Oral 9-cis retinoid for childhood blindness due to Leber congenital amaurosis caused by RPE65 or LRAT mutations: an open-label phase 1b trial

Robert K Koenekoop, Ruifang Sui, Juliana Sallum, L Ingeborgh van den Born, Radwan Ajlan, Ayesha Khan, Anneke I den Hollander, Frans P M Cremers, Janine D Mendola, Ava K Bittner, Gislin Dagnelie, Ronald A Schuchard, David A Saperstein

Summary

Background Leber congenital amaurosis, caused by mutations in RPE65 and LRAT, is a severe form of inherited retinal degeneration leading to blindness. We aimed to assess replacement of the missing chromophore 11-cis retinal with oral QLT091001 (synthetic 9-cis-retinyl acetate) in these patients.

Methods In our open-label, prospective, phase 1b trial, we enrolled patients (aged ≥6 years) with Leber congenital amaurosis and LRAT or RPE65 mutations at McGill University’s Montreal Children’s Hospital. Patients received 7 days of oral QLT091001 (10–40 mg/m² per day). We assessed patients at baseline and days 7, 9, 14, and 30, and then 2 months and every 2 months thereafter for up to 2–2 years for safety outcomes and visual function endpoints including Goldmann visual fields (GVF), visual acuity, and functional MRI assessment. We regarded patients as having an improvement in vision if we noted at least a 20% improvement in retinal area on GVF compared with baseline or a visual acuity improvement of five or more letters compared with baseline in two consecutive study visits (or any improvement from no vision at baseline). This study is registered with ClinicalTrials.gov, number NCT01014052.

Findings Between December, 2009, and June, 2011, we enrolled and treated 14 patients aged 6–38 years who were followed up until March, 2012. Ten (71%) of 14 patients had an improvement in GVF areas (mean increase in retinal area of 28–683%). Six (43%) patients had an improvement in visual acuity (mean increase of 2–30 letters). Self-reported or parent-reported improvements in activities of daily living supported these findings. After 2 years, 11 (79%) patients had returned to their baseline GVF retinal area and ten (71%) had returned to baseline visual acuity letter values. Thus, three (21%) patients had a sustained GVF response and four (30%) had a sustained visual acuity response. Four patients had functional MRI scans, which correlated with visual response or absence of response to treatment. No serious adverse events occurred, although we noted transient headaches (11 patients), photophobia (11 patients), reduction in serum HDL concentrations (four patients), and increases in serum triglycerides (eight patients) and aspartate aminotransferase concentrations (two patients).

Interpretation Non-invasive oral QLT091001 therapy is well tolerated, and can rapidly improve visual function in some patients with Leber congenital amaurosis and RPE65 and LRAT mutations.

Introduction Leber congenital amaurosis is a severe inherited form of retinal degeneration that occurs in about one in 81000 births.1 Patients have significant vision loss from infancy, often leading to nystagmus (oscillations of both eyes) and then progression to severe vision loss or eventual total blindness in most patients. Poor pupillary responses and severely diminished electroretinograms (ERGs) show the loss of light-induced neural circuits in the retina.2 3 19 19 genetic subtypes of Leber congenital amaurosis are known to exist,7 with about 10% of all patients having mutations in LRP65 or RPE65,14 which encode proteins that function in the retinoid cycle. These genetic forms of the disease are characterised by a deficiency of 11-cis retinal,7 8 the visual chromophore that binds to rod and cone opsins and forms the visual pigments (rhodopsin and cone pigments). Normally, visual pigments are activated by light,7 initiating the phototransduction cascade and subsequent signalling to the visual cortex.8 Without activation of visual pigment, vision is not possible.

Chronic deficiency of 11-cis retinal eventually leads to photoreceptor degeneration.9 The interval between the loss of visual function and photoreceptor degeneration creates an opportunity for restoration of visual function. LRAT10 and RPE65 knockout mice1 and RPE6512–14 Briard dogs treated with RPE65 gene replacement15 or substitute chromophore (9-cis retinal)16 have shown recovery of visual function. In addition, recovery of partial vision in some patients with Leber congenital amaurosis due to RPE65 mutations has been reported after surgically delivered recombinant adenovirus-associated virus-mediated gene transfer of wild-type RPE65 cDNA.17–19

11-cis retinal is a very unstable aldehyde and is not conducive to pharmaceutical development.19 QLT091001 (QLT) is a stable synthetic compound converted in the body to 9-cis retinal. 9-cis retinal combines with opsin to...
form isorhodopsin, which also starts the phototransduction cascade when activated by light.19 Oral gavage of 9-cis retinal introduced in RPE65 and LRAT knockout mice rapidly improved vision as measured by ERG, pupillometry, and behaviour.13,20 Administration of 9-cis retinal also helped to preserve the morphology of the retina by improving interface contact between retinal pigment epithelium and rod outer segments. In addition, treatment with 9-cis retinal decreased the content of apo-opsin (unbound to chromophore) in the mice, reducing constitutive activation of the phototransduction cascade (which causes the degeneration in RPE65 mutants19) and thus slower photoreceptor degeneration.13,20 In dogs with RPE65 deficiency, QLT091001 and 9-cis retinal were injected into the vitreous cavity resulting in rapid and significant visual rescue as measured by visual behaviour and ERG.20

These findings led to human clinical trials with QLT091001. A Phase 1a trial in healthy human volunteers was completed (NCT00765427). In this phase 1b, proof of concept trial, we aimed to assess QLT091001 in patients with Leber congenital amaurosis due to RPE65 and LRAT deficiency.

Methods
Study design and patients

In this phase 1b trial, we enrolled patients referred to the McGill University’s Montreal Children’s Hospital by specialists worldwide. Eligible patients were diagnosed with Leber congenital amaurosis attributed to mutations in either LRAT or RPE65. Mutations were confirmed twice, first by a research laboratory (McGill Ocular Genetics Laboratory, Montreal Canada) and second by a Clinical Laboratory Improvement Amendments-certified laboratory (Carver Laboratory, Iowa City, IA, USA, or Nijmegen Diagnostics Laboratory, Nijmegen, Netherlands). The appendix contains a full description of the genotyping. We enrolled patients with a best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of three letters or better at 1 m (equivalent to a Snellen test score of 20/800).

Patients or guardians provided written informed consent or assent. Ethical approval was provided by McGill University Health Center and Montreal Children’s Hospital Research Ethics Board.

Procedures

Patients received an oral dose of 40 mg/m² QLT091001 (ie, a dose within the highest well tolerated dose in healthy volunteers) or a reduced dose of 10 mg/m² QLT091001 once daily for 7 days. After baseline measurements of efficacy and safety outcomes, patients were followed up on days 7, 9, and 14, and at month 1 and month 2, with follow-up once every 2 months when possible thereafter (many patients travelled substantial distances) as long as a therapeutic effect was noted. Baseline visual acuity and GVF scores were the average of two separate pretreatment study visit measurements.

We assessed several visual function endpoints in this trial, including visual acuity (ETDRS chart), visual field area (Goldmann manual kinetic perimetry), photoreceptor activity (rod and cone ERGs according to the International Society for Clinical Electrophysiology of Vision standardised protocol), and colour vision (Ishihara colour plates). We recorded GVFs in each eye and with multiple test lights ranging from V4e to 14e, depending on patients’ visual sensitivity. GVF charts were digitised and isotherm outlines converted to total seeing retinal area for each test light. We took structural measurements of in-vivo retinal architecture (with spectral domain optical coherence tomography) and lipofuscin (fundus autofluorescence) in the central macular retina. Finally, we assessed a subset of patients for changes in visual cortex activity with blood-oxygen-level dependent (BOLD) functional MRI scans (each lasting 256 s) done in a 3T Siemens TRIO scanner with a voxel resolution of 4 mm³. These patients viewed four types of stimuli: greyscale images of faces, greyscale images of houses, high contrast black letters on a white background, and a homogeneous mid-level grey background with a fixation mark only. All scans for all patients occurred within 1 month of baseline. Safety assessments included vital signs, physical examinations, review of systems, electrocardiographs, and clinical laboratory tests.

We converted Goldmann visual field (GVF) areas to retinal area as described by Dagnelie.21 Because of the study design of this phase 1b study, we did not do a statistical analysis to assess significant differences in efficacy measures. We regarded patients as having a positive response to therapy if they had at least a 20% improvement in retinal area on GVF compared with baseline, based on a cross-sectional comparison of GVF area and self-reported everyday activities from Turano and colleagues22 and test–retest results of a similar patient population from Bittner and colleagues,23 and a visual acuity improvement of five or more letters compared with baseline in two consecutive study visits. For GVF, normal symmetrical fields run from about 60° nasally to 90° temporally (horizontal span of 150° in each eye). We regarded patients who had no measurable GVF or visual acuity at baseline to have a positive response if they had GVF or visual acuity measurements on two consecutive visits after treatment. We recorded all self-reported subjective comments about the treatment effects.

This study is registered with ClinicalTrials.gov, number NCT01014052.

Role of the funding source

QLT was the sponsor of the study and provided financial support for the study design, data collection, and data analysis. QLT also provided editorial assistance for figures and tables. The corresponding author had full access to all the data in the study and had final access to all the data in the study and had final
responsibility for the decision to submit for publication. RAS and DAS had full access to all study data.

Results

We enrolled and treated 14 participants between December, 2009, and June, 2011. No patient was excluded from the study and all enrolled patients completed the study. Enrolled patients were aged 6–38 years (table 1). One patient (number 3) was enrolled with a visual acuity score that was lower than the eligibility criteria because spectral domain optical coherence tomography and fundus autofluorescence showed evidence of a viable photoreceptor layer. 12 patients received seven doses of 40 mg/m² per day and 2 patients received a reduced dose of 10 mg/m² per day.

We noted no systemic or ocular serious adverse events. Six of 14 patients developed a transient, moderate-to-severe headache and seven patients developed transient, moderate-to-severe photophobia 12–36 h after receipt of the first dose of QLT091001 (table 2, appendix). Two patients with headache received ibuprofen or acetaminophen (one for 1 day and one for 3 days) and headaches resolved in all patients within 1–2 days after the last daily treatment dose of the study drug. Incidence of photophobia corresponded with patients’ initial vision improvement. Headache and photophobia occurred on the same treatment days in six patients, but not always every day in any patient (appendix). We noted no significant decrease of safety outcomes in any structure related to vision on optical coherence tomography, fundus autofluorescence, or ERG. Serum triglycerides were increased in eight patients and aspartate transaminase concentrations were increased in three patients and HDL was decreased in four patients. These values returned to baseline in all patients by day 60 (appendix).

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<th>Visual acuity response (number of letters)*</th>
<th>Baseline GVF retinal area</th>
<th>Day 14 GVF retinal area</th>
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A list of all adverse events is shown in the appendix.

Table 1: Baseline demographics and visual response data after treatment from day –1 to month 2

Table 2: Adverse events regarded as related to treatment (occurring in ≥2 patients)

Figure 1: Normal GVF assessment
Normal GVF sizes with the V4e and II4e targets in an adult. GVF=Goldmann visual field. OU=both eyes. OD=right eye. OS=left eye.
All 14 patients returned for several follow-up visits beyond day 14 and no patient withdrew from the study. ERGs and measures of colour vision were generally non-detectable at baseline and did not change with treatment. In addition, optical coherence tomography and fundus autofluorescence measurements did not change with treatment.

Six (43%) of 14 patients had improvements in visual acuity, ranging from two to 30 letters (table 1). The median duration of the visual acuity response was 315 days (IQR 111–534). Three (21%) patients had a bilateral response.

Ten (71%) of the 14 patients had improvements in GVF compared with baseline (average of two log retinal

**Figure 2: GVF assessment of patient 1 (responder)**
On several baseline GVFs (for 5 years before enrolment), patient 1 had relatively symmetrical circular 30° fields with the V4e target and could not identify the I4e target. After 7 days of dosing, she developed new symmetrical temporal islands on day 7 OU and saw the I4e target in OD. At 4 months, the GVFs with the V4e target were symmetrical from 50° nasally to 90° temporally, and she identified the I4e target in both eyes (~5°). GVF size more than doubled compared with baseline. At 19 months, the GVF by the V4e target decreased to 50–80°, and although the I4e target was visible, it was much smaller than it had been. At 26 months after dosing, GVF by the V4e target declined further to 40–70°. The GVF area for the I4e target declined by more than 50% since 19 months and at 26 months the I4e target was not visible (suggesting return to baseline field). GVF=Goldmann visual field. OU=both eyes. OD=right eye. OS=left eye.

**Figure 3: GVF assessment of patient 3 (responder)**
On day 2, symmetrical central islands of vision developed with the V4e target light, which remained until day 8, corresponding to patient 3 seeing herself in a mirror and an increase in visual acuity from 0 to 2 letters. On day 13, the results are unreliable, but at 1–2.5 months after dosing she sees the V4e again; only to return to baseline by 3 months. GVF=Goldmann visual field. OU=both eyes. OD=right eye. OS=left eye.
area values): nine had bilateral responses and one had a unilateral response (figures 1–6, table 1). The magnitude of response ranged from a mean increase of 28% to 683% in GVF area with a median duration of response of 163 days (table 1, appendix). On day 14, 7 days after end of treatment, the overall mean GVF improvement was almost 100% compared with baseline (figure 7) in the 13 patients with detectable GVF at baseline. Patients with small to medium baseline GVF areas (up to 70° average diameter or 250 mm² retinal area) tended to have greater improvements than did patients with larger baseline GVF sizes (figure 7). The appendix contains details of the subjective patient responses.

Figure 4: GVF assessment of patient 5 (responder)
Baseline V4e is relatively normal, but IV4e, I4e, and I4e are severely decreased in size. IV4e is especially abnormal in the superior field. On day 9, patient 5 had enlargement of the GVF, especially to the IV4e target, the II4e target, and the I4e target. At 18 months, GVF is starting to decrease back to baseline. Notably, the superior field measured by the IV4e target decreased first. GVF=Goldmann visual field. OU=both eyes. OD=right eye. OS=left eye.

Figure 5: GVF assessment of patient 9 (responder)
After receipt of the 10 mg/m² dose, little change in GVF was noted between baseline and day 7. However, at 2 months after dosing, we noted a large increase in the GVF measured by the III4e target. GVF=Goldmann visual field. OU=both eyes. OD=right eye. OS=left eye.

Figure 6: GVF assessment of patient 16 (non-responder)
Severe central and pericentral abnormalities in the GVF that did not improve after treatment. GVF=Goldmann visual field. OU=both eyes. OD=right eye. OS=left eye.
very large baseline GVF retinal areas had very low treatment effects (ceiling effect). GVF = Goldmann visual field.

Data for 13 patients with detectable GVF at baseline. Error bars show standard error of the mean. Patients with Figure 7: Mean percentage change in GVF size retinal area compared with baseline

Overall, we regarded 11 patients (79%) as visual function responders with two consecutive study visit improvements in GVF retinal area of at least 20%, and/or at least a five letter improvement in visual acuity (or new ability to see any letters) with at least one eye within 2 months of treatment. Of these responders, five responded in terms of GVF and visual acuity, five in GVF only, and one in visual acuity only (table 1). Ten responders had self-reported improvements in activities of daily living.

We assessed four patients with functional MRI (one GVF responder [patient 9] and three non-responders [patients 13, 15, and 16]). Scans were done between day –13 and day –2 before treatment and at day 8 to day 13 after treatment. The time between scans was 12 days for patient 9, 15 days for patient 13, 19 days for patient 15, and 14 days for patient 16. Functional MRI data were analysed separately by participant to yield a contrast map for each session and its corresponding variance (p=0.01 to p=0.0001, false discovery rate). We combined session level maps in a second-level fixed-effects analysis to test whether there was a difference between the session-level responses. Figure 8 shows that when face targets were shown to patient 9 (a responder by GVF criteria), a change in visual cortical activation occurred after treatment. Primarily, the activated area of occipital cortex was larger than it was at baseline. This finding was confirmed with intersession statistics corrected for multiple comparisons with a cluster-based Monte Carlo simulation with a cluster-forming threshold of p<0.001, 10 000 iterations, and a cluster cutoff of p<0.05. These increases in cortical activity were consistent with the increases in visual field area (GVF) of patient 9 (figures 1–6). Second, two new areas of cortical activation appeared that were not present at baseline (figure 8, arrows). Furthermore, when house and letter visual targets were shown to patient 9, we noted another increase in occipital cortical activity compared with baseline (figure 8). Functional MRI data for participant 16 and the other two patients with no increase in GVF retina area did not show any changes, which is consistent with the absence of notable changes in GVF after treatment (appendix).

Discussion

In our phase 1b trial of 14 patients with Leber congenital amaurosis caused by RPE65 and LRAT mutations, treatment for 7 days with oral QLT091001 led to restoration of clinically meaningful visual function in most patients. These findings were supported by self-reported or parent-reported improvements in vision related activities of daily living (appendix) and in a subgroup of patients studied objectively with functional MRI (panel).

GVF and visual acuity proved to be reliable and sensitive measures of efficacy. Because of their relevance in clinical assessment of visual function, we focused on analysis of these endpoints. Such analysis is in accordance with several previous natural history studies of Leber congenital amaurosis. Jacobson and colleagues noted that the GVF was measurable in 29 of 30 patients aged 4–55 years old with Leber congenital amaurosis and RPE65 mutations. None of their patients was able to detect the smallest test light of the GVF in the central retinal area, the I-4e. In our trial, as a result of treatment, four patients developed the ability to see the I-4e target. Longitudinal data documenting the natural history of kinetic fields (GVF) in patients with Leber congenital amaurosis and RPE65 mutations from Jacobson, Paunescu, and colleagues suggest a relatively rapid and inexorable decline of GVF size between 10 years and 30 years of age. These studies suggest that the GVF test accurately measures the progressive vision loss in patients with Leber congenital amaurosis and RPE65 mutations and that the GVF improvements in this study are attributable to treatment.

ERG measures did not improve in this trial or three gene replacement trials. However, animal models of treatment have shown notable improvements in ERG amplitudes. The absence of response in the human trials is probably attributable to the level of retinal degeneration at the time of therapy. In the preclinical trials most, if not all, of the animals were treated within days (mice) or weeks (dogs) after birth with relatively moderate retinal degeneration. The mass effect necessary to produce a measurable ERG response is not possible if a significant portion of the retina has degenerated irretrievably. However, the lack of ERG improvement from the retina does not preclude functional improvement.

The treatment effect in six patients lasted to their last study visit (≥12 months; appendix). Several reasons could explain the long duration of action. Preclinical studies showed that restoration lasted beyond the dosing schedule in dark-reared animals tested under dim light conditions. Learning effects have been raised as a possible explanation, but most patients had many years of experience with both GVF and visual acuity measurements.
A placebo effect is also unlikely because of the robust and stable, symmetric bilateral improvements, and the variable timing of the drop-off back to baseline visual function. A drug depot could have occurred either in the retina or retinal pigment epithelium, in adipose tissue, or in the liver of patients with RPE65 deficiency. Further preclinical work is underway to better understand this long-term effect of treatment noted in some patients.

We noted no serious adverse events in this trial. QLT091001 is a retinoid compound and the safety signals are consistent with this drug class, including transient headaches relieved with over the counter NSAID treatment. Patients with headaches had normal eye examinations, with no evidence of intracranial hypertension, which is a known side-effect of retinoid class drugs. What might be unique to this compound is the photophobia that accompanied the headaches. Such an effect might be attributable to an increase in photoreceptor activity conferred by supplementing the chromophore in previously inactive cells. Because the onset of headaches was often accompanied by photophobia and preceded the development of the improved visual response, the headache might also be due in part to visual recovery. Noseda and colleagues28 discovered a mechanism for exacerbation of headache by light, prevalent in blind individuals who maintain non-image-forming photoregulation with massive rod and cone photoreceptor degeneration. On the basis of these findings, headaches in the patients might in part be caused by the increased activity of retinal pathways that modulate the activity of dura-sensitive thalamocortical neurons.

Non-randomised, prospective gene therapy clinical trials to treat Leber congenital amaurosis related to RPE65 deficiency have reported visual function improvements in some patients and have garnered much attention in the medical and lay literature. This therapy requires the patient to undergo a surgical procedure to remove vitreous and create a small retinal detachment by injection of the gene vector under the retina. In addition to the potential side-effects from the vector, patients were also exposed to potential surgical side-effects such as anaesthesia risks, retinal detachment, macular hole, and cataract formation. At present, only a small portion of the retina can be treated at one time, and another surgery is needed to treat the contralateral eye. Gene replacement could theoretically cure the disease with one treatment, but a recent report by Cideciyan and colleagues29 suggests that although RPE65 replacement might improve vision for a period of time, it does not stop the degeneration of the retina. For this reason, alternative therapies might be needed. Oral chromophore replacement therapy is non-invasive, reaches the entire retina of both eyes, and can be withdrawn if necessary. A synthetic retinoid is not without safety concerns as well. Because such therapy would involve a retinoid class drug, known systemic side-effects exist, some of which were noted in patients of this trial. Potentially, ocular side-effects could also occur, although no such

![Panel: Research in context](image)

**Systematic review**

We searched PubMed for controlled trials published in English before Nov 1, 2013, that assessed oral drug treatments for Leber congenital amaurosis and retinitis pigmentosa attributable to mutations in RPE65 and LRAT. We used the MeSH terms (“inherited retinal disease” OR “LCA” OR “RP” OR “RPE65” OR “LRAT”) AND “trial”. We also searched reference lists from selected clinical trial studies for secondary resources. We only identified gene therapy treatment studies (as cited in the report) related to vision loss caused by RPE65 mutations. For example, human gene replacement experiments30–32 have shown that local rescue in the operated eye can improve local function in patients with RPE65 deficiency. All other controlled studies (eg, vitamin supplement studies in patients with retinitis pigmentosa) did not investigate the inherited retinal diseases due to mutations in specific genes. Recently MacLaren and colleagues33 showed the same gene treatment effect for advanced choroideremia.

**Interpretation**

To our knowledge, our study showed for the first time that an oral drug (QLT 091001) can bypass the block in the retinoid cycle (created by loss of RPE65 and LRAT), reach the retinas of both eyes, and improve visual function as measured by Goldmann visual field, visual acuity, and functional MRI, and that these controlled efficacy measures correlate with subjective observations of the patients. Sustained treatment effects with multiple dosing need further assessment.
events were reported in patients of this trial. Notably, the patients in this trial were treated with the maximum dose tested in initial safety studies. Most retinoid side-effects seem to be dose dependent.19 In our phase 1b trial, the drug was also tested at a reduced dose (10 mg/m² per day) in two patients and still had an effect but with fewer reported adverse events. Trials to further explore the efficacy and potential side-effects of the drug are ongoing.

Although the significance of the trial is restricted because of the small number of patients enrolled, the single course of therapy, and the open-label design, the trial showed that treatment with QLT091001 was well tolerated and resulted in clinically meaningful improvements in visual function in most patients.

Contributors
RKK was the principal investigator and responsible for study design, genetic testing, data collection, data interpretation, and writing. RS, JS, and LvdB were responsible for data collection, genetic testing, and recruitment of patients. RA and AK were responsible for data collection. AIdH was responsible for genetic testing and patient identification. FPMC was responsible for genetic testing, patient recruitment, and patient identification. JDM, AKB, GD, RAS, and DAS were responsible for study design, data collection, and writing. JDM was responsible for the collection and interpretation of the fMRI data, and was masked to the other visual function results.

Declaration of interests
RKK, AKB, and GD are independent researchers (basic and clinical scientists) at academic institutions (McGill and John’s Hopkins University), and worked as consultants of QLT on the drug development trial. RAS and DAS are consultants for QLT. DAS has an equity stake in QLT and is an inventor on patents directly involved with the technology. Foundation Fighting Blindness Canada, Canadian Institutes for Health Research (CIHR), Fonds de la Recherche en Santeé et Bien-être du Quebec (FRSQ), and Reuse Vision contributed to the genotyping of the patients by research grants to RKK. All other authors declare that they have no competing interests.

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References