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IDEBENONE: efficient food supplement at LHON, will it be in DOA as well?

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Abstract:

Leber's Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA) are rare hereditary optics diseases due to mutations in mitochondrial DNA that lead to mitochondrial dysfunction and posteriorly to damages in the retinal ganglion cell.

The cause of LHON is a primary mutation in the mitochondrial DNA. In 90% of the cases, LHON is caused by one out of three primary mutations of the mitochondrial DNA (mtDNA), m.11778G>A in the *MT-ND4* gene, m.14484T>C in the *MT-ND6* gene, or m.3460G>A in the *MT-ND1* gene. It affects mainly young adult men and is maternally transmitted.

DOA develops due to the degeneration of the optic nerve it is characterised by the loss of visual acuity, optic disc pallor, changes in the visual camp and has its beginning in childhood. In 75% of patients, the gene responsible for the disease is the *OPA1* gene.

The idebenone antioxidant used in LHON is a synthetic analogue of the Q10 coenzyme, has a short lipophilic chain and counteracts the deficiency of complex I when transporting the electrons directly to complex III, promoting the production of cellular energy (ATP) and reactivating the retinal ganglion cells.

The objective of the article is to verify if the treatment with idebenone could be equally effective in DOA as verified in LHON.

Twenty-three articles were used and chosen using inclusion and exclusion criteria.

Through the analysis of the articles, it is concluded that idebenone is effective in LHON when used at the onset of the disease, but in DOA significant conclusions cannot yet be drawn. Even though idebenone has already shown benefits for this disease, more trials have to be carried out in the future and at earlier stages of the disease such as seen in LHON.

Keywords: LHON, DOA, Idebenone, Neuropathy

Introduction

Hereditary diseases are rare and their prevalence is estimated at 1 in every 10,000 people. In the field of ophthalmology, the most common hereditary diseases are Leber's Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA). These diseases are mainly due to deficiencies in mitochondria that lead to mitochondrial dysfunction, with a reduction of available energy and subsequent damage to retinal ganglion cells. The previously mentioned hereditary optic neuropathies manifest themselves alone or as a symptom of another disease, usually neurological (1). LHON is a hereditary disease, as the name implies, being the most common among mitochondrial cytopathies (2). It is due to a primary mutation in mitochondrial DNA, with three hotspot mutations found in about 90% of patients, represented in the following table (3).

Table 1. *Most frequent hotspot mutations in LHON disease, all of which happen in complex I o mithocondrial respiratory chain.*

Mutation	**m.11778G>A**	**m.3460G>A**	**m.14484T>C**
Location	*MT-ND4*	*MT-ND1*	*MT-ND6*
Protein	p.R340H	p.A52T	p.M64V

LHON is characterised by the loss of vision, without pain, first in one eye, followed by symptoms in the other eye after 6 to 8 weeks. If the second eye is not affected, the disorder is not considered as LHON (4). The incidence of this disease is between 1:31,000 and 1:54,000 people and it mainly affects young adult men (between 20 and 30 years old). Being a mitochondrial disease means it is maternally transmitted. The prognosis of LHON is not very favourable, since most affected people end up blind and with visual acuity of 20/200, and with a high chance of dyschromatopsia. The pupillary light reflex remains unchanged due to the preservation of a specific group of retinal ganglion cells that contain melanopsin and therefore become more resistant to mitochondrial dysfunction (4). Figure 1 shows the development of LHON in the left eye at its beginning (A), after three months (C) and after 5 months (E). It reveals a gradual decrease in optic disc swelling, but an increase in the whiteness and progression in the right eye at the same time as for the left eye (B, D, F). This demonstrates that optic disc swelling started within the first three months and that the atrophy of the temporal region of the optic disc happened at 5 months (5).

Dominant Optic Atrophy is a mitochondrial cytopathy that also occurs due to optic nerve degeneration where, initially, the retinal ganglion cells and their axons, which constitute the optic nerve, are affected (6). This optic neuropathy is mainly characterised by loss of visual acuity, whitening in the optic disc (Figure 2), visual field changes, usually bilateral and predominantly with childhood onset. Optical coherence tomography demonstrates a decrease in the retinal nerve fibre layer. Vision loss in this disease occurs slowly, its progression starting in childhood and continuing all through to adulthood (7). DOA is a disease of the central nervous system, since the retinal ganglion cells, originating in the diencephalon, are affected; however, mitochondrial dysfunction occurs, because the genes responsible for this neuropathy encode proteins that will act in the mitochondria. Concerning its prevalence, it is 3:100,000 people. In 75% of patients, the gene responsible for this optic neuropathy is the *OPA1* gene, which acts mainly on the fusion and fission of the inner mitochondrial membrane (8). The discovery of the association of this gene with DOA occurred more than ten years ago, however, a complete cause-effect relationship has not yet been found. However, one of the main questions to understand, to be able to develop treatment, is how this degeneration of retinal ganglion cells occurs (6).

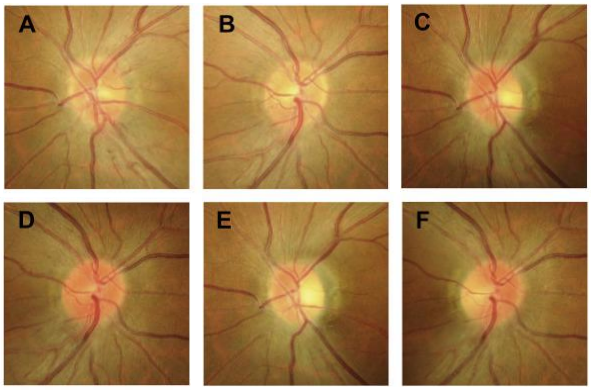

Figure 1. *Evolution of retina in LHON (5).*

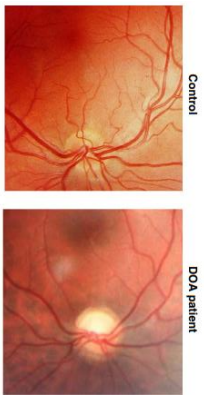

Figure 2. *Difference between retina in DOA and in person without DOA (6).*

The diagnosis of these two rare hereditary diseases may consist only of anamnesis or require other tests that involve the need for specific ophthalmological tests (1).

Traditionally, the treatment of LHON is based on the administration of food supplements, such as activators of mitochondrial synthesis, brimonidine, phytoestrogens, cyclosporine A, vision aids and special attention to nutritional and environmental changes. Food supplements are taken in combinations of vitamins, coenzyme Q10, carnitine, and creatine, among others. The use of these supplements will help in the function of the mitochondria allowing it to reduce the reactive oxygen species. Mitochondrial synthesis is a process through which cells increase mitochondrial mass and mitochondrial copy number so that there is a greater production of ATP and thus a decrease in the symptoms of the disease. New therapies consist of gene therapy and taking idebenone (4).

For DOA, there is still no treatment, as a preventive indication, there is only advice on healthy lifestyle habits, such as avoiding the consumption of alcohol, tobacco and medications that may affect mitochondrial functioning. In LHON, these cautions do also apply. Although LHON and DOA are rare, some studies have been carried out to find an effective treatment to correct the genetic defect and prevent its transmission to offspring (6). So far, the most successful treatment that has been achieved has been for LHON, with the antioxidant idebenone.

Idebenone is a synthetic analogue of coenzyme Q10, synthesised in Japan in 1980. It is a molecule that has a lipophilic short chain that easily allows its penetration into mitochondrial membranes and the blood-brain barrier (9) (10).

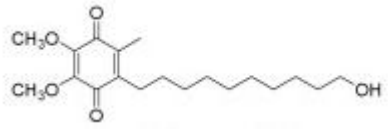

Figure 3. *Idebenone (9).*

The only approved treatment for Leber's hereditary optic neuropathy is Raxone ®, the trade name for idebenone since, through its mechanism of action, it manages to combat the deficiency of complex I of the respiratory chain, due to the mutation in the mitochondrial DNA and transport the electrons directly to complex III, promoting cellular energy production (ATP) and reactivating retinal ganglion cells (11).

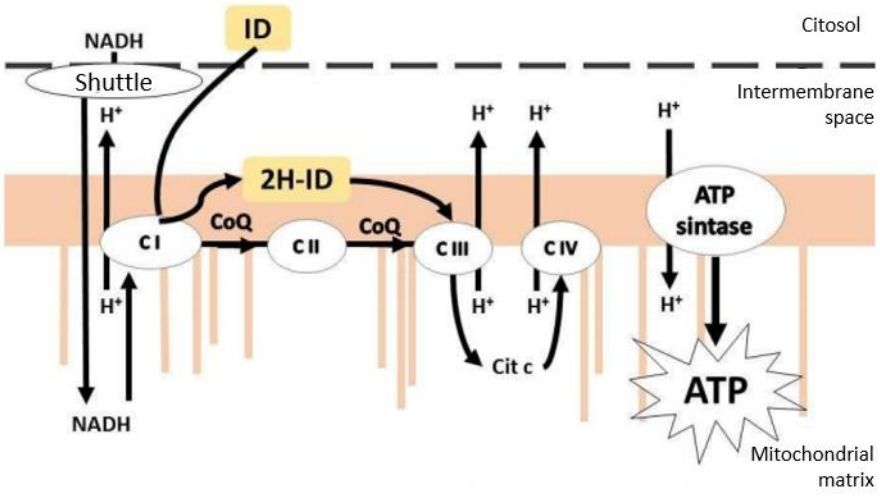

Figure 4. *Action mechanism for idebenone in mitochondrial respiratory chain. (C I - Complex I; C II - Complex II; C III - Complex III; C IV - Complex IV).*
Adapted from Amanda Harduim Valduga, 2016 (12).

The oral administration of this molecule demonstrated good availability in the brain and eye. Through pre-clinical studies in mouse models, an increase in ATP production and a reduction in the levels of reactive oxygen species in fibroblasts were verified. Results from preclinical studies were positive and continued to be in clinical studies (9).

Pre-clinical trials aim to identify, as early as possible, problems that the compounds under study can bring, being the longest and most expensive phases, with many of them not progressing from this stage. These tests ensure that several criteria, such as efficacy and safety, are passed before they reach humans. Pre-clinical tests are further divided into *in vitro* and *in*

vivo tests, with *in vitro* tests carried out in laboratories, in cells or tissues, and *in vivo* tests carried out in animals, in order to make comparisons with humans (12). After the pre-clinical trials, we move on to clinical trials, which are studies carried out on human beings to evaluate the effects and results of the study in question (13).

Objectives

With the present work we intend to collect information on the proposed theme: "Idebenone: efficient food supplement in LHON, will it also be in DOA?", since idebenone is a food supplement already used in LHON with proven effectiveness, we intend to verify if there will also be a positive action of idebenone in DOA. With this work, we also intend to understand the conditions/stages of pre-clinical and clinical trials necessary to allow us to conclude on the question initially posed.

Materials and Methods

This study is a systematic review that is defined as “a clear formulation of questions that use systematic and explicit procedures to identify, select, and critically evaluate important research, and to compile and analyze data from that research” (14). For the development of this work, several databases were used, such as “Pubmed”, “Scielo” and “OMIM”, with the keywords “LHON”, “DOA”, “Idebenone” and “neuropathy”. In order to carry out this article, 20 articles related to the topic were selected after applying the inclusion and exclusion criteria. One of the selection criteria was the period of publication, with articles published preferably between 2011 and 2020 being selected, however older articles were used because they were relevant to the work. Articles that, by reading the title or abstract, were not related to the work were excluded.

All rules of ethical conduct were complied with throughout the investigation, always referencing the sources used in the work. This article has an exclusively academic purpose and there is no personal or economic interest.

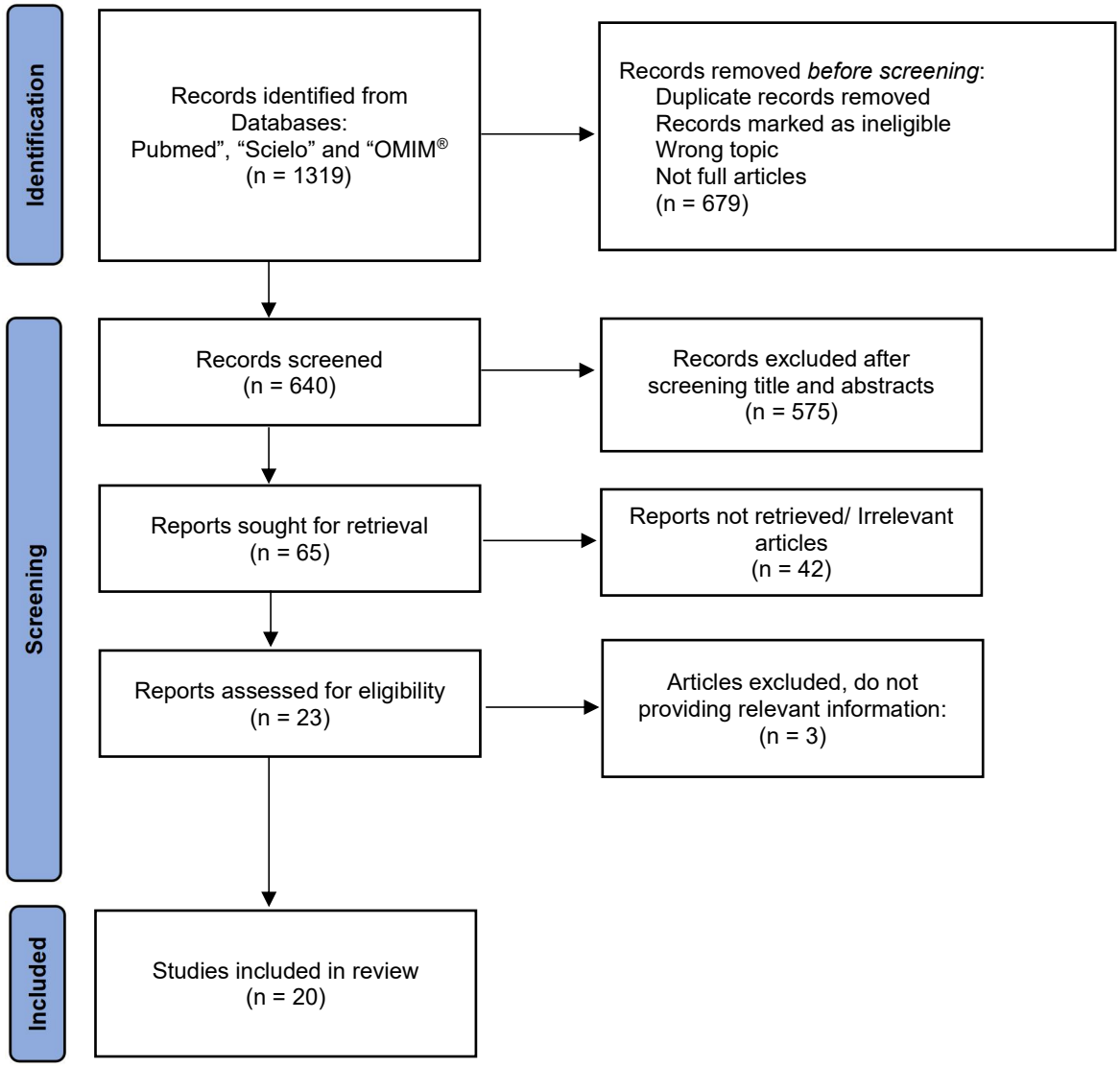

Figure 5. PRISMA flowchart of study selection process.

Results

The results of this investigation are presented in the following table.

Table 1. Summary of selected studies

Author/Year	Type of study	Synthesis
Klaus Rüther (2018)	Revision	Hereditary ophthalmologic diseases in general.

(1)		Symptoms, diagnosis, threatment, prevalence.
Victor A. McKusick (2011) (2)	Revision	Description of LHON, its symptoms, physiopathology and mutations.
Yu Ding et al. (2020) (3)	Revision	Characterisation of Leber's hereditary optic neuropathy. Provides information on the disease's mutations and early detection of the disease.
Anna Theodorou-Kanakari et al. (2018) (4)	Revision	Presents the current and innovative treatments of Leber's hereditary optic neuropathy emphasizing the antioxidant idebenone.
Mitsuhiro Matsuzaki et al. (2018) (5)	Case report	Addresses changes in the retinal nerve fiber layer and full-thickness retina in a patient with Leber's hereditary optic neuropathy.
Guy Lenaers et al. (2012) (6)	Revision	Defines DOA, addresses several points such as the characteristic symptoms, the prevalence of the disease, the types of mutations and the most common one, the prognosis of the disease, the methods of diagnosis and treatments.
Eduardo Scaldini Buscacio et al. (2013) (7)	Case report	Characterisation of dominant optic atrophy, describing the genetic and clinical features, and advice on how not to worsen the symptoms of the disease.
Bo Young Chun, Joseph F. Rizzo (2017) (8)	Revision	Defines dominant optic atrophy and Leber's hereditary optic neuropathy. Explains the pathophysiology, progression and treatment of both hereditary optic diseases.
Giulia Amore et al. (2020) (9)	Revision	Discusses idebenone and other possible treatments for hereditary optic neuropathies and presents several options to improve or circumvent the disease.
Lucia Montenegro et al. (2018) (10)	Revision	Addresses the antioxidant idebenone, explains its discovery and its physicochemical characteristics. It also reports the functions of this molecule and its analogues.
Katherine A. Lyseng-Williamson (2016) (11)	Revision	Characterisation of idebenone, regarding its mechanism of action and its function in LHON disease.
Amanda Harduim Valduga (2016)	Master's thesis	Addresses Duchenne Muscular Dystrophy. Analyses the antioxidant idebenone when a mitochondrial mutation occurs,

(12)		and the mitochondrial respiratory chain.
Mariana Varela Alves da Silva Salgueiro (2015) (15)	Master's thesis	Addresses mitochondria and their role in cellular energy production, reactive oxygen species, oxidative stress and antioxidants.
Fabrice D. Heitz et al. (2012) (16)	Clinical case	Reports a pre-clinical placebo-controlled trial with the molecule idebenone, carried out in mice with LHON disease. It describes the entire procedure of introducing the disease into the animal and the entire analysis process after treatment with idebenone.
Thomas Klopstock et al. (2011) (17)	Revision	Addresses a double-blind, randomized, multicentre placebo-controlled clinical trial, run for 24 weeks in 85 patients with Leber's hereditary optic neuropathy using idebenone in a daily dose of 900mg. The aim of the study is to see if patients who took idebenone improved their vision when compared to placebos.
Claudia B. Catarino et al. (2020) (18)	Clinical case	Multicentre, retrospective and uncontrolled clinical trial, using idebenone at a dose of 900mg per day, to verify improvements in the acuity of 111 patients.
P.A Williams, J.E. Morgan, M. Votruba (2011) (19)	Revision	Explains the two mouse models most used to carry out tests on dominant optic atrophy.
T.G. Smith, S. Seto, P. Ganne, M. Votruba (2016) (20)	Clinical case	Analyses a randomized, placebo-controlled preclinical trial of *OPA1*-mutated and wild-type mice. 2000 mg/kg/day of idebenone used. Assesses cellular responses in the retina, brain and retinal ganglion cells.
Piero Barboni et al. (2013) (21)	Clinical case	Clinical trial with patients with dominant optic atrophy, using off-label idebenone for one year. Checks for improvement in the patient's visual acuity.
Martina Romagnoli et al. (2020) (22)	Clinical case	Cohort study that addresses a clinical trial with 87 patients with dominant optic atrophy, using idebenone as treatment. Comparison of treated and untreated patients.

Discussion

Mitochondria is an intracellular organelle, whose main functions are cellular respiration and cellular energy production (ATP) through the process of oxidative phosphorylation. Cellular respiration occurs in a complex molecular process, called the mitochondrial respiratory chain, composed of four protein complexes, complex I, II, III and IV (15). These complexes successively transfer electrons to each other, through redox reactions, coupling to the generation of an electrochemical gradient that allows the phosphorylation of ADP into ATP (Figure 4).

LHON

LHON, as previously mentioned, is essentially caused by three primary mutations in mitochondrial DNA, all of which affect genes encoding the mitochondrial subunits of complex I, of the mitochondrial respiratory chain (Table 1). Since complex I is affected by mutations, it consequently affects the entire functioning of the mitochondrial respiratory chain, since there will be a deficit in the transport of electrons. This leads to lower production of cellular energy (ATP), an increase in reactive oxygen species (ROS), which increases levels of oxidative stress and decreased glutamate transport, leading to retinal ganglion cell dysfunction and their death by apoptosis (16).

The only treatment so far for LHON disease is idebenone. Idebenone is an endogenous antioxidant that is found in all mitochondrial membranes and protects them from oxidative stress, due to its inhibitory action on lipid peroxidation. One of the advantages of using idebenone in LHON is the fact that it interacts with the mitochondrial respiratory chain, especially when there is a deficiency in complex I (16). When idebenone enters the mitochondrial respiratory chain, it is reduced by complex I. The reduced form of idebenone can transport electrons from the cytoplasm directly to complex III. This mechanism of action of idebenone restores the ATP levels in the cell (12).

In recent years, several preclinical trials and clinical trials have been conducted to test the effectiveness of idebenone on LHON.

Pre-clinical trials

The study by Heitz *et al.* (2012) presents a preclinical trial with idebenone. This study aimed to demonstrate the protective effect of idebenone on LHON using a retinal ganglion cell line

from a mouse model with LHON (16). The models used were 7-week-old male wild-type mice weighing 25 grams and were divided into two batches (16).

In batch 1 mice were treated with dietary doses of idebenone or with a placebo for 21 days. In batch 2 mice were treated with a single dose of 60mg/kg of idebenone orally or via tube. All mice were injected with rotenone, a complex I inhibitor that thus prevents the transport of electrons along the mitochondrial respiratory chain, which causes the effects associated with LHON (15). The results of the study demonstrated that idebenone concentrations above 10nM protect retinal ganglion cells from complex I inhibition and confirmed the mechanism of action of idebenone through the presence of quinone oxidoreductase in retinal ganglion cells. This study also demonstrated that idebenone penetrates the ocular fluid after oral administration since in batch 1, 21 days after taking idebenone, its concentration in aqueous humour, vitreous and plasma and its concentration had increased proportionally to the administered dose and they noticed the rapid penetration of idebenone into the eye. Idebenone was also found to have the ability to prevent the thinning of the retina caused by LHON. Finally, this preclinical trial demonstrated that animals pre-treated with idebenone significantly regained vision after 70 days of rotenone administration compared to animals that were treated with placebo alone (16).

Clinical trials

Clinical trials follow pre-clinical trials. There are already several reports of clinical trials carried out with idebenone.

The first clinical trial performed with idebenone in LHON was a prospective, randomised, double-blind, placebo-controlled study. The study had 85 patients enrolled, and the criteria are described in the following table (17).

Table 2. *Inclusion and exclusion criteria of clinical trial from Klopstock et al. (2011)*

Inclusion criteria	**Exclusion criteria**
Ages between 14 and 64 years old	Pregnant women
One of the 3 known mitochondrial DNA mutations for LHON	Nursing women
Loss of vision due to disease in a period of 5 years	Abuse drugs' users

A centralised randomisation process was carried out in which patients were randomly chosen to receive a dose of 900mg per day of idebenone, in doses of 300mg, three times a day, with meals, for 24 weeks, taking the placebo to the control group was performed according to the same dosage schedule (17).

Of the 85 patients, 55 took the 900 mg idebenone/day and 30 took the placebo. Seven patients withdrew from the study due to adverse effects such as an infected epidermal cyst and one case of epistaxis, however, no adverse effects were considered to occur due to taking idebenone (18). In evaluating the results of the study, the authors found that there was no significant difference in visual acuity between these two groups. However, they found that participants with discordant visual acuities at baseline who took idebenone recovered their visual acuity more significantly than those with identical visual acuities. They also found that after treatment with idebenone, 20% of patients who could not read any letter at the beginning could read at least one full line after the 24th week of treatment and patients who took the placebo had no changes. Finally, they concluded that idebenone is more effective in patients who are still early in the disease, where one eye is more affected than the other (17).

In another study by Catarino *et al.* (2020), a multicentre, retrospective, uncontrolled clinical trial is reported to test visual acuity in a group of 111 subjects with LHON and the long-term safety of idebenone. Of the 111, only 87 participants were carriers of one of the three LHON hotspot mutations and had had the onset of disease symptoms for less than a year (18). They collected all data on visual acuity and adverse reactions that might already be common. The 111 patients were from 38 different places and 10 different countries (18). Treatment with idebenone was carried out for 25 weeks, with 40 of the 87 patients regaining vision in the left eye. The magnitude of recovery in the 111 patients increased, using the parameter of the logarithm of the minimum angle of resolution (logMAR) it rose from logMAR 0.45 to logMAR 0.72, which allowed us to conclude that the magnitude of recovery is greater the longer the duration of the treatment (18). It should also be noted that the 32 patients who reported adverse effects were not related to the administration of idebenone. This clinical trial allowed us to conclude that long-term treatment with idebenone brings very positive results, however, it also highlights the need for an early start on the treatment (18).

DOA

DOA is caused by mutations in the *OPA1* gene, located on chromosome 3, which encodes

mitochondrial proteins located in the inner mitochondrial membrane and ubiquitously expressed. Mutations present in the *OPA1* gene that lead to DOA promote the synthesis of a mutated RNA, which will give rise to a non-functional protein and therefore there is a 50% decrease in the amount of *OPA1* protein available in the mitochondria/cell (6).

An important question in this disease is to understand why retinal ganglion cells are most affected if *OPA1* proteins are expressed in all cells of the body. The study by Lenaers *et al.* (2012) put 3 hypotheses, and it is still unknown which one is right. The first hypothesis put forward for this situation is the fact that the *OPA1* gene when present in cells and in particular the unmyelinated region of the axons, emphasises the importance of the mitochondrial network in the functions of the axons and the synapse networks. Therefore, a mutation in the *OPA1* gene can cause problems in these retinal ganglion cells (6). The second hypothesis is that retinal ganglion cells are the only ones exposed to daylight, which can cause an increase in reactive oxygen species and lead to the death of retinal ganglion cells by apoptosis. The third and final hypothesis is related to the energy needs of retinal ganglion cells, which may be affected due to the organisation of blood vessels in the macula and the deficiency in the mitochondrial respiratory chain that does not produce enough ATP for cell survival, resulting in cell death by apoptosis (6).

Pre-clinical trials

The study by Williams *et al.* (2011) performed a pre-clinical *in vivo* trial with two mouse models that were previously used as good models to verify the symptoms of DOA: B6; C3-Opa^{1Q285STOP} and the B6; C3-Opa$^{1329\text{-}355del}$. Both mutated models demonstrated a 50% decrease in the transcription of the *OPA1* gene and consequently in the production of the *OPA1* protein (19).

A randomised, placebo-controlled, 56 B6; C3-Opa^{1Q285STOP} mouse model trial mice with visual loss and 63 wild-type mice was developed by Smith *et al.* (2016). This study aimed to understand the effects of idebenone in mice and whether or not it can be used in humans with the disease. The trial used 119 mice that were divided into four groups, some received idebenone and others placebo and two protocols were carried out, the first lasting 60 days contained mice aged 12 to 14 months intending to check ATP levels and oxidative stress. The second protocol, lasting 42 days, involved mice aged only 11 months and aimed at visual assessment and quantification of quinone oxidoreductase. After the mice were sacrificed, the

retinas were used for labelling retinal ganglion cells (20). The study concluded that idebenone has a negligible effect on the protection of retinal ganglion cells based on the results obtained, as the levels of *OPA1* protein were maintained, ATP levels increased among B6;C3-Opa^{1Q285STOP} mice and recovery in dendritic length increased, but ultimately reported the occurrence of vision deterioration in mice similar to baseline after 6 weeks of treatment. Due to these results, it was hypothesised that the dosage of idebenone used was insufficient and that it should be increased. An important aspect is the levels of quinone oxidoreductase (NQO1), which in this case remained unchanged in the retina in both types of mice. (20).

Clinical trials

The study by Barboni *et al.*, carried out in 2013, used idebenone in the treatment of seven patients with dominant optic atrophy, under the regulation of off-label drug use in Italy, and with the informed consent of all participants. With the study running for one year, idebenone was used at daily doses of 270 mg in children, between 540 and 675 mg in adults, and one participant received 1000 mg of idebenone. (21).

This study demonstrated an improvement in visual acuity and visual function in both eyes, and one patient improved colour discrimination. Regarding the thickness of the retinal nerve fibre layer, there were no changes and the older patients did not recover their vision compared to the younger ones. Younger patients improved visual function after 6 months due to having had the disease for less time and therefore a easier recovery (21).

In a second clinical trial performed by Romagnoli *et al.* (2020), and using information from previous work (20), studied 87 patients with AOD and divided them into 2 groups: idebenone-treated, 50, and untreated, 37. Regarding the doses of idebenone, they described that they were varied, 24 patients took 540mg/day, 10 patients took 270mg/day, another 10 received 405mg/day, 5 took 675mg/day and 1, with only 10 years, received 135mg/day (22). One of the assessments carried out in the study was the change in visual acuity between the beginning of the study and the last follow-up, using logMAR, with < -0.1 logMAR meaning that there is an improvement in visual acuity and > 0.1 logMAR when there is a decrease in visual acuity. With the initial verification of the patients' visual acuities, they were divided into two groups, the stabilisation/recovery group and the vision-worsening group (22).

They classified 74 eyes as stable/recovering and 13 as vision worsening. Comparing baseline to the last follow-up, there was a significant difference in the idebenone-treated group

demonstrating greater stability of visual acuity (Figure 6). Treated AOD patients benefited four times more than the untreated group (22).

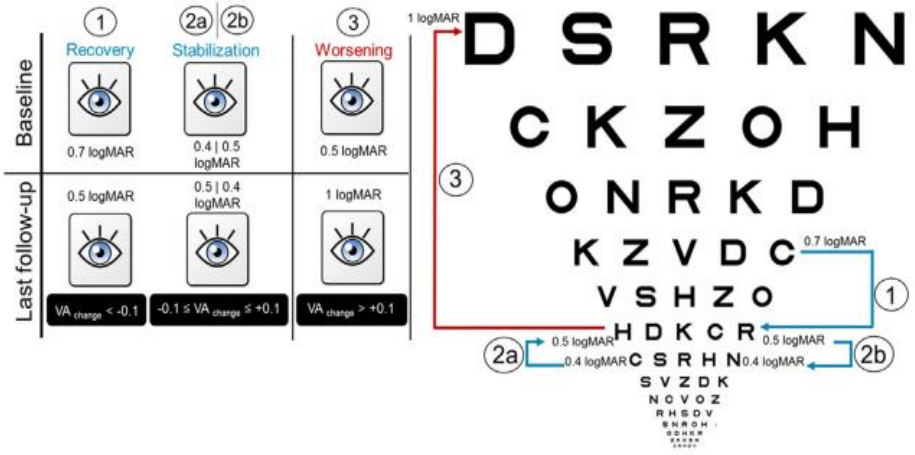

Figure 6. *Visual acuity at the beginning of the study and at last follow-up, and division by groups.*
Image from Romagnoli *et al.* 2020 (22)

Conclusion

LHON and DOA, although they are the two ophthalmic diseases associated with mitochondrial alterations, have differences between them, such as the age at which the disease manifests, DOA usually occurs in childhood while LHON begins to manifest in young adults. The mechanisms responsible for the diseases are different, in LHON there are mutations in complex I of the MRC that lead to its dysfunction, decreasing the production of ATP, promoting greater production of reactive oxygen species, the dysfunction of retinal ganglion cells and finally its death by apoptosis. On the other hand, DOA occurs due to mutations in the *OPA1* gene, decreasing the production of *OPA1* proteins, which also leads to mitochondrial dysfunction and, consequently, retinal ganglion cell dysfunction. However, and despite the differences, they have points in common, such as the degeneration of the axons of the papillomacular bundle, the first to be affected, which leads to pallor of the optic disc, loss of central vision and decreased visual acuity. Another common point between diseases is the increased production of reactive oxygen species and the decrease in cellular energy.

Due to the common characteristics, it is assumed that idebenone can be effective in DOA, as

it has already been proven in LHON, and clinical trials have shown an improvement in patients with DOA who have been treated with idebenone. However, the trials carried out so far are not sufficient to allow idebenone to be approved for treatment, since in the trials carried out, the number of subjects was small and there were no placebo-controlled trials. Another issue is the fact that DOA has not yet been fully studied, nor is its mechanism known and therefore idebenone can help in some parts of the disease but may worsen in others.

In conclusion, with the information currently known, idebenone cannot be considered effective in dominant optic atrophy, lacking further studies both on the pathology itself and on the interaction of idebenone in DOA.

Future perspectives

In the future, it will be important to carry out double-blind, placebo-controlled, randomised clinical trials with idebenone in DOA, as was done in LHON, so that the results are controlled and significant to be able to conclude on the efficacy and safety of administration of idebenone in DOA.

Greater investment in the study of rare diseases will be important, because although each one of them affects few people, as a whole there are many rare diseases, which usually cause very serious changes, which affect the life people in such a way that they cannot have an independent life, needing caregivers.

It will also be relevant to investigate the possibility of other food supplements, which are coadjuvants of idebenone in the treatment of these pathologies.

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