Long-Term Experience from an Expanded Access Program with Idebenone in Pediatric Leber's Hereditary Optic Neuropathy (LHON) Patients

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Background

- LHON results in bilateral, severe central vision loss, and is caused by mitochondrial DNA mutations
- LHON is typically diagnosed between 15 – 30 years of age, although it can be detected earlier
- Idebenone, the only approved treatment for LHON in Europe*[1] has been shown to be efficacious and safe in a large proportion of adult patients, but pediatric data is limited
- Priglinger C. et al.[2] observed good safety in 32 LHON patients between 4 and 16 years of age, treated with idebenone (300 mg three times a day) under real-world conditions. Patients below the age of 13 seemed to have better efficacy than patients between 13 and 16 years of age. Erdei Z. et al. observed improvement of visual acuity (VA) and visual fields in a 10 year old female treated over 12 months with idebenone (900 mg/day)[3]

Objectives

To investigate the safety and benefit of long-term idebenone treatment on the VA in pediatric patients treated under routine clinical practice in an Expanded Access Program (EAP)[4]

Methods

- Retrospective medical chart analysis of patients who were under 12 years of age at start of therapy
- All patients received idebenone 900 mg (Raxone® 150 mg tablets) in 3 divided doses through a Named Patient Scheme under routine clinical practice
- VA expressed as logMAR; all Snellen converted VA > 1.68 logMAR and off-chart values are imputed to 1.8 logMAR
- Safety measured through frequency and severity of adverse events

Results

Demographics and Baseline

- Five pediatric patients, 2 female and 3 male, age between 6.9 and 11 years at baseline (BL; median age 9.8 years)
- Time since onset ranged from 1.7 months to 5 years
- Patients carried one of the following mutations, G3460A (1) T14484C (2) G11778A (1) A14495G (1)
- Best VA at BL ranged between 0.16 to 1.20 logMAR (median 0.94 logMAR)
- For all patients, Nadir occured at BL for at least one eye

Time in Treatment

- Median time in treatment was 33.64 months, range between 6.8 to 40 months

Change in Visual Acuity

- Median best VA at last visit (LV) was 0.08 logMAR (range -0.18 to 1.36)
- Magnitude of recovery 2 to 9 ETDRS lines at first observation of clinically relevant recovery (CRR), which increased to 4 to 12 ETDRS lines by LV

Safety

- No new safety signals were observed

Discussion

Patient 1

The most recent eye deteriorated to a Nadir despite treatment with idebenone for nearly 4 months. With maintained treatment both eyes improved although at a different rate and with different magnitude

Patient 2

Patient showed an initial (erratic) improvement over the first 12 months but deteriorated (despite therapy) back to BL levels over the next 2 years. VA never deteriorated to off-chart

Patient 3

This patient showed a positive response after the first 3 months of therapy which normalized the VA after 25 months of treatment

Patient 4

A rare mutation carrier with a moderate visual function loss and a fast and progressive response, resulting in normalization of VA after approximately 3 months on treatment

Patient 5

Treatment was started after 4 years since disease onset. Visual deterioration was very asymmetric and VA in the worst eye showed a temporary improvement (artefact?). Overall, VA was maintained at initial levels

Dose in LHON pediatric population

The safety and efficacy of Raxone in LHON patients under 12 years of age have not yet been established[1]

Pharmacokinetic data from population pharmacokinetic studies, which included pediatric Friedreich's Ataxia patients of age 8 years and above, did not reveal any significant differences in the pharmacokinetics of idebenone. In clinical trials in Friedreich's Ataxia, 32 patients between the ages of 8 and 11 years and 91 patients between the ages of 12 and 17 years received idebenone at ≥ 900 mg/day for up to 42 months[1]

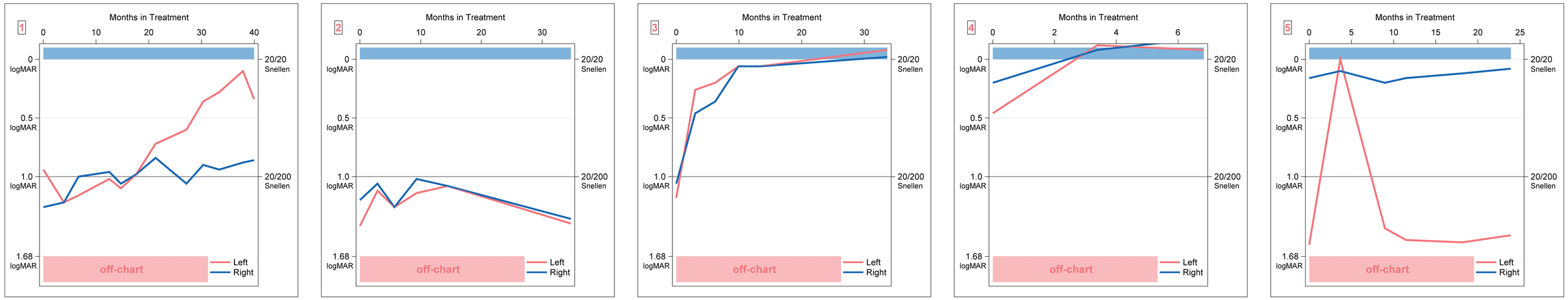
The data presented here indicates that the safety profile of idebenone is not different from that observed in adolescents and adults and VA in pediatric patients as young as 7 years of age can improve/prevent deterioration to off-chart VA with idebenone

Conclusions

Results of this real-world program with idebenone in LHON pediatric patients suggest:

- Safety at the administered doses seems to be in line with that of adult patients
- Treatment with idebenone can result in both stabilization of good residual VA and relevant recovery of lost vision in some patients
- In some eyes/subjects the beneficial effect can continue to progressively improve even after 30 months of therapy. None of the eyes treated deteriorated to off-chart VA over the observation period
- These data indicate that long-term idebenone treatment could be a safe and efficacious therapeutic approach in pediatric LHON patients

Figure 1 - 5. Patient eyes VA along treatment



G3460A carrier, 6.9 years at BL

Left
1.7 months onset at BL
0.94 logMAR at BL
Nadir 3.9 months post BL
Gain of 6 lines from BL
Gain of 8 lines and 4 letters from Nadir

Right
3.5 months onset at BL
1.26 logMAR at BL
Nadir at BL
Gain of 4 lines from BL/Nadir

T14484C carrier, 9.1 years at BL

Left
7.9 months onset at BL
1.42 logMAR at BL
Nadir at BL
Gain of 1 letter from BL/Nadir

Right
7.9 months onset at BL
1.20 logMAR at BL
Nadir at LV
Loss of 1 line and 3 letters from BL

T14484C carrier, 9.8 years at BL

Left
6.0 months onset at BL
1.18 logMAR at BL
Nadir at BL
Gain of 12 lines and 3 letters from BL/Nadir

Right
6.0 months onset at BL
1.06 logMAR at BL
Nadir at BL
Gain of 10 lines and 4 letters from BL/Nadir

A14495G carrier, 11 years at BL

Left
2.4 months onset at BL
0.46 logMAR at BL
Nadir at BL
Gain of 5 lines and 2 letters from BL/Nadir

Right
1.7 months onset at BL
0.20 logMAR at BL
Nadir at BL
Gain of 3 lines and 4 letters from BL/Nadir

G11778A carrier, 11 years at BL

Left
4.1 years onset at BL
1.58 logMAR at BL
Nadir at BL
Gain of 4 letters from BL/Nadir

Right
4.1 years onset at BL
0.16 logMAR at BL
Nadir 9 months post BL
Gain of 4 letters from BL
Gain of 1 line and 1 letter from BL/Nadir

Acknowledgements

The authors would like to thank all patients and health care professionals participating in this Expanded Access Program for their contribution in collecting the data. If you have any questions about this data please contact Dr Xavier Llòria (Xavier.Lloria@Santhera.com)

Conflict of interest

XL and MS are regular employees of Santhera Pharmaceuticals Switzerland Ltd ("Santhera"). TK has been investigator in Santhera - sponsored trials, has been serving on the Scientific Advisory Board and received speaker honoraria from Santhera. FL and CC have received speaker honoraria from Santhera

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2. Priglinger C. et al. A retrospective analysis of childhood onset Leber's Hereditary Optic Neuropathy (LHON) treated with idebenone. Poster Presentation. European Pediatric Ophthalmological Society (EPOS). Budapest, Hungary. 7-8 September 2018
3. Erdei Z. et al. Clinical experience with idebenone in the treatment of adolescents with Leber's Hereditary Optic Neuropathy – 3 case reports. Poster Presentation. European Pediatric Ophthalmological Society (EPOS). Budapest, Hungary. 7-8 September 2018
4. Raxone® EPAR, European Medicines Agency, September 2015

Raxone®, Santhera Pharmaceuticals (Deutschland) GmbH, idebenone 150 mg tablets is not approved in USA

* In the European Union, Raxone® is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON)

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Natural History of Leber's Hereditary Optic Neuropathy (LHON): Findings from a large Patient Cohort

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Background

- LHON is a mitochondrial (mt) disease, affecting both genders but predominantly young men, which leads to functional loss of retinal ganglion cells and subsequent progressive, severe, visual impairment[1-3]
- Rates of spontaneous recovery are low[4]. However, existing knowledge of the disease course and the rate and nature of visual recovery is based on a small group of studies in which recovery outcomes of visual acuity (VA) are inconsistently defined and observation times are variable[5-7]
- We report natural history data up to 60 months (m) follow-up from an international, multicenter LHON medical record survey (MRS)

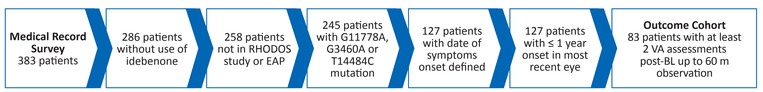
Objectives

- To describe the demographic characteristics and establish the clinical course of VA over 60 m of follow-up, in a standardized natural history dataset, from a large cohort of untreated LHON patients

Methods

- Population: genetically confirmed diagnosis of LHON. No other exclusion criteria were applied
- Collected data: year of birth, gender, mtDNA mutation, medical history, use of idebenone, date of symptoms, onset for each eye, VA assessments (VAA) including date and VA method (ETDRS, Snellen) expressed as logMAR
- Analysis: long term VA evolution in the Outcome Cohort (**Figure 1**)
- Clinically Relevant Recovery (CRR): defined as an improvement from off-chart to reading 1 line on the ETDRS chart, or an on-chart improvement of 2 lines

Figure 1. Patient selection for Outcome Cohort



Results

MRS patient demographics (Table 1)

- Medical records for 383 patients were collected
- Primary mutations represent 95.8% of the LHON subjects (**Table 1**)
- Male gender was more frequent across primary mutation carriers compared to non-primary carriers (> 70% vs. 58.8%, not shown (NS))
- Age at onset has maximum incidence from 15 to 35 years (y) across all mutations
- Onset of symptoms was bilateral in around half of patients across all primary mutations but occurred in nearly two thirds of non-primary patients
- In sequential onset cases, the 2nd eye is affected within a median of 3 m across all mutations but can be as long as 42 y

Outcome Cohort demographics (Table 2)

- 83 patients provided long term VA data (Outcome Cohort)
- Demographic distribution (mutation, gender, age) are representative of the known disease characteristics of LHON (**Table 2**)
- Overall, 59% of the patients were in the 15 to 35 y age range (NS)
- Mean time since symptoms onset in most recent eye was 2 m
- Observation time was from 2.3 m up to 58.7 m with a median of 14.9 m

Change in patient Best VA along observation time (N = 83 patients) (Table 2)

- At baseline (BL), 66.3% of patients in the Outcome Cohort had a VA < 1.0 logMAR
- At Nadir only 4.8% remained in VA < 1.0 logMAR with 63.9% of patients off-chart (> 1.68 logMAR)
- At last visit (LV), nearly half of all patients were off-chart, a 10-fold increase from BL. 18.1% of patients had a final VA < 1.0 logMAR, 3.7 times fewer than at BL

Change in VA from BL at LV (N = 166 eyes) (Figure 2 and 3)

- At LV, 16.3% had a spontaneous VA gain equivalent to at least 2 lines on the ETDRS chart, 20.4% had no Clinically Relevant Change, 63.3% deteriorated by 2 or more lines. The number of eyes deteriorating was 3.9 times higher than those spontaneously improving (**Figure 3, right**)
- 29 eyes (58.6%) that were off-chart at BL never improved from off-chart (NS)
- Worsening can happen regardless of the VA at BL (**Figure 3, left**)
- By VA category, 53% of eyes are off-chart at LV (NS) (**Figure 3, left**)

Table 1. MRS Patient Demographics

	Patients, N = 383
G11778A **G3460A** **T14484C** **Non-primary**	256 (66.8%) 65 (17%) 45 (11.7%) 17 (4.2%)
Male	295 (77%)
Age at onset: **< 12 years** **12 to 15 years** **15 to 35 years** **> 35 years** **Unknown**	 30 (7.8%) 23 (6%) 238 (62.1%) 84 (21.9%) 8 (2.1%)
Bilateral onset	214 (55.9%)
Delta[1] symptoms onset	3 (1.8 – 6) 1 d – 42 y

Values are given as N (%), or median (Q1-Q3) min-max

Table 2. Outcome Cohort

	Patients, N = 83
G11778A **G3460A** **T14484C**	61 (73.5%) 13 (15.7%) 9 (10.8%)
Male	69.8%
Age at onset (years)	26 (19 – 37) 6.0 – 75.0
Months since most recent symptoms onset at BL	1.3 (0.6 – 3.0) 0.0 – 8.6
Months since BL at Last Visit	14.9 (6.4 – 29.7) 2.3 – 58.7
Best VA at BL **< 1.0 logMAR** **1.0 – 1.68 logMAR** **off-chart**	 55 (66.3%) 24 (28.9%) 55 (66.3%)
Best VA at Nadir **< 1.0 logMAR** **1.0 – 1.68 logMAR** **off-chart**	 4 (4.8%) 26 (31.3%) 53 (63.9%)
Best VA at LV **< 1.0 logMAR** **1.0 – 1.68 logMAR** **off-chart**	 15 (18.1%) 28 (33.7%) 40 (48.2%)
CRR from BL **G11778A** **G3460A** **T14484C**	18 (21.7%) 9 (14.8%) 7 (53.8%) 2 (22.2%)
CRR from Nadir **G11778A** **G3460A** **T14484C**	29 (34.9%) 17 (27.9%) 8 (61.5%) 4 (44.4%)

Values are given as N (%), or median (Q1-Q3) min-max

Figure 2. Change in VA at BL, Nadir and LV.
Left: eyes by VA category;
Right: eyes VA logMAR

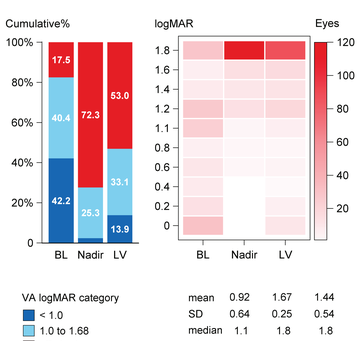
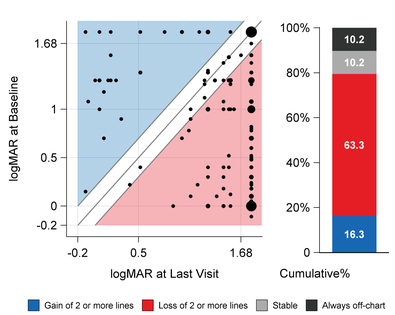


Figure 3. Change in VA at LV from BL (eyes). Left: Final VA with respect to BL value (colors indicate direction of change: blue = improvement; red = deterioration; white = no change); Right: Cumulated % by direction of change



Discussion

- This study provides a new insight into LHON's epidemiology and natural course over time. Despite the large number of patients involved, the lack of mutation testing availability in older historical patient records may represent a potential geographic and time bias. Furthermore, the requirement of having a confirmed mutation might result in an underrepresentation of non-primary mutations
- While G11778A also shows high prevalence in adulthood, non-primary mutations show a trend towards childhood and adolescence. G3460A has the highest percentage of childhood onset amongst all mutations
- The high number of simultaneous onset cases is probably due to lack of precise dates in the medical records (in some cases exact day was not recorded)

Conclusions

- Overall, gender and age of onset and sequential interval time of eye onset are in line with published data. G11778A is the most prevalent mutation, followed by G3460A and then T14484C
- Of the primary mutations, G11778A presents the most frequent cause of disease onset in patients over 35, with G3460A the most frequent in childhood
- Despite this, in terms of Best VA at onset, G11778A and G3460A show very similar profiles. T14484C shows the Best VA values at onset
- Non-primary mutations represent just 4% of the cases collected and include the highest percentage of female patients, children below the age of 15 and the highest percentage of patients with Best VA < 1.0 logMAR at BL (together with T14484C)
- Overall, the spontaneous evolution during the first 5 y after onset is that of a relevant and profound deterioration of VA in nearly two thirds of the eyes. Only 16% of eyes show some spontaneous improvement

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BL: baseline (1st visit after onset); ETDRS: early treatment diabetic retinopathy study; LV: last visit; logMAR: logarithm of the minimum angle of resolution; mt: mitochondrial; m: months; Nadir: worst VA observed during the follow-up; NS: not shown; VA: visual acuity; VAA: VA assessment; y: years

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