

Introduction

Background: Little is known about the pharmacokinetics (PK) of anidulafungin (ANF) given in alternate dosing strategies other than the standard once daily schedule, though these may offer a more convenient way of providing prophylaxis to patients at high risk for invasive fungal diseases. We set out to explore this in a cohort of patients admitted for an allogeneic HSCT or to receive intensive chemotherapy for AML.

Methods

Primary objective: To determine the pharmacokinetics of anidulafungin given as 200mg once in every 2 days (q48h) or 300mg once in every 3 days (q72h) to patients undergoing an allogeneic haematopoietic stem cell transplant or receiving first remission induction treatment for AML-MDS.

Secondary objective: To determine whether adequate exposure is attained by patients undergoing an allogeneic haematopoietic stem cell transplant or receiving first remission induction treatment for AML-MDS when using a q48 hours dosing regimen.

- To determine whether infusion time can be increased to 2 mg/min
- To determine the safety of anidulafungin in this patient population

Patient population and treatment plan:

Patients receiving a allogeneic haematopoietic stem cell transplant or patients receiving first remission induction treatment for AML-MDS.

An open-label, non-randomised, non-controlled, single-centre, phase IV trial.

Day 1-15: anidulafungin 200mg q48h IV (8 dosages) or anidulafungin 300mg q72h IV (5 dosages)
Day 16-21: washout period to determine elimination of anidulafungin.

2 PK curves on days 4 (q72h) or 5 (q48h) and 13 were drawn at t=0 (pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours post infusion (15 samples).
Additional trough samples were drawn on all other study days and until 7 days after stopping anidulafungin. Patients were eligible if at least the first PK curve was completed.

Modeling was done using Non Linear Mixed Effect Modeling (NONMEM 7.2) with Pirana interface. Simulation files were created using R.

Safety:
Medical history, physical examination: Upon inclusion.
Vital signs: Daily.
Laboratory safety: Following routine practice.
Adverse events: Subjects were asked to report any adverse experiences (including vomiting and diarrhoea) in addition to medical and nursing observations on all study days.

Results

26 patients gave written informed consent. 6 patients were not evaluable due to a wide variety of reasons leaving 20 patients to be fully evaluable (table 1).
All available drug concentrations were simultaneously modelled rendering a total of 581 samples and 92 dosing records.

	Group 1 (q48h)	Group 2 (q72h)	Total
Median Age (years + range)	55 (26 - 62)	55 (21 - 64)	55 (21 - 64)
Median Weight (kg + range)	77 (52 - 101)	77 (61 - 113)	77 (52 - 113)
Median Height (cm + range)	176 (160 - 185)	180 (168 - 183)	180 (160 - 185)
Gender	3 female, 7 male	2 female, 8 male	5 female, 15 male

Table 1: baseline characteristics

A two compartment model best described the data. The model improved by allowing variance on CL and V1. Adding variance on Q and V2 in the model did not result in improvement of diagnostics as well as a reduction in objective function.

Results

Parameter	Basic model	Final Model	Bootstrap (n=1000)	Dowell et al (J Clin Pharm)
Typical Value				
CL (L/h)	1.12 (6%)	1.49 (8%)	1.49	0.95
CL with CsA (L/h)		1.02 (6%)	1.02	
V1 (L)	31.4 (6%)			9.97
V1 (L) FFM		31.8 (5%)	31.78	
Q (L/h)	0.59 (24%)	0.59 (25%)	0.60	24.2
V2 (L)	23.2 (13%)	23.1 (13%)	23.02	23.2
Interpatient % CV				
IIV CL (RSE) [shrinkage]	25.7% (12%) [-1%]	20.2% (20.2%) [-1%]	19.2%	34.9%
IIV V1 (RSE) [shrinkage]	24.5% (16%) [4%]	19.7% (16%) [4%]	18.9%	Fix
IIV Q (RSE)	fix	fix		fix
IIV V2 (RSE)	fix	fix		fix
Residual error (RSE) [shrinkage]				
	22.1% (6%) [3%]	22.1% (6%) [3%]	21.9%	24.6%

Table 2: Population PK parameters estimates of the simple model, final model and the bootstrap analysis. A comparison with literature (Dowell et al is presented).

Significant covariates that were selected from the stepwise approach are the use of cyclosporine A (CsA) on clearance and fat free mass (FFM) on volume of distribution of compartment 1 (V1). None of the other drugs had sufficient patients using these drugs to make a valid statement.

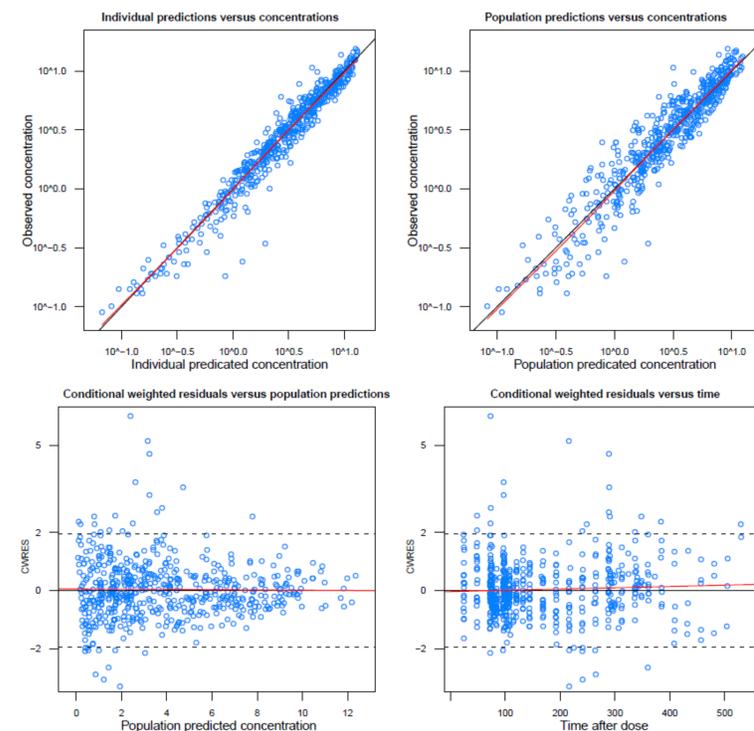


Figure 1: Goodness-of-Fit plots of the final model

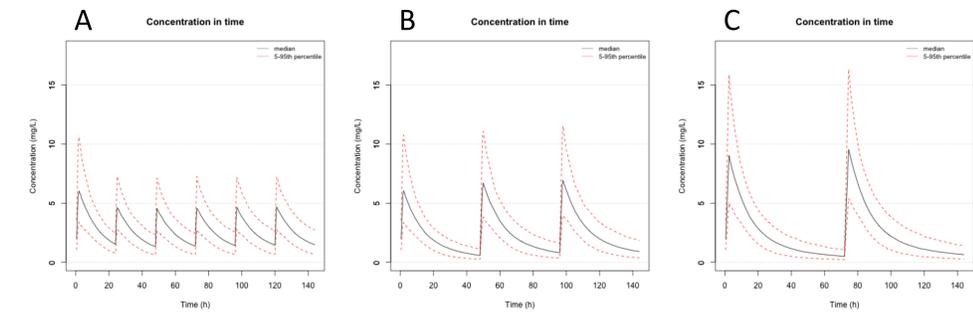


Figure 2: Typical PK profile (median + IQR) after simulations of licensed dose (A), 200mg q48h (B) and 300mg q72h (C) of each 3000 patients

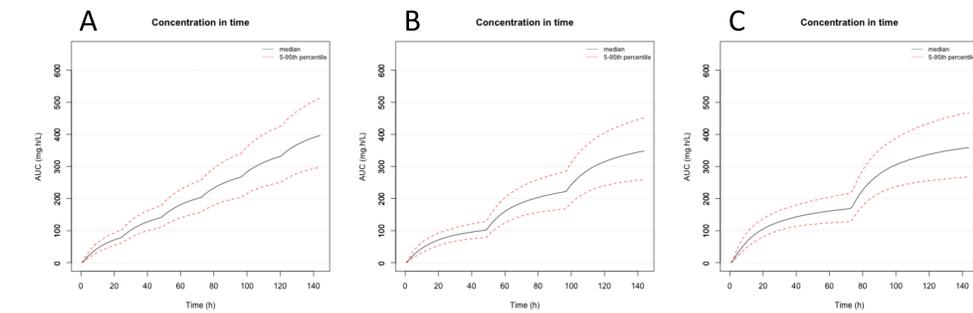


Figure 3: simulations of cumulative AUC (median + IQR) for the regimens: licensed dose (A), 200mg q48h (B) and 300mg q72h (C) of each 3000 patients

SAFETY:

Three serious adverse events (SAE) were recorded in 26 patients. Patient A3 was diagnosed with a life threatening bacterial sepsis one day after start anidulafungin treatment. Patient A12 died within 30 days after completion of the study due to "serum sickness" and/or graft versus host disease and/or PTLD because of occlusion of the coronaria sinistra. Patient B12 was admitted to the hospital within 30 days after completion of the study due to septic shock. None of the SAEs were considered related to the study drug.

All adverse events were mild and transient and resolved, and treatment was not discontinued in any of the assessable cases. No important laboratory abnormalities were reported. The increased infusion rate of 2 mg/min infused over a central venous catheter was well tolerated in all of the patients.

Conclusions

This is the first study to define extensive PK of alternate dosing strategies of anidulafungin with either 200mg q48h or 300mg q72h using a non-linear mixed effect modelling approach.

FFM was identified as relevant covariate on V1. Concomitant use of CsA resulted in a reduced clearance as also described in literature.

PK results were comparable to results published in healthy volunteers using standard dosages of anidulafungin.

We have now sufficient evidence to define an optimal regimen for less frequent prophylaxis regimens based on modelling and simulation and demonstrate its value in clinical practice.