Author's response to reviews

Title: Laser therapy for onychomycosis in patients with diabetes at risk for foot complications: Study protocol of a randomised, double blind controlled trial.

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Dear editors,

We would like to thank the editors for considering our manuscript “Laser therapy for onychomycosis in patients with diabetes at risk for foot complications: a study protocol of a randomised, double blind controlled trial” for publication in your journal. We think the comments of the reviewers have led to an improved manuscript.

Below you’ll find a point by point rebuttal to the questions and points raised by the reviewers.

1. Complications in diabetic patients with neuropathy undergoing this type of laser treatment for onychomycosis have been documented previously in the literature (Moutran et al 2014) As the current study title suggest a “safety” dimension, how will this aspect be managed? This should be documented in the study protocol.

   Reply: We first would like to thank the reviewer for his or her time and effort invested in reviewing of our manuscript.  
   Firstly, we can reassure that the patient described in the mentioned paper would never have been included in our trial. Furthermore, we have reasons to believe that this patient, who received 3 laser sessions, could have received a higher than recommended laser dose. One session is one horizontal and one vertical passing over the nail. Because our patients with a neuropathy have no pain sensation we have opted to a maximum of two sessions.  
   In our experience in many patients we have treated, not suffering from neuropathy, the third session is sometimes accompanied with intense pain sensation. The last session can’t be finished in that situation. Furthermore our pulse energy is lower.  
   At an earlier stage we amended the study protocol and accounted for this article and amended the research protocol and changed the in- and exclusion criteria. We will only include patients with either neuropathy or peripheral artery disease, not both. And in the amended study protocol, we will exclude patients with known and relevant arterial disease (defined as either having an
ankle brachial index below 0.9, ischaemic rest pain, or a toe pressure below 50 mmHg. Furthermore, patients with renal failure (eGFR<30 ml/ min) are also excluded to avoid the possibility of a false negative ankle brachial index due to the arterial incompressibility\textsuperscript{2,3}. These values are also used in the Dutch guideline for the treatment of the diabetic foot, for identifying patients who are at risk for delayed ulcer healing\textsuperscript{4}.

We have added the following sentence to the protocol; A maximum of two sessions (one session is one horizontal and one vertical sequential passing) will be applied to eliminate potential safety issues in those patients with neuropathy and lack of protective sensibility.

2. In the PCR analysis, the authors wish to detail how patients with multiple pathogen onychomycosis would be documented / analysed.

Reply: The reviewer is right in pointing out this point to us. Nail dust is collected from the target nail for microbiologic confirmation with blankophor microscopy, culture and polymerase chain reaction (PCR). PCR is regarded as the gold standard. The PCR is a real-time multiplex PCR based on amplification of ribosomal internal transcribed spacer regions and identification by probes specific for Trichophyton mentagrophytes species complex, Trichophyton tonsurans, Trichophyton violaceum, Trichophyton rubrum species complex, Microsporum canis, Microsporum audouinii and Epidermophyton floccosum as described by Arabatzis et al\textsuperscript{5}.

We have added the following sentence to the study protocol; In case multiple fungi are detected in PCR, microbiologic cure can only be established when the PCR at follow-up is completely negative.

Yours sincerely,

On behalf of all authors,

Leonie Nijenhuis – Rosien, Podiatrist, Isala Diabetes Centre