A rationale for reduced-frequency dosing of anidulafungin for antifungal prophylaxis in immunocompromised patients

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Objectives: Reduced-frequency dosing strategies of anidulafungin may offer a more convenient way of providing adequate antifungal prophylaxis to patients at high risk of invasive fungal diseases. We aimed to provide the pharmacological rationale for the applicability of reduced-frequency dosing regimens.

Methods: We defined two groups of 10 patients that were to receive anidulafungin at 200 mg every 48 h or 300 mg every 72 h. Blood samples were drawn daily and two pharmacokinetic curves were constructed after 1 and 2 weeks of treatment. A population pharmacokinetic model was developed using non-linear mixed-effects modelling. ClinicalTrials.gov identifier: NCT01249820.

Results: The AUC over a 6 day period (IQR) for a typical patient on 200 mg every 48 h or 300 mg every 72 h resulted in 348 mg.h/L (310.6–386.7) and 359 mg.h/L (319.1–400.9), respectively, comparable to the licensed regimen [397.0 mg.h/L (352.4–440.5)]. In the final model, the volume of distribution proved to be dependent on the lean body mass and CL of cyclosporine A. All three regimens resulted in comparable dose-normalized exposure over time.

Conclusions: We now have sufficient evidence to start using less frequent dosing regimens and demonstrate their value in clinical practice. These less frequently applied infusions enable more personalized care in an outpatient setting with reduced costs.

Keywords: antifungal drugs, pharmacokinetics, modelling and simulation, reduced-frequency dosing strategies

Introduction

Azole antifungal drugs, specifically posaconazole and voriconazole, are currently used as primary and secondary antifungal prophylaxis in haematology patients experiencing prolonged neutropenia and specific cellular immune dysfunction, resulting from the disease itself and therapies used to treat them.1–4 Unfortunately, azole use frequently results in severe hepatotoxicity and liposomal amphotericin B shows dose-dependent renal toxicity. There are also concerns about the emergence of azole resistance among isolates of Aspergillus fumigatus.5,6 New strategies need to be identified to offer adequate prophylaxis to this group of vulnerable patients. Anidulafungin is a suitable candidate because of its more favourable safety profile. Furthermore, anidulafungin lacks drug–drug interactions, thereby improving the management of other drugs commonly used in the haematological setting.7

Anidulafungin seems the ideal candidate to fulfil this need but daily intravenous administration provides a substantial challenge, especially when patients may be treated in an outpatient setting. The solution might be the administration of a higher dose with a reduced frequency. The patterns of microbial kill (at least for Candida infections) for echinocandins are described by two pharmacokinetic/pharmacodynamic indices: the AUC/MIC ratio or the Cmax/MIC ratio.8 The above-mentioned argument provides a rationale for intermittent anidulafungin dosing in humans.9–11 This has, however, not been tested before. Therefore, it seemed prudent to conduct a trial to elucidate the use of reduced-frequency dosing regimens.

Briefly, this strategy may prove simple and convenient for patients in whom azoles can be a challenge or contraindicated due to reasons such as emerging resistance, interactions or toxicity. Less frequent dosing is less burdensome than the customary daily intravenous dosing. In addition, this strategy seems more
feasible in the expanding group of haematology patients who receive outpatient-based HSCT and chemotherapy.

Methods

This open-label, Phase II study (ClinicalTrials.gov identifier: NCT01249820) was approved by the Ethics Committee of Radboud University Medical Center, Nijmegen in 2010 and was conducted in compliance with the Declaration of Helsinki. Patient informed consent was obtained before enrolment. From 2010 to 2012, adults aged 18–65 years who were admitted to receive an allogeneic HSCT were eligible if they were to receive either myeloablative or reduced-intensity conditioning regimens to prepare for the partially T-cell-depleted transplant or to receive remission induction chemotherapy for AML or high-risk myelodysplastic syndrome (MDS). Each patient was managed with a four-lumen central venous catheter to allow the fourth lumen to be reserved exclusively for anidulafungin administration. Any signs or symptoms of invasive fungal disease (IFD) or the use antifungal drugs within the previous month was grounds for exclusion identical to previous studies. This study was a two-cohort, open-label, Phase II study in which anidulafungin was administered intravenously the day following HSCT or directly after completing remission induction chemotherapy. Two cohorts of 10 patients each received 200 mg of anidulafungin every 48 h or 300 mg of anidulafungin every 72 h. All infusions were given at 8 A.M. at an infusion rate of 2 mg/min. This high infusion rate was tested to allow shorter infusions more appropriate for future use in the outpatient setting. Treatment was followed by a period of 14 days during which drug concentrations were measured daily and 1 week after the last dose to allow determination of terminal elimination.

Treatment protocol and supportive care

Remission induction chemotherapy consisted of idarubicin and cytarabine. Myeloablative conditioning consisted of idarubicin, cyclophosphamide with either total body irradiation or busulfan for matched related donors. Matched unrelated donors received thymoglobulin and cyclophosphamide with either total body irradiation or busulfan. Reduced-intensity conditioning consisted of fludarabine, cyclophosphamide and melphalan. In allogeneic HSCT graft-versus-host disease prophylaxis consisted of cyclosporine A (1 mg/kg twice a day intravenously) starting on the day of HSCT. Supportive care measures, including the use of antibacterial prophylaxis, management of the central venous catheter and the diagnostic approach for IFD, have previously been described in detail for the HSCT setting.

Blood sampling

Blood was obtained to determine sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, glucose, total cholesterol, triglycerides, blood urea nitrogen, creatinine, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, GGT and lactate dehydrogenase. Blood was also obtained to determine haemoglobin, leucocyte differential counts and platelet counts.

Vital signs, temperature, pulse, oxygen saturation and blood pressure were monitored immediately before starting the infusion and hourly for the first 4 h afterwards.

Blood samples were drawn into lithium heparin-containing tubes and centrifuged for ~10 min at 1000 g (2500 rpm) within 30 min of collection. Plasma was aspirated and transferred in two plastic tubes and stored at ~80°C.

Two pharmacokinetic curves were determined on days 5 (three doses) and 15 (eight doses) and on days 4 (two doses) and 13 (five doses) for the every 48 h regimen and the every 72 h regimen, respectively. Blood samples for the full pharmacokinetic analysis were taken at pre-defined times of t=0 (pre-dose) and then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 h post-infusion. Additional daily samples at 24 h intervals were taken once daily on all other study days and for 7 days after stopping anidulafungin.

Analytical assay

Anidulafungin samples were measured by UPLC with fluorescence detection. Samples were pre-treated using a protein precipitation procedure (acetonitrile/methanol (50/50) and formic acid (0.1%)). A seven-point calibration curve with three quality control samples was used. All measurements were done in duplicate. The dynamic range of the assay was 0.008–8.4 mg/L and the accuracy range (n=15), which was dependent on the concentration, was 94.2%–103.5%. The intraday precision varied between 0.9% and 1.8% and the interday precision was between 0.5% and 1.6%. Three freeze–thaw cycles did not impact the stability of anidulafungin. Recovery was 93% (coefficient of variation: 4%).

Pharmacokinetic model

The pharmacokinetic data were analysed using non-linear mixed-effects modelling with NONMEM 7.2 (Giuborgo, Hanover, MD, USA). The gfortran compiler (version 4.6.1) was used with NONMEM, with Pirana (version 2.8; http://www.pirana-software.com/) and Perl-Speaks-NONMEM (version 3.5.3; http://psn.sourceforge.net/) used for model execution. Data visualization was performed with R (version 2.15.2; http://www.r-project.org/) and Xpose (version 4.4; http://xpose.sourceforge.net/).

Discrimination between different models was achieved by comparing the objective function value (OFV; i.e. −2 log likelihood). A significance level of P<0.05, corresponding to a decrease in OFV of 3.8, was considered statistically significant. For diagnostic purposes, goodness-of-fit plots (GOF) were used. The CI of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the models.

Pharmacokinetic models incorporating either one-, two- or three-compartment models with linear elimination were investigated. The first-order conditional estimation method with interaction was used throughout model development. Proportional, additive and combined additive and proportional residual error models were evaluated.

All covariates were plotted independently against the individual pharmacokinetic parameters and the weighted residuals of the model without covariates to visualize relations. Potential covariates were formally tested in the model as follows: for continuous covariates such as body weight [and derived parameters such as BMI or lean body mass (LBM)], the influence of the covariate on each pharmacokinetic parameter was tested throughout model development. Proportional, additive and combined additive and proportional residual error models were evaluated.

All covariates were plotted independently against the individual pharmacokinetic parameters and the weighted residuals of the model without covariates to visualize relations. Potential covariates were formally tested in the model as follows: for continuous covariates such as body weight [and derived parameters such as BMI or lean body mass (LBM)], the influence of the covariate on each pharmacokinetic parameter was tested using a linear or allometric function. Other covariates such as the use of concomitant drugs were modelled as dichotomous variables using linear functions. Statistical evaluation of the incorporated covariate relationships was performed by forward inclusion and backward deletion. A P value <0.005 was applied to evaluate the covariates in the forward inclusion (an OFV value of ≥7.8 points), while the backward deletion procedure used a stricter criterion (OFV >10.83; P<0.001).

The covariates tested were body weight, BMI and LBM as well as renal function, bilirubin levels, white blood cell counts, absolute neutrophil counts, the liver function tests alkaline phosphatase, bilirubin, AST, ALT and GGT and the concomitant use of cyclosporine A, tacrolimus or prednisolone (as dichotomous variables). The Jannmahasatian et al. formula was used to calculate the LBM and renal function was estimated from the serum creatinine using Modification of Diet in Renal Disease formula.

Bootstrap analysis was used to validate the internal model for which the current datasets were resampled 1000 times to produce a new data set of the same size containing a different combination of individuals. The parameter estimates were summarized in terms of mean values with their standard errors and were compared with the estimates obtained from the final model dataset. A visual predictive check (VPC) was done to assess the predictive performance of the model.
Monte Carlo simulation

The pharmacokinetic model was then employed for the simulations to establish what exposure would be achieved using a wide variety of regimens. To build a valid dataset we used the population distribution of a cohort of 1706 AML/MDS and stem cell transplant patients from the haematology department (2007–14) (mean age (range) was 57 years (18–81), mean height (range) was 174.4 cm (135–204) and mean weight (range) was 76.4 kg (39–145)). The 1706 patients were replicated to a total of 18000 individuals with identical distribution of relevant parameters using R (http://www.r-project.org). We argued this would render a realistic distribution representing the average patient on a haematology ward. These 18000 virtual patients were equally distributed over six groups consisting of 3000 subjects each: licensed dose of anidulafungin at 200/100 mg with or without cyclosporine A; 200 mg of anidulafungin every 48 h with or without cyclosporine A; and 300 mg of anidulafungin every 72 h with or without cyclosporine A (dichotomous). A ‘waste’ compartment was defined to determine the cumulative AUC after 6 days of therapy. Day 6 was chosen as in this situation the same cumulative dose over time was given for the every 48 h regimen and the every 72 h regimen. The licensed regimen resulted in a cumulative dose of 700 mg instead of 600 mg for the every 48 h group and the every 72 h group.

Safety

All adverse events were recorded regardless of treatment or potential causal relationship to anidulafungin. Events involving adverse drug reactions, illness that developed during the study or exacerbations of pre-existing illnesses were considered adverse events. In addition, abnormal measurements (e.g. ECG changes and abnormal laboratory test results) that resulted in anidulafungin discontinuation or required intervention or diagnostic evaluation to assess the risk to the subject were also recorded as adverse events.

Results

Twenty-six patients gave written informed consent to participate in this study but only 20 patient episodes were fully evaluable. The every 48 h group \( (n = 10) \) consisted of 3 females and 7 males and the every 72 h group \( (n = 10) \) consisted of 2 females and 8 males. Their mean age was 55 years (range 21–64) and their mean weight was 77 kg (range 52–113). A detailed overview of the demographic characteristics of these 20 patients is given in Table 1.

Pharmacokinetic model

All available drug concentrations were simultaneously modelled involving a total of 581 samples and 92 dosing records. A structural three-compartment model \([\text{CL} \text{ and the volume of distribution of the central compartment (compartment 1) (V1) and two peripheral compartments (compartments 2 and 3) (V2 and V3)}]\) best described the data. Both the GOF and the OFV improved compared with the two-compartment model. However, this model could not be retained when LBM was added because of a correlation between \( V_1 \) and intercompartmental CL \( (Q_{1-3}) \). As a result, the model was simplified by equalizing \( V_3 \) to \( V_2 \) (a 2.5-compartment model). This did not result in any improvement. Hence, a two-compartment model was the final structural model. A combined error model was tested, but this did not improve the OFV or GOF. In the final model, the pharmacokinetic parameters were as follows: \( \text{CL} \) (without cyclosporine A) \( = 1.49 \text{ L/h} \); \( \text{CL} \) (with cyclosporine A) \( = 1.02 \text{ L/h} \); \( V_1 = 31.8 \text{ L} \) (for median LBM of 57 kg); \( V_2 = 23.1 \text{ L} \); and \( Q = 0.59 \text{ L/h} \). Parameter estimates of the structural model with interindividual variability are provided in Table 2.

Covariate model

Treatment with cyclosporine A on CL and LBM on \( V_1 \) were selected as significant covariates from the stepwise approach. Both covariates were modelled as linear variables. Allometric functions did not improve the GOF or OFV. The impact of other concomitant drugs on anidulafungin pharmacokinetics could not be determined as there was an insufficient number of patients using

| Table 1. Patient demographics for the total cohort and the two subcohorts |
|-------------------------------------------------|-----------------|-------------|
| Age (years), median (range)                     | 55 (26–62)      | 55 (21–64)  |
| Weight (kg), median (range)                     | 77 (52–101)     | 77 (61–113) |
| Height (cm), median (range)                     | 176 (160–185)   | 180 (168–183) |
| Gender                                          | 3 females and 7 males | 2 females and 8 males | 5 females and 15 males |
| Haematological disease                          |                 |             |
| AML/MDS                                         | 7               | 8           | 15          |
| other                                           | 3               | 2           | 5           |
| Treatment                                       |                 |             |
| H SCT                                           |                 |             |
| myeloabla tive conditioning                     | 7               | 9           | 16          |
| reduced-intensity conditioning                  | 0               | 1           | 1           |
| remission induction chemotherapy                | 3               | 0           | 3           |
| Day of first ANF dose from start of chemo/conditioning, median (range) | 10 (9–13) | 10 (8–13) |
| Neutropenia (duration in days), median (range)  | 15 (14–22)      | 15 (13–21) |

q48h, 200 mg of anidulafungin every 48 h; q72h, 300 mg of anidulafungin every 72 h; ANF, anidulafungin.
these drugs to draw any valid conclusion. Apart from LBM and cyclosporine A, no parameter yielded a significant result. Liver function tests and renal function had no impact on either the V or CL of anidulafungin. In the three-compartment model, there was a correlation between the estimate of V1 and the intercompartmental CL between compartments 1 and 3 (Q1–3) when LBM was added as a covariate. Setting V2 and V3 as identical compartments did not resolve this issue. Therefore, we chose to return to a two-compartment model rather than dropping LBM as a covariate on V1 as described in the structural model paragraph (Figure S1, available as Supplementary data at JAC Online).

Model validation
The results of the 1000 patient bootstrap confirmed the robustness of the model (Table 2). VPC demonstrated the validity of the final covariate model (Figure 1a and b).

Monte Carlo simulation
The median AUC at 23.99 h on day 5 for the three regimens (licensed dose, 200 mg every 48 h and 300 mg every 72 h) without cyclosporine A was 396.9 mg.h/L (297.3–512.9), 348.4 mg.h/L (259.9–586.6) and 359.4 mg.h/L (267.7–468.1), respectively. In the case of coadministration with cyclosporine A, the cumulative AUC at 23.99 h on day 5 for the three regimens amounted to 522.8 mg.h/L (403.3–662.9), 462.0 mg.h/L (355.9–586.6) and 482.6 mg.h/L (368.8–614.1), respectively (Table 3 and Figures 2–4).

Safety
Three serious adverse events were recorded among the 26 patients. Patient A3 was diagnosed with a life-threatening bacterial sepsis 1 day after starting anidulafungin treatment. This patient dropped out of the study at that moment. Patient A12 died within 30 days after completion of the study (while having graft-versus-host disease and post-transplant lymphoproliferative disorder) due to a myocardial infarction. Patient B12 was admitted to the hospital within 30 days after completion of the study due to septic shock. None of the serious adverse events was considered related to the study drug.

All other adverse events were mild, transient and resolved and it was not necessary to discontinue treatment. No ECG abnormalities were observed, there were no important laboratory abnormalities observed and the changes from baseline were moderate and not related to anidulafungin administration. The increased infusion rate of 2 mg/min was well tolerated by all the patients.

Fungal infections
None of the patients had a breakthrough fungal infection.

Discussion
From our study, we demonstrated that higher dosage of anidulafungin with less frequent administration resulted in comparable exposure over time (defined as cumulative exposure from day 1 to day 6) and that these less frequent administrations had identical exposure to daily dosing regimens. Furthermore, we demonstrated that dosages up to 300 mg resulted in linear pharmacokinetics. In the literature, dose-escalation studies to determine the linearity of pharmacokinetics were only investigated up to maintenance dosages of 130 mg once daily.17 Taking the AUC/MIC as the pharmacokinetic/pharmacodynamic index, it is not unreasonable to assume that identical exposure using reduced-frequency dosing strategies will be as effective. In animal studies, dose escalation with increased dosing interval demonstrated the importance of the AUC/MIC and Cmax/MIC concentration-dependent indices.9,18,19 In the clinical setting, however, this is not confirmed. Several studies have tried to use higher dosages of echinocandins to boost performance of these drugs against Candida species.20,21 Betts et al.20 did not find any

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model</th>
<th>Final model</th>
<th>Bootstrap (n=1000), mean (97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (L/h) (RSE)</td>
<td>1.12 (6%)</td>
<td>1.49 (8%)</td>
<td>1.49 (1.22–1.69)</td>
</tr>
<tr>
<td>CL with CsA (L/h) (RSE)</td>
<td></td>
<td>1.02 (6%)</td>
<td>1.03 (0.91–1.15)</td>
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<tr>
<td>V1 (L) (RSE)</td>
<td>31.4 (6%)</td>
<td>31.8 (5%)</td>
<td>31.8 (28.7–35.1)</td>
</tr>
<tr>
<td>V1 (L) LBM (for a median LBM of 57 kg) (RSE)</td>
<td></td>
<td>0.59 (24%)</td>
<td>0.60 (0.28–0.91)</td>
</tr>
<tr>
<td>Q (L/h) (RSE)</td>
<td>23.2 (13%)</td>
<td>23.1 (13%)</td>
<td>23.0 (17.0–28.4)</td>
</tr>
<tr>
<td>Interpatient %CV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIV CL (RSE) [shrinkage]</td>
<td>25.7% (12%) [−1%]</td>
<td>20.2% (20.2%) [−1%]</td>
<td>19.2% (12.6–24.5)</td>
</tr>
<tr>
<td>IIV V1 (RSE) [shrinkage]</td>
<td>24.5% (16%) [4%]</td>
<td>19.7% (16%) [4%]</td>
<td>18.9% (12.1–25.1)</td>
</tr>
<tr>
<td>IIV Q (RSE)</td>
<td>fix</td>
<td>fix</td>
<td></td>
</tr>
<tr>
<td>IIV V2 (RSE)</td>
<td>fix</td>
<td>fix</td>
<td></td>
</tr>
<tr>
<td>Residual error (RSE) [shrinkage]</td>
<td>22.1% (6%) [3%]</td>
<td>22.1% (6%) [3%]</td>
<td>21.9% (18.9–24.8)</td>
</tr>
</tbody>
</table>

CL, clearance; V1, volume of distribution of compartment 1; V2, volume of distribution of compartment 2; Q, intercompartmental clearance; IIV, interindividual variability; RSE, root square error; CV, coefficient of variation; CsA, cyclosporine A.
Figure 1. (a) VPC for the total group of anidulafungin patients. The solid red line connects the observed median values per bin, whereas the solid blue lines represent the observed 5th and 95th percentiles of the observations. Blue areas indicate the 95% CIs of the 5th and 95th percentiles of the predicted (simulated) value, whereas the red area indicates the CI of the median. The filled circles are the observations. The independent variable is ‘time after dose (h)’ and the dependent variable is ‘concentration (mg/L)’. (b) VPC for the two subgroups. The independent variable is ‘time after dose (h)’ and the dependent variable is ‘concentration (mg/L)’. q48h, every 48 h; q72h, every 72 h.
significant gain when using 150 mg of caspofungin compared with regular dosing of 50 mg of caspofungin for invasive candidiasis. Contrary to the findings of Betts et al., Andes et al. demonstrated that micafungin at higher dosages with less frequent administrations resulted, although not significantly differently, in a trend towards better outcome in oesophageal candidiasis. If one accepts that $C_{\text{max}}/\text{MIC}$ is the driving parameter this would possibly mean that from a pharmacological view point a better efficacy can be expected. A drawback of higher dosages and subsequent $C_{\text{max}}$ has been associated with a paradoxical effect, but this has never been demonstrated in humans. Another drawback of higher dosing is the chance of increased risk of toxicity. In the literature, reports have emerged on concentration-dependent side effects. In our study, anidulafungin was well tolerated. Specifically, no infusion-related toxicity was noted even with the increased infusion rate of 2 mg/min (the regular rate is 1.1 mg/min). It must be noted that all administrations were done through a central venous catheter.

In addition to improved efficacy of reduced-frequency dosing strategies of echinocandins in in vivo models, it may also provide benefits in the setting of prophylaxis. No IFD occurred in the 20 patients [background incidence (invasive aspergillosis + candidaemia) ~10%; unpublished data, J. P. Donnelly and W. J. F. M. Van Der Velden].

### Table 3. Modelling and simulation of 18000 patients (six cohorts)

<table>
<thead>
<tr>
<th>Name</th>
<th>Median AUC</th>
<th>5th percentile</th>
<th>25th percentile</th>
<th>75th percentile</th>
<th>95th percentile</th>
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<tr>
<td>q24h</td>
<td>396.97</td>
<td>297.30</td>
<td>352.43</td>
<td>440.48</td>
<td>512.87</td>
</tr>
<tr>
<td>q24h with CsA</td>
<td>522.75</td>
<td>403.27</td>
<td>470.93</td>
<td>577.83</td>
<td>662.86</td>
</tr>
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<td>q48h</td>
<td>348.45</td>
<td>259.61</td>
<td>310.58</td>
<td>386.67</td>
<td>452.24</td>
</tr>
<tr>
<td>q48h with CsA</td>
<td>462.05</td>
<td>355.91</td>
<td>416.15</td>
<td>509.55</td>
<td>586.55</td>
</tr>
<tr>
<td>q72h</td>
<td>359.36</td>
<td>267.68</td>
<td>319.11</td>
<td>400.93</td>
<td>468.08</td>
</tr>
<tr>
<td>q72h with CsA</td>
<td>482.56</td>
<td>368.80</td>
<td>433.94</td>
<td>534.61</td>
<td>614.10</td>
</tr>
</tbody>
</table>

CsA, cyclosporine A; q24h, licensed regimen of anidulafungin with a loading dose of 200 mg on the first day followed by a maintenance dose of 100 mg every 24 h as of day 2; q48h, 200 mg of anidulafungin every 48 h; q72h, 300 mg of anidulafungin every 72 h; median AUC, the median exposure achieved at the start of day 6 of therapy.

![Typical exposure of the population resulting from the simulation experiment. Typical profiles for the licensed regimen (a1), 200 mg every 48 h (a2) and 300 mg every 72 h (a3). (b1), (b2) and (b3) are the same dosing regimens but with coadministration of cyclosporine A.](image-url)
lipid formulations of amphotericin B are contraindicated due to specific organ dysfunction or due to drug interactions. In the future, a more prominent role due to emerging azole resistance can be attributed to the echinocandins and anidulafungin may thus provide a suitable alternative as prophylaxis in this cohort. The drawback of echinocandins is the limitation of intravenous administration. Less frequent dosing will provide a patient-friendly alternative to customary daily dosing regimens. Reduced-frequency dosing seems more feasible in the growing group of haematology patients that receive outpatient-based HSCT and chemotherapy. Moreover, patients requiring prolonged prophylaxis because of chronic graft-versus-host disease might be more easily managed and in an outpatient setting.

A number of papers have described the pharmacokinetics of anidulafungin at licensed dosing regimens. Our findings on pharmacokinetic parameters in the haematology population corroborate with the findings in other populations. Specifically, the work of Dowell et al. and Liu and Mould, who both used non-linear mixed-effects modelling, showed similar findings to our work. We found cyclosporine A to influence the CL of anidulafungin. If cyclosporine A was coadministered, the CL of anidulafungin was reduced resulting in a higher exposure. This has been described with a similar effect size by Dowell et al.

Next, weight and derived parameters were identified as a significant covariate on V1. Specifically, LBM correlated best with V1 in which higher LBM resulted in a larger volume of distribution for anidulafungin. The finding that body weight impacts

Figure 3. Cumulative exposure over time defined as the AUC from time 0 to day 6 of treatment for the licensed regimen (a1), 200 mg every 48 h (a2) and 300 mg every 72 h (a3). (b1), (b2) and (b3) are the same dosing regimens but with coadministration of cyclosporine A.

Figure 4. Boxplots for the simulated regimens. CsA, cyclosporine A; q24h, licensed regimen of anidulafungin with a loading dose of 200 mg on the first day followed by a maintenance dose of 100 mg every 24 h as of day 2; q48h, 200 mg of anidulafungin every 48 h; q72h, 300 mg of anidulafungin every 72 h. Scenario A = licensed regimen without cyclosporine A. Scenario B = licensed regimen with cyclosporine A. Scenario C = 200 mg every 48 h without cyclosporine A. Scenario D = 200 mg every 48 h with cyclosporine A. Scenario E = 300 mg every 72 h without cyclosporine A. Scenario F = 300 mg every 72 h with cyclosporine A.
pharmacokinetic parameters is also noted for other echinocandins.\textsuperscript{29,30} We chose to explore LBM using the formula of Janmahasatian et al.\textsuperscript{16} in addition to weight and BMI as anidulafungin is freely water soluble, has a low log P and the V of anidulafungin is limited. Hence, it was argued that LBM might best reflect the distribution of anidulafungin as eventually was demonstrated in this trial. The clinical relevance is subject to debate. As stated based on the physico-chemical properties of anidulafungin, it is not surprising that similar findings are found for this drug as for caspofungin and micafungin.

The clinical efficacy of reduced-frequency regimens with higher dosages still needs to be clinically validated. We believe this study provides the necessary background for the justification of reduced-frequency dosing and are firmly of the opinion that the next step is to set up a clinical Phase III trial.

Acknowledgements

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Transparency declarations

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Author contributions

R. J. M. B., W. J. F. M. V. D. V., D. M. B. and J. P. D. designed the study. W. J. F. M. V. D. V. and N. M. A. B. recruited patients. A. C. and S. H. assisted in data collection. C. A. J. K. assisted in the pharmacokinetic analysis. R. J. M. B. analysed the data and drafted the manuscript. All of the authors read and approved the final version of the manuscript accepted for publication.

Supplementary data

Figure S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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