Clinical science

Three-year efficacy and safety of repeated low-level red-light therapy for myopia control: a multicentre real-world study

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ABSTRACT

Background To evaluate the efficacy and safety of repeated low-level red-light (RLRL) therapy for controlling myopia progression over 3 years in real-world settings.

Methods This multicentre cohort study included participants currently undergoing RLRL treatment, identified from electronic medical databases in three hospitals (myopic children and adolescents aged 7–18 years, who were prescribed RLRL therapy from 1 June 2018 to 1 June 2023), using stratified random sampling based on RLRL treatment duration (≥0.5–1 year, ≥1–2 years, ≥2–3 years and ≥3 years), with approximately 90 participants in each group. All participants voluntarily received RLRL therapy twice a daily (3 min/session, ≥4-hour interval), 5–7 days/week.

Results Among 362 participants, 90 were treated for ≥0.5–1 year (median 0.64 year), 91 for ≥1–2 years (median 1.40 years), 90 for ≥2–3 years (median 2.30 years) and 91 for ≥3 years (median 3.65 years). The satisfactory myopia control rate (defined as annual axial elongation ≤0.10 mm) was 72.53% (95% CI 62.17 to 81.37) over ≥3 years of RLRL treatment, with annual axial length change of 0.06 mm/year (95% CI 0.03 to 0.08). No subjective visual function damage was documented by best-corrected visual acuity, and no treatment duration-dependent changes in objective full-field electroretinogram were observed. A minimal, reversible optical coherence tomography change was noted in four eyes which did not impact visual function.

Conclusions This real-world study demonstrates that RLRL therapy provides promising long-term efficacy and safety in myopia control over 3 years among Chinese myopic children and adolescents.

Trial registration number NCT05871840.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Repeated low-level red-light (RLRL) therapy has been shown in randomised controlled trials to slow axial elongation and refractive error progression in children with myopia.
⇒ The efficacy of RLRL treatment has been demonstrated for up to 2 years with good safety in controlled trial settings.
⇒ The longer-term (≥3 years) effectiveness and safety of RLRL therapy in real-world populations remain unknown.

WHAT THIS STUDY ADDS

⇒ This multicentre real-world study shows that RLRL therapy maintains myopia control efficacy over 3 years among myopic children and adolescents, with 72.5% of children achieving satisfactory axial elongation control (annual axial elongation ≤0.10 mm).
⇒ The myopia control effect declined slightly after the first 2 years but remained clinically meaningful.
⇒ No subjective visual function loss was detected by best-corrected visual acuity, and objective full-field electroretinogram parameters showed no treatment duration-related changes.
⇒ Minimal, reversible OCT changes were noted in four eyes, without impact on visual function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates that RLRL therapy remains effective and safe for myopia control over 3 years in real-world settings, providing valuable long-term evidence.
⇒ Future research is warranted to elucidate the underlying mechanisms of RLRL therapy.

INTRODUCTION

Repeated low-level red-light (RLRL) therapy is an emerging approach for myopia prevention and control, with the innovative and effective myopia control method highlighted in the latest 2023 Digest of the International Myopia Institute (IMI).[1] A number of randomised controlled trials (RCTs) have revealed that RLRL slowed axial elongation and refraction progression by 36.2%–69.4% and 53.9%–76.6% over 1 year when comparing with single-vision spectacles (SVS), with particularly strong efficacy seen in highly myopic populations.[2–5] This myopia control effect was sustained over 2 years in a subsequent post-trial follow-up

study.[6] Furthermore, the combination of RLRL therapy with orthokeratology has also been shown to optimise axial elongation management among myopic children.[7] However, the longer-term (3 years and beyond) efficacy and safety of RLRL remains unclear.

Although RCTs serve as the gold standard of clinical evidence, they are conducted under highly controlled conditions with strict selection criteria, which might not reflect the actual effect of an intervention and requires validation in real-world settings.[8] In China, more than 100 000 children and teenagers have been or are currently treated with RLRL therapy as of 2023. This extensive duration of RLRL therapy's market presence, combined with the large number of active users, provides a unique opportunity to conduct a real-world study to address the gaps in the understanding of long-term efficacy and safety of RLRL therapy in real-world circumstances.

Therefore, this study aims to answer the following questions: (1) What is the long-term efficacy of RLRL therapy for myopia control over 3 years? (2) Does the RLRL efficacy for 3 years decrease compared with 6 months, 1 year and 2 years? (3) What is the long-term safety profile of RLRL therapy in terms of subjective and objective visual function as well as structural assessments?

METHODS

Study design and population

This observational multicentre cohort study was conducted at three tertiary hospitals in China, including Shenzhen Guangming District People's Hospital, The Second Affiliated Hospital of Wannan Medical College and The First Affiliated Hospital of Baotou Medical College. Using hospital electronic databases, we identified 2529 children and adolescents aged 7–18 years who received RLRL therapy between 1 June 2018 and 1 June 2023 with myopia ≤ −1.00 dioptres (D) in both eyes (spherical equivalent refraction (SER) by cycloplegic or non-cycloplegic refraction). Exclusion criteria were: not currently undergoing RLRL therapy; incomplete baseline data (axial length (AL), SER, best-corrected visual acuity (BCVA)); strabismus; binocular vision abnormalities; ocular/systemic diseases; or history of intraocular surgery/laser treatment. After exclusions, 924 children and adolescents were eligible.

To obtain a representative cohort, we implemented stratified random sampling based on both treatment duration (≥0.5–1 year, ≥1–2 years, ≥2–3 years and ≥3 years) and study centre. The required number of participants for each treatment-duration group was determined a priori, as detailed in the 'Sample Size' section. Accordingly, in each of the three centres, eligible participants were assigned to the four duration strata, and computer-generated random sequences were used to select approximately 30 participants per stratum per centre. All selected participants were contacted strictly following this predetermined random order via telephone, with no manual selection. If an invitee declined, the next individual in the random sequence was contacted. This standardised prespecified sampling procedure was applied consistently across centres to minimise selection bias and enhance reproducibility.

The study protocol was approved by the Institutional Review Board of Shenzhen Guangming District People's Hospital (LL-KT-2023006) and subsequently obtained by all study sites. Oral and written informed consent was obtained from participants and their legal guardians. The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. This study was registered on ClinicalTrials.gov (NCT05871840) and followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

RLRL therapy

In addition to wearing SVS, participants voluntarily purchased and received RLRL therapy using a home desktop device (Eyerising, Suzhou Xuanjia Optoelectronics Technology, Jiangsu, China) with semiconductor laser diodes delivering low-level red light (650±10 nm).[2] Children and adolescents used the device at home twice daily for 3 min/session, ≥4 hour apart, 5–7 days/week, under guardian supervision. Treatment compliance was tracked through an online automated log. If two consecutive sessions were missed, the system sent reminder messages to guardians. Treatment cessation details (reason, duration, resumption date) were collected via questionnaire. Treatment duration was calculated as the interval between initial therapy and follow-up and classified as ≥0.5–1 year, ≥1–2 years, ≥2–3 years or ≥3 years.

Data collection

Given the retrospective nature, baseline data were extracted before initiation of RLRL therapy. Baseline demographics, examination date, RLRL start date and ophthalmic data (biometrics, refraction, visual acuity, eye position, slit-lamp assessment) were obtained from medical records or participant-provided reports. The interval between baseline evaluation and therapy initiation was within 2 weeks. Full-field photopic electroretinogram (ffERG) and optical coherence tomography (OCT) were not performed at baseline.

Follow-up uncorrected visual acuity (UCVA) and BCVA at 4 m were measured with the ETDRS logMAR E chart (Guangzhou Xieyi Weishikang or Shijia SJ-LED-03) by trained optometrists under adequate lighting. AL was assessed before cycloplegia using non-contact partial coherence interferometry (IOL Master XP/500, Carl Zeiss Meditec; or SW-9000, Suoer). The same device model was used at baseline and follow-up to ensure measurement comparability. Five AL readings were averaged, with error ≤0.05 mm. Non-cycloplegic and cycloplegic autorefraction was performed three times (Topcon KR 800 or Nidek ARK-1), and averaged to a precision of 0.25 D. Cycloplegia was induced with three drops of compound tropicamide (0.5% tropicamide, 0.5% phenylephrine) at 0, 5 and 10 min. Full cycloplegia was confirmed when pupil diameter ≥5 mm and light reflex was absent after an additional 15 min.

Follow-up ffERG was recorded using the RETeval system (LKC Technologies) following the ISCEV standards with Sensor Strip skin electrodes.[9] Considering the RLRL device's visible red light and the difficulty of prolonged testing in children, two photopic responses (2.0 Hz and 28.3 Hz, 85 Td/s on 850 Td background) were measured in both eyes after 10 min adaptation under around 300 lux.[10] Three reliable measurements were averaged by experienced examiners. OCT images were obtained with Topcon DRI OCT Triton, Zeiss Cirrus 5000 or Big Vision BV1000 using horizontal/vertical and radial scans under cycloplegia. Fundus photographs centred on the fovea were taken with Topcon DRI OCT Triton, GAUSH Toka TNF507 or Suoer SW-8800. OCT and fundus images with poor quality, blinking or motion artefacts were retaken until sufficient quality was achieved.

Follow-up data were first recorded in paper medical records and reports, then entered into the Electronic Data Capture (EDC) system on the same day. Study coordinators supervised

data integrity and verified entries against original reports to ensure accuracy.

Outcomes

Outcomes included satisfactory myopia control rate, annual changes in AL and SER, and changes in UCVA and BCVA post ≥0.5–1 year, ≥1–2 years, ≥2–3 years and ≥3 years of RLRL usage. Satisfactory myopia control was defined as annual axial elongation ≤0.10 mm.[7 11] This threshold is supported by evidence from the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study and IMI report, showing that children and teenagers exhibit a normal physiological axial elongation of approximately 0.10 mm/year.[12 13] Although physiological axial growth varies with age, a single unified threshold was adopted in this study to allow consistent comparisons across treatment-duration groups and to align with prior myopia research.[12 13]

At follow-up, participants and parents completed questionnaires on potential adverse events (including but not limited to dazzling, short-term glare and flash blindness). Duration of afterimages, especially those >5 min, was documented. Serious adverse events were defined as sudden vision loss ≥2 lines or new central scotoma. All adverse events were recorded in the EDC system and reported individually.

ERG waveforms, OCT images and fundus photographs were reviewed at the reading centre by two independent ophthalmologists (Y.C., W.W.) masked to participant characteristics. ERG records with poor compliance (eg, low signal-to-noise ratio causing unmeasurable implicit time/amplitude or abnormal eye widening on screenshots) were excluded. Auto-generated a-wave, b-wave and 28.3 Hz flicker implicit times and amplitudes were compared across treatment groups. OCT and fundus images were carefully reviewed with reference to a prior case report of RLRL-related retinal damage.[14] Discrepancies were resolved by a senior ophthalmologist (M.H.).

Sample size

Based on previous research,[6 11] about 55% of children achieved satisfactory myopia control after 6 months to 2 years of RLRL. Assuming a decrease to 30% after 3 years, 81 participants per treatment-duration group were needed for a two-sided α=0.05 and 90% power. To improve reliability, the sample size was increased by 10% to 90 per group.

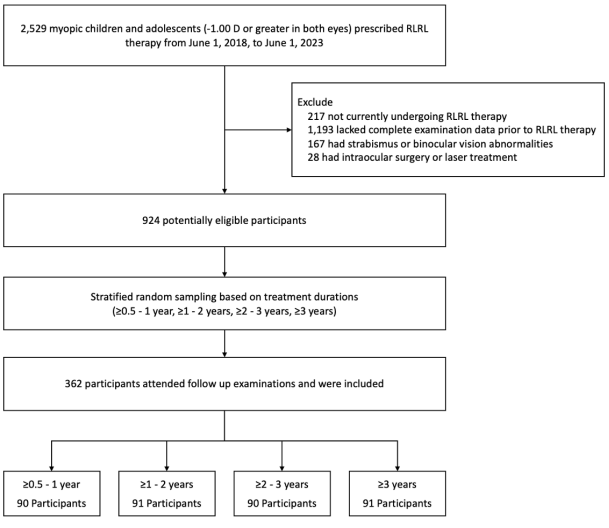

Figure 1 Study flowchart. D, dioptre; RLRL, repeated low-level red-light.

Statistical analyses

Baseline demographics, ophthalmic data, RLRL duration and photopic ffERG parameters were summarised descriptively by treatment duration. Quantitative variables were presented as mean (SD) or median (IQR), and categorical variables as number (percentage). Continuous variables were compared using ANOVA or Kruskal-Wallis tests, and categorical variables using $\chi 2$ or Fisher's exact tests. Ocular parameters were analysed from the right eye only (n=362).

The incidence of satisfactory myopia control and the exact 95% CIs were calculated with the Clopper-Pearson method for all duration groups. Annual AL and SER change rates were computed as mean change from baseline to follow-up divided by treatment duration. Cycloplegic objective SER and non-cycloplegic objective/subjective SER were compared between baseline and follow-up. Differences in satisfactory control rates, AL and SER outcomes were evaluated for ≥0.5–1, ≥1–2 and ≥2–3 year groups versus ≥3 years. Multivariate logistic and linear regression identified baseline factors associated with satisfactory control and annual axial elongation. UCVA and BCVA changes were categorised as loss ≥2 lines, no change (±1 line) or gain ≥2 lines; follow-up BCVA was further classified as Snellen 20/25 or 20/20. Subgroup analyses compared satisfactory control and annual axial change by baseline age, sex, ethnicity, cycloplegic SER and AL. The proportion with annual axial shortening >0.05 mm was also analysed.[15] All analyses were performed using Stata (V.17, StataCorp, Texas, USA). A two-sided $p<0.05$ indicated statistical significance.

RESULTS

Participant characteristics

Of 924 potentially eligible participants, 362 myopic children and adolescents were randomly invited and examined from July to December 2023: 90 treated for ≥0.5–1 year (median 0.64), 91 for ≥1–2 years (median 1.40), 90 for ≥2–3 years (median 2.30) and 91 for ≥3 years (median 3.65) (figure 1). Participant distribution across study sites is shown in online supplemental table S1. Fifteen children reported temporary discontinuation of RLRL (1 week-3 months) due to travel or illness, all resuming therapy afterward.

Table 1 shows the baseline demographic and ocular characteristics and treatment years among participants by treatment duration. Participants with ≥3 years' RLRL treatment were younger than those in the ≥0.5–1 year group at baseline (mean (SD), 9.24 (1.80) vs 10.47 (2.03)] years, $P_{Bonferroni}<0.001$). No significant differences were observed among groups in baseline sex, ethnicity, cycloplegic SER, AL, UCVA or BCVA.

Satisfactory myopia control

Over ≥3 years of RLRL, the satisfactory myopia control rate was 72.53% (95% CI 62.17 to 81.37) (table 2). The rates for ≥0.5–1, ≥1–2 and ≥2–3 years were 88.89% (95% CI 80.51 to 94.54), 89.01% (95% CI 80.72 to 94.60) and 82.22% (95% CI 72.74 to 89.48), respectively. The efficacy declined after ≥3 years compared with ≥0.5–1 and ≥1–2 years, but was similar to ≥2–3 years. Multivariate logistic regression showed older age (Odds ratio (OR)=0.79; 95% CI 0.67 to 0.93; P=0.004) and shorter treatment duration (OR=1.43; 95% CI 1.14 to 1.80; P=0.002) was associated with higher achievement of satisfactory myopia control (online supplemental table S2).

Table 1 Baseline characteristics and treatment years of participants stratified by RLRL treatment duration

	≥0.5–1 year	≥1–2 years	≥2–3 years	≥3 years	P value
No. of participants	90	91	90	91	—
Age, years					**0.001***
4–7	7 (7.78)	11 (12.09)	23 (25.56)	27 (29.67)	
8–13	80 (88.89)	77 (84.62)	65 (72.22)	63 (69.23)	
14–17	3 (3.33)	3 (3.30)	2 (2.22)	1 (1.10)	
Mean	10.47 (2.03)	10.00 (2.09)	9.62 (2.05)	9.24 (1.80)	
Median	10.24 (8.84, 12.23)	9.54 (8.60, 11.36)	9.30 (7.98, 11.08)	8.92 (7.83, 10.64)	
Sex, %					0.404†
Male	45 (50.00)	47 (51.65)	54 (60.00)	54 (59.34)	
Female	45 (50.00)	44 (48.35)	36 (40.00)	37 (40.66)	
Ethnicity, %					0.234*
Han	83 (92.22)	83 (91.21)	88 (97.78)	86 (94.51)	
Others	7 (7.78)	8 (8.79)	2 (2.22)	5 (5.49)	
SER, D					0.806‡
Mean	−2.83 (1.73)	−3.22 (2.02)	−3.33 (2.23)	−2.74 (1.44)	
Median	−2.12 (-3.38, −1.75)	−2.50 (-3.75, −2.00)	−2.88 (-4.62, −1.75)	−2.31 (-3.44, −1.75)	
AL, mm					0.517§
Mean	24.97 (1.01)	24.85 (1.24)	24.88 (0.97)	24.74 (0.85)	
Median	24.84 (24.20, 25.74)	24.62 (24.16, 25.40)	24.87 (24.13, 25.48)	24.60 (24.16, 25.07)	
UCVA, logMAR					0.483§
Mean	0.70 (0.34)	0.66 (0.30)	0.67 (0.28)	0.61 (0.22)	
Median	0.65 (0.40, 0.95)	0.60 (0.50, 0.90)	0.70 (0.40, 1.00)	0.60 (0.40, 0.70)	
BCVA, logMAR					0.809‡
Mean	0.01 (0.03)	0.01 (0.04)	0.01 (0.03)	0.01 (0.04)	
Median	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Treat duration, years					**<0.001**§
Mean	0.69 (0.17)	1.41 (0.28)	2.32 (0.25)	3.75 (0.61)	
Median	0.64 (0.55, 0.84)	1.40 (1.16, 1.61)	2.30 (2.10, 2.53)	3.65 (3.23, 4.22)	

Data were presented as mean (SD) or median (IQR) for continuous variables or number (%) for categorical variables. Boldface indicates statistical significance.
*Data were compared using Fisher's exact test.
†Data were compared using $\chi 2$ test.
‡Data were compared using Kruskal-Wallis test.
§Data were compared using analysis of variance test among groups.
logMAR=logarithm of the minimum angle of resolution.AL, axial length; BCVA, best corrected visual acuity; D, dioptre; RLRL, repeated low-level red-light; SER, spherical equivalent refraction; UCVA, uncorrected visual acuity.

Changes in AL, SER and visual acuity

The mean annual AL changes were −0.22 mm/year (95% CI −0.27 to −0.17) for ≥0.5–1 year, −0.07 mm/year (95% CI −0.10 to −0.04) for ≥1–2 years, 0.008 mm/year (95% CI −0.02 to 0.03) for ≥2–3 years and 0.06 mm/year (95% CI 0.03 to 0.08) for ≥3 years. The axial change per year increased with treatment duration (table 2). Age and treatment duration correlated significantly with annual AL change (both Ps <0.001; online supplemental table S2). The mean annual cycloplegic objective SER changes were 0.02 D/year (95% CI −0.10 to 0.14) for ≥3 years (online supplemental table S3).

UCVA change distribution across groups is shown in online supplemental table S4 (baseline UCVA available for 163 participants, 45.03%). All participants achieved BCVA ≥20/25 at follow-up, and no BCVA loss ≥2 lines occurred in any group (online supplemental table S4).

Table 2 Satisfactory myopia control rate and annual change in AL following RLRL therapy by treatment duration

		Satisfactory myopia control rate		Annual change in AL	
	N	% (95% CI)*	Difference (95% CI)	mm/year (95% CI)	Difference (95% CI)
≥0.5–1 year	90	88.89 (80.51 to 94.54)	16.36 (5.12 to 27.60)	−0.22 (−0.27 to −0.17)	−0.27 (−0.33 to −0.22)
≥1–2 years	91	89.01 (80.72 to 94.60)	16.48 (5.29 to 27.68)	−0.07 (−0.10 to −0.04)	−0.12 (−0.16 to −0.09)
≥2–3 years	90	82.22 (72.74 to 89.48)	9.69 (−2.41 to 21.80)	0.008 (−0.02 to 0.03)	−0.05 (−0.08 to −0.02)
≥3 years	91	72.53 (62.17 to 81.37)	—	0.06 (0.03 to 0.08)	—

Satisfactory myopia control rate was defined as annual AL change ≤0.1 mm/year following treatment. Differences in satisfactory myopia control rates and annual changes in AL were calculated for the ≥0.5–1 year, ≥1–2 years and ≥2–3 years groups compared with the ≥3 years group, respectively.
*CIs were calculated with Clopper-Pearson method.
AL, axial length; RLRL, repeated low-level red-light.

Table 3 Implicit time and amplitude of photopic full-field ERG in participants following RLRL therapy stratified by treatment duration

	≥0.5–1 year	≥1–2 years	≥2–3 years	≥3 years	P for trend*
Photopic cone a-wave†					
Implicit time (ms)	12.38 (0.72)	12.38 (0.87)	12.28 (0.71)	12.43 (0.65)	0.694
Amplitude (μV)	8.31 (2.66)	7.91 (2.66)	8.36 (2.36)	7.80 (2.48)	0.508
Photopic cone b-wave†					
Implicit time (ms)	27.15 (0.78)	27.15 (0.77)	27.15 (0.78)	27.31 (0.85)	0.691
Amplitude (μV)	35.39 (12.39)	34.70 (11.10)	36.42 (10.07)	32.89 (11.09)	0.557
Photopic flicker†					
Implicit time (ms)	23.95 (0.50)	23.80 (0.53)	23.86 (0.54)	23.93 (0.65)	0.095
Amplitude (μV)	29.98 (8.07)	28.75 (7.68)	31.03 (7.50)	27.52 (8.14)	0.587

Data were presented as mean (SD).
*Adjusted for age, sex and axial length.
†Full-field ERG data (n=34, 9.42%) with poor compliance or improper inspection operation were excluded in the analysis for each step.
ERG, electroretinogram; RLRL=repeated low-level red-light therapy.

Safety

No serious adverse events, including sudden vision loss ≥2 lines or central scotoma, were observed. No participant reported glare or flash blindness. Among 358 participants (98.90%), afterimages lasted 1–2 min in 290 (81.01%) and 3–5 min in 68 (18.99%); none exceeded 5 min.

At follow-up, 361 children (99.72%) completed ffERG on two photopic responses; one child did not due to intolerance. After excluding 34 records (9.42%) for poor compliance or improper operation, no significant differences were found in photopic cone a-wave/b-wave implicit times and amplitudes across treatment durations (≥0.5–1, ≥1–2, ≥2–3, ≥3 years). Photopic flicker response (implicit time and amplitude) also remained consistent among groups. These results indicate RLRL does not cause measurable retinal function changes or adverse effects regardless of duration (all P_{raw}s and $P_{adjusted}$s for trend >0.05; table 3).

Four children (1.10%) were detected with OCT changes characterised by linear discontinuity of their ellipsoid zone on radial scans at follow-up (two right eyes, two left; figure 2). Case 3 and case 4 additionally showed a tiny yellowish-grey spot in the foveal region of the fundus photograph. The characteristics of the four cases are detailed in online supplemental table S5). These four children (2 girls and 2 boys, aged 9–13 years) had RLRL durations of 2.01 to 4.84 years, maintained BCVA≥20/20 at baseline and follow-up, reported afterimages of 1–2 min and showed no ffERG-detected visual function damage. Three reported gradual afterimage shortening over therapy. None had baseline OCT before RLRL, limiting temporal comparison. No other OCT structural changes were found in the cohort.

Subgroup analysis

As shown in online supplemental tables S6 and S7, axial shortening occurred in 77.78% (95% CI 67.79 to 85.87) of the ≥0.5–1 year group, 59.34% (95% CI 48.53 to 69.52) of ≥1–2 years, 24.44% (95% CI 16.00 to 34.64) of ≥2–3 years, and 14.29% (95% CI 7.83 to 23.19) of ≥3 years.

DISCUSSION

In this multicentre real-world study, RLRL therapy achieved a satisfactory myopia control rate of 72.53%, with mean annual AL change of 0.06 mm/year (95% CI 0.03 to 0.08) over a median follow-up of 3.65 years. The efficacy of RLRL therapy for myopia control over ≥3 years was sustained and comparable to ≥2–3 years, though slightly lower than ≥0.5–1 year and ≥1–2 years. No subjective visual function damage was observed in BCVA, and there were no treatment duration-related changes in ffERG across the four groups. Tiny ellipsoid zone discontinuities on OCT radial scans without visual function alteration were detected at a low incidence of 1.10%. No adverse or serious events were reported.

Sustained efficacy of RLRL over 3 years

This real-world study confirmed sustained RLRL efficacy, with >70% satisfactory myopia control and annual axial elongation of 0.06 mm/year over >3 years. It provides the first real-world evidence of long-term RLRL effectiveness in axial elongation management. Compared with other anti-myopia treatments with ≥2 year follow-up (online supplemental table S8), RLRL appears superior: satisfactory myopia control rates were 5.9%–31.5% for specially designed spectacles,[16 17] 19.4% for 0.01% atropine,[18] 18.9%–20% for orthokeratology[18–20] and 35.3%–39.5% for combined 0.01% atropine and orthokeratology.[19] Direct comparisons should be interpreted cautiously due to differences in study design, populations and age.

Slightly reduced efficacy across treatment duration

For ≥3 years of RLRL, satisfactory myopia control rates were 16.36% and 16.48% lower than in the ≥0.5–1 and ≥1–2 year groups, respectively, but comparable to ≥2–3 years. Longer treatment was noted to be associated with decreased control efficacy and higher annual axial elongation. This decline may reflect the therapy's initial strong effect gradually diminishing, as seen with other myopia interventions (eg, atropine).[6 21] In addition, participants in the ≥3 years group were younger at baseline, which may contribute to faster eye growth, as axial elongation slows with age.[22]

Long-term safety

No adverse events or subjective visual function damages were observed after long-term RLRL usage, consistent with previous RCTs.[2 7 23] This 3-year study showed no treatment duration-dependent effect of RLRL on ffERG, indicating no objective visual function changes over time. This aligns with multifocal ERG evidence showing no macular function change after 1-year

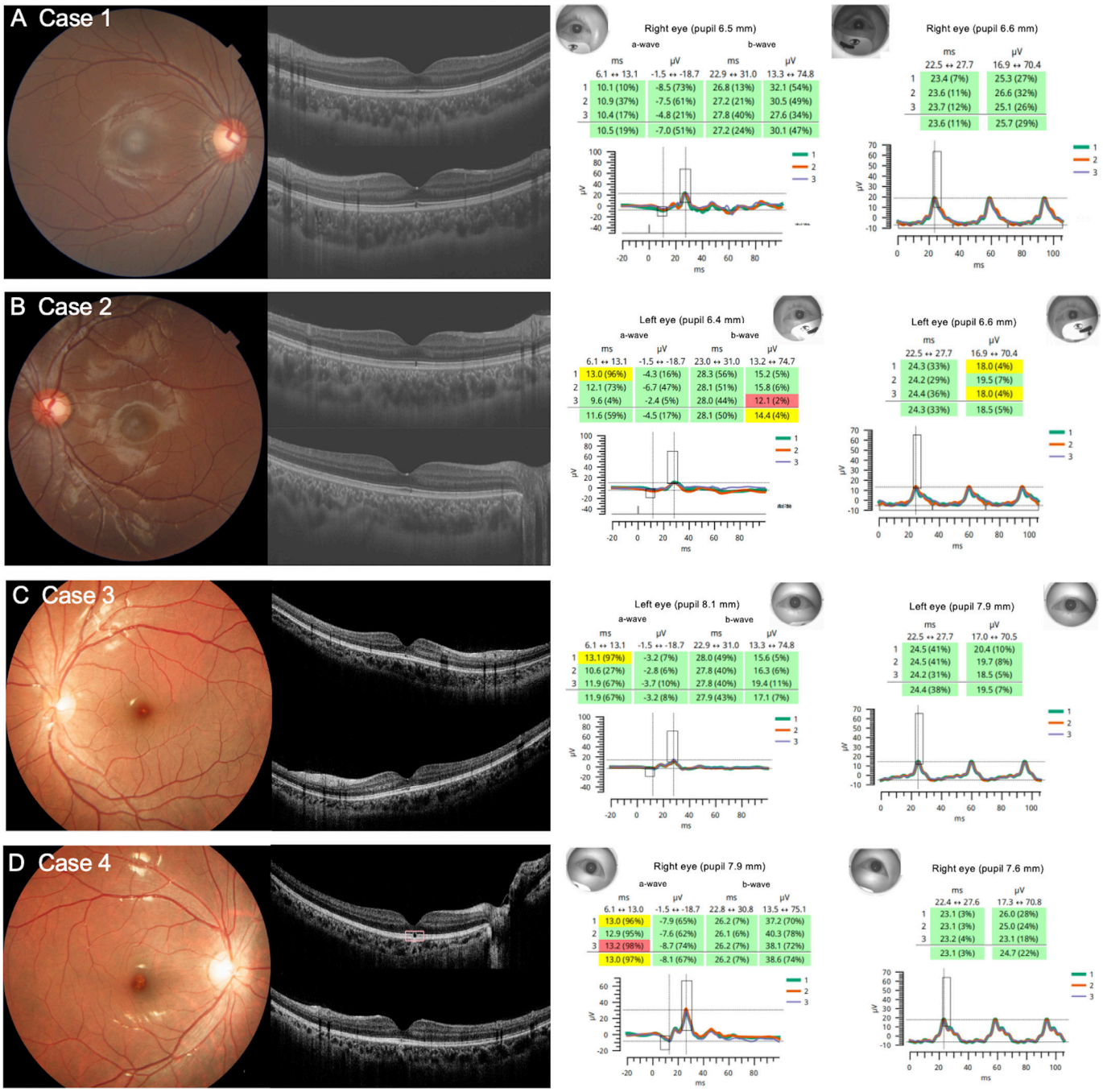

Figure 2 Fundus photographs and OCT images of four cases with linear discontinuity of ellipsoid zone without ERG functional damage. Linear discontinuity of the ellipsoid zone was detected in two OCT cross sections of radial scan in four children, with no discontinuity observed in both horizontal and vertical line scans. Two cases (C, D) additionally showed a tiny yellowish-grey spot in the fundus photograph foveal region. ERG, electroretinogram; OCT, optical coherence tomography.

RLRL.[24] Baseline ffERG data were unavailable, precluding direct within-participant comparisons.

Four children exhibited OCT changes marked by linear discontinuity in the ellipsoid zone, without subjective or objective visual function detriments or delayed afterimages. All maintained BCVA of Snellen 20/20 or better throughout treatment and discontinuation. These findings differ from previous reports of retinal damage following RLRL,[14] and from conditions, such as acute zonal occult outer retinopathy, multiple evanescent white dot syndrome[25] or solar/laser maculopathy, where outer retinal disruption typically caused vision decline.[26 27] Although the lack of baseline OCT data prevents establishing the cause of these changes, the absence of visual function deficits and improvements after RLRL discontinuation suggests the discontinuity is a reversible, physiological treatment response rather than permanent damage (online supplemental figure S1-3). Of note, OCT revealed a microdefect in the ellipsoid zone at the fovea,[28 29] characterised by outer segments disruption with preserved intact inner segments of foveal photoreceptors and RPE, allowing regeneration through normal renewal.[30] Given no subjective symptoms and potential rapid recovery for the microdefects, these likely represent transient change. We hypothesise

that RLRL may stimulate mitochondrial activity and increase the metabolic demand of the photoreceptor in the fovea,[31] which is particularly rich in mitochondria,[32] thereby overloading the renewal cycle of the outer segments. Combined with ffERG findings, these observations support the safety of RLRL and provide insight into its possible mechanism.

Strengths and limitations

This multicentre study benefitted from the study design closely mirroring real-world conditions and employing stratified random sampling to capture the long-term efficacy and safety of RLRL therapy in real-world settings. No higher efficacy was observed in ≥3 years versus shorter durations for satisfactory control or axial elongation, suggesting minimal selection bias from continued treatment among good responders. These findings provide real-world validation of prior RCT evidence.[2 3 5 7 33] RCTs may be limited by strict selection, often enrolling children at high risk of myopia progression and thus showing lower treatment effects (reported 53.2%–54.4% satisfactory control in 1-year RCTs of RLRL).[11 34] Comprehensive assessments of visual function, ocular structure and key inclusion of ffERG strengthened safety evaluation.

Several limitations should be acknowledged. First, no SVS or sham control group was included due to the observational design; controlled studies are needed to strengthen the evidence. Second, ERG and OCT were measured only at follow-up, limiting longitudinal analysis. Third, although we adopted a conservative unified definition of satisfactory myopia control (≤0.10 mm/year),[12 13] physiological axial growth varies with age, with typical rates of approximately 0.26 mm/year in younger children (6–12 years) and 0.08 mm/year in adolescents (13–17 years).[35 36] To account for this, we performed a sensitivity analysis using age-specific thresholds, and the results were consistent with the main findings (online supplemental table S9). Finally, the generalisability to non-Chinese populations warrants further study.

CONCLUSIONS

In conclusion, this real-world study demonstrates that RLRL therapy offers promising long-term efficacy and safety in controlling myopia over 3 years in Chinese myopic children and adolescents. Future research is needed to understand the underlying mechanisms of RLRL therapy.

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Competing interests MH and ZZ are listed as inventors on the patents and patent applications related to the study (CN201910490186.6). MH is a director and shareholder in Eyerising Ltd and Eyerising International Pty Ltd. No other potential conflicts of interest relevant to this article were reported.

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