Int. j. adv. multidisc. res. stud. 2024; 4(6):1184-1185

Received: 02-12-2024
Accepted: 12-12-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

More in-depth Studies are needed before the Microsomal Prostaglandine E1 Inhibitor Sonlicromanol can be Recommended for m.3243A>G-related Mitochondrial Disorders

Josef Finsterer
Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

DOI: https://doi.org/10.62225/2583049X.2024.4.6.3575
Corresponding Author: **Josef Finsterer**

We were interested to read the article by Smeitink *et al*. on a randomized controlled phase 2b study (RCT) on the efficacy of sonlicromanol, a microsomal prostaglandin E1 inhibitor, in 27 patients carrying the mtDNA variant m.3243 A>G, which manifested in four phenotypes (maternally inherited diabetes and deafness (MIDD, n=15), myopathy (n=10), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS, n=1), and chronic progressive external ophthalmoplegia (CPEO, n=1)) [1]. The primary endpoint (identification task test (IDN)) did not reach statistical significance [1]. However, significant improvements were observed in patient- and clinician-reported outcome measures after the extension phase (Test of Attention Performance 7 (TAP) with alarm, TAP without alarm, Beck Depression Inventory (BDI) somatic, BDI total, 12-item Short Form Questionnaire (SF12) physical component and seven domains of the RAND Short Form Questionnaire 9 (SF-36) such as pain [1]. The study is impressive, but some points should be discussed.

The first point relates to the selection of outcome parameters [1]. m.3243A>G carriers, especially MELAS- CPEO-plus and MIDD-plus patients, not only exhibit muscle weakness, fatigue, pain or cognitive decline, but more frequently also headache, hypoacusis, seizures, stroke-like episodes (SLE), hypertrophic cardiomyopathy or gastrointestinal impairment [2]. Therefore, it is recommended that these common phenotypic characteristics also be used as outcome variables to assess whether sonlicromanol also has a positive effect on these phenotypic characteristics. Since one of the hallmarks of MELAS is SLE, which may dominate the phenotype, it is critical to know whether the frequency or intensity of SLE was reduced in the one patient included by the use of sonlicromanol. Since SLE and MELAS in general can be associated with epilepsy, we should also know whether the type, frequency and intensity of seizures were reduced with sonlicromanol. In addition, the 10 patients with pure myopathy will have no cognitive impairment, so they will not meet the primary endpoint with or without the study drug.

The second point is that the study group was homogeneous only in terms of the underlying mtDNA mutation, but not in terms of phenotype, biochemical defect and functional impairment [1]. The included patients were inhomogeneous with respect to heteroplasmy rate in the different affected tissues and presumably also with respect to mtDNA copy number, mtDNA polymorphisms and variants in nuclear genes involved in mitochondrial metabolism and function. The inhomogeneity of the study group relativizes the significance of the results. Different clinical, biochemical and functional phenotypes may respond differently to sonlicromanol. Accordingly, MIDD, myopathy, MELAS and CPEO patients may respond differently to the study drug.

The third point is that the concomitant medication of the included patients was not reported [1]. Patients with mitochondrial disorders (MID) often require medication for comorbidities or take “mitochondrial cocktails”. Knowing the total medication that the included patients were taking regularly is crucial not only for assessing drug-drug interactions, but also for assessing whether the beneficial effect may be due to any of these concomitant medications.

The fourth point is that the time period for dose-finding and safety assessment was only four weeks [1]. Long-term side effects can only be assessed if patients are observed over a much longer period of time. Were any side effects reported during the extension phase of the study?

The fifth point is that the statement that the m.3243A>G variant is the most common mtDNA mutation is not substantiated. There are no large-scale epidemiologic studies that systematically compare the prevalence rates of different pathogenic mtDNA variants worldwide. In a Korean study of 118 MID patients, the m.16189T>C allele was the most common, occurring in a quarter of patients [3].

The sixth point refers to the statement that the m.3243A>G variant causes an isolated or compound complex I defect, as stated in the introduction [1]. This statement is contradictory as there are no "compound complex I" defects. The m.3243A>G variant is usually associated with compound defects of respiratory chain complexes I, III and IV, but not with isolated complex I of the respiratory chain [4].

The final point is that at least four of the authors were affiliated with the company that makes sonlicromanol (Khondrion), which may be a significant bias in favour of the positive results of the study.

Since sonlicromanol rescues retinal ganglion cells (RGCs), it would also be interesting to know whether patients with retinal involvement in particular benefited from the study drug.

Overall, this interesting study has significant limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and support the message of the study. Randomized, placebo-controlled, double-blind studies with a crossover phase in a large homogeneous group of m.3243AQ>G subjects are needed before the conclusion can be drawn that sonlicromanol has a beneficial effect on symptomatic m.3243A>G subjects.

Declarations

Ethical approval: Not applicable.

Consent to participation: Not applicable.

Consent for publication: Not applicable.

Funding: None received.

Availability of data and material: All data are available from the corresponding author.

Completing interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval.

Acknowledgements: None.

Keywords: Sonlicromanol, m.3243A>G, MELAS, MIDD, Respiratory Chain, mtDNA

References

1. Smeitink J, van Es J, Bosman B, Janssen MCH, Klopstock T, Gorman G, *et al*. Phase 2b program with sonlicromanol in patients with mitochondrial disease due to m.3243A>G mutation. Brain, Nov 6, 2024. :awae277. Doi: 10.1093/brain/awae277.
2. Alves CAPF, Zandifar A, Peterson JT, Tara SZ, Ganetzky R, Viaene AN, *et al*. MELAS: Phenotype Classification into Classic-versus-Atypical Presentations. AJNR Am J Neuroradiol. 2023; 44(5):602-610. Doi: 10.3174/ajnr.A7837.
3. Pham VH, Nguyen VL, Jung HE, et al. The frequency of the known mitochondrial variants associated with drug-induced toxicity in a Korean population. BMC Med Genomics. 2022; 15:3. Doi: https://doi.org/10.1186/s12920-021-01153-0
4. Richter U, McFarland R, Taylor RW, Pickett SJ. The molecular pathology of pathogenic mitochondrial tRNA variants. FEBS Lett. 2021; 595(8):1003-1024. Doi: 10.1002/1873-3468.14049.