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

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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 years)

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) 1

Methods

Retrospective medical chart analysis of patients who were under 12 years of age at start of therapy

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) 1

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,4 has been shown to be efficacious and safe in a large proportion of adult patients, but pediatric data is limited

• Priglinger C. et al.1 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. Erdis E. et al. observed improvement of visual acuity (VA) and visual fields in a 10 year old female treated over 12 months with idebenone (500 mg/day)1

• The safety and efficacy of Raxone® in LHON patients under 12 years of age have not yet been established2

• Pharmacokinetic data from population pharmacokinetic studies, which included pediatric Friedrich’s Ataxia patients of age 8 years and above, did not reveal any significant differences in the pharmacokinetics of idebenone. In clinical trials in Friedrich’s Ataxia, 31 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 months3

• 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

• Safety measured through frequency and severity of adverse events

• 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 (rapid) improvement over the first 12 months but deteriorated (despite therapy) back to BL levels over the next 2 years. Never deteriorated to off-chart

Patient 3

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

Acknowledgements

The authors would like to thank all patients and healthcare professionals participating in this Expanded Access Program for their contribution in collecting the data. In any question about the data please contact Dr. Xavier Llória (xavier.lloria@santhera.com)

Conflict of interest

FL and CC have received speaker honoraria from Santhera 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 and Fl"obenon (Raxone® 150 mg tablets) in 3 divided doses through a Named Patient Scheme under routine clinical practice

All patients received idebenone 900 mg (Raxone® 150 mg tablets) in 3 divided doses through a Named Patient Scheme under routine clinical practice

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 established3

Pharmacokinetic data from population pharmacokinetic studies, which included pediatric Friedrich’s Ataxia patients of age 8 years and above, did not reveal any significant differences in the pharmacokinetics of idebenone. In clinical trials in Friedrich’s Ataxia, 31 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 months3

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/subject 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

References

1. Raxone® Summary of Product Characteristics (SmPC), European Medicines Agency, 2018


4. 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)

Job code: 0-ML-021-0319-V1-1
Natural History of Leber’s Hereditary Optic Neuropathy (LHON): Findings from a large Patient Cohort

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Objective: 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, mDNA 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) and 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.

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 (Table 1)
- 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)

Overview: 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).

References:

9. 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

Acknowledgements

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