Can we predict the influence of inflammation on voriconazole exposure? An overview

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Running title:

Inflammation's impact on voriconazole exposure

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Synopsis

Voriconazole is a triazole antifungal indicated for invasive fungal infections that exhibits a high degree of inter-individual and intra-individual pharmacokinetic variability. Voriconazole pharmacokinetics is non-linear, making dosage adjustments more difficult. Therapeutic drug monitoring is recommended by measurement of minimum plasma concentrations. Several factors are responsible for the high pharmacokinetic variability of voriconazole: age, feeding (which decreases absorption), liver function, genetic polymorphism of the *CYP2C19* gene, drug interactions, and inflammation. Invasive fungal infections are indeed very frequently associated with inflammation, which engenders a risk of voriconazole overexposure. Many studies have reviewed this topic in both the adult and pediatric populations, but few studies have focused on the specific point of the prediction, to evaluate the influence of inflammation on voriconazole pharmacokinetics. Predicting the impact of inflammation on voriconazole pharmacokinetics could help optimize antifungal therapy and improve patient management. This review summarizes the existing data on the influence of inflammation on voriconazole pharmacokinetics in adult populations. We also evaluate the role of C-reactive protein, the impact of inflammation on patient metabolic phenotypes, and the tools that can be used to predict the effect of inflammation on voriconazole pharmacokinetics.

INTRODUCTION

Voriconazole is a triazole antifungal agent indicated for invasive fungal infections (IFIs). The main indication of voriconazole is invasive aspergillosis, a life-threatening and dreaded disease that occurs in high-risk patients, such as patients with hematological malignancies, solid organ transplantation, or patients in intensive care units with severe immunosuppression due to immunosuppressors or viral-induced acute respiratory distress syndrome. Voriconazole exhibits a high degree of inter-individual and intra-individual pharmacokinetic variability. Voriconazole pharmacokinetics is non-linear, which leads to more difficult dosage adjustments.[1] Therapeutic drug monitoring is recommended by measurement of minimum plasma concentrations (C_{min}), with a therapeutic target range between 1 to 5.5 mg/L for prophylactic and curative treatment, and 2 to 5.5 mg/L for optimal curative treatment in severe and complex infections.[2,3–5] Several factors are responsible for voriconazole's high degree of pharmacokinetic variability: food consumption (which affects absorption), liver function, genetic polymorphism of the *CYP2C19* gene, drug interactions, and inflammation.[6] The *CYP2C19* gene is highly polymorphic: the *CYP2C19**2 or *3 alleles are associated with enzymatic loss-of-function, which results in an intermediate or poor metabolizer phenotype leading to an increase in voriconazole exposure. The *CYP2C19**17 allele conducts to a rapid or ultrarapid metabolizer phenotype and leads to a decrease in voriconazole exposure. There is limited evidence for an association between variants within the *CYP3A4* gene and its impact on voriconazole pharmacokinetics apart from Gautier-Veyret and He's studies.[7,8] Inflammation can affect voriconazole pharmacokinetics and may induce a risk of voriconazole overexposure.[9] Several studies have reviewed this topic in adult and pediatric populations.[10] The C-reactive protein (CRP) level is an interesting marker of inflammation that is readily available in clinical practice, and several authors have attempted to predict its influence on

voriconazole C_{min}. In addition, another predictive approach is evaluation of the hepatic metabolic capacity by the measurement of voriconazole N-oxide C_{min}, which is the main metabolite of voriconazole. Voriconazole is intensively metabolized by cytochrome P450 (CYP) iso-enzymes, with only 2% excreted unchanged in urine. The main circulating metabolite, voriconazole N-oxide, accounts for 72% of the radiolabeled metabolites found in human plasma.[11] CYP2C19 is the primary enzyme responsible for the metabolism of voriconazole into voriconazole N-oxide. CYP3A4, CYP2C9 and members of the flavin containing monooxygenase family also contribute to the metabolism of voriconazole.[12] Measurement of both voriconazole and voriconazole N-oxide C_{min} allows for calculation of the metabolic ratio (MR) ([voriconazole N-oxide C_{min}]/[voriconazole C_{min}]) and constitutes a viable phenotyping approach.[13] This ratio is theoretically decreased during inflammation episodes. Predicting the impact of inflammation on this ratio and then on voriconazole pharmacokinetics could help optimize antifungal therapy. Therefore, it seems relevant to summarize the studies that have sought to predict the influence of inflammation on voriconazole pharmacokinetics. Invasive fungal infections are indeed very frequently associated with inflammation, which contributes to voriconazole C_{min} variability and complicates patient management. This review summarizes the existing data on the influence of inflammation on voriconazole pharmacokinetics, its impact on patient metabolic phenotypes, and the role of CRP. Moreover we present and discuss three types of tools that can be used to predict the effect of inflammation on voriconazole pharmacokinetics: (i) formulas developed for the prediction of the influence of CRP on voriconazole $C_{min,}$ (ii) a phenotyping approach involving calculation of a MR, and (iii) population pharmacokinetics models integrating CRP as a covariate. The final aim is to optimize voriconazole dosing to improve patient care.

METHODOLOGY

A systematic literature search was performed using the PubMed® database with the following keywords: “voriconazole” AND “inflammation”, AND “concentration” OR “level” OR “pharmacokinetics”. Twenty studies were identified with the aforementioned keywords. The search was limited to English-language articles, studies conducted in adult subjects, and publication dates between 2003 and 2023. The abstracts of these articles were read, and relevant articles were selected for this review. Articles concerning pediatric populations were excluded, as were articles with paid access. The analysis of these articles resulted in the selection of 15 articles of interest linked to the subject of the present review. However, few articles directly address this topic. Formulas developed for prediction of the influence of CRP on voriconazole C_{min} have been taken from the literature and tested using data from the Boglione-Kerrien study.[14]

RESULTS

Impact of inflammation on voriconazole C_{min} and the role of CRP

The influence of inflammation on voriconazole metabolism is now well-established. Inflammatory cytokines cause modulation of the activity of drug-metabolizing enzymes and transporters (DMET). The concentrations of specific proteins, such as CRP, increase during inflammatory episodes due to the stimulation of hepatocytes by interleukin (IL)-6 cytokines. Inflammation plays an inhibitory role on DMETs, with a significant impact on drugs with a narrow therapeutic index, such as voriconazole.[15] There is a decrease in the metabolic activity of CYP2C19 and CYP3A after an acute inflammatory state (e.g., during surgery), which has been assessed by intake of a phenotyping cocktail containing several drugs called "the Geneva cocktail” in the study by Lenoir *et al.*[16]

Because of its wide availability, CRP is a useful marker for the evaluation of inflammatory status, particularly during IFIs. In a study conducted in hematological patients exhibiting invasive fungal infections, CRP was shown to be increased during inflammation: CRP was measured with a median equal to 108 mg/L on Day 0 (range 5–326), and CRP >100 mg/L in 72% of cases between D0 and D12 of the IFI diagnosis.[17] Gautier-Veyret *et al.* have demonstrated that CRP > 96 mg/L leads to an increased risk of voriconazole overexposure and thus represents a useful predictive marker.[18] The intensity of inflammation needs to be taken into account, and a high inflammatory response highlighted by high CRP concentrations strongly impacts voriconazole pharmacokinetics.[19] Indeed, more severe inflammation has a greater impact on voriconazole C_{min} and the MR.[20] Concomitant measurement of CRP in patients treated with voriconazole as proposed by Le Daré *et al*, may help predict voriconazole overexposure episodes.[21] An observational study of hematological patients showed the predictive value of a combination of biomarkers associating high CRP (> 120 mg/L) with low concentrations of procalcitonin or presepsin for IFIs.[22] In a prospective study that included 61 patients, the impact of the CRP level on voriconazole C_{min} was evaluated, and an extract of 12 profiles of inflammatory patients is presented in Figure 1. The voriconazole C_{min} changes concomitantly with the CRP concentration. However, there is significant variability in the inflammatory profiles encountered (i.e., the duration of inflammation, the time of inflammation in relation to the treatment and, therefore, to the infection).[14]

The relevance of measuring another marker of inflammation with a better predictive value was also highlighted within the literature. Rather than CRP, IL-6 can be measured because its effect is more directly related to the inflammatory process, and it may provide more precise information. Vreugdenhil *et al.* found a significant but moderate correlation between IL-6 and voriconazole C_{min}. Thus, taking IL-6 into account as an inflammatory marker does not appear

to be more informative than using CRP.[23] A positive correlation has also been shown between IL-18 or transforming growth factor (TGF)-β1 and voriconazole C_{min}, but the authors did not indicate whether practical and predictive use could be considered.[24]

The significant variability of the inflammatory profile between patients shows that prediction can, therefore, be difficult, but CRP measurement is nevertheless useful.

Formulas to predict the influence of CRP on voriconazole C_{min}

Several authors have sought to predict the influence of CRP on voriconazole C_{min} and the MR.[9,25–28] Of these studies, only one was prospectively conducted.[26] In Table 1, the different formulas used in the literature to predict the influence of CRP on voriconazole C_{min} are compared. To assess the relevance of these formulas, 15 inflammatory patients from the Boglione-Kerrien *et al.* study were tested. Considering a maximum bias of 20% between the concentrations predicted with the formulas and the observed value of the concentrations that were measured (maximum measurement bias based on bioanalytical guidelines used by pharmacology learning societies), no formula appears satisfactory, since a bias greater than 20% was obtained in approximately half of the patients. A tendency to overestimate the voriconazole C_{min} was observed for certain predicted concentrations. Therefore, using this small sample of external data, no prediction formula based on CRP was appropriate for voriconazole C_{min} prediction.

Inflammation and metabolic phenoconversion

During acute inflammation episodes, voriconazole clearance by cytochromes is reduced by a phenomenon called metabolic phenoconversion. The phenotype, which is mainly determined by the patient's genotype but also influenced by other factors, is modified by the inflammatory process. Metabolic capacity is transiently inhibited during the inflammatory process, and

irrespective of the patient's genotype, the patient's phenotype can then switch to a poor metabolizer phenotype. The impact is significant in rapidly metabolizing patients because, in this case, the profile determined by genotyping is entirely masked by the inflammation: inflammatory cytokines cause a decrease in CYP450 activity leading to an increase in voriconazole C_{min}.[15] Although changes in CRP do not allow accurate prediction of voriconazole C_{min} changes during an inflammatory episode, its measurement can be informative regarding the risk of phenoconversion.[15]

Patient management is, therefore, difficult in this context. It should also be noted that approximately 20% of the Caucasian population are rapid voriconazole metabolizers.[29] Some centers undertake *CYP2C19* and *CYP3A* genotyping to determine a genetic score, but this has highlighted the lack of prediction of voriconazole C_{min} in inflammatory patients.[30] The genotype impacts the voriconazole C_{min} and the MR only in cases with mild to moderate inflammation (CRP < 40 mg/L) according to Aiuchi *et al.* Thus, when the CRP level is > 40 mg/L, *CYP2C19* polymorphisms are not an independent factor influencing voriconazole C_{min} and the MR.[31] The determination of genetic scores should be combined with inflammation to improve prediction, as inflammation is an important parameter to be taken into account.[25] Physiologically based Pharmacokinetics (PBPK) models also use this approach, which combines *CYP2C19* and *CYP3A4* genotypes and inflammation by measuring CRP.[32] The usefulness of genotyping downstream of infection in order to optimize patient care remains to be demonstrated, particularly in cases of phenoconversion. It would be interesting to obtain continuous CRP monitoring over a period of several days in order to understand the dynamics of the phenomenon and to cover the entire inflammatory process from its beginning to its decrease. In addition, CRP measurement is immediately available to the clinician, whereas genotyping is not.

Figure 2 illustrates the case of a metabolic phenoconversion in a rapid-metabolizer patient during an inflammatory episode.

The use of phenotyping as a prediction tool: calculation of the MR

The MR reflects the change in the inflammatory status. It is determined according to the following formula: MR= [voriconazole N-oxide C_{min}]/[voriconazole C_{min}]. The higher the CRP, the lower the MR, which results in reduced metabolic capacity and increased voriconazole C_{min}.[33] MR thresholds of 0.48 and 1.15 were determined based on receiver operating characteristic (ROC) curve analysis in the Boglione-Kerrien *et al.* study, in which MR values > 1.15 and < 0.48 were determined to be the best predictors for having a voriconazole C_{min} lower than 2 mg/L and above 5.5 mg/L, respectively, at the next visit. Sixty-eight percent of observations with a low MR (< 0.48) had a CRP > 96 mg/L, compared to 45% for an MR between 0.48 and 1.15 and 10% for an MR greater than 1.15. There was a 7.35-fold increased risk of the MR being < 0.48 when the CRP was greater than 96 mg/L, which suggests decreased metabolism with inflammation, with a median MR equal to 1. A low MR may then indicate a risk of accumulation of voriconazole and an increased risk of voriconazole overexposure.[14] The voriconazole N-oxide concentration is generally not determined routinely, but its measurement and the calculation of the MR could provide additional information regarding patient metabolic capacity. The quantification of both voriconazole and the main metabolite voriconazole N-oxide by a multiplex method allows determination of the MR.[34,35] According to Veringa and colleagues, this can improve patient care.[26] The suggested MR threshold of 0.48 could be an alert for the pharmacologist and may help them assess the patient's metabolic capacity, the impact of inflammation, and ultimately personalize and optimize the patient's dosage and follow-up. In a retrospective study conducted by Encalada *et al.*, an

association was shown between CRP and MR in the case of severe inflammation with CRP > 100 mg/L measured on the same day as the voriconazole C_{min}.[9] Niioka *et al.* highlighted the fact that CYP2C19 activity can be assessed by measuring the MR, but that voriconazole C_{min} prediction is improved by taking into account CRP, age, and the route of administration, in addition to the patient's genotype.[36]

Population pharmacokinetic model – Model-informed precision dosing

The use of a population pharmacokinetic model integrating an inflammation marker such as CRP as a covariate, appears to be a useful tool for implementation and evaluation in real life, allowing voriconazole C_{min} prediction according to the level of inflammation. Van den Born *et al.* integrated CRP into a one-compartment model with non-linear elimination, based on 1060 voriconazole blood sample measurements from 54 patients. Several covariates were tested, including body weight and liver enzymes (alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, and gamma-glutamyl transferase), but only CRP improved the model. An exponential factor of 0.0048 on voriconazole clearance was found, which means that the metabolic rate decreased by 50% for each 150 mg/L increase in CRP. The authors specified that future research is necessary to improve the prediction of voriconazole concentrations and allow a better estimation of pharmacokinetic parameters. In addition, this model should be evaluated with external data to assess the performance of its predictive capacity.[37] Furthermore, the study by Jiang *et al*. integrated CRP into a population pharmacokinetic model, albeit with a more limited number of blood samples used for the construction of the model (233 blood samples from 69 patients with talaromycosis endemic fungal infection).[38]

CONCLUSION

The impact of inflammation on voriconazole exposure is substantial, but prediction of the change in voriconazole C_{min} in an inflammatory context remains difficult, with high inter- and intra-individual variability. To date, there are still limited studies on the impact of inflammation on voriconazole C_{min}. Moreover, the dynamic of the inhibitory effect of inflammation on voriconazole metabolism is still to decipher. Thus, it is still challenging to offer a comprehensive algorithm to guide voriconazole drug adjustment in the case of inflammation. As the majority of studies have been conducted in adults, this review focused only on adult patients, and no therapeutic recommendations for children can be inferred from the available data. However, CRP is a widely-used, easy-to-obtain, biological parameter, and its monitoring during fungal infections may help optimize voriconazole C_{min}. Indeed, CRP monitoring, as a reflection of inflammatory status influencing voriconazole pharmacokinetics, appears to be an essential tool in the management of patients treated with voriconazole for invasive fungal infections, in addition to therapeutic drug monitoring. A CRP threshold close to 100 mg/L could constitute an alert threshold for clinicians and represent an aid for pharmacologists in proposing dosage adjustments. This would allow further improvement and personalization of treatment. MR determination by measuring the main metabolite voriconazole N-oxide concentration is also a promising tool, and this could be implemented gradually in pharmacology laboratories. Ideally, CRP and MR should be included as new markers of variability in model-informed precision dosing approaches to optimize voriconazole C_{min} prediction and personalize voriconazole treatment. Finally, further studies should focus on evaluating the added value of a CRP-driven approach on the actual TDM of voriconazole.

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Conflict of interest statement

FL received institutional research grants from Sandoz, Astellas, and Chiesi and received fees to attend meetings from Pfizer, MSD, Gilead, and Viiv. JPG received fees from Gilead, Pfizer, MundiPharma, and Shionogi for lectures. The other authors have no conflicts of interest to declare.

Author contributions: CBK and FL designed the work. CBK participated in the compilation of studies. CBK and FL performed the analysis of studies and wrote the manuscript. JPG, MCV, and EB provided final approval of the manuscript in its submitted form. All authors revised the manuscript for important intellectual content and approved the manuscript in its submitted form.

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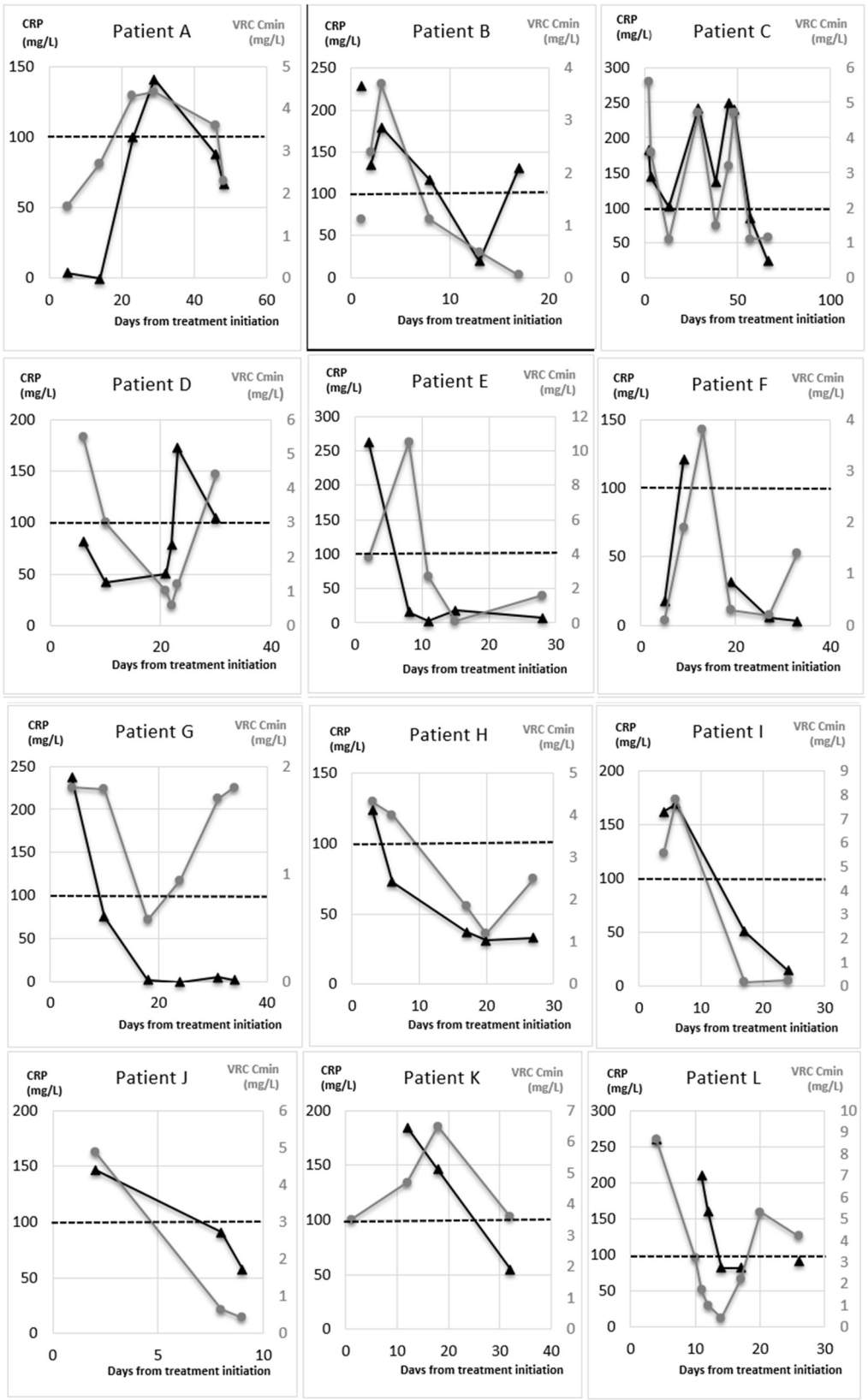
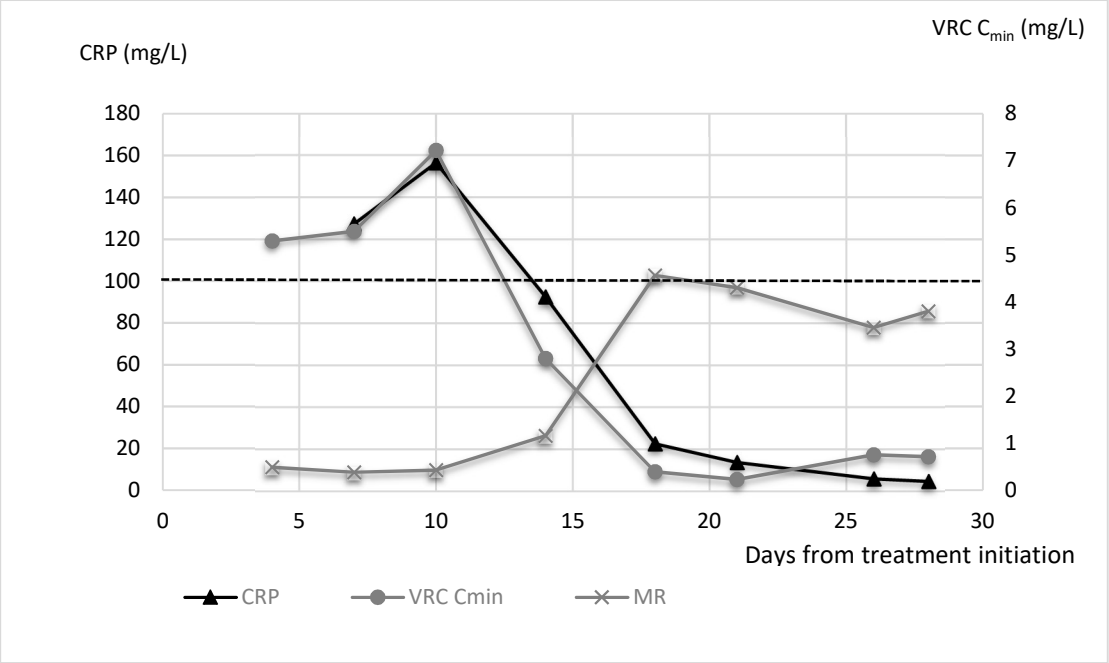
FIGURES

Figure 1. CRP and voriconazole C_{min} changes in inflammatory patients (from Boglione-Kerrien *et al.*[14])



VRC Cmin: voriconazole minimum concentration; *CRP: C-reactive protein (threshold at 100 mg/L represented by the black dotted line)*

Figure 2. Voriconazole C_{min} and MR changes in parallel with CRP changes: case of a phenoconversion (from Boglione-Kerrien *et al.*[14])



VRC C_{min}*: voriconazole minimum concentration; MR: metabolic ratio; CRP: C-reactive protein (threshold at 100 mg/L represented by the black dotted line)*

*The genotype of the patient was *17/*17 for CYP2C19, the patient was an ultra-rapid metabolizer of voriconazole. Phenotype and MR determination: MR was measured at 0.43 during the first 10 days (MR < 0.48) and increased towards a very high MR at 4.03 from the 18th day, revealing ultra-rapid metabolism masked by inflammation. This is referred to as phenoconversion.*

TABLES

Table 1. Comparative table of predicted voriconazole C_{min} and MR results, integrating CRP influence

	Mathematical Formula	Bias < 20% on VRC C_{min}	Bias < 20% on MR	Reference
Veringa	VRC +VRC x1.005321^{N} MR-MR x 0.99229 ^{N}	53% (8/15)	20% (3/15)	***[26]***
Van Wanrooy	increase 0.015 mg/L VRC C_{min} for every 1 mg/L increase in CRP	53% (8/15)	/	***[27]***
Encalada Ventura	VRC: increase 0.021mg/L VRC C_{min} for every 1 mg/L increase in CRP. MR : decrease 0.010 mg/L for every 1 mg/L increase in CRP	53% (8/15)	20% (3/15)	***[9]***
Bolcato	Increase 100 mg/L in CRP: increase of 82% VRC C_{min}	55% (6/11)	/	***[25]***

VRC C_{min}: voriconazole minimum concentration; CRP: C-reactive protein; MR: metabolic ratio.
Formulas were tested on n=15 patients from the Boglione-Kerrien et al study[14] (only 11 patients for the Bolcato formula because the increase in concentration was not specified in the event of variation in CRP greater than 100 mg/L with this formula).
The analysis was based on a predicted/measured threshold variation = 20%.