Observational Study of the Clinical Efficacy of Voriconazole and Its Relationship to Plasma Concentrations in Patients

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Voriconazole is approved for treating invasive fungal infections. We examined voriconazole exposure-response relationships for patients from nine published clinical trials. The relationship between the mean voriconazole plasma concentration (Cavg) and clinical response and between the free Cavg/MIC ratio versus the clinical response were explored using logistic regression. The impact of covariates on response was also assessed. Monte Carlo simulation was used to estimate the relationship between the trough concentration/MIC ratio and the probability of response. The covariates individually related to response were as follows: study (P < 0.001), therapy (primary/salvage, P < 0.001), primary diagnosis (P < 0.001), race (P = 0.004), baseline bilirubin (P < 0.001), baseline alkaline phosphatase (P = 0.014), and pathogen (yeast/mold, P < 0.001). The Cavg for 72% of the patients was 0.5 to 5.0 μg/ml, with the maximum response rate (74%) at 3.0 to 4.0 μg/ml. The Cavg showed a nonlinear relationship to response (P < 0.003), with a lower probability at the extremes. For patients with Cavg < 0.5 μg/ml, the response rate was 57%. The lowest response rate (56%) was seen with a Cavg ≥ 5.0 μg/ml (18% of patients) and was associated with significantly lower mold infection responses compared to yeasts (P < 0.001) but not with voriconazole toxicity. Higher free Cavg/MIC ratios were associated with a progressively higher probability of response. Monte Carlo simulation suggested that a trough/MIC ratio of 2 to 5 is associated with a near-maximal probability of response. The probability of response is lower at the extremes of Cavg. Patients with higher free Cavg/MIC ratios have a higher probability of clinical response. A trough/MIC ratio of 2 to 5 can be used as a target for therapeutic drug monitoring.

Therapeutic drug monitoring (TDM) is advocated increasingly for antifungal agents (13, 36) and is potentially an important tool to optimize the therapeutic outcome of patients with invasive fungal infections (3, 15). However, before TDM can be used widely, it is first necessary to establish the relationships between drug exposure and both clinical efficacy and toxicity. This information can then be used to guide optimal antifungal regimens for individual patients. Unfortunately, the determination of these exposure-response relationships in patients with invasive fungal infections is frequently confounded by multiple factors that have an impact upon clinical outcome.

Voriconazole is a triazole with broad spectrum antifungal activity and is currently considered the first line agent for the treatment of invasive aspergillosis (27, 42). The relationship between mean voriconazole plasma concentrations and drug-related toxicity was described by Tan et al. in 2006 (39). That study, in over 1,000 patients, suggested a relationship between mean voriconazole plasma concentrations and the probability of visual adverse events, as well as with elevated liver function tests. However, the relationship between voriconazole concentrations in plasma and clinical response has only been investigated in relatively small studies (9, 18, 23, 24, 25, 37). Despite a variety of methodological approaches being used, there do appear to be clinically important exposure-response relationships. Voriconazole TDM may improve clinical efficacy (18, 23, 24, 37), but this has not been formally demonstrated. Furthermore, the optimal target concentration range for this antifungal compound is not known.

Laboratory animal models of disseminated Candida albicans infection suggest that the pharmacokinetic-pharmacodynamic index that optimally links drug exposure with outcome for voriconazole and other triazole antifungal agents is the AUC/MIC ratio (2). Furthermore, a free AUC/MIC value of ~25 is associated with half-maximal antifungal effect in murine models of disseminated candidiasis (3). Unfortunately, there is a relative paucity of high-quality population pharmacokinetic data from patients with invasive fungal infections (5). This makes assessment of a correlation between triazole concentrations and efficacy difficult. For voriconazole this situation is further complicated by nonlinear pharmacokinetics in adults, but not in pediatric patients aged 2 to 11 years (43), and high inter-individual pharmacokinetic variability (30). The most important factor accounting for inter-individual variability is the CYP2C19 genotype (17). However, voriconazole plasma concentrations, like those of other triazoles, may also be affected by various drug-drug interactions (5, 6, 20). In addition, the impact of underlying condition on the pharmacokinetics of voriconazole has only been described in a small number of hematopoietic cell transplant recipients, where the pharmacokinetics appear to be similar to healthy volunteers (7).

We explore here the relationship between plasma voriconazole concentrations and clinical response in a population of 825 patients from nine, previously published clinical trials. We
Initially explore the relationship between mean plasma concentrations (C_{avg}) and clinical efficacy and then describe the impact of the voriconazole MICs on drug exposure-response relationships. Logistic regression modeling enables the potential effect of a number of covariates on the drug exposure-response relationships to be examined. Finally, we use Monte Carlo simulation to estimate the relationship between the trough concentration/MIC ratio and the clinical response, thereby providing further insight into drug exposure targets for TDM.

### Table 1. Clinical studies included in the efficacy versus voriconazole plasma concentration analysis

<table>
<thead>
<tr>
<th>Indication*</th>
<th>No. of patients (% success)</th>
<th>Voriconazole dose[^a]</th>
<th>Maximum duration of therapy (wks)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic IFIs in non-neutropenic patients</td>
<td>52 (60) p.o., 200 mg q12h[^b]</td>
<td>24</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>110 (63) i.v., 6 mg/kg x2 q12h → 3 mg/kg q12h; p.o., 200 mg q12h[^b]</td>
<td>24</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Esophageal candidiasis in AIDS</td>
<td>185 (76) p.o., 200 mg q12h</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Empirical therapy[^c]</td>
<td>166 (63) i.v., 6 mg/kg x2 q12h → 4 mg/kg q12h; p.o., 200 mg q12h[^b]</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Invasive fungal infections[^d]</td>
<td>13 (40) i.v., 6 mg/kg x2 q12h → 3 mg/kg q12h; p.o., 200 mg q12h[^b]</td>
<td>12</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Non-neutropenic candidemia</td>
<td>313 (51) i.v., 6 mg/kg x2 q12h → 4 mg/kg q12h; p.o., 200 mg q12h[^b]</td>
<td>12</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>252 (75) i.v., 6 mg/kg x2 q12h → 4 mg/kg q12h; p.o., 200 mg q12h[^b]</td>
<td>8</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

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[^a]: Two separate studies.
[^b]: Dose escalation allowed. p.o., peroral; i.v., intravenous; q12h, every 12 h; x2, administered twice.
[^c]: Only patients with data review committee-determined baseline infections were included.
[^d]: Salvage therapy, intolerance, no approved therapy.

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**Materials and Methods**

Sources of data. The data are from nine primary or salvage therapy clinical studies totaling 1,091 patients, with 1,007 having both a clinical outcome and measured voriconazole concentrations in plasma. These phase II and III clinical trials were completed before year 2000, and the results have all been published (Table 1). The modified intent to treat from the population of these studies included 896 patients. To be included in our primary analyses, these patients had to have one of the following: prospective, investigator-determined, outcomes at the end of therapy: a complete, partial, stable, or failed response to therapy (34) or to have died (any causality) or to have discontinued therapy due to an adverse event or laboratory abnormality (any causality). Of the 896 patients, 71 (7.9%) had one of the following outcomes—protocol violation (n = 16), withdrew consent (n = 16), other (n = 15), or lost to follow-up (n = 24)—and were thus excluded, giving a final population of 825 patients for primary analysis.

Organism and MIC. Invasive fungal isolates were identified to the species level using standard phenotypic techniques. Voriconazole MICs were obtained for fungi isolated at the start of therapy from 404 of the 825 (49%) patients in six of the clinical studies (Table 1) (1, 14, 21, 26). These MICs were measured at two reference laboratories according to Clinical and Laboratory Standards Institute methodology (M27-A2 and M38-A for yeasts and molds, respectively, with 48-h MIC readings) and have been published elsewhere (12, 19).

Voriconazole concentrations in plasma. Voriconazole concentrations were measured at a central reference laboratory using a well-validated, high-performance liquid chromatography assay (38). Voriconazole exhibits plasma protein binding at ca. 60% in humans (31). This value was used to estimate the mean unbound plasma fraction for each patient infected with a fungal isolate for which an MIC had been determined.

Drug exposure, pharmacokinetics, and efficacy. Plasma samples were taken at various times during the voriconazole dosing interval. Differences in clinical protocol design (including the voriconazole intravenous [i.v.]/peroral [p.o.] dosing regimen and the duration of therapy) led to considerable variation in the number and timing of plasma samples obtained from each patient. Furthermore, these samples were not necessarily obtained at optimally informative times, and there were relatively few samples for which there was reliable information on the time of collection relative to the time of drug administration. In addition, the CYP2C19 genotype was not available for any patient. Consequently, these data could not be used to develop a population pharmacokinetic model. Nevertheless, phase I studies suggest that there is low intra-individual variation in plasma concentrations relative to inter-individual variability (22, 29, 30), thus allowing the mean plasma concentration per patient (C_{avg}) to be used as a measure of drug exposure.

Data analysis. The relationship between C_{avg} and efficacy was investigated by logistic regression using the logarithm of an individual’s mean plasma concentration and the binary outcome measure (i.e., success or failure). A range of covariates (listed in Table 4) that could have an impact upon the probability of obtaining a clinical response to voriconazole were also investigated. In addition to graphical displays using splines, quadratic functions of linear terms were used to explore nonlinearity. There is no supposition of the exact form of the nonlinear relationships. Data analysis used SAS/STAT software (33).

Subset analysis of the impact of MICs on clinical outcome. The relationship between the C_{avg} free plasma concentration/MIC ratio and clinical response was also investigated using logistic regression, as described above. Three additional covariates only available for this particular subset of patients were included in the modeling: geographic location, underlying condition, and site of infection (Table 4).

Relationship between C_{avg} and trough concentration. To provide a more clinically tractable measure of drug exposure, Monte Carlo simulation was used to estimate the relationship between C_{avg} and trough voriconazole concentrations (40). The population pharmacokinetic model used in this analysis was fitted to data from healthy volunteers and patients with invasive aspergillosis. The structural model included the parameters V_{max} and K_{m} (the maximum rate of enzyme activity and the voriconazole concentration at which enzyme activity is half-maximal, respectively) to enable the nonlinear pharmacokinetics to be estimated (W. Hope, unpublished data). The mean population parameter values and their associated variances were inserted into subroutine PRIOR of ADAPT 5. A 5,000-patient simulation was performed.

The simulation module in ADAPT 5 was used to calculate the AUC at the end of the first week of i.v. therapy after the administration of 6 mg/kg every 12 h (q12h) i.v. on day 1, followed by 4 mg/kg i.v. administered q12h thereafter (8). The average concentration was calculated by dividing the AUC_{0-12} by the dosing interval (i.e., 12 h). The C_{avg} free fraction was obtained by multiplying this value by 0.4. The probability of clinical response was determined from the logistic regression parameters that described the relationship between the C_{avg}/MIC ratio and the probability of clinical response. The corresponding trough concentration at the end of the first week of therapy in each of the simulated patients was determined. The trough/MIC ratio was determined for each patient by using MIC values of 0.125 to 64 mg/liter. To further estimate the overall likelihood of a given outcome across the simulated population, an expectation across the distribution was calculated by using an approach described elsewhere (10, 11). The expectation for the trough/MIC ratio and probability of clinical response was calculated in the following manner. The distribution of trough/MIC ratio and the probabilities of successful outcomes for the 5,000 simulated patients were described by using a histogram with 20 subgroups. The midpoint value for each subgroup was multiplied by the fraction of simulated patients in each respective subgroup (e.g., if the subgroup contained 1,000 patients with trough/MIC values of 100 to 150, the midpoint value of 125 is multiplied by 1,000/total population; this process was repeated across the entire distribution). The overall estimate for the simulated population was then determined by summation of each of these products.
RESULTS

Patient population. There were 825 patients with a recorded clinical response and voriconazole plasma level measurements used in the primary analysis. The individual clinical studies from which they came, the voriconazole regimens and the overall response rates of the studies are summarized in Table 1. These 825 patients had an investigator-determined overall clinical response rate of 68.8%.

The patients were from approximately 200 centers in over 25 countries; 546 (66%) were male, and 650 (79%) were Caucasian. The age range was 12 to 90 years (median, 44 years), and the weight range was 26 to 132 kg (median, 64 kg). Seventy-two patients with a lower response rate (57%) compared to yeast infections (70% to 78%) (mean, 74%). This concentration range also included differences between categories of race, regions, studies, sites of infection, and underlying conditions. Clearly, some of success rates associated with the various concentration intervals for patients infected with yeasts and molds were 77% and 60%, respectively (Table 2). However, the maximum clinical response for yeasts or molds (81% or 74%, respectively) was achieved at C avg levels of 3.0 to 4.0 μg/mL. Patients infected with yeasts had higher response rates than those infected with molds across the entire range of voriconazole concentration intervals used in this analysis. Mold infections were also associated with a significantly lower clinical response rate compared to yeast infections (P < 0.001) for patients with plasma concentrations of ≥5.0 μg/mL (Table 2).

There were 87 (11%) patients with a C avg of <0.5 μg/mL. These patients had a lower response rate (57%) compared to patients with a C avg of 0.5 to <5.0 μg/mL (Table 2). However, the lowest response rate (56%) occurred in the 147 (18%) patients, where the C avg was ≥5.0 μg/mL. Dosage escalation, for any reason, occurred in only 4.8% of these patients (7/147; four successes and three failures). The outcomes for the 147 patients with a C avg of ≥5.0 μg/mL are summarized in Table 3.

Just over half (83/147 [56%]) of these patients completed therapy successfully, while the remaining 64 (44%) had stable or failed outcomes. These 64 patients included 36 receiving primary therapy and 28 receiving salvage therapy. There were 32/64 (50%) patients who died due to their underlying disease or fungal infection, while the remainder discontinued therapy (lack of efficacy, adverse events, or laboratory abnormalities, Table 3). In only 4/18 (22%) patients who discontinued therapy due to an adverse event or laboratory abnormality was this discontinuation ascribed, by the investigator, to voriconazole (1 elevated transaminases, 1 elevated bilirubin, 1 elevated alkaline phosphatase, and 1 hypoglycemia). None of the 18 patients discontinued therapy due to central nervous system adverse events of any causality.

Mean plasma concentration and efficacy. The simple response rate was significantly better for patients with the following characteristics: patients in primary therapy not salvage, patients infected with yeasts and not molds, patients with candidiasis not aspergillosis, and patients with lower baseline bilirubin and alkaline phosphatase levels (Table 4). There were also differences between categories of race, regions, studies, sites of infection, and underlying conditions. Clearly, some of

### Table 2. Investigator-determined success at end of therapy for 825 patients categorized by mean plasma voriconazole concentration interval

<table>
<thead>
<tr>
<th>Mean plasma conc (μg/mL)</th>
<th>Total, n = 825 (69)</th>
<th>Yeast infected, n = 432 (77)</th>
<th>Mold infected, n = 388 (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>87 (57)</td>
<td>52 (63)</td>
<td>34 (47)</td>
</tr>
<tr>
<td>0.5—&lt;1.0</td>
<td>75 (71)</td>
<td>34 (82)</td>
<td>40 (60)</td>
</tr>
<tr>
<td>1.0—&lt;1.5</td>
<td>94 (71)</td>
<td>38 (84)</td>
<td>56 (63)</td>
</tr>
<tr>
<td>1.5—&lt;2.0</td>
<td>100 (74)</td>
<td>47 (87)</td>
<td>53 (62)</td>
</tr>
<tr>
<td>2.0—&lt;3.0</td>
<td>151 (75)</td>
<td>70 (80)</td>
<td>80 (70)</td>
</tr>
<tr>
<td>3.0—&lt;4.0</td>
<td>100 (78)</td>
<td>53 (81)</td>
<td>47 (79)</td>
</tr>
<tr>
<td>4.0—&lt;5.0</td>
<td>71 (70)</td>
<td>46 (65)</td>
<td>25 (44)</td>
</tr>
<tr>
<td>5.0—&lt;6.0</td>
<td>47 (60)</td>
<td>24 (71)</td>
<td>23 (48)</td>
</tr>
<tr>
<td>6.0—&lt;8.0</td>
<td>55 (51)</td>
<td>37 (54)</td>
<td>17 (47)</td>
</tr>
<tr>
<td>8.0—&lt;10.0</td>
<td>26 (62)</td>
<td>18 (76)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>≥10.0</td>
<td>19 (58)</td>
<td>13 (85)</td>
<td>5 (0)</td>
</tr>
</tbody>
</table>

* A total of five patients were not confirmed to have either yeast or mold infection.

### Table 3. Outcomes of 147 patients with mean plasma concentrations of >5.0 μg/mL

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy success</td>
</tr>
<tr>
<td>Therapy failure</td>
</tr>
<tr>
<td>Reasons for therapy failure</td>
</tr>
<tr>
<td>Insufficient efficacy</td>
</tr>
<tr>
<td>Died (all causes)</td>
</tr>
<tr>
<td>Discontinued due to adverse event or laboratory abnormality</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Adverse event/laboratory abnormality due to voriconazole</td>
</tr>
</tbody>
</table>

* Includes (two) patients not confirmed to have yeast or mold infection.
these variables are likely to be confounded. In contrast, patient gender, age, weight, and baseline alanine aminotransferase (ALT), aspartate transaminase (AST), or creatinine levels were not related to clinical outcome.

Logistic modeling for the 825 patients revealed a significant, nonlinear relationship (as exemplified by a quadratic polynomial term, \( P < 0.003 \)) between mean voriconazole plasma concentrations and clinical response. The parametric polynomial model does not describe the nonparametric spline fit well where data are sparse (Fig. 1), but it does confirm that a more complex model than a simply linear one is required. The inclusion of covariates (from Table 4) in this nonlinear model did not change the significance of the curved relationship between the \( C_{\text{avg}} \) and response, although some had additional explanatory power (infection type, study, and baseline bilirubin). Furthermore, the relationship was not affected by the removal of a large study of esophageal candidiasis in AIDS patients (\( n = 154 \)) that contained the highest response rates (Table 1) and may conceivably have obfuscated any underlying relationship for the invasive infections.

### Mean free plasma concentration/MIC ratio and efficacy

The impact of the MIC on the drug exposure-response relationships was explored by using the free \( C_{\text{avg}}/\text{MIC} \) ratio as the independent variable in a logistic regression model. The \( C_{\text{avg}} \) versus-response relationship for the 404 patients in whom an MIC was available was also nonlinear, with a shape similar to that shown in Fig. 1, and was not affected by the inclusion of covariates in Table 4. Importantly, however, the relationship between \( C_{\text{avg}}/\text{MIC} \) ratio-versus-response was best described by using a linear term (parameter estimates for the final model are shown in Fig. 2), reflecting the fact that higher \( C_{\text{avg}}/\text{MIC} \) ratio values were associated with progressively better clinical responses. Of note, this relationship was only statistically significant when the data from yeasts and molds were combined. The relationships of the free \( C_{\text{avg}}/\text{MIC} \) ratio versus response for yeast (295 patients) and mold (109 patients) when examined separately were not statistically significant (\( P = 0.368 \) and 0.172 for yeasts and molds, respectively).

### Relationship between trough/MIC ratio and clinical response

The population parameter values and their dispersions were readily recapitulated in the Monte Carlo simulation. The administration of the currently recommended i.v. regimen resulted in a median trough concentration ± the standard deviation of \( 2.48 \pm 6.44 \mu \text{g/ml} \). The estimated relationship between the trough/MIC ratio and the probability of clinical response is shown in Fig. 3. Although the probability of a clinical response

### TABLE 4. Simple relationship of covariates with efficacy in logistic modeling for all 825 patients and/or 404 patients from the MIC data set

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category, % success</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>&lt;0.001 Salvage, 55%; primary, 72%</td>
<td></td>
</tr>
<tr>
<td>Infection type</td>
<td>&lt;0.001 Mold, 60%; yeast, 76%</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td>&lt;0.001 Aspergillosis, 60%; candidiasis, 77%; other, 55%</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>0.004 Caucasian, 66%; other, 78%</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.080 Female, 65%; male, 71%</td>
<td></td>
</tr>
<tr>
<td>Region*</td>
<td>0.016 Americas, 67%; Europe, 74%; Asia/Oceania, 84%; Africa, 87%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>&lt;0.001 See Table 1 for full population</td>
<td></td>
</tr>
<tr>
<td>Site of infection*</td>
<td>&lt;0.001 54 to 87%</td>
<td></td>
</tr>
<tr>
<td>Underlying condition*</td>
<td>&lt;0.001 57 to 86%</td>
<td></td>
</tr>
<tr>
<td>Baseline variants(^b)</td>
<td>Wt (kg) 0.637 55, 69.4%; 74, 68.5%</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin/ULN(^c)</td>
<td>&lt;0.001 0.34, 74.4%; 0.92, 69.6%</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase/ULN</td>
<td>0.033 0.66, 71.5%; 1.45, 69.1%</td>
<td></td>
</tr>
<tr>
<td>AST/ULN</td>
<td>0.296 0.47, 70.4%; 1.21, 69.8%</td>
<td></td>
</tr>
<tr>
<td>Creatinine/ULN</td>
<td>0.132 0.57, 71.1%; 0.93, 69.1%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Determined by logistic regression, except as noted. \(^*\) Determined using the MIC data set only.

\(^b\) Baseline variant values represent the percent predicted success and are presented as “25th percentile; 75th percentile”.

\(^c\) Upper level of normal.

FIG. 1. Binomial data and quadratic logistic fit for investigator outcome versus the mean voriconazole plasma concentration for 825 patients. ○, Data points separated as clinical success or clinical failure; - - -, spline (moving average); ------, line of predicted fit; - - -, upper and lower 95% confidence intervals. The curvature was significant at \( P < 0.003 \).
progressively increased with a higher trough concentration/MIC ratio, the probability of a successful outcome was near maximal with trough/MIC values of ca. 2 to 3.

**DISCUSSION**

The relationship between both mean plasma voriconazole concentrations and mean concentration/MIC ratios with efficacy were analyzed for patients from nine phase II and III clinical studies. These studies used the currently recommended voriconazole clinical dose regimens for adults, which was also used in the Monte Carlo simulations. The median \( C_{\text{avg}} \) of 2.37 \( \mu \text{g/ml} \) for these 825 patients falls well within the range of steady-state voriconazole mean concentrations achieved after multiple i.v. and p.o. dosing in healthy volunteers or in hematopoietic cell transplant recipients (7, 28). This is also the largest patient population used to date to examine the voriconazole drug exposure and clinical response relationship and provides useful insights into potential drug exposure targets for TDM.

There is a significantly lower rate of clinical response at the extremes of drug exposure. Although the poorer clinical response in patients with lower drug exposures is intuitively obvious and consistent with other studies (16, 20, 23), the lower rate of clinical response at higher concentrations is more difficult to understand. The extent of curvature, depicted in Fig. 1, did not change with the incorporation of any of the covariates (including primary or salvage therapy and yeast or mold pathogen) or with the removal of the majority of noninvasive yeast infections (esophageal candidiasis study) from the analysis. This suggests that none of these factors have a simple impact upon \( C_{\text{avg}} \) response relationships. Dose escalation was reported for only 4.8% of the 147 patients with mean plasma levels of \( \geq 5.0 \mu \text{g/ml} \) and so cannot account for the vast majority of these concentrations. Furthermore, there is no evidence that the lower response rate seen at these high mean concentrations is related to voriconazole toxicity, suggesting that other unidentified factors (or combinations of factors) may be important. Patients with mold infections did exhibit a significantly worse response than those with yeast infections at mean plasma levels of \( \geq 5.0 \mu \text{g/ml} \), but the reason for this is not clear. Potentially the severity of illness of these patients not only led to worse responses but also impaired their ability to clear voriconazole.

One factor that clearly has a powerful impact upon exposure response relationships is the MIC. The use of \( C_{\text{avg}}/\text{MIC} \) ratio as the independent variable yields a linear relationship, reflecting the fact that patients with higher free \( C_{\text{avg}}/\text{MIC} \) values are significantly more likely to respond to voriconazole therapy. This finding also suggests that the MIC conveys important information that can be used to optimize voriconazole therapy at the bedside. Interestingly, the free \( C_{\text{avg}}/\text{MIC} \) ratio that is associated with a higher probability of clinical response is
largely concordant with pharmacodynamic targets derived from experimental models of disseminated candidiasis (2, 4). A free voriconazole AUC/MIC ratio of \( \sim 24 \) for various Candida albicans strains is associated with half-maximal antifungal effect and is consistent with other members of the triazole antifungal class (4). A free AUC/MIC ratio of 24 is comparable to a free \( C_{\text{avg}}/\text{MIC} \) ratio of \( \sim 1 \), which is associated with a clinical response of \( \sim 65\% \) in this analysis (Fig. 2).

One problem with using \( C_{\text{avg}} \) as a measure of drug exposure is that it is cumbersome in a clinical context. Although a trough concentration is not necessarily optimally precise, it is more clinically tractable. Monte Carlo simulation provides an estimate of the relationship between total voriconazole trough concentration/MIC ratio and the clinical response. Figure 3 suggests that a progressively higher trough/MIC ratio is associated with a progressively higher probability of clinical response. The probability of clinical response is near maximal with a trough/MIC ratio that is somewhere between ca. 2 and 5. This finding can help guide therapy for patients when the MIC of the invading pathogen is known and enables prompt decision-making role in the design, execution, analysis or reporting of this research.

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ERRATUM

Observational Study of the Clinical Efficacy of Voriconazole and Its Relationship to Plasma Concentrations in Patients

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Volume 55, no. 10, p. 4782–4788, 2011. Page 4786: The x axis values for Fig. 2 were incorrect; the figure should appear as shown below.

FIG. 2. Binomial data and linear logistic fit for investigator outcome versus the mean voriconazole free drug/MIC ratio for 404 patients. ○, Data points separated as clinical success or clinical failure. Curves: - - - - , spline; ——, line of predicted fit; - - - - , upper and lower 95% confidence intervals. The slope was significant at $P = 0.005$. Note that the free ratio is $0.4 \times$ the ratio. Calculation: logit ($P$) = $(0.766 + 0.139) \times \log_{10}$ free ratio, where $P$ is the probability of response.