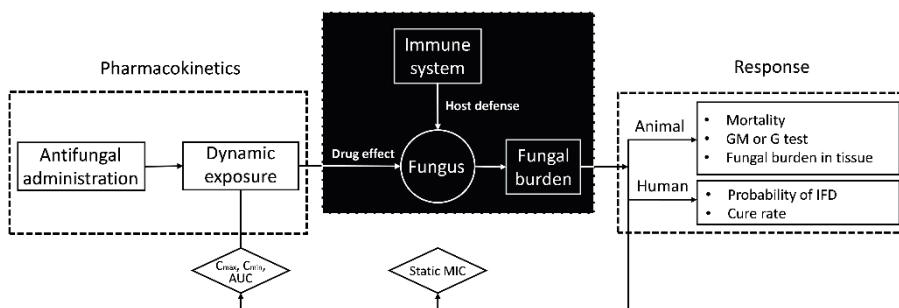


Fig. 3 Schematic illustration of the pharmacological and physiological processes driving antifungal drug response and how they link to the currently used PK/PD indices.

C_{max} = peak concentration; C_{min} = trough concentration; AUC = area under the concentration-time curve; MIC = minimum inhibitory concentration; GM test = detection of galactomannan; G test = detection of (1-3)-β-D-glucan; IFD = invasive fungal disease.

2.3.4 Toxicity

No clear relationship between posaconazole exposure and treatment-related toxicity has been identified to date [32, 87]. During the development process of the delayed-release tablet and the intravenous formulation, an upper toxicity limit of 3.75 mg/L was selected, which was derived from the 90th percentile of the exposure achieved from previous clinical studies that characterized safety for approval of the posaconazole oral suspension [32]. The most frequently reported adverse events during posaconazole treatment included gastrointestinal disorders, such as diarrhea, nausea, vomiting, and also hypokalemia, pyrexia, which are of little clinical concern and considered acceptable [2, 77, 78]. In the following sections we summarize the two posaconazole-related toxicities that are of most clinical concern, namely hepatotoxicity and cardiotoxicity.

Hepatotoxicity

Hepatotoxicity is usually considered a common adverse event (AE) of azole antifungal drugs. The occurrence of treatment-related increases in hepatic enzymes was 1 - 3% reported in 605 patients receiving the posaconazole suspension in two prophylaxis studies [77, 78]. Other treatment-related serious hepatotoxicities, such as hepatic failure and hepatocellular damage, appeared to be very rare ($\leq 1\%$) among these hematological patients [77, 78]. The incidence of treatment-related abnormal liver function test (LFT) in 447 hematological patients receiving delayed-release tablets or intravenous injections was $\leq 2\%$ which is similar to the suspension despite significant higher exposure [32, 34]. It was also reported that switching from suspension to delayed-release tablet can significantly increase posaconazole concentration more than 2-fold without worsening its hepatotoxicity [105]. Apart from hematological patients, posaconazole also showed a low occurrence of hepatotoxicity in patients with chronic pulmonary aspergillosis, refractory IFD and lung transplantation [106-108].

Some studies indicated that the incidences of LFT abnormalities are generally transient and reversible for long-term posaconazole use [2, 109, 110]. Most studies

found no correlation between posaconazole exposure and hepatotoxicity occurrence [108, 111-113]. Nevertheless, in 343 hematological patients receiving delayed-release tablets or intravenous injections, a posaconazole concentration of >1.83 mg/L was proven to be correlated with grade 3/4 hepatotoxicity using classification and regression tree analysis, although no association was found using logistic regression [114]. In general, even though the incidence is low, monitoring LFT is necessary and TDM together with dose adjustments or discontinuation and alternative medication should be considered when treatment-related liver toxicity is assessed.

Cardiotoxicity

QT interval prolongation is also a class effect of the azoles. Posaconazole was reported to be associated with a prolonged QT interval and other cardiac AEs, such as atrial fibrillation and torsades de pointes [77]. Treatment-related prolongation of the QT interval or corrected QT (QTc) interval occurred in 4% of 304 neutropenic patients receiving posaconazole suspension in one active-controlled prophylaxis study [77]. However, QT prolongation was not observed in healthy volunteers [2]. The incidences of the treatment-related atrial fibrillation and torsades de pointes are less than 1% [77]. There is no evidence of an increased risk of cardiotoxicity in hematological patients receiving posaconazole delayed-release tablets or intravenous injections. Surprisingly, the incidence rates of the treatment-related prolonged QT interval is slightly lower for these two new formulations ($\leq 1\%$) [34].

Coadministration with CYP3A4 substrates, such as pimozide and quinidine, can increase the exposure of these drugs and result in a higher risk of cardiotoxicity, including QTc prolongation and torsades de pointes [114], therefore these drugs are contraindicated with posaconazole. Besides, posaconazole is also contraindicated to be used in patients receiving drugs that are known to prolong the QTc interval or those identified with potentially proarrhythmic conditions such as cardiomyopathy and QTc prolongation. Potassium, magnesium, and calcium should be corrected before posaconazole administration, in order to reduce the risk of posaconazole-related cardiotoxicity [2]. There are less safety concerns with respect to prolonged QT or QTc in patients with persistent febrile neutropenia or refractory IFD, patients with chronic pulmonary aspergillosis, and lung transplant patients [106-108]. No discernable correlation between posaconazole exposure and cardiotoxicity was found to date [30, 111].

2.3.5 Posaconazole resistance

Although the use of azole monotherapy is precluded in most patients with azole-resistant *Aspergillus* disease, a modest role of azole therapy may remain in infections caused by isolates with low-level azole resistance. If the azole MIC is close to the resistance breakpoint, dose escalation might be a feasible strategy provided that drug toxicity is avoided. The posaconazole MICs of azole-resistant *A. fumigatus* often remain close to the wild-type MIC distribution (i.e. MIC ≤ 0.5 to 1 mg/L) [115, 116]. Preclinical studies indicated that isolates with a posaconazole MIC of 0.5 mg/L can be treated successfully with increased exposure [7, 9]. The required AUC/MIC in patients to treat isolates with increased posaconazole MICs was calculated based on these experiments and bridged to human infections. Thus for each posaconazole MIC the required exposure was calculated. As the posaconazole AUC is linearly

correlated with C_{min} , target C_{min} values could be extracted from this correlation [97]. Thus, it is postulated that these isolates with relatively low MICs (but classified as resistant based on the EUCAST breakpoint) may be treated with augmented posaconazole dosing in order to achieve high drug concentrations [23]. One should bear in mind that clinical evidence on the efficacy of this strategy is absent. A major concern of a strategy using augmented dosing is the revelation of adverse events (AEs). One study evaluated the AE in patients with posaconazole high dosing regimen and incidental high posaconazole serum concentrations. This study concluded that the number of AEs in these groups were comparable to previous reports on standard dosing. A direct comparison between high dosing and standard dosing has not been reported [23].

2.3.6 New strategies for posaconazole targeted therapy

The finding that posaconazole accumulates in human peripheral blood mononuclear cells and polymorphonuclear leukocytes triggered an investigation on the impact of posaconazole-loaded leukocytes on the antifungal activity and functional capacity of different leukocytes [117-120]. High posaconazole intracellular concentrations did not show a significant impact on the functional capacities of human neutrophils and macrophages *in vitro* [118]. Natural killer cells also have proven to still be viable and they maintained their capacity under therapeutic concentration of posaconazole [120]. Similar results were also found in neutrophil-like leukocyte cells. Furthermore, an improved antifungal activity was observed both *in vitro* and in an *in vivo* mouse model with invasive pulmonary aspergillosis, which indicates the potential of posaconazole-loaded leukocytes as a novel antifungal strategy, in which leukocytes serve as a vehicle to target the infection site and further increase the antifungal effect [119]. Apart from this, these endogenous vehicles are supposed to be associated with less safety problems and are considered as a promising strategy for the prophylaxis and treatment of IFD.

2.4 Special populations

2.4.1 Patients with hepatic or renal impairment

Posaconazole showed slightly lower CL/F in patients with mild, moderate and severe hepatic impairment (corresponding to Child-Pugh class A, B and C, respectively) in comparison with healthy subjects after a single 400 mg dose of the oral suspension [121], which might be attributable to decreased metabolism by UGT1A4. The AUC was increased by 36% in patients with hepatic dysfunction compared to patients with normal hepatic function. Due to this minor change in the pharmacokinetics and the observed safety in patients with hepatic impairment, no dose adjustments are proposed for the posaconazole suspension in patients with hepatic impairment. This recommendation was directly applied to the later released formulations, without clear evidence on the influence of liver function on posaconazole pharmacokinetics nor the safety profile with these formulations in this population [2]. Future studies may still be needed to investigate the long-term pharmacokinetics and safety of all posaconazole formulations in patients with hepatic impairment.

No clinically significant difference in posaconazole CL/F or the exposure was

observed between patients with mild, moderate, and severe chronic renal disease (corresponding to creatinine clearance levels at 50-80, 20-49, <20 mL/min, respectively) and healthy subjects after a 400 mg single dose of oral suspension [122]. Posaconazole suspension also appears to be effective and well-tolerated in patients with refractory IFD and renal impairment (creatinine clearance <50 mL/min or serum creatinine level >2 mg/dL) [123]. Therefore, no dose adjustment was suggested in patients with mild and moderate renal impairment receiving the posaconazole suspension. There is still a necessity for monitoring of the symptoms of IFD just like other patients with IFD. This is due to the high variability in exposure of the oral suspension [3]. This recommendation was also directly applied to posaconazole delayed-release tablets without support by a clinical study [3]. The posaconazole intravenous formulation is not recommended for patients with moderate or severe renal impairment, because of the expected accumulation of the sulfobutylether- β -cyclodextrin excipient in the kidneys. However, from the experience with voriconazole, also containing sulfobutylether- β -cyclodextrin, we have learned that the benefits may outweigh the risk. In addition, the sulfobutylether- β -cyclodextrin appeared to accumulate by about six fold in kidney, but was not nephrotoxic itself [124-126]. Data on pharmacokinetics, efficacy and safety upon long-term posaconazole using are lacking in this special population, for which future studies are expected to fill the gap.

2.4.2 Obesity

For patients weighing ≥ 120 kg, the product label suggests to closely monitor for IFD due to the increased risk of lower posaconazole exposure [3]. Additionally, in patients with hematological malignancies, significantly lower trough concentrations were also observed between patients ≥ 90 kg compared to those <90 kg (0.65 vs. 1.31 mg/L), as well as between patients with body mass index ≥ 30 and those with a body mass index <30 (0.89 vs. 1.29 mg/L) receiving posaconazole delayed-release tablets [127]. The delayed-release tablet administration showed a significantly lower exposure and longer washout half-life in healthy obese subjects (weight of 116.8 ± 19.6 kg and 140.4 ± 32 kg, mean $\pm$ SD) compared to healthy normal-weight subjects (weight of 71.2 ± 8.2 kg and 67.9 ± 9.1 kg, mean $\pm$ SD) [128, 129]. The lower exposure can be attributed to an increased clearance and distribution volume [129]. In addition to this, the washout half-life is further prolonged by an increase in the already large distribution volume resulting from the extensive distribution of posaconazole into adipose tissue, which can also lead to a prolonged drug-drug interaction with of CYP3A4 substrates in obese patients [128, 129].

A recent population pharmacokinetic study in 16 obese patients receiving posaconazole by peripheral venous catheter, showed that a maintenance dose of 300 mg QD can only ensure target attainment in patients weighing less than 180 kg for prophylactic purpose (using $C_{\min} > 0.7$ mg/L as target). For patients with higher weights, 400 mg is required. For treatment purpose (using a $C_{\min} > 1.0$ mg/L), the maintenance dose needs to be increased to 400 mg and 500 mg for patients weighing between 120 and 170 kg, and more than 170 kg, respectively [130].

2.4.3 ICU patients

Limited studies on the use of posaconazole were performed in patients admitted

to the intensive care unit (ICU). The posaconazole oral suspension given via nasogastric tube showed very low systemic exposure in 27 ICU patients with only 17% of the cohort achieving a steady-state C_{min} above 0.25 mg/L after a treatment of 400 mg BID or 200 mg QID, which indicates the posaconazole oral suspension to be unsuitable in this population and indicated the use of intravenous formulations [131].

A recent study reported the pharmacokinetic profiles of a single intravenous dose of posaconazole in 8 ICU patients [55]. Clearance and V_d were more than twice the value reported in healthy volunteers (16.8 L/h vs 6.9 L/h and 529 L vs 236 L, respectively) [29]. This could result from hypoalbuminemia increasing the unbound posaconazole, which can then distribute into the tissue and be eliminated by clearing organs, but unfortunately there are no studies available on the influence of hypoalbuminemia on the pharmacokinetics of posaconazole. The AUC and C_{max} in these patients are comparable to patients with AML/MDS, but lower than in healthy volunteers [29, 33, 55].

In brief, the posaconazole intravenous injection displays encouraging pharmacokinetic characteristics in ICU patients and further studies with larger cohorts are required to demonstrate the efficacy and safety of this formulation in this special population.

2.4.4 Pediatrics

While the posaconazole oral formulations are approved in patients older than 13 years (USA) or 18 years (Europe), the intravenous form is only labeled for patients older than 18 years, due to the potential toxicity to brain ventricle development observed in juvenile dogs [2, 30]. However, many studies have reported its off-label use in pediatric patients, which could be attributed to the promising efficacy and safety profile in adults [132-134]. A recent population pharmacokinetic model was developed for 171 pediatric immunocompromised patients aged between 5 month and 18 years receiving one of the oral formulations, with nearly 96% of the samples being obtained after administration of the suspension [52]. The estimated values of CL/F and V/F related to the delayed-release tablet formulation and standardized to a 70-kg individual are comparable to those reported in adults [40, 41]. These children showed a higher inter-individual variability on CL/F compared to that of adults (63.0% vs. 24.2% or 37.9%) [40, 41]. This might be partly attributable to the age-associated maturation of hepatic UGT1A4 [135].

A twice daily allometric dosing algorithm based on body-weight (index at 0.75) resulted in adequate posaconazole concentrations at day 10 in 12 children aged 3-16 years with chronic granulomatous disease [136]. In children aged ≤ 13 years, a bodyweight-based dosing regimen of the oral suspension of 4 mg/kg TID or body surface area-based regimen of 120 mg/m² TID, showed a considerable proportion of hematologic children to reach <0.7 mg/L steady-state plasma concentrations [137-140]. Therefore, higher initial dosing strategies of ≥ 20 mg/kg/day were recommended and expect to ensure adequate concentrations [141, 142]. Experience with the posaconazole delayed-release tablet in pediatric patients is limited. A model-derived dosing strategy was applied in 34 children and adolescents (range 5-17 years) receiving the posaconazole delayed-release tablet and more than 90% of the patients were reported to have steady-state trough concentrations above the target of 0.7 mg/L [134]. However, to implement such size-based dosing approaches in younger children, the delayed-release tablet displays an unattractive prospect as it

is indivisible and large in size. A new delayed-release tablet formulation of smaller dosage and size or a new oral suspension formulation with better bioavailability might benefit young children.

High variability in posaconazole concentrations was also reported in this population as a result of the erratic bioavailability for which TDM was recommended [138-141, 143]. Consistent with the previous findings in adult patients [37-39], diarrhea and concomitant PPI use also had a negative impact on the bioavailability of the suspension in children [52]. A population pharmacokinetic analysis in children illustrated the insufficient therapeutic target attainment even on the highest feasible dose of oral suspension in children with diarrhea and/or PPI administration [52]. Based on the model-based simulations, this study recommended different dosing regimens for different age groups for both prophylactic and treatment purpose in children patients aged <13 years. Due to the poor and saturable bioavailability of the suspension, the delayed-release tablet formulation is considered a superior choice compared to the oral suspension once the children are able to take it [52, 100, 134].

The establishment of pediatric target exposure is currently based on the concentration targets recommended in adults, which assumes that the same exposure will result in the same effect in adults and children. Although the susceptibility of fungi to antifungals can reasonably be expected to be the same in adult and pediatric patients, it still remains to be established whether differences in the developmental status of the immune system result in different required target concentrations *in vivo*. Differences in target concentrations could be likely, because despite the fact that the proportion of the target attainment was not high in children, the posaconazole oral suspension was demonstrated to be effective, safe and well-tolerated in preventing and treating IFD in immunocompromised children [137, 138, 140, 144-147].

2.4.5 Patients with cystic fibrosis

As the steady-state trough concentration for posaconazole delayed-release tablet is significantly higher than for the suspension both in cystic fibrosis (CF) (1.1 mg/L vs 0.19 mg/L) and in non-CF lung transplant patients (1.9 mg/L vs 0.47 mg/L) [54, 148], the delayed-release tablet form is considered a promising alternative for the suspension with satisfactory drug exposure and good tolerance. In lung transplant patients, patients with CF showed significant lower posaconazole concentrations compared to non-CF patients with both oral formulations [54, 148, 149], which can increase the risk of subtherapeutic concentration in this subgroup, especially for the suspension.

Higher posaconazole concentrations were found to be correlated with lower *Aspergillus* Immunoglobulin E levels [150]. Posaconazole oral formulations, especially the delayed-release tablet, exhibited satisfactory exposure in children (median age 13 years, range 3 - 17 years) with CF and was proven to be generally safe and well tolerated [151]. Overall, posaconazole delayed-release tablet appears to be a suitable antifungal agent in patients with CF due to the improved absorption and the wide intrinsic distribution into the lung tissue. Further studies are still needed to confirm the efficacy of posaconazole in CF patients.

2.5 Conclusions

Posaconazole is widely used for the prevention and treatment of IFD. As this drug is going off patent, new generic formulations are expected to enter the European market in the beginning of 2020, which will likely result in an increased clinical use due to anticipated price drops. The current review will help those that are less familiar with the use of posaconazole to better understand the behavior of this drug. We want to alert clinicians that especially the absorption profile and bioavailability of posaconazole appear to be highly dependent on the formulation, meaning that proposed dosages may not always be directly translatable to other formulations.

There is a plethora of pharmacokinetic information available for the oral suspension, while new information on the pharmacokinetics of both the intravenous formulation as well as the delayed-release tablet is emerging rapidly. These studies are predominantly performed in healthy volunteers and hematological patients. There is therefore an urgent remaining need for more (population) pharmacokinetic knowledge on both the critically ill patients as well as the pediatric population. For all populations three distinct pharmacological issues should be further explored:

- 1) differences in oral absorption profiles, bioavailability, and exposure of the three pharmaceutical formulations need to be clarified for each special patient population,
- 2) protein binding, the variability in protein binding, and its relation to PD must be investigated. This is typically relevant for populations with a high likelihood of altered protein binding such as critically ill patients, (pediatric) leukemic patients, and patients with renal failure,
- 3) more information on site specific penetration of posaconazole, specifically brain tissue, is needed. Now that higher and more predictable plasma concentrations are attained with the new formulations, it might be possible to achieve detectable brain concentrations thereby opening up treatment strategies, but also toxicological risks. Some neurological side effects have been described pointing towards an increased exposure in the brain [152], but this has yet to be confirmed.

There is a paucity of data related to the PD of posaconazole, especially on a mechanistic level. Past work on exposure response relationships needs to be revisited using unbound concentrations and taking into account dynamic exposure profiles. Simultaneously, the scientific community could invest in detecting new biomarkers that could provide useful information on the efficacy of treatment. Such markers should perform better than current measures of outcome that leave room for interpretation such as mycological response. These biomarkers should be subsequently linked to the dynamic pharmacokinetic profiles to define the PK-PD relations. Finally, knowledge should be gained on how to treat fungal disease with pathogens with attenuated MICs. Adaptive targets, i.e. targets based on the pathogens MIC, have been investigated in animal models, but its clinical utility needs to be validated. Ultimately, information on the hosts' immune response should also be utilized to complete the understanding on the interplay between pathogen, host, and drug to predict treatment outcome.

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