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Three-Year Clinical Trial of Low-Concentration Atropine for Myopia Progression (LAMP) Study: Continued Versus Washout

Phase 3 Report

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Purpose: (1) To compare the efficacy of continued and stopping treatment for 0.05%, 0.025%, and 0.01% atropine during the third year. (2) To evaluate the efficacy of continued treatment over 3 years. (3) To investigate the rebound phenomenon and its determinants after cessation of treatment.

Design: A randomized, double-masked extended trial.

Participants: A total of 350 of 438 children aged 4 to 12 years originally recruited into the Low-Concentration Atropine for Myopia Progression (LAMP) study.

Methods: At the beginning of the third year, children in each group were randomized at a 1:1 ratio to continued treatment and washout subgroups. Cycloplegic spherical equivalent (SE) refraction and axial length (AL) were measured at 4-month intervals.

Main Outcome Measures: Changes in SE and AL between groups.

Results: A total of 326 children completed 3 years of follow-up. During the third year, SE progression and AL elongation were faster in the washout subgroups than in the continued treatment groups across all concentrations: -0.68 ± 0.49 diopters (D) versus -0.28 ± 0.42 D ($P < 0.001$) and 0.33 ± 0.17 mm versus 0.17 ± 0.14 mm ($P < 0.001$) for the 0.05%; -0.57 ± 0.38 D versus -0.35 ± 0.37 D ($P = 0.004$) and 0.29 ± 0.14 mm versus 0.20 ± 0.15 mm ($P = 0.001$) for the 0.025%; -0.56 ± 0.40 D versus -0.38 ± 0.49 D ($P = 0.04$) and 0.29 ± 0.15 mm versus 0.24 ± 0.18 mm ($P = 0.13$) for the 0.01%. Over the 3-year period, SE progressions were -0.73 ± 1.04 D, -1.31 ± 0.92 D, and -1.60 ± 1.32 D ($P = 0.001$) for the 0.05%, 0.025%, and 0.01% groups in the continued treatment subgroups, respectively, and -1.15 ± 1.13 D, -1.47 ± 0.77 D, and -1.81 ± 1.10 D ($P = 0.03$), respectively, in the washout subgroup. The respective AL elongations were 0.50 ± 0.40 mm, 0.74 ± 0.41 mm, and 0.89 ± 0.53 mm ($P < 0.001$) for the continued treatment subgroups and 0.70 ± 0.47 mm, 0.82 ± 0.37 mm, and 0.98 ± 0.48 mm ($P = 0.04$) for the washout subgroup. The rebound SE progressions during washout were concentration dependent, but their differences were clinically small ($P = 0.15$). Older age and lower concentration were associated with smaller rebound effects in both SE progression ($P < 0.001$) and AL elongation ($P < 0.001$).

Conclusions: During the third year, continued atropine treatment achieved a better effect across all concentrations compared with the washout regimen. 0.05% atropine remained the optimal concentration over 3 years in Chinese children. The differences in rebound effects were clinically small across all 3 studied atropine concentrations. Stopping treatment at an older age and lower concentration are associated with a smaller rebound. *Ophthalmology 2022;129:308-321 © 2021 by the American Academy of Ophthalmology*

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Myopia is a worldwide public health threat with increasing prevalence in most regions over the past decades, especially in East Asia.[1-3] Low-concentration atropine eye drops are an emerging therapy for myopia control.[4-7] However, the optimal concentration and long-term treatment approaches are yet to be defined. In the Phase One and Phase Two results of the Low-concentration Atropine for Myopia Progression (LAMP) study, 0.05% atropine was shown to be the most effective concentration for treatment over 2 years among the 3 low concentrations of atropine at 0.05%,

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0.025%, and 0.01%.[5,6] The efficacy of 0.05% atropine in reducing spherical equivalent (SE) progression was doubled from that observed for 0.01% atropine over 2 years.[6] In both the Atropine for the Treatment of Myopia Studies (ATOM1 and ATOM2), a "rebound phenomenon" was observed.[8,9] Faster progressions of myopia occurred following treatment cessation after 2 years of continuous atropine therapy for subjects treated with 1%, 0.5%, and 0.1% atropine, but not for those treated with 0.01% atropine.[8,9] Moreover, the results of the 3-year ATOM2 study (including 2-year treatment and 1-year washout phases) showed that children in the 0.01% atropine group progressed on average by only −0.72 diopters (D) in terms of SE refraction, less than the children in both the 0.1% atropine (−1.04 D) and 0.5% atropine (−1.15 D) groups.[9] Results of the ATOM2 study suggested an optimal balance between efficacy and side effects by 0.01% atropine compared with higher concentrations.[9]

Several questions regarding atropine treatment strategies remained to be answered. First, clinicians must decide whether atropine treatment should be continued or stopped during the follow-up period. One strategy proposed for children study subjects is to begin with 2 years of initial treatment, followed by withholding treatment for 1 year for monitoring.[4,9-11] Treatment can be restarted in those with fast progression after 1 year.[10-12] Continuous atropine treatment until late adolescence has also been advocated.[11] Second, the magnitude of the rebound effect following treatment cessation after using 0.05%, 0.025%, and 0.01% atropine must be determined to evaluate the long-term efficacy and to determine the optimal concentration. Third, the factors associated with the rebound effect must be identified for deciding the cessation strategy. In this third phase of the LAMP study, we aim to evaluate whether the efficacy of continued treatment (0.05%, 0.025%, 0.01% atropine) is better than stopping treatment during the third year; the long-term efficacy of continued treatment of these low concentration atropine over 3 years; and the rebound effect and its associations with low-concentration atropine after treatment cessation.

Methods

The study design has been described for the LAMP Phase 1 and 2 studies.[5,6] In brief, children aged 4 to 12 years with a myopic refraction of at least −1.0 D in both eyes, astigmatism of less than 2.5 D, and documented myopic progression of at least 0.5 D in the previous year were enrolled in a double-blinded, single-center clinical trial. In Phase 1, the children were randomly assigned to 4 treatment groups (0.05%, 0.025%, 0.01% atropine, and placebo), with follow-up at 4-month intervals after initial treatment. In Phase 2, all children in the placebo group for Phase 1 were switched to receiving 0.05% atropine at the beginning of the second year until the end of the phase due to ethical consideration, after we have proved the efficacy of low-concentration atropine for myopia control compared with placebo at the end of the first year. Children in the original atropine treatment groups still received the same concentrations throughout this second year.

For the current Phase 3 study, the children study subjects in each of the 3 original treatment groups for Phase 1 (0.05%, 0.025%, and 0.01% atropine) were randomized in a 1:1 ratio into a continued treatment subgroup and a treatment cessation or "washout" subgroup, stratified further by sex and age (6−8 years, 9−11 years, and 12−14 years). For the continued treatment subgroups, the subjects continued receiving eye drops of the same concentration once nightly in both eyes throughout the third year. For the washout subgroups, all subjects stopped receiving eye drops. Children in the switchover group for Phase 2 continued treatment using 0.05% atropine in the third year. As in the previous 2 phases, subjects in the continued treatment subgroups for Phase 3 remained masked to their specific treatment concentrations. However, all study subjects and their parents were informed about whether they were assigned to a continued treatment subgroup or a washout subgroup. Likewise, clinical investigators remained masked to all group and subgroup allocations. All parents or guardians gave written informed consent, with verbal assent from the study subjects. The study is registered with the Chinese Clinical Trial Registry (identifier: ChiCTR-TRC-13004032) and the Clinical Trials Registry of the Centre for Clinical Research and Biostatistics, The Chinese University of Hong Kong (identifier: CUHK_CCT00383). It was approved by the ethics committee of The Chinese University of Hong Kong. All procedures were conducted according to the tenets of the Declaration of Helsinki.

Trial medication was prepackaged as mono-dose eye drops with atropine sulfate concentrations of 0.05%, 0.025%, and 0.01% (0.5-ml unit concentration, preservative free) by Aseptic Innovative Medicine Co. Ltd. The expiration duration for each batch of eye drops was 2 years. The manufacturer provided certificates of analysis for all 3 concentrations, and the Hong Kong Department of Health granted drug trial certificates. Compliance with trial medication was classified according to the mean number of days per week that trial medication was used as reported by the subjects; compliance rates of >75% (i.e., a mean of 5.25 days/week) were considered acceptable.

Subjects were offered photochromic glasses if they experienced glare or if their parents or guardians were worried about excessive exposure to light. They would be given progressive glasses as reading aids if they experienced difficulty with near vision or on parental request. All subjects were prescribed with best-corrected spectacles. The Chinese 25-Item Visual Function Questionnaire, along with validated questionnaires on outdoor time and near work, were administered to the parents or guardians at the end of the third year.[13]

The ophthalmic examinations conducted in Phase 3 were the same as for the previous 2 phases.[5,6] Ophthalmic parameters collected at each visit included distance best-corrected visual acuity (BCVA) as measured using a logarithm of the minimum angle of resolution chart, in addition to near visual acuity under best-corrected distance spectacle correction at 40 cm, the near point of accommodation. Accommodation amplitude was calculated as the inverse of the near point of accommodation. Photopic and mesopic pupil sizes were measured using an OPD-Scan III unit (Nidek). Cycloplegic autorefraction was performed using an autorefractor (Nidek ARK-510A) after a cycloplegic regimen, which consisted of at least 2 cycles of eye drops. In the first cycle, 2 separate eye drops, cyclopentolate 1% (Cyclogyl; Alcon-Convreur) and tropicamide 1% (Santen) were administered to both eyes at 5 minutes apart. A second cycle of the same cycloplegic drops was administered 10 minutes after the first cycle. Ocular AL was measured using a Zeiss IOL Master unit (Carl Zeiss Meditec Inc.).

Primary outcomes included (1) the difference in myopia progression, measured by changes in SE and AL, between the continued treatment and washout subgroups at each concentration during the third year; (2) cumulative myopia progression over the course of 3 years (combined results for all 3 phases of the LAMP study), for continued treatment and washout subgroups at each

concentration; and (3) the rebound effect and its associated factors. Secondary outcomes included side effect parameters such as changes in accommodation amplitude, mesopic and photopic pupil sizes, distance BCVA, near visual acuity, and Chinese 25-Item Visual Function Questionnaire scores. All parameters were monitored and compared with the baseline measurements from 3 years ago. During each visit, the children and their parents were invited to freely report any side effects, medical illness, or hospitalizations since the previous visit. Adverse events were documented regardless of whether they appeared related to atropine use, including symptoms related to allergies, glare, and blurred near vision.

Statistical Analysis

To calculate the required number of study subjects, we estimated the myopia progression rates during the third year to be −0.28 D,[14] −0.56 D,[15] and −0.49 D[4] for the 0.05%, 0.025%, and 0.01% continued treatment subgroups, and −0.75 D[14] for all the washout subgroups, respectively. The cumulative myopia progression rates over 3 years were estimated to be −0.84 D, −1.69 D, and −1.47 D for the 0.05%, 0.025%, and 0.01% continued treatment subgroups, and −1.31 D, −1.88 D, and −1.73 D for the 0.05%, 0.025%, and 0.01% atropine washout subgroups, respectively. The common standard deviation within a concentration group was assumed to be 0.6 D.[16] To detect significant differences in myopia progression during the third year and over all 3 years between corresponding continued treatment and washout subgroups, a sample size of 432 eyes in 216 subjects (72 subjects per concentration group) should achieve 80% power at a significance level of 0.05. Assuming an attrition rate of 10%, a sample size of 480 eyes in 240 subjects (80 subjects per concentration group) would be required. For this study, we successfully recruited 93, 86, and 91 subjects (186, 172, and 182 eyes) for the 0.05%, 0.025%, and 0.01% atropine groups, respectively, which were adequate to achieve 80% power at a 0.05 significance level.

All data were analyzed according to the modified intention-to-treat principle.[17] Modified intention-to-treat is a subset of the intention-to-treat population and allows the exclusion of some randomized subjects in a justified way.[18] The modified intention-to-treat analysis allows a subjective approach in entry criteria, which may lead to confusion, inaccurate result, and bias.[17] Mean values for ocular parameters were calculated from both eyes. Changes in parameters were calculated as the difference between the baseline visit and the designated follow-up visit. Our analysis was based on complete case data, excluding subjects who had dropped out of the study before completing the 3 years.[19] Group differences in categorical data were tested by the chi-square test and Fisher exact test. Generalized estimating equations with robust standard errors for longitudinal data analysis[20,21] were used to adjust the inter-eye correlations and incorporate all valuable data. P values were generated using generalized estimating equation models[22] and adjusted for multiple comparisons using the Bonferroni adjustment procedure.[23] The software SPSS (version 24.0; IBM Corp.) was used for data analyses. P values less than 0.05 were considered statistically significant.

Results

Of the 438 children aged 4 to 12 years originally randomized into the 0.05%, 0.025%, 0.01% atropine treatment groups and the switchover group for the first 2 phases of the LAMP study, 350 (79.9%) continued in the extended trial in Phase Three. Among them 93, 86, 91, and 80 subjects were in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switchover groups, respectively (Fig 1). The dropout rates in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switchover groups are 17.4%, 27.8%, 21.8%, and 35.1% over 3 years, respectively. A higher dropout rate was in the switchover group ($P = 0.02$) and older subjects ($P < 0.001$) (Fig 1). The baseline demographic characteristics of the extended trial subjects in the continued treatment and washout groups across all concentrations studied were similar (Table 1). Furthermore, the characteristics of the 326 subjects who completed 3 years of follow-up were similar to those of the 112 subjects who did not (Table S1, available at www.aaojournal.org).

Changes in SE Refraction and AL During the Third Year

During the third year, the respective SE progressions for the continued treatment subgroups of the 0.05%, 0.025%, and 0.01% atropine treatment groups were −0.28 ± 0.42 D, −0.35 ± 0.37 D, and −0.38 ± 0.49 D ($P = 0.65$; Table 2), and the respective AL elongations 0.17 ± 0.14 mm, 0.20 ± 0.15 mm, and 0.24 ± 0.18 mm ($P = 0.19$; Table 2). After treatment cessation during the third year, the SE progression and axial elongation for the washout subgroups followed concentration-dependent response, that is, faster progressions at higher concentrations. There were no significant differences in SE progression across concentration groups, with respective SE progressions of −0.68 ± 0.49 D, −0.57 ± 0.38 D, and −0.56 ± 0.40 D ($P = 0.15$; Table 2), but a large axial elongation in higher concentration, with the respective AL elongations 0.33 ± 0.17 mm, 0.29 ± 0.14 mm, and 0.29 ± 0.15 mm ($P = 0.003$; Table 2). Comparing the continued treatment and washout subgroups for each concentration group, both the SE progressions ($P < 0.001$, $P = 0.004$, and $P = 0.04$ for 0.05%, 0.025%, and 0.01% concentrations, respectively; Table 2) and AL elongations ($P < 0.001$, $P = 0.001$, and $P = 0.13$ for 0.05%, 0.025%, and 0.01% concentration, respectively; Table 2) were less for the former subgroups. The differences between continued treatment and washout subgroups were dependent on both atropine concentration and age; the lower the treatment concentration and the older the subject's age, the smaller the difference in myopia progression in continued treatment and washout subgroups (Table S2, available at www.aaojournal.org).

Changes in SE Refraction and AL Over 3 Years

Over the 3 years of continuous treatment, the cumulative mean SE progressions were −0.73 ± 1.04 D, −1.31 ± 0.92 D, and −1.60 ± 1.32 D for the 0.05%, 0.025%, and 0.01% atropine groups, respectively, with significant differences among groups ($P = 0.001$; Table 2, Table S3, available at www.aaojournal.org, and Fig 2). The respective cumulative mean AL elongations were 0.50 ± 0.40 mm, 0.74 ± 0.41 mm, and 0.89 ± 0.53 mm ($P < 0.001$; Table 2, Table S3, available at www.aaojournal.org, and Fig 3). Among the subjects who received 3 years of continuous treatment, the proportions of those who exhibited SE progression of less than 1.50 D were 76.9%, 61.8%, and 47.6% for the 0.05%, 0.025%, and 0.01% atropine groups, respectively. In contrast, the proportions of subjects who exhibited a progression of 3.0 D or more were much lower, at 5.1%, 0%, and 11.9%, respectively (Fig 4).

Among the washout subgroups, the cumulative mean SE progressions over 3 years were −1.15 ± 1.13 D, −1.47 ± 0.77 D, and −1.81 ± 1.10 D for the 0.05%, 0.025%, and 0.01% atropine groups, respectively ($P = 0.03$; Table 2 and Fig 2). The respective cumulative mean AL elongations were 0.70 ± 0.47 mm, 0.82 ± 0.37 mm, and 0.98 ± 0.48 mm ($P = 0.04$; Table 2 and Fig 3).

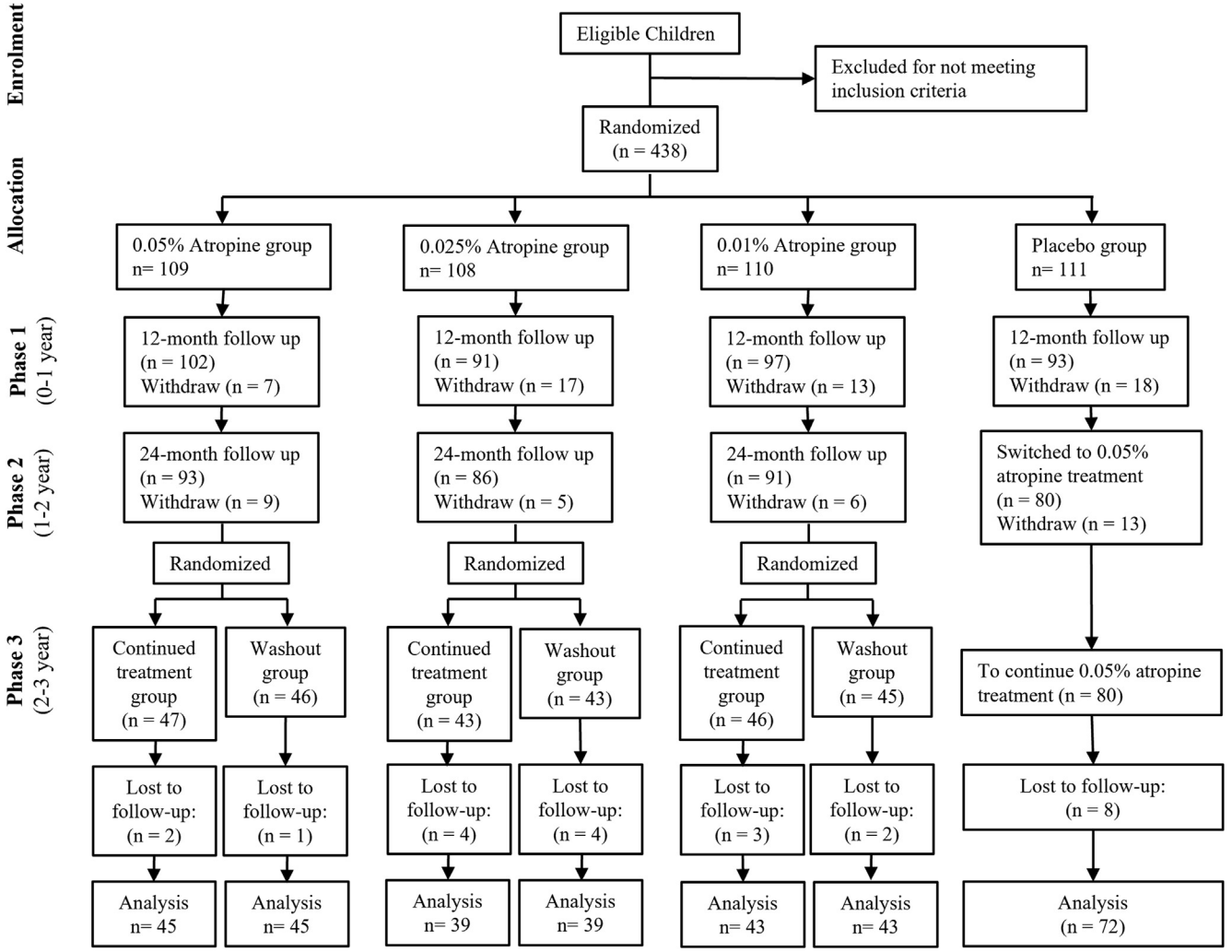

Figure 1. Subject progression throughout the Low-concentration Atropine for Myopia Progression (LAMP) Study.

Changes in SE Refraction and AL for the Switchover Group

The mean SE progression and AL elongation for the switchover group were −0.29 ± 0.28 D and 0.15 ± 0.11 mm during the third year and −1.27 ± 0.87 D and 0.76 ± 0.38 mm, respectively, over the course of 3 years. These changes were similar to those for the washout subgroup of the 0.05% group over 3 years ($P = 0.94$ for SE progression and $P = 0.92$ for AL elongation).

Factors Related to Rebound Effects During the Third Year

During the third year, older age and lower atropine concentration before treatment cessation were associated with a smaller rebound effect in both SE progression and AL elongation (Table 3). A 1-year increase in the subject's age was related to a 0.08 D decrease in SE rebound and 0.05-mm decrease in AL elongation, whereas a prior treatment concentration of 0.01% atropine was related to a SE rebound that was 0.20 D SE less and 0.08-mm AL elongation less when compared with 0.05% atropine (Table 3). As age increased, the difference in rebound magnitude among 0.05%, 0.025%, and 0.01% atropine groups become smaller (Table 4). For the ages 6 to 8 years, higher concentration atropine at 0.05% resulted in a greater SE rebound compared with 0.01% atropine, showing a concentration-dependent effect (P trend = 0.02). For the older age groups of 9 to 11 years and 12 to 14 years, the SE rebound magnitudes related to the 3 concentrations became similar (P trend > 0.05 for both groups, Table 4).

Changes in Side Effects and Vision-Related Quality of Life During the Third Year

For washout subgroup subjects, pupil size and accommodation amplitude returned to baseline levels for all atropine concentration groups following treatment cessation during the third year (Table S4, available at www.aaojournal.org). In the continued treatment subgroups of the 0.05%, 0.025%, and 0.01% atropine groups, changes in accommodation amplitude by the end of the third year were similar to those at the ends of the previous 2 years in concentration-dependent responses (Table S4, available at www.aaojournal.org, and Table 5). Likewise, changes in pupil size by the end of the third year were similar to those at the ends of the previous 2 years in concentration-dependent responses (Table S4, available at www.aaojournal.org, and Table 5). Distance

Table 1. Demographics and Characteristics at 24 Months in the 0.05% Atropine, 0.025% Atropine, 0.01% Atropine, and Switchover Groups that Completed 3 Years

	0.05% Atropine (n = 90)		0.025% Atropine (n = 78)		0.01% Atropine (n = 86)		Switchover Group* (n = 72)
	Continue (n = 45)	Washout (n = 45)	Continue (n = 39)	Washout (n = 39)	Continue (n = 43)	Washout (n = 43)	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
Age (yrs)	10.86 (1.51)	11.07 (1.81)	10.93 (1.73)	10.88 (1.63)	10.54 (1.73)	10.44 (1.83)	11.12 (1.90)
Sex (Male, %)	22 (48.9%)	23 (51.1%)	23 (59.0%)	22 (56.4%)	21 (48.8%)	25 (58.1%)	45 (62.5%)
BMI (kg/m^2)	17.29 (3.05)	17.51 (2.95)	18.57 (3.20)	18.00 (2.91)	17.59 (3.70)	18.34 (4.47)	17.14 (2.90)
SE (D)	−4.49 (1.95)	−4.42 (2.42)	−5.11 (2.47)	−4.65 (2.10)	−5.65 (3.04)	−5.45 (2.18)	−5.24 (2.08)
SE changes in the first 2 yrs (D)	−0.45 (0.83)	−0.47 (0.83)	−0.96 (0.73)	−0.90 (0.69)	−1.22 (1.00)	−1.24 (0.87)	−0.99 (0.73)
Axial length (mm)	25.13 (0.90)	25.20 (0.86)	25.53 (1.00)	25.38 (0.92)	25.49 (1.33)	25.54 (1.11)	25.46 (0.91)
Axial length changes in the first 2 year (mm)	0.34 (0.30)	0.36 (0.37)	0.54 (0.32)	0.53 (0.29)	0.65 (0.39)	0.68 (0.38)	0.60 (0.30)
Central corneal thickness (μm)	558.85 (27.49)	558.61 (31.47)	555.62 (29.22)	560.87 (30.59)	557.86 (25.87)	550.87 (25.72)	555.99 (34.78)
IOP (mmHg)	16.24 (1.80)	15.48 (1.75)	15.73 (1.44)	16.10 (2.21)	15.88 (2.14)	15.34 (1.73)	15.35 (2.10)
Photopic pupil size (mm)	5.05 (0.90)	5.04 (0.94)	4.28 (0.79)	4.59 (0.79)	4.02 (0.69)	4.29 (0.85)	5.10 (0.93)
Mesopic pupil size (mm)	7.47 (0.76)	7.42 (0.55)	7.22 (0.67)	7.04 (0.60)	6.77 (0.61)	6.85 (0.67)	7.34 (0.63)
Accommodation amplitude (D)	10.84 (1.99)	10.29 (2.09)	10.92 (2.28)	10.66 (2.36)	11.44 (1.94)	11.38 (1.89)	10.10 (2.13)
Distance VA (logMAR)	−0.02 (0.08)	−0.02 (0.06)	−0.01 (0.08)	−0.02 (0.05)	0.00 (0.07)	−0.01 (0.07)	−0.02 (0.05)
Near VA (logMAR)	0.02 (0.05)	0.02 (0.09)	0.02 (0.09)	0.00 (0.06)	0.03 (0.07)	0.03 (0.07)	0.04 (0.06)
Outdoor activity (hours per day)†	2.16 (0.86)	2.26 (0.83)	2.20 (1.01)	2.16 (0.78)	2.29 (0.82)	2.14 (0.81)	2.26 (0.86)
Near work (dioptic hours per day)‡	16.08 (3.79)	15.47 (5.03)	16.41 (3.99)	15.62 (3.01)	16.41 (2.51)	15.81 (4.32)	15.92 (4.44)

D = diopter; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; SE = spherical equivalent; VA = visual acuity.
*Switchover group: subjects receiving placebo during the first year and were then switchover to 0.05% atropine group at the beginning of the second year.
†Outdoor activity = outdoor exercise + outdoor leisure activity.
‡Near work = 3*(homework + reading + playing cell phone) + 2*(using computer + playing video game) +1*(watching TV).

Table 2. Change in Ophthalmic Parameters over Three Years in the 0.05% Atropine, 0.025% Atropine, and 0.01% Atropine Groups

Change	0.05% Atropine (n = 90)		0.025% Atropine (n = 78)		0.01% Atropine (n = 86)		Overall P values	Pairwise Comparisons P values‡ (3 vs. 2; 3 vs. 1; 2 vs. 1)
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*		
SE (D)								
Baseline to 36 mos								
Continue	−0.73	1.04	−1.31	0.92	−1.60	1.32	**0.001***	0.01,* 0.002,* 0.99
Washout	−1.15	1.13	−1.47	0.77	−1.81	1.10	**0.03***	0.13, 0.03,* 0.99
P values	**0.04***		0.34		0.45			
24 to 36 mos†								
Continue	−0.28	0.42	−0.35	0.37	−0.38	0.49	0.65	0.99, 0.99, 0.99
Washout	−0.68	0.49	−0.57	0.38	−0.56	0.40	0.15	0.58, 0.16, 0.99
P values	**<0.001***		**0.004***		**0.04***			
Axial length (mm)								
Baseline to 36 mos								
Continue	0.50	0.40	0.74	0.41	0.89	0.53	**<0.001***	0.003,* <.001,* 0.99
Washout	0.70	0.47	0.82	0.37	0.98	0.48	**0.04***	0.14, 0.04,*0.99
P values	**0.04***		0.28		0.54			
24 to 36 mos†								
Continue	0.17	0.14	0.20	0.15	0.24	0.18	0.19	0.54, 0.24, 0.99
Washout	0.33	0.17	0.29	0.14	0.29	0.15	**0.003***	0.33, 0.002,* 0.46
P values	**<0.001***		**0.001***		0.13			

D = diopters; SD = standard deviation; SE = spherical equivalent.
Mean and SD were calculated with both eye data.
P values were generated by generalized estimating equation models with age, sex, and baseline SE adjustment for SE comparisons.
P values were generated by generalized estimating equation models with age, sex, and baseline AL adjustment for AL comparisons.
*Significance was set at 0.05.
†Spherical equivalence at 24 months was used as the baseline SE for SE comparison over 24 to 36 mos; AL at 24 mos was used as the baseline AL for AL comparison over 24 to 36 mos.
‡Bonferroni correction was applied for the pairwise comparisons.

BCVA and near BCVA were not affected in all subgroups (Table S4, available at www.aaojournal.org, and Table 5).

The number of subjects that had photophobia remained similar between continued treatment and washout subgroups during the third year. In general, few subjects required progressive lens spectacles in both the continued (4.4% for 0.05% group, 10.3% for 0.025% group, 9.3% for 0.01% atropine group) and washout groups (4.4% for 0.05% group, 2.6% for 0.025% group, 7% for 0.01% group) (Table S5, available at www.aaojournal.org). The occurrence rate of allergic conjunctivitis was similar among the concentration groups (Table S5, available at www.aaojournal.org). Twenty subjects reported severe adverse events requiring hospitalization, but none were related to topical atropine therapy (Table S5, available at www.aaojournal.org). Compliance rates of >75% (expected use of >5 days/week) were 82.6%, 94.4%, 84.7%, and 83.9% for the 0.05%, 0.025%, 0.01%, and switchover groups, respectively ($P = 0.24$). No differences were observed in vision-related quality of life across all concentration groups and between subgroups (Table S6, available at www.aaojournal.org).

Discussion

In this Phase 3 report of the LAMP study, the results show the following: (1) During the third year, continued atropine treatment at any of the 3 concentrations (0.05%, 0.025%, and 0.01%) confers better efficacy than stopping treatment. (2) Over the 3-year study period, the efficacy of 0.05% atropine was more than double that of 0.01%. (3) A greater rebound effect was associated with higher atropine concentration and younger age at treatment cessation. The differences in rebound effects among the 3 atropine concentration groups (0.05%, 0.025%, and 0.01%) were small from a clinical perspective. (4) All atropine concentration groups showed good tolerance in the current study of Chinese children. Among the washout subgroups, pupil size and accommodation amplitude returned to baseline levels after treatment cessation. These findings support the continuation of 0.05% atropine treatment during the third year in Chinese children.

Continuing Atropine Treatment During the Third Year

The optimal long-term atropine treatment strategies are currently not established, given that most studies report an active treatment period of only 1 to 2 years.[15,24-32] According to the findings of the ATOM2 study,[4,9] the World Health Organization suggested in 2015 that treatment cessation for 1 year should be considered if good treatment responses are observed after 2 years of continuous therapy, and those who show progression after the 1-year cessation can be offered further treatment.[10]

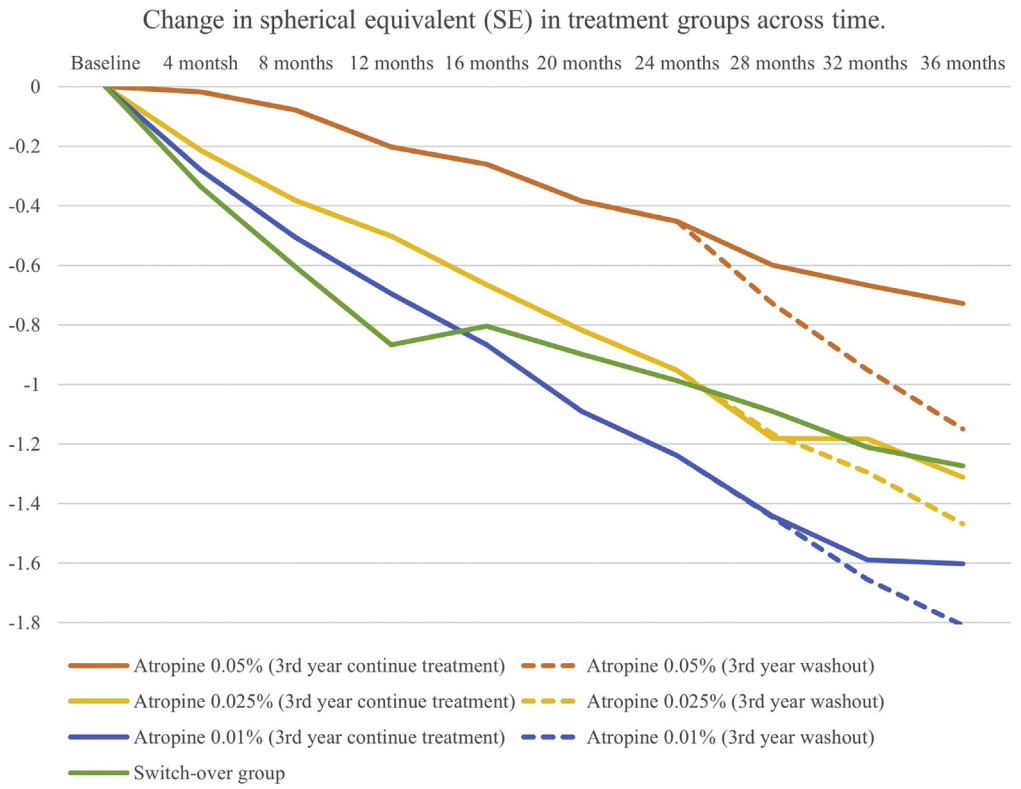

Figure 2. Changes in spherical equivalent (SE) progression for treatment groups over time. The switchover group received placebo during the first year and was then switched over to 0.05% atropine at the beginning of the second year and continued 0.05% treatment at the third year. D = diopters; M = months.

Our results show significant differences in SE and AL between continued treatment and washout subgroups. Therefore, we suggest continuation of atropine treatment at any concentration during the third year. In our study, the mean age of the study subjects was 8.34 years and 10.89 years at the start of the first and third year, respectively. Myopia progression continues during childhood and only gradually slows down when reaching adolescence. Progression in the study subjects is expected after treatment cessation. The difference in myopia progression between continuing and stopping treatment is most prominent in the 0.05% group (0.4 D) compared with the 0.025% (0.22 D) and 0.01% (0.18 D) groups. At 0.05% concentration, continued treatment resulted in better efficacy, whereas treatment cessation resulted in a greater rebound when compared with concentrations of 0.025% and 0.01%. The progression difference also becomes smaller at older ages as the progression slows down. Atropine effect between continued treatment and stopping treatment becomes smaller with age. Some studies reported that myopia may still progress during the late-teens in the university student although the progression is age-dependent.[33-35] Both myopia progression rate and age factors should be considered when determining the cessation of atropine treatment. Accordingly, we suggest a weaning strategy from higher concentration to lower concentration and at an older age for stopping treatment, when myopia progression becomes minimal.

Efficacy of Different Concentration Atropines Over 3 Years

The ATOM2 study suggested that 0.01% atropine was the optimal concentration based on an optimal balance between efficacy and safety. There was significant myopia rebound among the 0.1% and 0.5% groups on a treatment regimen of a 2-year treatment period followed by a 1-year washout period.[9] The overall myopia progression over 3 years was the lowest for the 0.01% atropine group (-0.72 ± 0.72 D), followed by the 0.1% group (-1.04 ± 0.83 D) and the 0.5% group (-1.15 ± 0.81 D) ($P < 0.001$).[6] Following the release of the ATOM2 results, the low concentration of 0.01% atropine has been widely used across Asia.[24,36] Based on these findings, our LAMP study further investigated the optimal concentration among low concentration atropine 0.05%, 0.025%, and 0.01% for myopia control.[5,6,37,38] We show in the LAMP study phase 3 that 0.05% atropine confers better treatment efficacy compared with 0.01% under both a 3-year continuous treatment regimen and a washout regimen. The mean SE progression for continuous 0.05% atropine treatment was 0.72 D over 3 years, less than the first-year natural progression (0.81 D) for the placebo group. The AL elongations observed over 3 years were 0.50 mm, 0.75 mm, and 0.89 mm for the 0.05%, 0.025%, and 0.01% groups, respectively. Table S7 (available at www.aaojournal.org) summarizes comparisons between our study and the

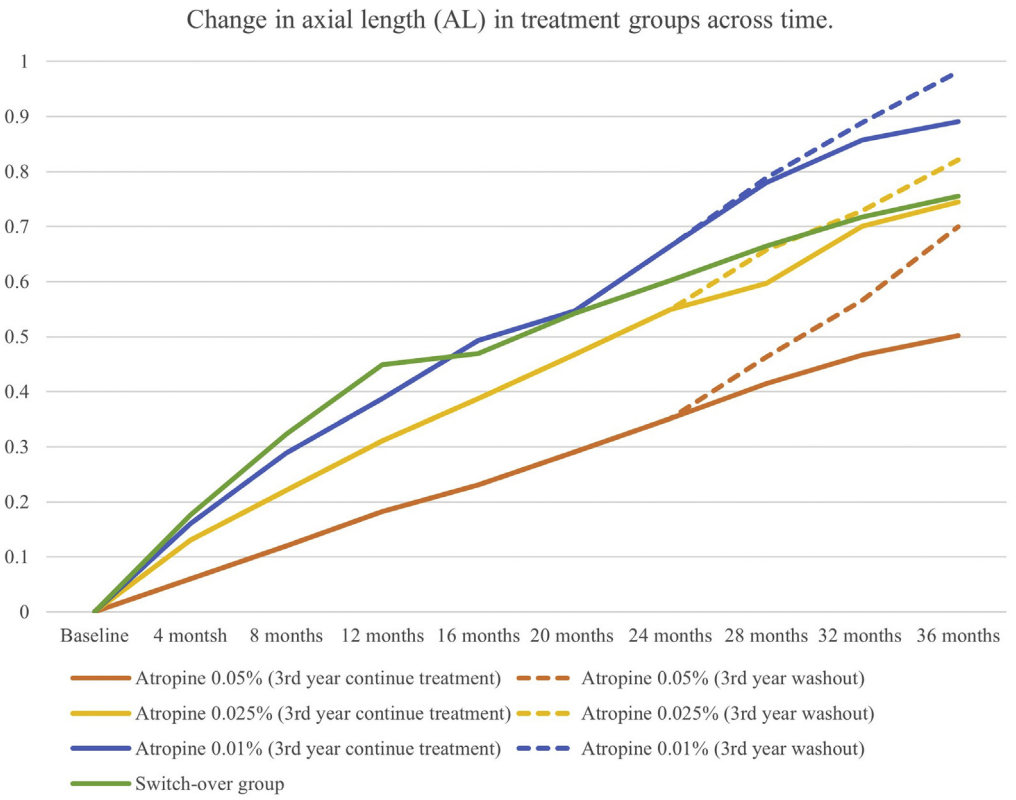

Figure 3. Changes in axial length elongation for treatment groups over time. The switchover group received placebo during the first year and was then switched over to 0.05% atropine at the beginning of the second year and continued 0.05% treatment at the third year. D = diopters; M = months.

ATOM1 and ATOM2 studies. Both the ATOM2 and LAMP studies were conducted on a majority of East Asian children.[4-6,12,37,38] There is a racial variation in sensitivity to atropine that relates to the amount of pigmentation within the iris.[39] Possible side effects might be higher in the White populations.[40] Our findings of 0.05% atropine as the optimal concentration may not be generalizable to other non-Asian children.

Rebound Effects for Low-Concentration Atropine Followed a Concentration-Dependent Response

In the ATOM2 study, the cessation of 0.1% and 0.5% atropine treatment resulted in greater myopic rebounds, resulting in faster myopia progressions overall for higher atropine concentration.[9] In line with the ATOM2 study, the

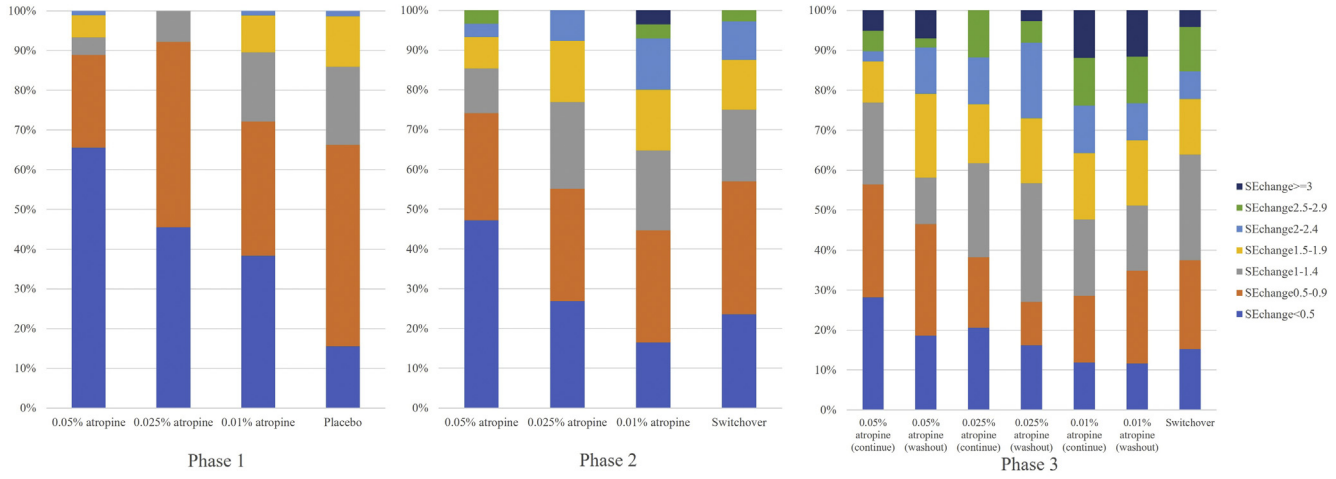

Figure 4. Bar graph showing the distribution of the various rates of progression of myopia during the LAMP Study phase 1 (12 months), phase 2 (24 months), and phase 3 (36 months).

Table 3. Multiple Regression Models of Spherical Equivalent/Axial Length Changes during Third Year in Washout Group

Spherical Equivalent (D) Change at Third year				Axial Length (mm) Change at Third year			
	Beta (β)	*Standard Error*	P *Values*		*Beta (β)*	*Standard Error*	P *Values*
Age at Treatment Cessation (yrs)	0.08	0.02	**<0.001***	**Age at Treatment Cessation (yrs)**	−0.05	0.01	**<0.001***
Sex (Male as Reference)	−0.10	0.07	0.14	**Sex (Male as Reference)**	−0.01	0.03	0.61
SE at Treatment Cessation (D)	0.01	0.02	0.46	**SE at Treatment Cessation (D)**	−0.01	0.01	0.39
Parental Myopia Status				**Parental Myopia Status**			
≤1 moderate or high myopia	0			≤1 moderate or high myopia	0		
Both moderate or high myopia	0.03	0.07	0.64	Both moderate or high myopia	0.01	0.02	0.55
Outdoor Activity (hours per day)†	0.03	0.04	0.41	**Outdoor Activity (hours per day)**†	−0.03	0.01	0.09
Near work (dioptic hours per day) ‡	−0.01	0.01	0.33	**Near work (dioptic hours per day)**‡	0.00	0.00	0.11
Treatment Groups				**Treatment Groups**			
0.05% Atropine	−0.20	0.08	**0.02***	0.05% Atropine	0.08	0.03	**0.01***
0.025% Atropine	−0.03	0.08	0.74	0.025% Atropine	0.03	0.03	0.29
0.01% Atropine	0			0.01% Atropine	0		

D = diopter.
Generalized estimating equations were used to adjust the correlation between eyes.
*Significance was set at 0.05.
†Outdoor activity = outdoor exercise + outdoor leisure activity.
‡Near work = 3*(homework + reading + playing cell phone) + 2*(using computer + playing video game) + 1*(watching TV).

rebound effects among the studied concentrations (−0.68 D, −0.57 D, and −0.56 D for the 0.05%, 0.025%, and 0.01% atropine groups, respectively) also follow a concentration-dependent response in our study, but at a smaller amplitude. The differences between concentration groups were too small to be of significant clinical and statistical implications (Table 2). Consequently, taking into consideration the rebound effects at different concentrations, 0.05% atropine was shown to be the most effective concentration over 3 years among the 0.05%, 0.025%, and 0.01% atropine groups. The mechanisms of concentration-dependent differences in rebound of SE and AL have not been fully explained yet. It was postulated that the lower concentration of atropine acts at the anterior segment of eyeball and affects various muscarinic receptors to different degrees, resulting in a more modulated adaptive response

Table 4. Estimated Mean of SE/AL Progression in Washout Groups at Third Year with Different Age Groups

Dependent Variable *Spherical Equivalent (D) Change at Third Year*					
	0.05% Atropine	*0.025% Atropine*	*0.01% Atropine*		*Pairwise comparisons*
Age (yrs)	*Estimated mean (95% CI)*	*Estimated mean (95% CI)*	*Estimated mean (95% CI)*	P *Trend*	P *values*† *(3 vs. 2, 3 vs. 1, 2 vs. 1)*
6–8 (n = 35)	−1.01 (−1.20, 0.81)	−0.70 (−0.93, −0.47)	−0.66 (−0.78, −0.53)	**0.02***	0.21, 0.02,* 0.99
9–11 (n = 58)	−0.72 (−0.89, −0.54)	−0.55 (−0.74, −0.36)	−0.54 (−0.75, −0.33)	0.37	0.68, 0.67, 0.99
12–14 (n = 34)	−0.50 (−0.67, −0.33)	−0.43 (−0.57, −0.28)	−0.42 (−0.54, −0.29)	0.74	0.99, 0.99, 0.99
P values	**0.004***	0.37	0.17		
Axial Length (mm) Change at Third Year					
	0.05% Atropine	*0.025% Atropine*	*0.01% Atropine*		*Pairwise comparisons*
Age (yrs)	*Estimated mean (95% CI)*	*Estimated mean (95% CI)*	*Estimated mean (95% CI)*	P *Trend*	P *values*† *(3 vs. 2, 3 vs. 1, 2 vs. 1)*
6–8 (n = 35)	0.46 (0.39, 0.53)	0.37 (0.27, 0.48)	0.34 (0.26, 0.41)	0.11	0.65, 0.12, 0.99
9–11 (n = 58)	0.35 (0.30, 0.41)	0.28 (0.21, 0.34)	0.26 (0.19, 0.33)	0.07	0.27, 0.13, 0.99
12–14 (n = 34)	0.24 (0.19, 0.29)	0.24 (0.19, 0.30)	0.19 (0.15, 0.22)	0.11	0.99, 0.28, 0.30
P values	**<0.001***	0.10	**0.01***		

CI = confidence interval; D = diopter.
Estimated means were generated in generalized estimating equations by adjusted age at treatment cessation, sex, refraction at 24 months, outdoor time, near work activities, parental myopia status and treatment groups.
*Significance was set at 0.05.
†Bonferroni correction was applied for the pairwise comparisons.

Table 5. Difference of Biometric Parameters in the Continue Treatment 0.05% Atropine, 0.025% Atropine, and 0.01% Atropine Groups

	0.05% Atropine (n = 45)		0.025% Atropine (n = 39)		0.01% Atropine (n = 43)			
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	**Overall *P* Values**	**Pairwise Comparisons *P* Values[†] (3 vs. 2; 3 vs. 1; 2 vs. 1)**
Photopic pupil size (mm)								
Baseline to 12 mos	0.92	0.99	0.83	0.92	0.59	0.79	0.16	0.99, 0.21, 0.62
Baseline to 24 mos	1.01	1.03	0.67	0.73	0.58	0.69	0.07	0.23, 0.06, 0.99
Baseline to 36 mos	0.97	1.19	0.66	0.68	0.61	0.82	0.22	0.41, 0.27, 0.99
24 to 36 mos	−0.04	1.04	−0.01	0.88	0.02	0.90	0.92	0.99, 0.99, 0.99
P values[‡]	0.89		0.49		0.97			
Mesopic pupil size (mm)								
Baseline to 12 mos	0.62	0.55	0.43	0.51	0.31	0.42	**0.004***	0.20, 0.002,* 0.57
Baseline to 24 mos	0.64	0.69	0.30	0.52	0.23	0.52	**0.001***	0.02,* <0.001,* 0.81
Baseline to 36 mos	0.56	0.74	0.33	0.54	0.20	0.54	**0.02***	0.30, 0.02,* 0.70
24 to 36 mos	−0.09	0.51	0.03	0.52	−0.02	0.46	0.64	0.99, 0.99, 0.99
P values[‡]	0.77		0.32		0.41			
Accommodation amplitude (D)								
Baseline to 12 mos	−2.23	2.36	−1.48	2.17	0.22	2.83	**<0.001***	0.39, <0.001,* 0.01*
Baseline to 24 mos	−2.27	2.80	−1.29	2.79	−0.15	3.24	**0.01***	0.40, 0.003,* 0.27
Baseline to 36 mos	−3.12	3.29	−1.45	3.19	−0.38	4.05	**0.002***	0.07, 0.002,* 0.79
24 to 36 mos	−0.86	2.63	−0.16	2.96	−0.23	3.05	0.49	0.99, 0.99, 0.99
P values[‡]	0.10		0.91		0.59			
Distance VA (logMAR)								
Baseline to 12 mos	−0.02	0.06	−0.02	0.06	−0.03	0.11	0.80	0.99, 0.99, 0.99
Baseline to 24 mos	−0.03	0.05	−0.05	0.08	−0.04	0.07	0.52	0.77, 0.99, 0.99
Baseline to 36 mos	−0.04	0.07	−0.05	0.07	−0.07	0.07	0.35	0.99, 0.44, 0.99
24 to 36 mos	−0.01	0.05	0.00	0.08	−0.03	0.07	0.11	0.99, 0.17, 0.43
P values[‡]	0.50		0.38		0.18			
Near VA (logMAR)								
Baseline to 12 mos	0.02	0.10	0.00	0.09	0.00	0.12	0.44	0.61, 0.99, 0.99
Baseline to 24 mos	0.00	0.09	−0.03	0.09	−0.02	0.08	0.16	0.19, 0.56, 0.99
Baseline to 36 mos	−0.03	0.10	−0.06	0.08	−0.08	0.08	0.11	0.74, 0.11, 0.49
24 to 36 mos	−0.04	0.09	−0.03	0.09	−0.06	0.06	0.12	0.99, 0.64, 0.15
P values[‡]	0.11		0.08		0.06			

Mean and SD were calculated with both eye data.
P values were generated by generalized estimating equation models with age, sex.
D = diopter; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; VA = visual acuity.
*Significance was set at 0.05.
[†]Bonferroni correction was applied for the pairwise comparisons.
[‡]Comparisons among baseline to 12 mos, baseline to 24 mos, and baseline to 36 mos.

than that which occurs with higher concentration of atropine.[4,8] However, we found that low concentrations of atropine had no clinical effect on corneal or lens power, which ascertained that antimyopic effects of low-concentration atropine acted mainly on reducing AL elongation in our previous study.[38]

Another important finding was the effect of age on the rebound magnitude: The older the subject's age, the smaller the rebound effect. This can be related to the slower inherent physiological progression of children at older ages, as demonstrated by results of the LAMP study Phases 1 and 2.[5,6,37] We have recently shown strong association of young age with poor treatment outcomes. Younger children required higher concentrations to achieve similar reductions in myopic progression as older children who were treated by lower concentrations.[37] The concentration-dependent effect among 0.05%, 0.025%, and 0.01% atropine lessened with age (Table 5). For the ages 9−11 years and 12−14 years, the myopic rebound during the third year was similar across all the 3 atropine concentration groups. Moreover, according to estimated means for SE progression and AL elongation after treatment cessation, younger children treated by lower concentrations showed rebound at a similar magnitude as that for older children treated by higher concentrations. For example, the rebound for the ages 9 to 11 years in the 0.05% group was similar to that for the ages 6 to 8 years in the 0.025% group, and the rebound for ages 12 to 14 years in the 0.05% group was similar to that for ages 9−11 years in the 0.025% group. In the ATOM2 study, children with myopia progression of >0.5 D in the washout phase were restarted on 0.01% atropine with promising results. The ATOM2 study also suggested that younger children and those with greater myopic progression in year 1 were more likely to require retreatment, which supports our findings.[12] We suggest that low-concentration atropine treatment in children should be ended at older ages when both the natural myopic progression rate and the rebound effect become smaller. Meanwhile, the optimal age for treatment cessation remains to be evaluated in our subsequent reports.

All Concentrations Remain Well Tolerated

Across the continued treatment subgroups, all concentrations were well tolerated over the 3-year study period. In the current cohort, photopic pupil sizes increased on average by 0.97 mm, 0.45 mm, and 0.61 mm in the 0.05%, 0.025%, and 0.01% atropine groups, respectively. These changes in pupil size did not increase with time throughout the study. It was reported that an increase in photopic pupil size of more than 3 mm is a potential threshold of significant discomfort.[41,42] However, such a low concentration that proved tolerable and acceptable in Asian children may not be applicable to White children with lighter pigmented eyes that may be less tolerant of the side effects.[39,43] Another study in Europe suggested high-concentration atropine (0.5%) can be a treatment option for children at risk of developing high myopia, even though they have a large proportion (22%) of children who ceased treatment because of a relatively high occurrence of side effects.[44] In this Phase 3 study covering the third year, we found that across the washout subgroups for all concentrations, pupil size and accommodation amplitude returned to baseline levels at the first 4-month visit after treatment cessation, indicating that the side effects of atropine due to pupil mydriasis are reversible after 2 years of continuous treatment.

Study Limitations and Strengths

The primary limitation of the study is the switch of the placebo group to 0.05% atropine treatment during the second year, therefore missing the opportunity to continue comparisons with a placebo group. This had to be done based on medical ethics. Thus, the current study cannot evaluate the difference of SE progression and AL elongation among 0.05%, 0.025%, and 0.01% with placebo groups over 3 years. Nevertheless, our results include an arm-to-arm comparison among atropine concentrations of 0.05%, 0.025%, and 0.01% over a 3-year period, followed by 1:1 randomization into continued treatment and washout groups, on a randomized control design to determine the optimal concentrations. This re-randomization allows us to evaluate the longer term efficacy between continuing treatment versus stopping treatment during the third year. Second, the sample sizes for each group were halved due to re-randomization, which limited the sensitivity for the detection of differences between concentration groups. Nevertheless, the statistical power was able to detect a 0.25 D difference between the concentration groups for both the 3-year continuous treatment regimen and the washout regimen. Third, the unmasking of subjects in the washout subgroups may lead to biases. Providing a placebo to the washout group would decrease both the biases in self-reported questionnaires and potentially the dropout rates. Nevertheless, all treatment concentrations were well tolerated. In addition, the rates for photophobia, near vision disturbances, and vision-related quality of life were similar between continued treatment and washout subgroups at all atropine concentrations. Finally, our participants were Chinese, so the generalizability of our study results to other ethnic populations may be limited, especially for Whites with lighter pigmented iris.

Perspectives

Although our results confirmed that continuing atropine treatment into the third year is better than stopping at the third year for monitoring, long-term treatment strategies remain to be defined. For children at older ages and growing into adolescence, the natural myopic progression rate slows. The difference between continuing treatment and stopping treatment becomes smaller. We postulate that good treatment effects can be obtained by withholding treatment for 6 months after 3 years of treatment if the progression has stabilized and then restarting treatment when progression is observed again. We have started the subsequent Phase 4 study, in which all continued treatment subgroups will be switched to using 0.05% atropine continuously until the end of the fifth year. All washout groups will be continued based

on a pro re nata approach for subjects showing progressions of 0.5 D or more to resume treatment using 0.05% atropine. We will be able to determine the long-term efficacy of low-concentration atropine over a 5-year period.

In conclusion, the results of this phase 3 LAMP study show that 0.05% atropine is the optimal concentration among the 0.05%, 0.025%, and 0.01% atropine groups for myopia control over a 3-year period in Chinese children, even when considering the rebound phenomenon for each concentration group. During the third year, continuing treatment using 0.05% atropine confers a better efficacy than stopping treatment. A greater rebound effect is associated with higher treatment concentration and younger age at treatment cessation. However, the rebound effects across the concentration groups studied were small from a clinical perspective. All atropine concentrations were well tolerated without apparent adverse effects on vision-related quality of life. Taking into account that the efficacy of 0.05% atropine over 3 years is more than double that for 0.01% atropine, with only minor rebound effects, we suggest that treatment using 0.05% atropine should be continued into the third year in Asian children.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The study was approved by the Ethics Committee of The Chinese University of Hong Kong. All procedures were conducted according to the tenets of the Declaration of Helsinki. Child subjects who participated in this study gave verbal consent, and written informed consent was obtained from their parents or guardians.

No animal subjects were used in this study.

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Obtained funding: Yam, Chen

Overall responsibility: Yam, Zhang, Zhang, Wang, Tang, Li, Young, Tham, Chen, Pang

Abbreviations and Acronyms:
AL = axial length; **ATOM** = Atropine for the Treatment of Myopia Study; **BCVA** = best-corrected visual acuity; **D** = diopter; **LAMP** = Low-concentration Atropine for Myopia Progression Study; **SE** = spherical equivalent.

Keywords:
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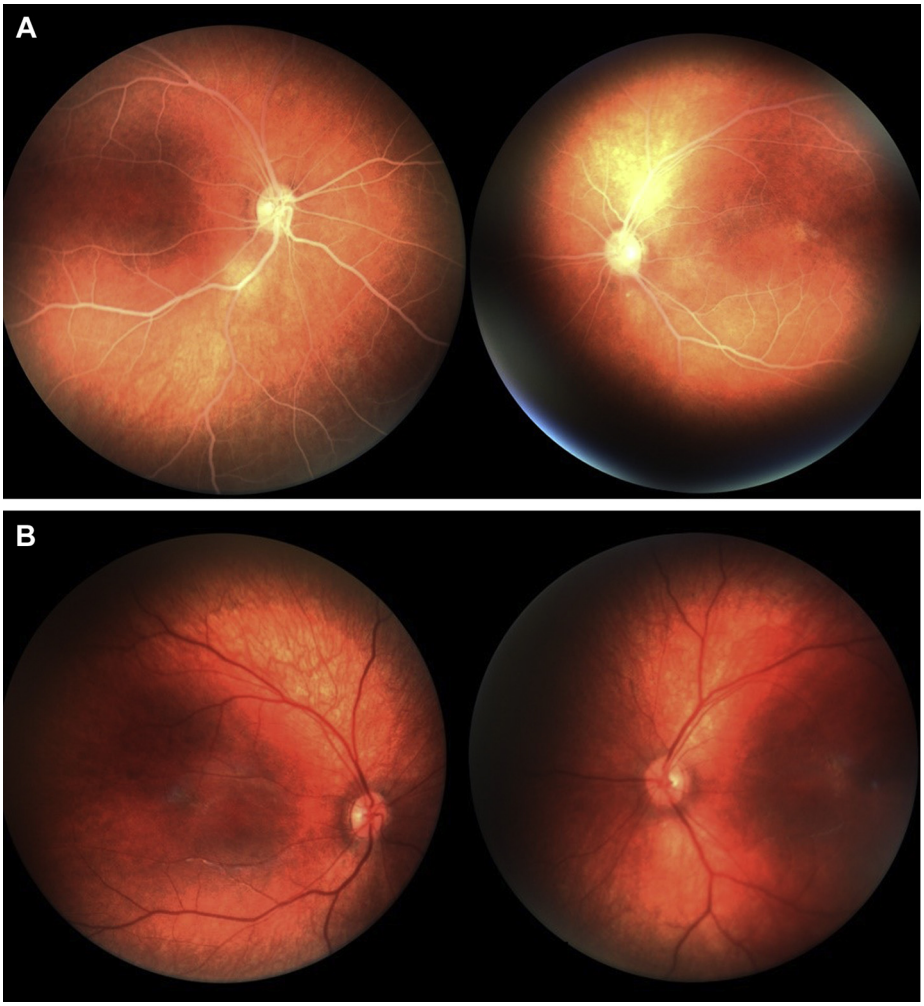
Pictures & Perspectives



Lipemia Retinalis in a Baby with Hyperlipoproteinemia

A 3-week-old boy presented with fever and restlessness. Blood work-up (complete blood count, biochemical profile, and lipid profile) revealed severe hypertriglyceridemia and acute pancreatitis. Examination of the fundi showed creamy arterioles and veins consistent with a diagnosis of lipemia retinalis (Fig **A**). Gene testing detected c.809G>A (p.ARG270HIS) homozygous mutation in the lipoprotein lipase gene. After a few days of treatment with medium chain triglyceride-based enteral formula, triglyceride levels decreased, and the color of the retinal blood vessels returned to normal (Fig **B**). (Magnified version of Fig **A**-**B** is available online at www.aaojournal.org).

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