READERS' COMMENTS

Characteristics of Japanese patients with Leber's hereditary optic neuropathy and idebenone trial: a prospective, interventional, non-comparative study

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To the Editor,

With interest we read the article by Ishikawa et al. about an uncontrolled, prospective, intervention study of 51 patients with Leber's hereditary optic neuropathy (LHON) due to the ND4 variant m.11778G>A treated with idebenone (900 mg/day) over 24 weeks [1]. Improvement of > 0.2 logMAR was achieved in 25.5% after 24 weeks and in 33.3% after 48 weeks of follow-up [1]. We have the following comments and concerns.

The main shortcoming of the study is its design [1]. The study is uncontrolled, why it remains unclear if the figures provided as success rates are truly reliable. Baseline values of best corrected visual acuity (BCVA), visual fields, clinical fusion frequency (CFF), and retinal ganglion cell layer complex thickness (RGCLcT) were compared with those at 24 and 48 weeks after starting treatment respectively. These parameters were neither compared with a group of healthy or disease controls. If the therapeutic effect of idebenone depends on the severity at onset, misleading results may ensue.

Another shortcoming is that heteroplasmy rates of the variant were not provided. Knowing heteroplasmy rates is crucial as they may determine the phenotype, and the course and outcome. Though heteroplasmy rates are usually high in LHON patients or even homoplasmic (100%), exact figures are essential.

A further shortcoming is that it is not described how adherence to taking the study medication was controlled.

Another shortcoming refers to the reporting of side effects. Though idebenone is usually well tolerated, side effects, such as nausea, vomiting, stomach pain, loose

stools, tachycardia, or an increased risk of infection have been reported [2]. However, the article does not mention anything about side effects except that all patients tolerated the study drug. Thus, we should be informed how many patients experienced any of the previously described or new adverse reactions.

Spontaneous remission varies between the different LHON mutations. Spontaneous remission of the m.11778G>A variant is rare but has been occasionally reported [2]. Thus, we should know in how many of the included patients was the presumed treatment effect rather attributable to spontaneous remission than to idebenone.

In patients to whom idebenone is given after onset of the disease the therapeutic effect may be limited or even absent. We should know if the therapeutic effect correlated negatively with the latency between onset and beginning of the treatment.

The authors assume that reduced ATP production leads to oxidative stress and consecutively to necrosis of retinal ganglion cells (RGCs) and thus optic atrophy [1]. However, spontaneous recovery has been reported in 6–8% of the LHON cases. How do the authors explain recovery if RGCs no longer exist? How do the authors explain that RGCLcT remains unchanged under idebenone whereas BCVA improves? Is there a need to replace the pathophysiological concept of cell death to functional impairment with only cell atrophy?

It is not conceivable why patients with elevated transaminases, epilepsy, delirium, or hallucinations, patients with agranulocytosis, and patients with chronic renal failure were excluded. In all studies on idebenone carried out in LHON so far hardly any side effects were reported. Thus, it is quite unlikely that idebenone would have enhanced the abnormalities used as exclusion criteria.

Overall, the interesting study by Ishikawa et al. has a number of shortcomings, which should be met before drawing conclusion as have been provided. Testing the therapeutic

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effect of idebenone requires an appropriate study design, heteroplasmy rates, monitoring of adherence, reporting of adverse reactions, discussion of spontaneous remission, and revision of the pathophysiological concept of LHON.

Sincerely,

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References

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Author's Reply

We appreciate the interest and concern that Dr. Finsterer has expressed in our study.

We agree with Dr. Finsterer's comment that "If the therapeutic effect of idebenone depends on the severity at onset, misleading results may ensue." This study was performed between October 2013 and May 2016, and 57 Japanese patients with LHON were ultimately enrolled. This relatively small number meant that we could not divide the patients into multiple groups, including placebo, study drug, new onset, and chronic groups. Therefore, we had to design a one-armed study, in which we could then compare the visual function at baseline and post-therapy. However, we just showed the observational results, and did not mention the therapeutic effect of idebenone.

To detect the mitochondrial mutation(s) in the present study, BML Inc. (Tokyo, Japan) performed the qualitative testing on a commercial basis. Although we asked BML for the heteroplasmy rates, the laboratory did not determine the actual rates. So, we cannot provide the rates in the present study.

Enrolled patients were instructed to take each 300 mg idebenone 3 times per day. However, we could not directly monitor the patients.

As we mentioned in the present study, the enrolled patients never complained about side effects, such as those

that Dr. Finsterer cited, so, we did not mention any side effects.

We agree with the comment that "we should know in how many of the included patients was the presumed treatment effect rather attributable to spontaneous remission than to idebenone." Our study had only one arm, so we could not answer that question. Therefore, we conclude, in the present manuscript, that further studies are needed.

The improvement rate in the late-intervention patients was significantly higher than that in the early-intervention patients, suggesting that the idebenone could not protect against disease progression, but that it might be effective even when optic nerve atrophy was present.

This dissociation between anatomical damage and functional improvement is unclear in studies of LHON, as Dr. Finsterer mentioned. Owing to preliminary MRI data, our hypothesis regarding the mechanism of action of idebenone is as follows. 1. LHON causes RGC death. 2. Idebenone affects surviving or residual intact RGCs. 3. Signals from the surviving RGCs are amplified. 4. Visual cortex is functionally activated. 5. Visual field improves. We have relevant data, but only from four patients. So, again, we conclude further study is needed.

We also agree with Dr. Finsterer's comment about the exclusion criteria. The patients with elevated transaminases, epilepsy, delirium, or hallucinations, agranulocytosis, and chronic renal failure were not enrolled in this study. We should have clearly stated the exclusion criteria including these diseases.

We agree with some of Dr. Finsterer's several concerns. As we mentioned in the present manuscript, there are several limitations. However, we will seriously reflect on the various problems, including Dr. Finsterer's concerns, and relentlessly work to solve these problems. In addition, we will perform further study to investigate pharmacological efficacy of idebenone.

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