

## SUMMARY

Leishmaniasis is a disease affecting predominantly people in the developing countries; 350 million people worldwide are at risk and yearly more than 2 million new cases occur. Leishmaniasis is caused by protozoan parasites of the genus *Leishmania* which are transmitted by the bite of the infected female sand flies. In general, leishmaniasis is a zoonotic infection (i.e. transmitted from non-human mammals to humans, not between humans). Only under extreme conditions it can be transmitted between humans (anthroponotic transmission). The infection with *Leishmania* parasites may result in three clinical syndromes depending of the infecting species, and the host immunity:

- Visceral leishmaniasis a generalized disease in which different internal organs e.g. liver, spleen, bone marrow and lymph system may be infected;
- Cutaneous leishmaniasis with only skin involvement: single to multiple skin ulcers, satellite lesions and nodular lymphangitis.
- Mucocutaneous leishmaniasis, the cutaneous form with metastasis to mucous and cartilage tissues of mouth and upper respiratory tract causing extensive destruction.

Around 20 *Leishmania* parasites are known to cause disease in man. The species are divided in two subgenera; *Leishmania* and *Viannia*. The *Leishmania* is present in the Old and New World and *Viannia* is restricted to the New World. The vector, the sand fly usually belongs to the genus *Lutzomyia* or *Phlebotomus*.

In Suriname the main causative species is the *Leishmania Viannia guyanensis*. This species causes mainly cutaneous leishmaniasis and sporadic mucocutaneous leishmaniasis (MCL). Reservoirs are probably mammals living in the forested interior e.g. sloths, ant-eaters and rodents. Cutaneous leishmaniasis is endemic in Suriname and incidence of 0.66

per 1000 inhabitants has been reported from 1979-1985. At present the figures are probably higher since the last decade the economic activities in the hinterlands of Suriname has grown. Gold digging, logging and eco-tourism are activities which have increased and persons who participate in these activities are at risk for acquiring cutaneous leishmaniasis. At present there are no vaccines or prophylactic drugs available for leishmaniasis. Protection against the vector (via the use of insect repellents and covering clothing) is the only form of prevention available against this vector borne disease but this often fails. Therefore early diagnosis and treatment is important. Pentamidine isethionate is the only available drug in Suriname for cutaneous leishmaniasis. It has been used since 1994. Current cure entails a standard treatment of 3 intramuscular injections of 300mg pentamidine (salt) per injection every 3 days (over a period of 7days total). Recently in standard clinical practice more patients with therapy failure after the three IM injections of 300 mg pentamidine are seen. Reasons for this might be that *Leishmania* species exists in Suriname which are less sensitive to pentamidine, patients receiving a sub therapeutic dose of pentamidine or incomplete treatment. The compliance to treatment is rather low. Patients frequently return to the forest without taking the full course of pentamidine often because of financial reasons.

This thesis reports the evaluation of the standard treatment of cutaneous leishmaniasis, three intramuscular injections of 4mg/kg (salt) pentamidine in 7 days (day 1, 4 and 7) compared to the shorter treatment of two intramuscular injections of 7mg/kg (salt) pentamidine in 3 days (day 1 and 3), the PELESU study (**PE**ntamidine isethionate regimen for cutaneous **LE**ishmaniasis in **SU**riname) (chapter 2). The cost-effectiveness of the standard treatment and the short treatment are presented in chapter 3. The impact of the body location of lesions on the health related quality of life of patients with cutaneous leishmaniasis is presented in chapter 4. Lastly the identification of a new leishmaniasis causing species is described with implications for clinicians (chapter 5).

**Chapter 1.** An introduction of the thesis is presented in this chapter. Epidemiology, clinical aspects, diagnostic procedures and treatment of cutaneous leishmaniasis are presented. The epidemiology and current treatment of cutaneous leishmaniasis in Suriname are discussed.

**Chapter 2** describes the results of the PELESU study: the clinical, parasitological and pharmaco-economical evaluation of a short (3 days) versus standard (7 days) pentamidine isethionate regimen for cutaneous leishmaniasis in Suriname, a randomized non-inferiority trial. Clinical- and parasitological cure of cutaneous leishmaniasis lesions, patients reported side effects and clinically determined drug related toxicity events and health related quality of life regarding patients in the PELESU study are described. Eligible patients with cutaneous leishmaniasis were randomized in one of the two treatment arms: short regimen pentamidine, two IM injections of 7mg/kg in 3 days and standard regimen pentamidine, three IM injections 4mg/kg in 7 days, in this non-inferiority study. One hundred sixty three patients were included, 84 in the standard regimen and 79 in the short regimen. Patients were evaluated during treatment and follow up (1 week, 6 weeks and 12 weeks after treatment) visits. Primary objective was to evaluate if a short pentamidine regimen is non-inferior compared to the standard pentamidine regimen with respect to clinical cure 6 weeks after the end of treatment. The secondary objective of the study was to establish whether a short pentamidine regimen is non-inferior compared to the standard pentamidine regimen with respect to clinical cure at 12 weeks and parasitological cure at 6 and 12 weeks, adverse events and drug related toxicity events recorded one week after the end of treatment. Furthermore, we assessed if a short regimen of pentamidine affects quality of life equally compared to the standard regimen of pentamidine before the first injection and 6 weeks after the end of treatment. The number of lost to follow up patients was very high, at 6 weeks 18% (15/84) and 33% (26/79), in the 7 days and 3 days regimen respectively. The numbers of lost to follow up at the end of the study (12 weeks after treatment) were 30% (25/84) and 38% (30/79). Six weeks

after end of treatment 39% (31/79) individuals in the intervention group and 49% (41/84) individuals in the control group were cured as based on the clinical pictures (ITT analysis). When only including those patients who attended the visits in our study (PP analysis), clinical cure rate at 6 weeks were 58% (31/53) in the 3 days and 59% (41/69) in the 7 days regimen. Parasitological cure rates were slightly higher than the clinical cure rates. Based on this study we cannot conclude that the 3 days regimen is not worse (non-inferior) to the 7 days regimen in clinical and parasitological cure at 6 weeks and 12 weeks follow up. Nausea, fever, taste changes, swelling at injection site and the presence of other side effects were more frequent in 3 days regimen. Furthermore, hemolysis, nephrotoxicity, pancreas toxicity appeared to be more frequent in the 3 days regimen. Regarding subjective side effects and laboratory toxicity events it cannot be concluded that the short regimen is non-inferior to standard regimen for in the short regimen there were more side effects and toxicity events than in the standard regimen. The present study assessed the health related quality of life (HRQL) using the Skindex-29 and EQ-5D/VAS. Our results showed an impairment in HRQL in both treatment regimens which was improved 6 weeks after treatment. Before treatment and 6 weeks after treatment there were no statistical significant differences between the two treatment regimens. The high number of lost to follow up patients might have biased the outcome of present study. If most patient returned for follow up the outcome might have been that the short treatment was non-inferior to the standard treatment. Therefore in future studies special attention should be paid to minimization of lost to follow up

**Chapter 3** presents the results of the cost-effectiveness analysis (CEA) of the short (3 days) treatment and the standard (7 days) treatment of the PELESU study. The cost-effectiveness of both treatments was estimated. Cost-effectiveness was expressed as cost per patient treated and cured at 6 and 12 weeks by using provider and patient cost data. The DALY (disability-adjusted life year) averted was also assessed. Cost per patient treated and cured at 6 weeks was calculated to be US\$295,42

for the 7 standard and \$241,40 for the short treatment. Cost per DALY averted in the standard arm was \$12.844,44 versus \$10.495,67 in the short treatment arm. At the end of the study on 12 weeks after treatment the cost per patient treated and cured was \$269,16 for the standard versus \$202,25 for the short treatment arm. Cost per DALY averted was \$11.702,71 in the standard versus \$8.793,67 in the short treatment. The results from the PELESU study indicate that the shorter treatment regimen of two injections of pentamidine is more cost-effective than the standard treatment regime of three injections of pentamidine. Although the short treatment was found to be associated with higher direct costs for patients, the short treatment was found to be less costly from a provider perspective and also resulted in large indirect cost savings for patients. Additionally, the short treatment resulted in a lower cost per patient treated and cured as well as a lower cost per DALY averted. A weak point in the present study is the high number of loss to follow up patients. Assuming all patients lost to follow up were cured further lowers the cost per DALY averted of the short treatment to below the GDP per capita of Suriname, making it a highly cost-effective intervention. It is not possible to compare the current findings with other cutaneous leishmaniasis endemic areas where pentamidine is used for the treatment of cutaneous leishmaniasis. Very little is published on CEA in cutaneous leishmaniasis treatment and more CEA studies should be done.

**Chapter 4** reports the effect of the body localization of cutaneous leishmaniasis lesions on the patient's health related quality of life (HRQL). This is the first study which uses Skindex-29 and EQ-5D/VAS as measurements for HRQL in cutaneous leishmaniasis patients. One hundred sixty three patients of the PELESU study were assessed with Skindex-29 and EQ-5D/VAS questionnaires before the first treatment was given. Out of these, 46 patients also participated in a qualitative anthropologic study involving in depth interviews. All patients were allocated in 4 groups: head and face, upper limbs, lower limbs and trunk. Patients with lesions on the lower limbs have significant higher

Skindex-29 scores in the symptom scale compared to lesion on head/face and trunk. The lower limb group was more likely to report problems in the dimensions self-care, mobility, usual activities and pain/discomfort of the EQ-5D. Women had lower HRQL than men; in female participants the Skindex-29 scales emotions, functioning and overall were significantly higher, they were more likely to report problems in the EQ-5D dimension pain/discomfort and the EQ VAS score was significantly lower. In conclusion, the location of cutaneous leishmaniasis lesions in Suriname on the lower limbs is significantly associated with a lower HRQL compared to lesions on the head/face, trunk and upper limbs. In general the finding of the study suggests that cutaneous leishmaniasis patients were not stigmatized because of their illness. Studies performed in other cutaneous leishmaniasis endemic areas are needed to evaluate the effects of the body localization of cutaneous leishmaniasis on the HRQL of patients. The use of Skindex-29 and EQ-5D should be considered as tools for outcome measure for HRQL in cutaneous leishmaniasis.

**Chapter 5** presents a case report, the first case of cutaneous leishmaniasis caused by *L. (V.) braziliensis* in Suriname. The patient in whom the *L. braziliensis* was detected was included in the PELESU study on January 2010. He presented with three ulcers, one on his left nostril and two on his right lower arm, which he acquired after a hunting trip to West-Suriname. No apparent mucosal lesions were noticed. Species identification (PCR-RFLP and sequence based techniques) performed on a skin biopsy of the ulcer on the lower arm revealed *L. braziliensis*. The patient was cured after receiving two intramuscular injections of 7 mg/kg pentamidine. The patient did not return after the trial and could not be traced after completion of the study. This case indicates that *L. braziliensis* species are present in Suriname. Cutaneous leishmaniasis lesions showing failure of cure after pentamidine treatment could be due to infection with *L. braziliensis* and mucocutaneous leishmaniasis may develop in patients infected with *L. braziliensis*. Therefore clinicians should be alert. Further investigation

and species identification should be performed for patients who show treatment failure to the standard pentamidine regime.