Atropine for the Treatment of Childhood Myopia: Effect on Myopia Progression after Cessation of Atropine

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Purpose: The aim of this study was to assess the effect on myopia progression after cessation of topical atropine treatment.

Design: Parallel-group, placebo-controlled, randomized, double-masked study.

Participants: Four hundred children aged 6 to 12 years with refractive error of spherical equivalent −1.00 to −6.00 diopters (D) and astigmatism of −1.50 D or less.

Intervention: No intervention was administered. Subjects were followed up for 12 months after stopping treatment, which consisted of either 1% atropine or vehicle eyedrops once nightly for 2 years. Only 1 eye of each subject was chosen through randomization for treatment.

Main Outcome Measures: The main efficacy outcome measures were change in spherical equivalent refraction as measured by cycloplegic autorefraction and change in ocular axial length as measured by ultrasonography.

Results: After cessation of atropine drops, the mean progression in the atropine-treated group was −1.14±0.80 D over 1 year, whereas the progression in placebo-treated eyes was −0.38±0.39 D ($P<0.0001$). However, after 3 years of participation in the trial (with 2 years on atropine treatment), eyes randomized to atropine have less severe myopia than other eyes. Spherical equivalent was −4.29±1.67 D in the atropine-treated eyes compared with −5.22±1.38 D in the placebo-treated eyes ($P<0.0001$). Spherical equivalents in atropine-untreated and placebo-untreated eyes were −5.00±1.62 D and −5.28±1.43 D, respectively. Over the 3 years, the increase in axial length of the atropine-treated eyes was 0.29±0.37 mm compared with 0.52±0.45 mm in the placebo-treated eyes ($P<0.0001$). After cessation of atropine, the amplitude of accommodation and near visual acuity returned to pretreatment levels.

Conclusions: After stopping treatment, eyes treated with atropine demonstrated higher rates of myopia progression compared with eyes treated with placebo. However, the absolute myopia progression after 3 years was significantly lower in the atropine group compared with placebo.

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Myopia is an important public health problem because of its frequency and the consequent public health spending.[1] It is not only a refractive error that requires optical correction but also an ocular state that is associated with an increased risk of sight-threatening conditions, such as myopic macular degeneration, retinal detachment, and glaucoma.[2–4] The risk of these complications increases with the severity of myopia.[1,3]

Because myopia commonly develops in childhood and stabilizes after a period of progression,[1,5,6] it may be possible to reduce the lifetime risk of retinal complications by reducing the severity of the "final myopia" with a treatment modality targeting children with myopia. We recently published the 2-year results of a randomized controlled trial that evaluated the treatment of children with myopia using atropine 1.0% eyedrops.[7]

The study showed that topical atropine was well tolerated and effective in slowing the progression of low and moderate myopia and ocular axial elongation in Asian children, even though the exact mechanism of the drug in retarding myopia is unknown. Childhood myopia progression often extends beyond 2 years. It is not known whether the slower rate of myopia progression and axial length elongation will be maintained after stopping treatment or there will be a rebound phenomenon that will negate the positive treatment effect.

Atropine inhibits accommodation resulting in reduced near visual acuity. It is not known, however, whether prolonged use of atropine will result in permanent paralysis of accommodation or accelerated decrease in accommodative amplitude, thus leading to earlier onset of presbyopia.

To address these issues, we report the results of refractive error and axial length changes, as well as accommodation, 1 year after the cessation of atropine.

Materials and Methods

Study Design

The design and methods of the Atropine in the Treatment of Myopia study, which commenced in 1997, have been published[7] and are

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summarized in this article. This was a single-center randomized, double-masked, placebo-controlled trial designed primarily to study whether topical atropine can prevent the progression of low and moderate myopia effectively and safely in children. The study and protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Singapore Eye Research Institute Review Board. Recruitment of participants was from the general public, primary schools, and ophthalmology practices through the distribution of standardized brochures and letters describing the Atropine in the Treatment of Myopia study, as well as public talks. The participants were children between 6 and 12 years of age with refractive error of spherical equivalent between −1.00 and −6.00 diopters (D) who met the eligibility criteria published previously. Every child gave assent, and written informed consent was also obtained from the parents or legal guardians after thorough explanation of the nature and risks of the study before enrollment. Overall study performance and child safety were reviewed by an independent data and safety monitoring committee.

Randomization

Assignments to treatment were allocated with concealment according to a computer-generated randomization list after eligibility criteria were verified. The children had an equal probability of assignment to either atropine or placebo. Only 1 eye of each child was chosen for treatment. The chosen eye also was selected using the randomization process. A child was considered to be enrolled in the study once the randomization assignment and study number were issued and the child received the assigned eyedrops, which were handed out on the spot promptly after randomization.

Intervention

There was no active intervention during the third year of the study. In the previous 2 years, the eyes assigned for treatment were treated with either 1% atropine sulfate or vehicle eyedrops once nightly for 2 years. Both the atropine and vehicle eyedrops, the latter consisting of 0.5% hydroxypropyl methylcellulose and 1:10,000 benzalkonium chloride, were specially prepared by Alcon Laboratories (Puurs, Belgium).

Masking

To minimize observational bias, neither the study participants nor the investigators responsible for measuring the study outcomes were aware of the intervention given. Several steps were taken to preserve and monitor masking. The atropine and placebo eyedrops were packaged in identical bottles so that no one was able to identify the contents. Labels on the bottle had only the study number, the eye to be treated, and the expiration date. Parents or guardians were asked to seek advice from only the coordinating investigator regarding matters pertaining to their child's treatment and not to discuss any issues related to the study with the investigators measuring the study outcomes. To mask these study investigators, both pupils of every child were dilated fully and checked by the coordinating investigator before being seen by the study investigator.

Study Procedures

Cycloplegic autorefraction was used to assess refractive errors. As with all data-collection procedures, autorefraction was performed only by investigators who were trained and certified on study protocols. A Canon RK5 autorefractor-autokeratometer (Canon Inc. Ltd., Tochigiken, Japan) was used throughout the study to take 5 reliable readings, both before and after cycloplegia. All 5 readings had to be 0.25 D or less apart in both the spherical and cylindrical components before they were accepted. The cycloplegic regimen consisted of 1 drop of proparacaine hydrochloride (Alcaine, Alcon-Couvreur, Puurs, Belgium) followed by 3 drops of 1% cyclopentolate hydrochloride (Cyclogyl, Alcon-Couvreur) administered approximately 5 minutes apart. Cycloplegic autorefraction measurements were taken at least 30 minutes after instillation of the third drop of cyclopentolate. Cycloplegic subjective refraction also was performed primarily for the purpose of prescribing spectacles. After cycloplegic refraction, ocular biometry (anterior chamber depth, lens thickness, vitreous chamber depth, and overall axial length) was measured by A-scan ultrasonography with the Nidek US-800 EchoScan (Nidek Co. Ltd., Tokyo, Japan). Six measurements were obtained for each eye. The axial length measurement was based on the average of the 6 values with a standard deviation of less than 0.12 mm.

Before inducing cycloplegia, the amplitude of accommodation was assessed. With full distance correction in the trial frame placed at 15 mm from the eye, the near point of accommodation (NPA) was measured, 1 eye at a time, using an RAF rule. The NPA was measured with the patient trying to read the smallest letter (N5) on the RAF rule. With the RAF rule in place, the target was moved from 50 cm to the point where the last line became slightly blurred. Then the target was slowly pushed back until the last line was just clearly read. This point was taken as the NPA. The reciprocal of the NPA in meters was calculated as the amplitude of accommodation. Near best-corrected visual acuity was documented using the reduced logarithm of the minimal angle of resolution chart held at 30 cm.

After the first 2 years of the study, data collection was performed at the 30-month and 36-month time points. After the second year visit (Fig 1), all study subjects ceased application of any study medications.

Outcome Measures

Efficacy. The primary outcome was progression of myopia, defined as the change in spherical equivalent refractive error relative to baseline. The baseline assessment took place 2 weeks after commencement of treatment; that is, the pretreatment visit.

This was necessary because atropine induces an additional cycloplegic effect that could lower further the spherical equivalent refractive error. As such, a run-in period allowed for stabilization of the cycloplegic effect, thus making comparison of spherical equivalent refractive error between the baseline and subsequent visits more meaningful. The secondary outcome was change in axial length during follow-up relative to baseline measured by A-scan ultrasonography.

Safety. The safety outcomes have been described[7] and will focus on the near corrected visual acuity and the amplitude of accommodation in the 30- and 36-month measurements compared with the pretreatment visit. The visual acuity was measured using the Early Treatment Diabetic Retinopathy study chart and recorded as the minimum angle of resolution (logarithm of the minimal angle of resolution) values. The chart uses a balanced distribution of Sloan letters that are graded in difficulty; each of the 5 letters in each line counts for a score of 0.1/5 or 0.02.

Statistical Analyses

Two independent sample *t* tests were used to compare the spherical equivalent and progression rate of myopia between atropine and placebo-treated eyes during the 3-year period. Similarly, 2 independent sample *t* tests were performed to assess the difference in progression rate of myopia between atropine and placebo-treated

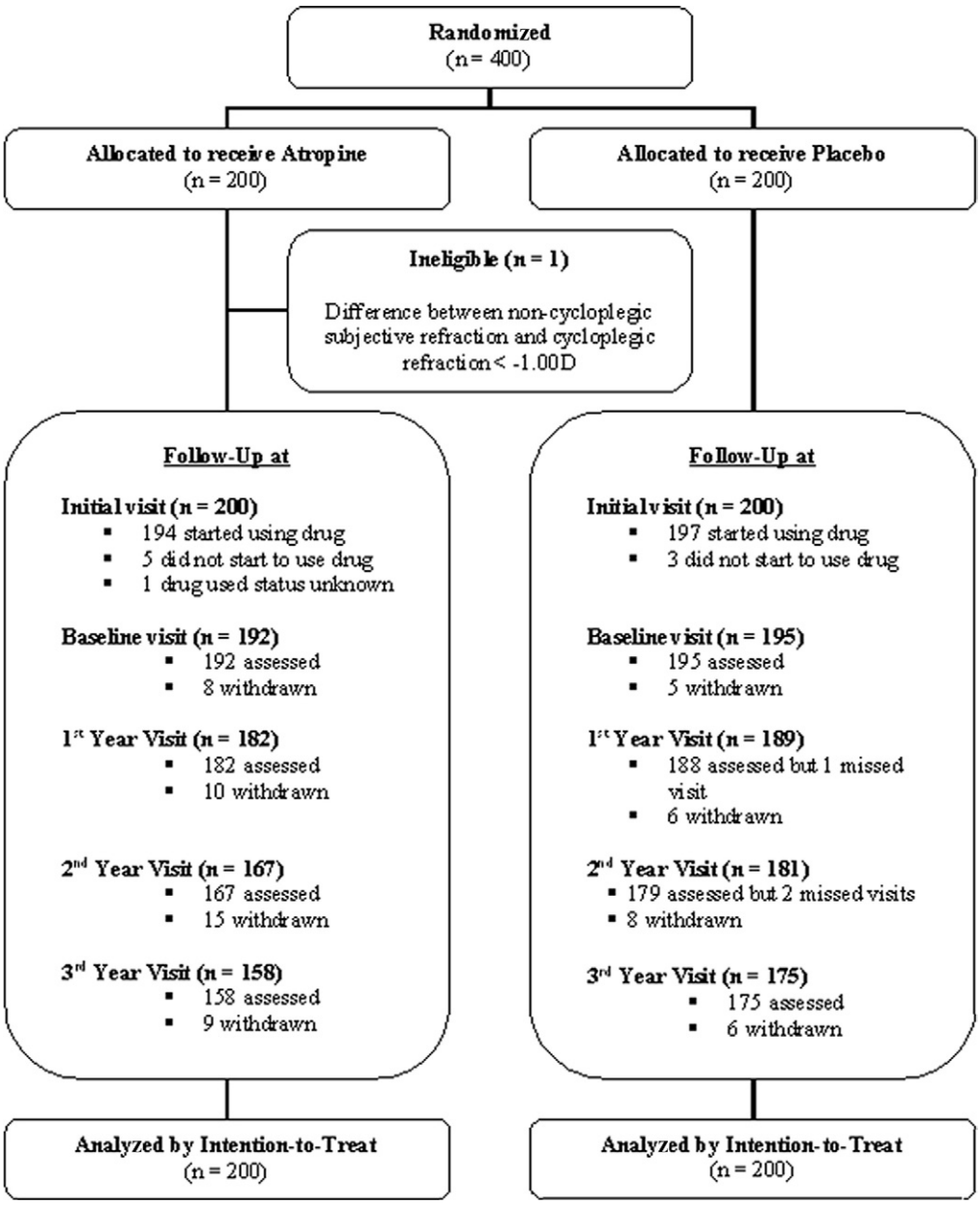

Figure 1. Flow chart showing the trial outline. D = diopters.

eyes in the last year of the study and the first and second halves of the third year. Paired *t* tests were used to examine the difference in progression rate of myopia within atropine and placebo-treated eyes in the first and second halves of the third year, as well as the second half versus the first 2 years.

The number of subjects whose myopia had progressed by more than 2.0 D and 1.5 D at the end of the 3 years was presented. Two independent sample *t* tests were used to compare the mean axial length and increase in axial length between atropine-treated and placebo-treated eyes. To compare the difference in amplitude of accommodation and near visual acuity between atropine and placebo-treated eyes, the 2 independent sample *t* tests were used. Paired *t* test was used to compare between atropine-treated and atropine-untreated eyes. The number of subjects with abnormal lenticular opacities was investigated.

Date Quality and Integrity

The trial data were collected on printed forms and entered into CLINTRIAL (Domain Pharma Corporation, Lexington, MA). The statistical analysis were generated using SAS version 9.1 (SAS Inc., Cary, NC) and performed according to intention-to-treat.

Results

As reported by us previously,[7] 400 children were enrolled between April 1999 and September 2000. The trial outline and the randomization of the children are shown in Figure 1. A total of 333 subjects completed the third-year study. Only a small number of children dropped out after the second-year assessment, with the

majority completing the third-year assessment; 175 of 181 (97%) of the children were randomized to receive placebo, and 158 of 167 (95%) of those were randomized to receive atropine.

The demographics and pretreatment characteristics of the subjects have been published[7] with spherical equivalent and axial lengths comparable between treatment arms. The mean age at the time of registration was 8.75 years for those who did not finish the 3-year follow-up and 9.21 years for those who finished the 3-year follow-up ($P = 0.177$). Our analyses indicate no significant difference (all $P>0.05$) in axial length or spherical equivalent between the dropout group (who had 2-year data but not the last year) and follow-up group (who had completed all 3 years).

Figure 2 shows the mean spherical equivalent of the subjects. The mean spherical equivalent of the atropine-treated eyes was significantly less myopic than those subjects with placebo-treated eye at baseline and first and second years (all $P<0.0001$). The difference in the spherical equivalents of the atropine-treated eye from other eyes persisted in the third-year visits. After 3 years of participation in the trial, the spherical equivalent of the atropine-treated eyes was -4.29 ± 1.67 D compared with -5.22 ± 1.38 D for placebo-treated eyes ($P<0.0001$). Spherical equivalents in atropine-untreated and placebo-untreated eyes were -5.00 ± 1.62 D and -5.28 ± 1.43 D, respectively.

The difference in the spherical equivalents of the atropine-treated eyes and the other eyes narrowed in the last year. The mean rate of increase of myopia in the last year of the study in the atropine-treated eyes was significantly higher than the eyes in the placebo-treated group ($P<0.0001$). After cessation of atropine drops, the mean progression in the atropine-treated group was -1.14 ± 0.80 D, whereas in the corresponding period, the progression in placebo-treated eyes was -0.38 ± 0.39 D. Nevertheless, the average rate of myopia progression of the atropine-treated eyes over the entire 3-year period was still less than the rate in other eyes: -0.46 ± 0.26 D/year, compared with -0.53 ± 0.30 D, -0.52 ± 0.30 D, and -0.54 ± 0.30 D/year in the atropine-untreated, placebo-treated, and placebo-untreated eyes, respectively ($P = 0.043$, on comparing atropine-treated and placebo-treated eyes).

In the first half of the third year, the mean progression rate of myopia was -1.51 ± 1.40 D/year in the atropine-treated eyes and -0.40 ± 0.65 D/year in the placebo-treated eyes. The mean progression rate of myopia was -0.76 ± 0.70 D/year in the atropine-treated eyes and -0.38 ± 0.58 D/year in the placebo-treated eyes during the second half of the third year. The progression rate of myopia in the atropine-treated eyes was significantly higher than in the placebo-treated eyes during both periods ($P<0.0001$). For the atropine-treated eyes, the rates of the myopia progression were significantly less steep in the second half of the last year compared with the rate in the preceding 6 months ($P<0.0001$). Not surprisingly, for the placebo-treated eyes, the progression rate in the first half of the third year was not significantly different from that in the second half ($P>0.05$). Although the rate of myopia progression in the atropine-treated eyes was less severe in the second 6 months than in the first 6 months after drug cessation, it was still significantly more severe than that in the 2-year period while on drug ($P<0.0001$).

Figure 3 shows the distribution of myopia progression in the 4 groups after 3 years. Over the course of the trial (3 years), only 36 atropine-treated eyes progressed by more than 2.0 D. In contrast, 57, 52, and 62 of the atropine-untreated, placebo-treated, and placebo-untreated eyes progressed by more than 2.0 D, respectively. Only 69 atropine-treated eyes progressed by more than 1.5D, compared with 82, 98, and 102 in the atropine-untreated, placebo-treated, and placebo-untreated eyes, respectively.

The mean axial lengths of the eyes in each group are plotted in Figure 4. The mean axial length at the third year measurement was 24.16 ± 0.91 mm in the atropine-treated eyes, compared with 25.45 ± 0.89 mm, 25.45 ± 0.89 mm, and 25.47 ± 0.89 mm in the atropine-untreated eyes, placebo-treated eyes, and placebo-untreated eyes, respectively ($P = 0.0031$ on comparing atropine-treated with placebo-treated eyes). Although the axial lengths in the atropine-

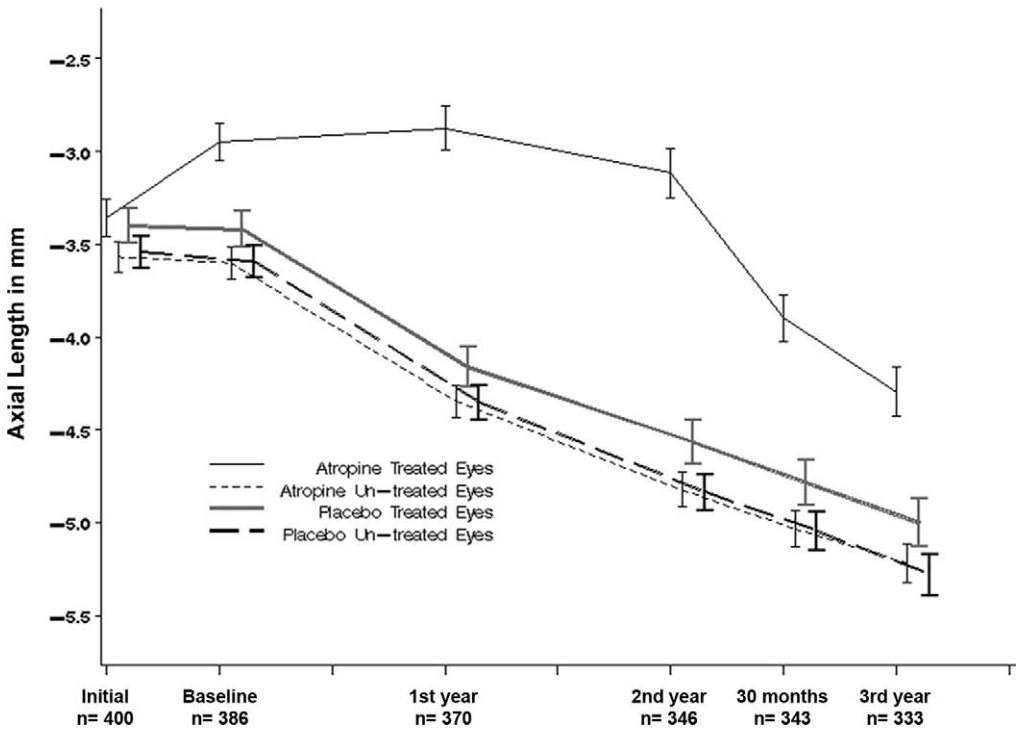

Figure 2. Line chart showing the mean spherical equivalents of the subjects in the 4 groups of eyes. Error bars show the standard errors of the means.

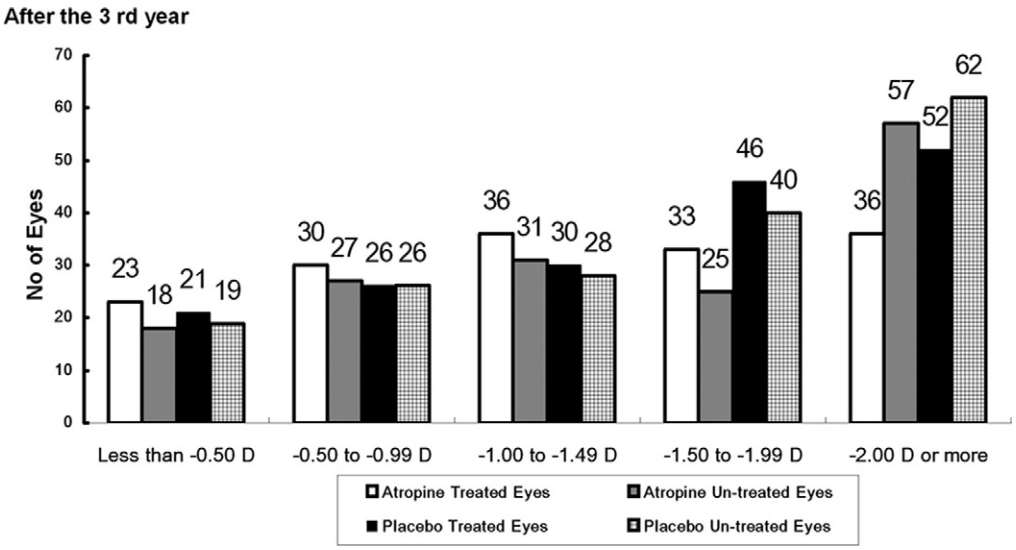

Figure 3. Bar chart showing the distribution of progression of myopia after 3 years of the trial. The numbers above the bars indicate the number of subjects corresponding to the respective bars. D = diopters.

treated eyes were still shorter than the other eyes at the end of the 3 years, the difference was reduced compared with earlier years. Over the course of the 3 years, the increase in axial length of the atropine-treated eyes was 0.29±0.37 mm, compared with 0.50±0.48 mm, 0.52±0.45 mm, and 0.58±0.48 mm in the atropine-untreated, placebo-treated, and placebo-untreated eyes, respectively. The change in axial length of the atropine-treated eyes was significantly smaller than of the placebo-treated eyes ($P<0.0001$).

There were no significant differences in the amplitude of accommodation (Table 1) or the near visual acuity (Table 2) at the initial visit. At the baseline visit (after 2 weeks of atropine), the atropine-treated eyes showed a significant decrease in the amplitude of accommodation (Table 1) and worsening of near visual acuity (Table 2) corrected with the distance glasses from the initial visit (all $P<0.0001$).

The decrease in the amplitude of accommodation in the atropine-treated eyes had recovered (reverted to their "normal" value) by 6 months after cessation of the drug. At 6 months after stopping treatment, the amplitude of accommodation was not only not reduced but also rather significantly improved from the initial visit's measurement (all $P<0.001$).

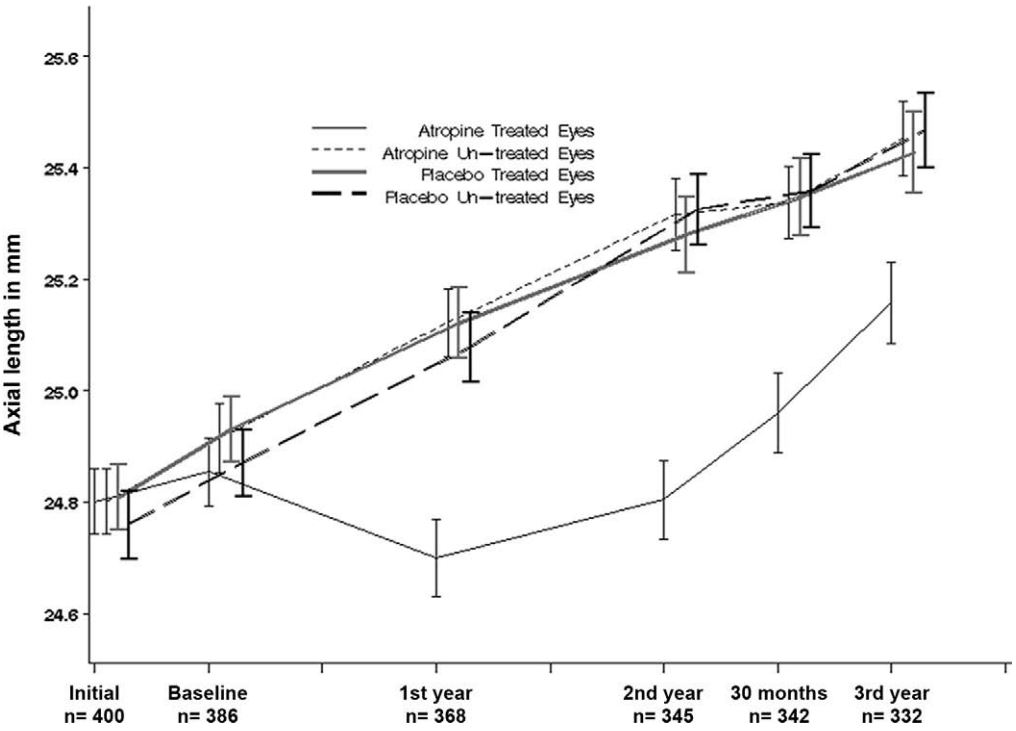

Figure 4. Line chart showing the mean axial lengths of the subjects in the 4 groups of eyes. Error bars show the standard errors of the means.

Table 1. Amplitude of Accommodation

Visit	Amplitude of Accommodation (D), Mean ± SD, n			
	Atropine-treated Eyes	*Atropine-untreated Eyes*	*Placebo-treated Eyes*	*Placebo-untreated Eyes*
Initial	13.76±3.45, 200	13.86±3.58, 200	14.25±3.56, 200	14.10±3.73, 200
Baseline	2.81±2.58, 191	12.71±3.84, 192	14.11±3.57, 194	14.01±3.27, 194
30 mo	14.96±2.71, 164	16.73±13.27, 164	15.93±2.78, 179	15.85±2.84, 179
3 y	14.64±2.56, 158	15.22±2.63, 158	15.93±2.81, 175	16.01±2.89, 175
Visit	**Difference in Amplitude of Accommodation from Initial Visit (D), Mean ± SD, n**			
Baseline	−11.0±3.88, 191 ($P<0.0001$)	−0.07±3.65, 192 ($P = 0.786$)	−1.15±3.98, 194 ($P<0.0001$)	−0.03±3.51, 194 ($P = 0.895$)
30 mo	1.21±3.87, 164 ($P<0.0001$)	1.82±3.82, 164 ($P<0.0001$)	2.83±13.7, 179 ($P = 0.0009$)	1.87±4.02, 179 ($P<0.0001$)
3 y	0.89±3.76, 158 ($P = 0.003$)	1.78±3.84, 158 ($P<0.0001$)	1.42±3.96, 175 ($P<0.0001$)	2.02±3.86, 175 ($P<0.0001$)

D = diopters; SD = standard deviation.

At 6 months after stopping atropine (30 months visit), there was no significant difference in near visual acuity for atropine-treated eyes from the other eyes ($P = 0.7313$ for placebo-treated eyes, $P = 0.3376$ for atropine-untreated eyes, and $P = 0.1195$ for placebo-untreated eyes). Slit-lamp microscopy in the third year of the study did not detect any lenticular opacities. In addition, the loss of best-corrected distance visual acuity in the third year (cycloplegic readings) was ≤3 letters (0.06) in all eyes when compared with the initial, baseline, or second-year visits (Table 3), although there was a small but statistically significant decrease in eyes whether atropine was given or not (all $P<0.001$).

Discussion

Key Findings

In the third-year follow-up of the Atropine in the Treatment of Myopia study, in which no atropine was administered, an overall reduction in the progression of childhood myopia was observed in the atropine-treated eyes compared with placebo-controlled eyes. Although atropine was only used in the first 2 years of the study, the beneficial effect of the drug on myopia progression was still evident 1 year after cessation of atropine. Although the effect of the drug on myopia was relatively reduced after cessation for 1 year, the change in the axial length of the eyes over the entire study duration was significantly less than in eyes not treated with atropine. These results suggest that the effect of atropine on the axial elongation of myopic eyes was not completely abrogated by the cessation of its use for 1 year.

This study also showed that the impairment of accommodation and consequent blurring of near vision as a result of atropine treatment was only temporary and reversible after cessation of treatment. In addition, there was absence of any cataracts 1 year after cessation of atropine drops.

Comparison with Other Studies

There has been no previous longitudinal study that evaluated the effect of cessation of atropine eyedrops on myopia progression.

Possible Mechanisms

Why is there a rebound effect after cessation of atropine? The data suggest that atropine may have a short-term reversible action and a longer-term action on children's refractive errors. The short-term change may be responsible for the reduction in the spherical equivalent in the atropine-treated eyes as early as the baseline measurement (Fig 2), which was obtained 2 weeks after the initial visit, that is, 2 weeks after the commencement of treatment. This difference is probably related to cycloplegic effects of atropine because there was a difference in accommodation (Table 1) but not the axial length (Fig 4). After cessation of atropine treatment, the progression rate in the first 6 months differed

Table 2. Near Corrected Visual Acuity

Visit	Near Corrected Visual Acuity, Mean ± SD, n			
	Atropine-treated Eyes	*Atropine-untreated Eyes*	*Placebo-treated Eyes*	*Placebo-untreated Eyes*
Initial	0.50±0.11, 200	0.50±0.11, 200	0.51±0.13, 200	0.51±0.13, 200
Baseline	1.58±0.50, 192	0.50±0.15, 192	0.50±0.15, 194	0.49±0.13, 194
30 mo	0.39±0.05, 164	0.39±0.06, 164	0.39±0.06, 179	0.38±0.05, 179
3 y	0.38±0.06, 158	0.38±0.06, 158	0.39±0.06, 175	0.39±0.06, 175

D = diopters; SD = standard deviation.

Table 3. Change in Best-corrected Cycloplegic Distance Visual Acuity

Group	Difference in Cycloplegic Best-corrected Visual Acuity, Mean ± SD, n			
	Atropine-treated Eyes	*Atropine-untreated Eyes*	*Placebo-treated Eyes*	*Placebo-untreated Eyes*
30 mo from initial visit	−0.05±0.07, 164 (P<0.0001)	−0.04±0.06, 164 (P<0.0001)	−0.05±0.07, 179 (P<0.0001)	−0.05±0.07, 179 (P<0.0001)
3 y from initial visit	−0.06±0.07, 158 (P<0.0001)	−0.05±0.06, 158 (P<0.0001)	−0.06±0.06, 175 (P<0.0001)	−0.06±0.07, 175 (P<0.0001)
3 y from baseline visit	−0.03±0.06, 158 (P<0.0001)	−0.03±0.06, 158 (P<0.0001)	−0.05±0.06, 175 (P<0.0001)	−0.04±0.07, 175 (P<0.0001)
3 y from 2-y visit	−0.02±0.05, 157 (P = 0.0004)	−0.01±0.05, 157 (P = 0.001)	−0.02±0.05, 174 (P<0.0001)	−0.02±0.05, 174 (P = 0.0003)

D = diopters; SD = standard deviation.

from that in the following 6 months. This suggests that the cycloplegic effect of the drug wore out within 6 months of cessation.

Notwithstanding the "rebound phenomenon" observed in the first 6 months after stopping treatment, the rate of myopia progression beyond 6 months in the atropine-treated eyes, although less than the prior 6 months, was still slightly higher than that of control eyes. It is not known whether the rate of progression will plateau or continue unabated resulting in the myopia catching up with the control eyes.

Strengths and Limitations

The merits of this study include those of a randomized, double-masked, placebo-controlled design and the inclusion of ocular biometry as secondary outcome in all subjects. A weakness of the study was that the duration of follow-up after the cessation of the atropine drops was only 1 year. Although there was a rebound phenomenon in the myopia progression in atropine-treated eyes after stopping the drug for 1 year, it was not sufficient to negate the earlier positive treatment effects. It remains to be seen whether a longer period of drug-free treatment will obliterate the earlier benefits, but of course reinstitution of atropine treatment to enhance or complement further myopia reduction may be considered in the clinical setting of progressive myopia. The natural history of childhood myopia is to progress for a few years and stabilize thereafter.[1,5,6] Because of the relatively short duration of drug cessation, it is not known if 2 years of atropine use is sufficient to obtain a final spherical equivalent that is significantly less myopic than atropine-untreated subjects. One can make the case that atropine administration should be advocated if it reduces the final spherical equivalent, because the risk of retinal complications in myopia is associated with the magnitude of the spherical equivalent later in life.[1,3]

Treatment with 1% atropine produces some unwanted adverse effects, such as glare and photophobia, because of mydriasis and blurring of near vision from induced cycloplegia. Therefore, it is not envisaged that the administration of atropine for myopia be extended for excessively long periods. In a clinical setting, it would be feasible to consider a goal of reducing final refractive error in children with progressive myopia, which could be achieved by titrating the duration of atropine administration in children according to the number of years of previous myopia progression. By assuming that the total duration of myopia progression is intrinsic to each child and is not affected by any atropine administration, a child with more years of progression should be treated with a shorter duration of atropine. Alternatively, it may also be possible to cease atropine use in older myopic children, such as early to mid-teenaged children, regardless of the duration of atropine use, because epidemiologic evidence shows an association between age and stabilization of refractive error.[5,6] It would be ideal if atropine use could be restricted to short periods when maximal myopia progression occurs, with cessation and subsequent retreatment according to progression rate. Further research is required to identify the optimal duration of treatment of myopia with atropine by evaluation of refractive errors for a longer period of time after the cessation of atropine treatment.

The Atropine in the Treatment of Myopia Study showed that the progression of low and moderate myopia could be slowed pharmacologically, with effects still persisting after stopping the active drug for 1 year. Despite long-term use of atropine, the amplitude of accommodation and blurred near vision returned to normal after stopping treatment.

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