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### Clinical pharmacology in leishmaniasis: treatment optimization of a neglected disease

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CHAPTER 6  
**CONCLUSIONS &  
PERSPECTIVES**



## Conclusions and perspectives

Leishmaniasis remains one of the world's most devastating neglected tropical diseases, with an estimated 2 million new cases of infection per year resulting in approximately 50,000 deaths annually [1]. Sadly, the available treatment options for this parasitic disease have only marginally improved within the past century: the mainstay of treatment still consists of toxic antimony-compounds; 'newer' treatment options such as (liposomal) amphotericin B and miltefosine are often out of reach for the patients most in need. These treatment regimens urgently require further evaluation and optimization. Unlike malaria, leishmaniasis has largely been neglected by clinical pharmacologists and this thesis is the first work in this field of research. The studies presented in this thesis aim at further optimization and rationalization of miltefosine therapy for both cutaneous (CL) and visceral leishmaniasis (VL), with an emphasis on the clinical application of population pharmacokinetics and pharmacodynamics, the evaluation and establishment of novel pharmacodynamic measures and the impact of poor-quality medicines and guidelines. The most salient conclusions of this thesis are discussed here, presented in a broader context of the use and application of clinical pharmacology in the development and optimization of drug therapies for CL, VL and other neglected tropical diseases.

### Pharmacokinetics

Pharmacometrics, or the science of quantitative clinical pharmacology [2], plays an increasingly important role in the optimization of the clinical use of medicines. Tropical medical research is often tormented by non-optimal clinical trials performed in resource-constrained settings in arduous circumstances. Certainly under these conditions, pharmacometrics can be a great asset in the eventual analysis of collected pharmacokinetic data to explore rational treatment regimens and drug exposure-response relationships or rather can provide rational predictions thereof when data are unavailable. This potential of pharmacometrics is demonstrated in this thesis, for instance in chapters 3.2 and 4.3 for which we were only able to collect sparse pharmacokinetic data from India and Nepal or in chapter 3.3 in which the power and translational value of modeling and simulation are demonstrated in an instance where it was plainly impossible to collect data. In this thesis we focused specifically on the pharmacokinetics of miltefosine. Miltefosine has been in experimental use for the treatment of VL since the mid-1990s and was eventually licensed for this specific indication in 2002, in India, which is described in the review in chapter 1.1. Historically, very limited dose-finding studies were performed for the treatment of VL, all in Indian patients, with little attempt to establish an exposure-effect relationship or to accurately describe its pharmacokinetics and the most important covariates influencing it. When the Dutch military force was confronted with an outbreak of CL among their troops in Afghanistan, miltefosine was chosen as the treatment of choice. Little was known how to extrapolate the dosage used for

malnourished Indian VL patients to relatively healthy and much larger Dutch CL patients. To this end a bioanalytical assay was developed and validated (chapter 2.1), samples were collected and a population pharmacokinetic study was undertaken to fully characterize the pharmacokinetics of miltefosine, described in chapter 3.1. This population analysis revealed that miltefosine was eliminated much slower from the body than previously thought and expected, with a terminal elimination half-life of 31 days, resulting in detectable levels of miltefosine up to at least 6 months after end of therapy. The expected impact of these findings on emergence of drug resistance and contraceptive protection for this teratogenic drug has been discussed in this thesis.

The clinical drug development of miltefosine for the treatment of leishmaniasis was performed within a public-private partnership. Nevertheless, this unique development and registration process suffered from several shortcomings and led to various issues remaining to be addressed [3]. Although our first population pharmacokinetic study of miltefosine was of exploratory nature, mainly because of the scarcity of data on this particular topic, further studies were designed based on these results to further explore various imminent issues in the treatment of leishmaniasis with miltefosine. Pediatric patients make up more than 50% of all VL and CL patients, but typically little attention was attributed to this vulnerable group during the clinical drug development phase of miltefosine, mainly due to ethical and practical constraints. In chapter 3.2, we demonstrate that children are currently relatively underexposed compared to adults using the same mg/kg body weight dose. This was investigated by making use of the only scarce pharmacokinetic data available for pediatric patients from India and a population pharmacokinetic analysis approach. A new optimal allometric dose was proposed, which will probably improve clinical outcome in these pediatric patients. The clinical appropriateness of allometric dosing, instead of linear dosing based on mg/kg, is firmly rooted in the biological principles supporting it and is increasingly adopted in the drug development process, specifically in the design of first-in-human and pediatric studies [4,5].

Using pharmacometrics, another imminent and relevant problem related to miltefosine's toxicity profile was further investigated: the recommended duration of contraceptive cover after the last dose of miltefosine. Based on reproductive toxicity studies in animals, miltefosine is most probably teratogenic and therefore pregnancy is a strong contraindication and women of childbearing potential require contraception during but also after treatment. The appropriate duration of contraception remained a topic of debate since miltefosine's introduction. Also for the newly proposed shorter combination regimens containing miltefosine, it was unknown how long contraception should be reasonably provided. Based on a large anthropometric dataset of Indian VL patients, the reported dose-levels showing (no) reproductive toxicity in animals, and population pharmacokinetic model-based simulations, rational yet conservative periods of contraception after various different miltefosine regimens were recommended. Following our recommendations, duration

of post-treatment contraception should be extended from the currently advised 2 months to 4 months after a 28-day miltefosine treatment course. This last finding has important implications for the rollout of miltefosine but also stipulates the need for implementation of shorter combination treatment regimens. The novel translational approach to provide recommendations for duration of contraception duration for women based on preclinical reproductive toxicity studies in animals, described in chapter 3.3, may be methodologically generalized to the drug development of other teratogenic drugs.

Pharmacokinetics is often neglected in tropical medicine research and during the development of drugs for tropical diseases, due to for instance the difficulties of collecting samples or plainly the local unavailability of the equipment needed to analyze the samples. As shown in various chapters in this thesis, in such instances a population pharmacokinetic modeling approach can be an extremely powerful tool either to make use of the sparsely collected data or on the other hand to provide rational assumptions based on state-of-the-art model-based simulations to provide a solution to important outstanding clinical issues.

## Pharmacodynamics

In leishmaniasis, final cure is typically evaluated by following patients for several months after end of therapy to verify whether parasite biomass, and thus clinical symptoms, do return (i.e. relapse of disease) or will permanently subside. This clinical algorithm is far from ideal to compare drug efficacy and effectiveness: a myriad of factors is influencing the processes leading to eventual relapse of disease which may not (all) be influenced by the drug under investigation. Moreover, this elaborate and demanding process of long-term follow-up visits is difficult to maintain under routine conditions for both the patient as well as the health system. This results in a high proportion of patients who get lost to follow-up, certainly in the typical VL settings where access to care is limited by geographical distances and patients need to travel long distances to reach the health center.

Assessment and comparison of drug efficacy for antileishmanial treatments is especially relevant since there is renewed public interest and substantial efforts are being made to discover and develop drugs for neglected tropical diseases through various public-private partnerships, for instance through OneWorldHealth and the Drugs for Neglected Diseases initiative (DNDi) [6]. All these efforts stand or fall with the possibility and availability of a good, and objective, measure of clinical efficacy of the drugs. On another note but in a similar context is the clinical relevance of emergence of drug-resistant parasites in the field. Antimony resistance or non-susceptibility is already rampant in large parts of the VL endemic areas in India. But also for miltefosine drug-resistance is looming: parasite clones were easily induced *in vitro* to express resistance and emergence of resistant clones in endemic areas is feared, certainly in areas where there is mainly anthroponotic transmission of disease. However, the detection of the emergence of resistance remains cumbersome

and difficult to interpret: *Leishmania* parasites are genetically highly heterogeneous and known genetic markers of resistance from *in vitro* studies have not been identified *in vivo* yet despite observed reduced susceptibility of some clinical isolates. Also the aspect of emerging resistance is currently monitored by and extrapolated from increasing failure rates or relapse rates of VL in the field within six months after end of treatment.

For both of these outstanding issues – (1) comparison of (new) treatment regimens and (2) early detection of emerging drug resistance – pharmacodynamic markers of disease, permitting the monitoring and capturing of the early response to treatment in a (population of) patient(s), are needed. In chapter 4.4 the first overview is provided of an inventory of plausible and available tools that might be useful as pharmacodynamic markers in CL and VL. Also, we propose a benchmark for the required specifications of biomarkers which would allow their pharmacodynamic application in VL or CL. Unfortunately, as is the case for so many aspects of pathophysiology and pharmacology in leishmaniasis, little effort has been made till date to evaluate the pharmacodynamic potential of several of these potential markers in relation to the clinical efficacy of treatment regimens for both VL and CL. It will be pivotal for the leishmaniasis drug development pipeline to further investigate useful pharmacodynamic markers to be able to fully characterize and compare exposure-response relationships of existing drugs and those currently still in the pipeline. In this thesis, we focused on the use of a direct assessment of the parasite biomass in skin lesions of patients (CL; chapter 4.1) and in blood (VL; chapter 4.2) using a specific quantitative polymerase chain reaction (qPCR). For VL, blood is not the main target site of action of drugs and may even be regarded as a so-called ‘proxy’ site only, since parasites mainly reside and replicate within bone marrow, spleen and other viscera. Although patient numbers were small and sensitivity of the assay appears not very high in East African VL patients, the blood parasite biomass in terms of *Leishmania* rRNA reduced rapidly after initiation of treatment in those patients with a detectable parasite load in blood at initiation of treatment. In this particular chapter we compared two different treatment schedules of liposomal amphotericin B (a single dose versus a multiple dose schedule). The unexpected large observed difference in initial cure rates, which led to early discontinuation of this trial, correlated significantly with the observed differences in parasite clearance rates between the two treatment arms. Despite the small numbers, this first attempt at establishing a pharmacodynamic measure in leishmaniasis has led to the implementation of this qPCR methodology in various clinical trials on VL currently ongoing in East Africa. First results of these trials, including a pharmacokinetic-pharmacodynamic analysis are expected to be reported early 2013. Additionally, a proof-of-principle study is described in this thesis in which we assessed the dynamics of parasite clearance in CL skin lesions using a repetitive biopsy approach (chapter 4.1). Parasite clearance was successfully assessed in this manner and proofed a relevant addition to the subjective clinical assessment of the



lesions. It provided not only an estimate of the rate of parasite clearance, it also demonstrated that parasites remain in the lesions still after the end of miltefosine treatment, corresponding with a relatively slow clinical response. The exact role of this approach in the evaluation of new treatment options for CL requires further evaluation, which may be complicated by the invasiveness of this biopsy approach. Pharmacokinetics and -dynamics can be regarded as one of the major gaps still existing in research and development (R&D) for new drugs to treat neglected tropical diseases. Fortunately, this gap has been recognized both by the R&D organizations which are thriving the development of these new drugs, but also by international regulatory organizations and the scientific community. As exemplified in this thesis, evaluation of pharmacokinetics and -dynamics should be prioritized during drug development for neglected tropical diseases, particularly in rare and vulnerable populations, to help rationalize and optimize both dose regimens and informed clinical risk management.

### **Impact of the quality of medicines**

Access to medicines for neglected tropical diseases is a complicated and intricate topic with various challenges: on the one hand there is high cost of the available treatments and on the other hand there is the plain absence of appropriate treatments that affect patients in resource-limited countries, as shortly discussed above. To further complicate issues, manufacturers of medicines for tropical neglected diseases often cease or interrupt production or the products that need to be used are labelled for other indications, leading to confusion in guidelines and dose recommendations, as we have shown for pentamidine in chapter 5.5. The high costs of available treatments in combination with, among others, the often complete lack of drug regulatory oversight in the affected countries, have led to a situation of multiple quality standards. This opened the way for poor-quality medicines – but also medical devices and diagnostics – to become particularly prevalent in low- and middle-income countries. Poor-quality medicines can be counterfeit and/or substandard, which is, again, a complicated discussion on terminology and inadequate definitions further described in chapters 5.3 and 5.4. To date, concerted international actions have mainly focused on tackling and detecting counterfeits and have largely neglected the (structural) production and distribution of substandards in poorly regulated countries. Tragically, poor quality medicines in poorly regulated countries are typically only detected after they have caused severe morbidity and mortality. We described such a discovery and its aftermath concerning a ‘miltefosine’ medicine not containing any miltefosine in Bangladesh in chapter 5.2. For this purpose, a state-of-the-art platform of chemical analytical techniques was developed to identify counterfeit or substandard miltefosine capsules (chapter 5.1), including a rapid simple color test which can be easily used at the level of primary health care facilities. Nevertheless, despite our own efforts in this direction, the problem of poor quality drugs, certainly substandards, cannot be solely and sustainably

solved with these *post hoc* detection techniques – often only deployed long after the damage has already been done. As we have proposed in chapter 5.3, more extensive remedial measures should be put in place to prevent the (structural) production of substandards, negligence of quality standards and the existence of multiple quality standards. It is expected that a very recently instituted member-state mechanism of the World Health Assembly may finally take care of these urgently needed measures, putting back the emphasis on protection of public health and patients instead of intellectual property. Instead of *a posteriori* detection, *a priori* solutions to prevent poor-quality medicines should be prioritized.

Concluding, this thesis presents various novel applications of clinical pharmacokinetics and pharmacodynamics in the treatment of CL and VL, by which diverse clinically relevant issues, mainly related to the efficacy and safety of miltefosine, could be elucidated. Throughout this thesis, the added value of population modeling and simulation in clinical pharmacology has been exemplified, for instance by making full use of sparse datasets, translational preclinical-to-clinical extrapolation of toxicity and drug exposure, and design and *in silico* evaluation of optimal dosing regimens specifically aimed at pediatric populations. Whereas pharmacokinetics and pharmacodynamics are often marginalized or even neglected in the (pre)clinical development process of drugs for neglected diseases, due to various practical constraints, we here demonstrated that population-based modeling is an elegant and very effective way of analysis when there is limited data available on exposure and response. Furthermore, in this thesis we solved various critical issues which enabled further optimization of miltefosine in the treatment of leishmaniasis, pertaining for instance to the optimal dosage in children and adults, identification of poor quality miltefosine capsules, safety (the required duration of contraceptive protection) and efficacy (parasite clearance dynamics and the probability of relapse).

Future clinical trials in leishmaniasis should aim to incorporate both pharmacokinetics and pharmacodynamics to further rationalize treatment comparison and allow for the establishment of exposure-response relationships, which may not only differ geographically between the highly heterogeneous populations affected by leishmaniasis (host factor), but also between the diverse causative *Leishmania* species (parasite factor). New drugs for both CL and VL are urgently needed, since none of the currently available treatments is optimal or affordable. The future development of new treatment modalities currently in the drug development pipeline for leishmaniasis, such as fexinidazole and a range of combination therapy strategies, can only be successful when exposure and response are accurately characterized and compared to the currently available treatments. Patient-friendly and non-invasive ways of sampling should be developed and employed to allow these pharmacological studies in the most vulnerable patients in resource-constrained settings. Available simulation techniques should be used as much as possible prior to initiation of clinical trials to bridge prior (pre)clinical data to the clinical reality. As such, clinical pharmacology and the application of

pharmacometrics cannot longer be ignored in the current major momentum of efforts to forward the development of drugs for neglected tropical diseases.

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