A short-form paper for Antimicrobial Agents and Chemotherapy (AAC)

Title: Isavuconazole therapeutic drug monitoring associated to a pharmacogenetic exploration is far from being a pharmacologists' whim.

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ABSTRACT

Isavuconazole is a new antifungal prodrug to treat invasive aspergillosis and mucormycosis, theoretically not requiring drug monitoring. However, we reported 4 clinical cases with toxic concentrations. Based on Desai's population pharmacokinetic model, we estimated patients' kinetic profile. Clearance was abnormally low, likely related to CYP3A4/5 polymorphisms. Thus, we recommend to collect blood sample just before the first maintenance dose to estimate pharmacokinetic profile and individualized dose. For patients presenting high concentrations, pharmacogenetics can be done.

Recently, Stott et al. [1] mentioned that "the novel broad-spectrum azole drug isavuconazole does not currently appear to require TDM but 'real-world' data are awaited and TDM could be considered in selected clinical cases". It did not take very long to confirm these proposals and even go further in the recommendations.

Isavuconazole is a new antifungal prodrug approved in the USA and Europe for the treatment of invasive aspergillosis and mucormycosis in adults. The recommended dose is 200 mg (IV or PO) every 8 h for 48 h, followed by 200 mg once daily for maintenance dose applied 12–24 h after the last loading dose. The median trough plasma concentrations of isavuconazole (i.e. value determined just before drug readministration) at steady state (> 7 days of treatment) in patients who received the drug in the SECURE and VITAL trials [2-3], were 3–4 µg/mL. Recently, we observed 4 cases of unexpected high concentrations a few days after the last loading dose, without obvious explaining factors (no drug-drug interactions and no previous hepatic injury). For 2 patients, these high levels were concomitant with adverse effects (patellar tendinopathy and discomfort, respectively).

Isavuconazole plasma concentrations were determined using a validated chromatographic technique according to ISO15189 standards. Using the population pharmacokinetic model published by Desai et al [4], firstly we simulated 50000 pharmacokinetic profiles of isavuconazole for the recommended loading (200 mg/8h x 6) and maintenance doses (200 mg/day). Secondly, for each patient, we computed the Empirical Bayes Estimates (EBE) of the pharmacokinetic parameters (Table 1) and deduced the most likely kinetic profile (Fig. 1-4). Because these patients were extremes with respect to Desai's model, their EBE's where computed using an individual parameter distribution with heavier tails than the classical multidimensional log-normal distribution.

As isavuconazole is mainly metabolized by hepatic CYP3A4 and 3A5 [5-6], a pharmacogenetic exploration of *CYP3A4*22* (rs35599367) and *CYP3A5*3* (rs776746) polymorphisms, likely to explain low isavuconazole metabolism [7], was performed in these patients by real-time PCR.

This pharmacokinetic-pharmacogenetic exploration was routinely done as part of the hospital care of patients according to the regulations applied in France (patient's informed consent for genotyping).

For all patients, pharmacokinetic parameters were different from the median values (clearance 2.36 L/h, peripherical distribution volume 241.28 L, elimination half-life 90.57 h) reported by Desai [4] and in particular the clearance that was systematically lower (Table 1). In accordance with clinicians, an individualized dose adjustment could be proposed for two patients (Fig.3 and 4, Table 1) and the therapeutic drug monitoring confirmed in each case that the estimated values were very closed to the measured ones (2.54 µg/mL and 2.57 µg/mL vs. 2.22 µg/mL and 2.55 µg/mL respectively for patient 3; 2.09 µg/mL vs. 1.83 µg/mL for patient 4). Among the 4 patients studied, all of them carried the homozygous variant *CYP3A5*3*, associated to a lake of CYP3A5 activity, while 2 patients were homozygous for the *CYP3A4*22*. In the Caucasian population, that is close to the Desai's study population (83.2% of Caucasian's and 16.8% of Asian's patients [4]), more than 80-90% of patients possess *CYP3A5*3* polymorphism [8]. Consequently, this information cannot explain over-exposure in our patients. On the contrary, *CYP3A4*22* polymorphism is present in less than 8-10% of the Caucasian population [9]. Only 2 patients (50% of our population, patient 2 and 4) presented this polymorphism suggesting that other(s) explaining factor(s) is(are) likely elsewhere.

Based on these unexpected high concentrations and as previously suggested by Stott et al [1], we propose two recommendations. The first one consists in collecting a blood sample just before the first maintenance dose to estimate precociously the patient's likely kinetic profile using Desai's population pharmacokinetic model. Based on this profile, an individualized dose adjustment can be proposed as necessary. The second recommendation consists in screening CYP3A4 and 3A5 genetic polymorphisms, besides those usually explored (*CYP3A4*22* and *CYP3A5*3*), including the nonfunctional alleles *CYP3A4*17* (rs4987161) [10], *CYP3A5*6* (rs10264272) [8] and *CYP3A5*7* (rs76293380) [8] for patients presenting unexpected kinetic profiles. To date for patients in real life, too much sparse information concerning factors affecting pharmacokinetic profiles is available.

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FIGURE LEGENDS

Fig. 1 Patient 1: Kinetic profile of isavuconazole. Median kinetic profile (curve in white), "extremes" profiles found in less than 5% and 95% of the population (black curves) and estimated kinetic profile of the patient (red curve); the black stars represent the measured concentrations.

Fig. 2 Patient 2: Kinetic profile of isavuconazole. Median kinetic profile (curve in white), "extremes" profiles found in less than 5% and 95% of the population (black curves) and estimated kinetic profile of the patient (red curve); the black stars represent the measured concentrations.

Fig. 3 Patient 3: Kinetic profile of isavuconazole. Median kinetic profile (curve in white), "extremes" profiles found in less than 5% and 95% of the population (black curves) and estimated kinetic profile of the patient (red curve); the black stars represent the measured concentrations while the green ones represent the estimated trough concentrations in case of individualized dosage adjustment and the therapeutic drug monitoring confirmed the estimated values.

Fig. 4 Patient 4: Kinetic profile of isavuconazole. Median kinetic profile (curve in white), "extremes" profiles found in less than 5% and 95% of the population (black curves) and estimated kinetic profile of the patient (red curve); the black stars represent the measured concentrations while the green ones represent the estimated trough concentrations in case of individualized dosage adjustment and the therapeutic drug monitoring confirmed the estimated values.

Table 1 Pharmacokinetic-pharmacogenetic exploration of isavuconazole for 4 French patients presenting high unexpected plasma levels: this exploration was done as part of the hospital care of patients**.**

TDM therapeutic drug monitoring

Column 1: patient's number

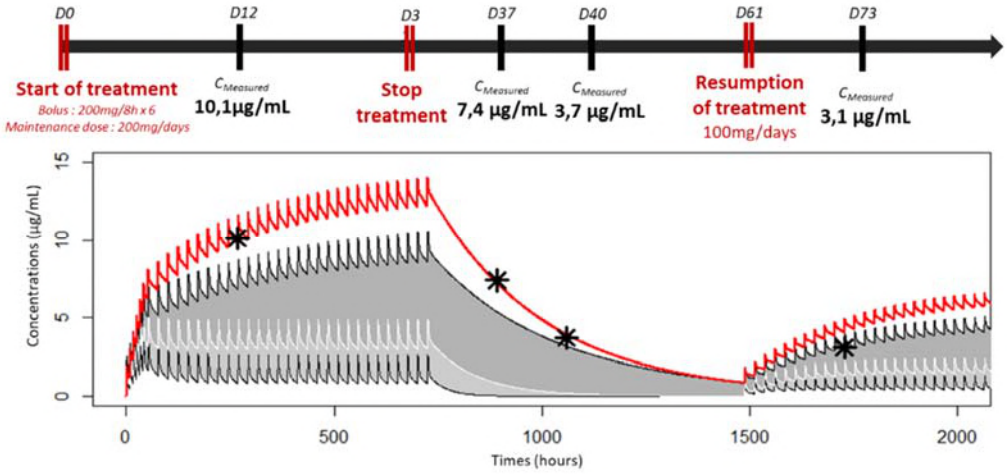
Column 2 to 7: Clinical information found for each patient

Column 8: Pharmacogenetic polymorphisms found for each patient according to a real-time PCR technique

Column 9 to 11: Pharmacokinetic parameters of isavuconazole estimated from Desai's population pharmacokinetic model [4] and plasma concentrations measured at different times depending on each patient

Column 12 to 13: The estimated trough concentrations in case of individualized dosage adjustment

161 Fig. 1



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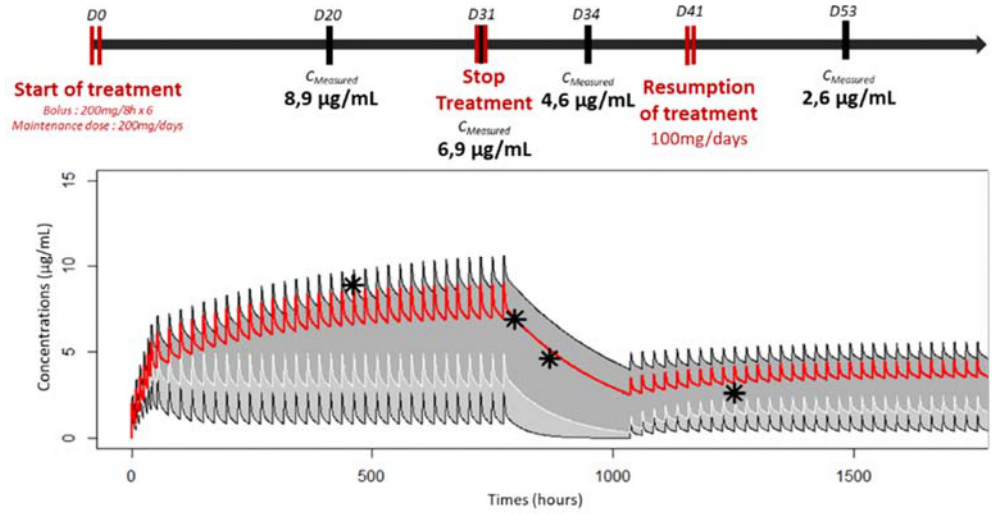
163 Fig. 2



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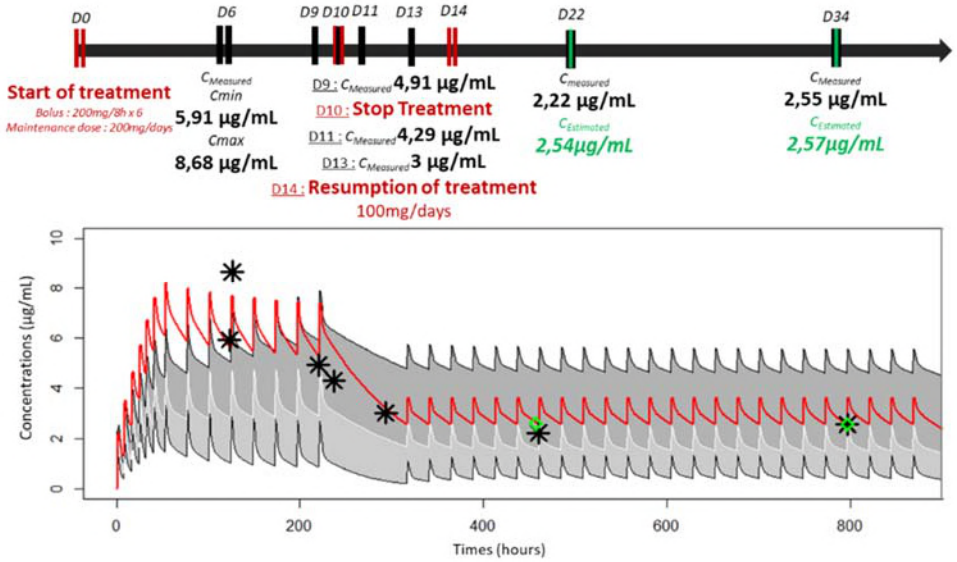
165 Fig. 3



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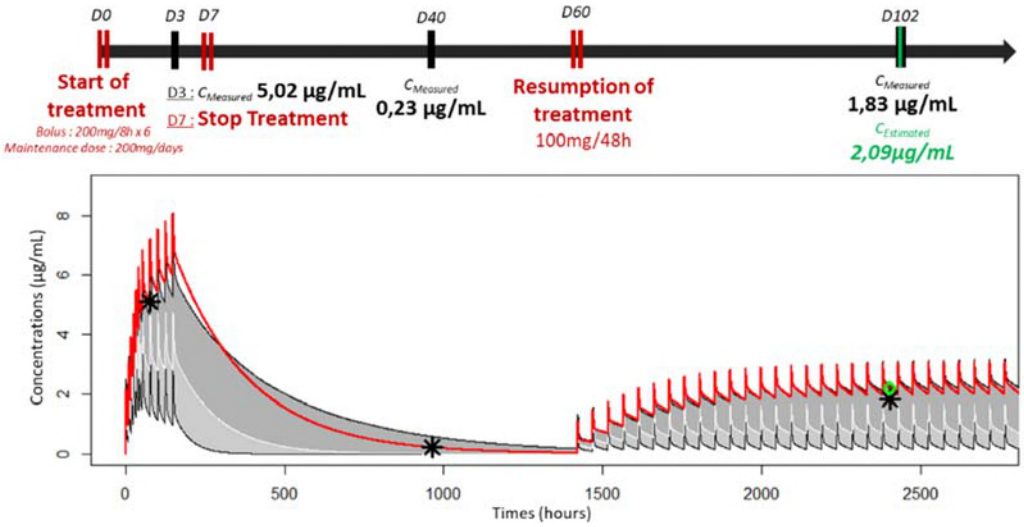
167 Fig. 4



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171 Table 1

Patient	Clinical information						Pharmacogenetics	Pharmacokinetic parameters			Individualized dose adjustment	
	Sex	Age	Ethnic group	BMI (kg/m^2)	Coprescription	Adverse effects	CYP3A4*1 CYP3A5*3	Clearance (L/h)	Distribution volume (L)	Half-life (h)	New dose	TDM
1	Male	70 years	Caucasian	20.8	Methotrexate Prednisone Esomeprazole	Patellar tendinopathy	CYP3A4 : 1*/1* CYP3A5 : 3*/3*	0.62	120.23	190.01	100 mg/24h	
2	Female	52 years	Caucasian	20.2	Prednisone	Discomfort	CYP3A4 : 1*/22* CYP3A5 : 3*/3*	1.09	196.77	161.28	100 mg/24h	
3	Male	38 years	Caucasian		Prednisone		CYP3A4 : 1*/1* CYP3A5 : 3*/3*	1.41	88.14	69.00	100 mg/24h	2.22µg/mL measured for 2.54µg/mL estimated 2.55µg/mL measured for 2.57µg/mL estimated
4	Female	50 years	Caucasian		Levothyrox Oxazépam Zopiclone Clonazepam		CYP3A4 : 1*/22* CYP3A5 : 3*/3*	1.03	141.23	134.40	100 mg/48h	1.83µg/mL measured for 2.09µg/mL estimated

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3	Male	38 years	Caucasian		Prednisone		CYP3A4 : 1*/1* CYP3A5 : 3*/3*	1.41	88.14	69.00	100 mg/24h	2.22µg/mL measured for 2.54µg/mL estimated 2.55µg/mL measured for 2.57µg/mL estimated
4	Female	50 years	Caucasian		Levothyrox Oxazépam Zopiclone Clonazepam		CYP3A4 : 1*/22* CYP3A5 : 3*/3*	1.03	141.23	134.40	100 mg/48h	1.83µg/mL measured for 2.09µg/mL estimated

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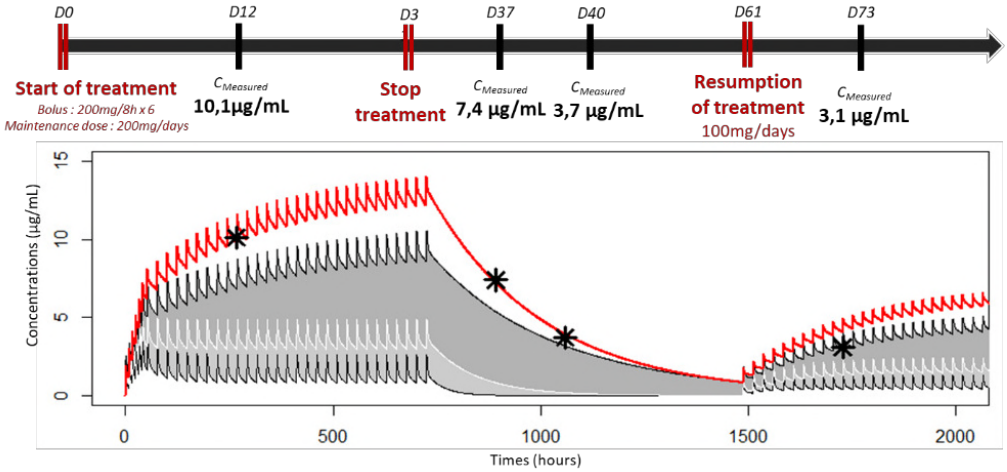

Fig. 2

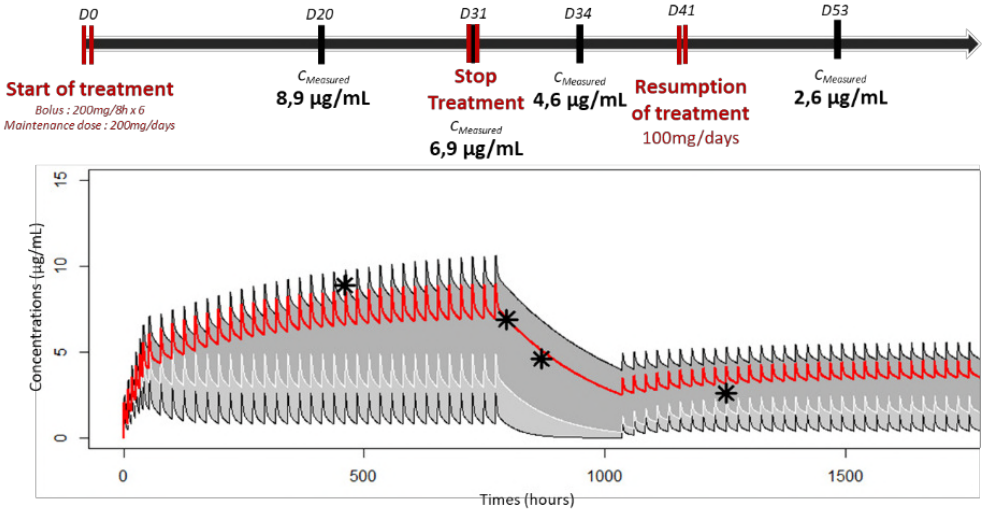

Fig. 3

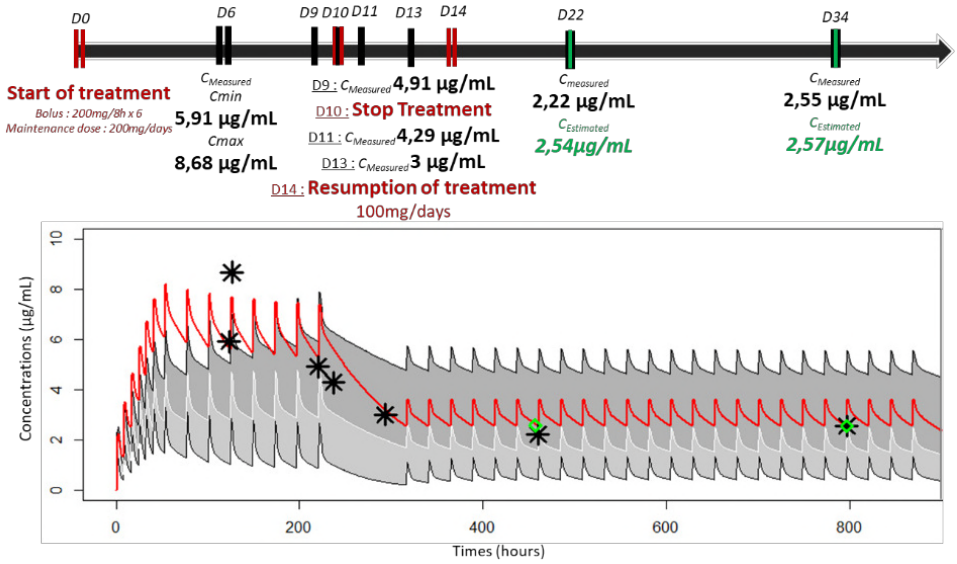

Fig. 4