Review
of the doctoral thesis

Prepared by Monika Łukaszewicz
Titled
Evaluation of selected etiopathogenic and clinical parameters of painful diabetic neuropathy during treatment with alpha-lipoic acid used intravenously at a dose of 600mg daily.

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Diabetic neuropathy is the most common complication of diabetes. It is often asymptomatic and is recognized in advanced stages of the disease. Neuropathy is a risk factor for diabetic foot syndrome and a cause for increased mortality in diabetic patients. The painful form of the neuropathy is the most discomforting to patients, causing complaints and worsening the quality of life. The pathogenesis of diabetic neuropathy is not fully understood, therefore factors influencing the onset of pain as well the pathogenetic mechanisms in patients with neuropathy are still sought. Unfortunately, in the vast majority of patients, the only possible treatment in painful neuropathy is symptomatic treatment. One of the few substances having proven causal effect in neuropathy is alpha-lipoic acid (ALA). It works through mechanisms that reduce oxidative stress, one of the key mechanisms activated by hyperglycemia and responsible for the development of chronic complications of diabetes including neuropathy.
The aim of the dissertation of Monika Łukaszewicz was to assess the effect of treatment with alpha-lipoic acid on oxidative stress parameters in diabetic patients and to explain the biochemical mechanisms of action of the drug.

In the expanded introduction M. Łukaszewicz describes in detail molecular mechanisms of redox imbalance in diabetes and its involvement in the pathogenesis of diabetic neuropathy. The introduction part is well illustrated with several figures. In my opinion the introduction section is well written and proves the high knowledge of the Candidate in the studied field.

The aim of the study should be stated more clearly. Some information given in section 3 is unnecessarily repeated. Some methodological issues might be avoided in this part of the dissertation.

In the Research Design and Methods section MD Monika Łukaszewicz provides a clear description of the study population, which contains type 1 (T1DM) as well as type 2 diabetic patients (T2DM). I have some concerns regarding this part of the dissertation. As the total number of patients is limited to 31 a more homogenic group of subjects (limited to only one type of diabetes) could give more convincing and reliable results of the study.

In the next paragraph the inclusion and exclusion criteria are given in detail. The author should probably state why type 2 diabetic patients not treated with insulin were excluded. Moreover, the recruitment phase of patients should be described and more information concerning enrollment process should be included in this section. The dose of insulin should be calculated and provided as units per kg of body mass. MD Monika Łukaszewicz describes the method of measuring the blood pressure, however these results are not given in the table 1. The next part of the methodology includes the laboratory testing. The laboratory part is described in detail. MD Monika Łukaszewicz provides the methods of clinical examination of peripheral neuropathy, however in the recruitment part the criteria of neuropathy diagnosis are missing as well as current guidelines as a reference. Based on neuropathy diagnosis at the beginning the patient was regarded as eligible for the study. This diagnosis requires solid clear guidelines and recommendations. The description of the statistical methods is in the majority correct. However, the author should be aware of the fact that using mean and standard error to express the data does not show the data dispersion.
It the Results Chapter of the dissertation MD Monika Łukaszewicz describes the influence of the treatment with alpha-lipoic acid on the biochemical parameters, oxidative stress, parameters of neuropathy in nerve conduction studies as well as based on questionnaires. Most of the results are presented in figures that clearly illustrate statistically significant and nonsignificant findings. In my opinion, in addition to the charts, actual mean A1c values and their changes should be reported, including standard deviation or range. The study is not a randomized clinical trial and does not include control group. Therefore, the slight decrease in A1c level might be just related to the participation in the study, only partially with the treatment with ALA. Of course, 15 days of the study duration is too short to notice a significant, substantial lowering of A1c level. In this context, the obtained results might be even more clinically relevant.

In the table 6 the author presents data regarding microalbuminuria as mean and probably standard deviation (SD) or standard error (the abbreviation Str. used). All the abbreviations used should be explained. Moreover, the list of abbreviations on the first page should be alphabetically ordered to make searching easier. If the data presentation is mean and SD, the standard deviation is surprisingly large, suggesting significant dispersion of the results. If so, this requires more accurate characteristics of the study group in terms of proteinuria (this might suggest that the study group contains two different groups – with small and large proteinuria). Moreover, generally the distribution of the data and consequently the tests used should be provided in my opinion in the whole results chapter.

Subsequently, MD Monika Łukaszewicz provides the results of the nerve conduction (NC) studies, which were measured twice: before and a month after treatment with alpha-lipoic acid. In the abstract the author states that a lot of nerve conduction studies parameters were enhanced, and median nerve motor conduction velocity improved significantly. However, none of the change in the parameters of NC presented in the dissertation is statistically significant (defined as the level of p<0.05). Based on the results presented, the author has no sufficient data to draw conclusions about the positive effect of treatment with ALA in diabetes on the nerve conduction. The most valuable part of the work is a biochemical part that includes evaluation of markers of oxidative stress during treatment with alpha-lipoic acid: plasma proteins' carbonyl, plasma protein and plasma proteins' SH groups. MD Monika Łukaszewicz shows a significant increase of plasma proteins’ SH groups in patients with T1DM after 15 days of treatment. Finally, the pain symptoms described with
Visual Analog Scale diminished significantly at the end of the study. Moreover, the use of additional analgesics decreased along with the treatment with alpha-lipoic acid.

In the discussion MD Monika Łukaszewicz presents current knowledge concerning the ALA redox effects mechanisms and the concepts that are based on the study results. So far, the protective mechanisms of ALA were referred to antioxidant activities. The results of MD Monika Łukaszewicz revealed ALA as a critical redox-active thiol channel oxidant resulting in the closure of the channel and reduction of pain sensation. Conclusions are clearly stated, however could be provided in points which correspond to the objectives of the work. Such a composition facilitates the arrangement and understanding of the results and implications for clinical practice. Some of the conclusions are in fact the study results. The references contain the most important and up-to-date works in the subject area of the author. In my opinion the author should additionally provide any current position statement or the recommendations of the working group regarding the diagnosis and treatment of diabetic neuropathy.

In summary, the dissertation of dr Monika Łukaszewicz presents high scientific level and is an important contribution to the current knowledge in the topic. It is important to emphasize that the results contribute to the knowledge of biochemical mechanisms of action of alpha-lipoic acid, but they also have important clinical implications for patients with painful diabetic neuropathy. Monika Łukaszewicz’s dissertation meets the requirements of the dissertation for the PhD degree. The doctoral thesis corresponds to the conditions specified in the Article 13 (1) of the Act of 14th March 2003 on scientific degree and academic title.

Therefore, I refer to the Medical Faculty of Gdansk Medical University for the admission of Monika Łukaszewicz to further stages of the doctoral degree.