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Editorial

Leber hereditary optic neuropathy: What are the therapeutic perspectives?☆

Neuropatía óptica hereditaria de Leber: ¿de qué perspectivas terapéuticas disponemos?

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An old saying in medicine enunciates that «a disease without treatment has many treatments». However, in the presence of several research lines on a specific pathological process it is possible to envisage the possibility of providing patients an efficient therapeutic option. In the case of Leber's hereditary optic neuropathy (LHON), several recent research studies focused on modifying the natural course of the visual impairment (which in most cases is quite severe) have reported interesting results.

In said disease, mitochondrial DNA mutations give rise to alterations in the proteins involved in complex one of the mitochondrial respiratory chain, leading to ATP deficit in the cell and increased levels of oxygen free radicals which could end up in apoptosis. In addition to appropriate genetic counseling, restricting consumption of tobacco and alcohol, and the contraindication for several medicaments (ethambutol, linezolid, erythromycin, antiretrovirals), the therapeutic options for LHON comprise treatments with idebenone and potentially treatments with phytoestrogens and gene therapy.

Idebenone is a benzoquinone, a synthetic analog of coenzyme Q_{10} that has a preventive effect on the oxidative action of oxygen-reactive species in mitochondria. After being utilized in isolated cases with uncertain results, Carelli carried out a retrospective, non-randomized study comparing the evolution of patients affected by LHON who were given different dosages of idebenone (Mnesis®, Takeda Pharmaceutical, Osaka, Japan) with patients previously visited and not treated.[1] His conclusions were that the visual recovery rate was higher in treated patients, particularly if they had mutation 11778, and that in monocular cases the involvement of the second eye could not be avoided with idebenone. In parallel, the randomized, double-blind RHODOS study compared the effect of idebenone (Raxone®, Santhera Pharmaceuticals, Liestal, Switzerland) at a dose of 900 mg/day with the effect of placebo on visual acuity (VA) of patients with LHON.[2] The main objectives were not achieved although the results improved, mainly in the mutation 11778 cases, by focusing on the subgroup of individuals with discordant vision and therefore with presumably recent onset. However, a high significance was not reached until one patient was justifiably removed. Even so, the results indicated that the number of patients in this subgroup was small. In addition, the discordant vision criteria is inadequate when taken globally as it includes a large range of cases, including single eye involvement, 2 eye involvement in various stages or cases with different residual VA in each eye. After interrupting treatment and a follow-up of 30.7 ± 4.9 months, the RHODOS-OFU study demonstrated a parallel development, maintaining the difference between the Raxone® group (Santhera

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Pharmaceuticals, Liestal, Switzerland) and placebo.[3] However, both in the RHODOS and RHODOS-OFU studies the vision-related quality of life studies (HRQoL) did not demonstrate favorable results for patients who had been given idebenone.

Subsequently, the *Expanded Access Program* (EAP) was implemented, administering 900 mg/day of Raxone® (Santhera Pharmaceuticals, Liestal, Switzerland) to patients affected by LHON with under one year of evolution, and the *Natural History Case Record Survey* (CRS) that assessed visual loss and recovery in untreated LHON patients.[4] At the end of said studies and in the subsequent post hoc analysis, the authors concluded that the proportion of clinically relevant recovery (CRR) after 6 months was of 30.2% in the idebenone group against 10.3% in the placebo group (RHODOS), and of 30.6% in the idebenone group against 19.1% in the untreated group (EAP & CRS). However, a therapeutic result considered in this study as CRR on the basis of the tests with ETDRS optotypes may not agree with quality of life improvements experienced by patients, which demonstrates the occasional discrepancy between statistical significance and clinical efficacy. In turn, *EPI-743* is a parabenzoquinone having antioxidant activity superior to that of idebenone, and the only study published to date on its utilization reported that out of 5 LHON treated patients, VA improved in 4 and normalized in 2.[5]

Similarly, it has been demonstrated in vitro that phytoestrogens can correct the pathological phenotype associated to LHON irritations, both in cybrids and in fibroblasts derived from patients.[6] These compounds of natural origin bind in a highly selective manner to beta-type estrogen receptors which regulate neuroprotective effects. Alpha-type receptors account for the undesirable effects of estrogens, i.e., gynecomastia and diminished libido in males, and increased breast and endometrium cancer risk in females.

In fact, the most fascinating and promising therapy is gene therapy. The fact that LHON primarily affects retinal ganglion cells, particularly in the papillo-macular array, makes the target tissue easily accessible with intravitreal injections. In addition, the involvement of the second eye within a period under one year in most cases, with the window of therapeutic opportunity this involves, makes NHOL the ideal "in vivo" laboratory candidate for researching new therapies. The difficulty lies in introducing a gene in the mitochondrial matrix where the DNA encounters the mutation that causes the disease, due to the relative imperviousness of the internal mitochondria membrane. In order to overcome this problem, various approaches have been designed and are present in various experimentation phases, and only the allotopic expression[7,8] has reached the phase of study in humans. This approach consists in relocating and expressing a gene from one cellular compartment to another and, in the specific case of LHON, a viral vector is used for inserting exogenous DNA in the nucleus. This DNA includes the gene without limitation as well as a signal sequence for directing the protein toward the inside of the affected mitochondria. The mutation-free genetic material is transcribed to messenger RNA, which is exported to cytosol where the synthesis of the normal protein and the signal sequence takes place. This new, structurally normal protein is inserted in the respiratory chain with the ensuing improvement in its performance. At present 5 clinical trials on a gene therapy in LHON are ongoing, of which 2 are already in phase III.[7]

By way of conclusion, nowadays the only possible available treatments for Leber's optic neuropathy is idebenone and, in the absence of confirmation about its actual efficacy on the final visual condition of patients, it can be administered as a trial in cases having under one year or at the most 2 years of evolution. Similarly, it is indispensable to review the therapeutic benefits criteria, correlating the visual acuity data assessed with ETDRS optotypes with the most appropriate vision-related quality of life tests or HRQoL.

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REFERENCES

1. Carelli V, La Morgia C, Valentino ML, Rizzo G, Carbonelli M, De Negri AM, et al. Idebenone treatment in Leber's hereditary optic neuropathy. Brain. 2011;134:e188.
2. Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain. 2011;134:2677–86.
3. Klopstock T, Metz G, Yu-Wai-Man P, Büchner B, Gallenmüller C, Bailie M, et al. Persistence of the treatment effect of idebenone in Leber's hereditary optic neuropathy. Brain. 2013;136:e230.
4. European Medicines Agency. 25 June 2015 EMA/480039/2015 Committee for Medicinal Products for Human Use (CHMP). Assessment report. Raxone. International non-proprietary name: idebenone. Procedure No. EMEA/H/C/003834/0000.
5. Sadun AA, Chicani CF, Ross-Cisneros FN, Barboni P, Thoolen M, Shrader WD, et al. Effect of EPI-743 on the clinical course of the mitochondrial disease Leber hereditary optic neuropathy. Arch Neurol. 2012;69:331–8.
6. Pisano A, Preziuso C, Iommarini L, Perli E, Grazioli P, Campese AF, et al. Targeting estrogen receptor β as preventive therapeutic strategy for Leber's hereditary optic neuropathy. Hum Mol Genet. 2015;24:6921–31.
7. ClinicalTrials.gov [Internet]. Bethesda (MD): US National Library of Medicine [cited 15 June 2016]. Available in: http://www.clinicaltrials.gov.
8. Feuer WJ, Schiffman JC, Davis JL, Porciatti V, González P, Koilkonda RD, et al. Gene therapy for Leber hereditary optic neuropathy: initial results. Ophthalmology. 2016;123:558–70.