Clinical pharmacology in leishmaniasis: treatment optimization of a neglected disease
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PREFACE
Preface

“I hope that the interest which must always attach to the discovery of new parasites of man will suffice to excuse me for adding yet another paper on this subject to those already contributed on this subject by Leishman, Donovan, Laveran, and myself”

Sir Ronald Ross (1857-1932) in the British Medical Journal of November 28th 1903

Over a century ago, the dispute regarding a newly discovered parasite causing disease in man was settled by the revered Nobel Prize laureate Sir Ronald Ross by naming it after its concurrent discoverers Lt. Gen. Leishman and Col. Donovan: *Leishmania donovani* [1]. The tropical infection that is caused by these parasites was then known by the Sanskrit or Hindi term *kala-azar*, which translates as *black* or *fatal fever*, and was feared for its devastating epidemics in the last decades of the 19th century which decimated the populations of Assam and Bihar states of India. *Leishmania* parasites occur in tropical regions worldwide - from the Indian subcontinent to East Africa and Latin America - and are transmitted from human and animal reservoirs back to human by minuscule sand flies. They come in a multitude of species complexes and are not only the cause of a fatal infection of the inner viscera (hence *visceral leishmaniasis*; VL), but can also result in stigmatizing skin lesions known as *cutaneous leishmaniasis* (CL). Leishmaniasis is still a major burden of disease and accounts for over 50,000 deaths per year, which makes it after malaria the second largest killer of all parasitic diseases [2]. It affects the poorest of the poor and is regarded as a neglected tropical disease, mainly because the options to treat these vulnerable patients have only very marginally changed since its discovery more than a century ago by Ross, Leishman and Donovan. Toxic compounds containing the metal element antimony are still the mainstay of treatment. The antimony-containing drugs require elaborate series of injections and have been in use to treat leishmaniasis as early as 1913 [3]. These compounds are far away from the desired antiparasitic ‘magic bullet’ (*Zauberkugel*) proposed by Paul Ehrlich: they do not selectively kill the parasite, but are very toxic to the patient as well. Only a decade ago, in 2002, miltefosine, the long-awaited first oral drug to treat leishmaniasis, became available to VL patients in India. With its reasonable toxicity profile and the easy oral route of administration, miltefosine was a highly valued addition to the available repertory of antileishmanial drugs.

This thesis, “yet another paper” on the subject of leishmaniasis, focuses on various significant pharmacological aspects of the drug miltefosine which merited further scientific investigations. Miltefosine was originally developed as an anticancer drug, after which the activity of miltefosine against *Leishmania* parasites was only discovered by serendipity. As an introduction to this thesis, a comprehensive overview of the history, pharmacological aspects and therapeutic safety and efficacy of miltefosine in the treatment of visceral and cutaneous leishmaniasis is presented in chapter 1.1. Measuring miltefosine drug concentrations in patient materials
is one of the pivotal basic research methodologies used throughout this thesis, in chapter 2.1 the development and validation of a bioanalytical method using state-of-the-art liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) equipment used for the quantification of miltefosine in biological matrices is described.

Chapter 3 focuses on miltefosine drug exposure (or pharmacokinetics) in leishmaniasis patients. In chapter 3.1 miltefosine drug exposure in patients was investigated for the first time, making use of population pharmacokinetic modeling, performed in a cohort of Dutch soldiers who were treated with miltefosine for CL contracted in Afghanistan. In chapter 3.2 a more optimal dosing algorithm for miltefosine is proposed, using population modeling and simulation of miltefosine pharmacokinetic observations in Indian children, Indian adults and European adults. The main safety concern for miltefosine is its possible reproductive toxicity to fetus and embryo, which severely comprises its use in women. Little is known about the periods of contraceptive cover required in women of child-bearing potential. In chapter 3.3 a novel translational method is discussed to estimate how long contraception should be provided to prevent any reproductive toxicity after various miltefosine treatment regimens.

Chapter 4 focuses on the effects of miltefosine (or pharmacodynamics) in leishmaniasis patients. Parasites are quantified in biopsies of skin lesions of European cutaneous leishmaniasis patients (chapter 4.1) and in blood of visceral leishmaniasis patients in East Africa (chapter 4.2), to describe the dynamics of parasite clearance in patients. Furthermore, a first attempt to investigate the concentration-effect relationship of miltefosine is provided in chapter 4.3, in which the correlation between miltefosine exposure and high treatment failure rates in Nepalese VL patients is studied in depth. This chapter ends with an overview and benchmark of possible pharmacodynamic biomarkers which could be used in clinical trials to better and earlier assess treatment outcome (chapter 4.4).

Chapters 3 and 4 collectively discuss the optimization of treatment of patients suffering from leishmaniasis from a pharmacokinetic and pharmacodynamic perspective to increase individual efficacy and safety of the drug. Optimization of therapy is only of use when patients suffering from tropical diseases have access to medicines - of good quality - to treat their fatal diseases, which is certainly not always the case. Sadly these vulnerable patients are confronted with an additional fatal scourge: fake and bad quality medicines. Chapter 5 discusses the impact of spurious and poor quality medicines specifically in the treatment of neglected tropical diseases. The discovery of ‘miltefosine capsules’ not containing any miltefosine in Bangladesh is elaborately described in chapter 5.2, in response to which a comprehensive platform of analytical chemistry methods, including a simple and rapid color test, was developed for the identification of miltefosine in pharmaceutical formulations (chapter 5.1). In chapters 5.3 and 5.4, issues relating to the current definitions of poor quality drugs and corresponding remedial measures are further critically discussed with a focus on drugs used in the treatment of leishmaniasis and other neglected
tropical diseases.

Altogether, this thesis presents a broad collection of clinical pharmacological investigations mainly related to the drug miltefosine in the treatment of leishmaniasis, with the overall aim to further rationalize and optimize the treatment of this neglected tropical disease.

References