



Miltefosine treatment failure in visceral leishmaniasis in Nepal is associated with low drug exposure

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Background

Visceral leishmaniasis (VL) is a fatal neglected tropical parasitic disease and miltefosine is the only oral drug available for it (28 day regimen). Recent reports indicated increased miltefosine **treatment failure rates** on the Indian subcontinent [1,2], compared to clinical trials performed a decade ago. In **Nepal** a cohort study was performed in which miltefosine-treated VL patients were followed-up for 12 months to identify **relapsing patients** [2]. Comparing end-of-treatment miltefosine concentrations (equivalent to C_{ss} or C_{max}) did not show a significant difference between relapses versus cures. However, this could be obscured by the large interindividual variability in sampling times (single sparse sampling), variability in individual doses (children vs. adults) and susceptibility of the parasite.

Aim

To further **explore the pharmacological factors associated with miltefosine treatment failures**. The relationship between miltefosine drug exposure and treatment failure was assessed in a cohort of Nepalese VL patients treated with miltefosine monotherapy, **linking *in vivo* PK to *in vitro* drug susceptibility of the parasite**.

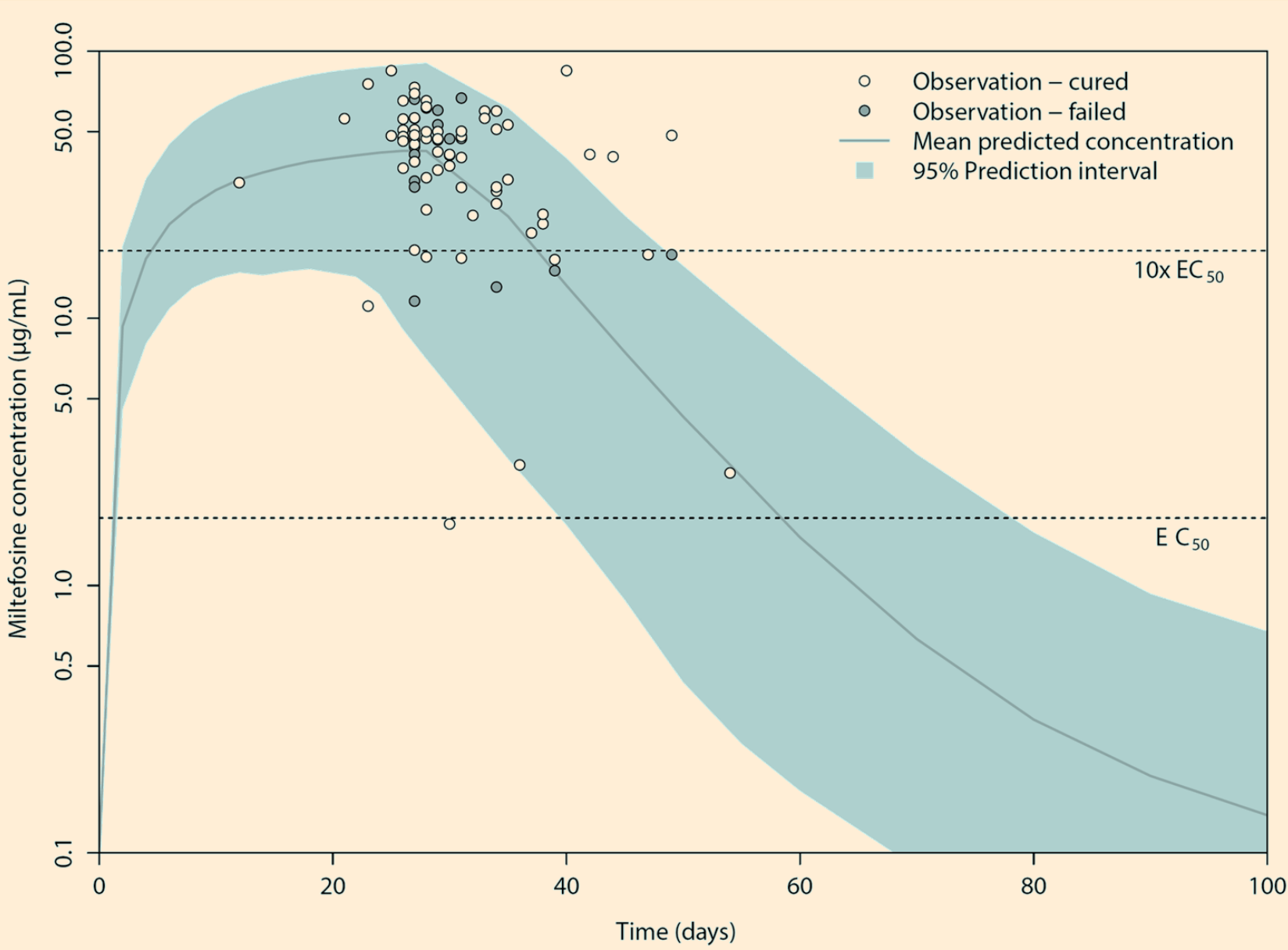
Methods

Single **sparse** blood samples were collected nominally at the end of treatment (EOT) and miltefosine concentrations in these samples were analyzed in our lab using LC-MS/MS. A **population PK-PD** analysis was performed in a sequential manner using non-linear mixed-effects modeling (NONMEM 7.2) and a logistic regression model for the binary treatment outcome (treatment failure vs. cure). Sparse data from Nepal was modeled **simultaneously** with three other miltefosine PK datasets from India and the Netherlands, using fat-free mass and allometric scaling [3,4]. The population PK model for miltefosine was used to derive several measures of individual drug exposure for the patients in the cohort, linked to ***in vitro* intracellular drug susceptibility** of the *Leishmania* clinical isolates from these Nepalese patients (e.g. C_{EOT}, AUC_{0-EOT}, AUC_{0-∞}, Time>EC₅₀, Time>10xEC₅₀). The following **logit-function for probability of failure (p_i)** was used, where *MIL* is the miltefosine exposure covariate centered around its population mean:

$$\text{Logit}_{p_i} = \ln\left(\frac{\text{BASE}}{1 - \text{BASE}}\right) + \theta \cdot (MIL_i - MIL_\mu)$$

Demographics

Parameter	Mean (95% CI)
No. of patients enrolled	81
Age (yrs)	22.9 (19.5 – 26.2)
No. of patients aged <12 yrs	20
Body weight (kg)	35.9 (32.9 – 39.0)
Body Mass Index (kg/m ²) ^a	17.9 (17.2 – 18.6)
No. of days of miltefosine treatment	29.3 (28.4 – 30.2)
Daily miltefosine dose (mg/kg/day)	2.4 (1.67 – 4)
- children (<12 yrs)	2.5 (1.67 – 3)
- adults (≥12 yrs)	2.4 (1.79 – 4)
No. of patients included in the PD analysis	76
No. of patients failed/cured	16/60



Visual predictive check of the final 2-compartment PK model for Nepalese EOT miltefosine concentrations; broken lines indicate the mean *in vitro* susceptibility parameters EC₅₀ and 10xEC₅₀. Open dots indicate observations from cured patients, filled dots from treatment failures.

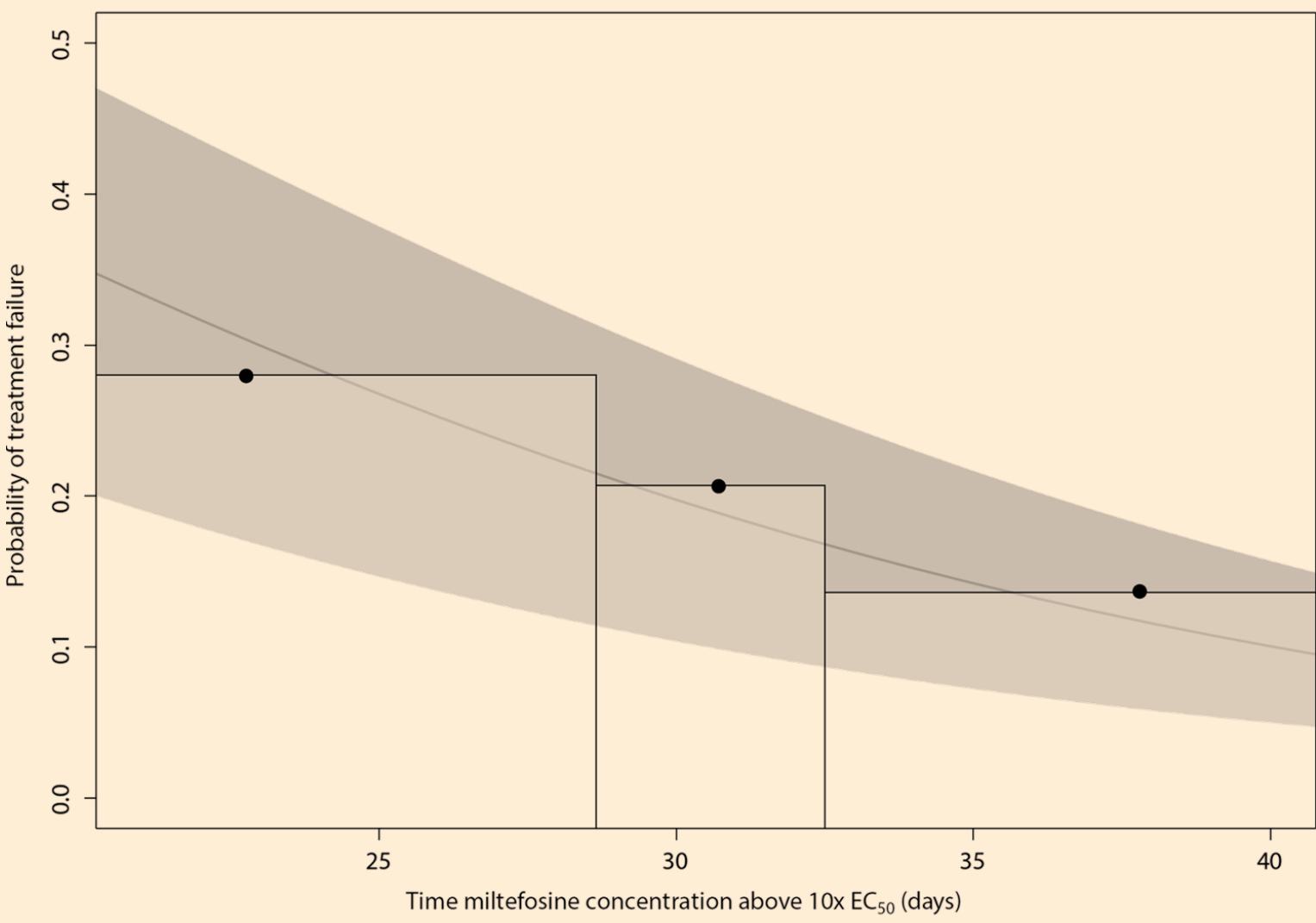
PK model parameters

Parameter	Estimate	Precision (RSE)	Between-subject variability
Absorption rate (/day)	9.6	Fixed	19.4%
Clearance/F (L/day)	3.69	3.4%	35.1% ^a
Q/F (L/day)	0.0316	16.6%	NE
Central volume/F (L)	38.5	4.5%	31.6% ^a
Peripheral volume/F (L)	1.69	8.6%	NE
Res. variability (%) ^b	24.5	36.4%	

^a BSV of CL and V_c were correlated by 87%.
^b Res. variability specifically for the Nepalese subset of data; separate res. variabilities were estimated for other datasets (unreported)

Results

A 2-compartment PK model was successfully fitted, with only modest shrinkage of η_{EBE}'s (14,5% & 34,5% for CL/F and V_c/F, resp.), given the extreme sparseness of the data. **Probability of miltefosine treatment failure** was 21% in our cohort of Nepalese VL patients. The **only significant PK risk factor** identified for treatment failure was **Time>10xEC₅₀** (mean 30.2 days), with an increased **odds ratio for treatment failure of 1.08** (95% CI 1.01-1.17, p=0,02) for each day decrease of Time>10xEC₅₀. As previously observed in Indian patients, we here confirmed that children are less exposed to miltefosine than adults while using the conventional 2.5 mg/kg/day miltefosine dose.



Probability of treatment failure
Mean **predicted probability** (solid line) and 95% CI (grey area) of **treatment failure** versus the time that miltefosine concentrations were above 10xEC₅₀. The dots indicate the mean *observed* probability per bin, with equal number of observations per bin (within the bars)

Conclusion

Treatment failure in Nepalese VL patients is significantly associated with the time miltefosine concentrations are above 10xEC₅₀. Evaluation of the recently proposed optimal allometric miltefosine dosing algorithm is therefore needed [4]. This study is the first step towards the definition of PK-PD targets to be attained in VL.