Treatment of cutaneous leishmaniasis with pentamidine isethionate in Suriname; a comparison study between two treatment regimes, 3 days vs 7 days.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23868

Source
Nationaal Trial Register

Brief title
N/A

Health condition

The disease leishmaniasis, caused by protozoan Leishmania parasites and transmitted via infected
female sandflies and reservoir hosts is endemic in 88 countries and 350 million people are at risk. Leishmaniasis prevalence is >12 million cases/year and the incidence is >2.5 million cases/year. The estimated disease burden is 2.4 million DALYs. Leishmaniasis is a category 1 disease (Emerging or uncontrolled diseases) and the World Health Organization (WHO) has acknowledged it as a severely neglected disease and urged intensified research programs to improve vector control, diagnostics and therapeutic arsenal to contain further incidence and morbidity.
An infection with Leishmania parasites can, depending of the infecting species, give rise to several distinct clinical manifestations, ranging from localized cutaneous leishmaniasis (CL) with single to multiple skin ulcers, satellite lesions or nodular lymphangitis or possibly mucosal involvement and systemic visceral leishmaniasis (VL) with involvement of different organs (like liver and spleen) and bone marrow, which may be lethal.
Currently, Pentamidine isethionate is the only drug available for patients with CL in Suriname. Usual care at this moment in Suriname entails a standard treatment regimen of three doses

of 4mg/kg body weight Pentamidine Isethionate im. (in 7 days)

Sponsors and support

Primary sponsor: Koninklijk Instituut voor de Tropen (KIT)
Source(s) of monetary or material Support: WOTRO

Intervention

Outcome measures

Primary outcome

To establish if a short course pentamidine isethionate 7 mg/kg body weight given intramuscular at days 1 and 3 (short course) is equally effective as the standard course pentamidine isethionate 4mg/kg intramuscular at days 1, 4 and 7 (standard course) in patients with CL. CL is diagnosed by the detection of leishmaniasis organisms (in a skin smear or a biopsy by light microscope or by the detection of leishmaniasis nucleic acid sequences through NAAT) in a clinically suspected lesion.

1. A clinical relapse is defined as persistence of one or more leishmaniasis lesions at 6 or 12 weeks after completion of treatment documented by one dermatologist with at least 4 years diagnostic experience in leishmaniasis. All lesions will be photographed (both healed and persisting lesions) and evaluated per visit by a second dermatologist with at least 4 years diagnostic experience in leishmaniasis, who is blinded from the results of the first evaluator. In case of discrepancy between the 2 dermatologist observers, the discrepancy will be solved by a third dermatologist with at least 4 years diagnostic experience in leishmaniasis on the basis of the photographs of the discrepant lesions. The expected success of the standard treatment group is approximately 90%10. To determine whether the treatment success of the short course is equal to that of the standard course, no less than an expected 70% treatment success is considered effective.

2. To establish if the short course is equally effective as the standard course as far as parasitological cure rate 6 and 12 weeks after completion of the treatment. A parasitological cure is defined as elimination of leishmania RNA 6 and 12 weeks after completion of the treatment course, in one designated proven leishmania RNA positive lesion before treatment. The short course is considered to have an equal parasitological cure rate, if in the short course arm the rate does not exceed the cure rate in the standard course arm by more than 20% (compared per visit).

Secondary outcome

1. To establish if the short course has an equal rate of patient reported side effects and

clinically determined drug related toxicity events as the standard course.
Side effects (recorded at the last treatment visit) are:

a. nausea (as indicated by the patient);

b. erythema exsudativum multiforme (occurrence of blisters in skin and/or mucosal tissue);

c. unknown/other side effects.

Drug related toxicity events (recorded 1 week after treatment and compared to the screenings visit) are:

d. hypotension (10mm Hg drop in diastolic blood pressure compared to: the pressure before the injection, measured halfway the injection and 10 minutes after the injection);

e. hemolysis (>1mmol drop in hemoglobin count);

f. leucopenia (drop in leukocytes count < 4 x 10(9)/l);

g. thrombocytopenia (drop in thrombocytes < 150 x 10(9)/l);

h. hypoglycemia (drop in glucose < 4 mmol/l);

i. liver toxicity (>2 fold rise in serum transaminases, normal values = <40 U/l));

j. nefrotoxicity (kreatinin level rise >10umol/l, normal values = 70-110 umol/l));

k. pancreas toxicity (3 fold rise in amylase, normal value = 32 U/l)).

The short course is considered to have an equal rate of side effects or drug related drug toxicity events if in the short course arm the rate does not exceed the rate in the standard course arm by more 20%.

2. To establish if the short course is equal to the standard course as far as health related quality of life measured by validated self-report questionnaires. Generic QoL measured by the EQ-5D and EQ-VAS questionnaires and disease-specific QoL measured by the SKINDEX questionnaire. The short course is considered to affect the quality of life equally as the standard course if the quality of life outcome in the short course arm is no lower than the quality of life outcomes in the standard course group by more than 20%.

3. To establish if the short course is equal to the standard course as far as the cost-effectiveness based on a cost survey questionnaire. The appropriate type of economic evaluation is conditional on the results of the primary objective (relapse rate) and health related quality-of-life (HR-QoL). In the case of one clearly superior strategy, a cost-effectiveness analysis (CEA) would be required to combine clinical and economic outcomes. In case of comparable outcomes in clinical effectiveness, a cost-minimization analysis (CMA) would suffice.

4. To establish the effect on the patient compliance of the short course regimen versus the standard course regimen. A patient is considered non-compliant for a study visit in case he/she fails to show up more than 24 hours after the consented date and time, without a notification beforehand. The short course is considered to affect the compliance compared to the standard course if the compliance rates between the two regimens differs by more than 20%.

Study description

Background summary

In this randomized, non-inferior 2 arm, trial cutaneous leishmaniasis patients will be treated with pentamidine isethionate (PI). In the control arm, 110 patients will be administered 3 IM injections of 4mg/kg bodyweight per injection, on days 1, 4 and 7. In the other arm, the intervention arm, 110 patients will be administered 2 IM injections of 7mg/kg bodyweight per injection, on days 1 and 3. Effectiveness of both arms will be compared. Also the side effects, drug related toxicity, patients' compliance, cost-effectiveness and Quality of Life.

During sample size considerations for our non-inferiority trial, we assume that the cure rate will be at least 90% in both arms. The non-inferiority margin was predefined as 20%, power factor 80% and alpha 5%. Previous sample size calculation resulted in 110 patients per study arm. This was wrong because according to power (sample size) calculator, the sample size should be 28 patients per treatment arm, 56 patients in total. www.sealedenvelope.com/power_binary_noninferior.php. During the trial we detected that the cure rate in both arms was lower than the expected 90%. The cure rate for both treatment arms was around 85%. If we consider this trial a non-inferiority trial with cure rate of 85%, significance level (alpha) 5%, power (1-beta) 80% and non-inferiority margin 15% than the sample size calculation will be 71 patients per treatment arm, total of 142 patients. In a paper by Luisa C. Rubiano et al. "Noninferiority of Miltefosine Versus Meglumine Antimoniate for Cutaneous Leishmaniasis in Children" JID 2012:205, the sample size was 62 patients per group, non-inferiority limit was 15%, cure rate 80%/85%, one sided alpha 5% and power of 90%. After reading this paper and having evaluated our data we came to the conclusion that we have sufficient patients to stop the inclusion. At the moment we have included 83 patients in the control arm and 78 in the intervention arm.

We regret not having reported earlier this change in sample size.

Study objective

The parasitic disease cutaneous leishmaniasis (CL), caused by single cell Leishmania parasites, is an increasing health threat in Suriname, mainly affecting poor populations in the

interior. It is a chronic infection with a spectrum of clinical presentations, most excessive is the extensive ulceration and disfiguring scar formation. In Suriname CL is known as Boschyaws or Boessie-Yassi.

Diagnosis of CL can be difficult and treatment options are few, with serious side effects, and increasingly failing, possibly due to emerging drug resistance against the first line treatment.

The primary objective of the clinical trial is to establish whether a short course of pentamidine isethionate (PI) is equally effective as the standard course of pentamidine isethionate which is presently used for patients with CL.

As secondary objectives, side effects, drug related toxicity, compliance, cost-effectiveness and quality of life effects related to the standard versus the short course treatment regimen will be compared.

In this project, Pentamidine Isethionate treatment will be studied in a randomized controlled trial with 2 treatment arms:

1. 4mg/kg body weight at day 1, 4 and 7 (control / usual care arm) or

2. a short course regime of 7mg/kg body weight on day 1 and day 3 (case/ intervention arm).

Study design

Primary outcomes are measured at 6 weeks and 12 weeks after treatment. Lesions are measured, photographed and skin biopsies are taken.

Secondary outcomes are measured after each threatment, at 6 weeks and 12 weeks after treatment. Questionnaires are filled in and blood samples are taken before and 1 week post therapy for analysis.

Intervention

In this project, Pentamidine Isethionate treatment will be studied in a randomized controlled trial with 2 treatment arms:

1. 4mg/kg body weight im. at day 1, 4 and 7 (control / usual care arm) or

2. a short course regime of 7mg/kg body weight im. on day 1 and day 3 (case/ intervention arm).

Assuming remission rates of 10% under both treatments, a sample size of 100 patients in each treatment arm was calculated to achieve an 80% power to yield a statistical significant result. Due to an expected 10% dropout in both arms, we aim to enroll a total of 220 patients, with 110 in the usual intervention arm and 110 in the short intervention arm.

Considering side effects of treatment, in the control arm these are rarely seen. In the case arm with higher dosage in shorter time, it will be interesting to compare this with the control arm.

Contacts

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Eligibility criteria

Inclusion criteria

1. Patient is 16 years and older of age;

2. Histopathology and/or smear of skin biopsy confirms diagnosis CL;

3. Willingness to attend all visits (treatment (1, 2 and 3) and follow-up (1, 2 and 3) regarding the study;

4. Patient can be contacted by phone, either directly or through family living (in the vicinity of Paramaribo.

Exclusion criteria

1. Patients with CL treated in the past 6 months;

2. Pregnancy or lactation;

3. Potential loss to follow up (unable to attend one of the study visits, either treatment or follow-up visits;

4. Patients with a history of liver disease and/or elevated transaminasen levels of more than 2 times the normal value (normal values = <40 U/l) at the time of enrollment;

5. Patients with a history of kidney disease and/or elevated plasma creatinine level of > 40% the upper limit of the normal range (normal values = 70-110 umol/l) at the time of enrollment;

6. Patients with a history of pancreas disease and/or elevated amylase levels of more than 3 times the normal value (normal value = 32 U/l) at the time of enrollment;

7. Patients with anemia (hemoglobin level < 7.5 mmol/l), leucocytopenia (leucocytes < 4x109/l) and thrombopenia (thrombocytes < 150x109/l) at the time of enrollment;

8. Patients with a history of heart disease;

9. Patients with diabetes;

10. Patients with a known allergy for Pentamidine Isethionate.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-01-2009
Enrollment:	220
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	25-09-2009
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL1959
NTR-old	NTR2076
Other	WOTRO : WO 16531300
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results