Doxycycline therapy for improvement of lymphedema of filarial and non-filarial origin

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Introduction

Doxycycline treatment improves mild to moderate lymphedema independent of ongoing infection. (Mand S. *et al*, CID 2012)

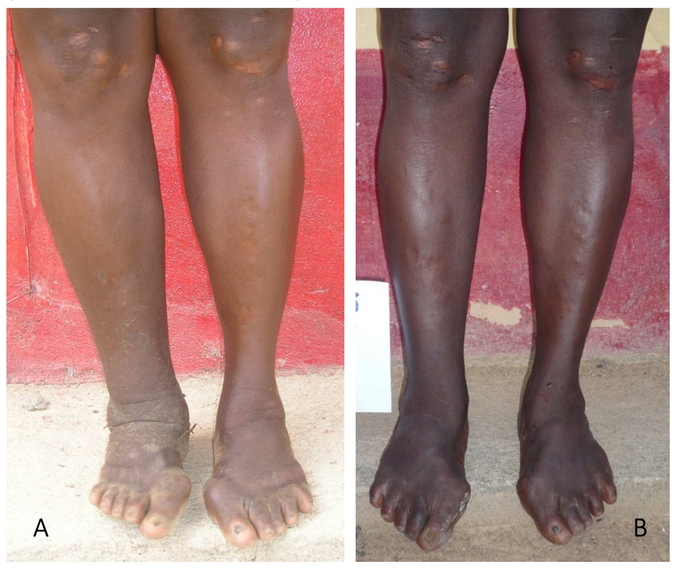


Figure 1: Woman with a lymphedema (LE) stage 3 of the right leg before treatment with DOX200 for 6 weeks (A) and LE stage 1 of the right leg 24 months after treatment onset (B). Staging was done according to Dreyer, G. *et al*, 2002.

Lymphedema (LE) can have various origins. One cause is the infection with filarial worms like *Wuchereria bancrofti* that can cause severe lymphedema. A previous study showed that a 6-week treatment with 200 mg doxycycline did not only exert macro- and micro-filaricidal effects but also improved the lymphedema in lymphatic filariasis (LF) patients. We designed three clinical trials to confirm and expand these findings. These trials are a part of the TAKeOFF project which aims to establish structures for further clinical trials within the scope of NTD research in the African partner countries.

Structure

The three LEDoxy trials, funded by the TAKeOFF project, take place in Ghana, Tanzania and Cameroon. Three additional study sites are funded by the USAID conducted in collaboration with the NTD Support Center (Taskforce for Global Health, Atlanta, USA).
The study design is harmonized but the studies are conducted independently in each country by a local study team supported by researchers from Germany.

Figure 2: Countries in which the LEDoxy trials are conducted
created at https://www.amcharts.com/visited_countries/#

Ghana (ISRCTN14042737) and Tanzania (ISRCTN65756724)

- Multi-national interventional randomized double-blind placebo-controlled phase II trial with LF patients with LE Stage 1-3
  - Efficacy of 200 mg DOX for 6 weeks compared to placebo
  - Efficacy of 100 mg DOX for 6 weeks compared to placebo
- Phase II pilot trial in patients with LE Stage 4-6
  - Efficacy of 200 mg DOX for 6 weeks compared to placebo

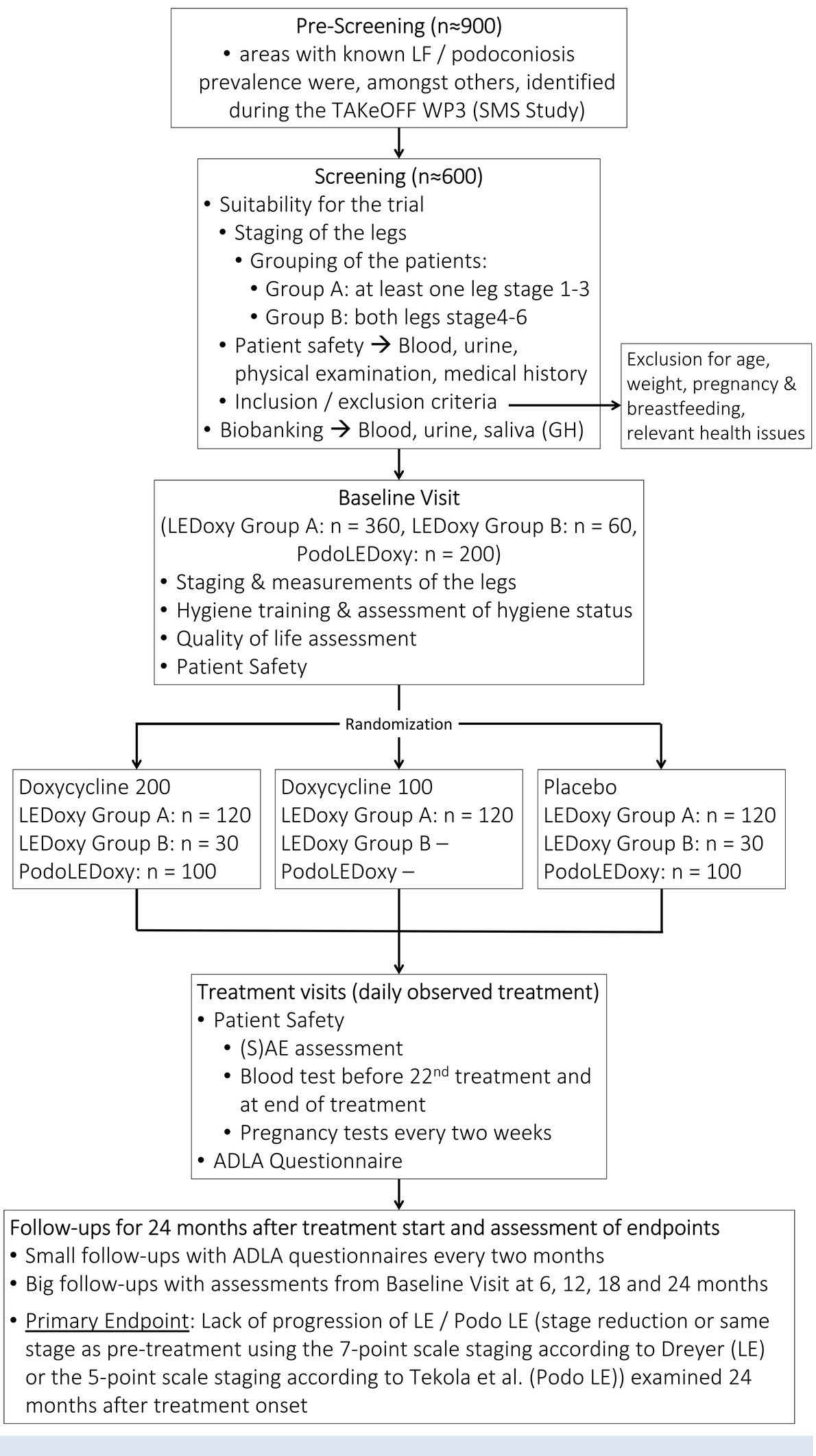
Cameroon (ISRCTN11881662)

- Interventional randomized double-blind placebo-controlled phase II trial with podoconiosis patients with LE Stage 2-4
  - Efficacy of 200 mg DOX for 6 weeks compared to placebo

Mali (NCT02927496), Sri Lanka (NCT02929134), India (NCT02929121)

- Harmonization with the TAKeOFF trials
- Efficacy of 200 mg DOX for 6 weeks compared to placebo

Study Flowchart



Aims

Confirm the efficacy of DOX 200. The treatment of lymphatic filariasis is mainly based on the elimination of the parasite but leaves the pathology behind. Establishing DOX to improve lymphedema in international guidelines (e.g. WHO) for morbidity management could greatly improve the life of affected patients.

Reduce the dose to 100 mg DOX. 100 mg DOX is widely used in malaria prophylaxis and against other infections. A previous RCT has shown that the macrofilaricidal effect of 100 mg DOX in LF is as good as the 200 mg dose. A dose reduction would reduce possible side effects if any and costs for health care providers.

Test DOX 200 in severe LE stages. The study by Mand *et al.* focused on patients with LE stage 2-3. A pilot trial with 30 patients per group (DOX 200 and placebo) will investigate whether also patients with LE stages 4-6 profit from treatment with DOX200 in the trials in Ghana and Tanzania (as well as in the three USAID funded trials).

Expand the findings to Podo LE. The original study found that the positive effects on lymphedema in LF were independent of the infection status. Therefore it is possible that DOX can also exert its effects in lymphedema of other origins like podoconiosis LE which is caused by irritant red clay soil.

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Research Networks f Health Innovations Sub-Saharan Afri
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