Pharmacokinetic-pharmacodynamic modelling of *Leishmania* blood parasite kinetics in visceral leishmaniasis patients

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Introduction

- To achieve long-term cure of visceral leishmaniasis (VL), sufficient parasite depletion during treatment, as well as adequate suppression of parasite regrowth by the host's immune system might be needed
- A more detailed understanding of the parasite dynamics is instrumental to identify risk factors for parasite recrudescence and clinical relapse
- Variable blood parasite plasma profiles were observed among patients (Figure 1), i.e., partial or complete initial parasite clearance during treatment, and variable regrowth after treatment, in some cases later suppressed, presumably caused by the host's immune system

Objectives

- To characterise parasite eradication by different VL therapies, as well as parasite proliferation and parasite suppression after treatment
- To evaluate haematological or parasitological markers associated with either parasite regrowth, parasite suppression, or clinical outcome

Methods

- Data originated from three clinical trials in which Eastern African VL patients received different VL therapies (Table 1)
- *Leishmania* kDNA was quantified with real-time quantitative PCR in whole blood samples during and up to 6 months after treatment[1]

An integrated PK-PD model was developed using NONMEM (v 7.3):

- PK-PD models (miltefosine [4] and fexinidazole and its active metabolites), and K-PD models (amphotericin B and SSG), were evaluated to induce drug-dependent killing of parasites
- To allow for parasite recrudescence after complete drug-induced parasite depletion, the parasite compartment was restricted to ≥1 parasite/mL
- The structural model parameters were estimated sequentially, by estimating 1) parasite proliferation, 2) drug-dependent parasite clearance during treatment, and 3) suppression of parasite growth after treatment
- Different parasitological and haematological markers were evaluated by a covariate analysis to explain the host's immune response

Table 1. Overview included studies

Study	Age	Treatment	N	N cured (%)
FEXI-VL-001 (NCT01980199)	adults	Fexinidazole 1800 mg (4 days), 1200 mg (6 days)	13	2 (15.4)
LEAP0208[2] (NCT01067443)	7-60 yrs	Amphotericin B 10 mg/kg (1 day) + SSG 20 mg/kg (10 days)	40	37 (92.5)
		Amphotericin B 10 mg/kg (1 day) + miltefosine 2.5 mg/kg (10 days)	44	37 (84.1)
		Miltefosine 2.5 mg/kg (28 days)	46	35 (76.1)
LEAP0714[3] (NCT02431143)	4-12 yrs	Miltefosine allometric dosing (ranging between 30 and 100 mg/day) (28 days)	29	27 (93.1)

Results

- Parasite proliferation was best described by an exponential growth model, with an *in vivo* parasite doubling time of 7.8 days
- Drug-dependent parasite killing was best described by first-order linear PK-PD models (fexinidazole and miltefosine[4]) or K-PD models (amphotericin B and SSG) (Figure 2)
- Parasite growth was suppressed by k_{imm}, a first-order elimination process, representing the onset and magnitude of parasite suppression by the host's immune system after start of treatment

Figure 1. Typical parasite profiles in a selection of patients. Dots: observations. Solid green line: population predictions. Dashed green line: individual predictions. Dashed grey line: end of treatment

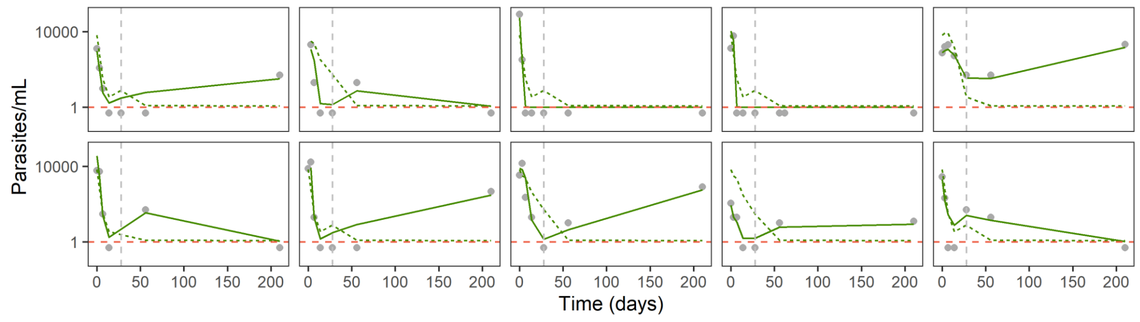


Table 2. PD parameter estimates in the final population PK-PD model

Parameter	Typical value	RSE (%)	BSV (CV%)	RSE (%)	Shrinkage (%)
E_{BASE} (p/mL)	3650	18	247.4	7	7
k_{GR} (h^{-1})	0.0037	8	-	-	-
λ_{fexi} ($\mu g^{-1}*L*h^{-1}$)	0.0011	27	44.2	44	3
λ_{MF} ($\mu g^{-1}*L*h^{-1}$)	0.0009	0	123.7	8	33
λ_{Amb} ($mg^{-1}*kg*h^{-1}$)	0.0114	22	146.6	19	51
λ_{SSG} ($mg^{-1}*kg*h^{-1}$)	0.0145 (fixed)[a]	-	66 (fixed)[a]	-	61
$E_{max,IMM}$ (h^{-1})	0.0239	0	400	20	62
$EC_{50,IMM}$ (h)	906	0	205.2	13	52
Proportional residual error (var)	-	-	77.7	0	16
Additive residual error (var)	-	-	70.7 (fixed)[b]	-	16

A_{Amb}: Amphotericin B dose (mg/kg) * k_e (0.1155 h^{-1}); A_{SSG}: SSG dose (mg/kg) * k_e (0.3465 h^{-1}); BSV: between-subject variability; C_{fexi}: summed concentration of the active metabolites fexinidazole sulfoxide and fexinidazole sulfone; CMF: miltefosine concentration; CV: coefficient of variation; E_{BASE}: Baseline blood parasite load; $E_{max,IMM}$: maximum inhibition by immune response; $EC_{50,IMM}$: time at half-maximum inhibition; k_{GR}: parasite growth constant; λ_{Amb}: linear drug effect Amphotericin B; λ_{fexi}: linear drug effect fexinidazole; λ_{MF}: linear drug effect miltefosine; λ_{SSG}: linear drug effect SSG; RSE: relative standard error; Time: time after start of treatment (hours)

[a]Fixed because of model instability

[b]Fixed to half the lower limit of quantification

Figure 2. Schematic of the PK-PD model

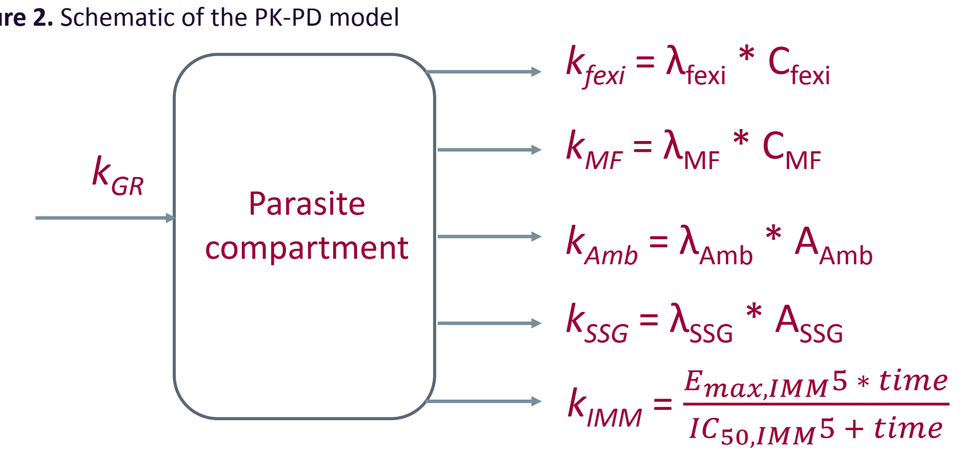
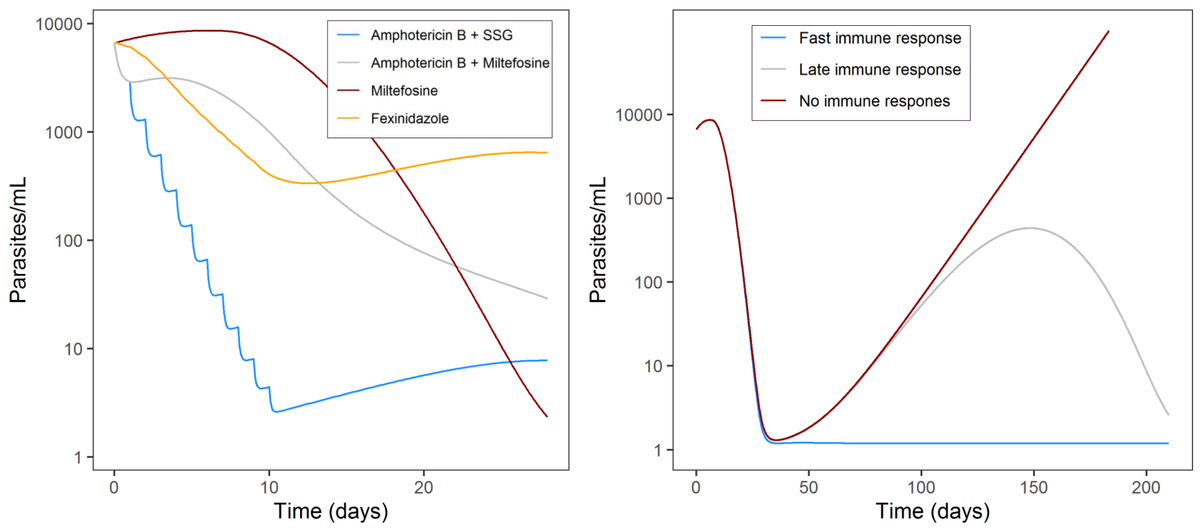


Figure 3. Simulations of parasite suppression in a typical patient by different drug effects during treatment (left), and by different immune responses after treatment (right)



Conclusions

- This is the first semi-mechanistic PK-PD model of *Leishmania* parasite kinetics in VL, which provides insight into the *in vivo* parasite growth rate and parasite clearance rates by different drugs
- Future work will be focused on model stabilization, and evaluation of markers to predict parasite response or clinical outcome, which could not yet be identified

References:
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Disclosure

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